الجامعة التقنية الشمالية/ المعهد التقني الموصل

قسم تقنيات التمريض

الصف الاول / فرع التمريض + فرع الاسعاف الفوري

الاحياء المجهرية

د. ندوه محمد خضر

Microbiology

Lecture 1:

Microbiology is divided into four branches:

1. Medical Microbiology
2. Industrial Microbiology
3. Food Microbiology
4. Soil Microbiology

What is Medical Microbiology?

Medical Microbiology deals with microorganisms, such as bacteria, viruses, fungi and parasites, which are of medical importance and are capable of causing diseases in human beings. It deals with etiology, pathogenesis, laboratory diagnosis, treatment, epidemiology and control of infection.

Medical Microbiology includes six sciences:-

1. Parasitology: deals with parasites causing diseases in human.
2. Mycology: deals with fungus causing diseases in human.
3. Bacteriology: deals with bacteria.
4. Immunology: includes mechanism involved in the development of resistance by body to infectious diseases.
5. Genetics: is the study of heredity and variations.
6. Virology: is the study of viruses.

Definition of Bacteria:

Bacteria are unicellular free living organisms, without chlorophyll, having both RNA and DNA, capable of performing all essential processes of life growth, metabolism and reproduction. They have rigid cell wall containing muramic acid.

Classification of bacteria

According on their shape, bacteria are classified into several varieties:

1. Cocci: are spherical or oval cells.

2. Bacilli: are rod shaped cells.

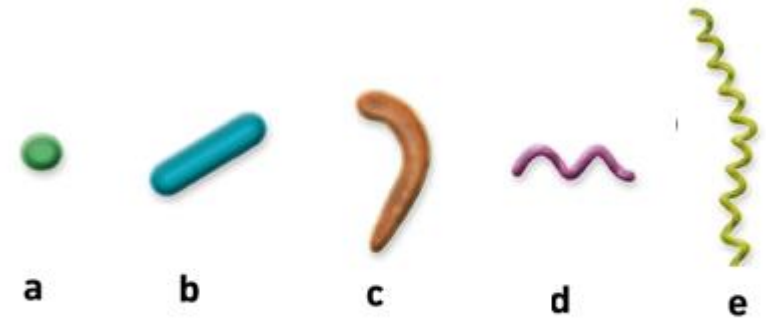
3. Vibrios: are comma shaped curved rods.

4. Spirilla: are rigid spiral forms.

5. Spirochetes: are spiral forms.

6. Actinomycetes: are branching filamentous bacteria.

7. Mycoplasma: are bacteria that lacks to cell wall, therefore, do not possess a stable morphology.



Examples of bacteria

According to the shape, bacteria are classified as:-

1. Cocci (spherical shape) due to arrangement:

a. Cocci in cluster ---------- *Staphylococci*
b. Cocci in chain ---------- *Streptococci*
c. Cocci in pair ---------- *Diplococci*

2. Bacilli (rod or cylindrical shape)
3. Vibrio (comma shaped)
4. Spirochaetes (several coils and flexible)
5. Actinomycetes (branching filamentous bacteria)
6. Mycoplasma (Do not possess a stable morphology, due to lack cell wall), appears rounded or oval bodies with interlacing filaments.

General structure of bacteria

The general structure of bacteria includes:

1- Capsule (slime layer): It is gelatinous secretion of bacteria, which organized as a thick coat a round cell wall.

Function:-

a. Protection against deleterious agents, e.g. lytic enzymes.
b. Contribute to the virulence of pathogenic bacteria by inhibiting phagocytosis.

2- Wall: Is the outer supporting layer, which protects the internal structure. Cell wall composed of mucopeptide (muerin), scaffolding formed by N-acetyleglucosamine and N- acetyle muramic acid molecules alternating in chain cross linked by peptide chain.

Function:

1. Protects the internal structure (supporting layer).
2. Gives shape to the cell.
3. Role in division of bacteria.
4. Offers resistance to harmful effect of environment.

* Cell wall synthesis could be inhibited by many factors.

Lysozyme: enzyme present in many tissue fluid cause lysis of bacteria.

They act by splitting cell wall mucopeptide linkages.

3- Flagella: These are long, sinuous, contractile filamentous appendages known as flagella. They are organ of locomotion. They are antigenic and composed of protein.

4- Pili (fimbriae): Are filamentous, short, thin, straight, hair like.
(0.5 *M* long less than 10nm. thick).

Function:

1. Organ of adhesion.
2. Conjugation tube through which genetic material is transmitted from donor to recipient cell.
3. They are antigenic.

Flagella	Pili
1. Size: larger, thicker.	1. Smaller and thinner.
2. Arise from cytoplasm or Cytoplasmic membrane, but not attached to cell wall.	2. Attached to cell wall.
3. Organ of movement.	3. Organ of adhesion and conjugation.
4. Not straight.	4. Straight.

5- Ribosome: These are ribonucleoprotein granules. They are sites of protein synthesis, measuring (100-200) Angstrom unit.

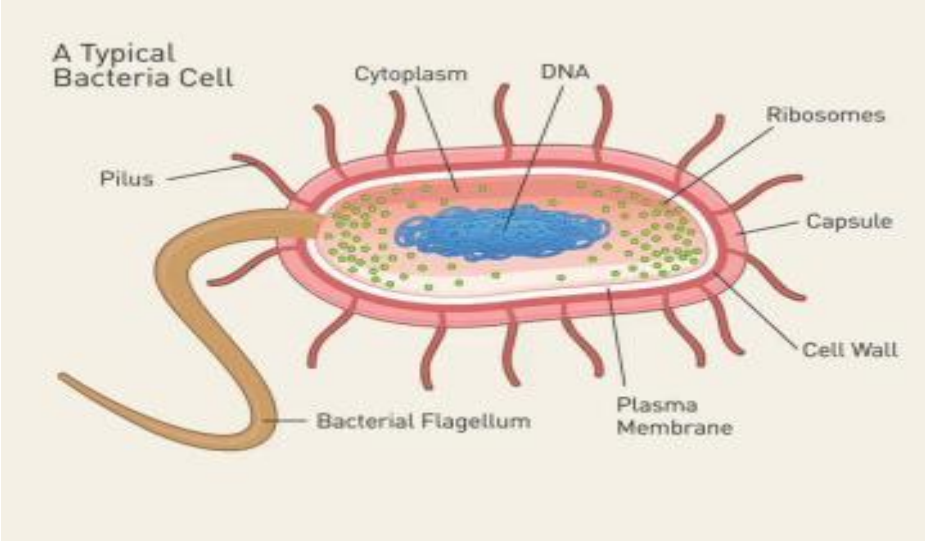
6- Mesosome: Sites of respiratory enzymes in bacteria.

7- Cytoplasm: Bacterial cytoplasm is a suspension of organic and inorganic solutes in viscous watery solution.

8- Cytoplasmic membrane: It is thin semi permeable membrane which lies just beneath the cell wall.

Function:

1. Controls in flow and out flow of metabolites to and from protoplast.
2. Presence specific enzyme (permease) plays important role in passage through membrane.



The Typical bacterial cell

Comparison between Eukaryotic and Prokaryotic cells

Characters	Prokaryotes	Eukaryotes
Examples	Bacteria, green algae	Fungi, protozoa Slime moulds
Membrane-bound organelles	Absent	Present
Nucleus Nuclear membrane Nucleolus Chromosome Mitotic division	 Absent Absent One Absent	 Present Present More than one Present
Cytoplasm Mitochondria Golgi apparatus Endoplasmic reticulum	 Absent Absent Absent	 Present Present Present
Chemical composition Steroids Muramic acid	 Absent present	 Present Absent

Environmental conditions of bacterial growth

In order to have a sufficient bacterial growth, the following environmental conditions are required:

1. Temperature
2. Oxygen
3. Moisture
4. Hydrogen ion concentration (pH).

1. Temperature: divided into 3 groups:

a. Psychrophilic: (0–25˚C) mostly soil and water bacteria.

b. Mesophilic: (25–45˚C) includes bacteria producing disease.

c. Thermophilic: (50–60˚C) Bacillus, Algae.

2. Oxygen: Bacteria are classified into groups due to oxygen requirement:

a. Aerobes: Grow only in presence of oxygen, e.g. *Bacillus*, *Pseudomonas*.

b. Facultative anaerobes: Can live with or without oxygen .e.g. *E. coli*, *Salmonella, Staphylococcus, Shigella.*

c. Obligate anaerobes: Multiply only in the absence of oxygen . e.g. *Clostridium*, *Bacteroides*.

Carbon dioxide: Some types of bacteria need CO_2 for metabolic activities, e.g. *Neisseria gonorrhoeae*.

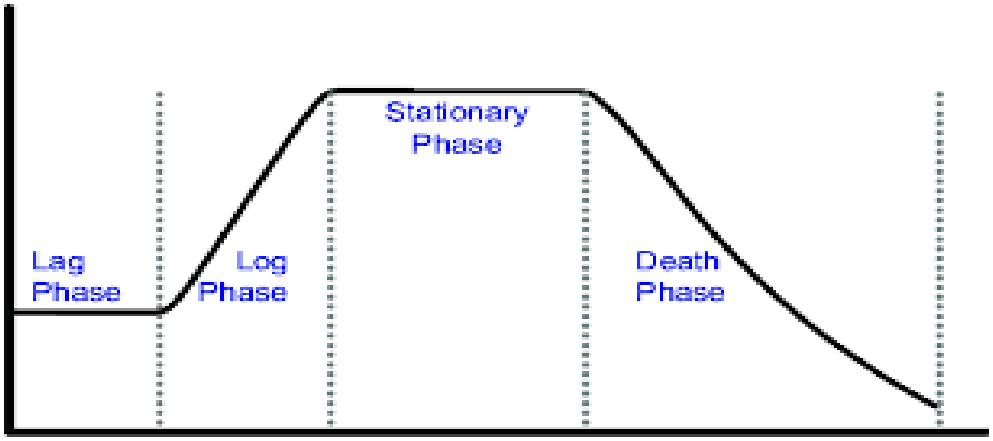
3. Moisture: Bacteria requires water for growth, desiccation may kill most of bacteria.

4. pH: Optimum pH for the bacterial growth ranged between (7.2-7.6), e.g. Vibrio grow at alkaline pH, but Lactobacilli grow at acidic pH.

Stages of bacterial growth

The bacterial growth curve represents the number of live cells in a bacterial population over a period of time. There are four distinct phases of the bacterial growth, i.e., lag, exponential, stationary and death or decline phase. The initial phase is the lag phase, where bacteria are metabolically active but not dividing. After that, the exponential phase begins, which is time of exponential growth.

In the stationary phase, growth reaches a plateau, as the number of dying cells equals the number of dividing cells. Finally, the death phase is characterized by an exponential decrease in the number of living cells, as the population growth begins to decline, due to depletion of nutrients and accumulation of waste products.



The bacterial growth curve

Generation time

The time required for bacterium to produce two daughter cells under optimum condition is called generation time. For example, the generation time of *E. coli* is 20 minutes.

Lecture 2:

Bacterial growth inhibition by sterilization and disinfection

Sterilization: Is the process by which all forms of life (bacteria, fungi, viruses….etc) killed or eliminated. Various agents are used in sterilization such as:

A: Physical

1- Sun light.

2- Drying.

3- Heat. This divided into dry heat and moist heat.

4- Filtration.

5- Radiation.

6- Ultrasonic vibration.

B: Chemical

1- Acid.

2- Alkalis.

3- Salts.

4- Halogens.

5- Oxidizing agent.

6- Reducing agents.

7- Formaldehyde.

8- Phenol.

9- Soap.

10- Dyes.

11- Aerosol

Physical methods

1- Sun light: This is one of the natural methods of sterilization in case of water in tanks, river and lakes, due to ultraviolet rays.

2- Drying: Drying in air has a serious effect on many spores

3- Heat: The factors influencing sterilization by heat are

1) Type of heat: a- Dry. b- Moist.

2) Temperature and time.

3) Number of organisms present.

4) Whether organism has sporing capacity.

Types of heat

1) Dry heat

a. Red heat: It is used to sterilize metallic object by holding them in flame till they are red hot e.g. inoculating wires, needles, scalpels, and forceps.

b. Flaming: The subject is passed over flame without allowing it to become red hot e.g. cotton wool plugs and glass slides.

c. Incineration: It is an excellent method for rapidly destroying material e.g. soiled dressing, animal's carcasses, bedding and pathological material.

d. Hot air oven: Sterilization by hot air oven requires temperature of 160° C for one hour for sterilizing glass, syringes, Petri dishes, test tubes.

2) Moist heat

A) Temperature blow 100° C

Pasteurization of milk: Temperature employed is either 63° C for 30 minutes (Holder method) or 72° C for 15-20 seconds (Flash method) to kill organisms like *Mycobacterium, Salmonella* and *Brucella*.

B) Temperature at 100° C

Tynddallization: This is the process by which medium is exposed to steam at 100° C for 30 minutes each on 3 successive days.

Boiling: Most of vegetative form of bacteria fungi and viruses are killed at 50-70° C in short time.

Steam at atmosphere pressure (100° C): Free steam is used to sterilize culture media which may decompose if subjected to higher temperature.

Steam under pressure: For bacteriological and surgical work boiling is not sufficient because spore can survive hence high pressure sterilizer or autoclave is used.

4- Filtration

This method of sterilization is useful for antibiotic solutions and serum.

5- Radiation

Ultraviolet radiation is a chief bactericidal factor present in sun light, as it causes following changes in the bacterial cell:

1- Denaturation of protein.

2- Damage of DNA.

3- Inhibition of DNA replication.

Ultraviolet lamps are used in:

a- Killing microorganisms.

b- Producing bacterial and viral vaccines.

6- Ultrasonic and sonic vibrations: Are bactericidal causing mechanical agitation and rupture of bacteria.

Chemical methods

1- Acids and alkalis: Are inhibitory agents for the bacterial growth, e.g., *Mycobacteria* are more resistant to acid than alkalis.

2- Distilled water: causes loss of viability, which could be due to traces of metal in distilled water.

3- Metallic ions: $HgCl_2$ and $AgNO_3$ prevents the growth of many bacteria in concentration less than 1ppm (part per million).

4- Oxidizing agents: Are weak antiseptic e.g H_2O_2 and potassium permanganate.

5- Halogens: Iodine is used for skin, chlorine combines with water to form hypochloric acid, which is bactericidal.

6- Formaldehyde: 5-10% solution in water kills many bacteria. It is bactericidal sporicidal and lethal to viruses also.

7- Phenol: It is used for sterilizing surgical instruments and for killing culture accidentally spread in the laboratory.

8- Soap and detergents: Are bactericidal and bacteriostatic for gram positive organisms.

9- Alcohol: Ethyl alcohol is most effective in 70% solution than 100% alcohol fort killing spores.

10- Dyes: Gentian violet and malachite green etc. are active against gram positive bacteria.

11- Aerosols and gaseous disinfectant: such as, SO_2, chlorine and formalin vapour have been used as gaseous disinfectant.

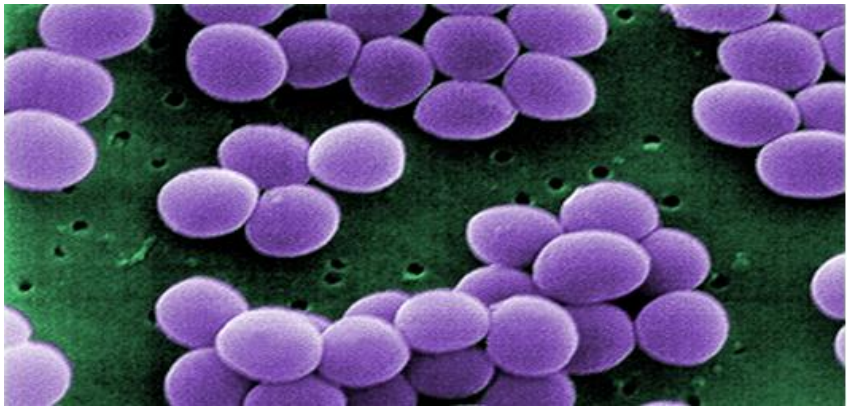
Disinfection: Refers to the elimination of all pathogenic organisms that cause infection. There are two major methods:

1. Chemical method: by using chemical agents such as, chlorine, ozone, halogens bromide, iodine, phenol, ethanol, formaldehyde and hydrogen peroxide.

2. Physical method: includes, UV (ultraviolet) light, gamma-ray irradiation, sonification and heat.

Staphylococcus aureus

General characters: Bacteria are oval or spherical (0.8 to 0.9m) non motile, non-capsulated, non sporing, Gram positive, arranged in cluster (grape like). Cluster formation is occurs by active aggregation of multiple cells into one location.



Virulence factors: Virulence is defined as the capacity of a pathogen, usually a micro-organism, to cause disease. The broad range of infections caused by *Staph. aureus*, is related to a number of virulence factors that allow it to adhere to surface, invade or avoid the immune system and cause harmful toxic effects to the host. These Factors are:

1. Adherence factor: One major class of *Staph. aureus* adhesions comprises protein that attached to the cell peptidoglycan, which in turn, attached to the plasma or extracellular matrix components.

2. Exoprotein: Nearly all strains of *Staph. aureus* secret a group of exoprotein such as, exotoxins and enzymes, including nucleases, proteases, lipases… etc. The main function of these proteins may be to convert host tissues into nutrients required for the bacterial growth.

Pathogenesis: *Staphylococci* are one of the most important causative agents of hospital acquired infection, especially post-operative wound infection. It causes the majority of acute pyogenic lesions in human. Staphylococcal diseases are classified as:

a. Cutaneous lesions: boils, abscess, impetigo, eye infection in new born, (*pemphigus neonatorum*).
b. Deep infection: acute osteomyelitis, tonsillitis, pharyngitis, abscess breast (mastitis), *Staphylococcal septicameia*.
c. Staphylococcal food poisoning. This occurs when food (meat, fish, milk products) contaminated with enterotoxin B, which produced by staphylococci after 6 hours of consuming, leading to diarrhea and vomiting.

Toxins:

1-Haemolysin: *Staph. aureus* produces at least 3 types of haemolysine known as alfa, beta, and gamma.

2- Leukotoxins lyse white blood cells

3- Staphylococcal enterotoxins (SEs) cause vomiting and diarrhea and the toxins are one of the most common causes of food-borne diseases.

4- Fibrinolysin: *Staph. aureus* produces staphylo kinase during the later stage of growth, which causes lysis of fibrin.

Other toxins:

(a) Nucleases
(b) Lipases
(c) Proteases
(d) Scarlatina toxin.

Treatment: The antibiotic therapy for *S. aureus* infections includes cephalexin (keflex), dicloxacillin, linezolid and nafcillin.

Culture media: Selective media are widely used to detect small numbers of *S. aureus* such as, broth of mannitol salt agar.

Lecture 3:

Streptococcus

General characters: spherical or oval cells about 1*M* in diameter, arranged in chains, gram positive, non-motile, non-sporing and sometimes capsulated, required media enriched

with blood, serum or ascetic fluid for their growth. *Streptococcus* can be classified into the following groups due to their hemolytic activity:

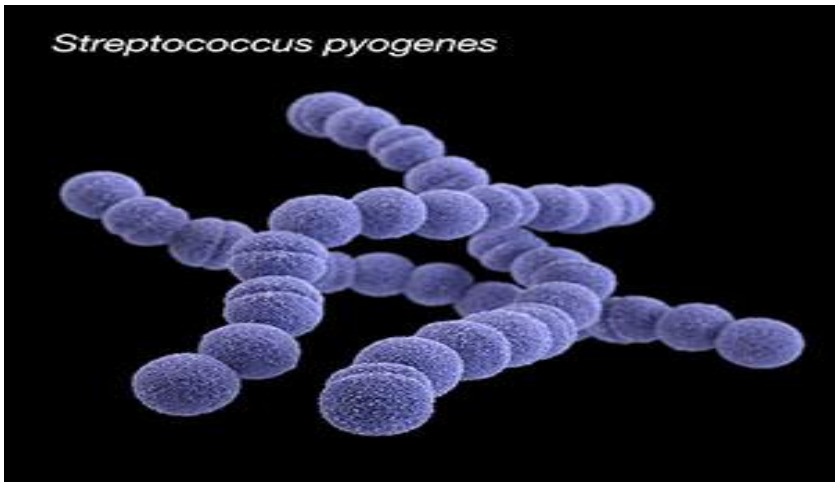
1. Beta- hemolytic: Breaks down the red blood cells and hemoglobin completely. This leaves a clear zone around the bacterial growth or colony, e.g. *Streptococcus pyogenes*.

2. Alfa- hemolytic: Partially breaks down the red blood cells and leaves a greenish color behind on blood agar plates due to oxidizing hemoglobin, e.g. *Streptococcus viridans.*

3. Gamma-hemolytic: (non-haemolytic) many streptococci do not produce any kind of haemolysis, generally commensal, e.g. *Streptococcus faecalis.*

Streptococcus includes the following species:

***Streptococcus pyogenes*:**



Virulence factors include:

1. M protein and lipoteichonic acid for attachment.
2. Hyaluronic acid capsule that inhibits phagocytosis.
3. Other extracellular products such as, pyrogenic toxin, which causes the rash of scarlet fever.

