Bacterial Pathogenicity

Infection: is the invasion of the human body tissue by disease causing agents, their multiplication, and the reaction of host tissues to the infectious agents and the toxin they produce.

Mixed infection: Several microbes grow simultaneously at the infection site.

Disease: Any deviation from health, disruption of a tissue or organ caused by microbes or their products.

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

Human body defenses

There are two kinds of body defenses against microbial infections:

- **humoral immunity** the aspect of immunity that is mediated by macromolecul , such as secreted antibodies , complement proteins and certain Antimicrobial peptide.
- **Cell-mediated immunity** is an Immune response that does not involve Antibody but rather involves the activation of body immunity cells like Phagocytes, Antigen -specific Cytotoxic T-lymphocytes.

According to its way of living bacteria can be classified to

1. **Nonpathogenic:** A microorganism that does not cause disease.
2. **Opportunistic pathogen:** An agent capable of causing disease only when the host's resistance is impaired (e.g. when the patient is "immunocompromised).
3. **Pathogenic bacteria:** is parasitic bacteria that are the causative agents of bacterial infections.
4. **Saprophytic bacteria:** which live freely in the soil and feed on decaying organic matters.
5. **Commensals:** Are parasitic bacteria live on external or internal surfaces of the body without causing disease, these bacteria may even be beneficial to the host e.g. commensals of the gut digest polysaccharides and are source of certain vitamins, these bacterial flora also compete with pathogenic bacteria for nutrition thus inhibiting their growth.

Bacterial Pathogenicity:

refers to the ability of an organism to cause disease, using its virulence factors**.** **Virulence** usually refers to the degree of pathogenicity within a group or species of microorganisms. virulence of a microorganism is not generally attributable to a single factor, but depends on several parameters that are related to the organism, the host, and the dynamic interaction between them. Bacterial virulence, can be measured by bacterial **infectivity** (their ability to initiate an infection) and the **severity** of the condition produced.

In the lab, Virulence can be designated as LD_{50} or ID_{50} (These values are determined by inoculation of laboratory animals):

the LD_{50} (50% lethal dose) is the number of organisms needed to kill half the hosts, and ID_{50} (50% infectious dose) is the number needed to cause infection in half the hosts.

Pathogenicity depends on:

1- Virulence factors (Adherence factors, Invasiveness, Toxin production).

2- Number of initial organisms.

3- Immune status.

Table 5.2 Examples of surface virulence factors which interfere with host defences

Organism	Virulence factor	Used in vaccine
Bacteria		
Streptococcus pneumoniae	Polysaccharide capsule	Yes
Streptococcus pyogenes	M protein	No
Staphylococcus aureus	Protein A	No
Neisseria meningitidis	Polysaccharide capsule	Yes
Haemophilus influenzae	Polysaccharide capsule	Yes
Klebsiella pneumoniae	Polysaccharide capsule	No
Escherichia coli	Protein pili	No
Salmonella typhi	Polysaccharide capsule	No
Mycobacterium tuberculosis	Mycolic acid cell wall	No
Fungi		
Cryptococcus neoformans	Capsule	No

STAGES OF PATHOGENICITY

1-Transmission

2-Attachment (adhesion, adherence).

3-Colonization and multiplication of microorganism.

4-Avoidance of host defense mechanisms like phagocytosis.

5-Damage of host cells by:

A- Invasiveness.

B -Toxin production.

C- Both of them.

TRANSMISSION Most infections are acquired by transmission from external sources, they are **exogenous** in origin. Others are caused by members of the normal flora behaving as opportunist pathogens, i.e. they are **endogenous** in origin. Transmission can be by:

- inhalation- the airborne route
- ingestion - faecal contamination of food and water.
- Inoculation - by sexual contact, contaminated needles, skin contact, blood transfusions or biting insects.

There are four important portals (or gates) of pathogens

1- Skin.

2- Respiration.

3- Gastrointestinal tract.

4- Genitourinary tract.

