Chapter 2.5. General Bacteriology: Normal Flora and Bacterial Pathogenesis

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MICROBIOLOGY OF NORMAL FLORA

Normal microbial flora refers to the diverse group of microbial populations that every human being harbors on skin and mucous membranes. They do not cause harm; rather they have a beneficiary effect on the host.

- Humans acquire the normal flora soon after the birth and then continue to harbor it until death
- In humans, the normal flora is located in various sites such as the gastrointestinal tract (GIT), respiratory tract, genitourinary tract, and skin
- Most of the normal flora predominantly contain bacteria and to a less extent some fungi and parasites
- GIT is the predominant site of normal flora, where the most common flora is *Bacteroides fragilis* (anaerobic flora). Among aerobes, *Escherichia coli* is the most common.

The microbiological profile of the normal flora in various sites of the human body is given in *Table 2.5.1*.

Role of Normal Flora

Various microorganisms present as the normal flora have a different relationship with the host. They may have a beneficiary effect on the host, or may be harmful to the host.

Table 2.5.1. Common normal flora of human host.

Anatomical site	***Organisms as normal flora***
Oral cavity	Nonsporing anaerobes

Anatomical site	***Organisms as normal flora***
	Viridans streptococci, Yeast
Nasopharynx	Nonsporing anaerobes Streptococci, *Neisseria* (non-pathogenic) *Staphylococcus epidermidis*
Gastrointestinal tract	Nonsporing anaerobes (e.g. *Bacteroides fragilis)* Enterobacteriaceae and other gram-negative rods Enterococci *Candida* species Commensal *Entamoeba* species*
Vagina	Nonsporing anaerobes Diphtheroids *Lactobacillus* *Streptococcus agalactiae* *Candida*
Skin	Nonsporing anaerobes *Staphylococcus epidermidis* Diphtheroids, *Micrococcus*
*Parasites as a part of normal flora	

Beneficial Effects

The normal microbial flora has several beneficial effects on the host:

- **Prevent colonization of pathogen:** By competing for attachment sites or essential nutrients
- **Synthesize vitamin:** Human enteric bacteria secrete several vitamins such as vitamin K and B complex (e.g. vitamin B12) in excess
- **Waste produced antagonizes other bacteria:** Normal flora may inhibit or kill other nonindigenous organisms by producing a variety of waste substances such as—fatty acids, peroxides, lactic acid, etc.
- **Immune stimulation:** Normal microbiota being foreign to the host stimulates the host's immune system.

Disturbed Normal Flora Promote Infection

When the composition of normal flora is disturbed, it facilitates pathogenic organisms to enter and cause disease. Several mechanisms by which the normal flora is disturbed are as follows:

- **Injudicious use of broad-spectrum antimicrobial agent:** It may completely suppress the normal flora thus permitting the pathogen to take the upper hand and cause infection
- **Host factors** such as immune suppression, reduced peristalsis may promote the pathogen to grow
- **Physical destruction** of the normal flora by irradiations, chemicals, burns, etc.

Harmful Effects

Members of the normal flora may cause various endogenous disease.

- When the host immunity is lowered, *or*
- If they enter the wrong site or tissue—then even the resident flora can produce disease **(Table 2.5.2)**.

Probiotics

The term "Probiotics" is defined as the live microorganisms (part of normal flora) that, when administered in adequate amounts, confer a health benefit to the host.

- They are extremely useful in the conditions where the normal intestinal flora is suppressed
- Probiotics are commercially available in the form of capsules or sachets, consisting of a mixture of some important beneficiary bacteria and yeast of human intestinal flora such as *Bifidobacterium, Lactobacillus,* etc.
- Probiotics are found to have a beneficiary role in treating the following conditions:
  - Gastroenteritis due to any cause
  - Antibiotic-associated diarrhea
  - Lactose intolerance
  - Irritable bowel syndrome and colitis
  - Necrotizing enterocolitis
  - *Helicobacter pylori* infection.