Pathogenesis

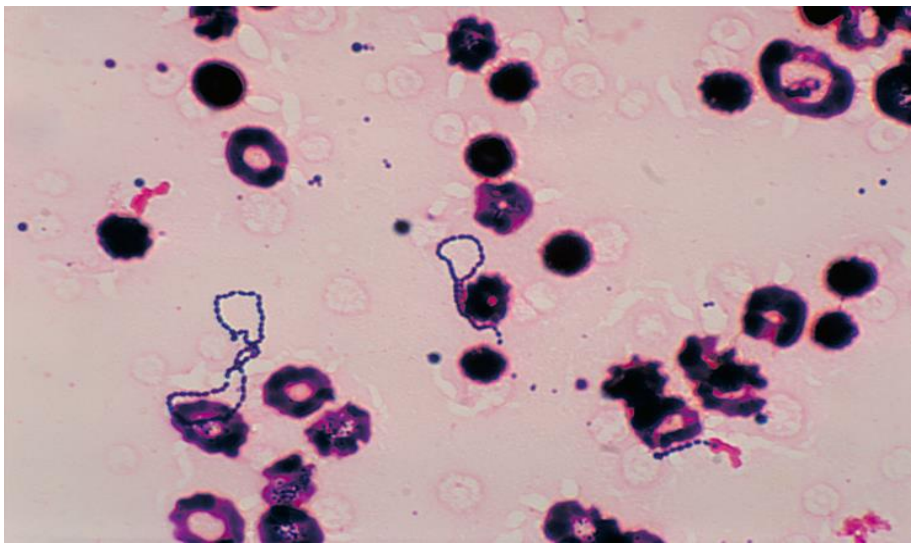
1. Respiratory infection like throat infection, tonsillitis, pharyngitis.
2. Skin infection like suppurative infection of skin e.g. wound and burn.
3. Scarlet fever is caused by a strain producing erthrogenic toxin. It is characterized by a bright red rash on the body, usually accompanied by a high fever and sore throat.
4. Genital tract infection causing puerperal sepsis.

Toxins: Erythrogenic toxins also referred to as *Strep. Pyogenic* toxins, which induces inflammation.

Treatment: Penicillin or amoxicillin is the antibiotic that treats *Strep. Pyogens* infections.

Culture media: usually grown on agar media supplemented with blood, which allows the detection of β-hemolysis for subsequent identification of *Streptococcus*.

***Streptococcus viridans*:**



Virulence factors include:

Binding to platelets, binding to fibrin, exopolysaccharide production, and binding to fibronectin have been identified as factors associated with virulence of *S. viridans.*

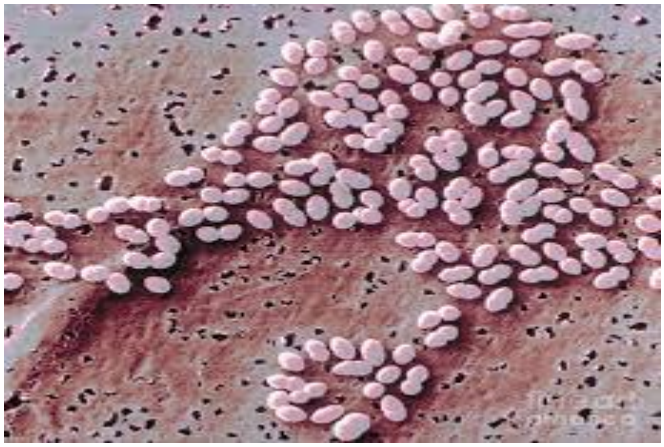
Pathogenesis: Causes subcute bacterial endocarditis, which is an infection of the heart involving damaged valves or endothelium.

Toxins: Erythrogenic toxins also referred to as *Strep. Pyogenic* toxins, which induces inflammation.

Treatment: Penicillin or amoxicillin is the antibiotic that treats *Strep. Pyogens* infections.

Culture media: usually grown on agar media supplemented with blood, which allows the detection of β-hemolysis for subsequent identification of *Streptococcus*.

***Streptococcus faecalis*:**



Virulence factors include:

1. Aggregation substance is a pheromone-responsive, plasmid-encoded bacterial adhesion that mediates efficient contact between donor and recipient bacterium.
2. The contribution of the surface protein to colonization and persistence of *E. faecalis* in urinary tract infections has been shown in an animal model.

3. Lipoteichoic acid (LTA): They are often present on the cell surface. The LTA molecule has been found to bind to a variety of eukaryotic cells, including platelets, erythrocytes, lymphocytes and epithelial cells.

Pathogenesis: It may cause disease in human being when introduced into the blood stream or urinary tract accidentally.

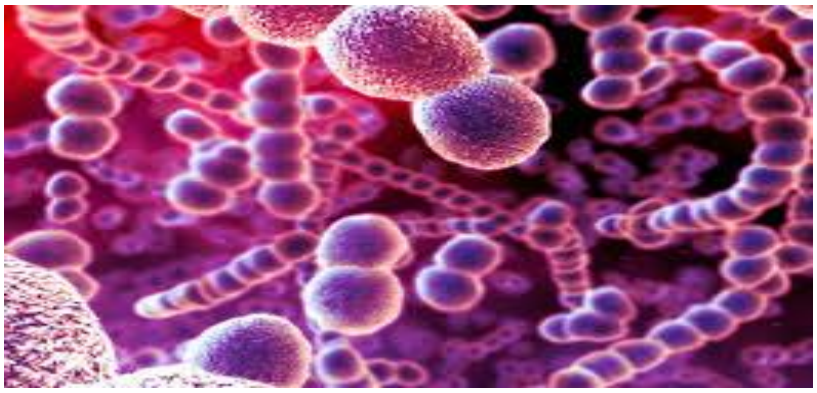
Toxin: A plasmid called cytolysin, is important for pathogenesis in animal models of infection, and the cytolysin in combination with high-level gentamicin increase the risk of death in human beings.

Treatment: Penicillin or amoxicillin

Culture media: Usually grown on media containing bile salt. On blood agar, colonies are little bigger than *Streptococcus pyogenes* on Mac Conkey agar, as they are tiny and dark pink in colors.

Pneumococcus

General characters: Gram positive, lancet shaped, which arranged in pairs or short chains. They are capsulated, surrounded by poly- saccharide capsule. They are non-motile and non-sporing.



Virulence factor: one virulence factor is a polysaccharide capsule that releases *pneumococci* from the host by preventing phagocytosis. Another factor is pneumolysin, which inhibits antibody synthesis.

Pathogenesis: *Diplococcus pneumoniae* cause lobar pneumonia, bronchopneumonia, pneumococcal meningitis, otitis media sinusitis, conjuctivitis, etc…

Toxins: Pneumolysin (a pore-forming hemolysin) is the primary component of live *pneumococci*, stimulating NO (nitric oxide) production in macrophages, which is an essential element of antimicrobial immunity but can also contribute to host-induced tissue damage.

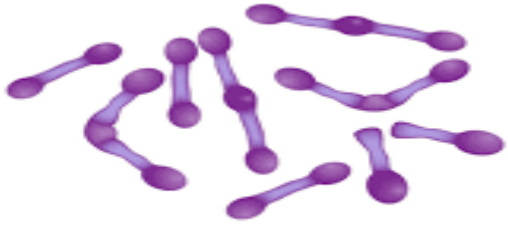
Treatment: penicillin, ampicillin and cefitraxone.

Culture media: *Pneumococci* grow best on blood agar, colonies are surrounded by alfa- haemolytic zone. Tryptic Soy Agar is also used.

Lecture 4:

Corynebacterium diphtheria

General characters: Is a Gram-positive, non-motile, aerobic, rod-shaped bacterium. Strains grow in tissues or old cultures, causing diphtheria, can be characterized as toxigenic or non-toxigenic, or those causing diphtheria and those that don't, respectively.



Corynebacterium diphtheriae

Virulence factors: *C. diphtheriae* has two main virulence factors, i.e., pilli and toxin that contribute to its survival in the host. They help the process of adherence in the host and the colonization of the respiratory tract to cause infection.

Pili

The pilli found on the surface of *C. diphtheriae* are beneficial in the adherence to host cells. There are three distinct types of pili. First type allows for the adherence to pharyngeal epithelial cells, while second and third type display for binding to lung and laryngeal epithelial cells.

Toxin

The main virulence factor of *C. diphtheriae* is diphtheria toxin (DT), an exotoxin, released by the bacteria after entering the human body. The major function of the toxin is to enter the cytoplasm and inhibit protein synthesis in host cells.

Pathogenesis: Diphtheria can cause a thick gray coating to build up in throat or nose making it difficult to breathe and swallow. Diseased individuals may experience a sore throat, overall weakness, fever, and swollen glands. Respiratory involvement typically begins with sore throat and mild pharyngeal inflammation.
Development of a localized or coalescing pseudomembrane can occur in any portion of the respiratory tract. The pseudomembrane is characterized by the formation of a dense, gray debris layer composed of a mixture of dead cells, fibrin, RBCs, WBCs, and organisms.

Treatment: The common form of treatment is the administration of erythromycin or penicillin.
Culture media: Loeffler Medium is used for growing Corynebacterium diphtheria, which contains horse serum, beef extract, dextrose and proteose peptones.

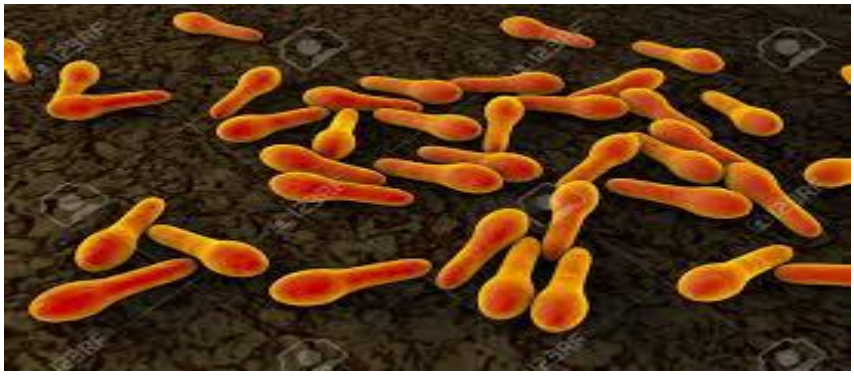
Vaccination: There are four vaccines that have been developed to treat diphtheria: DTaP, DT, Td, and Tdap. DTaP and DT are given to children under the age of seven, while Td and Tdap are administered during adulthood. The latter two vaccines are used as boosters and are not given at the same time.

Lecture 5:

Clostridium

The genus *Clostridium* is Gram positive, anaerobic, (4-6) micron in length, spore forming, pleomorphic bacilli and spindle shape.

1- *Clostridium tetani*: Spore is terminal, oval and allocated outside the bacilli, this appearance is called drum stick.



Virulence factors: *C. tetani* grows at the wound site, it releases the toxins tetanolysin and tetanospasmin. The function of tetanolysin is unclear, although it may help *C. tetani* to establish infection within a wound. Tetanospasmin ("tetanus toxin") is responsible for the symptoms of tetanus. Tetanospasmin spreads via the lymphatic system and bloodstream throughout the body, where it is taken up into various parts of the nervous system.

Toxins: It is an obligate anaerobic bacterium whose spores produce two distinct toxins, i.e., tetanolysin, which causes local tissue destruction and tetanospasmin that leads to causes clinical tetanus.

Pathogenesis: Spores implanted in wound multiply only if conditions are favorable. The toxin produced by the bacterium is absorbed by motor nerve ending. Toxin travels along the axis cylinders of peripheral nerve and reach central nervous system. It exacts mode of action is not known but it may act at synaptic junctions between anterior horn cell and related internuncial neurons leading to abolition of spinal inhibition.

Treatment: Acute treatment of tetanus is based on wound cleaning and the administration of antibiotic, such as intravenous metronidazole or penicillin.

Culture media: When grown on blood agar medium, it produces alfa haemolysis.

2. *Clostridium perfringens*:

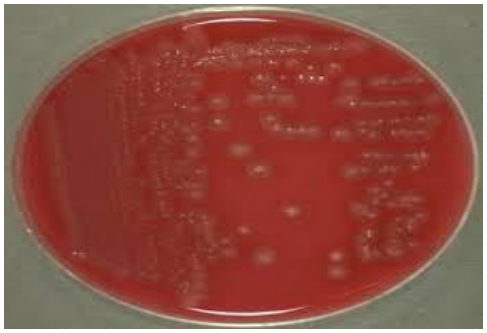
General characters: Gram-positive, anaerobic bacterium that is widely distributed in the environment; it is found in soil, however, commonly inhabits are the gastrointestinal tract of humans and animals. This bacterium is a major cause of histotoxic and enteric diseases.

Toxins: Toxins are the main cause of lesions and symptoms associated with diseases caused by its infection. There are two main groups of toxins; major and minor. The major toxins are alpha, beta, epsilon and iota toxins. Theses toxins are lethal and necrotizing agents. Minor toxins are eta, theta, kappa and enterotoxin.

Pathogenesis: Toxins produced by the bacterium results in a broad range of diseases including gas gangrene, various enterotoxaemias, food poisoning and necrotic enteritis.

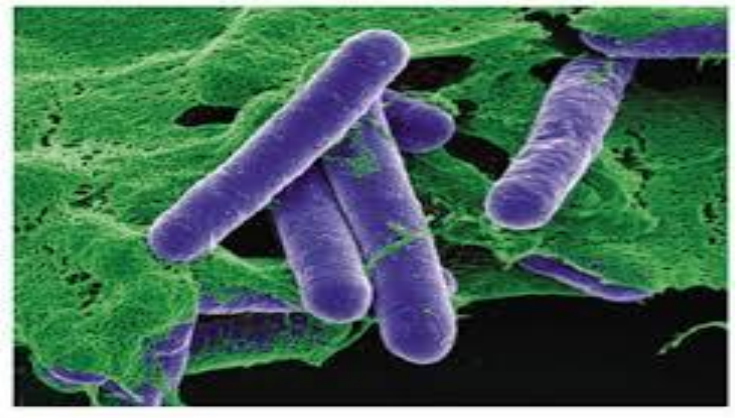
Treatment: Oral rehydration or, in severe cases, intravenous fluids and electrolyte replacement can be used to prevent or treat dehydration. Antibiotics are not recommended.

Culture media: Lactose-gelatin medium and Sporulation broth.



3. *Clostridium botulinum*:

General characters: Gram positive, obligate anaerobic, spore-forming, rod-shaped bacterium. *C. botulinum* organisms are commonly found in soils and marine sediments throughout the world. It also colonizes the gastro-intestinal tract of fishes, birds and mammals.



Virulence factors: The only virulence factor of *C. botulinum* is neurotoxin. It targets the peripheral nervous system and has similar functions to that of the tetanus toxin. It is secreted and absorbed into the blood stream.

Toxins: The toxin types are classified as A, B, C, D, E, F and G. Human botulism has been described with the strains of Clostridium botulinum that produce toxin types A, B and E.

Pathogenesis: includes the following:

1. Transmission: *C. botulinum* can be transmitted through home canned foods, poorly packaged preserved foods, open wounds, injections and honey products. Since spores can be dormant for several years canned foods are highly susceptible for contamination.

2. Infectious dose, incubation and colonization: One reason Botulism is so toxic is due to its low infectious dose. It only takes 75 mg of toxin to kill a 75 kg person or 1 mg/1 kg weight of an individual. The incubation period can last for years because of the spore resistance to heat and relatively low acidities.

Colonization can occur at the site of infection like a wound. Since the toxin is produced in the tissues the bacteria grow near blood vessels so the toxins can be absorbed easily into the blood.

Disease:

Botulism is caused by *C. botulinum*. This is classified as a single species but consists of at least three genetically distinguishable groups of organisms that have been recognized as toxic for humans. They share the ability to produce neurotoxins with similar pharmacological activities but diverse serologic properties. it has five clinical categories of botulism:

1) Foodborne botulism.
2) Wound botulism.
3) Infant Botulism.
4) Adult infectious botulism.
5) Inadvertent botulism

Treatment:
Foodborne botulism: If diagnosed early, antitoxin should be administered to block the actions of the exotoxin. If respiratory failure has set in, mechanical ventilator and intensive care are required.

Wound botulism: Administration of antitoxins to neutralize the exotoxin, surgical debridement and excision of the affected area, followed by the required supportive treatment.

Infant botulism: Remove the contaminated food by inducing vomiting and enemas. Good supportive care is further required for recovery.

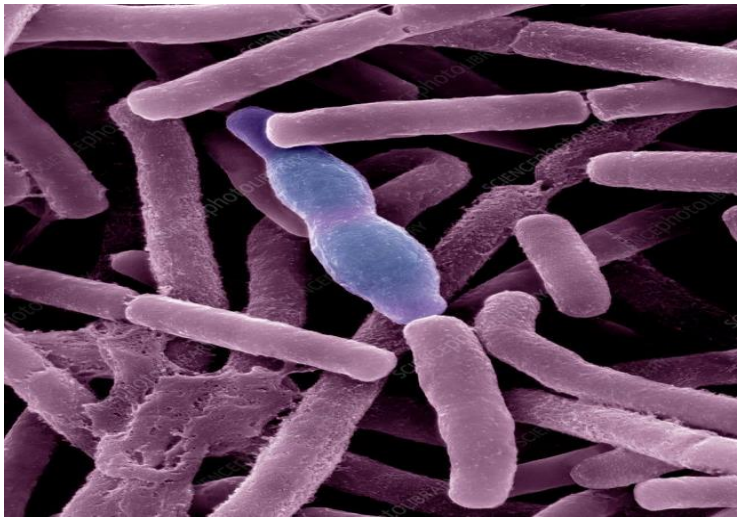
Adult infectious botulism: It occurs as a result of intestinal colonization with *C. botulinum* and in vivo toxin production in a manner similar to that of infant botulism. These patients often have a history of abdominal surgery or recent antibiotic treatment.
Inadvertent botulism: This has been reported in patients who have been treated with intramuscular injections of botulinum toxin.

Culture media: Blood agar and egg yolk agar (EYA) (94) serve as the most common unselective plating media.

Lecture 6:

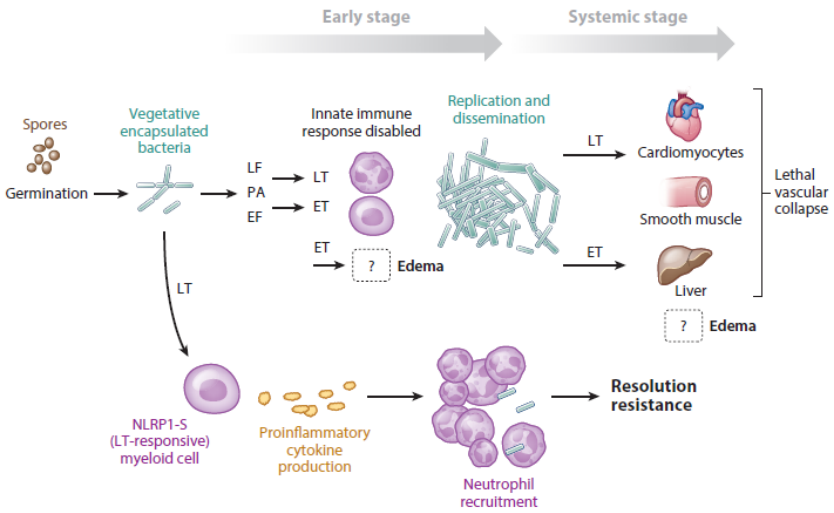
Bacillus anthracis

General characters: It is a Gram-positive, rod-shaped bacterium, with a width of 1.0–1.2 µm and a length of 3–5 µm. When grown in culture, they tend to form long chains of bacteria. On agar plates, they form large colonies that are generally white or cream colored.
Most *B. anthracis* strains produce a capsule that gives colonies a slimy mucus-like appearance.



Virulence factors and toxins: Virulent forms of *B. anthracis* are two large pathogenicity related plasmids, i.e., pXO1, which encodes the anthrax toxin genes and pXO2, which carries the genes responsible for capsule synthesis and degradation. *B. anthracis* bacterium (responsible of anthrax disease) express its pathogenic activity mainly through the capsule (anti-phagocytic activity) and the production of a toxic complex consisting of three proteins known as protective antigen (PA), lethal factor (LF), and edema factor (EF).

Pathogenesis: The anthrax toxins are believed to play roles in two stages of infection. Early during infection, they target the immune response to allow survival in the host and to facilitate dissemination. In systemic disease, they target tissues and induce lethality, as shown below:



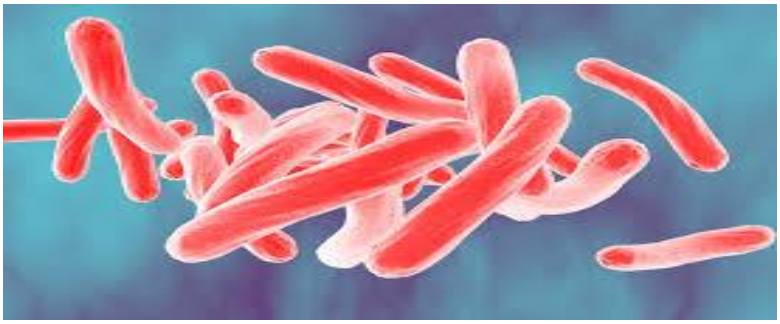
Treatment: Many antibiotics target *B. anthracis*, including penicillin, amoxicillin, levofloxacin, and ciprofloxacin.

Culture media: It can be grown in an ordinary nutrient medium under aerobic or anaerobic conditions. In particular, Blood Agar (ABA) and Cereus Ident Agar (CEI) are selective growth media for the isolation of *Bacillus anthracis*.

Mycobacterium tuberculosis

General characters: *M. tuberculosis* is an aerobic, Gram negative, non-spore forming, non-motile bacillus with a high cell wall content of high molecular weight lipids, which comprise approximately 60% of the cell wall structure.

According to cell wall composition, mycobacteria stain poorly with Gram stain but are described as acid-fast, as once stained with hot carbol-fuchsin it resists decolourisation with acidified organic solvents (Ziehl–Neelsen stain). The high lipid concentration in the cell wall accounts for its resistance to antimicrobial agents, and resistance to killing by acidic and alkaline compounds in both the intra and extracellular environment.

