وزارة التعليم العالي والبحث العلمي

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المرحلة الرابعة

Pathogenic bacteria/ Theory

Lec. 1 : Pathogenic Bacteria (Overview)

The science of medical microbiology dates back to the pioneering studies of Pasteur and Koch. The methods they developed lead to the first golden age of microbiology (1875–1910). When many bacterial diseases and the organisms responsible for them were defined. In the first half of the 20th century, scientists studied the structure, physiology, and genetics of microbes in detail and began to answer questions relating to the links between specific microbial properties and disease.

The contributors:

- **Louis Pasteur (1822-1895)**

A French microbiologist, He is considered as **"Father of Microbiology"**.

1862– Proposed germ theory of disease

1867 – Pasteur devised the process of destroying bacteria known as pasteurization.

1881 – Development of anthrax vaccine. Resolved Pebrine problem of silkworms.

1885 – Development of a special vaccine for rabies (the **Pasteur : treatment).**

- **Robert Koch (1843 - 1910)**

A German scientist, He perfected many bacteriological techniques and known as **"Father of Practical Bacteriology"**

1876 - Koch demonstrated that anthrax is caused by Bacillus anthracis.

1882 - Isolated the bacterium--Mycobacterium tuberculosis--that causes tuberculosis.

1883 - Isolation of Vibrio cholerae, the cause of cholera.

1883 - Verification of the germ theory of disease by relating a specific organism to the specific disease.

1884 – Koch put forth his postulates-known as Koch's postulates.

The four Original postulates are:

1- The suspected microorganism must always be found in diseased but never in healthy individuals.

2- The microorganism must be isolated in pure culture (one free of all other types of microbes) on a nutrient medium.

3- The same disease must result when the isolated microorganism is inoculated into a healthy host.

4- The same organism must be reisolated from the experimentally infected host. (Fig. 1).

Proposed fifth postulate

5- Elimination of the disease-causing microbe from the infected host or prevention of exposure of the host to the microbe should eliminate or prevent disease,

KOCH'S POSTULATES
The suspected: pathogenic organisms should be present in all cases of the disease and absent from healthy animals.
The suspected organism should be grown in pure culture.
Cells from a pure culture of the suspected organism should cause disease in healthy animal.
The organism should be desolated as shown to be the same ??? the original

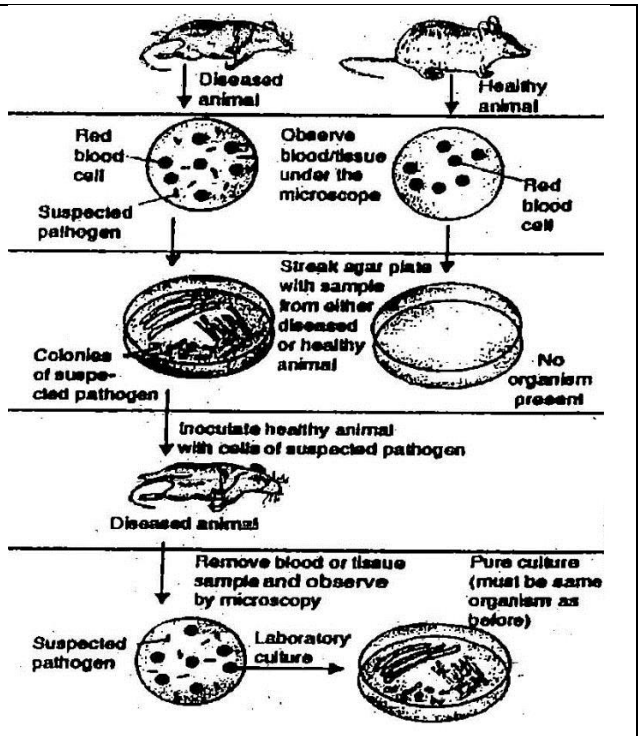


Fig. 1: Koch's postulates

- **Joseph Lister (1827-1912)**

British surgeon, he first introduced the technique to reduce microbes in a medical setting and prevent wound infections in 1867. Lister will always be known as the Father of antiseptic surgery or father of modern surgery.

Specific relationships between human and germs:

From the moment of birth human been are continuously exposed to microorganisms including bacteria. Some of the interactions between the human and microorganisms are essential for the wellbeing of individual but other result in disease.

• Parasite is an organism that resides on or within another living organism in order to find the environment, nutrient that required for growth and reproduction.

Symbiotic relationships:

The surface tissue of the skin, oral cavity, respiratory tract, gastrointestinal tract, genital and urinary tract are populated by bacteria and other microorganisms.

- **Normal micro flora (Microbiota)** are microbial population frequently found in association with particular tissue in normal, healthy individuals.
- **Transients or Transient flora** are acquired from the environment and establish themselves briefly but tend to be excluded by competition from residents or by the host's innate or immune defense mechanisms. They found in association with skin and mucous membrane, they may be present for hours, days, few weeks, they may or may not be pathogenic.
- **Residents or Resident flora** are strains that have an established niche at one of the many body sites, which they occupy indefinitely. They found regularly inside the body (endosymbiosis) or on surface (ectosymbiosis) usually not pathogenic but may be opportunistic.

Microbiota of the skin:

- Staphylococcus epidermidis
- Staphylococcus aureus (in small numbers)
- Micrococcus species
- α-Hemolytic and nonhemolytic streptococci (eg, Streptococcus mitis).
- Corynebacterium species
- Propionibacterium species
- Peptostreptococcus species
- Acinetobacter species
- Small numbers of other organisms (Candida species, Pseudomonas aeruginosa, etc)

Microbiota of the mouth

- Staphylococcus
- Neisseria
- Lactobacillus
- Bacteriodes

The muocus membrane of mouth and pharynx are often sterile at birth, after birth some viridans streptococci become established.

Microbiota of the upper respiratory tract

- α-Hemolytic and nonhemolytic streptococci
- Haemophilus species
- Pneumococci
- Mycoplasma
- Bacteroides

Microbiota of the eye:

- Staphylococcus spp.

- Streptococcus spp.
- Corynebacterium xerosis

Microbiota of the ears

- Staphylococcus spp.
- Streptococcus spp.
- Bacillus spp.