Table 2.5.2. Diseases produced by normal flora.

Diseases	Anatomical site from which the flora is transferred
Urinary tract infection	Intestinal flora such as *Escherichia coli, Klebsiella*
Endocarditis	Oral flora (Viridans streptococci)
Dental caries	Oral flora
Peritonitis	Intestinal flora

MECHANISM OF BACTERIAL PATHOGENESIS

The ability of bacteria to produce disease or tissue injury is referred to as 'pathogenesis'. It involves several steps such as—transmission of the organism, infective dose, adhesion, invasion, intracellular survival, and expression of several virulence factors (like toxins and enzymes, etc.).

Route of Transmission

The route of transmission of infection plays a crucial role in the pathogenesis of certain bacteria. This difference is probably related to the modes by which different bacteria can initiate tissue damage and establish themselves **(Table 2.5.3)**.

Infective Dose

The infective dose of the bacteria is referred to as the minimum inoculum size that is capable of initiating an infection.

- **Low infective dose:** Certain organisms require a relatively small inoculum to initiate infection
  - *Shigella*: Very low (as low as 10 bacilli)
  - *Campylobacter jejuni* (500 bacilli).

Table 2.5.3. Mode of transmission of bacterial infections.

Transmission	***Bacterial agents/diseases***
Contact	Multi-drug resistant organisms in hospitals such as *S. aureus, E. coli, Klebsiella, etc.*
Droplet	Meningococcus, *C. diphtheriae* Pneumococcus
Aerosol	*M. tuberculosis*
Ingestion	*Salmonella* and *Shigella* *Vibrio* and diarrheagenic *E. coli*
Vector-borne	Rickettsiae and *Borrelia*
Sexual	Gonococcus, *Chlamydia trachomatis* *Treponema pallidum*
Vertical	*Treponema pallidum*
Birth canal	*Listeria, Streptococcus agalactiae*

- **Large infective dose:** In contrast, bacteria with a high infective dose can initiate the infection only when the inoculum size exceeds a particular critical size
  - *Salmonella* (10^2–10^5 bacilli)
  - *Vibrio cholerae* (10^6–10^8 bacilli).

The infective dose varies depending upon the factors, such as:

- **Virulence of the organism:** Higher the virulence, the lower is the infective dose
- Host's age and overall immune status
- The ability of the organism to resist gastric acidity: *Shigella* can survive gastric acidity, even a low infective dose can initiate the infection. In contrast, *Vibrio* is extremely acid labile, hence requiring a heavy inoculum to bypass the gastric barrier.

Adhesion

Adhesion of the bacteria to body surfaces is the initial event in the pathogenesis of the disease. It is mediated by specialized molecules called adhesins that bind to specific host cell receptors.

- **Fimbriae or pili:** They are the most important adhesins present in some bacteria. They directly bind to the sugar residues on host cells
- **Other adhesins:** Apart from pili, there are other adhesins found in certain bacteria, such as M protein *(Streptococcus pyogenes),* lipoteichoic acid (gram-positive cocci), etc.
- **Biofilm formation:** It is another mechanism by which certain bacteria mediate strong adherence to certain structures, such as catheters, prosthetic implants, and heart valves. Biofilm is a group of bacterial cells which stick to each other on a surface and are embedded within a layer of a self-produced matrix of the glycocalyx.

Invasion

Invasion refers to the entry of bacteria into host cells, leading to its spread within the host tissues.

- Highly invasive pathogens produce spreading or generalized lesions (e.g. streptococcal infections)
- While less invasive pathogens cause localized lesions (e.g. staphylococcal abscess).

Important virulence factors that help in invasion include:

- Virulence marker antigen or invasion plasmid antigens in *Shigella*
- **Enzymes:** The invasion of bacteria is enhanced by many enzymes such as hyaluronidase, collagenase, streptokinase, IgA proteases.