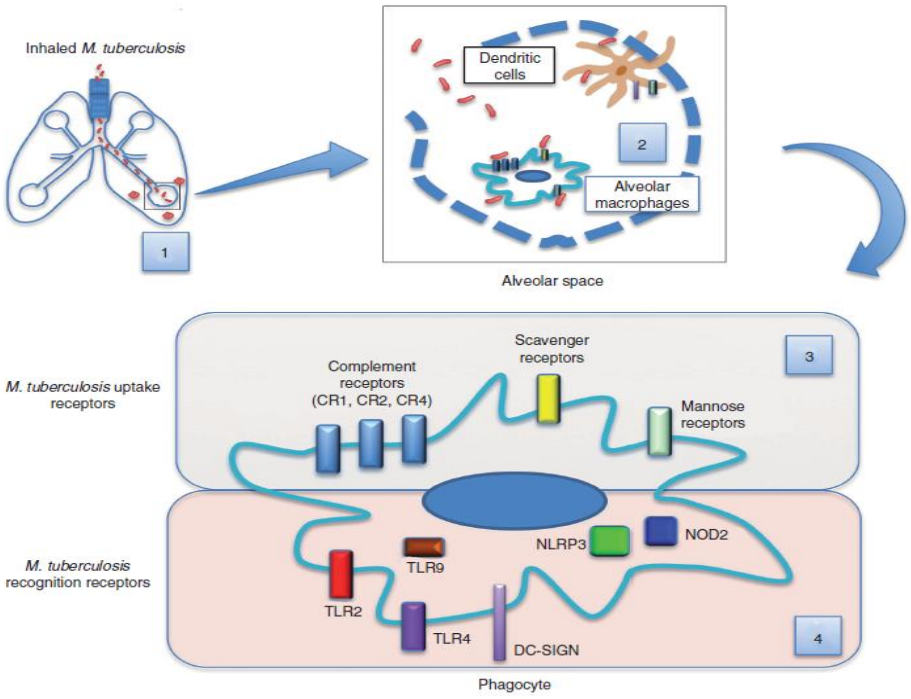


Virulence factors: are recognized by mycobacterial virulence genes that bacilli employ to survive and persist in the hosts. Most of these virulence genes encode enzymes of several lipid pathways, cell surface proteins, regulators and proteins of signal transduction systems.

Another group of relevance is the one involved in mycobacterial survival inside the aggressive microenvironment of the host macrophages. It is noticeable that mycobacteria lack classical virulence factors such as toxins, which are typical of other bacterial pathogens.

Pathogenesis: Early steps of infection: *M. tuberculosis* is a highly successful bacterial pathogen that mainly targets host macrophages, (key mediators of both innate and adaptive immune response).

In lung infections, *M. tuberculosis* is typically inhaled into the body, passes through the airways and reaches the alveolar space. Here, it interacts with dendritic cells, alveolar macrophages and pulmonary epithelial cells, but its optimal hosts are alveolar macrophages and other mononuclear phagocytes.



Toxins: *Mycobacterium tuberculosis* (Mtb) induces necrosis of infected cells to evade immune responses. Mtb utilizes the protein CpnT to kill human macrophages by secreting tuberculosis necrotizing toxin (TNT) that induces necrosis.

Disease: TB is caused by *M. tuberculosis* and is one of the most intensively studied human diseases. It can target practically any organ of the body. Humans are the only reservoir for the *M. tuberculosis* species, although many animals are also susceptible to infection.

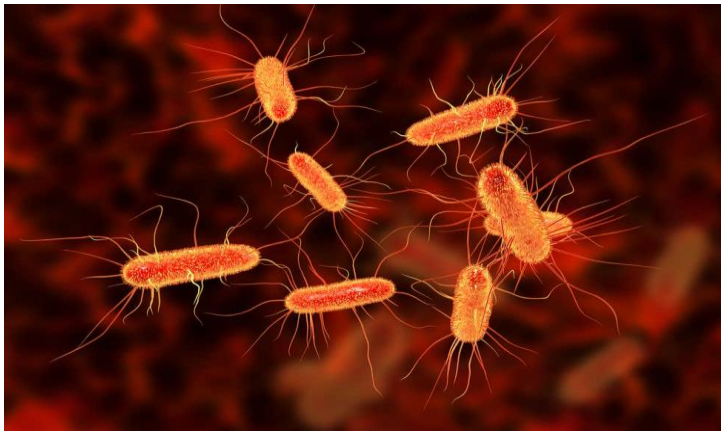
Treatment: For initial empiric treatment of TB, the administration of 4-drug regimen: isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin.

Culture media: Some new technologies have been endorsed by the World Health Organization (WHO), such as implementation of automated liquid cultures, fluorescence microscopy and light-emitting diode (LED) fluorescence microscopy.

Lecture 7:

Escherichia coli

General characters: *Escherichia coli* also known as *E coli* are Gram-negative bacilli. They are facultative anaerobes, rod-shaped and non-spore forming.



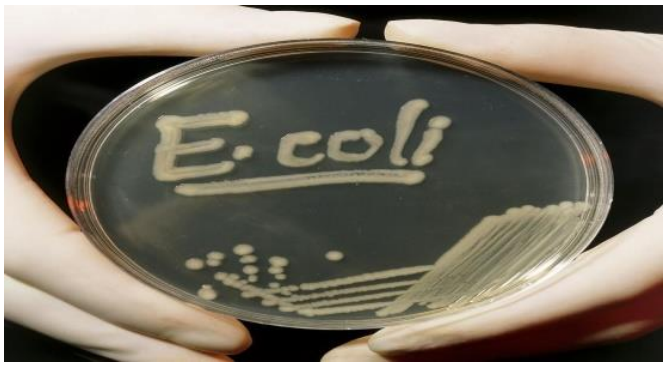
It is commonly found in the gut of humans and warm-blooded animals. Most strains of *E. coli* are harmless, which are part of the normal flora of the gut, and can benefit their hosts by producing vitamin K_2 and preventing colonization of the intestine with pathogenic bacteria, having a symbiotic relationship.

Virulence factors and toxins: Virulence factors are related to the pathogenicity of extra-intestinal pathogenic *E. coli* (ExPEC) that are numerous and have a wide range of activities, from those related to bacteria colonization to those related to virulence, including adhesions, toxins, iron acquisition factors, lipopolysaccharides and polysaccharide capsules, which are usually encoded on plasmids.

Disease: Virulent strains can cause gastroenteritis, urinary tract infections and neonatal meningitis. Common signs and symptoms include severe abdominal cramps, diarrhea, vomiting and sometimes fever.
Some strains however, such as Shiga toxin-producing *E. coli* (STEC) can cause severe foodborne disease. It is transmitted to humans primarily through consumption of contaminated foods, such as raw or undercooked ground meat products, raw milk, and contaminated raw vegetables and sprouts.

Treatment: Currently, the antibiotics of choice are fluoroquinolones or azithromycin, with an emerging role for rifaximin.

Culture media: *E. coli* grows in a variety of defined laboratory media, such as lysogeny broth, or any medium that contains glucose, ammonium phosphate monobasic, sodium chloride, magnesium sulfate, potassium phosphate dibasic, and water.



***Salmonella spp*.**

General characters: *Salmonella spp*. are a group of bacteria, which reside in the intestinal tract of human beings and warm blooded animals and are capable of causing disease. They are facultative anaerobic, motile, Gram negative rod-shaped bacteria. *Salmonella spp*. are members of the Enterobacteriaceae group.

The genus *Salmonella* contains 2 species:

• *Salmonella enterica*

• *Salmonella bongori*.

Virulence factors: Classic virulence factors include virulence-plasmids, toxins, fimbriae and flagella. However, effector proteins involved in survival and have been characterized recently.

Toxins: *Salmonella enterica* serovar Typhi (*S. Typhi*) is the cause of typhoid fever in humans, which results from secreting Typhoid toxin. Typhoid fever is accompanied by various symptoms including fever and abdominal pain.

Pahogenesis: *Salmonella* can invade different cell types, including epithelial cells, and macrophages, Most infections are due to ingestion of food contaminated by animal feces, or by human feces. *Salmonella* serotypes can be divided into two main groups, i.e., typhoidal and nontyphoidal.
Nontyphoidal serotypes are more common, and usually cause gastrointestinal disease. They can infect a range of animals, and are zoonotic, meaning they can be transferred between humans and other animals. Typhoidal serotypes include *Salmonella* Typhi and *Salmonella* Paratyphi A, which are adapted to humans and do not occur in other animals.

Disease: Salmonellosis in humans is typically transmitted via the alimentary route. Another possible route of transmission is contact with infected animals, such as pets, that are often kept in direct contact with humans, may also constitute a risk group

Treatment: Nontyphoidal *Salmonella* (NTS) infections do not usually require treatment with antibiotic drugs, however complications such as meningitis and septicaemia do occur and require treatment with antibiotic drugs, including ciprofloxacin, ceftriaxone and ampicillin.

Infections caused by *S. Typhi* and *S. Paratyph*i may involve serious complications such as meningitis and septicaemia and require treatment with antibiotics such as cefixime, chloramphenicol, amoxicillin, azithromycin and ceftriaxone to prevent death.

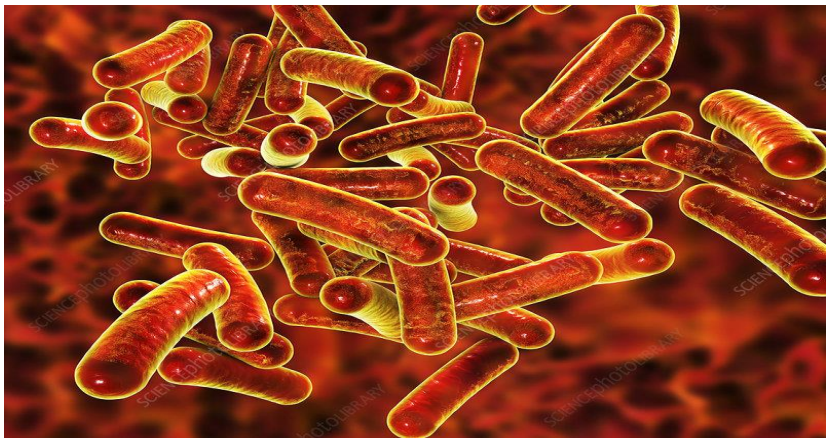
Culture media: Blood culture is the gold standard method for diagnosis of *S. Typhi* and *Salmonella Paratyphi* infections.

Shigella spp.

General characters

Shigella spp. are Gram-negative, non-spore forming rod-shaped bacteria and are members of the family Enterobacteriaceae. The genus *Shigella* is divided into four species based on their O antigen type and biochemical characteristics, i.e., *S. dysenteriae, S. flexneri, S. boydii and S. sonnei.*

Shigella spp. are bacteria that cause shigellosis, also known as bacillary dysentery. They are highly infectious organisms.



Virulence factors

Shigella spp. has a virulence plasmid that encodes genes involved in the invasion process and intra cellular spread. Other genes involved in the invasion process are located on the chromosome.

Toxins

Shiga toxins are cytotoxins that cause severe gastrointestinal disease caused by *Shigella dysenteriae* serotype 1. (*S. dysenteriae* 1) produces the prototype Shiga toxin. Vascular damage caused by Shiga toxins in the colon, kidneys, and central nervous system may result in hemorrhagic colitis, or more severe conditions such as hemolytic uremic syndrome.

Pathogenesis

Shigella spp. are transmitted by consumption of contaminated food or contaminated water, which is used for drinking and food preparation or fecal contamination of water.

Once ingested, *Shigella spp*. use the acidic environment of the stomach and invade the epithelial cells of the colon to enable infection. *Shigella spp*. multiplies inside the colonic epithelial cells and spread to adjacent cells, leading to the death of the infected cells.

The colon becomes inflamed and ulcerated resulting in the bloody mucoid diarrhea.

Disease

The clinical symptoms of shigellosis range from mild diarrhea to severe dysentery, depending on the *Shigella* serotype causing infection, dose and the immunity and age of the host. The incubation period is 1–7 days (usually 3 days) and symptoms typically last for 1–2 weeks.

Initial symptoms include watery diarrhea, fever and fatigue. In more severe cases, as the case for *S. dysenteriae* serotype 1 infection, symptoms include abdominal cramps, nausea and vomiting. All *Shigella spp*. can cause acute bloody diarrhea.

Treatment: ciprofloxacin, Pivmecillinam, ceftriaxone and Azithromycin.

Culture media: Mac Conkey Lactose Agar (MLA) and Xylose Lysine Deoxycholate Agar.

Lecture 8:

Vibrio cholerae

General characters

A Gram-negative, facultative anaerobic, comma-shaped bacterium. The bacterium's natural habitat is saltwater and has a flagellum at one cell pole as well as pili.

Virulence factors and toxins

V. cholerae pathogenicity genes code for proteins directly or indirectly involved in the virulence of the bacteria. During infection, *V. cholerae* secretes cholera toxin, a protein that causes profuse, watery diarrhea (known as "rice-water stool"). Colonization of the small intestine also requires the toxin coregulated pilus (TCP), a thin, flexible, filamentous appendage on the surface of bacterial cells.

Pathogenesis

In the intestinal lumen, *V. cholerae* bacterium uses fimbriae (short pilli) to attach to the intestinal mucosa. After that it secretes cholerae toxin that leads to secreting of water into the intestinal lumen, causing watery stool or rice watery stool.

V. cholerae can cause syndromes ranging from asymptomatic to cholera gravis. Symptoms include watery diarrhea (a grey and cloudy liquid), occasional vomiting, and abdominal cramps.

Disease

V. cholerae bacterium causes Cholera, which is a major infectious disease. Infections are particularly common after ingesting contaminated water or food. Cases are occasionally seen in people, who have eaten raw or undercooked shellfish. Cholera appears suddenly with painless, watery diarrhea, sometimes accompanied by vomiting.

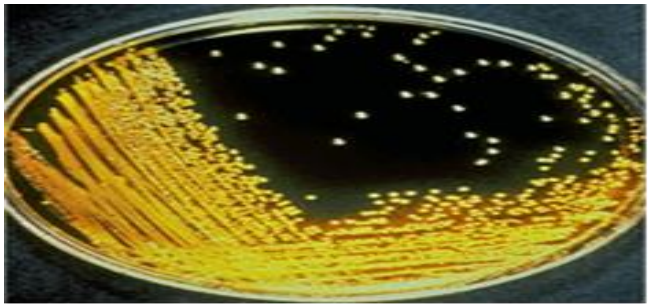
Infections may be subclinical, mild or severe. Severe fluid loss can be seen in more serious cases; thirst, oliguria, severe dehydration, acidosis, muscle cramps and shock may result. Most cases last approximately 2 to 7 days but death may occur within a few hours if the fluid loss is high.

Treatment

- Rehydration therapy, meaning prompt restoration of lost fluids and salts through rehydration therapy is the primary goal of treatment.
- Antibiotic treatment, which reduces fluid requirements and duration of illness, is indicated for severe cases of cholera. Doxycycline is recommended as first-line treatment for adults, while azithromycin is recommended as first-line treatment for children and pregnant women.
- Zinc treatment has also been shown to help improve cholera symptoms in children.

Culture media

Selective thiosulfate–citrate–bile salts agar (TCBS) is ideal for isolation and identification.



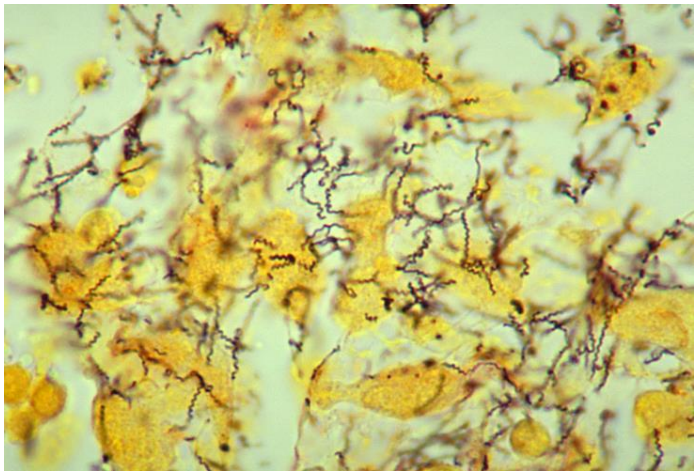
Treponema spp.

General characters

Treponemes are anaerobic, helically coiled, corkscrew-shaped cells (spiral shaped bacteria), 6 to 15 μm long and 0.1 to 0.2 μm wide. They have an outer membrane which surrounds the periplasmic flagella.

The genus *Treponema* contains both pathogenic and nonpathogenic species. Human pathogens cause four treponematoses: syphilis (*T pallidum* subsp *pallidum*), yaws (*T pallidum* subsp *pertenue*), endemic syphilis (*T pallidum* subsp *endemicum*), and pinta (*T carateum*).

Nonpathogenic Treponemes may be part of the normal flora of the intestinal tract, the oral cavity, or the genital tract. Some of the oral Treponemes have been associated with gingivitis and periodontal disease.



Virulence factors

The potential virulence factors of this microorganism include adherence factors, motility, evasion mechanisms from host defenses and cytotoxic factors for host tissues.

Pathogenesis

Treponemes are highly invasive pathogens. Evasion of host immune responses appears to be, at least in part, due to the unique structure of the treponemal outer membrane (i.e., it's extremely low content of surface-exposed proteins). Although treponemes lack classical lipopolysaccharide (endotoxin), they possess abundant lipoproteins which induce inflammatory processes.

Disease

Treponemes cause syphilis, Syphilis is a systemic disease caused by the spirochaete, *Treponema pallidum*. The infection can be classified as congenital (transmitted from mother to child in utero) or acquired (through sex or blood transfusion).

Acquired syphilis is divided into early and late syphilis. Early syphilis comprises the primary, secondary and early latent stages. Late syphilis refers to late latent syphilis, neurological and cardiovascular syphilis.

Treatment

A treponemicidal level of antimicrobials needs to be achieved in the serum and cerebrospinal fluid (CSF) to provide effective treatment for syphilis.
A penicillin level of greater than 0.018 mg per litre is considered sufficient, and needs to be maintained for at least 7–10 days in early syphilis, and for a longer duration in late syphilis.

Long-acting benzathine benzylpenicillin, at a dose of 2.4 million units is recommended for late syphilis treatment. Parenteral, rather than oral, penicillin treatment is preferred for treatment.

Culture media

Treponema cannot be cultured, it is only found in humans.

Lecture 9:

Parasitology

Medical Parasitology is the branch of medical sciences that deals with organisms (parasites), which lives temporarily or permanently, on or within the human body (host).
The competition between the host and the parasite is referred to as host-parasite relationship. The parasite usually obtains nourishment and protection, while offering no benefit in return. Consequently, the host suffers from various disease, infections and discomfort. However, in some cases, the host may show no signs of infection by the parasite.
Human parasites are either unicellular (protozoa) or multicellular (helminthes and arthropods).
The parasites may live inside the host (endoparasites) or on the host surface (ectoparasites).
Endoparasites are classified into intestinal, atrial or they may inhabit body tissues causing serious health problems. Ectoparasites are arthropods that either cause diseases or act as vectors transmitting other parasites.

Classification of parasites

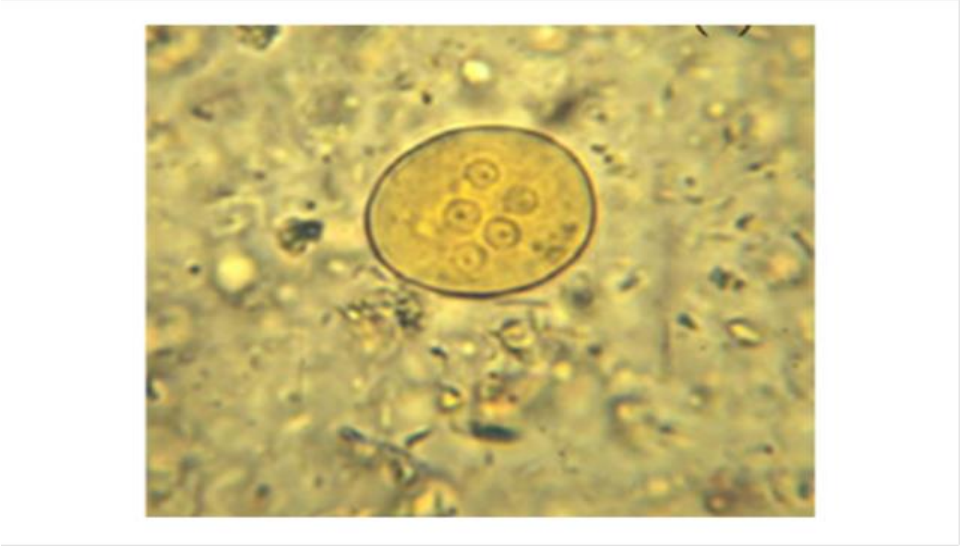
According to the nature of the host-parasite interactions and the environmental factors, the parasite may be one of the following types:

- An obligatory parasite that is completely dependent on its host and cannot survive without it e.g. hookworms.
- A facultative parasite that can change its life style between free-living in the environment and parasitic according to the surrounding conditions. e.g. *Strongyloides stercoralis*.
- An accidental parasite that affects an unusual host e.g. *Toxocara canis* (a dog parasite) in man.
- A temporary parasite that visits the host only for feeding then leaves it. e.g. Bed bug visiting man for a blood meal.
- A permanent parasite that lives in or on its host without leaving it e.g. Lice.
- An opportunistic parasite that is capable of producing disease in an immune-deficient host (like AIDS and cancer patients). In the immuno-competent host, it is either found in a latent form or causes a self-limiting disease e.g. *Toxoplasma gondii*.
- A zoonotic parasite that primarily infects animals and is transmittable to humans. e.g. *Fasciola* species.

***Entamoeba* histolytica**

General features

Entamoeba histolytica is an invasive, pathogenic protozoan, causing amoebiasis, and an important cause of diarrhea in developing countries. The organism can be prevalent in cold regions as well as tropical and subtropical regions that have contaminated water.



Cyst of *E. histolytica* in raw water samples stained with iodine

Life cycle

The life cycle of the parasite is represented by two forms: the cyst and the trophozoite. The cyst is the infective and non-motile form of the parasite. It is excreted in the feces and can survive for weeks in the environment. Mature cysts possess 4 nuclei and average 20 µm in diameter.