Microbiota of the gastrointestinal tract

✓ Upper intestine

- Lactobacillus
- Enterococcus

✓ Colon

96 - 99% of bacteria.consist of anaerobic;

- Lactobacillus spp.
- Streptococci.
- Fusobacterium spp.
- Bifidobacterium
- Bacteroides
- Clostridium perfringens
- Small numbers of Proteus and Pseudomonas

The important functions of intestinal microbiota can be divided into three major categories:

1. **Protective functions:** in which the resident bacteria displace and inhibit microbial pathogens indirectly by competing for nutrients and receptors or directly through the production of antimicrobial factors, such as bacteriocins and lactic acid.

2. **The development and function of the mucosal immune system**. Such as induce the secretion of IgA.
3. **Metabolic functions**. Such as synthesize vitamin K, biotin, and folate and enhance ion absorption. Certain bacteria metabolize dietary carcinogens and assist with fermentation of nondigestible dietary residue.

Pathogenicity of microorganisms:

Pathogenicity: The ability or capacity of an infectious agent (microorganism) to cause disease. I

Pathogen: A microorganism capable of causing disease. There are two types of pathogens:

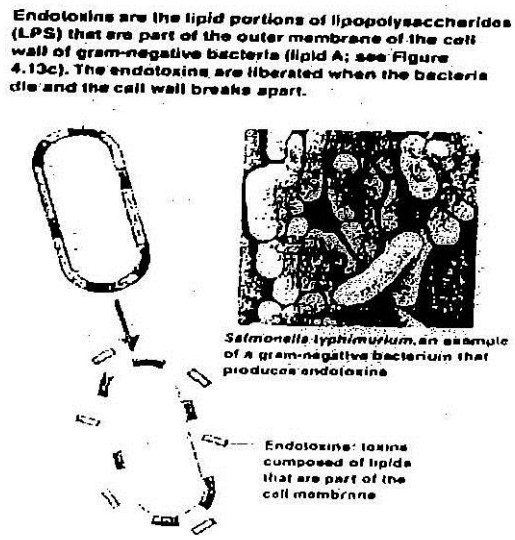
1. **Opportunistic pathogens:** agents capable of causing disease only when the host's resistance is impaired (ie, when the patient is "immunocompromised").Or they are normal flora cause disease when the immune response of the host is suppressed. For example: Clostridium perfringens is normal flora in colon but cause "gas gangrene" in locally damaged tissue.
2. **True pathogens:** they possess properties that enable them to overcome the body defenses and infect the tissue of normal healthy subject.

The microbial factors contributing infection:

A few substances play role in reproduction of diseases:

1. **Toxins**

Toxins produced by bacteria are generally classified into two groups: exotoxins and endotoxins. Exotoxins are proteins that are most often excreted from the cell. However some exotoxins accumulate inside the cell and are either injected directly into the host or are released by cell lysis. Endotoxins are lipid molecules that are components of the bacterial cell membrane. The primary features of the two groups are listed in Table 1.



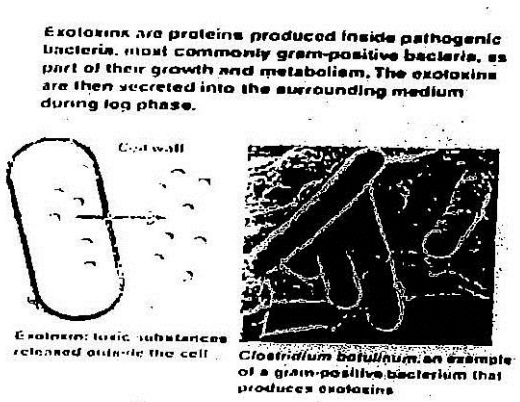


Table 1: Essential features of exotoxin and endotoxin

Exotoxin	Endotoxin
Excreted by living cell; found in high concentrations in liquid medium	Integral part of the cell wall of gramnegative bacteria; released on bacterial. death
Produced by both gram-positive and gram-negative bacteria	Found only in gram-negative bacteria
Polypeptides with a molecular weight. of 10,000-900,000	Lipopolysaccharide complexes, lipid A portion probably responsible for toxicity
Relatively unstable; toxicity often destroyed rapidly by heating at temperatures above 60°C	Relatively stable; withstand heating at temperatures above 60°C for hours without loss of toxicity.
Highly antigenic, stimulate formation of high-titer antitoxin; antitoxin neutralizes toxin	Weakly immunogenic; antibodies are antitoxic and protective
Converted to antigenic, nontoxic toxoids by formalin, acid, heat, and so on	Not converted to toxoids
Highly toxic; fatal to animals in microgram quantities or less	Moderately toxic; fatal for animals in tens to hundreds of micrograms
Usually do not produce fever in the host	Usually produce fever in the host

2. Extracellular enzymes: Many species of bacteria produce enzymes that are not intrinsically toxic but do. Play important roles in the infectious process.

A. Tissue-Degrading Enzymes

Many bacteria produce tissue-degrading enzymes. The best-characterized are enzymes from C. perfringens, and, to a lesser extent, anaerobic bacteria, S. aureus, and group a streptococci.

- **collagenase** a proteolytic enzyme degrades collagen, the major protein of fibrous connective tissue, and promotes spread of infection in tissue. Produce from C. perfringens
- **coagulase,** many pathogenic Staphylococcus produce this enzyme which works in conjunction with blood factors to coagulate plasma. Coagulase contributes to the formation of fibrin walls around staphylococcal lesions, which helps them persist in tissues.
- **Hyaluronidases** are enzymes that hydrolyze hyaluronic acid, a constituent of the ground substance of connective tissue. They are produced by many bacteria (eg, staphylococci, streptococci, and anaerobes) and aid in their, spread through tissues.
- **Streptokinase** (fibrinolysin), this enzyme is able to dissolve coagulated plasma and probably aids in the rapid spread of streptococci through tissues. Many hemolytic streptococci produce it.
- **Cytolysins**—that is, they dissolve red blood cells (hemolysins) or kill tissue cells or leukocytes (leukocidins). Many bacteria produce these substances such as Clostridia and Staphylococci. Most gram-negative rods isolated from sites of disease produce hemolysins. For example, whereas E. coli strains that cause urinary tract infections typically produce

hemolysins, strains that are part of the normal gastrointestinal flora may or may not produce hemolysins.

