Unit – 1 Host parasite relationship

Microorganisms are constantly associated with the body surfaces of animals. There are more bacterial cells on the surface and inside the body of an animal than the cells that make up the body of an animal. The bacteria and other microbes that are consistently associated with an animal are called the **normal flora**, or more properly the "**indigenous microbiota**". These bacteria have a full range of **symbiotic interactions** with their animal hosts.

In biology, **symbiosis** is defined as "life together", i.e., those two organisms live in an association with one another. Thus, there are three types of symbiotic associations.

Types of Symbiotic Associations

1. **Mutualism**. Both members of the association benefit. E.g. Lactic acid bacteria that live in intestine and on the vaginal epithelium of a woman. The bacteria are get constant temperature and supply of nutrients (glycogen) and they produce lactic acid, which protects intestine and vagina from colonization and disease caused by yeast and other potentially harmful microbes.

2. **Commensalism**. There is no benefit or harm to either member of the association. E.g. *Staphylococcus epidermidis*, and skin of humans. The bacterium produces lactic acid that protects the skin from colonization by harmful microbes that are less acid tolerant.

3. **Parasitism**: **Parasite** refers to an organism that grows and is sheltered on or in a different organism while contributing nothing to the survival of its host. In microbiology, the parasite is capable of causing damage to the host. This type of a symbiotic association draws our attention because a parasite may become pathogenic if the damage to the host results in disease. Other nonindigenous parasites generally always cause disease if they associate with a nonimmune host.

Parasitology: It refers to the scientific study of parasitism.

Pathogen is a microorganism that is able to produce disease.

Pathogenicity is the ability of a microorganism to cause disease in another organism, namely the **host** for the pathogen.

Opportunistic pathogens: In humans, some of the normal bacterial flora (e.g. *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae)* is **potential pathogens** that live in a commensal or parasitic relationship without producing disease. They do not cause disease in their host unless they have an opportunity brought on by some compromise or weakness in the host's anatomical barriers, tissue resistance or immunity. Furthermore, the bacteria are in a position to be transmitted from one host to another, giving them additional opportunities to colonize or infect.

Obligate pathogens: These are pathogens that cause disease definitely when entered and multiplied in the body.

Normal flora of Human Body

In a healthy animal, the internal tissues, e.g. blood, brain, muscle, etc., are normally free of microorganisms. However, the surface tissues, i.e., skin and mucous membranes are constantly in contact with environmental organisms and become readily colonized by various microbial species. The mixture of microorganisms regularly found at any anatomical site is referred to as the **normal flora** or **indigenous microbiota**. The normal flora of humans consists of a few eukaryotic fungi and protists, but bacteria are the most numerous and obvious microbial components of the normal flora.

Beneficial Effects of the Normal Flora

1. The normal flora synthesizes and excretes vitamins:

These vitamins are absorbed as nutrients by their host. For example, in humans, enteric bacteria secrete Vitamin K and Vitamin B12, and lactic acid bacteria produce certain B-vitamins in intestine.

2. The normal flora prevents colonization by pathogens:

It prevents colonization by pathogens by competing for attachment sites or for essential nutrients. This is thought to be their most important beneficial effect, which has been demonstrated in the oral cavity, the intestine, the skin, and the vaginal epithelium.

3. The normal flora may antagonize other bacteria by producing antimicrobial substances:

Normal flora produces substances which inhibit or kill nonindigenous species. The intestinal bacteria produce a variety of substances ranging from relatively nonspecific fatty acids and peroxides to highly specific bacteriocins, which inhibit or kill other bacteria.

4. The normal flora stimulates the development of certain tissues:

Development of certain tissues such as the caecum (part of large intestine near joining of small intestine) and certain lymphatic tissues (Peyer's patches) in the GI tract are developed in presence of normal flora. The caecum of germ-free animals is enlarged, thin-walled, and fluid-filled, compared to that organ in conventional animals. Also, the intestinal lymphatic tissues of germ-free animals are poorly-developed compared to conventional animals.

5. The normal flora stimulates the production of natural antibodies:

Since the normal flora behaves as antigens in an animal, they induce an immunological response, in particular, an antibody-mediated immune (AMI) response. Low levels of antibodies produced against components of the normal flora are known to cross react with certain related pathogens, and thereby prevent infection or invasion. Antibodies produced against antigenic components of the normal flora are sometimes referred to as "natural" antibodies, and such antibodies are lacking in germ-free animals.

Harmful Effects of the Normal Flora

Harmful effects of the normal flora, some of which are observed in studies with germ-free animals, can be put in the following categories.

1. Bacterial synergism: It is between a member of the normal flora and a potential pathogen. This means that one organism is helping another to grow or survive. There are examples of a member of the normal flora supplying a vitamin or some other growth factor that a pathogen needs in order to grow. This is called **cross-feeding** between microbes. Another example of synergism is the normal flora shares its drug resistance with pathogens.

2. Competition for nutrients: Bacteria in the gastrointestinal tract must absorb some of the host's nutrients for their own needs. However, in general, they

transform them into other metabolisable compounds, but some nutrient(s) may be lost to the host.

3. Induction of a low grade toxemia: Minute amounts of bacterial toxins (e.g. endotoxin) may be found in the circulation.

4. The normal flora may be agents of disease: Members of the normal flora may cause **endogenous disease** if they reach a site or tissue where they cannot be restricted or tolerated by the host defenses. Many of the normal floras are potential pathogens, and if they gain access to a compromised tissue from which they can invade, disease may result.

5. Transfer to susceptible hosts: Some pathogens of humans that are members of the normal flora may also rely on their host for transfer to other individuals where they can produce disease. This includes the pathogens that colonize the upper respiratory tract such as *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Staphylococcus aureus,* and potential pathogens such as *E. coli*, *Salmonella* or *Clostridium* in the gastrointestinal tract.

6. Dental Caries, Gingivitis and Periodontal Disease: The most frequent and economically-important condition in humans resulting from interactions with our normal flora is probably dental caries. Dental plaque, dental caries, gingivitis (inflammation of roots of teeth) and periodontal disease result from actions initiated and carried out by the normal bacterial flora.

Dental plaque: The dominant bacterial species in dental plaque are *Streptococcus sanguis* and *Streptococcus mutans*, both of which are considered responsible for plaque.

Plaque formation is initiated by a weak attachment of the streptococcal cells to salivary glycoproteins forming a pellicle on the surface of the teeth. This is followed by a stronger attachment by means of extracellular sticky polymers of glucose (glucans) which are synthesized by the bacteria from dietary sugars (principally sucrose).

Dental Caries: is the destruction of the enamel, dentin or cementum of teeth due to bacterial activities. Caries are initiated by direct demineralization of the enamel of teeth due to lactic acid and other organic acids which accumulate in dental plaque. Lactic acid bacteria in the plaque produce lactic acid from the fermentation of sugars and other carbohydrates in the diet of the host.

Streptococcus mutans and *Streptococcus sanguis* are most consistently been associated with the initiation of dental caries, but other lactic acid bacteria are probably involved as well. These organisms normally colonize the occlusal fissures and contact points between the teeth, and this correlates with the incidence of decay on these surfaces.

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❖ **Normal Flora of various parts of human body**

1. **Normal Flora of the Skin**
2. **Normal Flora of the Conjunctiva (Eyes)**
3. **Normal Flora of the Respiratory Tract**
4. **Normal Flora of the Urogenital Tract**
5. **Normal Flora of the Oral Cavity**
6. **Normal Flora of the Gastrointestinal Tract**

1. **Normal Flora of the Skin**

Skin is the organ of the human body that protects from the pathogens, from the environment and retards the loss of excessive water. Its other functions are insulation, temperature regulation, sensation and synthesis of vitamin D. The skin is composed of the epidermis, dermis and fat cells.

Epidermis: This layer consists of dead cells (without nucleus) and constantly in contact with microorganism from the environment.

Dermis: Consists of connective tissues and cushions the body from heat and strain. It has sebaceous gland, sweat gland, hair follicles and nerve endings.