The trophozoite is the motile form, with a size ranging from 10 to 60 µm. It colonizes the intestinal tract leading mainly to tissue destruction and secretory bloody diarrhea.

Entamoeba histolytica is monogenetic, meaning that its life cycle is completed only in one host, which is usually humans, and does not need an intermediate host. The ingestion of infective mature cysts from contaminated food, water, or hands, is followed by their excystation (Excystation is the process of transformation of the cysts into trophozoites by disruption of the cyst wall) only when they reach the terminal part of the small intestine (Ileum).

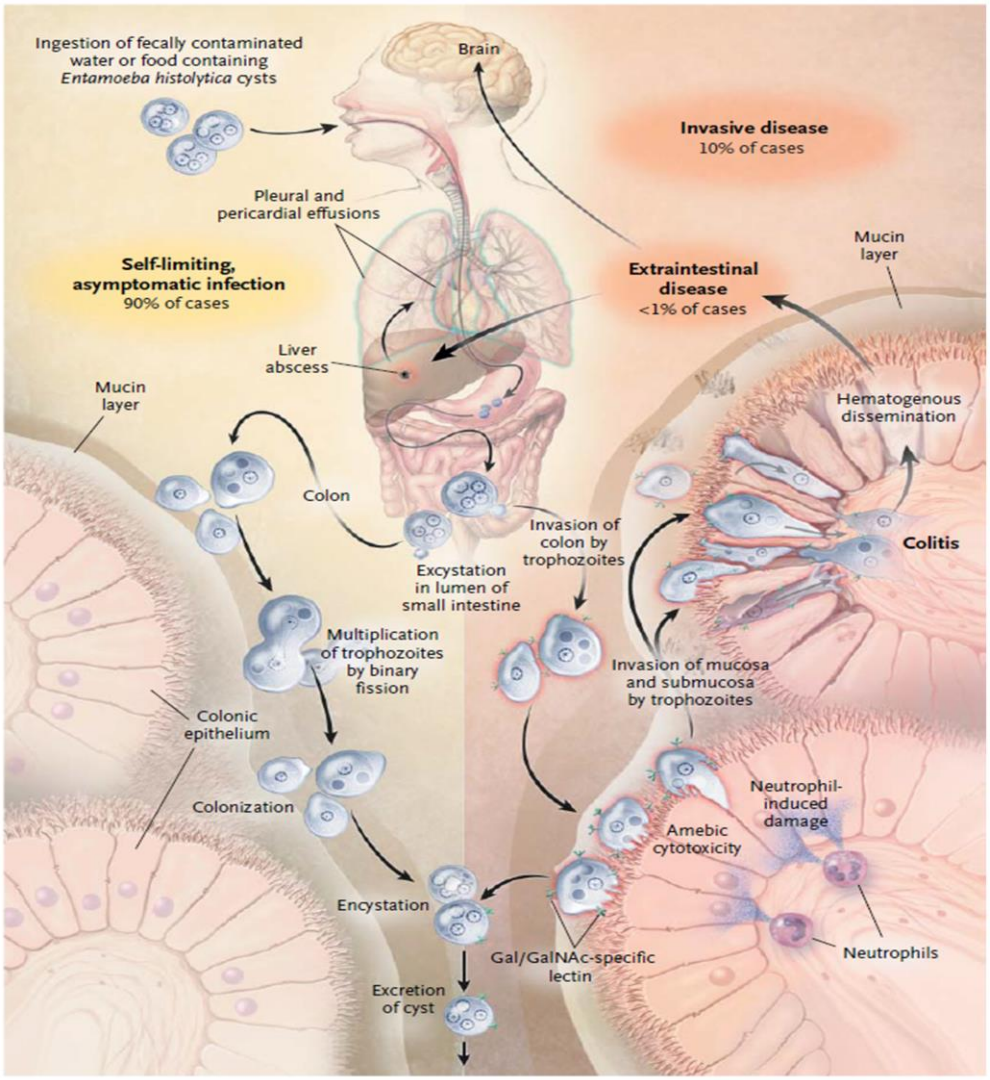
The gastric juice has no effect and cannot dissolve the cyst wall through the trypsin enzyme action, allowing amoeba to emerge and to start proliferation.

The amoeba undergoes a round of nuclear division followed by cytokinesis (cell division) to produce 8 small uni-nucleated trophozoites, called amebula. After that,

both stages are passed in the feces: trophozoites are usually present in loose stool, whereas cysts are found in firm stools.

According to the protection provided by their walls, cysts are able to resist environmental conditions for days to weeks and can be responsible for disease transmission. However, once outside the body, trophozoites passed in the stool are rapidly damaged, and if ingested do not survive exposure to the gastric environment.

When the trophozoites colonize the intestine by adhering to colonic mucin glycoprotein, they feed on bacteria and undergo repeated rounds of binary division.



The life cycle of *E. histolytica* in human after ingestion

Pathogenesis

Cysts are directly excreted in the stool and spread through the environment via contaminated water, soil, and fresh vegetables as well as unsanitary household conditions.

Following ingestion, cysts transform into vegetative forms or trophozoites, which is the motile stage that moves with the aid of pseudopodia and colonize the intestinal mucosa of the large bowel.

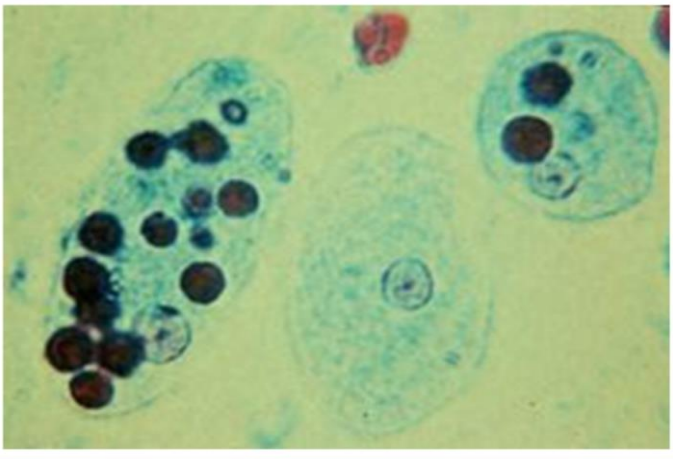
Trophozoites can also invade the intestinal mucosal barrier and, via the bloodstream, disseminate to the liver, lung, and other sites with resultant pathologic manifestations.

Disease

Amoebiasis is basically an acute disease acquired by:

(i) Ingestion of cysts present in contaminated food, water, or plants.
(ii) Through person to person contact.
(iii) Exposure in endemic areas.
(iv) Swimming in contaminated water.

Clinical manifestations range from the asymptomatic carrier state to dysenteric symptoms represented by abdominal pain and bloody diarrhea.



Trichrome stain of *E. histolytica* trophozoites in amebiasis

Treatment

Several drugs are available for amebiasis treatment and their choice depends mainly on the clinical stage. Diagnosis has to be adopted before the treatment as it differs from intestinal and invasive disease.

				Entamoeba histolytica
Amebic liver abscess	Metronidazole followed by a luminal agent	750 3 times For 7–10 days	35–50 mg/kg of body weight in 3 divided doses	Primarily gastrointestinal: anorexia, nausea, vomiting, diarrhea, abdominal discomfort, unpleasant metallic taste; disulfuram-like intolerance reaction with alcohol, etc.
	Tinidazole followed by a luminal agent	800 3 times For 5 days	60 mg/kg (maximum 2 g)	Primarily gastrointestinal and disulfuram-like intolerance reaction as for metronidazole
	Paromomycin	25–35 mg/kg 3 divided doses For 7 days		Primarily gastrointestinal: diarrhea, gastrointestinal Upset
	Diloxanide furoate	500 3 times a day For 10 days	20 mg/kg 3 divided doses	Primarily gastrointestinal: flatulence, nausea, vomiting, pruritus, urticaria
Amebic colitis	Metronidazole followed by a luminal agent (as for amebic liver abscess)	750 3 times a day For 7–10 days	35–50 mg/kg in 3 divided	As for amebic liver abscess
Asymptomatic intestinal Colonization	Paromomycin	25–35 mg/kg 3 divided doses For 7 days		Primarily gastrointestinal: diarrhea, gastrointestinal upset
	Diloxanide furoate	500 3 times a day For 10 days	20 mg/kg 3 divided doses	Primarily gastrointestinal: flatulence, nausea, vomiting, pruritus, urticaria

Giardia lamblia

General features

Giardia lamblia is a flagellated unicellular eukaryotic microorganism that commonly causes diarrheal disease throughout the world. It is colonize and reproduce in the small intestines of several vertebrates, causing giardiasis.

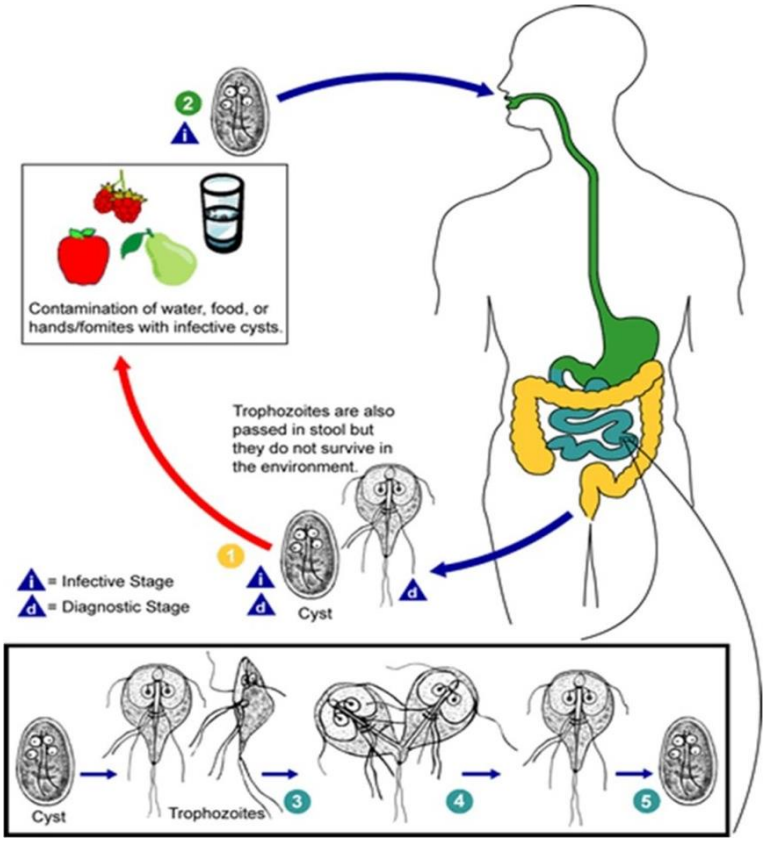
Life cycle

Giardia species have two major stages in the life cycle. Infection of a host is initiated when the cyst is ingested with contaminated water or, less commonly, food or through direct fecal-oral contact.

The cyst is relatively inert, allowing prolonged survival in a variety of environmental conditions. After exposure to the acidic environment of the stomach, cysts encyst into trophozoites in the small intestine.

The trophozoite (vegetative form) replicates in the small intestine, where it causes symptoms of diarrhea and malabsorption.

After exposure to biliary fluid, some of the trophozoites form cysts in the jejunum and are passed in the feces, allowing completion of the transmission cycle by infecting a new host.



Life cycle of *Giardia lamblia*

Pathogenesis

The symptoms of *Giardia*, which may begin to appear 2 days after infection, include violent diarrhea, excess gas, stomach or abdominal cramps, upset stomach, and nausea.

Resulting dehydration and nutritional loss may need immediate treatment. A typical infection can be slight, resolve without treatment, and last between 2–6 weeks, although it can sometimes last longer and/or be more severe. Coexistence with the parasite is possible (symptoms fade), but an infected individual can remain a carrier and transmit it to others.

Disease

Giardiasis is a gastrointestinal disease characterized by acute or chronic diarrhea, caused by protozoan parasites in the genus *Giardia*. People are considered to be the most important reservoir hosts for human giardiasis. This organism is carried in the intestinal tract of many animals and people, with clinical signs developing in some individuals, but many others remaining asymptomatic.

Treatment

Medication containing tinidazole or metronidazole decreases symptoms and time to resolution. Albendazole is also used.

Balantidium coil

General features

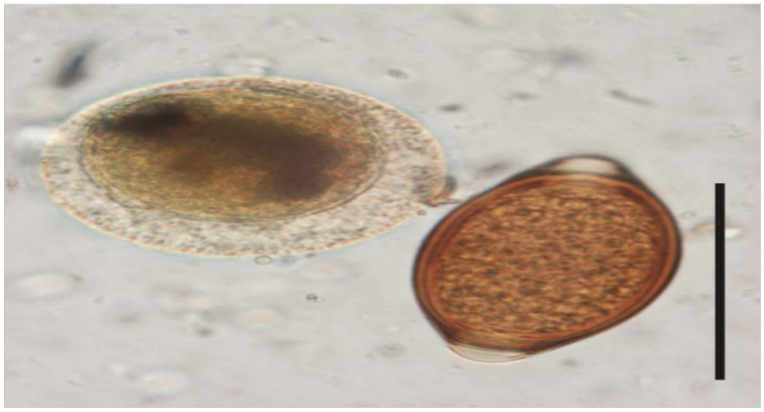
B. coli is a large, ciliated protozoan with a worldwide distribution, but rarely causes human disease. The parasite has been described in a wide range of mammalian hosts other than humans, including non-human primates, pigs and wild boars, cattle, sheep, goats, camels, equids and rodents.

Life cycle

Infection occurs when a host ingests a cyst, which usually happens during the consumption of contaminated water or food. Once the cyst is ingested, it passes through the host's digestive system. While the cyst receives some protection from degradation by the acidic environment of the stomach through the use of its outer wall, it is likely to be destroyed at a pH lower than 5, allowing it to survive easier in the stomachs of malnourished individuals who have less stomach acid.

Once the cyst reaches the small intestine, trophozoites are produced. The trophozoites then colonize the large intestine, where they live in the lumen and feed on the intestinal flora. Some trophozoites invade the wall of the colon using proteolytic enzymes and multiply, and some of them return to the lumen. In the lumen, trophozoites may disintegrate or undergo encystation.

Encystation is triggered by dehydration of the intestinal contents and usually occurs in the distal large intestine, but may also occur outside of the host in feces. Now in its mature cyst form, cysts are released into the environment where they can go on to infect a new host.



Balantidium coli cysts from a pig sample

Pathogenesis

Balantidium cysts are found in the feces of infected individuals. Balantidiasis is considered a waterborne and foodborne disease. The parasite is transmitted by the fecal-oral route, with the cysts, and possibly but less likely by the trophozoites, being ingested with fecally-contaminated water and food.

Disease

Balantidiasis is a zoonotic disease, but does not considered as a public health problem because infections are usually asymptomatic, however, in some circumstances the parasite could invade the intestinal mucosa causing a disease known as balantidial dysentery (balantidiasis), which could be fatal.

Although most infections are asymptomatic, acute balantidiasis manifests as persistent diarrhea, abdominal pain, weight loss, nausea, vomiting and occasionally dysentery, which may resemble amoebiasis.

Chronic infection and disease also occurs, characterized by intermittent diarrhea and occasional blood in the stools. The pig is regarded as the primary host for *B. coli*, in which it is a commensal organism and rarely associated with the mucosa.
Moreover, waterborne epidemics have occurred in areas of poor sanitation.
B. coli cysts are resistant to levels of chlorination used to treat drinking water; however, they are killed by boiling.

Treatment

Balantidium coli infections are easily treated with antibiotic therapy, such as T tetracycline (which is not recommended for pregnant women or for children under 8 years old) and metronidazole. It is advisable to give the patient a starch-free diet.

Lecture 10:

Toxoplasma gondii

General features

Toxoplasma gondii is an obligate intracellular protozoan parasite, causes high infection rate of disease in humans worldwide. Fields are the definitive hosts with complex life cycles.

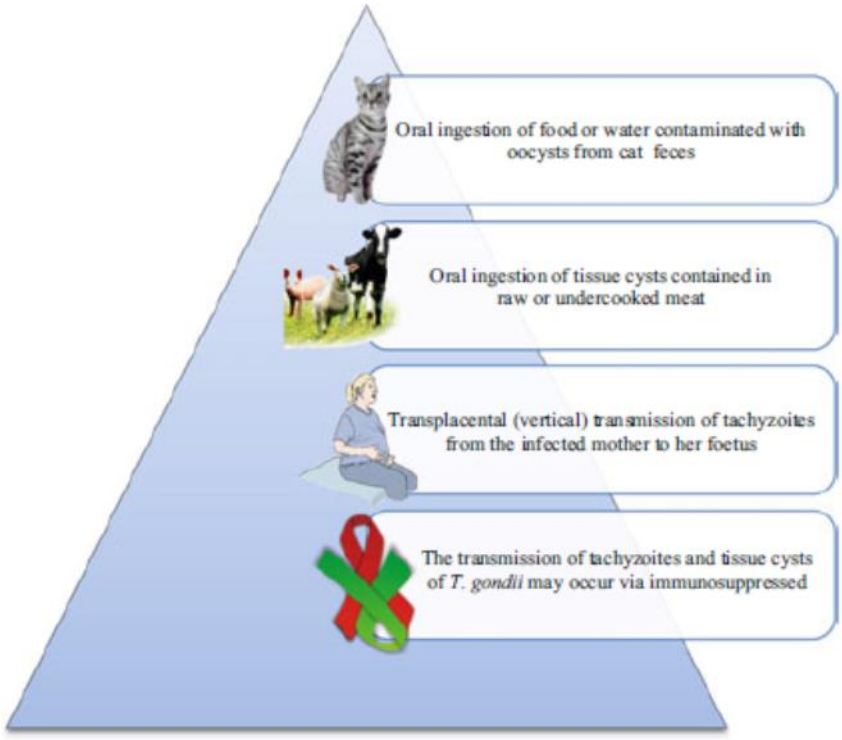
Life cycle

T. gondii undergoes an asexual reproductive cycle in all species. When the parasite is ingested, the tissue cyst or oocyst wall is dissolved during digestion, and releases bradyzoites or sporozoites, respectively. These organisms enter the small intestine and begin to multiply as tachyzoites.
Tachyzoites can disseminate to extraintestinal tissues within a few hours of infection, via the lymph and blood. They can enter nearly any cell and multiply; the host cell eventually ruptures and the released tachyzoites enter new cells. As host resistance

develops, tachyzoites begin to disappear, and form bradyzoites within tissue cysts.

Tissue cysts can be found in many organs, but are particularly common in skeletal muscle, myocardium and the central nervous system (CNS). They generally do not cause a host reaction, and can persist for many years, while bradyzoites in tissue cysts have traditionally been viewed as "resting".

Tissue cysts occasionally rupture and release parasites, which are readily controlled by the immune response in immunocompetent individuals, but may multiply and spread if the host becomes immunosuppressed.



The different routes of *T. gondii* transmission

Pathogenesis

Carnivores and omnivores, including humans, can be infected by eating raw or undercooked tissues containing tissue cysts (or possibly tachyzoites).

This is thought to be the more prominent route in cats. All animals, including herbivores, can become infected by ingesting sporulated oocysts from sources such as soil, cat litter, contaminated vegetables/ plants and water.

Milk-borne infections may be possible, although there is some debate about whether tachyzoites can survive digestion. In a recent study, tachyzoites remained viable in simulated gastric fluid for a time, especially when it was mixed with milk. *T. gondii* may also be present in transplanted organs or transfused blood. Heart transplants are a particularly common source of the parasite.

Disease

Toxoplasmosis is caused by *Toxoplasma gondii*. Some strains of *gondii* are more virulent than others. Infection with *T. gondii* is common in warm-blooded animals, including humans, and usually causes no illness or mild clinical signs in immunocompetent individuals and non-pregnant women.

Toxoplasmosis can have serious consequences in pregnant women, including those who are healthy. Congenital toxoplasmosis typically occurs when the mother becomes infected during (or, rarely, just before) pregnancy. The mother usually remains asymptomatic, but the organism can affect the developing fetal brain and/or retina.

Treatment

People with serious systemic signs and immunocompromised patients are treated with antibiotics. In animals, antibiotics may not eliminate *T. gondii* completely from the body. Corticosteroids are usually administered concurrently with antibiotics in eye disease.

Women who become infected during pregnancy may be given spiramycin, which may reduce the risk of fetal infection. Other antibiotics (e.g., pyrimethamine/ sulfonamide) can treat an infected fetus in utero, or a newborn. Infants may need to be treated for prolonged periods.

Plasmodium spp.

General features

These parasites are transmitted to vertebrate hosts by vectors (notably mosquito). In vertebrates, they form amorphous developmental stages (plasmodia) in blood cells

(mostly erythrocytes). Hundreds of species have been described in mammals, birds and reptiles; most causing no apparent harm but those infecting humans causing one of the worst fever scourges of mankind, malaria.

Malarial parasites form four developmental stages in humans (hepatic schizonts and then intraerythrocytic trophozoites, schizonts and gamonts) and three developmental stages in mosquitoes (ookinetes, oocysts and sporozoites).

Humans are hosts for 4 main species. On a global basis, ~40% of infections are due to *P. falciparum*, ~10% are due to *P. malariae*, ~50% to *P. vivax* and <1% to *P. ovale*.

