

Campylobacter:

- **curved, spiral or S shaped organism.**
- Microscopically resemble vibrio.
- **Gram-negative.**
- **Microaerophilic**, oxidase-positive, non-fermentative bacteria
Campylobacter species are typically spiral-shaped and able to move via unipolar or bipolar flagella.
- **Most *Campylobacter* species are pathogenic and can infect humans and other animals.**
- ***C. jejuni* and *C. coli* the most common.**
- ***C. jejuni* is now recognized as one of the main causes of bacterial foodborne disease in many developed countries.**
- *C. fetus* is a cause of spontaneous abortions in cattle and sheep, as well as an opportunistic pathogen in human.

Epidemiology:

- Commensals of many vertebrate species including mammals and fowl.
- These serve as reservoirs of infection
- **Can transmitted primarily through fecal/oral route-through.**
- **Direct contact.**

Pathogenesis:

- ***Campylobacter* may cause both intestinal and extra-intestinal disease.**
- They are now the leading cause of food borne disease in the united states.
- ***C.jejuni* causes acute enteritis ,Traveler's diarrhea and pseudoappendicitis.**
- **Bacteremia may occur most often in infant and elderly.**
- Complications include **septic abortion ,reactive artheritis** and **Guillain – Barre syndrome.**
- ***C.fetus* also may cause intestinal infections and bacteremia** it also causes infection of vascular sites and can infect CNS.
- In **compromised** hosts ,campylobacteriosis is more likely to result from infection with ***C.fetus*** than with ***C.jejuni*.**

Laboratory Identification:

- It can be isolated from feces using special media and microaerophilic conditions.
- Presumptive diagnosis can be made on the basis of finding curved organisms with rapid ,**darting motility** in wet mount of feces.

Treatment:

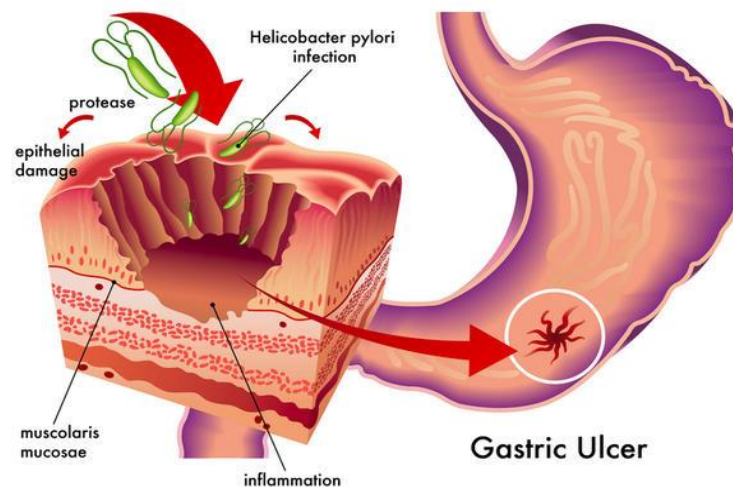
- Diarrhea should be treated symptomatically with fluid and electrolytes.
- For patients with systemic illness ,antibiotic should be administered.
- For *C.jejuni* ciprofloxacin is the drug of choice.
- For *C.fetus* ampicillin or cephalosporins are effective.

Prevention:

- Through cooking of contaminated food and pasteurization of milk and milk products.

Helicobacter:

- Member of the genus *Helicobacter* are **curve ,spiral organisms**.
- Rapid corkscrew motility due to **multiple flagella**.
- ***H.pylori*** the species of human significance is **microaerophilic**.
- **Produce urease**.
- Causes **acute gastritis** and **duodenal** and **gastric ulcers**.
- **unusual** in their ability to colonize the **stomach** ,whose pH protects against bacterial infection.



Pathogenesis:

- Transmission of *H.pylori* is thought to be from person to person.
- Untreated infections tend to be chronic and life-long.
- *H.pylori* colonizes gastric mucosal (epithelial) cells in the stomach.
- The organism survive in the mucus layer that coats the epithelium and cause chronic inflammation of the mucosa.
- Urease produce by *H.pylori* produces ammonia ions neutralize the stomach acid , Thus favoring bacterial multiplication.

Ammonia may cause:

- Injury.
- Potentiate the effects of a cytotoxin produced by *H.pylori*.

Clinical Significance:

- ***Helicobacter pylori*** initial infection causes.
 - Acute Gastritis.
- Both duodenal ulcer and gastric ulcers closely correlated with the infection with ***H.pylori***.
- ***H. pylori*** infection appear to be a risk factor for development of gastric carcinoma and gastric B-cell lymphoma.

Laboratory Identification:

- Serologic test (ELISA for serum antibodies to *H.pylori*).
- Breath tests for urease.
- Detection of *H.pylori* histologically.
- By culture.
- By a test of urease.

Treatment and prevention:

- Combination therapy with two or three antibiotics.
- A typical regimen include metronidazole ,tetracycline ,and bismuth.