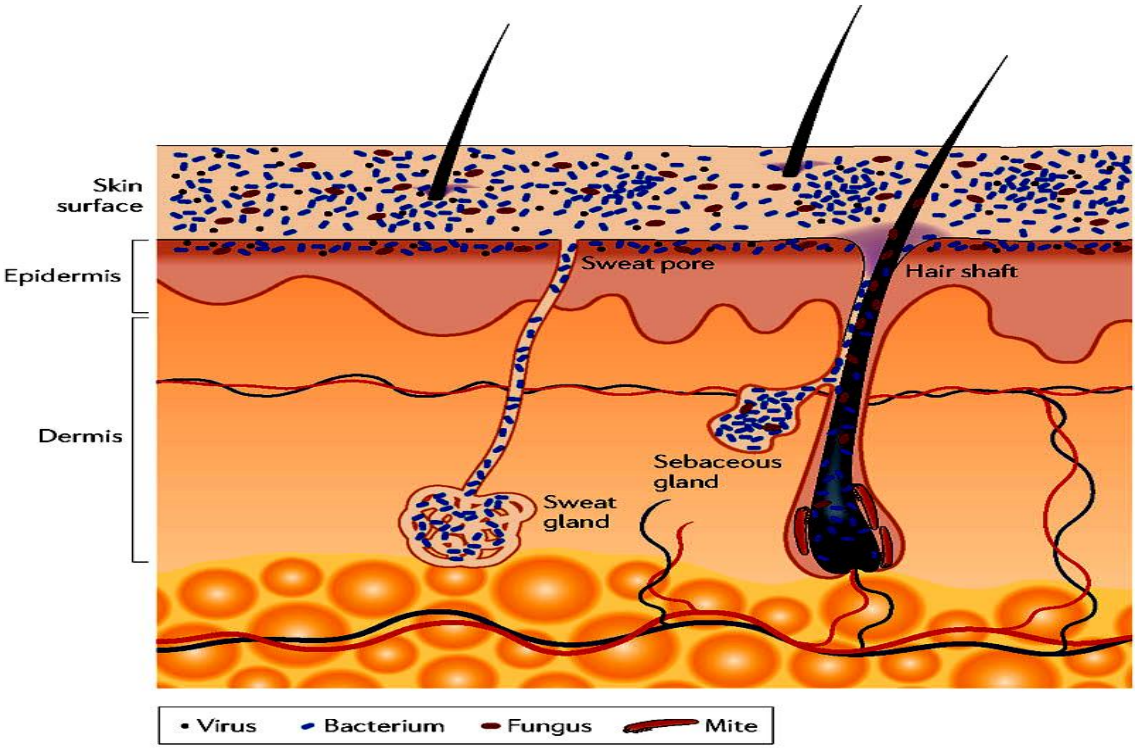
The adult human is covered with approximately 2 square meters of skin. Skin flora can be comensalistic, mutalistic or pathogenic. The flora depends on the area, the clothing, occupation and environment. The density and composition of the normal flora of the skin varies with anatomical conditions. Most bacteria on the skin are present in sweat glands.

Some of the common flora on skin are:

Bacteria: *Staphylococcus aureus, Staphylococcus epidermis, Micrococcus sp, Staphylococcus warneri, Propionibacterium acnes, Pseudomonas aeroginosa,*

Propionibacterium acnes, a normal inhabitant of the skin, become trapped in hair follicle, it may grow rapidly and cause inflammation and acne (PIMPLE).

Fungi: *Candida albicans, Trichosporon cutaneum, Microsporum gypseum*



Factors responsible for discouraging microbial colonization on skin

1. **Dryness**: Dry surface is inhibitory to microbial growth. Some regions of the skin are moist than others, e.g. The axillary region, toe webs and the perineum (skin at the lower end of the trunk between the thighs.) These regions have higher number of normal flora organisms than the drier area of skin.

2. **Low pH**: Skin has a normal pH between 3 and 5 and it is higher in moist regions. This low pH is due to the lactic acid or other organic acids produced by normal skin microorganisms such as staphylococci. This factor discourages the growth of other organisms.

3. Inhibitory Substances:

Sweat glands – secrete lyzozyme that destroys bacterial cell walls.

Sebaceous glands – secrete complex lipids which may be partially degraded by *Propionibacterium acnes*, that result in long chained unsaturated fatty acids e.g. Oleic acid. These fatty acids are highly toxic to other bacteria.

BENEFIT OF SKIN FLORA: The benefits bacteria can offer include preventing transient pathogenic organisms from colonizing the skin surface, either by competing for nutrients, secreting chemicals against them, or stimulating the skin's immune system.

DISADVANTAGE OF SKIN FLORA: Even resident microbes can cause skin diseases and enter the blood system creating life-threatening diseases particularly in immune-suppressed people.

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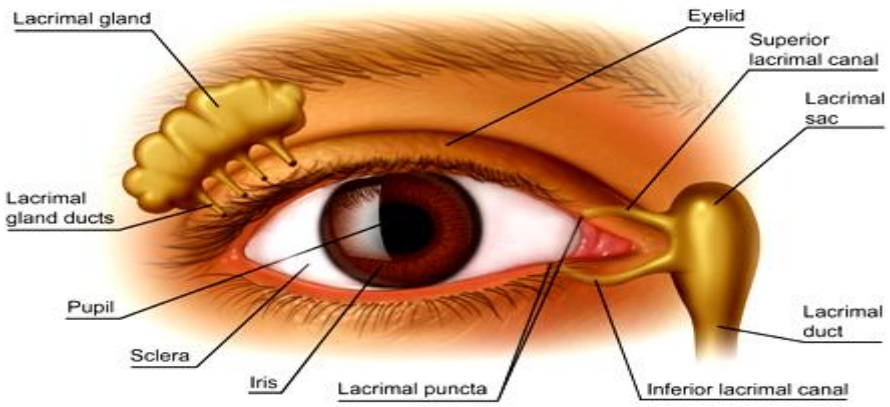
2. Normal Flora of the Conjunctiva (Eyes)

A variety of bacteria may be cultivated from the normal conjunctiva, but the number of organisms is usually small.

E.g. *Staphylococcus epidermidis* and *Propionibacterium acnes* are dominant. *Staphylococcus aureus, some Streptococci*, *Haemophilus* sp. and *Neisseria* sp. are occasionally found.

The conjunctiva is kept moist and healthy by the continuous secretions from the lachrymal glands. Blinking wipes the conjunctiva every few seconds mechanically washing away foreign objects including bacteria. Lachrymal secretions (tears) also contain bactericidal substances including lysozyme. There is little or no opportunity for microorganisms to colonize the conjunctiva without special mechanisms to attach to the epithelial surfaces and some ability to resist attack by lysozyme.



Pathogens which do infect the conjunctiva (e.g. *Neisseria gonorrhoeae* and *Chlamydia trachomatis*) are thought to be able to specifically attach to the conjunctival epithelium. Newborn infants may be especially prone to bacterial attachment. Since *Chlamydia* and *Neisseria* might be present on the cervical and vaginal epithelium of an infected mother, silver nitrate or an antibiotic may be put into the newborn's eyes to avoid infection after passage through the birth canal.