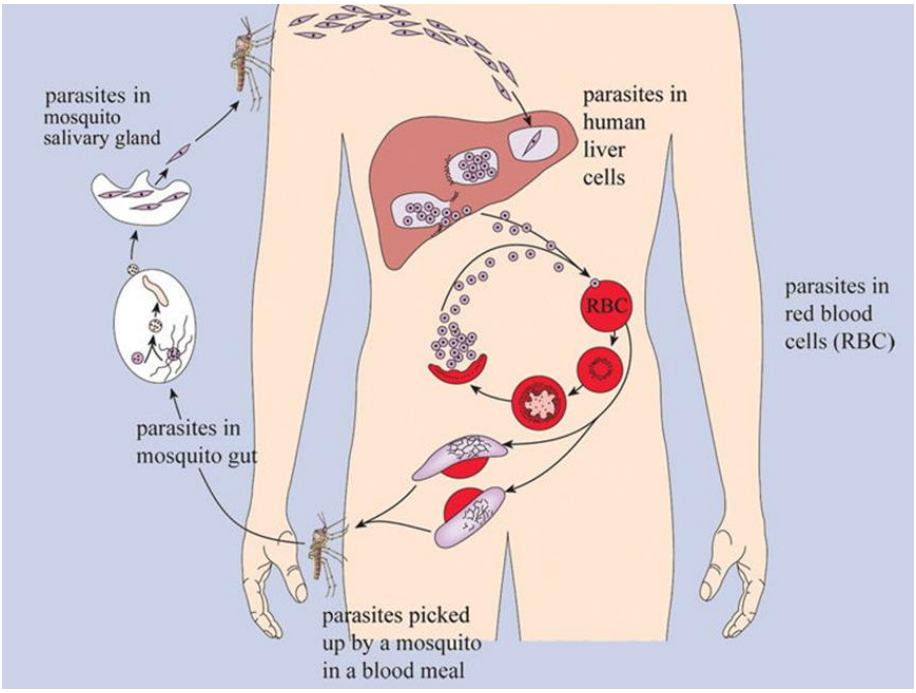
Life cycle

Plasmodium sporozoites injected by an infected mosquito migrate to the liver and initiate the hepatic stage of the parasite life cycle by invading hepatocytes, then multiply and differentiate into schizonts containing thousands of hepatic merozoites

.

These merozoites are released into the blood where they initiate the erythrocytic stage by invading and replicating within red blood cells (RBCs). Some of these asexual blood parasites differentiate into gametocytes that will ensure parasite transmission to the mosquito vector.

P. vivax and *P. ovale* show a slightly different life cycle within the mammalian host, as some sporozoites once in the liver do not develop immediately into schizonts, but remain at an uninucleate stage, in a form named hypnozoite, causing relapses for weeks, months or even years after the primary infection.



The life cycle of *Plasmodium*

Pathogenesis

The disease malaria is characterized by its long persistence in infected individuals in endemic areas, sometimes after years of infection. However, infections in highly susceptible individuals, such as children, pregnant women and travelers, can produce acute severe and even fatal disease.

Clinical signs is characterized by cyclic paroxysms of fever/chills (produced by host inflammatory responses), hemolysis and erythrophagocytosis (resulting in anemia), and organ hypo-perfusion due to ischemia.

Disease

Malaria remains a major cause of death and morbidity worldwide, with infections by *Plasmodium falciparum* accounting for the majority of malaria mortality, though the less virulent *P. vivax*, and probably *P. ovale*, also contributes significantly to morbidity.

Treatment

Antimalarial drugs of choice are primaquine, chloroquine (despite the emergence of chloroquine-resistant strains), sulfadoxine, pyrimethamine, mefloquine, quinine and tetracycline.

Leishmania spp.

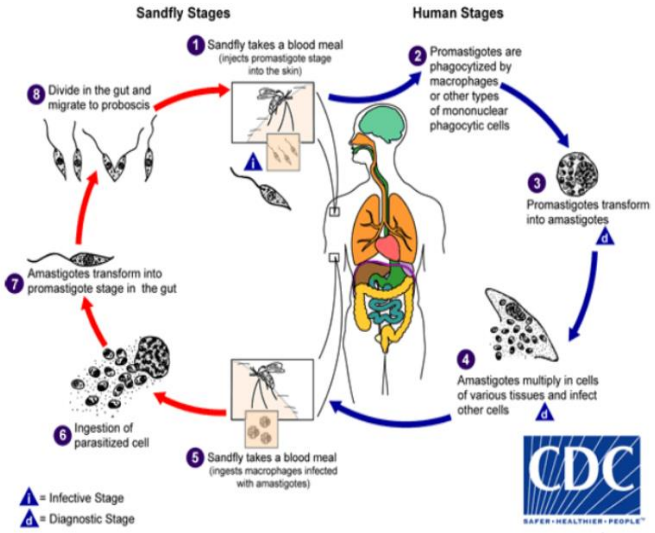
General features

A few of these organisms are primarily maintained in humans, but most circulate mainly in animals. Leishmaniasis is an important complex of protozoal vector-borne diseases that affects both humans and animals. It can be caused by many species of *Leishmania*. Leishmaniasis is transmitted by sandflies and can be difficult to prevent.

Life cycle

During their complex life cycle, *Leishmania* parasites are exposed to different extra- and intracellular environments. These organisms are digenetic parasites with two basic life cycle stages: one extracellular stage within an invertebrate host (phlebotomine sand fly) and one intracellular stage within a vertebrate host.

Thus, the parasites exist in two main morphological forms, amastigotes and promastigotes, which are found in vertebrate hosts and invertebrate hosts, respectively.



The life cycle of *Leishmania*

Pathogenesis

In humans, leishmaniasis has three general forms, cutaneous, mucocutaneous and visceral. Cutaneous leishmaniasis, a form that typically remains limited to the skin, can be caused by numerous organisms.

A few species of *Leishmania* regularly affect the mucous membranes, as well as the skin. Both cutaneous and mucocutaneous leishmaniasis may result in disfigurement, but mucosal involvement is generally more serious. Two organisms, *L. donovani* and *L. infantum*, cause visceral leishmaniasis, which is the most serious form.

Visceral leishmaniasis is characterized by damage to the internal organs, and fully symptomatic cases are considered life-threatening.

Sand fly salivary proteins might play a role in the recruitment of phagocytic neutrophils to the site of the bite, which then act as an inflammatory “silent” route for the parasite to enter macrophages.

Neutrophils are short-lived cells that undergo apoptosis, and are in turn phagocytosized by professional macrophages. Although Leishmania can invade a variety of phagocytic and non-phagocytic mammalian cells, the parasite has a marked preference for macrophages.

Disease

Leishmaniasis is a vector-borne zoonoticc disease caused by obligate intracellular parasite protozoa of the genus *Leishmania*. The disease gets into human population when human, flies and the reservoir hosts share the same environment. *Leishmania* infection is transmitted to humans and to other mammals by the bite of an infected sand fly vector.

The World Health Organization (WHO) has stated that leishmaniasis is one of the most neglected diseases. There are three clinical forms of leishmaniasis in human namely cutaneous, mucocutaneous, and visceral involving the skin, mucous membranes and visceral organs respectively. Cutaneous leishmaniasis is a less severe form of the disease which usually manifests self-healing ulcers. Mucocutaneous leishmaniasis results in disfiguring lesions of the nose, mouth and throat mucous membranes. Visceral leishmaniasis is the most severe form of the disease which can result in 100% mortality of infected patients if not treated.

Treatment

Pentavalent antimonials (e.g., sodium stibogluconate, meglumine antimoniate) can be used to treat leishmaniasis where the parasites are sensitive to these drugs, but drug resistance is a major problem in some areas. Other agents such as allopurinol, liposomal amphotericin B, paromomycin and miltefosine may also be employed.

Lecture 11:

Worm infections

Worm infections are the most common diseases affecting children from low and middle income countries. Major worm infections include Ascariasis, Trichuriasis, Hookworm, and Enterobiasis, which are transmitted through contaminated soil.

Although most helminthic infections are mild and are often asymptomatic, but moderate to heavy worm infections are generally associated with growth faltering, nutritional compromise, anemia and suboptimal academic performance among children from endemic regions.

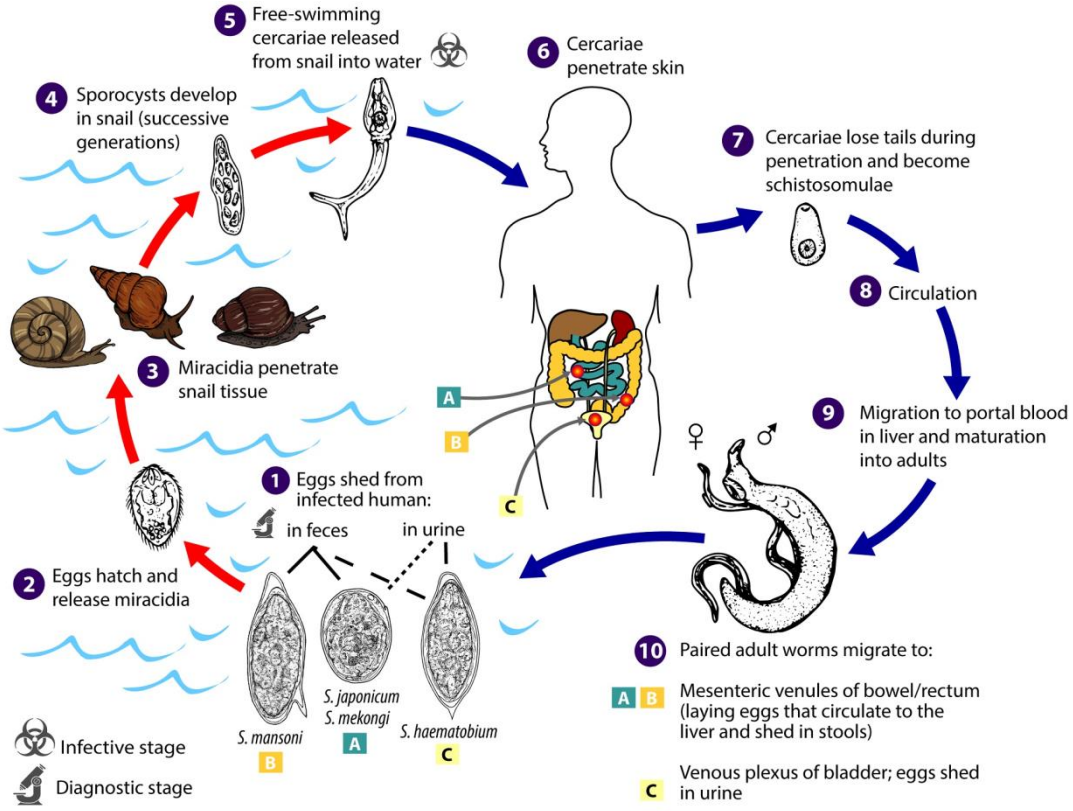
Schistosoma spp.

General features

Schistosoma has six species that can infect humans. *S. haematobium* has been reported in 54 countries and is the most common species, occurring in sub-Saharan Africa and the Middle East.

Life cycle

The schistosome life cycle occurs in 2 hosts: snails and mammals. The asexual or sexual reproduction depends on the type of host. Asexual reproduction occurs in freshwater snails. In the snail, this begins with the development of miracidia into a sporocyst. Sporocysts multiply and grow into cercariae. In the mammalian hosts, parasites grow to become mature, mate, and produce eggs. Mammalian hosts include humans, mice, and dogs.



Life cycle of *Schistosoma spp*.

Pathogenesis

Schistosome infection in humans occurs by contact with fresh water contaminated by cercariae, the free swimming, infectious stage of schistosomes that are released by the intermediate host snail then penetrate the intact human skin.

Disease

There are three distinct phases of clinical disease progression:

1- Acute infection: Acute schistosomiasis occurs in travelers to endemic areas. Common symptoms are myalgia, abdominal pain in the right upper quadrant, diarrhea (with or without blood), fatigue, malaise and fever.

2- Established active infection.

3- Late chronic infection.

Established active and late chronic disease affects mainly individuals from poor rural areas with long-standing infections. In established active and late chronic infections, immune-pathological reactions against Schistosome eggs trapped in host tissues lead to inflammatory and obstructive disease; the tissues and organs affected depend on the infecting *Schistosoma spp*.

Treatment

Praziquantel is cost-effective for treating schistosomiasis. The World Health Organization recommends a single dose of 40 mg/kg for all species and ages. However, this recommendation has a limitation: praziquantel does not kill immature worms present in the body at the time of treatment. Thus, treatment needs to be repeated after 2 to 4 weeks to increase effectiveness.

Ascaris

General feature

Ascaris is parasitic nematode, which infects humans and pigs. The human roundworm is one of the most common parasites in the world, infecting 1.2 billion people globally. Infections are most commonly documented in sub-Saharan Africa, U.S., China and East Asia.

Life cycle

1- Hosts infected with *Ascaris* via the fecal-oral route.

2- When infective eggs are ingested and hatch, *Ascaris* larvae develop in host tissues.

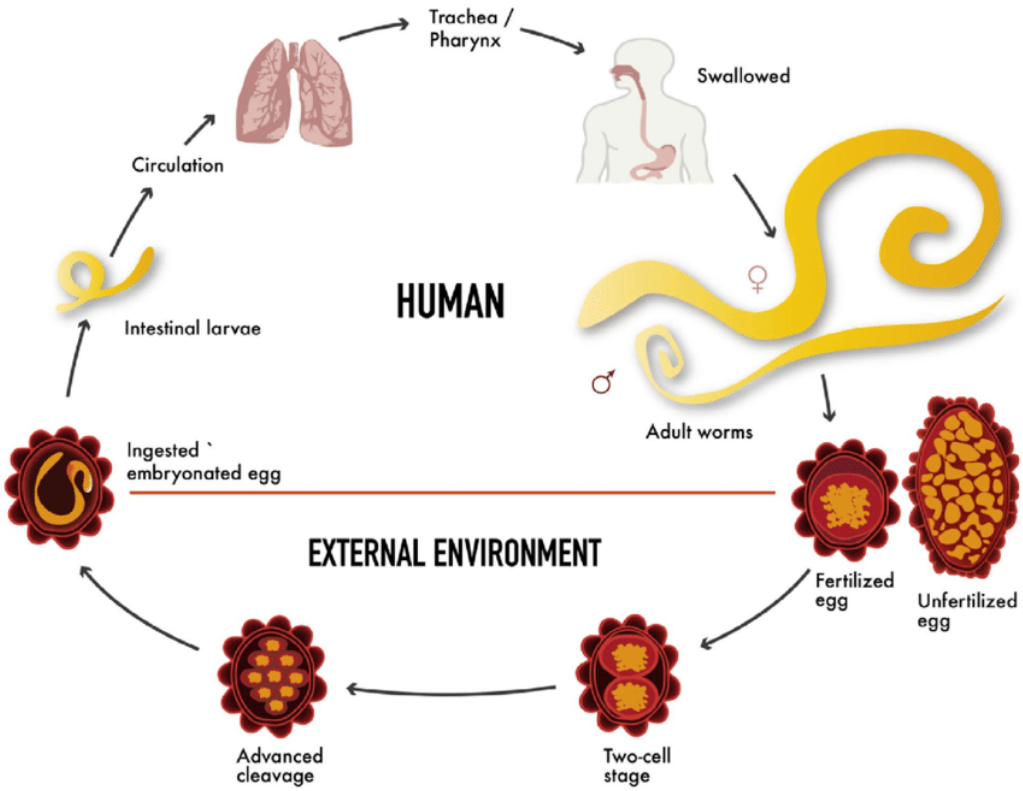
3- Larvae covered by the cuticle, hatch in the small intestine and migrate to the caecum and colon where they penetrate the mucosa.

4- The larvae then migrate via the portal blood to reach the liver, where the cuticle is shed.

5- After migration in the liver, the larvae advance to the lungs on days 6-8. The larvae penetrate the alveolar space and move to the pharynx where they are swallowed, resulting in returning to the small intestine on days 8-10.

6- Larvae mature and reach sexual maturity in the small intestine, moulting again on day 24.

7- The hepato-tracheal migration takes place over a 10-14 day period after the uptake of eggs in pigs and humans. Adult worms may reside in the intestines for approximately one year, but the majority of worms are expelled by the 23rd week of infection in pigs.



The life cycle of *Ascaris*

Pathogenesis:

Most *Ascaris*-induced pathogenicity is occur in school-age children due to their narrower intestinal lumen.When *Ascaris* larvae develop, different antigens are observed and various tissues are invaded, therefore the effects of infection differ over the course of larval migration and development.

Disease

1- The ascariasis can be characterized into acute and chronic symptoms.
2- Human hosts tend to experience acute lung inflammation, difficulty in breathing and fever as a result of larval migration through the pulmonary tissue.
3- Abdominal distension and pain, nausea and diarrhea are also characteristic symptoms of adult worm infection and chronic ascariasis.

Treatment

Several drugs are available and effective for treatment of ascariasis**,** such as Pyrantel pamoate, Mebendazole, Albendazole Levamisole and Piperazine citrate.

Taenia spp.

General features

Tapeworms of the genus *Taenia* include over 100 species. Members of the genus are characterised by a ribbon-like appearance containing segments called ‘proglottids.

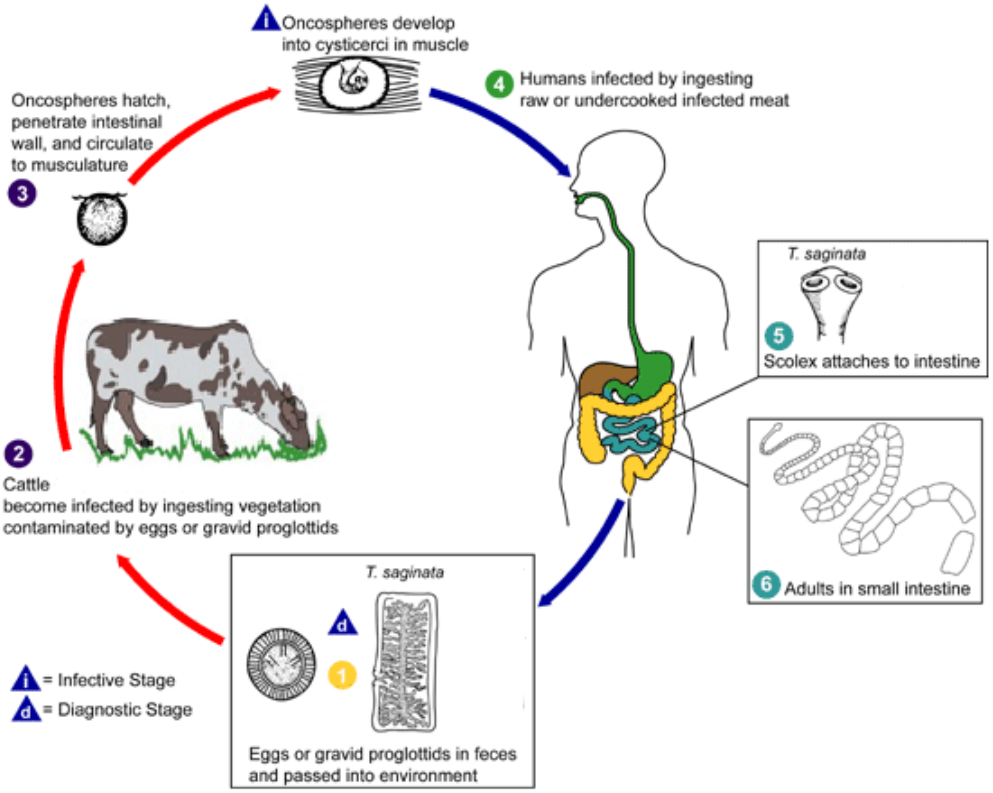
Life cycle

1- *Taenia spp*. lifecycle relies on a vertebrate intermediate host in which the infective larvae (cysticerci) develop.

2- The definitive host (human being) ingests the uncooked flesh of the intermediate host containing the cysticerci which develops in the small intestine into the adult tapeworm.

3- The tapeworm proglottids are released from the definitive host and intermediate hosts are infected by ingesting the tapeworm eggs from the proglottids.

4- *Taenia spp*. eggs have been demonstrated to survive for periods of months or years on pasture, with low to moderate temperatures and high humidity being associated with long survival times.



The life cycle of *Taenia saginata*

Pathogenesis

Key risk factors for *Taenia spp*. infection in both intermediate and definitive hosts includes poor sanitary conditions, contaminated water, outdoor and free-range animal husbandry, poor meat inspection and lack of health education. These risk factors are highly prevalent in less developed countries and are reflected in the high prevalence of *Taenia sp*p. found in these countries.

Disease

Intestinal taeniosis is generally asymptomatic, although mild abdominal discomfort has been reported. Intestinal taeniosis include Cholangitis (an infection of the biliary tract), gall bladder perforation, appendicitis and bowel obstruction. Some people suffering from taeniosis will notice the passage of proglottids (parasite segments containing eggs) in their feces.

Treatment

1- Human taeniosis infections (with the adult tapeworm) have generally mild clinical effects and are susceptible to praziquantel, niclosamide or triple dose albendazole.

2- Neurocysticercosis, however, requires careful surgical or medical management due to the sensitive location of the larval cysts and potential critical complications that can occur.

Lecture 12:

Virology

General structure of virus

Infectious virus particles – also referred to as virions – are constituted of various basic elements.

1- Inside, they contain an RNA genome or a DNA genome.

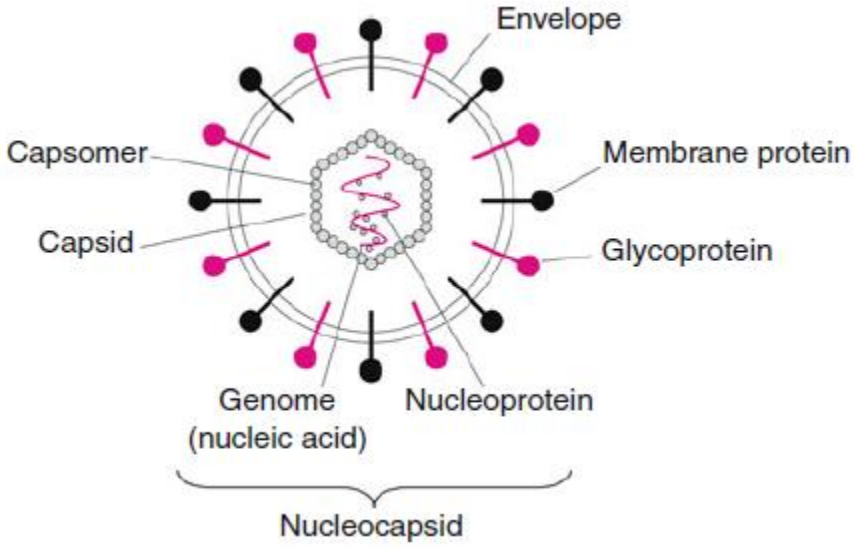
2- Depending on the virus type, the nucleic acid is single-stranded or double-stranded, linear, circular or segmented.