Table 5.1 Portals of entry of some common pathogens

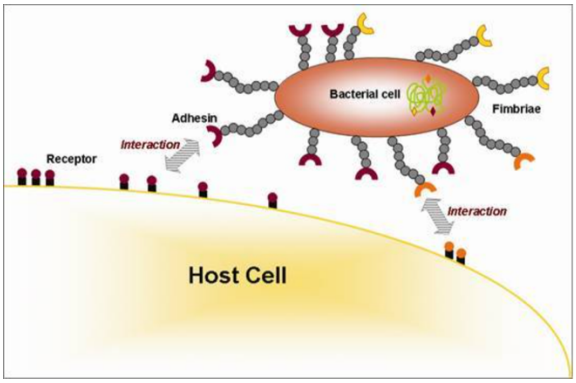
Portal of entry	Pathogen	Disease
Skin	*Clostridium tetani*	Tetanus
	Hepatitis B virus	Hepatitis B
Respiratory tract	*Streptococcus pneumoniae*	Pneumonia
	Neisseria meningitidis	Meningitis
	Haemophilus influenzae	Meningitis
	Mycobacterium tuberculosis	Tuberculosis
	Influenza virus	Influenza
	Rhinovirus	Common cold
	Epstein–Barr virus	Infectious mononucleosis
Gastrointestinal tract	*Shigella dysenteriae*	Dysentery
	Salmonella typhi	Typhoid fever
	Vibrio cholerae	Cholera
	Hepatitis A virus	Infectious hepatitis
	Poliovirus	Poliomyelitis
Genital tract	*Neisseria gonorrhoeae*	Gonorrhoea
	Treponema pallidum	Syphilis
	Human immunodeficiency virus (HIV)	Acquired immune deficiency syndrome (AIDS)
	Candida albicans (fungus)	Vaginitis

Adherence to host surfaces.

Adherence is the first step in the infection. Unless organisms have the ability to stick or adhere to host surfaces they will be unable to cause infection. Some bacteria and fungi have specialized structures or produce substances that facilitate their attachment to the surface cells (e.g. dentures, artificial heart valves), thereby enhancing their ability to colonize and cause disease. These adherence mechanisms are critical for organisms that attach to mucous membranes; mutants that lack these mechanisms are often non-pathogenic (e.g. the hair-like pili or Fimbriae, of *Neisseria gonorrhoeae* and *Escherichia coli* mediate their attachment to the urinary tract epithelium; the extracellular polysaccharides of *Streptococcus mutans* help it adhere to enamel surfaces).

Adherence factors.

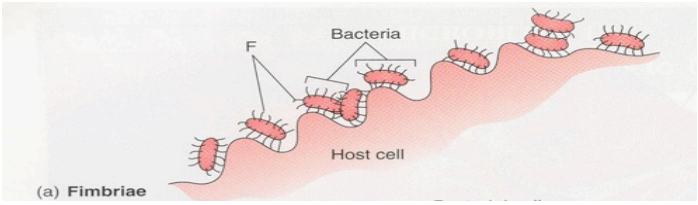
1-Fimbriae: Are the most common adhesion molecules e.g. *Neisseria gonorrhoeae* and *E coli* mediate the attachment to cell surfaces.



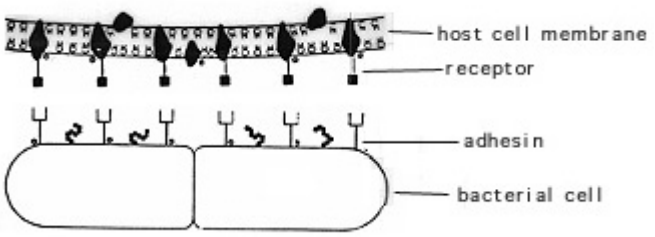
2- The **filamentous haemagglutinin adhesin (FHA)** is a large, filamentous Protein that serves as a dominant attachment factor for adherence to host Cilium Epithelium of the Respiratory tract.

3-Exopolysaccarides.Present on the surface of some-gram positive bacteria are also involving in adhesions.

4- Flagella act as adhesion *in Vibrio cholerae* and *Campylobacter jejani*.



5- In addition to above types of adherence factors **Specific adherence** involves permanent formation of many specific lock- key bonds between complementary molecules on each cell surface.

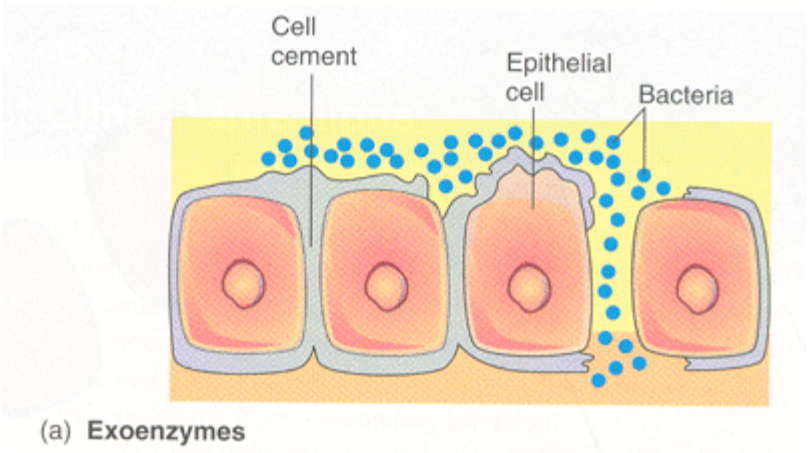


Colonization and invasion:

For many pathogenic bacteria, the initial interaction with host tissues occurs at a mucosal surface and then colonization is started. This allows the establishment of infection that may remain localized or may subsequently spread to other tissues in a process called **invasion**. Cell invasion confers the ability to avoid humoral host defence mechanisms .