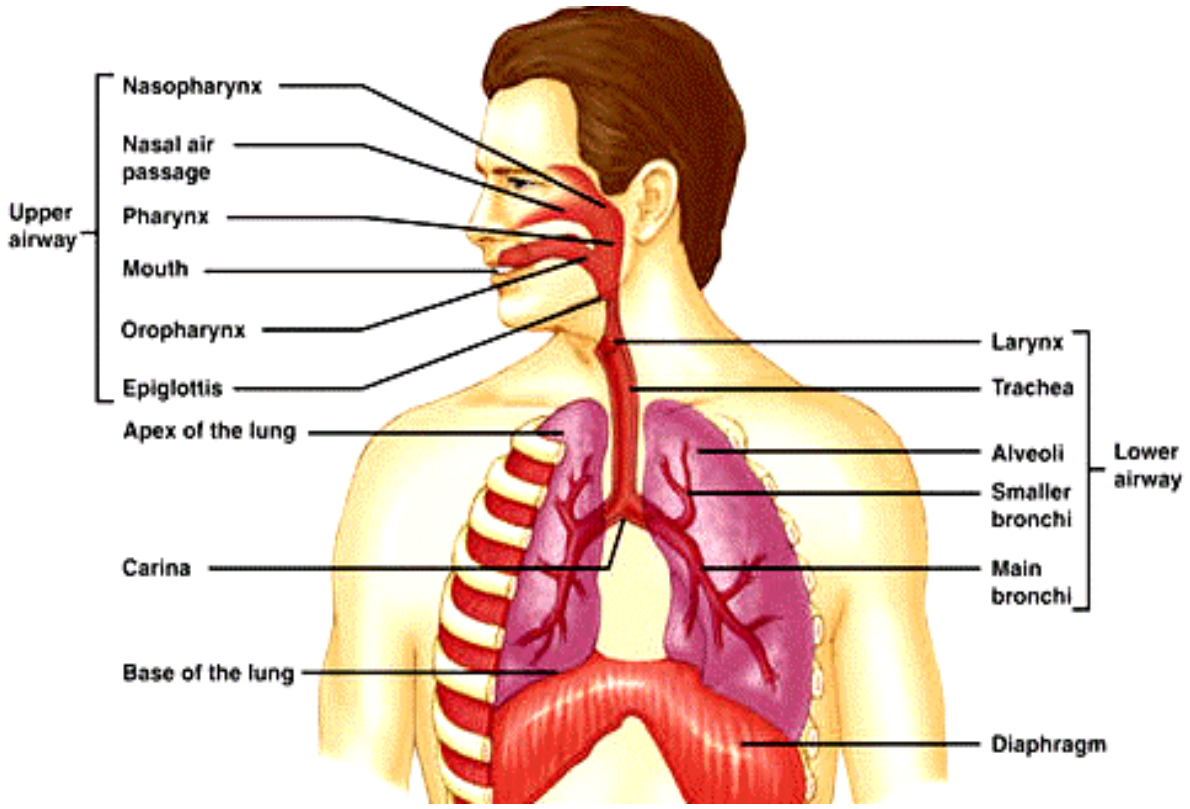
3. Normal Flora of the Respiratory Tract

A large number of bacterial species colonize the upper respiratory tract (nasopharynx).

E.g. **The nares (nostrils)** are always heavily colonized, predominantly with *Staphylococcus epidermidis*, corynebacteria and *Staphylococcus aureus*, this being the main carrier site of this important pathogen.

The healthy sinuses, in contrast are sterile.

The pharynx (throat) is normally colonized by streptococci and various Gram-negative cocci. Sometimes pathogens such as *Streptococcus pneumoniae, Streptococcus pyogenes, Haemophilus influenzae* and *Neisseria meningitidis* colonize the pharynx.



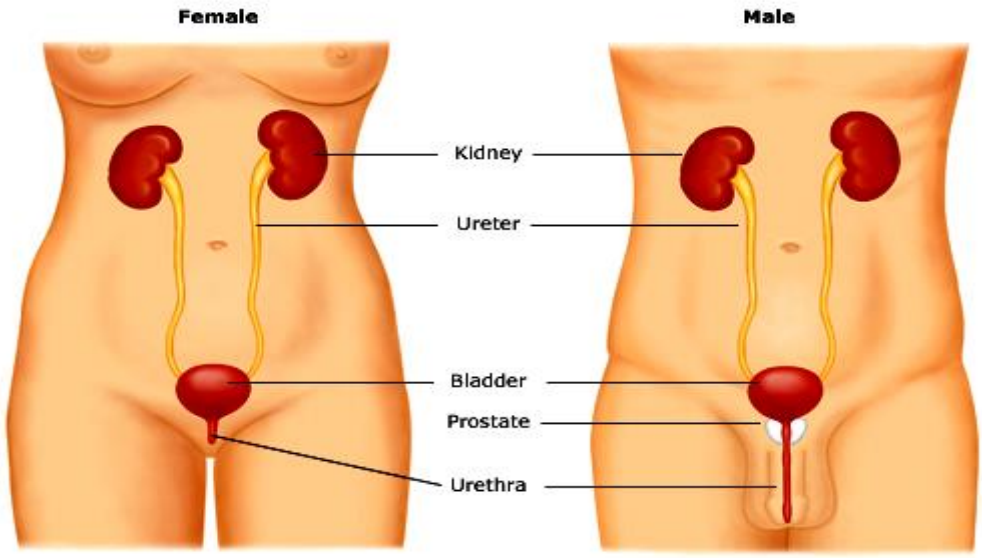
The lower respiratory tract (trachea, bronchi, and pulmonary tissues) is virtually free of microorganisms, mainly because of the efficient cleansing action of the ciliated epithelium which lines the tract. Any bacteria reaching the lower respiratory tract are swept upward by the action of the mucociliary blanket that lines the bronchi. These are then removed by coughing, sneezing, swallowing, etc.

If the respiratory tract epithelium becomes damaged, as in bronchitis or viral pneumonia, the individual may become susceptible to infection by pathogens such as *H. influenzae* or *S. pneumoniae* descending from the nasopharynx.

4. Normal Flora of the Urogenital Tract

Urine is normally sterile, and since the urinary tract is flushed with urine every few hours, microorganisms are unable to adhere and are removed.

E.g. The normal flora consists of S*taphylococcus epidermidis, Enterococcus faecalis* and some α-hemolytic streptococci. Their numbers are not plentiful, however in addition, some enteric bacteria (e.g. *E. coli, Proteus*) and corynebacteria, which are probably contaminants from the skin, vulva or rectum, may occasionally be found at the anterior urethra.



The vagina becomes colonized soon after birth with *corynebacteria, staphylococci, streptococci, E. coli*, and a *lactic acid bacterium* historically named "Doderlein's bacillus" (*Lactobacillus acidophilus*). During reproductive life, from puberty to menopause, the vaginal epithelium contains glycogen due to the actions of circulating estrogens. Doderlein's bacillus predominates, being able to metabolize the glycogen to lactic acid. The lactic acid and other products of metabolism inhibit colonization by all except this lactobacillus and a select number of lactic acid bacteria. The resulting low pH of the vaginal epithelium prevents establishment by most other bacteria as well as the potentially-pathogenic yeast, *Candida albicans.* This is a striking example of the protective effect of the normal bacterial flora for their human host.

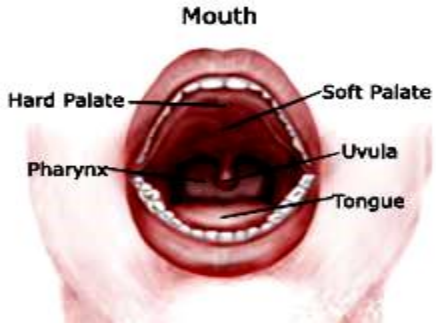
5. Normal Flora of the Oral Cavity

The presence of nutrients, epithelial debris, and secretions makes the mouth a favorable habitat for a great variety of bacteria.

E.g. *Streptococcus viridians, Lactobacilli, Staphylococci (S. aureus and S. epidermidis), Corynebacterium sp., Bacteroides sp., Streptococcus sanguis (dental plaque), Streptococcus mutans (dental plaque), Actinomyces sp.*

The mouth presents a succession of different ecological situations with age, and this corresponds with changes in the composition of the normal flora. At birth, the oral cavity is composed solely of the soft tissues of the lips, cheeks, tongue and palate, which are kept moist by the secretions of the salivary glands. At birth the oral cavity is sterile but rapidly becomes colonized from the

environment, particularly from the mother in the first feeding. *Streptococcus salivarius* is dominant and may make up 98% of the total oral flora until the appearance of the teeth (6 - 9 months in humans). The eruption of the teeth during the first year leads to colonization by *S. mutans* and *S. sanguis*. They will persist as long as teeth remain. Other strains of streptococci adhere strongly to the gums and cheeks but not to the teeth. The creation of the gingival crevice area (supporting structures of the teeth) increases the habitat for the variety of anaerobic species found. The complexity of the oral flora continues to increase with time, and bacteroides and spirochetes colonize around puberty.



On the other hand, the oral flora is the usual cause of various oral diseases in humans, including abscesses, dental caries, gingivitis, and periodontal disease. If oral bacteria can gain entrance into deeper tissues, they may cause abscesses of alveolar bone, lung, brain, or the extremities. Such infections usually contain mixtures of bacteria with *Bacteroides melaninogenicus* often playing a dominant role. If oral streptococci are introduced into wounds created by dental manipulation or treatment, they may adhere to heart valves and initiate subacute bacterial endocarditis.