3- The genome forms a nucleocapsid complex with cellular histones (polyomaviruses) or viral proteins.

4- This nucleic acid-protein complex can be surrounded by particular protein structures, which are the capsids (Capsids are rod-shaped or cubic-spherical protein structures).

5- In some cases (such as picornaviruses), the nucleic acid interacts directly with the capsids.

6- In viruses containing an envelope, the capsid layer can be absent (as in coronaviruses).



The structure of the virus

Classification of viruses

The classification of viruses into different families is based on the following main criteria:

1. The nature of the genome (RNA or DNA) due to a single or a double strand, linear or circular, segmented or continuous; also the arrangement of genes on the nucleic acid is important for the definition of virus families.

2. The form of the capsids (is the protein shell of a virus, which encloses the genetic material of the virus).

3. The presence of an envelope.

4. The size of the virion (the complete, infective form of a virus outside a host cell, with a core of RNA and a capsid).

5. The site of viral replication within the cell (cytoplasm or nucleus).

Differences between virus and bacteria

	Bacteria	Virus
1	Unicellular	Do not have cells
2	Considered as a living organism	Not considered
3	Larger and visible under light microscope	Smaller and visible under electron microscope
4	Contain a cell wall with peptidoglycan	Contain protein coat rather than a cell wall
5	Have a single, circular chromosome	Has DNA/RNA strand
6	Do not need a host organism for reproduction	Replicates only inside the host
7	Caused localized infections	Cause systemic infections
8	Can be either beneficial or harmful	Usually harmful
9	Infections can be prevented by Antibiotics.	Spread of viruses can be prevented by vaccines

Hepatitis virus types

Viral hepatitis is caused by infection with one of the five hepatitis viruses, which use the liver as their primary site of replication. Each of these, known as hepatitis A through E viruses (HAV to HEV), belong to different virus families, have unique morphology, genomic organization and replication strategy. These viruses cause similar clinical manifestations during the acute phase of infection but vary in their ability to cause chronic infection.

Hepatitis A virus (HAV)

General features

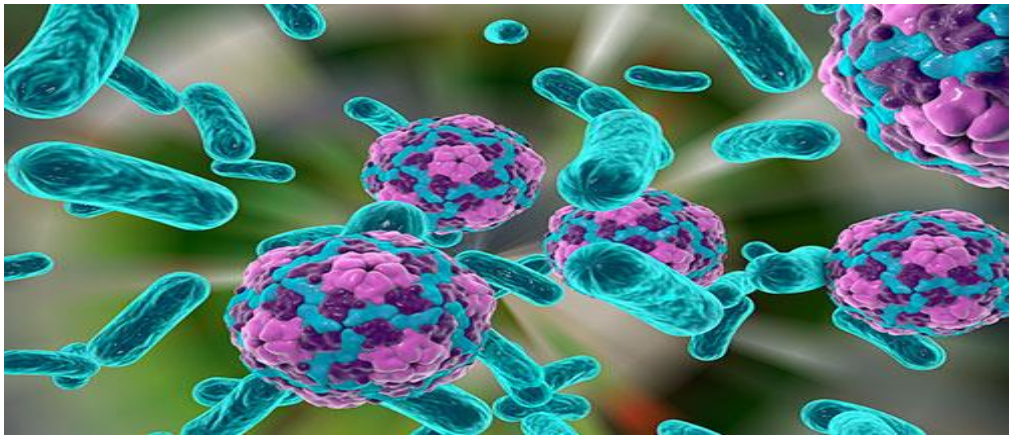
It is a non-enveloped virus, made up of a capsid of three or four proteins and a single-stranded, positive-sense polyadenylated RNA genome.

Pathogenesis

Humans are the only host, and hence the only source, of HAV. The virus is excreted in large amounts in faeces of infected people. The most important mode of transmission is close contact with an infected person, usually in a household or a school. Contaminated water and foods such as seafood, farm products, milk, hamburgers and salads are important modes of transmission. Although blood or blood products can also transmit HAV, they are uncommon. Sexual transmission of HAV has been also reported.

Disease

Hepatitis is a liver disease caused by HAV. Infection with HAV may be asymptomatic or may result in acute hepatitis of variable severity, including fulminant hepatitis. The incubation period is 2–6 weeks. The illness usually begins with a prodromal phase of 1–7 days characterized by non-specific, systemic symptoms, such as fatigue, malaise, low-grade fever, headache, myalgia, arthralgia, loss of appetite, nausea and vomiting, altered taste-sensation and aversion to fatty foods and smoking.



Replication

1- After infection, HAV replicates in the small intestine, from where it reaches the liver through portal circulation.

2- The major site of HAV replication is the hepatocytes.

3- After entry, the genomic RNA is translated into a polyprotein, which is subsequently processed into 11 different proteins.

3- Proteins replicate the genomic RNA.

4- Late in the replication cycle, the capsid proteins package the genomic RNA.

5- The newly formed virions are secreted across the surface of hepatocytes into liver sinusoids and bile canaliculi.

6- Finally, they enter the small intestine and are excreted in faeces.

Vaccine

Two different vaccines are used against hepatitis A, HavrixTM (Glaxo SmithKline) and VAQTATM (Merck). Both contain formalin-inactivated attenuated strains of HAV, are highly immunogenic and safe. For each vaccine, two doses separated by at least 4 weeks are recommended.

Hepatitis B virus (HBV)

General features

Hepatitis B virus (HBV) is an enveloped virus with nucleocapsid that contains double stranded circular DNA genome. The envelope comprises a small amount of lipid and three hepatitis b surface proteins large, medium and small.

Pathogenesis

Hepatitis B virus is transmitted by cutaneous and mucosal exposure to infected blood and other body fluids (semen and vaginal fluid). The highest concentrations of virus occur in blood and wound secretions. Moderate concentrations of HBV are found in semen and vaginal fluid. Lower concentrations occur in saliva. HBV is not spread by air, food or water. Common modes of transmission include mother to infant, child to child, unsafe injection practices and blood transfusions as well as sexual contact.

Disease

HBV can be a symptomatic disease (acute hepatitis B) or an asymptomatic infection with no sign or symptoms of disease. The hepatitis B virus (HBV) infects 350 million people worldwide, causing maladies ranging from acute hepatitis to chronic hepatitis,

cirrhosis and hepato-cellular carcinoma (HCC). Chronic HBV infection with cirrhotic liver is associated with the development of HCC, which are one of the most malignant cancers.

Replication

1- All three envelopes (or surface) proteins are encoded, i.e., the large envelope protein, the middle and small (S) envelope proteins.

2- All transcriptional regulatory elements including the promoters, enhancers, and the polyadenylation signal overlap with the protein-coding sequences.

Vaccine

The vaccine had included the development of an effective recombinant vaccine composed of purified HBsAg as well as Ig containing high-titer anti-HBsAg.

Hepatitis C virus (HCV)

General features

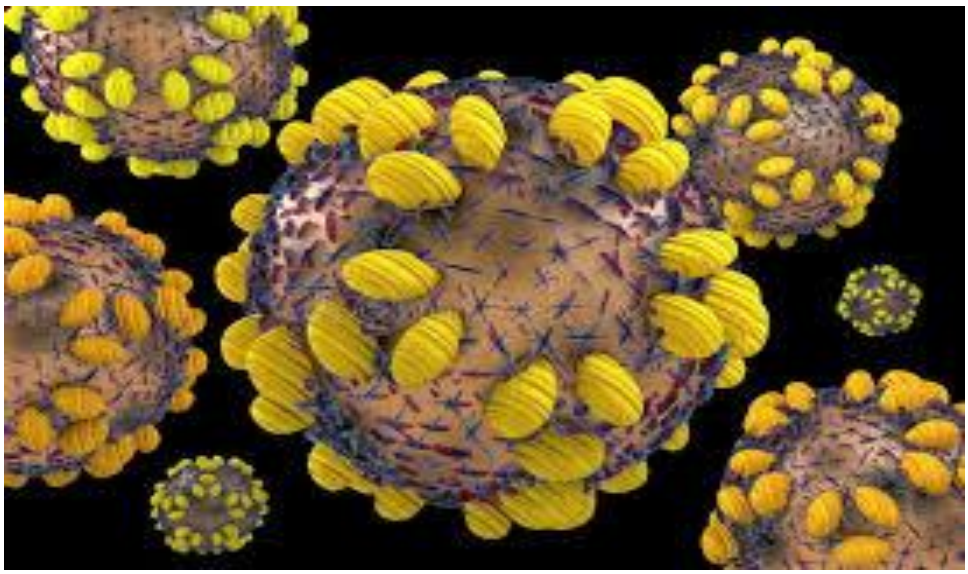
Hepatitis C virus is a small, enveloped virus. The genome consists of a single stranded RNA molecule.

Pathogenesis

HCV is transmitted through large or repeated percutaneous exposures to blood from transfusion and transplantation of infected organs.

Disease

Hepatitis C virus (HCV) is estimated to have infected almost 200 million people, representing almost 3% of world population. In 20–30% of patients HCV causes acute infection, but in the majority of patients, it causes a long-term chronic infection. Persistent infection with HCV is associated with the development of chronic hepatitis, hepatic steatosis, cirrhosis and hepato-cellular carcinoma (HCC).



Replication

1- The core protein interacts with HCV RNA and is largely involved in nucleocapsid assembly, oligomerization of the capsid protein and encapsidation of the viral genomic RNA.

2- Once the nucleocapsid is formed in the cytoplasm, it acquires the envelope proteins.

3- HCV particles are released.

Vaccine

A combination therapy of interferon with antiviral Ribavirin is usually given to patients. However, its efficiency varies with the HCV genotype and the viral loads at the start of therapy.

Lecture 13:

Herpes virus

General features

The structure of herpes viruses consists of a relatively large, double-stranded, linear DNA genome encased within a protein called the capsid, which is wrapped in a lipid bilayer called the envelope. The envelope is combined to the capsid by a membrane. This complete particle is known as the virion.

Pathogenesis

1-Transmission of HSV infections occurs through close contact with mucosal fluids, or in genital or oral secretions.

2- Infection occurs by inoculation of virus onto susceptible mucosal surfaces (e.g. Oropharynx, cervix, conjunctivae) or through small cracks in the skin.

3- During the primary infection:

* Virus infects the host at muco-cutaneous surfaces including the cornea, mouth, genital tract and skin.

* Invades the local sensory nerves by propagating via neurons.

* Establishes lifelong latency in the neuron bodies of sensory ganglia.

4- Following a primary infection, the virus enters at the site of primary infection, migrates to cell body of the neuron, and becomes latent in the ganglion.

5- As a result of primary infection; the body produces antibodies to particular type of HSV involved, preventing a subsequent infection of that type at a different site.

Disease

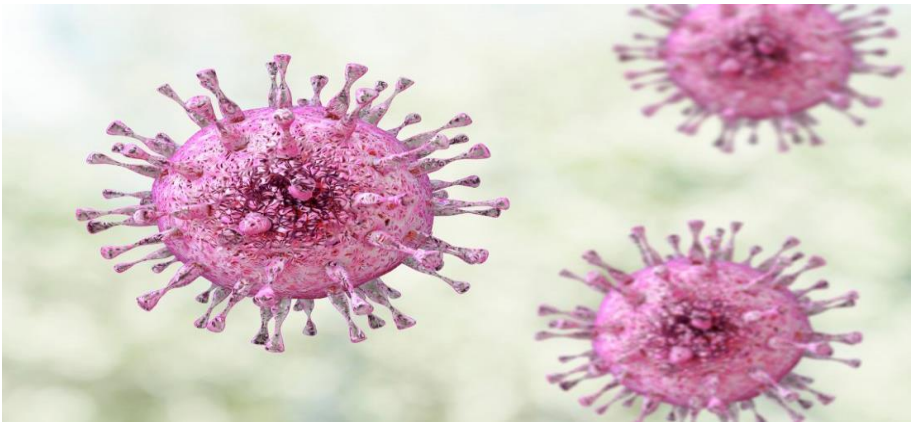
Herpes simplex virus (HSV) types 1 and 2 (HSV-1 and HSV-2) are two pathogenic agents that cause lifelong recurrent immune-pathologic diseases in man, ranging from fatal disseminated disease in newborns, to skin lesion (cold sores), genital ulcerations, blinding eye lesions and fatal encephalitis in adults.

1- Exposure to HSV at mucosal surfaces or abraded skin sites permits entry of the virus and initiation of its replication in cells of the epidermis and dermis.

2- Initial HSV infection is often subclinical, without apparent lesions.

3- Common infection of the skin or mucosa may affect the face and mouth (orofacial herpes), genitalia (genital herpes), or hands (herpetic whitlow).

4- More serious disorders occur when the virus infects and damage the eyes (herpes keratitis), or invades the central nervous system, damaging the brain (herpes encephalitis).



Replication

Viral replication occurs in ganglia and contagious neural tissue during primary infection only. After initial inoculation of the neural ganglion, virus spreads to other mucosal skin surfaces by centrifugal migration of infectious virions through peripheral sensory nerves.

Vaccine

Several antiviral drugs are effective for treating herpes, including acyclovir, valaciclovir (valacyclovir), famiciclovir and penciclovir. Acyclovir was the first discovered and is now available in generic.

Lipopeptide vaccines (i.e., topical ocular and intravaginal) provide a novel strategy that might target ocular and genital herpes and possibly provide protection from this virus.

Varicella-zoster virus

General features

Varicella zoster virus (VZV), also known as human herpesvirus is a herpesvirus with a double-stranded DNA genome. VZV only infects humans, with no animal reservoir. Its main targets are T lymphocytes, epithelial cells and ganglia.

Pathogenesis

1-VZV is highly communicable and spreads by the airborne route, with high transmission rate in temperate countries.

2- The virus spread to others from the respiratory tract.

3- Most viruses come from skin where it is highly concentrated in vesicles and skin cells.

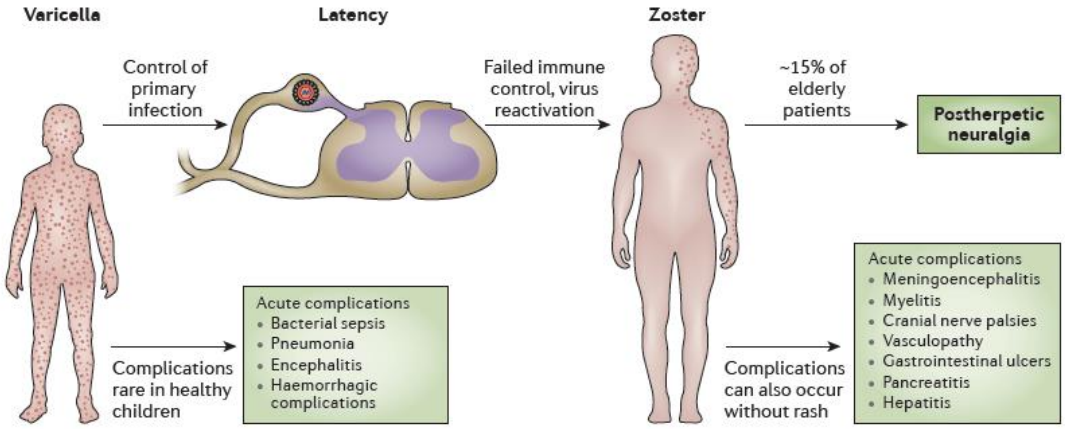
4- VZV particles enter cells by fusion of the virion envelope with the plasma membrane or by endocytosis followed by the transport of capsids and associated virion membrane proteins to the cell nucleus.

Disease

1-Primary infection causes varicella (chickenpox), as VZV
becomes latent in ganglionic neurons.

2- As cellular immunity to VZV decreases with advancing age or in immunocompromised individuals, VZV reactivates to cause zoster (shingles).

3- Zoster can be complicated by chronic pain (postherpetic neuralgia (PHN)) and other serious neurological and ocular disorders (for example, meningoencephalitis, myelitis), as well as multiple visceral and gastrointestinal disorders, including ulcers, hepatitis and pancreatitis.



Different phases of varicella zoster virus infection

Replication

varicella zoster virus (VZV) gene transcription is occur in a cascade that leads to the synthesis of viral proteins that are classified as immediate-early, early, and late, based on the time course of their expression after virus entry.

Vaccine

Live attenuated vOka consists of a mixture of distinct VZV genotypes, with 42 single nucleotide polymorphisms.

Cytomegalovirus (CMV)

General features

Cytomegalovirus (CMV) is a member of the human herpesvirus family. It has large, linear, double-stranded DNA. The genome is divided into a unique long (U_L) region and a unique short region. The U_L region contains two genes whose protein products are important in antiviral therapies.

Pathogenesis

Cytomegalovirus (CMV) is predominantly transmitted via:

• Breastfeeding

• Fomite spread

• Contact with other children

• The cervix during parturition

Infection with CMV can also occur via:

• Inhalation

• Sexual contact

• Blood transfusions

• Transfer with transplanted organs

• Transmission from mother to unborn child

Disease

1- Human cytomegalovirus (HCMV) causes severe illness and death in people, whose immune systems are weak, including organ and bone marrow transplant recipients, HIV infected people, those on immunosuppressive drugs and newborns infected during pregnancy, with recognized syndromes of fever, hepatitis, pneumonitis, encephalitis and retinitis.

2- After primary infection with CMV, the virus becomes latent and can be reactivated to produce a secondary infection, particularly during episodes of immunosuppression.

3- Cytomegalovirus is secreted in saliva, urine and breast milk.

Cytomegalovirus inside human cell

Replication

Human cytomegalovirus (HCMV) infects and replicates in a wide variety of cells, including epithelial cells of gland and mucosal tissue, smooth muscle cells, fibroblasts, macrophages, dendritic cells, hepatocytes and vascular endothelial cells.

HCMV undergoes latency in myeloid cells of the bone marrow leading to a life-long infection with sporadic reactivation.

Vaccine

A recombinant HCMV glycoprotein B (gB) vaccine has been shown to have some efficacy in prevention of infection in young women and adolescents.

Lecture 14:

Human Immunodeficiency Virus (HIV virus)

General features

Human Immunodeficiency Virus (HIV) are grouped into two types, HIV-type 1 (HIV-1) and HIV-type 2 (HIV-2). The worldwide main agent of AIDS is HIV-1, while HIV-2 is restricted to some regions of Western and Central Africa.

The retrovirus genome is composed of two identical copies of single-stranded RNA molecules and is characterized by the presence of structural genes.

Pathogenesis

Human Immunodeficiency Virus (HIV) cannot survive outside the bloodstream or lymphatic tissue. Furthermore, virus is easily inactivated by the exposure to common detergents and disinfectants. Thus, virus transmission requires the directed exposition to infected blood or secretions in the presence of skin damage, i.e. by needles or sharp tools, or abrasions in mucosal tissues within sexual intercourses. Transmission of HIV is highly dependent on the:

1- Biologic properties of the virus

2- Its concentration in the infected body fluid

3- Host susceptibility

HIV is mainly integrated or replicating into the infected cells, which are the main vehicles of virus transmission.

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Disease

Both viruses potentially cause AIDS, though disease of the central nervous system may be more frequent in HIV-2 infection. In addition, HIV-2 appears less virulent than HIV-1 and infection course takes longer to progress to AIDS. Ranging from few days to few weeks since exposure to HIV, most of the infected individuals present symptoms, e.g. flu-like illness, fever, maculopapular rash, oral ulcers, lymphadenopathy, pharyngitis, weight loss and myalgia.

It has been reported that individuals who display more severe and durable symptoms in the course of acute infection tend to progress more rapidly to AIDS. The symptomatic phase of acute HIV-1 infection lasts between 7 and 10 days, and rarely longer than 14 days.

Replication

Human Immunodeficiency Virus (HIV) viruses are characterized by other accessory/ regulatory genes that responsible of modulating virus replication. Among these, the tat gene encodes for a protein (Tat) that is expressed after infection and promotes the expression of HIV genes. The Rev protein, coded by the rev gene, ensures the export from nucleus to cytoplasm of the genomic RNA.

The HIV replication cycle can be summarized in six steps;

1) Binding and entry

2) Uncoating

3) Reverse transcription

4) Provirus integration

5) Virus protein synthesis and assembly

6) Budding

Vaccine

An effective HIV vaccine should induce powerful and durable immunity to prevent infection in healthy individuals and/or reduce viral replication and viral load in infected people, slowing or halting disease transmission and progression. These vaccines include:

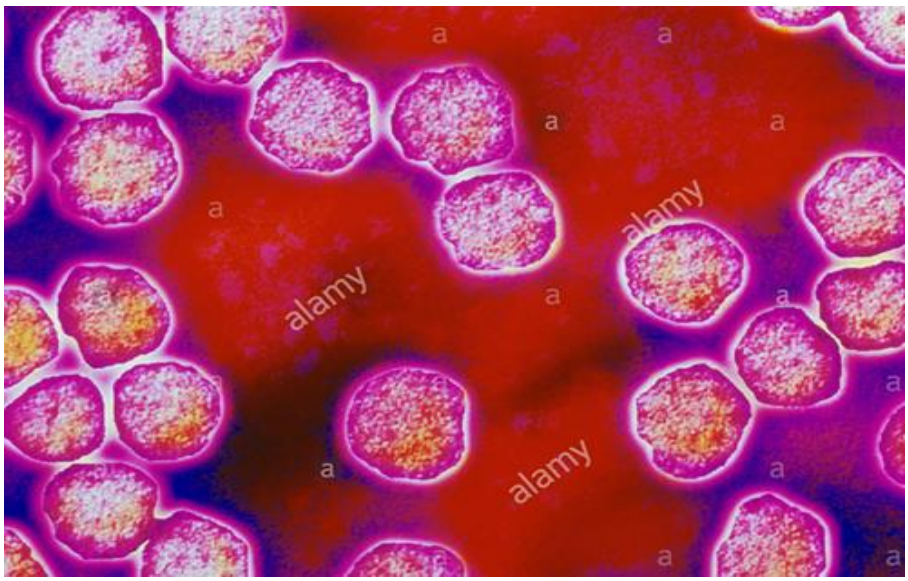
1- Live attenuated and inactivated virus vaccines

2- Protein subunit vaccines

Rubella virus

General features

The name rubella is derived from Latin word where rubella stands for “Little Red”. Rubella was initially considered as scarlet fever or measles. The rubella virus is roughly spherical in shape of diameter 40 - 60 nm. The virus carries a positive sense single stranded RNA genome enclosed within lipid capsid. The virus consists of three structural proteins, two envelope proteins glycoproteins E1 and E2 and one core protein C protein surrounding the genome.