B. IgA1 Proteases

Some bacteria that cause disease produce IgA1 proteases. IgA1 protease is an important virulence factor of the pathogens N.gonorrhoeae, N meningitidis, H influenzae, and S pneumoniae.

The enzymes are also produced by some streptococci associated with dental disease, and a few strains of other species that occasionally cause disease. Production of IgA1 protease allows pathogens to inactivate the primary antibody found on mucosal surfaces and thereby eliminates protection of the host by the antibody.

3 stage / pathogenic bacteria with Lec.1 .

Extracellular enzymes that play role in the infectious process

Enzyme	Work	M.O
collagenase	degrades collagen	C. perfringens
coagulase	coagulate plasma	Staphylococcus
Hyaluronidases	Hydrolyze hyaluronic acid	• Staphylococci • Streptococci • Anaerobes
Streptokinase (fibrinolysin)	dissolve coagulated plasma	Hemolytic streptococci
Cytech Veins 1. Hemolysins 2. leukocidins	dissolve RBCS kill tissue cells or leukocytes	• Clostridia • Staphylococci
IgA1 proteases	inactivate the antibody	• N.gonorrhoeae, • N.meningitidis, • H.influenzae, • S.pneumoniae.

Lec.2 Pathogenesis of bacterial infection

Infectious diseases are complex and involve a series of complex and shifting interactions between the invading organism and the host, these interactions include the following:

1. The organism's ability to breach host barriers and to evade destruction by innate local and tissue host defenses.
2. The organism's biochemical tactics to replicate, to spread, to establish infection, and to cause disease.
3. The microbe's ability to transmit to a new susceptible host.
4. The body's innate and adaptive immunologic ability to control and eliminate. The invading parasite.

Infection may imply colonization, multiplication, invasion or persistence of a pathogen on or within a host.

infectious disease is used to describe an infection that causes significant overt damage to the host. There are two broad qualities of pathogenic bacteria underlie the means by which they cause disease: invasiveness and toxigenesis.

Invasiveness is the ability to invade tissues. This encompasses mechanisms for colonization (adherence and initial multiplication), ability to bypass or overcome host defense mechanisms, and the production of extracellular substances ("invasins") which facilitate the actual invasive process.

Toxigenesis is the ability to produce toxins. Toxic substances may be transported by blood and lymph and cause cytotoxic effects at tissue sites remote from the original point of invasion or growth.

Pathogenesis is the process of causing disease. It depends on the:

- immune status of the host

- nature of the species or strain (virulence factors)
- Phase of microbial growth; bacteria in log phase are more likely to overcome host resistance than those in late phases.
- number of organisms in the initial exposure (dosage of pathogen): for example, Salmonella typhi infection need small dose, while Salmonella enteriditis infection need to large dose.

ID50 (Infectious Dose) is number of microbes required to produce infection in 50% of the population.

LD50 (Lethal Dose) is amount of toxin or pathogen necessary to kill 50% of the population in a particular time frame.

Virulence is a term which refers to the degree of pathogenicity of the microbe.

Virulence might be lost by the following:

1. Attenuation, successive transfer of pathogen.
2. Loss of capsule; for example loss of capsule in pneumococcus 3- Colony variation; conversion from smooth to rough, for example Salmonella & Shigella
3. Loss of temperate phage; for example Corynebacterium diphtheria.
4. Heat & desiccation

Enhancement of virulence by:

1. Successive passage in lab animals
2. Presence with other bacteria; for example Corynebacterium diphtheria & Streptococcus pyogenes

Conserving of virulence:

1. Lyophilization
2. Using enrichment culture media containing blood and store in dark at low temperature

3. Spore forming bacteria resist adverse conditions, therefore they have permanent virulence.

Bacterial virulence differs according to the host factors which include:

1. Age
2. Malnutrition
3. Drugs addiction
4. Metabolic diseases such as diabetes
5. Haemological disease
6. Immune deficiency disease
7. Sex
8. Race

Types of diseases:

1. **Local:** A disease that is restricted to a certain area in the body.
2. **Focal:** Localized site of disease from which bacteria and their products can spread to other body parts.
3. **Primary:** A disease caused by one microbial species.
4. **Secondary:** A primary disease complicated with second pathogen. For example, pneumonia following primary influenza especially in aged people.
5. **Mixed:** A disease caused by two or more microbial species.
6. In apparent: A disease that doesn't give rise to any detectable manifestation.
7. **Latent:** A disease that persist in the tissues in dormant state and later becomes manifested usually when the host resistance is lowered.

8. **Bacteremia:** A condition in which blood serves as site of presence of bacteria, but the bacteria usually cleared from the vascular system with no harmful effect.
9. **Septicemia:** A condition in which blood serves as a site of bacterial multiplication as well as a mean of transfers of infectious agents from one site to another.
10. **Pyemla:** The presence of pyogenic bacteria like Staphylococcus in the blood as they spread from one site to another.
11. **Toxemia:** The presence of bacterial toxins in the blood.

The Mechanisms of Bacterial Pathogenicity

To cause disease a pathogen must:

1. Gain access to the host (Entry into host)
2. Adhere to host tissues (Adhesion)
3. Penetrate or evade host defenses (Invasion)
4. Survival in the host
5. Damage the host, either:

- directly

- accumulation of microbial wastes

Entry into host

A. Mucous membranes (moist mucosa); most common route for most pathogens

1. Respiratory tract (most common)
2. Gastrointestinal tract
3. Urinary/genital tracts
4. Conjunctiva

B. Skin (keratinized cutaneous membrane);

-some pathogens infect hair follicles and sweat glands

-few can colonize surface

-unless broken, skin is usually an impermeable barrier to microbes

C. Parenteral route

-penetrate skin: punctures, injections, bites, cuts, surgery, etc.

-deposit organisms directly into deeper tissues

D. Many opportunistic pathogens are carried as part of the normal human flora, and this acts as a ready source of infection in the compromised host.

Adhesion:

Is an essential preliminary to colonization and then penetration through tissues. At the molecular level, adhesion involves surface interactions between specific receptors on the mammalian cell membrane (usually carbohydrates) and ligands (adhesin) (usually proteins) on the bacterial surface. The presence or absence of specific receptors on mammalian cells contributes significantly to tissue specificity of infection.