6. Normal Flora of the Gastrointestinal Tract

The bacterial flora of the gastrointestinal (GI) tract of animals has been studied more extensively than that of any other site. The composition differs between various animal species, and within an animal species. In humans, there are differences in the composition of the flora which are influenced by age, diet, cultural conditions, and the use of antibiotics.

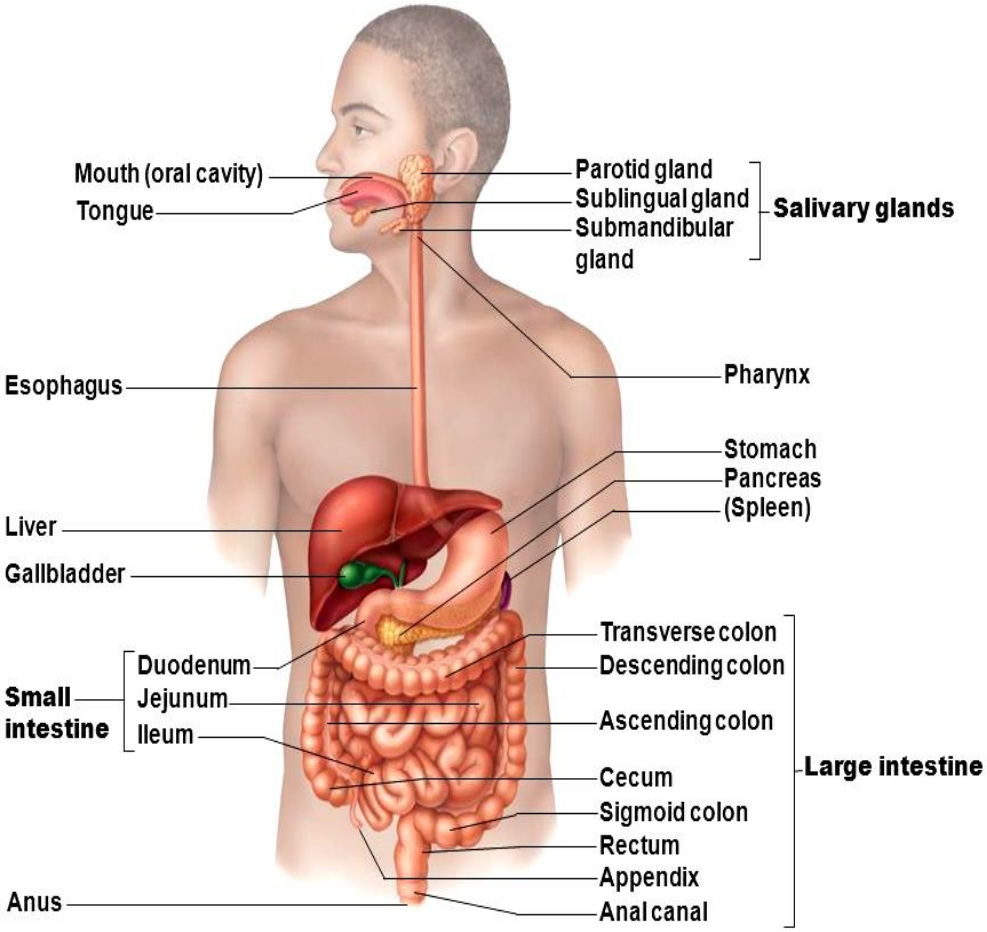
E.g. **In the upper GI tract** of adult humans, the esophagus contains only the bacteria swallowed with saliva and food. Because of the high acidity of the gastric juice, very few bacteria (mainly acid-tolerant **lactobacilli**) can be cultured from the normal stomach. However, at least half the population in the United States is colonized by a pathogenic bacterium, ***Helicobacter pylori***.

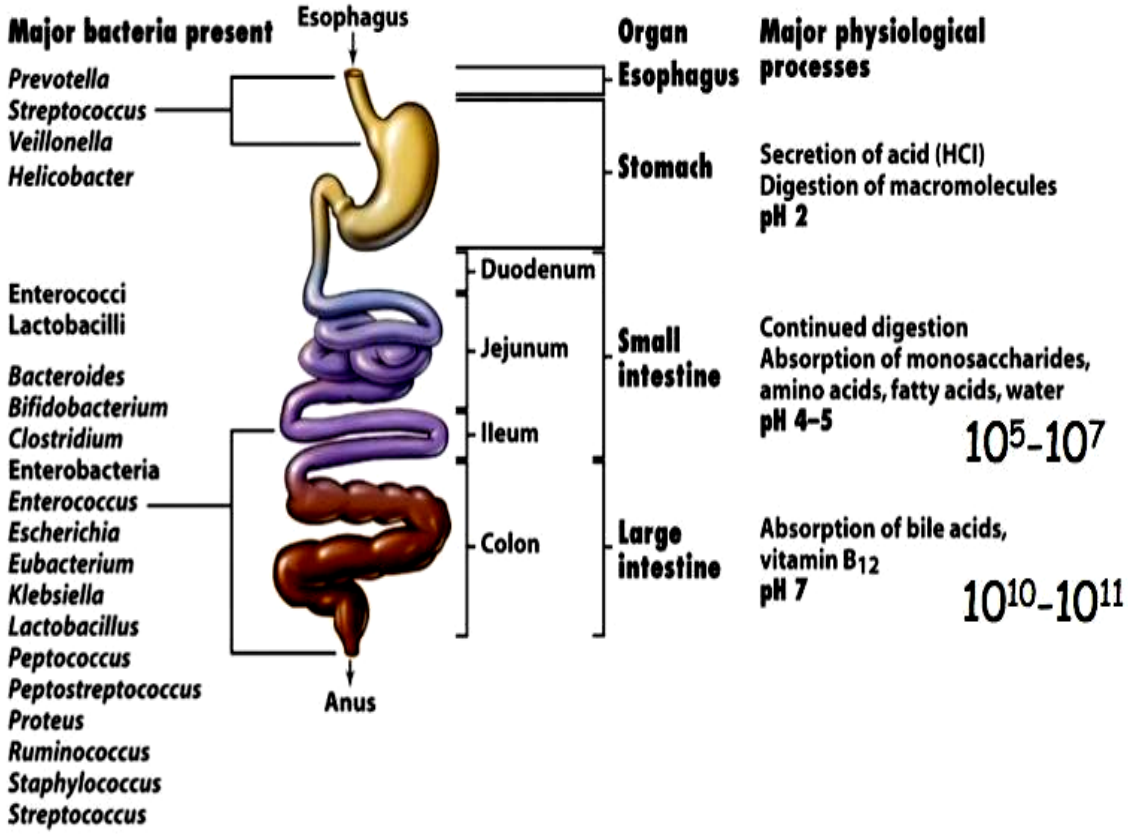
Since the 1980s, this bacterium has been known to be the cause of gastric ulcers, and it is probably a cause of gastric and duodenal cancer as well. (The Australian microbiologist, Barry Marshall, received the Nobel Prize in Physiology and Medicine in 2005, for demonstrating the relationship between *Helicobacter* and gastric ulcers.)

The proximal small intestine has a relatively less Gram-positive flora, consisting mainly of lactobacilli and *Enterococcus faecalis.* This region has about 10^5 - 10^7 bacteria per ml of fluid. The distal part of the small intestine contains greater numbers of bacteria (10^8/ml) and additional species, including coliforms (*E. coli* and relatives) and *Bacteroides,* in addition to lactobacilli and enterococci.

The flora of the large intestine (colon) is qualitatively similar to that found in feces. Populations of bacteria in the colon reach levels of 10^{11}/ml feces. *Coliforms* become more prominent, and *Enterococci, Clostridia and Lactobacilli* can be regularly found, but the predominant species are anaerobic *Bacteroides* and anaerobic lactic acid bacteria in the genus *Bifidobacterium* (*Bifidobacterium bifidum*). These organisms may outnumber *E. coli* by 1,000:1 to 10,000:1. Sometimes, significant numbers of anaerobic *Methanogens* (up to 10^{10}/gm) may reside in the colon of humans. This is our only direct association with archaea as normal flora.