Pseudomonas:

Pseudomonas aeruginosa

- *Pseudomonas aeruginosa* is a common Gram-negative, rod-shaped bacterium.
- **Widely distributed in nature (soil , water , plants and animals).**
- Motile (polar flagella).
- Encapsulated.
- Obligatory aerobic.
- **Nutritional requirements are minimal.**
- May colonize healthy human without causing disease.
- **Opportunistic pathogen.**
- **A major cause of nosocomial infections.**
- *P.aeruginosa* produce green and blue pigments(pyoverdin and pyocyanin respectively) also may produce red and black pigments.

Pathogenesis:

P.aeruginosa produce numerous **toxins** and **extracellular** products that promote invasion and dissemination of the organism.

- **Virulence factors:**
 - Cytotoxins (leukocidin), proteases, hemolysin, and pyocyanin
- **Systemic** disease is promoted by:
 - **Antiphagocytic capsule.**
 - **Endotoxin.**
 - **Exotoxin A & Exotoxin S.**

Clinical significance:

- *P.aeruginosa* **causes local and systemic** infections.
- Any tissue or organ system may be affected.

Risk factor:

- **Individuals with impaired immune defenses.**
- **Treatment with antibiotics that eliminate normal flora.**

Laboratory identification:

- *P.aeruginosa* can be isolated by a variety of media both nonselective (blood agar) and moderately selective media (MacConkey agar).
- Serology tests.

Treatment and prevention:

- Specific therapy varies with the clinical presentation and the antibiotic sensitivity pattern of the isolate.
- Difficult to find antibiotics effective against *P.aeruginosa* due to its rapid development of resistance mutations and its own innate mechanisms of antibiotic resistance.
- Need combination of antibiotic therapy (aminoglycoside antibiotic and β -lactam, or quinolone).

Bacteriodes:

- Is a genus of Gram-negative.
- **Members of the genus *Bacteriodes* are the predominant anaerobes found in the human colon.**
- **Part of the normal flora only cause disease when they gain access to blood during bowel penetration (surgery , trauma).**
- Slender rods or coccobacilli.
- Polysaccharide capsule is a virulence factor conveying resistance to phagocytosis.

Epidemiology:

- **Transmitted** from colon to the blood or peritoneum following abdominal trauma , thus the source of infection is endogenous (it not transmitted from person to person).

Pathology and Clinical Significance:

- *B.fragilis* cause bacteriodes.
- Produces enzymes (heparinase,collagenase,etc) contribute to tissue destruction when released into the blood Causes:
 - **Bacterimia.**
 - **Peritonitis.**
 - **Abdominal abscesses.**

Laboratory Identification:

- Exudates from mixed anaerobic lesions are often copious and noticeably **foul smelling.**
- Gram stain of exudates show numerous faint , slender **gram negative rods.**
- *B.fragilis* can be culture in blood agar under **anaerobic conditions.**
- **Biochemical tests determine its fermentation pattern.**

Treatment and prevention:

- Antibiotic resistance is common among *Bacteriodes*.
- Metronidazole is the drug of choice for *B.fragilis*.

Prevention:

- To avoid contamination of surgical wound preoperative antibiotic such as cefoxitin can be administered.

Haemophilus influenza:

- The major human pathogen of this genus.
- Pleomorphic: coccobacilli, slender filaments.
- *H. influenzae* may produce a capsule or may be unencapsulated.
- The capsule is the virulence factor.
- Serious, invasive *H. influenzae* disease is associated particularly with capsular type b (Hib).
- Nontypeable (**unencapsulated**) strains cause **pneumonia** among the elderly and individuals with chronic lung disease.

Epidemiology:

H. influenzae , Is a normal **upper respiratory tract flora** in humans.

- may also colonize:
 - **Conjunctiva.**
 - **Genital tract.**

Pathogenesis:

- *H. influenzae* is transmitted by respiratory droplets , colonize the upper respiratory tract mucosa.
- *H. influenzae* can enter the bloodstream and disseminate to distant sites.
- *H. influenzae* causes:
 - **First, disorders** such as **otitis media, sinusitis, epiglottitis, and bronchopneumonia (uncapsulated strains).**
 - **Second, disorders** such as **meningitis, septic arthritis, and cellulitis (Capsular type strains).**

Clinical significance:

- *H. influenzae* is the leading cause of meningitis, in infants and young children, frequently in conjunction with an episode of otitis media.
- Clinically, *H. influenzae* meningitis is indistinguishable from other purulent meningitides, and may be gradual in onset or fulminant.

Laboratory identification:

- Culture on **chocolate agar**.
- Isolation from blood, CSF or synovial fluid.
- Rapid diagnosis is crucial.
- In cases of meningitis, Gram staining of CSF commonly reveals pleomorphic, gram-negative coccobacilli .

Treatment:

- Ceftriaxone or cefotaxime should be **started** as soon as appropriate specimens have been taken for culture.
- Antibiotic sensitivity testing is **necessary**.
- upper respiratory tract infections are treated with trimethoprim-sulfamethoxazole or ampicillin plus clavulanate.