Invasion or invasiveness

It's the ability of microorganisms to enter host tissues, multiply and spread. it is mediated by a complex array of molecules, often described as 'invasins' which act against the host by breaking down defenses of the body.

Types of Bacterial Invasins

- **Spreading factors;** bacterial enzymes such as hyaluronidase, collagenase, etc.
- **Enzymes that cause cell lysis;** such as lecithinases, phospholipases, hemolysin, etc.
- **Staphylococcal coagulase**
- **Extracellular digestive enzymes,** such as proteases, lipases, glycohydrolases, nucleases, etc.

- **Toxins with short-range effects** related to invasion; such as anthrax toxin. Some bacteria, e.g. Corynebacterium diphtheriae or Clostridium tetani, (toxin producers) are non-invasive. Others such as Staphylococci & Streptococci are moderately invasive, while anthrax & plague bacilli are highly invasive.

Survival in the host

Most successful pathogens possess structural or biochemical features which allow them to resist the main lines of host internal defense against them, i.e., the phagocytic and immune responses of the host. For example;

- the poly-D-glutamate capsule of Bacillus anthracis protects the organisms against cell lysis by cationic proteins in sera or in phagocytes. The outer membrane of Gram-negative bacteria is a formidable permeability barrier that is not easily penetrated by hydrophobic compounds such as bile salts which are harmful to the bacteria.
- Pathogenic mycobacteria have a waxy cell wall that resists attack or digestion by most tissue bactericides. Intact lipopolysaccharides (LPS) of Gram-negative pathogens may protect the cells from complement-mediated lysis or the action of lysozyme.
- Almost all principal pathogens that cause pneumonia and meningitis have antiphagocytic polysaccharide capsules.

Damage the host

Tissue damage and the manifestations of disease may also result from interaction between the host's immune mechanisms and the invading organism or its products. Reactions between high concentrations of antibody, soluble microbial antigens, and complement can deposit immune complexes in tissues and cause acute inflammatory reactions and immune complex disease.

Epidemiology, it's derived from the Greek word "Epidemios" which means among people. It is the study of the distribution and determinants of health-

related states or events (including disease), and the application of this study to the control of diseases and other health problems.

Lab technique in Epidemiology

For epidemiological investigations the strains of bacteria can be divided into types, which are taxonomic categories below the species level. Various typing methods can be used: biotyping, antibiograms, serotyping, bacteriocin typing, and phage typing.

1. Biotyping: biochemical identification of isolates.
2. Serotyping: the use of antigenic differences among bacterial strains. For example; flageltar Ag, cell wall Ag, capsular Ag.
    - Commonly used to identify Salmonella, Shegilla and Enteropathogenic E.coli
    - M-protein serotyping is useful in epidemiology of glomeruli nephritis caused by Streptococcus pyogenes.
    - Capsular swelling test (Quelling test) is used in serotyping of Klebsiella spp.
3. Antibiogram: A test used to determine susceptibility of microorganisms to antibiotics or other antimicrobial substances.
4. Phage typing: Using the phages in identification of bacterial strains. For example: Saureus has 22 phages for identification,
5. Bacteriocin typing: Used in identification of Serratia marscence, E.coli, Proteus mirabilis & Shigella spp.
6. Genetic methods which including:
    - Direct method, hybridization of DNA
    - Indirect method, restricted endonuclease analysis

Pattern of infections or diseases:

- Endemic, a disease found constantly in low percentage with a certain area. For example, Cholera in Southeast Asia
- Epidemic, the outbreak that happens suddenly in high percentage of disease in susceptible persons within certain population. For example, Meningitis in Iraq at 1976
- Pandemic, communicable infections that are widespread in a region, sometimes worldwide, and have high attack rates. For example, Asian influenza

Patterns of transmission of diseases

1. **Horizontal:** Disease is spread through a population from one infected person to another (Kissing, sneezing)
2. **Vertical:** The disease is transmitted from parent to offspring (Ovum, sperm, placenta, milk)
3. **Contact Transmission:**
   - Direct - Kissing, sex
   - Droplets - Talking
   - Vertical – Mother to fetus
   - Vector
4. Indirect Contact:
   - Food, water, and biological products (blood, serum, tissue)
   - Fomite (door knobs, toilet seats, etc.)
   - Air

   – Droplet nuclei (dried microscopic residue)

   – Aerosols (dust or moisture particles)

Sporadic a disease occurs in an irregular pattern.

Prevalence is the total numbers of cases in the population at any given time.

Incidence is the number of new cases over a defined period of time.

Mortality rate is the number of individuals that die as a result of the outbreak of disease within certain period of time.

Nosocomial infections: hospital acquired infections.

Clinical stages of a disease in the host:

A. Acute diseases; are characterized by symptoms that usually appears quickly and become very intense, and then subsides when the host immune system has overwhelmed the pathogen or its toxic products. For example, childhood diseases like measles, mumps, various types of influenza and chicken box.

Stages of acute disease:

1. **Incubation period,** the time between exposure to the organism and appearance of the first symptoms of the disease.
2. **Acute period,** symptoms of the disease are at their peak. For example, fever and cough in respiratory, diarrhea and vomiting in intestinal tract, etc.
3. **Convalescent period,** a period characterized by a sharp decline in symptoms.

B. Chronic diseases and persistence; symptoms are expressed over a long period of time; infectious agent here is an intracellular parasite like brucellosis and tuberculosis.

Some microbes that persist in host give rise to mild symptoms or no symptoms, and its actively shed from the host, the individual shedding these microorganisms are called carriers and the microorganisms may be persist in the host for days, months or even year like bacteria of cholera, typhoid and diphtheria.

Reservoirs & sources of diseases:

1. Animate, which include;

- **Patients,** they represent the most important reservoirs for many viral and bacterial diseases like measles, mumps, poliomyelitis, whooping cough and sexually transmitted diseases.
- **Carriers,** infected healthy individuals, no symptoms (asymptomatic), or very mild form of disease, yet they both can spread disease to others - many bacterial pathogens.

Carriers can be:

1. **Convalescent carrier,** a person who has recovered from the symptoms of an infectious disease but is still capable of transmitting pathogens to others.
2. Healthy carrier, a person who or animal that harbors a specific infectious agent in the absence of discernible clinical disease and serves as a potential source of infection.
3. Chronic carriers, they carry infectious agents for long periods of time.