At birth the entire intestinal tract is sterile, but bacteria enter with the first feed. The initial colonizing bacteria vary with the food source of the infant. In breast-fed infants, *Bifidobacteria* account for more than 90% of the total intestinal bacteria. *Enterobacteriaceae* and *Enterococci* are regularly present, but in low proportions, while *Bacteroides, Staphylococci, Lactobacilli and Clostridia* are practically absent. In bottle-fed infants, *Bifidobacteria* are not predominant. When breast-fed infants are switched to a diet of cow's milk or solid food, *Bifidobacteria* are progressively joined by *Enterics, Bacteroides, Enterococci, Lactobacilli and Clostridia.* Apparently, human milk contains a growth factor that enriches for growth of *Bifidobacteria*, and these bacteria play an important role in preventing colonization of the infant intestinal tract by non indigenous or pathogenic species.


Mouth (oral cavity)
Tongue
Parotid gland
Sublingual gland
Submandibular gland
Salivary glands
Esophagus
Pharynx
Stomach
Pancreas
(Spleen)
Liver
Gallbladder
Small intestine
Duodenum
Jejunum
Ileum
Transverse colon
Descending colon
Ascending colon
Cecum
Sigmoid colon
Rectum
Appendix
Anal canal
Large intestine
Anus



It is in the intestinal tract that we see the greatest effect of the bacterial flora on their host. This is due to their large mass and numbers. Bacteria in the human GI tract have been shown to produce vitamins and may otherwise contribute to nutrition and digestion. But their most important effects are in their ability to protect their host from establishment and infection by alien microbes and their ability to stimulate the development and the activity of the immunological tissues.

- **Defensive mechanism of the host**

*** Immunity: -**

In Latin immunis means free of burden.

It refers to the general ability of a host to resist a particular infection or disease. There are mainly two types of immunity

A) Innate immunity or Native immunity or Natural resistance or Nonspecific defense mechanisms or General defense mechanisms.
B) Acquired immunity or specific resistance

Physical barriers (Mechanical barriers) [First line of defense]: -

a) Skin and mucous membranes
b) Respiratory system
c) Intestinal tract
d) Genitourinary tract
e) Eye

(Physical or mechanical barriers, along with the host's secretions [flushing mechanisms] are the First Line of Defense against organisms.)

a) <u>Skin and mucous membranes</u>: -

The intact skin forms a very effective mechanical barrier to parasitic invasion. There are several reasons for this—

→ Its outer layer consists of thick closely packed keratinized cells (components of hair, nails & outer skin cells) that organisms cannot enzymatically attack.

→ Continuous shedding of the outer squamous epithelial cells (desquamation) removes those organisms that do manage to adhere.

→ Relative dryness of the skin slows microbial growth.

→ Mild acidity (pH 5 to 6, due to the breakdown of lipids into fatty acids by the normal skin microbiota) inhibits the growth of many microorganisms.

→ The normal skin microbiota acts antagonistically against many pathogens; it also occupies attachment sites and competes for nutrients.

→ Sebum liberated from the oil glands (sebaceous) forms a protective film over the surface of the skin.

→ Normal washing (by humans) continuously removes organisms.

→ The mucous membranes of the respiratory, digestive, and urinogenital systems withstand parasitic organisms because the intact stratified squamous epithelium and mucous secretions form a protective covering that resists penetration and traps many microorganisms. Furthermore, many mucosal surfaces are bathed in specific antaparasitic secretions.

e. g. cervical mucous, prostatic fluid and tears are toxic to many bacteria. One antibacterial substance is 'Lysozyme' (muramidase), an enzyme that lyses bacteria by hydrolyzing the β (1-4) bond connecting N- acetylmuramic acid N-acetylglucosamine in the bacterial cell wall peptidoglycan. These mucous secretions also contain specific proteins that help to prevent the attachment of organisms and significant amounts of iron binding proteins (lactoferrin) that sequester iron away from these organisms.

b) <u>Respiratory system</u>: -

It has air filtration system at the upper and lower respiratory tracts. Organisms are deposited on the moist, sticky mucosal surfaces. The cilia in the nasal cavity beat towards the pharynx, so that mucus with its trapped microorganisms is moved towards the mouth and expelled. Humidification of the air by the nasal turbinate causes many hygroscopic organisms to swell and helps the phagocytic process.

Organisms less than 10 μm in diameter are transported by ciliary action away from the lungs and those larger than 10 μm are trapped by hairs and cilia lining the nasal cavity. Coughing and sneezing reflexes clear the respiratory system by expelling air forcefully from the lungs through the mouth and nose. Salivation also washes organisms from the mouth and nasopharyngeal areas into the stomach.

c) <u>Intestinal tract</u>: -

Once parasitic organisms reach the stomach, many are killed by its gastric juice (a mixture of hydrochloric acid, enzymes and mucous). The very high acidity of gastric juice (pH 2 to 3) is usually sufficient to destroy most organisms and their toxins. (except protozoan cysts, clostridium and

staphylococcus toxin). However, many organisms are protected by food particles and reach the small intestine.

Once in the small intestine, pathogens often are damaged by various pancreatic enzymes, bile, enzymes in intestinal secretions and secretory Ig A antibody. Peristalsis and normal loss of columnar epithelial cells remove intestinal microorganisms.

In addition, the normal microbiota of the large intestine is extremely important in preventing the establishment of pathogenic organisms by producing inhibitory substances (fatty acids) and by competing for attachment sites and for nutrients.

d) Genitourinary tract: -

Urine kills some bacteria due to its low pH and the presence of urea and other metabolic end products (uric acid, hippuric acid, indicant, fatty acids, mucin, and enzymes). The kidney medulla is so hypertonic that few organisms can survive. The urinary tract is flushed with urine and some mucus 4 to 10 times a day, eliminating potential pathogens.

In males, the anatomical length of the urethra (20 cm) provides a distance barrier that excludes microorganisms from the urinary bladder. Conversely, the short urethra (5 cm) in females is more readily traversed by microorganisms; this explains why general urinary tract infections are **14 times** more common in females than in males.

The vagina has another unique defense. Under the influence of estrogens, the vaginal epithelium produces increased amounts of **glycogen** that acid tolerant *Lactobacillus* species called *Doderlein's bacilli* degrade to form lactic acid. Normal vaginal secretions contain up to 10^8 *Doderlein's bacilli* per ml. Thus, an acidic environment is established. Cervical mucous also has some antibacterial activity.

c) Eye: -

The conjunctiva is specialized mucus secreting epithelial membrane that lines the interior surface of each eyelid and the exposed surface of the eyeball. It is kept moist by the continuous flushing action of tears (lacrimal fluid) from the lacrimal glands. Tears contain large amounts of lysozyme and other antimicrobial substances.

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Aggressiveness (Aggressive factors and mechanisms)

- **-** This is the ability of the organism to reproduce and spread in the body. Highly aggressive organisms escape the defense systems and spread rapidly throughout the body. Aggressiveness is dependent upon several factors.

- **(a) Capsules -** These help bacteria and fungi to resist and escape phagocytosis.

- **(b) Cell wall components -** These are chemicals that help the organism resist body defenses. The waxes in the wall of Mycobacterium are a case in point. The M protein of *Streptococcus pyogenes* is another example.

- **(c) Enzymes -** These are extracellular enzymes that help pathogens in the destruction of body tissues.

- **(d) Antigenic variation -** This is where certain pathogens alter their surface antigens which helps in escaping the immune system. Some have several sets of genes that control surface antigen that can be utilized. By the time one immune response has been mounted, the organism produces a new set of antigens that require a new immune response.

- **(e) Penetration of the cytoskeleton -** Many organisms produces proteins that rearrange the filaments of the cytoskeleton of the attacked cell. These so called invasins allow the organism to manipulate the cytoskeleton to bring the organism into the cell and then move it around in the cell.

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Infection

An **infection** is an **invasion** and **multiplication** of **pathogenic microbes** in the body tissues in which they are **not usually present**. *Pathogenic* means capable of causing disease. Infection does not always cause a disease.

Infection: a condition in which the body is invaded by an infectious microorganism (e.g., bacteria, virus, fungus).