INVASIVENESS

These are mechanisms that give bacteria its ability to invade tissues, multiply and spread rapidly (bacterial invasion). Invasiveness of bacteria plays a critical role in their pathogenesis by secretion of bacterial enzymes. Most are enzymes affecting physical barriers like tissue matrices and cell membranes. In this way, the bacterium can quickly spread through extracellular spaces.



(a) Exoenzymes

A few examples are:

a hemolysin or **listeriolysin O**: Which injects into the membrane of the vacuole and causes the formation of pores (e.g. that caused by *Listeria monocytogenes)* then enters the cytoplasm of the cell, where it continues to grow and multiply, after escaping the toxic environment of the phagolysosome.

Coagulase: Produced by *Staphylococcus aureus,* accelerates the formation of a fibrin clot (from fibrinogen). It helps protect the organisms from phagocytosis by walling off the infected area and by coating the organisms with a fibrin layer.

Collagenase : It breaks down collagen fibers & promote spread of infection.

Streptokinase and **staphylokinase :** produced from Group A streptococci and staphylococci that hydrolyze fibrin clots, which also facilitate the spread of organisms in the tissues.

Immunoglobulin A (IgA) protease: Degrades protective IgA on mucosal surfaces, allowing organisms such as *N gonorrhoeae, Haemophilus injluenzae* and *Streptococcus pneumoniae* to adhere to mucous membranes.

AGGRESSINS

In order to survive and multiply within the host, many organisms produce a variety of substances that allow them to avoid host defence mechanisms. These substances, termed aggressins, include capsules and extracellular slime substances, surface proteins, surface carbohydrates, enzymes, toxins, and other small molecules. The capsular structures of some bacteria enable the organisms to avoid phagocytosis by preventing interaction between the bacterial cell surface and phagocytic cells or by concealing bacterial cell surface components that would otherwise interact with phagocytic cells or complement and lead to ingestion. Some organisms produce capsules that are structurally similar to host tissues and, therefore, are not recognized as foreign by the body defense mechanisms. Organisms that possess capsules behave as aggressins include S. *aureus, S. pneumoniae, N. meningitidis, H. influenzas* type b, *K. pneumoniae* .

TOXIGENICITY

Toxin is a protein or conjugated protein produced by some pathogenic bacteria that is highly poisonous for other living organism. The ability of microorganism to produce a toxin that contributes to the development of disease called **toxigenicity.** Toxins are of two categories: endotoxins and exotoxins.

Endotoxins

Endotoxins are the cell wall lipopolysaccharides of Gram-negative bacteria (both cocci and bacilli) and are not actively released from the active cell, it is released after the cell death. Endotoxins cause fever, shock and other generalized symptom s.

It is an outer membrane chemical moiety consisting of three sections:

1-A toxic lipid (Lipid A) anchored in the outer membrane,

2-An immunogenic polysaccharide core, and

3-An O antigen proteins of oligosaccharides at the extracellular surface.

Exotoxins

Both Gram-positive and Gram-negative bacteria secrete exotoxins. Exotoxins in particular can cause disease in distant parts of the body as a result of diffusion of the toxin via systemic routes (e.g. tetanus bacillus infecting a lesion in the foot produces an exotoxin which causes 'lockjaw' or spasm of masseter muscles on the face).

Bacterial exotoxins can be broadly categorized as:

• neurotoxins

• enterotoxins

• miscellaneous exotoxins.

Neurotoxins. Tetanus toxin (produced by bacteria called *Clostridium tetan*i**)** , diphtheria toxin (by *Corynebecterium diphtheria*) and botulinum toxin (by Clostridium botulinum) are all neurotoxins and their action is mediated via neuronal pathways.

Enterotoxins. These toxins act on the gut mucosa and cause gastrointestinal disturbances. *Escherichia coli* enterotoxin is of two types: one heat-labile and one heat-stable.