- **Animals**

Zoonosis; it is any infection or disease that is transmitted to man from animals (a disease occurring primary in animal and transmitted secondary to human).

✓ For example; Salmonella transmitted from cattle and peltry through contaminated food causing salmonellosis.

✓ Two classes of arthropods serve as reservoirs and sources of infection:

1. **Insecta;** flies, mosquitoes, fleas and lice
2. **Arachnida;** ticks and mites

The relationship between infectious agents and arthropods;

1. **Mechanical;** arthropods carry infectious agents on their appendages and not involved in their life cycle like flies and Salmonella.
2. **Biological;** arthropods serve like hosts and reservoirs of the microbial agents like mosquitoes and malaria parasites.

2. **Inanimate,** which includes:

- Soil, example; Clostridium tetani and Clostridium perfrengens
- Water, example; Vibrio cholerae
- Food, example; Salmonella typhi, Clostridium botulinum & Campylobacter

Lec.3 The Enterobacteriaceae (enteric or coliforms)

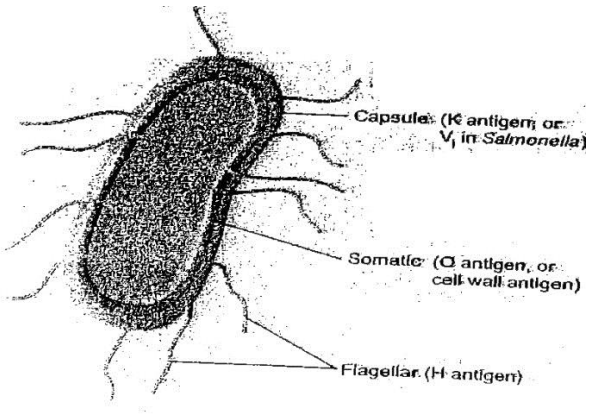
They are a large heterogeneous group of aerobes or facultative anaerobes, gramnegative rods, ferment a wide range of carbohydrates, possess a complex antigenic structure, and produce a variety of bacteriocins such as colicins, toxins (endotoxin & exotoxins) and other virulence factors. The natural habitat is the intestinal tract of humans and animals

Bacteriocins: proteins are produced by certain strains of bacteria active against some other strains of the same or closely related species.

The family includes 51 genera (Escherichia, Shigella, Salmonella, Enterobacter, Klebsiella, Serratia, Proteus, and others). The clinically significant Enterobacteriaceae comprise 20–25 species, and other species are encountered infrequently.

Antigenic Structure:

- more than 150 different heat-stable.somatic O (lipopolysaccharide) antigens
- more than 100 heat-labile K (capsular) antigens
- more than 50 H (flagellar) antigens



Diseases caused by Enterobacteriaceae other than Salmonella & Shigella Causative Organisms

E.coli, Proteus, Enterobacter, Klebsiella, Morganella, Providencia, Citrobacter, and Serratia species are found as members of the normal intestinal microbiota. They are sometimes found in small numbers as part of the normal microbiota of the upper respiratory and genital tracts. The bacteria become pathogenic only when they reach tissues outside of their normal intestinal or other less common normal microbiota sites,

The most frequent sites of clinically important infection are the urinary tract, biliary tract, and other sites in the abdominal cavity, but any anatomic site can be the site of disease.

Pathogenesis and Clinical Findings

A. E. coli

1. **Urinary tract infection (UTI):** E. coli is the most common cause of UTI and accounts for approximately 90% of first UTI in young women.
2. **E. coli-associated diarrheal diseases:**
   - **Enteropathogenic E. coll (EPEC)** are an important cause of diarrhea in infants, especially in developing countries. The duration of the EPEC diarrhea can be shortened and the chronic diarrhea cured by antibiotic treatment.

- **Enterotoxigenic E. coli (ETEC)** is a common cause of "traveler's diarrhea" and a very important cause of diarrhea in infants in developing countries. Some strains produce a heat-labile exotoxin (LT) and some produce the heat-stable enterotoxin Sta. Care in the selection and consumption of foods potentially contaminated with ETEC is highly recommended to help prevent traveler's diarrhea. Antibiotic treatment effectively shortens the duration of disease.
- **Shiga toxin-producing E. coli (STEC)** they produce two cytotoxic toxins, Shiga-like toxin 1 and Shiga-like toxin 2. Of the E. coli serotypes that produce Shiga toxin, 0157:H7 is the most common. STEC has been associated with hemorrhagic colitis, a severe form of diarrhea which can be prevented by thoroughly cooking ground beef and avoiding unpasteurized products such as apple cider.
- **Enteroinvasive E. coll (EIEC)** produces a disease very similar to shigellosis. The disease occurs most commonly in children in developing countries and in travelers to these countries.

The Shigellae

Antigenic Structure: There are more than 40 serotypes.

Pathogenesis and Pathology

Shigella infections (Shigellosis) are almost always limited to the gastrointestinal tract; bloodstream invasion is quite rare. Shigellae are highly communicable; the infective dose is on the order of 10% organisms. The pathogenic species of Shigella are S.dysenteriae, S. flexneri, S. boydii and S. sonnei.

Toxins

A.Endotoxin

B. Shigella dysenteriae Exotoxin.

S dysenteriae type 1 (Shiga bacillus) produces a heat-labile exotoxin that affects both the gut (acting as an enterotoxin) and the central nervous system (acting as neurotoxin). The exotoxin is a protein that is antigenic and lethal for experimental animals.

Clinical Findings

After a short incubation period (1-2 days), there is a sudden onset of abdominal pain, fever, and watery diarrhea. In more than half of adult cases, fever and diarrhea subside spontaneously in 2–5 days. However, in children and elderly adults, loss of water and electrolytes may lead to dehydration, acidosis, and even death. The illness caused by S dysenteriae may be particularly severe. On recovery, most persons shed dysentery bacilli for only a short period, but a few remain chronic intestinal carriers and may have recurrent bouts of the disease. Upon recovery from the infection, most persons develop circulating antibodies to shigellae, but these do not protect against reinfection.

Immunity: Injection of killed shigella'e stimulates production of antibodies in serum but fails to protect humans against infection.

Treatment: Ciprofloxacin, ampicillin, doxycycline, and trimethoprim-sulfamethoxazole.