Our environment is full of microorganisms (microscopic organisms) referred to as microbes. Microbes include bacteria, fungi, protozoa, and viruses. The majority of microbes are nonpathogenic, meaning they do not cause disease under normal conditions. Microbes that are capable of causing disease (i.e., pathogenic) are called pathogens. If a pathogen invades the body and the conditions are favorable for it to multiply and cause injurious effects or disease, the resulting condition is called an infection. The pathogen responsible for causing the infection is referred to as the infectious or causative agent. Infection can be local (restricted to a small area of the, body) or systemic, in which the entire body is affected.

Pathogens are microorganisms that are capable of producing disease in the host. Commensal microbes live in complete harmony with the host without causing any damage to it. The normal bacterial flora of the body consists largely of commensals. Many commensals behave as facultative pathogens in that they can produce disease when the host resistance is lowered.

It is necessary to distinguish between the term 'infection' and 'infectious disease'. The lodgement and multiplication of a parasite in or on the tissues of a host constitute infection. It does not invariably result in disease. In fact, disease is a rare result of infection, which is a common natural event.

Types of infections

1. Acute infection, like common cold, appears suddenly and lasts from few days to one month.

2. Asymptomatic infection causes no symptoms. Example: infection with Epstein-Barr virus (EBV), which can cause infectious mononucleosis, often triggers no symptoms in small children.

3. Atypical infection is one in which the typical or characteristic clinical manifestations of the particular infectious disease are not present.

4. Chronic infection, like tuberculosis or AIDS, may last from several weeks to several years.

5. Cross infection: When in a patient already suffering from a disease, a new infection is set up from another host or another external source, it is termed *cross infection.*

6. Endogenous infection: the source of infection is from the host's own body.

7. Exogenous infection: the source of infection is from the external sources.

8. Focal infection: The term *focal infection* indicates a condition where, due to infection or sepsis at localized sites such as appendix or tonsils, generalized effects are produced.

9. Iatrogenic infection: The term *iatrogenic infection* refers to physician-induced infections resulting from investigative, therapeutic or other procedures.

10. Inapparent or subclinical infection is one where clinical effects are not apparent.

11. Localized infection, like cellulitis, is limited to one or few body parts and presents with localized symptoms, like redness, swelling, pain or localized (nasal, ear, etc.) discharge.

12. Latent infection: Some parasites, following infection, may remain in the tissues in a latent or hidden form proliferating and producing clinical disease when the host resistance is lowered. This is termed *latent infection.*

13. N**osocomial infection** Cross infections occurring in hospitals are called *nosocomial infections.*

14. P**rimary infection**: the initial introduction of an infectious organism into the body. Initial infection with a parasite in a host is termed *primary infection.*

15. Recurrent infection is one that frequently affects a person, like folliculitis in those who share the same sport equipment, or fungal infections in those with **lowered immunity**.

16. Reinfection: Subsequent infections by the same parasite in the host are termed *reinfections.*

17. Secondary infection: infection with a second or subsequent infectious organism during the course of an initial infection. A secondary infection is an infection that occurs during or after treatment of another, already existing infection. It may result from the treatment itself or from alterations in the immune system. When in a host whose resistance is lowered by a preexisting

18. Systemic infection, like influenza, affects the whole body and causes systemic symptoms, like general malaise, muscle pains, fever, nausea, etc.

infectious disease, a new parasite sets up an infection, this is termed *secondary infection.*

Types of infectious diseases

1. Localised infections may be superficial or deep seated.

2. Generalized infection involves the spread of the infecting agent from the site of entry by contiguity, through tissue spaces or channels, along lymphatics or through the bloodstream.

3. Bacteraemia Circulation of bacteria in the blood is known as *bacteraemia.*

4. Septicaemia is the condition where bacteria circulate and multiply in the blood, form toxic products and cause high, swinging type of fever.

5. Pyaemia is a condition where pyogenic bacteria produce septicaemia with multiple abscesses in internal organs such as the spleen, liver and kidneys.

6. Endemic diseases are those which are constantly present in a particular area. Typhoid fever is endemic in most parts of India.

7. An epidemic disease is one that spreads rapidly, involving many persons in an area at the same time. Influenza causes annual winter epidemics in the cold countries.

8. A pandemic is an epidemic that spreads through many areas of the world involving very large numbers of persons within a short period. Influenza, cholera, plague and enteroviral conjunctivitis are pandemic diseases.

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Sources of infection

1. **Man (Person to person)**
2. **Animal**
3. **Insects**
4. **Food-Borne Infections**
5. **Waterborne Infections**
6. **Airborne Infections**
7. **Soil**
8. **Hospital Acquired Infections (HAIs)**

1. Man (Person to person)

Infection can be transmitted from person to person by:

Skin-to-skin contact, clothes, towels, sport equipment, etc. (**staphylococcal, including MRSA skin infections**, like **folliculitis**; **scabies**, **head lice**)

Droplets during **coughing**, **sneezing** (common cold, flu, swine flu, pneumonia, tuberculosis, bacterial meningitis, chicken pox, measles, rubella, mumps), or **kissing** (infectious mononucleosis, cold sores)

Stool-to-mouth (fecal-oral) spread, usually via **dirty hands** or **utensils** (stomach flu, hepatitis A, *Giardia*, pinworms, *Clostridium difficile*, cholera, poliomyelitis)

Sexually transmitted (gonorrhea, *Chlamydia*, genital herpes, pubic lice, genital warts (human papillomavirus – HPV), AIDS, syphilis)

Blood-to-blood contact by:

contaminated needles, usually by drug addicts or health workers (hepatitis B, C, AIDS)

blood transfusion (hepatitis B,C, AIDS, viral hemorrhagic fevers)

mosquitoes (malaria)

Spread from mother to fetus during pregnancy (hepatitis B, C, AIDS, HSV-1, HSV-2, rubella, parvovirus, toxoplasma, varicella, syphilis, bird flu), or delivery (*Chlamydia trachomatis*, *Neisseria gonorrheae*, CMV, group B *Streptococci*).

An **autoinfection** – the spread of an infection **from one body part to another**, usually by hands or clothes (folliculitis, impetigo).

2. Animal: Many pathogens are able to infect both man and animals. Animals may, therefore, act as sources of human infection. In some instances, the infection in animals may be asymptomatic. Such animals serve to maintain the parasite in nature and act as the *reservoir* of human infections. They are, therefore, called *reservoir hosts.* Infectious diseases transmitted from animals to man are called *zoonoses.* Zoonotic diseases may be bacterial *(e.g.* plague from rats), viral *(e.g.* rabies from dogs), protozoal *(e.g.* leishmaniasis from dogs), helminthic *(e.g.* hydatid disease from dogs) or fungal *(e.g.* zoophilic dermatophytes from cats and dogs).

3. Insects: Blood sucking insects may transmit pathogens to man. The diseases so caused are called *arthropod-borne diseases.* Insects such as mosquitoes, ticks, mites, flies, fleas and lice that transmit infections are called *vectors.* Transmission may be mechanical *(e.g.* transmission of dysentery or typhoid bacilli by the domestic fly). Such vectors are called *mechanical vectors.* In other instances, the pathogen multiplies in the body of the vector, often undergoing part of a developmental cycle in it. Such vectors are termed *biological vectors (e.g. Adies aegypti* mosquito in yellow fever, Anopheles mosquito in malaria).

4. Food-Borne Infections

Contaminated food materials may act as sources of infection. Presence of pathogens in food may be due to external contamination *(e.g.* food poisoning by staphylococcus) or due to pre-existent infection in meat or other animal products

Food poisoning is an infection of the gastrointestinal tract caused by microbes from contaminated food: bacteria, like *Salmonella* or *E. coli*, toxins from *Staphylococcus aureus* or *Clostridium botulinum*, parasites like *Giardia* or roundworm, viruses, like *Enterovirus*.

4. Waterborne Infections

By **drinking** contaminated water, one can suffer from stomach flu, cholera, dysentery, typhoid fever, amoebiasis, etc. Tap water in newly opened hospitals may contain *Legionella*.

By **swimming** in contaminated swimming or spa pools, or lakes, one can get **hot tub folliculitis**, intestinal parasite *Cryptosporidium*, eye and middle ear infections. Certain parasites may enter through the skin.

Water in **public showers** may hold *Legionella;* the floor may be contaminated by *Staphylococci* (from human skin infections)

Flood water may contain various pathogenic microbes.