Pathogenesis

1- The disease is contagious from 7 days after appearance of rash.

2- Postnatal rubella spreads by airborne respiratory droplets that result from coughing and sneezing, by direct contact with nasopharyngeal fluid of an infected person or from urine of infants with congenital rubella syndrome (CRS).

3- Infected individuals may be contagious as early as a week before the appearance of the rubella rash, and for up to a week after it first appears.

4- Children born with CRS may transmit the virus to others for more than a year.
5- Rubella cases typically peak in late winter or early spring

Disease

1- The infection starts from initial appearance of rash on face and then gradually spreads down the neck.

2- Infection occurs due to inhalation of aerosols and infects the upper respiratory tract where the virus enters the cell through cell - mediated endocytosis.

3- In case of children: Rash beginning on the face, which spreads to the rest of the body, low fever of less than 38°C and posterior cervical lymphadenopathy.

4- In older children and adults' additional symptoms may be present including: swollen glands, Coryza (cold like symptoms) and aching joints (especially in young women).

5- Serious problems can occur including brain infections, bleeding problems, birth defects (Congenital), inflammation of lymph nodes, cataracts, maculopapular rashes, heart defects and hearing loss

Replication

1- Rubella virus (RV) is characterized by slow replication, which is reflected in the long viral latent period of 8 to 12 h.

2- During viral replication, RV genomic RNA serves as a messenger for the nonstructural proteins and as a template for the synthesis of negative-polarity RNA strand.

3- RNA is packaged with the RV capsid protein to form nucleocapsids.

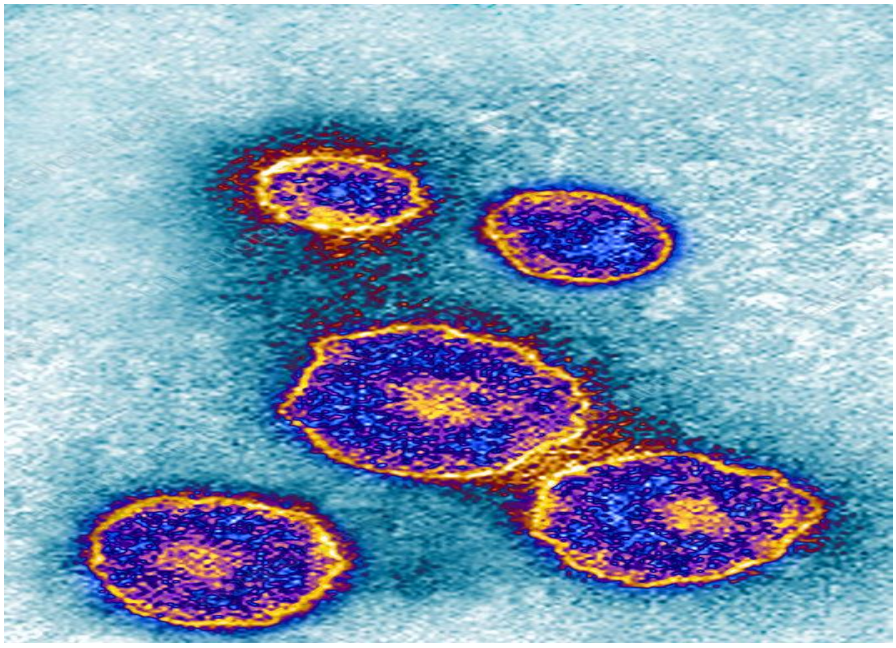
Vaccine

MMR II (Measles, Mumps and Rubella virus vaccine live) is the vaccine which is recommended to boost immune system and prevent serious, life threatening diseases. MMR II consists of live, attenuate strains Measles, Mumps and Rubella virus.

Mumps virus

General features

The virus is enveloped, has roughly spherical particles and containing a non-segmented negative strand RNA molecule. Virions are sensitive to treatment with lipid solvents, nonionic detergents, formaldehyde, oxidizing agents, and heat.



Pathogenesis

The virus is transmitted by respiratory droplets or by direct contact with infected respiratory secretions (e.g., kissing or shared utensils) or by contact with items in the environment contaminated with infected secretions.

Disease

1- Mumps or Epidemic parotitis is the common name of mumps disease. Symptoms include parotitis or swelling of sublingual or submandibular salivary glands for 2 or more days. Parotitis accompanied by fever, sore throat, and systemic symptoms of malaise and fever.

2- Less common manifestations, with or without parotitis, include benign orchitis, aseptic meningitis.

Replication

Mumps mostly colonizes and replicates along the upper respiratory tract. After entering the respiratory system, the virus locally replicates. To target tissues of the salivary glands and central nervous system, viremic dissemination occurs.

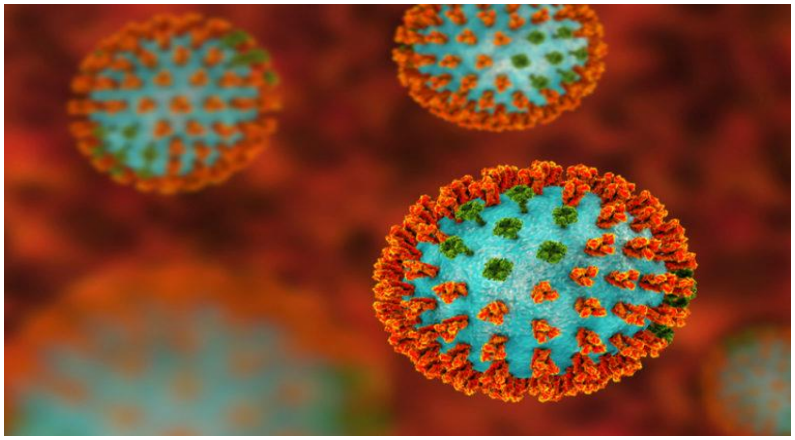
Vaccine

Live attenuated mumps virus vaccine is incorporated into combined MMR vaccine. For prevention of mumps, 2 doses of MMR vaccine are recommended routinely for children with the first dose at 12–15 months of age and the second dose at 4–6 years of age (school entry).

Orthomexovirus (Influenza virus)

General features

Helical enveloped viruse. It has Linear, 8 segmented RNA. These are important human pathogens as they cause both outbreaks and pandemics (infrequently) that kill thousands of people.



Pathogenesis

1- Typically, influenza is transmitted from infected mammals through the air by coughs or sneezes, creating aerosols containing the virus, and from infected birds through their droppings.

2- Influenza can also be transmitted by saliva, nasal secretions, feces and blood. Infections occur through contact with these bodily fluids or with contaminated surfaces.

3- Out of a host, flu viruses can remain infectious for about one week at human body temperature, over 30 days at 0°C (32 °F), and indefinitely at very low temperatures (such as lakes in northeast Siberia). They can be inactivated easily by disinfectants detergents.

Disease

1- Uncomplicated Influenza: Symptoms include chills, headache, dry cough, muscular aches. These may be induced by influenza A or B. In contrast, influenza C causes a common cold illness, Coryza.

2- Pneumonia: complications occur only in the elderly and debilitated. Influenza infection enhances the susceptibility of patients to bacterial superinfection, due to loss of ciliary clearance, dysfunction of phagocytic cells.

3- Reye's syndrome: an acute encephalopathy of children and adolescents (2-16 yrs).

Types of Influenza virus:

- Influenza A virus causes worldwide epidemics.

- Influenza B virus causes major outbreaks of Influenza.

- Influenza C virus cause mild respiratory tract infections and no outbreaks.

Replication

1- After viral hemagglutinins interact with the surface receptors, the virus enters the cell in vesicles and uncoats mediated by the M2 proteins and is facilitated by the low pH within the endosome/vesicle.

2- The viral nucleocapsid enters the cytoplasm and migrates to the nucleus where the genome RNA (8 segments) gets transcribed into mRNA by the viral RNA polymerase (transcriptase).

3- Most RNA's move to cytoplasm, some remain in the nucleus to serve as a template for the synthesis of negative polarity strand RNA genomes for the progeny, by a different subunit of viral RNA polymerase (replicase).

Vaccine

Vaccines are composed of either inactivated or live attenuated virions of the H1N1 and H3N2 human influenza A viruses, as well as those of influenza B viruses. Because the antigenicities of the wild viruses evolve, vaccines are reformulated annually by updating the seed strains.

Names of virus associated with human cancer

The main viruses associated with human cancers are:

1- Human papillomavirus

2- HPV and cervical cancer

3- HPV and other cancers

HPVs also have a role in causing some cancers of the penis, anus, vagina, and vulva. They are linked to some cancers of the mouth and throat, too.

4- Epstein-Barr virus (EBV)

5- Hepatitis B virus (HBV) and hepatitis C virus (HCV)

6- Human immunodeficiency virus (HIV)

7- Human herpes virus 8 (HHV-8)

8- Human T-lymphotrophic virus-1 (HTLV-1)

9- Merkel cell polyomavirus (MCV)

Lecture 15:

Mycology

General characteristics

1. They are eukaryotic cells contain membrane bound cell organelles including nuclei, mitochondria, Golgi apparatus, endoplasmic reticulum, lysosomes etc. They also exhibit mitosis.

2. Have a rigid cell wall and are non-motile, a feature that separates them from animals. All fungi possess cell wall made of chitin.

3. Are chemo-heterotrophs (require organic compounds for both carbon and energy sources) and fungi lack chlorophyll and are therefore not autotrophic. In particular, all are achlorophyllous - They lack chlorophyll pigments and are incapable of photosynthesis.

4. Fungi are osmotrophic; they obtain their nutrients by absorption.

5. They obtain nutrients as saprophytes (live off of decaying matter) or as parasites (live off of living matter).

6. Typically reproduce asexually and/or sexually by producing spores.

7. They grow either reproductively by budding or non-reproductively by hyphal tip elongation.

Taxonomy

Classification of the fungi includes:

1- All genera belong to one of three broad groups: Yeast, Mould, or Other. Yeast reproduces by budding and moulds reproduce by elongation at the tips of filamentous growth forms.

2- All fungal genera of medical importance can be placed into one of five sexual groups, even if sexual reproduction has not been observed. These groups correspond to the five phyla of the Kingdom Fungi and are the ascomycetes (Phylum Ascomycota), basidiomycetes (Phylum Basidiomycota), zygomycetes (Phylum Zygomycota), chytridiomycetes or chytrids (Phylum Chytridiomycota), and Fungi Imperfect.

3- Some genera are classified as dematiaceous, meaning that melanin in the cell walls of its conidia, hyphae, or both results in a darkly colored fungus.

4- Three genera are classified as dermatophytes. These fungi attack hair, nail and skin on the living patient.

5- Dimorphism is coded at the species level. Genera that contain dimorphic species are coded as moulds. For example, the genus Coccidioides is coded as a mould which contains a pair of dimorphic species.

Structure

The structure of a fungal cell includes:

1. All are eukaryotic - Possess membrane-bound nuclei (containing chromosomes) and a range of membrane-bound cytoplasmic organelles (e.g. mitochondria, vacuoles, endoplasmic reticulum).

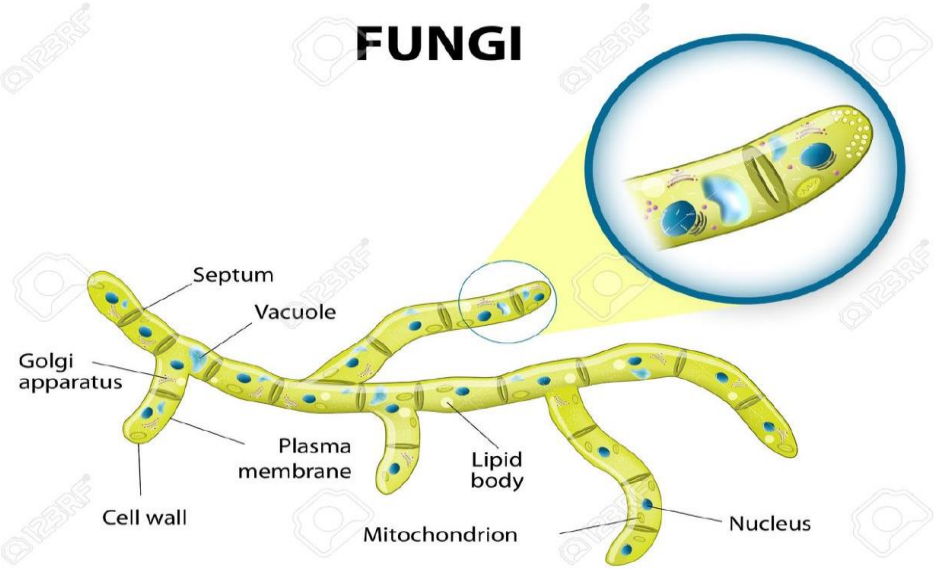
2. Most are filamentous - Composed of individual microscopic filaments called hyphae, which exhibit apical growth and branch to form a network of hyphae called a mycelium.

3. Some are unicellular - e.g. yeasts.

4. Protoplasm of a hypha or cell is surrounded by a rigid wall - Composed primarily of chitin and glucans, although the walls of some species contain cellulose.

5. Their nuclei are typically haploid and hyphal compartments are often multinucleate, although the oomycota and some yeast possess diploid nuclei.

6. Possess distinct storage compounds - e.g. glycogen, sugar alcohols and lipids.



Typical fungi cell (Fungal hyphae)

Cutaneous fungal infection (Superficial fungal infection)

1- Infections caused by pathogenic fungi and limited to the human hair, nails, epidermis, and mucosa are referred to as superficial fungal infections.

2- They are important because of their worldwide distribution, frequency, person-to-person transmission, and morbidity.

3- Severe infections may be the first indication of an underlying immunodeficiency.

4- Dermatophytosis (tinea or ringworm), pityriasis versicolor (formerly tinea versicolor) and candidiasis (moniliasis) are the three most common types of superficial fungal infections.

5- The dermatophytes are a large group that can infect human skin, hair, and nails; they are found in soil (geophilic organisms), on animals (zoophilic) and on humans (anthropophilic).

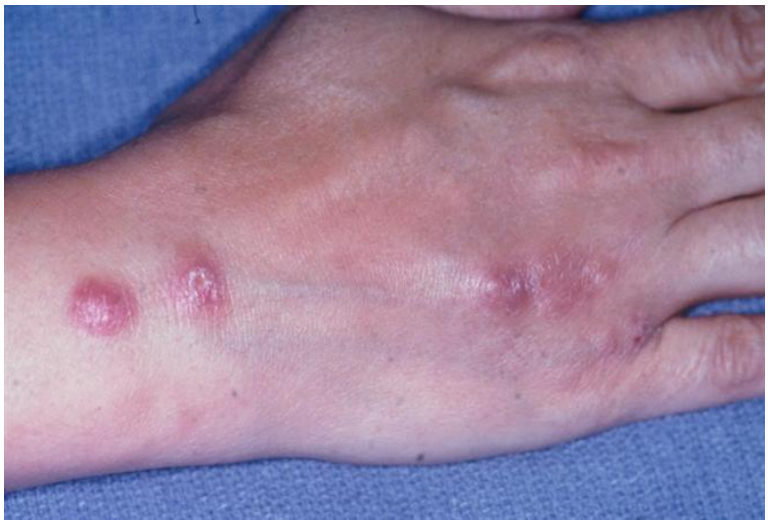
6- These fungi require keratin for growth and, therefore, they are unable to infect mucosal surfaces.

7- These fungi are found all over the world, although the specific species, and subsequent clinical presentation, vary from region to region.

8- Dermatophytosis is labeled by the involved area of the body (eg, *tinea corporis*, *tinea capitis*¸ *tinea pedis, tinea unguium*). Pityriasis versicolor is caused by the yeast form of a dimorphic fungus that is considered part of the normal human skin flora.

9- Candidiasis is caused by a yeast-like fungus of the genus *Candida* (most commonly *C. albicans*) that is part of the microflora in the human gastrointestinal tract (including the mouth) and the vagina.

10- Symptoms and signs of candidiasis manifest with a change in the normal host immune system.



Subcutaneous fungal infection

1- Subcutaneous fungal infection are a group of infections involving the skin, subcutaneous tissue, fascial planes, bones, or various organs systems.

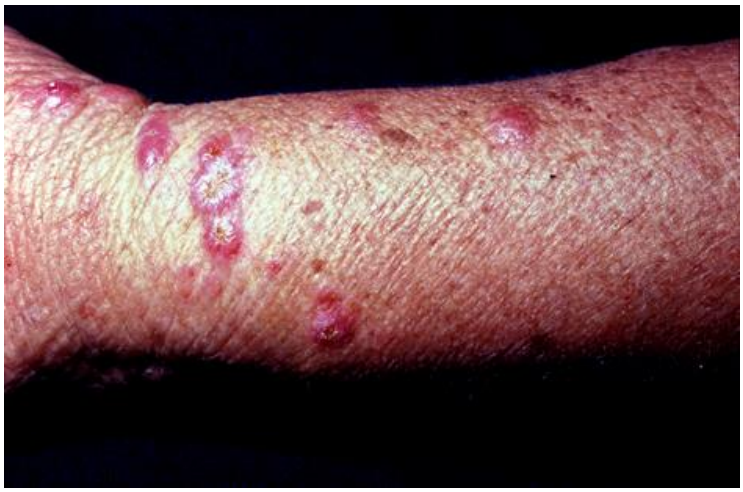
2- These include sporotrichosis, chromoblastomycosis and phaeohyphomycosis, mycetomas, subcutaneous zygomycosis (entomophthoromycosis and mucormycosis), and lobomycosis. Sporotrichosis remains the commonest subcutaneous mycosis worldwide.

3- These are prevalent in tropics/subtropics due to high temperature and humidity conducive to the growth of fungi.

4- The rural population is particularly at risk of being infected. The majority of patients are between 30 and 50 years of age.

5- The disease may either remain localized or involve adjacent tissues. Widespread dissemination may occur in immunocompromised host.

6- Treatment varies depending upon the site of infection, severity of the disease, and the pathogen involved.



Systemic fungal infection

1- Systemic fungal infection is an increasing cause of mortality and morbidity in patients with haematological malignancies and other conditions associated with profound immunosuppression.

2- Two groups of patients are at high risk of such infection, these are recipients of allogenic stem cell transplants and patients receiving intensive chemotherapy for de novo and relapsed acute leukaemias.

3- The majority of such infections are caused by *Aspergillus* and *Candida* species.

4- The etiology of systemic fungal infections can be classified into two groups: endemic mycoses due to true pathogenic fungi and opportunistic fungal infections due to a vast group of saprophytic fungi.

5- Common symptoms of candidemia (*Candida* infection of the bloodstream) include fever and chills that do not improve with antibiotics.

Candidemia can cause shock and therefore may include symptoms such as low blood pressure, fast heart rate, and rapid breathing. Systemic candidiasis may also affect other parts of the body such as the central nervous system (brain and spinal cord), abdomen, heart, kidneys, liver, bones, muscles, joints, spleen, and/or eyes.

Opportunistic fungal infection

1- Invasive fungal infections (IFI) have significantly increased in immunocompromised population.

2- Fungal species are widely distributed in soil, plant debris and other organic substrates.

3- Major risk factors for IFI include neutropenia <500 neutrophils/ml for more than 10 days, haematological malignancies, bone marrow transplantation, prolonged (>4 wk) treatment with corticosteroids; prolonged (>7 days) stays in intensive care, chemotherapy, HIV infection, invasive medical procedures, and the newer immune suppressive agents.

4- Other risk factors are malnutrition, solid organ transplantation, severe burns or prolonged stays in intensive care (>21 days), systemic corticosteroids for >7 days, and major surgery. There are also reports of the presence of infection in immunocompetent patients without signs or symptoms of conditions associated with immunocompromised status.

5- Infection can be transmitted by the inhalation of spores (aspergillosis, cryptococcosis, histoplasmosis), percutaneous inoculation in cutaneous and subcutaneous infections (dermatophytosis, madura foot), penetration into the mucosa by commensal organisms such as *Candida albicans*, and the ingestion of a toxin in contaminated food or drink (gastrointestinal disease).

6- Infections may be mild and only superficial or cutaneous (*e.g*. dermatophytosis and *Tinea versicolor*) or may cause life-threatening, systemic illness (*e.g*. candidiasis, aspergillosis and mucormycosis).

7- The clinical manifestations of the disease are related to host immunity and physiological condition. For example, *Candida* spp. can invade a local site (mucocutaneous or cutaneous candidiasis, onychomycosis) or cause systemic infections (renal, liver abscess, lung and nervous central system).

8- Allergic symptoms were reported in infections with other fungi such as *Aspergillus* spp. (allergic bronchopulmonary aspergillosis).

9- Treatment requires early diagnosis and is difficult because only a few antifungal agents are available, most usually have side effects, and some organisms have developed resistance.

Candida albicans pathogenesis

The polymorphic fungus *Candida albicans* is a member of the normal human microbiome. In most individuals, *C. albicans* resides as a lifelong, harmless commensal. Under certain circumstances, however, *C. albicans* can cause infections that range from superficial infections of the skin to life-threatening systemic infections.