Epidemiology, Prevention, and Control

Shigellae are transmitted by "food, fingers, feces, and flies" from person to person, Most cases of Shigella infection occur in children younger than 10 years of age. Because humans are the main recognized host of pathogenic shigellae, control efforts must be directed at eliminating the organisms from this reservoir by:

(1) Sanitary control of water, food, and milk; sewage disposal and fly control

(2) Isolation of patients and disinfection of excreta

- **Enteroaggregative E. coli (EAEC)** causes acute and chronic diarrhea in persons in developing countries, foodborne illnesses in industrialized countries and have been associated with traveler's diarrhea and persistent diarrhea in patients with HIV.

3. **Sepsis-**When normal host defenses are inadequate, E. coli may reach the bloodstream and cause sepsis.
4. **Meningitis**- Approximately 75% of E. coli from meningitis cases have the K1 antigen.

B. Klebsiella-K pneumoniae is present in the respiratory tract and feces of about 5% of normal individuals. It causes a small proportion (~1%) of bacterial pneumonias.

C. Serratia-S. marcescens is a common opportunistic pathogen in hospitalized patients. Serratia (usually nonpigmented) causes pneumonia, bacteremia, and endocarditis.

D. Proteus produce infections only when the bacteria leave the intestinal tract. They are found in urinary tract infections and produce bacteremia, pneumonia, and focal lesions in debilitated patients or those receiving contaminated intravenous infusions. P mirabilis causes urinary tract infections and occasionally other infections. P. vulgaris is important nosocomial pathogen.

Immunity: Specific antibodies develop in systemic infections, but it is uncertain whether significant immunity to the organisms follows.

Treatment

No single specific therapy is available. The sulfonamides, ampicillin, cephalosporins, fluoroquinolones, and aminoglycoșides have marked antibacterial effects against the enterics, but variation in susceptibility is great,

and laboratory tests for antibiotic susceptibility are essential. Multiple drug resistance is common and is under the control of transmissible plasmids.

Epidemiology, Prevention, and Control

Some of the enterics constitute a major problem in hospital infection; these bacteria commonly are transmitted by personnel, instruments, or parenteral medications. Their control depends on hand washing, rigorous asepsis, sterilization of equipment, disinfection, restraint in intravenous therapy, and strict precautions in keeping the urinary tract sterile (ie, closed drainage).

(3) Detection of subclinical cases and carriers, particularly food handlers

(4) Antibiotic treatment of infected individuals

The Salmonella-Arizona group

Salmonellae are often pathogenic for humans or animals when acquired by the oral route. They are transmitted from animals and animal products to humans, where they cause enteritis, systemic infection, and enteric fever.

Classification Currently, the genus Salmonella is divided into two species; S. enterica (contains subspecies; I, 11, illa, lib, IV & VI) and S. bongori. Most human illness is caused by the subspecies I strains, written as Senterica subspecies enterica. There are more than 2500 serotypes of salmonellae, including more than 1400 in DNA hybridization group I that can infect humans. Four serotypes of salmonellae that cause enteric fever can be identified: S. Paratyphi A (serogroup A), S. Paratyphi B (serogroup B), S. Choleraesuis (serogroup C1), and S. Typhi (serogroup D).

Pathogenesis and Clinical Findings

S. Typhi, S. Choleraesuis, and perhaps S. Paratyphi A and S. Paratyphi B are primarily infective for humans. The organisms almost always enter via the oral route, usually with contaminated food or drink. The mean infective dose to produce clinical or subclinical infection in humans is 105-108 salmonellae (but

perhaps as few as 100 S Typhi organisms): Among the host factors that contribute to resistance to salmonella infection are gastric acidity, normal intestinal microbiota, and local intestinal immunity. Salmonellae produce three main types of disease in humans:

A. **The "Enteric Fevers" (Typhoid Fever)**

This syndrome is produced by only a few of the salmonellae, of which S Typhi (typhoid fever) is the most important. The organisms multiply in intestinal lymphoid tissue and are excreted in stools. After an incubation period of 10–14 days, fever, malaise, headache, constipation, bradycardia, and myalgia occur.

B. **Bacteremia with Focal Lesions**

This is associated commonly with S choleraesuis but may be caused by any salmonella serotype.

C. **Enterocolitis** This is the most common manifestation of salmonella infection, enterocolitis can be caused by any of the more than 1400 group I serotypes of salmonellae. Eight to 48 hours after ingestion of salmonellae, there is nausea, headache, vomiting, and profuse diarrhea, 'With few leukocytes in the stools. Low-grade fever is common, but the episode usually resolves in 2-3 days.

Immunity: Infections with S. Typhi or S. Paratyphi usually confer a certain degree of immunity. .

Treatment: ampicillin, trimethoprim-sulfamethoxazole, or a third-generation cephalosporin.

Epidemiology

The feces of persons who have unsuspected subclinical disease or are carriers are a more important source of contamination than frank clinical cases that are promptly isolated, such as when carriers working as food handlers are "shedding" organisms. Many animals, including cattle, rodents, and fowl, are

naturally infected with a variety of salmonellae and have the bacteria in their tissues (meat), excreta, or eggs. The high incidence of salmonellae in commercially prepared chickens has been widely publicized.

A. Carriers

After manifest or subclinical infection, some individuals continue to harbor salmonellae in their tissues for variable lengths of time (ie, convalescent carriers or healthy permanent carriers). 3% of survivors of typhoid become permanent carriers, harboring the organisms in the gallbladder, biliary tract; or, rarely, the intestine or urinary tract.

B. Sources of infection

1. Water, milk and other dairy products (ice cream, cheese, custard)
2. Shellfish, meats and meat products
3. Dried or frozen eggs
4. “Recreational" drugs
5. Animal dyes
6. Household pets.

Prevention and Control

1. Sanitary measures must be taken to prevent contamination of food and water by rodents or other animals that excrete salmonellae.
2. Infected poultry, meats, and eggs must be thoroughly cooked.
3. Carriers must not be allowed to work as food handlers and should observe strict hygienic precautions.
4. Vaccination is recommended for travelers to endemic regions.