5. Airborne Infections

Industrial cooling or **hot water systems, air condition** and **room-air humidifiers** can be a source of *Legionella*. Common cold, Flu, Tonsilitis, Cough, Tuberculosis.

6. Soil

Some pathogens are able to survive in the soil for very long periods. Spores of tetanus bacilli may remain viable in soil for several decades and serve as the source of infection. Fungi *(e.g. Histoplasma capsulatum, Nocardia asteroides)* also survive in soil and cause human infection. Soil also serves as the source of parasitic infections such as roundworm and hookworm.

- During **walking barefoot**, *Clostridium tetani*, **sandworms,** or intestinal parasites, like *Strongyloides stercoralis or* hookworms can be contacted.
- **Eating with soil-contaminated hands** can also result in infection by parasites.

6. Hospital Acquired Infections (HAIs)

Infections acquired in hospitals can be dangerous, since causing microbes are often resistant to regular antibiotics, and patients infected are often already seriously ill. Common HAIs include:

- **Urinary tract infections (UTI)** from urinary catheters
- **Surgical-site infections (SSI)**
- **Staphylococcal** skin, lung and heart valve infections
- **Fungal** infections, like oral thrush in patients with **low immunity system** or cancer patients receiving chemotherapy
- ***Legionella*** may be sometimes found in the tap water in newly opened or poorly maintained hospitals.

Modes of transmission of infection

- **Transmission -** This is the movement of infectious organism from one host to the next. Transmission mechanisms include the following.

1. Contact transmission - This is spread by actual contact with the organism. It may include the following methods.

Direct contact - This is person to person. Kissing, sexual contact, or touching are major methods. Direct contact can also transmit disease from reservoir to humans. Rabies is a case in point.

2. Inhalation: Respiratory infections such as influenza and tuberculosis are transmitted by inhalation of the pathogen. Such microbes are shed into the environment by patients in secretions from the nose or throat during sneezing, speaking or coughing. Large drops of such secretions fall to the ground and dry there, Pathogens resistant to drying may remain viable in the dust and act as sources of infection. Small droplets, under 0.1 mm in diameter, evaporate immediately to become minute particles or *droplet nuclei* usually l-10 mm in diameter) which remain suspended in air for long periods, acting as sources of infection.

3. Ingestion: Intestinal infections are generally acquired by the ingestion of food or drink contaminated with the pathogens. Infection transmitted by ingestion may be water borne (cholera), food-borne (food poisoning) or hand borne (dysentery). The last occurs when small amounts of infective material remain on the hands, generally by faecal contamination and are transmitted while feeding, as in the case of nurses who may transmit diarrhea in this manner to infants.

4. Inoculation: Pathogens, in some instances, may be inoculated directly into the tissues of the host. Tetanus spores implanted in the depth of wounds, rabies virus deposited subcutaneously by dog bites and arboviruses injected by insect vectors are examples. Infection by inoculation may be iatrogenic when unsterile syringes and surgical equipments are employed. Serum hepatitis is transmitted by transfusion of contaminated blood or inoculation of material containing the virus.

5. Insects: Insects may act as mechanical or biological vectors of infectious disease.

6. Congenital: Some pathogens are able to cross the placental barrier and infect the fetus *in uterus.* This is known as vertical transmission. This may result in abortion, miscarriage or stillbirth. Live infants may be born with manifestations of the disease, as in congenital syphilis. Intrauterine infection with the rubella virus, especially in the first trimester of pregnancy, may interfere with organogenesis and lead to congenital malformation. Such infections are known as *teratogenic* infections.

7. Iatrogenic and laboratory infections: Infection may sometimes be transmitted during procedures such as injections, lumbar puncture and catheterization, if meticulous care in asepsis is lacking. Modern methods of treatment such as exchange transfusion, dialysis, and heart and transplant surgery increase the possibilities for iatrogenic infections. Laboratory personnel handling infectious material are at risk and special care should be taken to prevent laboratory infection.

Factors predisposing to microbial pathogenicity

Determining factors in infection

The terms ‘pathogenicity’ and ‘virulence’ refer to the ability of a microbe to produce disease or tissue injury, but it is convenient to make a fine distinction between them. 'Pathogenicity' is generally employed to refer to the ability of a microbial *species* to produce disease while the term ‘virulence’ is applied to the same property in a *strain* of microorganism and is capacity to produce disease. Thus the species *M. tuberculosis* or the polio virus is referred to as pathogenic. The pathogenic species *M. tuberculosis* and the polio virus contain strains of varying degrees of virulence including those which are avirulent, such as the vaccine strains. The virulence of a strain is not constant and may undergo spontaneous or induced variation. Enhancement of virulence is known as *exaltation* and can be

demonstrated experimentally by serial passage in susceptible hosts. Reduction of virulence is known as *attenuation* and can be achieved by passage through unfavourable hosts, repeated cultures in artificial media, growth under high temperature or in the presence of weak antiseptics, desiccation, or pro-longed storage in culture.

Virulence is the sum total of several determinants, as detailed below.

1. Adhesion: The initial event in the pathogenesis of many infections is the attachment of the bacteria to body surfaces. This attachment is not a chance event, but a specific reaction between surface receptors on the epithelial cells and adhesive structures on the surface of bacteria. These adhesive structures are called *adhesins.* Adhesins may occur as organized structures, such as fimbriae or fibrillae and pili, or as colonization factors. This specific adhesin may account for the tissue tropisms and host specificity exhibited by many pathogens. Adhesins serve as virulence factors. Loss of adhesins often renders the strain avirulent. Adhesins are antigenic. Specific immunization with adhesins has been attempted as a method of prophylaxis in some infections, as for instance against *Escherichia coli* diarrhoea in calves and piglets, and gonorrhoea in humans.

2. Invasiveness: This refers to the ability of a pathogen to spread in the host tissues after establishing infection. Highly invasive pathogens characteristically produce spreading or generalized lesions *(e.g.* streptococcal septicaemia following wound infection), while less invasive pathogens cause more localized lesions *(e.g.* staphylococcal abscess), Some pathogens though capable of causing serious or even fatal diseases lack in invasiveness altogether *(e.g.* tetanus bacillus which remains confined to the site of entry and produces the disease by elaborating a potent toxin).

3. Toxigenicity: Bacteria produce two types of toxins, exotoxins and endotoxins.

Sr No	Exotoxins	Endotoxins
1	Proteins.	Protein-Polysaccharide-Lipid complexes
2	Heat labile	Heat stable
3	Actively secreted by cells; diffuse into surrounding medium	Form part of cell wall; do not diffuse into surrounding medium
4	Readily separable from cultures by physical means such as filtration	Obtained only by cell lysis.
5	Action often enzymic	No enzymatic action
6	Specific pharmacological effect for each exotoxin	Effect nonspecific; action common to all endotoxins
7	Specific tissue affinities	No specific tissue affinity
8	Active in very minute doses.	Active only in very large doses.
9	Highly antigenic	Weakly antigenic
10	Action specifically neutralized by antibody	Neutralization by antibody ineffective
11	Can be toxoided	Cannot be toxoided
12	Produced mainly by Gram positive but also by some Gram negative bacteria	Produced by Gram negative bacteria bacteria

4. Communicability: The ability of a parasite to spread from one host to another is known as communicability. This property does not influence the production of disease in an individual host but determines the survival and distribution of a parasite in a community. A correlation need not exist between virulence and communicability. In fact, a highly virulent parasite may not exhibit a high degree of communicability due to its rapidly lethal effect on the host. In general, infections in which the pathogen is shed in secretions, as in respiratory or intestinal diseases, are highly communicable. In some instances, as in hydrophobia, human infection represents a dead end, there being an interruption in the spread of the pathogen to other hosts.

Development of epidemic and pandemic diseases requires that the strain of pathogen possesses high degrees of virulence and communicability.

5. Other bacterial products: Some bacterial products other than toxins, though devoid of intrinsic toxicity, may contribute to virulence by inhibiting the mechanisms of host resistance. Pathogenic staphylococci produce a thrombin-

like enzyme **coagulase** which prevents phagocytosis by forming a fibrin barrier around the bacteria and walling off the lesion. **Fibrinolysins** promote the spread of infections by breaking down the fibrin barrier in tissues. **Hyaluronidases** split hyaluronic acid which is a component of intercellular connective tissue and thus facilitate the spread of infection along tissue spaces. **Leucocidins** damage polymorphonuclear leucocytes. Many pathogens produce **haemolysins** capable of destroying erythrocytes but their significance in pathogenicity is not clearly understood.