Candida albicans exists often as a harmless commensal at various mucosal sites. As a pathogen, however, *C. albicans* is responsible for a wide range of infections, both mucosal and systemic, in both immunocompetent and immunocompromised individuals. *C. albicans* is acquired at or shortly after birth, often being transmitted from mother to child, and can remain a commensal or cause neonatal infections.

C. albicans can affect the oropharynx and/or the esophagus of persons with dysfunctions of the adaptive immune system.

Pathogenic factors

Several factors and activities have been identified which contribute to the pathogenic potential of this fungus. Among them are:

1- Molecules which mediate adhesion to and invasion into host cells.

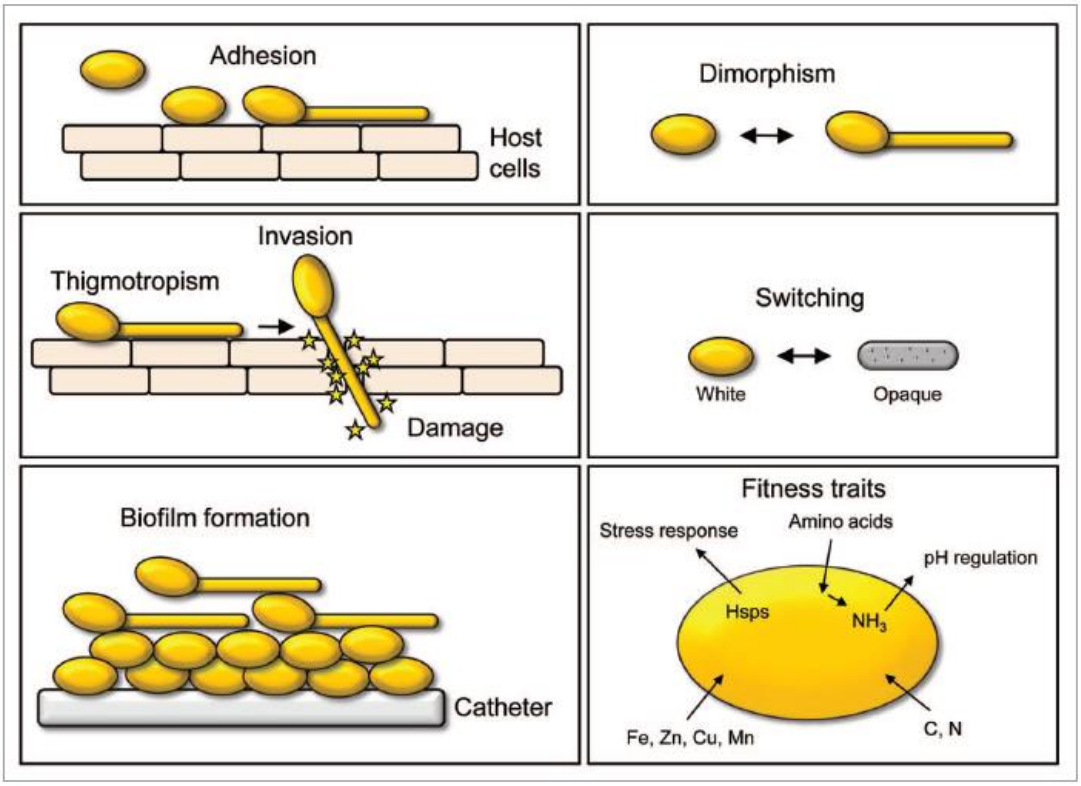
2- The secretion of hydrolases.

3- The yeast-to-hypha transition.

4- Contact sensing and thigmotropism.

5- Biofilm formation.

6- Phenotypic switching and a range of fitness attributes.



Pathogenicity mechanisms of *Candida albicans*

Cryptococcus neoformans pathogenesis

Cryptococcus neoformans (Cn) is a fungal pathogen, commonly found in urban environments that primarily affects immunocompromised individuals through inhalation of spores.

In healthy individuals Cn infection can remain in a latent form for prolonged periods of time. However, in individuals with impaired immune function, the infection may spread to the central nervous system (CNS), causing life-threatening meningitis. Thus, the disease is relatively common in AIDS patients and organ transplant recipients receiving immunosuppressive therapy.

Virulence Factors

1- The capsule of Cn is one of its major virulence factors because it is antiphagocytic required for intracellular replication and the polysaccharide functions as a major modulator of the host immune response

2- Melanin: Melanization is associated with virulence in Cn and other fungi. Melanins are dark pigments exists in cell wall. They absorb light across the UV and visible spectrum, have high physical and chemical strength and can resist degradation, even by strong acids.

3- Phospholipase B: is a secreted protein that is found in all Cn serotypes. The mechanism of action could involve damage to host tissues, nutrient acquisition, and immune modulation through alteration of lipid molecules.

References

Adam, R. D. (2001) 'Biology of Giardia lamblia', *Clinical Microbiology Reviews*, 14 (3), pp. 447–475.

Al-mohanna, M.T. (2016) 'Morphology and Classification of Bacteria'.

Al-Abri, S. S., Beeching, N. J.and Nye, F. J. (2005) 'Traveller's diarrhoea', *The Lancet.Infectious Diseases*, 5 (6), pp. 349–60

American Society for Microbiology (2006) 'Clinical Microbiology Reviews', 19 (2), pp. 298–314.

Asten, A. J. and Dijk, J. (2005) 'Distribution of classic virulence factors among Salmonella spp.', *FEMS Immunology and Medical Microbiology*, 44, pp. 251–259.

Ayed, L. B. and Sabbahi, S. (2015) 'Entamoeba Histolytica', Global Water Pathogen Project, Part Three. Specific Excreted Pathogens: Environmental and Epidemiology Aspects.

Alemayehul, B and Alemayehu, M. (2017) 'Leishmaniasis: A Review on Parasite, Vector and Reservoir Host', *Health Sci J*., 11(4), pp. 519.

Basil, D. (2016) 'Herpesviruses, Orthomyxoviruses, and Retro virus', pp. 1-16.

Bien, J., Sokolova, O. and Przemyslaw, B. (2011) 'Characterization of Virulence Factors of *Staphylococcus aureus*: Novel Function of Known Virulence Factors That Are Implicated in Activation of Airway Epithelial Proinflammatory Response', *J Pathog*,

Braun, J. S., Novak, R., Gao, G., Murray, P. J. and Shenep. J. L. (1999) ' Pneumolysin, a Protein Toxin of *Streptococcus pneumoniae*, Induces Nitric Oxide Production from Macrophages', *Infect Immun*, 67(8), pp. 3750–3756.

Brynestad, S., Sarker, M. R., McClane, B. R., Granum, P. E. and Rood, J. I. (2001) 'Enterotoxin Plasmid from *Clostridium perfringens* Is Conjugative', *Infect Immun*, 69 (5), pp. 3483–3487.

Baron, S. (1996) 'Medical Microbiology', 4th ed. University of Texas Medical Branch at Galveston.

Banuls, A., Hide, M and Prugnolle, F. (2007) 'Leishmania and the Leishmaniases A Parasite Genetic Update and Advances in Taxonomy, Epidemiology and Pathogenicity in Humans', *Advances in Parasitology*, 64.

Bharti, B., Bharti, S. and Khurana, S. (2017) 'Worm Infestation: Diagnosis, Treatment and Prevention', *The Indian Journal of Pediatrics*, 85(11):1-8.

Beltran, P. and Cristea, I. (2014) 'The Life Cycle and Pathogenesis of Human Cytomegalovirus Infection: Lessons From Proteomics', *Expert Rev Proteomics*, 11(6), pp. 697-711.

Bierle, C. J., Schleiss, M. R. and Anderholm, K. M. (2016) 'Cytomegalovirus Vaccines: Current Status and Future Prospects', *Drugs*, 76 (17), pp. 1625–1645.

Badiee, P. and Hashemizadeh, Z. (2014) 'Opportunistic invasive fungal infections: diagnosis & clinical management', *Indian J Med Res.*, 139 (2), pp. 195–204.

Chakrabarti, A. (2005) 'Microbiology of systemic fungal infections', *J Postgrad Med*, 51(1), pp. 16-20.

Chow, J. W., Thal, L. A., Perri, M. B., Vazquez, J. A., Donabedian, S.M., Clewell, D.B. and Zervos, M.J. (1993). 'Plasmid-associated hemolysin and aggregation substance production contribute to virulence in experimental enterococcal endocarditis' , *Antimicrob Agents Chemother*, 37 (11), pp. 2474–2477.

Chong, A., Lee, S., Yang, Y. and Song, J. (2017) 'The Role of Typhoid Toxin in Salmonella Typhi Virulence', Yale J Biol Med., 90 (2), pp. 283–290.

Centre for Disease Control (2013) 'Laboratory Methods for the Diagnosis of Vibrio cholerae'.

Centers for Disease Control and Prevention. U.S. Department of Health & Human Services.

Chalmers, R. M. (2013) '*Microbiology of Waterborne Diseases: Microbiological Aspects and Risks*', 2ed, London, Elsevier, http://orca.cf.ac.uk/id/eprint/60860.

Centers for Disease Control and Prevention (2009) 'Mumps virus', *Transfusion*, 49.

Dold, C. and Holand, C.V. (2011) 'Ascaris and ascariasis',*Microbes and Infection*, 13, pp. 632-637.

Dold, C. and Holland, C. V. (2011) 'Ascaris and ascariasis', *Microbes and Infection*, 13, pp. 632-637.

Dasgupta, G., Nesburn, A. B., Chentoufi, A. A. and Wechsler, S. (2009) 'New concepts in herpes simplex virus vaccine development: Notes from the battlefield', *Expert Rev Vaccines*, 8(8), pp. 1023–1035.

Douglas, C. (1994) 'Possible Pathogenic Mechanisms of Oral Streptococci', *Microbial Ecology in Health and Disease*, 7, pp. 175-177.

Elsify, A. M. (2015) 'A review on Clostridium perfringens toxins with special reference to Beta 2 toxin', *Minufiya Vet. J.*,9, pp. 85-100.

El-Tonsy, M. M. (2012) 'Introduction to medical parasitology', *Encyclopedia of Life .Support Systems (EOLSS)*.

Environmental & Public Health Consultants Since 1980.

Fasanella, A. (2013) '*Bacillus anthracis*, virulence factors, PCR, and interpretation of results', *Virulence*, 4(8), pp. 659–660.

Food Safety Authority of Ireland, (2011) 'Salmonella species', Microbial Factsheet, 1

Fanales-Belasio, E., Raimondo, M., Suligoi, B. and Buttò, S. (2012) 'HIV virology and pathogenetic mechanisms of infection: a brief overview', Ann Ist Super Sanità, 46 (1), pp. 5-14.

Gut, A. M., Vasiljevic, T., Yeager, T. and Donkor, O. (2018) 'Salmonella infection – prevention and treatment by antibiotics and probiotic yeasts: a review', Microbiology.

Gaurav, A., Singh, S. P., Gill, J. P., Kumar, R. and Kumar, D. (2013) 'Isolation and identification of Shigella spp. from human fecal samples collected from Pantnagar', pp. 376-379.

Gonzalez, A. and Thomas, L. (2018) 'Taenia spp.', Global Water Pathogen Project, Part Three. Specific Excreted Pathogens: Environmental and Epidemiology Aspects.

Gershon, A., Breuer, J., Cohen, J., Cohrs, R., Gershon, M., Gilden, D., Grose, C., Hambleton, S., Kennedy, P., Oxman, M., Seward, J. and Yamanishi, K. (2015) 'Varicella zoster virus infection', Nature Reviews | Disease Primers, 1, pp. 1-18.

Hamborsky, J. Kroger, A. and Wolfe, C. (2015) *'Chapter 21: Tetanus*', The Pink Book - Epidemiology and Prevention of Vaccine-Preventable Diseases, 13th ed., U.S. Centers for Disease Control and Prevention.

Herchline, T. E. (2019) 'Tuberculosis (TB) Treatment & Management'

Hudault, S., Guignot, J. and Servin, AL. (2001) 'Escherichia coli strains colonising the gastrointestinal tract protect germfree mice against Salmonella typhimurium infection', Gut, 49 (1), pp. 47–55

Howard-Jones, N. (1984). 'Robert Koch and the cholera vibrio: a centenary', *BMJ.*, 288 (6414), pp. 379–81.

Hu, J. (2016) 'Hepatitis B Virus Virology and Replication', *Hepatitis B Virus in Human Diseases*, Molecular and Translational Medicine.

International Programmeon Chemical Safety Poisons Information Monograph 858 Bacteria. World Health Organization.

Introduction to Mycology, Structures and Reproductive of Fungi, www.uobabylon.edu.iq › eprints › publication_1_13183_803

Jabra-Rizk, M., Kong, E., Tsui, C., Nguyen, M., Clancy, C., Fidel, P., Jr. and Noverr, M. (2016) '*Candida albicans* Pathogenesis: Fitting within the Host-Microbe Damage Response Framework', *Infection and Immunity*, 84 (10), pp. 2724-2739.

Kleep, L. I., Gioffre, A., Marina, J. S., Forrellad, Garcia, J. S., Morbidoni, H. R., Santangelo, M., Cataldi, A. A. and Bigi, F. (2013) 'Virulence factors of the Mycobacterium tuberculosis complex', *Virulence*, 4(1), pp. 3-66.

Katalinic, V., Furci, L. and Cirrillo, D. M. (2012) 'Microbiology of Mycobacterium tuberculosis and a new diagnostic test for TB', *Eur Respir Monogr*, 58, pp. 1–13.

Kelly, B. (2012) 'Superficial Fungal Infections', *Pediatrics in Review*, 33(4), pp. 22-37.

LaCour, M. (2003) 'Who Is Giardia? ', *Giardia*.

Lamba, K., Jennifer, A., Nelson, C., Poe, K., Collins, J., Kao, A., Cruz, L., Inami, G., Vaishampayan, J., Garza, A., Chaturvedi, V. and Vugia, D. (2016) 'Shiga Toxin 1–Producing Shigella sonnei Infections', *Emerging Infectious Diseases*, 22 (4).

Levine, M. M., Kotloff, K. L., Barry, E. M., Pasetti, M. F. and Sztein, M. B. (2007) 'Clinical trials of Shigella vaccines: Two steps forward and one step back on a long, hard road', *Nature Reviews Microbiology*, 5, pp. 540–553.

Lim, J. Y., Yoon, J., Hovde, C. J. (2010) 'A brief overview of Escherichia coli O157:H7 and its plasmid O157', *Journal of Microbiology and Biotechnology*, 20 (1), pp. 5–14.

Lightfoot, D. (2003) *'Shigella. Ch 17 In: Hocking AD (ed) Foodborne microorganisms of public health significance*'. 6th ed, Sydney, Australian Institute of Food Science and Technology (NSW Branch).

LaRock, D. L., Chaudhary, A. and Miller, S. I. (2015) 'Salmonellae interactions with host processes', *Nature Reviews. Microbiology*. 13 (4), pp. 191–205.

Lampel, K. A., Maurelli, A. T. (2007) '*Shigella species. Ch 15 In: Doyle MP, Beuchat LR (eds) Food microbiology', Fundamentals and frontiers*. 3rd ed, ASM Press, Washington D.C.

Lee, J. J. (2000) 'Illustrated Guide To The Protozoa', 2 ed. Allen Press.

Lema, D., Garcia, A. and Sanctis, J. (2014) 'HIV Vaccines: A Brief Overview', *Scandinavian Journal of Immunology*, 80, pp. 1–11.

Lee, J. and Bowden, D. S. (2000) 'Rubella Virus Replication and Links to Teratogenicity', *Clinical Microbiology Reviews*, 13 (4), pp. 571–587

Mahajan, V. (2005) 'Cutaneous sporotrichosis in Himachal Pradesh, India', *Mycoses*, 48, pp. 25-31.

McClelland, E., Casadevall, A. and Eisenman, H. (2007) 'Pathogenesis of *Cryptococcus neoformans*', *New Insights in Medical Mycology*, pp. 131-157.

Moayeri, M., Leppla, S. T., Vrentas, C., Pomerantsev, A. P. and Liu, S. (2015) 'Anthrax Pathogenesis', *Annu. Rev. Microbiol*., 69, pp.185–208.

McManus, D., Vennervald, B., Sacko, M. and Zhou, Z. (2018) 'Schistosomiasis', *Nature Reviews | Disease Primers*, 4(13).

Modrow, S., Falke, D., Truyen, W. and Schätzl, H. (2013) 'Molecular Virology', DOI 10.1007/978-3-642-20718-1_2.

Munro, C. and Macrina, F. (1994) 'Molecular pathogenesis of viridans streptococcal endocarditis', *Molecular Mechanisms of Bacterial Virulence*, pp. 249-265.

Mustafa, M., Muniandy, R., Elahee, M. I. and Mya, N. (2016) 'Herpes simplex virus infections, Pathophysiology and Management', *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 15 (7), pp. 85-91.

Mali, A. and Giri, P. (2018) 'A Mini Review on Rubella Virus', *Acta Scientific Medical Sciences*, 2 (9), pp. 10-14.

Mycoses study group, (2014) 'Taxonomy and Nomenclature'.

Mayer, F., Wilson, D. and Hube, B. (2013) 'Candida *albicans* pathogenicity mechanisms', *Virulence*, 4 (2), pp. 119-128.

Nissapatron, V., Lau, Y. and Fong, M. ()' *Toxoplasma gondii*: The Parasite in Trend, 8th ed.

Nygren, B. L., Schilling, K. A., Blanton, E. M., Silk, B. J., Cole, D. J. and Mintz, E. D. (2012) 'Foodborne outbreaks of shigellosis in the USA, 1998-2008', *Epidemiology and Infection*, 141(2), pp. 233–241.

Nelwan, M. L. (2019) 'Schistosomiasis: Life Cycle, Diagnosis, and Control', *Current Therapeutic Research*, 91, pp. 5–9.

Panawala, L. (2017) 'Difference Between Bacteria and Virus/Classification, Structure, Metabolism', *Pedia*.

Ponce-Gordo, F. and Jirků-Pomajbíková, K. (2015) '*Specific Excreted Pathogens: Environmental and Epidemiology Aspects*', Global Water Pathogen Project Part Three.

Plosa, E. J., Esbenshade, J. C., Fuller, M. P. and Weitkamp, J. (2012) 'Cytomegalovirus Infection', *Pediatrics in Review*, 33(4), pp. 156-163.

Potter, M. (2005) 'Strategies for managing systemic fungal infection and the place of intraconazole', *Journal of Antimicrobial Chemotherapy*, 56 (1), pp. 49-54.

Quantification of Human influenza A virus subtype (H3) genomes 2 Advanced kit handbook. 'Introduction to Human influenza A virus subtype (H3)', *Techne*.

Rawlinson, W. and Scott, G. (2003) 'Cytomegalovirus: A common virus causing serious disease ', *Australian Family Physician*, 32(10), pp. 789-793.

Roberts, L. S. and Janovy, J. R. (2009) *'Foundations of Parasitology'* 8th ed. McGraw-Hill.

Reichelt, M., Brady, J. and Arvin, A. (2009) 'The Replication Cycle of Varicella-Zoster Virus: Analysis of the Kinetics of Viral Protein Expression, Genome Synthesis, and Virion Assembly at the Single-Cell Level', *Journal of Virology*, 83 (8), pp. 3904-3918.

Shulman, S. T., Bisno, A. L., Clegg, H. W., Gerber, M. A., Kaplan, E. L., Lee, G. (2012) 'Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis', *Clinical Infectious Diseases*, 55, pp.1279–1282.

Siroy, A., Lokareddy, R. K., Speer, A., Doornbos, K. S., Cingolani, G. and Niederweis, M. (2015) 'The Tuberculosis Necrotizing Toxin kills macrophages by hydrolyzing NAD'**,** *Nat Struct Mol Biol*., 22(9), pp. 672–678

Spickler, A. R. (2012) 'Giardiasis' The Center for Food Security and Public Health. The U.S. Department of Agriculture Animal and Plant Health Inspection Service (USDA APHIS).

Soulard, V., Roucher, C., Bosson-Vanga, H. and Zanghi, G. (2015) 'Plasmodium falciparum full life cycle and Plasmodium ovale liver stages in humanized mice', *Nature Communications*, DOI: 10.1038/ncomms8690.

Samanta, I. (2015) 'Veterinary Mycology', Germany, Springer.

Ton-That, H. and Schneewind, O. (2003) 'Assembly of pili on the surface of *Corynebacterium diphtheriae*', *Mol Microbiol*, 50(4), pp.1429-1438

Tomastikova1, Z., Romero, S., Knotek, Z. and Karpiskova1, R. (2017) 'Prevalence and characteristics of Salmonella species isolated from captive reptiles in the Czech Republic', *Veterinarni Medicina*, 62 (8), pp. 456–469.

The Center for Food Security and Public Health. (2004).

Uzal, F. A., Freedman, J. C., Shrestha, A., Theoret, J. R., Garcia, J., Awad, M. M., Adams, V., Moore, R. J., Rood, J. I., McClane, B. A. (2014) 'Towards an understanding of the role of Clostridium perfringens toxins in human and animal disease', *Future Microbiol*., 9 (3), pp.361-77.

Warren, B. R., Parish, M. E., Schneider, K. R. (2006) 'Shigella as a foodborne pathogen and current methods for detection in food', *Critical Reviews in Food Science and Nutrition*, 46, pp. 551–567.

Weinstock, G. M., Hardham, J. M., McLeod, M. P., Sodergren, E. J. and Norris, s. j. (1998) 'The genome of Treponema pallidum: new light on the agent of syphilis', *FEMS Microbiology Reviews*, 22.

World Health Organization (2001) 'Introduction of Hepatitis B vaccine into childhood immunization services'.

World Health Organization (1999) 'Treatment of specific infections', Guidelines for the Management of Sexually Transmitted Infections.