Lec.4 Vibrios, Campylobacters, and Helicobacter

Vibrio, Campylobacter, and Helicobacter species are gram-negative rods that are all widely distributed in nature. The vibrios are found in marine and

surface waters. The campylobacters are found in many species of animals, including many domesticated animals. Vibrio cholerae produces an enterotoxin that causes cholera, a profuse watery diarrhea that can rapidly lead to dehydration and death. Campylobacter jejuni is a common cause of enteritis in humans. Helicobacter pylori has been associated with gastritis and duodenal ulcer disease.

The Vibrios

Vibrios are among the most common bacteria in surface waters worldwide. They are curved aerobic rods and are motile, possessing a polar flagellum. V. cholerae serogroups 01 and 0139 cause cholera in humans, and other vibrios may cause sepsis or enteritis. The medically important vibrios are listed in Table 1.

Table 1: The Medically Important Vibrios

Organism	Human Disease
V. cholerae serogroups 01and 0139	Epidemic and pandemic cholera
V. cholerae serogroups non-01/non-0139	Cholera-like diarrhea; mild diarrhea; rarely, extraintestinal infection
V. parahaemolyticus	Gastroenteritis, perhaps extraintestinal infection
Others V. mimicus, V. vulnificus, V. hollisae, V. fluvialis, V.damsela, V. anginolyticus, V. metschnikovii, V.cincinnatiensis	Ear, wound, soft tissue, and other extraintestinal infections (all uncommon)

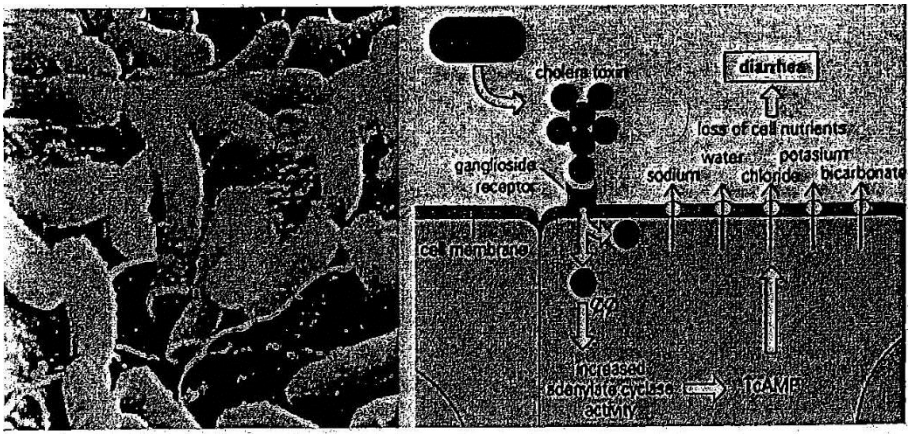
Vibrio cholera

V. cholerae has at least 206 O antigen groups. The V. cholerae serogroup 01 antigen has determinants that make possible further typing; the serotypes are Ogawa, Inaba, and Hikojima. Two biotypes of epidemic V. cholerae have been defined, classic and El Tor. The El Tor biotype tends to cause milder disease than the classic biotype.

$$\text{Vibrio cholerae}\begin{cases} 01\begin{cases}\text{classical}\begin{cases}\text{Ogawa}\\ \text{Inaba}\\ \text{Hikojima}\end{cases}\\ \text{El Tor}\end{cases} \\ \left.\begin{matrix}02-0138\\ 0140-0206\end{matrix}\right\} non-01\ non\ 0139 \\ 0139\ \text{Bengal}\end{cases}$$

Vibrio cholerae Enterotoxin

Vi-cholerae produce a heat-labile enterotoxin (MW 84,000), consisting of subunits A and B. Ganglioside GM1 serves as the mucosal receptor for subunit B, which promotes entry of subunit A into the cell. Activation of subunit A1 yields increased levels of intracellular cyclic adenosine monophosphate (CAMP) and results in prolonged hypersecretion of water and electrolytes. There is increased sodium-dependent chloride secretion, and absorption of sodium and chloride by the microvilli is inhibited. Electrolyte-rich diarrhea occurs as much as 20–30 U/day—with resulting dehydration, shock, acidosis, and death.



Pathogenesis and Pathology

A person with normal gastric acidity to become infected may have to ingest:

- $\geq 10^{10}$ V. cholerae when thie vehicle is water
- 10^2-10^4 organisms when the vehicle is food

Cholera is not an invasive infection. Virulent V. cholerae organisms attach to the microvilli of the brush border of epithelial cells. There they multiply and liberate cholera toxin and perhaps mucinases and endotoxin.

Clinical Findings

About 50% of infections with classic V. cholerae are asymptomatic, as are about 75% of infections with the El Tor biotype. The incubation period is 12 hours-3 days for persons who develop symptoms, depending largely on the size of the inoculum ingested. There is a sudden onset of nausea and vomiting and profuse diarrhea with abdominal cramps. Stools, which resemble "rice water," contain mucus, epithelial cells, and large numbers of vibrios. There is rapid loss of fluid and electrolytes, which leads to profound dehydration, circulatory collapse, and anuria. The mortality rate without treatment is between 25% and 50%.

Immunity

Gastric acid provides some protection against cholera vibrios. An attack of cholera is followed by immunity to reinfection, but the duration and degree of immunity are not known.

Treatment

- The most important part of therapy consists of water and electrolyte replacement to correct the severe dehydration and salt depletion.
- Many antimicrobial agents are effective against V. cholerae, oral tetracycline and doxycycline
- In children and pregnant women, erythromycin and furazolidine.

Epidemiology

- 1817 - 1993; 8 pandemics of cholera were occurred by V. cholerae 01 of the classic and El Tor biotype and serotype 0139 in Asia, Middle East, Africa,

South America and Central America

- The disease has been rare in North America,
- Cholera is endemic in India and Southeast Asia.

- The disease is spread:

1. By contact involving individuals with mild or early illness
2. By water, food, and flies.

- Only 1-5% of exposed susceptible persons develop disease.

Prevention and Control

- Control rests on education and on-improvement of sanitation, particularly of food and water.
- Patients should be isolated, their excreta disinfected, and contacts followed up.
- Chemoprophylaxis with antimicrobial drugs may have a place.
- Repeated injection of a vaccine containing either lipopolysaccharides extracted from vibrios or dense Vibrio suspensions can confer limited protection to heavily exposed persons (eg, family contacts) but is not effective as an epidemic control measure.