6. Bacterial appendages. Capsulated bacteria such as pneumococci, *K. pneumoniae* and *H. influenzae* are not readily phagocytosed. Some bacterial surface antigens such as the Vi antigen of *S. typhi,* K antigens of *E. coli* also help the bacteria to withstand phagocytosis and the lytic activity of complement.

7. Infecting dose: Successful infections require that, an adequate number of bacteria should gain entry. The dose may be estimated as the *minimum infecting dose* (MID) or *minimum, lethal dose* (MLD) which is respectively the minimum number of bacteria required to produce clinical evidence of infection or death in a susceptible animal under standard conditions. Animals exhibit considerable individual variation in susceptibility, these doses are more correctly estimated as statistical expressions, ID 50 and LD 50, as the dose required to infect or kill 50 per cent of the animals tested under standard conditions.

8. Route of infection; Some bacteria, such as streptococci, can initiate infection whatever be the mode of entry. Others can survive and multiply only when introduced by the optimal routes. Cholera vibrios are infective orally but are unable to cause infection when introduced subcutaneously. This difference is probably related to modes by which different bacteria arc able to initiate tissue damage and establish themselves. Bacteria also differ in their sites of election in the body after introduction into tissues. They also differ in the ability to produce damage to different organs in different species of animals. Tubercle bacilli injected into rabbits cause lesions mainly in the kidneys but infrequently in the liver and spleen, but in guinea pigs, the lesions are mainly in the liver and spleen, the kidneys being spared. The reasons for such selective multiplication in tissues are largely obscure, though they may be related to the presence in tissues of substances that may selectively hinder or favor their multiplication.

Process of infection - : entry and spread of infection in host body

I. INTRODUCTION

After adherence to the mucous membranes, many pathogenic bacteria and viruses multiply on (or in) the epithelial surface causing localized disease. Others have specialized virulence factors and strategies that allow them to invade across the epithelial cell surface (local invasion), or invade across the epthelial cell surface and spread systemically through the body.

II. VIRAL INFECTIONS

A. Review of viral entry into cells.

1. Direct penetration

2. Fusion with the cell membrane

3. Receptor mediated endocytosis

B Viral infections localized to the epithelial cell surfaces

1. Localized infections of the mucous membranes- “The HIT AND RUN” Infection Strategy

2. Warts – a localized viral infection of the skin

III. BASIC PRINCIPLES: HOW MICROBES SPREAD SYSTEMICALLY THROUGH THE BODY

A. What's under the epithelial cell surface?

1. The basement membrane

2. If the microbe reaches the subepithelial tissues it is exposed to 3 important host defenses:

a. Tissue fluids

b. The Lymphatic System

c. Phagocytic Cells

INFLAMMATION

B. Methods of systemic spread:

1. Direct Spread

2. Via the Lymphatics

a. Lymphatic vessels

b. Lymph nodes

c. Thoracic Duct ------Blood

3. Via the Blood

a. By directly entering a subepithelial vessel

b. By entering via the lymphatics and the lymph nodes

c. Microbes localize in the organs of the Reticuloendothelial (RES) System. What happens to pathogens that pass in the blood through the RES?

1. They many not be phagocytosed.

2. They are taken up and killed.

3. They are taken up and grow in the macrophages and/or the endothelial cells (cells that line the blood vessels)

4. There is transfer of the microbes from the macrophages to the neighboring tissue cells. (If into the hepatic cells – hepatitis)

d. What forms are microbes carried in the blood?

1. Free in plasma

2. Associated with white cells

3. Associated with red cells

4. Associated with platelets

4. Other routes of systemic spread:

a. Invasion of the CSF:

1. By the bloodstream (hematogenous spread)

2. By peripheral nerve fibers (neuronal spread)

b. Spread from organ to organ in the pleural or peritoneal cavities

C. SYSTEMIC VIRAL INFECTIONS (Steps in the Process):

1. Entry into the Body and Infection of the mucous membranes

Why do some pathogens invade and others don't?????

a. Temperature

b. The site of budding (for viruses)

c. Microbes must reach susceptible target tissues

i. Sometimes a different target tissue from where they started

ii. Sometimes they end up back where they started from

d. Infections may be confined because they are kept in check by host defenses.

2. Viruses reach the blood via a subepithelial vessel or the lymphatics

a. Primary viremia: May be short and silent for viruses

b. Growth of the viruses in primary target tissue

c. Reseeding of viruses into the blood

d. Multiplication in secondary target tissues

e. There may or may not be exit from the body

IV. Examples of systemic viral infections: measels, polio and mousepox

V. RASHES: There may be entry into the skin from above or below:

A. Through the epidermis:

1. A variety of skin and soft tissue infections

2. Formation of papillomas – warts

B. Through the dermis (caused by infections or toxins):

1. Macule

2. Papule

3. Vesicle

C. Ulcer

VI. Bacterial invasion and spread

A. One way of categorizing bacterial pathogens is whether they are primarily extracellular or intracellular pathogens. These two terms have broad and narrow meanings:

1. Extracellular pathogen – a bacterial pathogen that can grow and reproduce freely, and may move extensively within the tissues of the body.

(A more narrow meaning and one that we will use in this class- to describe the relationship between a pathogenic bacterium and the professional phagocytic cells (the neutrophils, monocytes and macrophages). In this context, an extracellular pathogen is one that cannot survive inside the phagocyte once it has been ingested.

2. Intracellular pathogens –pathogens that can live inside of host cells, especially phagocytes.

(Extracellular phases of intracellular pathogens: Note that no organism can be wholly intracellular all the time. If it is to replicate successfully (whether it is a viral or bacterial pathogen), there must be transmission between the host's cells and some exposure to the extracellular environment)

(A more narrow meaning with regards to the interaction of bacterial pathogens and the phagocytic cells. An intracellular pathogen is one that is able to survive and grow inside the professional phagocyte.)

a. Obligate intracellular pathogens - viruses,the rickettsiae, and the Chlamydiae, and includes some bacterial pathogens such as M. tubercuclosis, M. leprae, Legionella pneumophila, and Listeria monocytogenes.

b. Facultative intracellular pathogens – can survive and multiply inside or outside of professional phagocytes.

B. PATTERNS IN BACTERIAL PATHOGENESIS

1. Colonization of the mucosal surfaces with:

a. Local destruction of the microvilli – enteropathogenic E. coli

b. Production of an exotoxin that acts:

i. Locally – *V. cholerae* and cholera toxin (acts on the gut mucosa producing diarrhea)

ii. Systemically – *C. diptheriae* and diptheria toxin (*C. diptheriae* colonizes the bloodstream and acts on remote organs in the body especially the heart)

2. Initial colonization of the mucosal surface followed by invasion across the mucous membranes:

(Remember: The ability of bacterial pathogens to cross the mucous membranes either intracellularly or intercellularly) and reach the deeper tissues of the host is associated with specific virulence factors. Passive carriage can be accomplished without virulence factors – opportunistic pathogens.

1. Bacterial pathogens invade intercellularly with the help of enzymes:

a. hylauronidase - allow the bacteria to invade intercellularly by destroying the tight junctions.

b. collagenase – (formed by clostridia that cause gas gangrene) causes the breakdown of collagen, which is the ground substance of bone, skin, and cartilage. Helps with spread from the initial site of infection.

c. protease

Other enzymes and toxins associated with invasion once the microbes have breached the mucous membranes:

d. coagulase – produced by staphylococci; causes the coagulation of plasma, which produces a fibrin clot.

e. streptokinase – activates the proteolytic enzyme plasmin – which causes the dissolution of blood clots and, thus, allows the spread of streptococci. There is an essentially identical substance produced by the staphylococci that is called staphylokinase.

f. DNAses

g. hemolysins – damage RBC membranes releasing iron (a needed nutrient for microbial growth)

h. leukocidins – kill white blood cells

2. Bacteria invade directly into the epithelial cells with the help of a bacterial cell surface protein – invasin.

3. Bacteria invade by entering through the M cell