Intracellular Survival

Some organisms survive in the intracellular environment. They are grouped into obligate and facultative intracellular organisms **(Table 2.5.4)**. Various bacterial strategies that inhibit phagocytosis are:

- The bacterial capsule prevents the phagocyte from adhering to the bacterium. Examples of capsulated bacteria—*Neisseria meningitidis* and *Streptococcus pneumoniae*
- Inhibition of phagolysosome fusion by *Mycobacterium tuberculosis*

Table 2.5.4. Intracellular bacteria.

Facultative intracellular bacteria	***Obligate intracellular***
Salmonella typhi, *Brucella*	*Mycobacterium leprae*
Legionella, Listeria	*Rickettsia*
Neisseria meningitidis	*Chlamydia*
Mycobacterium tuberculosis	*Coxiella burnetii*

- Resistance to lysosomal enzymes by *Coxiella* species and *Mycobacterium leprae.*

Toxins

Endotoxins

Endotoxins are the lipid A portion of lipopolysaccharide (LPS).

- They are present as an integral part of the cell wall of gram-negative bacteria
- They are released from the bacterial surface by lysis of the bacteria
- They are responsible for various biological effects in the host such as—macrophage activation, platelet activation, activation of complement and coagulation pathway leading to disseminated intravascular coagulation (DIC) and septic shock and possibly death.

Exotoxins

They are heat-labile proteins; secreted by certain species of both gram-positive and gram-negative bacteria (examples are given in *Table 2.5.5)*.

- **High potency:** Exotoxins are highly potent even in minute amounts
- **Used for vaccine:** Exotoxins can be converted into toxoids by treatment with formaldehyde
- **Specific action:** They are highly specific for a particular tissue, e.g. tetanus toxin for CNS.

Exotoxins differ from endotoxins in several ways **(Table 2.5.6)**.

Table 2.5.5. Bacterial exotoxins.

Organisms	***Toxins (Exotoxins)***
Staphylococcus aureus	Exfoliative toxin Enterotoxin Toxic shock syndrome toxin
Streptococcus pyogenes	Pyrogenic exotoxin
Corynebacterium diphtheriae	Diphtheria toxin
Bacillus anthracis	Anthrax toxin
Clostridium tetani	Tetanus toxin
Clostridium botulinum	Botulinum toxin
Diarrheagenic *E. coli*	Heat labile toxin Heat stable toxin Verocytotoxin
Shigella	Shiga toxin
Vibrio cholerae	Cholera toxin
Pseudomonas	Exotoxin-A

Table 2.5.6. Differences between bacterial endotoxins and exotoxins.

Endotoxins	***Exotoxins***
Lipopolysaccharides in nature	Proteins in nature

Endotoxins	***Exotoxins***
Part of the cell wall of gram-negative bacteria	Secreted both by gram-positive and gram-negative bacteria
Produce nonspecific action (fever, shock, etc.)	Specific action on particular tissues
Less potent	More potent
Poorly antigenic	Highly antigenic
No effective vaccine is available using endotoxin	Toxoid forms are used as a vaccine, e.g. tetanus toxoid

EXPECTED QUESTIONS

1. I. Write short notes on:

1. Mechanisms of bacterial pathogenesis.
2. Differences between endotoxins and exotoxins.

2. II. Multiple Choice Questions (MCQs):

1. **The chemical nature of endotoxin is:**
    a. Protein
    b. Lipopolysaccharide
    c. Carbohydrate
    d. None
2. **The following are exotoxins,** *except:*
    a. Botulinum toxin
    b. Anthrax toxin
    c. Diphtheria toxin
    d. Lipid A portion of LPS
3. **Obligate intracellular bacteria are all,** *except:*
    a. *M. leprae*
    b. *Rickettsia*
    c. *Chlamydia*
    d. *M. tuberculosis*

Answers

1. b	**2.** d	**3.** d