Miscellaneous exotoxins. these exotoxins are produced by *Clostridium perfringens* and other species of clostridia that cause gas gangrene.

Antiphagocytic (Survival Inside of Phagocytes)

Many bacterial pathogens are rapidly killed once they are ingested by polymorphonuclear cells or macrophages. Some pathogens evade phagocytosis or leukocyte microbicidal mechanisms by adsorbing normal host components to their surfaces.

For example, *Staph..aureus* has surface protein A. Other pathogens have polysaccharide capsules that impede phagocytosis, e.g., *Streptococcus pneumoniae, N meningitidis.*

Streptococcus pyogenes (group A streptococci) have M protein, *N gonorrhoeae*(gonococci) have pili.

Most of these antiphagocytic surface structures show much antigenic heterogeneity. For example, there are more than 80 pneunococcal capsular polysaccharide types and more than 60 M protein types within group A *streptococci*.

Bacteria that can resist killing and survive or multiply inside of phagocytes are considered intracellular parasites. In this case, the environment of the phagocyte may be protecting bacteria during the early stages of infection or until they develop more virulence factors.

The role of bacterial biofilms

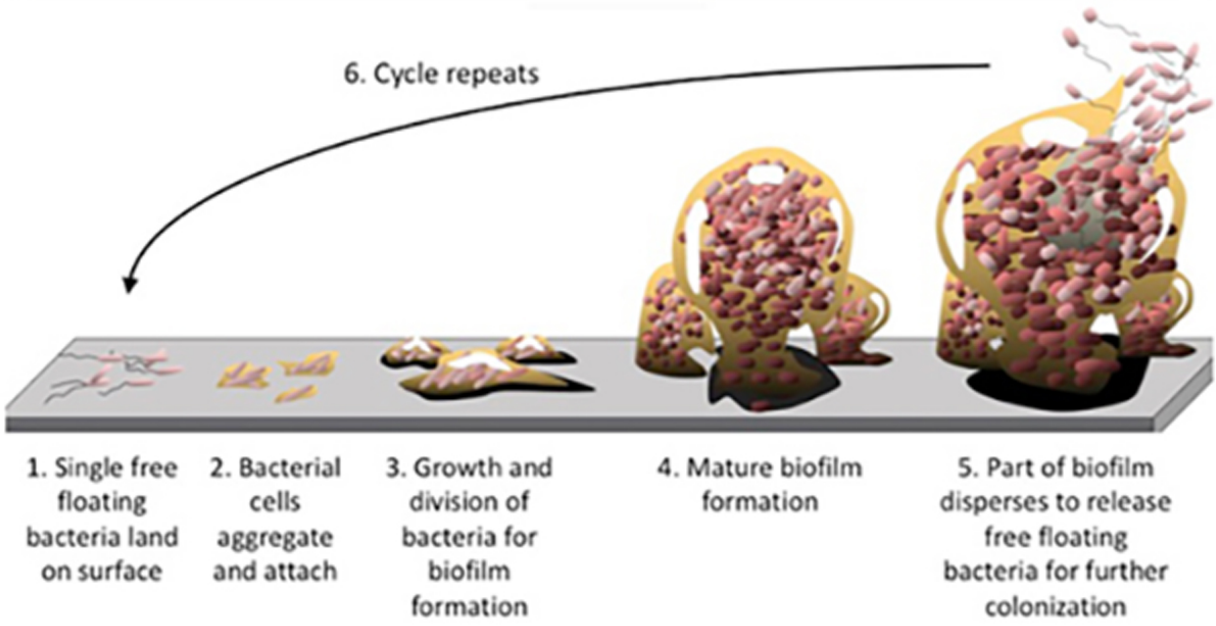
A biofilm is an aggregate of interactive bacteria attached to a solid surface or to each other and encased in an exopolysaccharide matrix. Biofilms form a slimy coat on surfaces and throughout nature. Bacteria of single species may coaggregate to form a biofilm. Fungi- including yeasts are occasionally involved.

Biofilms are:

- -formed when microbes adhere to each other and to the surface
- -each microbe secretes glycocalyx substances allowing other microbes to adhere; large mass is formed

the biofilm is resistant to disinfectants and antibiotics (outer layer protects inner layers), which makes serious problems for patients with catheters and surgical implants: serves as chronic reservoir.

Biofilms are important in human infections that are persistent and difficult to treat. A few examples include *Staphylococcus epidermidis* and *Staphylococcus aureus* infections of central venous catheters, eye infections such as occur with contact lenses and intraocular lenses, in dental plaque, and with *Pseudomonas aeroginosa* airway infections in cystic fibrosis patients.