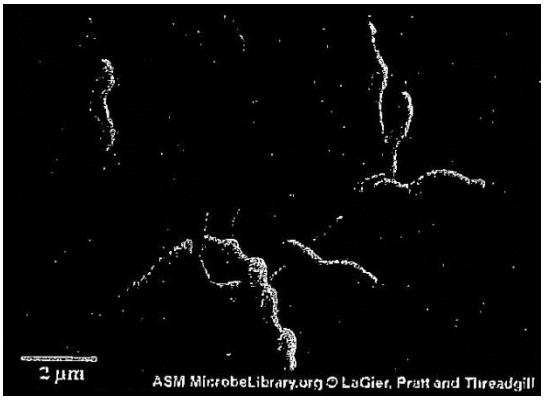
Campylobacter

Campylobacters cause both diarrheal and systemic diseases and are among the most widespread causes of infection in the world. C. jejuni and the other campylobacters are gram-negative rods with comma, S, or "gull wing" shapes. They are motile, with a single polar flagellum, and do not form spores. C. jejuni is a very common cause of diarrhea in humans.

The campylobacters have:

- LPSs with endotoxic activity.
- Cytopathic extracellular toxins
- Enterotoxins.

The significance of the toxins in human disease is not well defined.



Pathogenesis and Pathology

The source of infection may be:

1. Food, drink (eg, milk, undercooked fowl)
2. Contact with infected animals (especially poultry) or humans and their excreta,

C. jejuni is susceptible to gastric acid, and ingestion of about 104 organisms is usually necessary to produce infection. The organisms multiply in the small intestinie, invade the epithelium, and produce inflammation that results in the appearance of red and white blood cells in the stools. Occasionally, the bloodstream iś invaded, and a clinical picture of enteric fever develops.

Clinical Findings

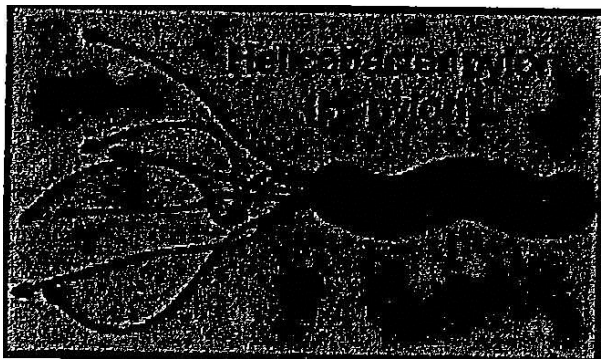
Clinical manifestations are acute onset of cramp abdominal pain, profuse diarrhea that may be grossly bloody, headache, malaise, and fever. Usually the illness is self-limited to a period of 5–8 days, but occasionally it continues longer.

Treatment

C. jejuni isolates are usually susceptible to erythromycin, most cases resolve without antimicrobial therapy; however, in about 5-10% of patients, symptoms may recur.

Helicobacter pylori:

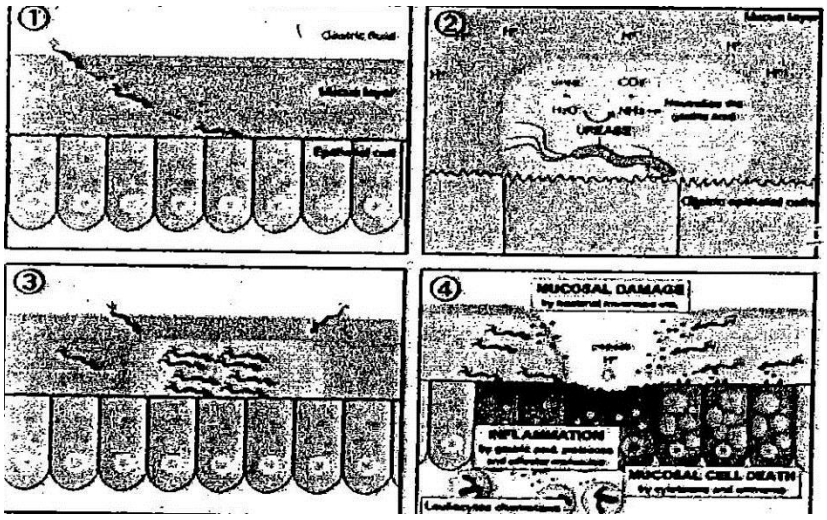
H. pylort is a spiral-shaped gram-negative rod. H. pylori is associated with antral gastritis, duodenal (peptic) ulcer disease, gastric ulcers, gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue (MALT) lymphomas. H. pylori is a major risk factor for gastric cancer.



Pathogenesis and Pathology

H. pylori grows optimally at a pH of 6.0-7.0 and would be killed or not grow at the pH within the gastric lumen. Gastric mucus is relatively impermeable to acid and has a strong buffering capacity. On the lumen side of the mucus, the pH is low (1.0-2.0); on the epithelial side, the pH is about 7.4. H. pylori is found deep in the mucous layer near the epithelial surface where physiologic pH is present. H. pylori also produces a protease that modifies the gastric mucus and further reduces the ability of acid to diffuse through the mucus. H. pylori produces potent urease activity, which yields production of ammonia and further buffering of acid. H. pylori is quite motilė, even in mucus, and is able to find its way to the epithelial surface. The mechanisms by which H. pylori causes' mucosal inflammation and damage are not well defined but probably involve both bacterial and host factors.

Helicobacter pylori pathogenesis overview



Clinical Findings

Acute infection can yield an upper gastrointestinal illness with nausea and pain; vomiting and fever may also be present. The acute symptoms may last for less than 1 week or as long as 2 weeks. After colonization, the H pylori infection persists for years and perhaps decades or evens a lifetime. About 90% of patients with duodenal ulcers and 50–80% of those with gastric ulcers have H. pylori infection.

Treatment

Triple therapy with metronidazole and either bismuth subsalicylate or bismuth subcitrate plus either amoxicillin or tetracycline for 14 days eradicates H. pylori infection in 70–95% of patients. An acid-suppressing agent given for 4 to 6 weeks enhances ulcer healing.

Epidemiology

H. pylori is present on the gastric mucosa of:

- Fewer than 20% of persons younger than years 30
- 40-60% of persons age 60 years, including persons who are asymptomatic.
- In developing countries, the prevalence of infection may be 80% or higher in adults.