Pathogenesis of viral infection

Pathogenesis is the process by which an infection leads to disease. Pathogenic mechanisms of viral disease include

(1) implantation of virus at the portal of entry,

(2) local replication,

(3) spread to target organs (disease sites), and

(4) spread to sites of shedding of virus into the environment.

Factors that affect pathogenic mechanisms are

(1) accessibility of virus to tissue,

(2) cell susceptibility to virus multiplication, and

(3) virus susceptibility to host defenses.

Virions (free viruses) implant onto living cells mainly via the respiratory, gastrointestinal, skin-penetrating, or urogenital routes although other routes can be used. The final outcome of infection may be determined by the dose and location of the virus as well as its infectivity and virulence.

Most virus types spread among cells extracellularly, but some may also spread intracellularly. Establishment of local infection may lead to localized disease and localized shedding of virus.

The incubation period is the time between exposure to virus and onset of disease. During this usually asymptomatic period, implantation, local multiplication, and spread (for disseminated infections) occur.

Depending on the balance between virus and host defenses, virus multiplication in the target organ may be sufficient to cause disease and death. (e.g. specific preference cells for rhinoviruses are upper respiratory epithelium and for human immunodeficiency virus (HIV) are CD4 T Lymphocytes)

Diverse viruses may be shed at virtually every site.

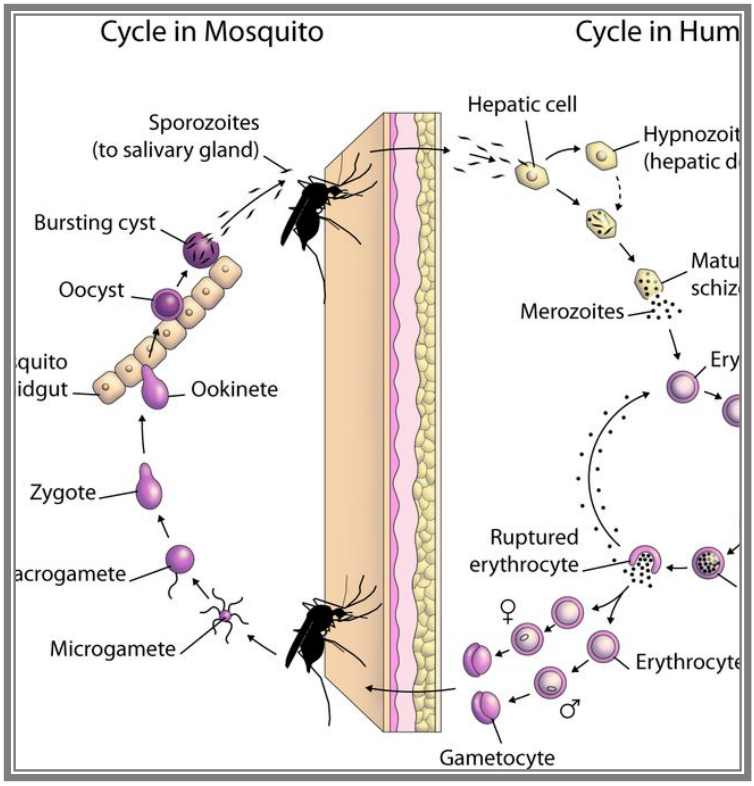
Pathogenesis of fungal infection

Fungal disease, particularly its life-threatening extreme, is relatively rare despite the some species of fungi present in the environment and on the human body surface. Most fungal infections appear to require a breach in host defenses in order to become established. Yeasts often cause mucosal inflammation following alteration of either vaginal or gastrointestinal flora. Dermatophytic fungi cause a variety of skin conditions but rarely cause more invasive disease in immunocompetent patients because they are restricted to the skin.

Pathogenesis of parasitic infections

Protozoal and helminth infections have a complex pathogenesis, which is best understood by referring to the parasite's life cycle. Some protozoal and helminth infections require transmission by a disease vector. The vector is often an arthropods. The development of disease depends on a three-way relationship between microorganism, vector and human victim in these infections.

In developed countries, parasitic infections are most common in international travelers, the sexually active, immunocompromised patients and poor people.



Life Cycle of Malaria Parasite

Opportunist infections

If an organism is capable of causing disease in an apparently healthy individual, it is clearly aggressively pathogenic. If it is normally incapable of causing disease but can do only when the human body immunity is compromised in some way, in this case infection called opportunist infection. These types of infections have a particular importance in hospitals patients and immunocompromised patients.