Prevention:

- Active **immunization** against Hib is effective in preventing invasive disease, and also reduces respiratory carriage of Hib.
- **Vaccine**, given to children younger than two years.
- **Rifampin** is given prophylactically to individuals in close contact with a patient infected with *H. influenzae*.

Neisseria:

- Genus *Neisseria* **gram-negative ,aerobic cocci.**
- Two *Neisseria* species pathogenic for humans.
 - ***Neisseria gonorrhoeae* (gonococcus)** causal agent of gonorrhea.
 - ***Neisseria meningitidis* (meningococcus),** causal agent of meningitis.
- **Gonococci and meningococci** are nonmotile diplococci that cannot be distinguished from each other under the microscope.
- **Both** bacteria are classified as **pyogenic cocci.**

***Neisseria gonorrhoeae*:**

- Gram-negative diplococcus,
- Is frequently observed inside **polymorphonuclear** leukocytes of clinical samples.
- Gonococci are **unencapsulated (unlike meningococci)** ,piliated, nonmotile, and resemble a **pair of kidney beans.**
- ***N. gonorrhoeae* is usually transmitted during sexual contact.**
- **Rarely**, during the **passage of a baby** through an infected birth canal.
- It does not survive long outside the human body because it is **highly sensitive to dehydration.**

Structure:

- Gonococci are **unencapsulated (unlike the meningococci)**, piliated and nonmotile, and resemble a pair of kidney beans.
- **Virulence factors:**
 - 1-Pili.**
 - 2-Lipooligosaccharide (LOS).**
 - 3-OMPs (outer membrane proteins).**

Pathogenesis:

- **Pili and OMP II**(outer membrane proteins) facilitate adhesion of the gonococcus to epithelial cells of the **urethra, rectum, cervix, pharynx, or conjunctiva**, and make colonization possible.
- **Pili** also enable the bacterium to resist phagocytosis.
- ❖ [Note: **Only piliated gonococci are virulent**].
- Both gonococci and meningococci produce an **IgA protease** that cleaves IgA , helping the pathogen to evade immunoglobulins of this subclass.

Clinical significance:

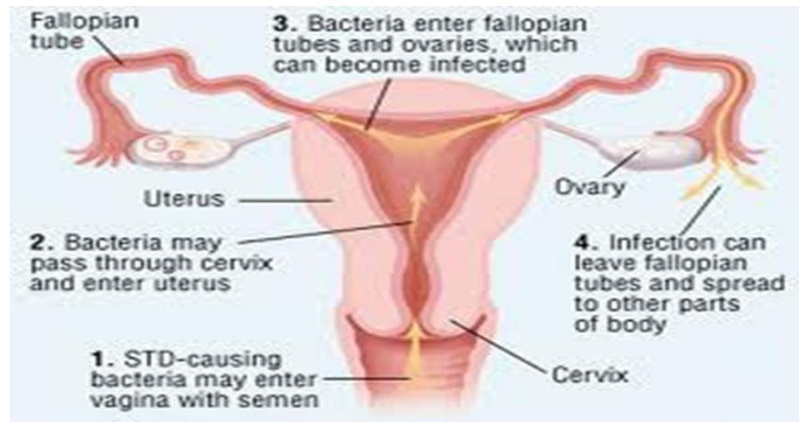
- Gonococci **most often** colonize the mucous membrane of the **genitourinary tract** or **rectum** .
- The organisms may cause a **localized** infection with the **production of pus**, or may lead to **tissue invasion, chronic inflammation**, and **fibrosis**.

A higher proportion of **females** than males are generally asymptomatic (**reservoir**).

1-Genitourinary tract infections:

- **In males** : Symptoms of gonococcal infection are more acute and easier to diagnose.
 - The patient presents with a **yellow**, purulent urethral discharge.
 - **Painful urination**.
- **In females**, infection occurs in the **endocervix** and extends to the **urethra** and **vagina**.
 - A **greenish-yellow** cervical discharge , often accompanied by intermenstrual bleeding.
 - The disease may progress to the uterus, causing **salpingitis**.
 - **Pelvic inflammatory disease (PID)**,and **fibrosis**.
 - **Infertility** occurs in 20% of women with gonococcal salpingitis, as a result of tubal scarring.

Genitourinary Infection



2-Rectal infections

- Prevalent in male homosexuals.

3-Pharyngitis

- Is contracted by oral-genital contact.
- Infected individuals may show a purulent exudate, and the condition may **mimic** a mild viral or a **streptococcal sore throat** .

4-Ophthalmia neonatorum

- is an infection of the conjunctival sac that is acquired by a newborn during passage through the birth canal of a mother infected with gonococcus .
- Gonococcal conjunctivitis can occur in adults.

5-Disseminated infection:

- Most strains of gonococci have a limited ability to multiply in the bloodstream. Therefore, bacteremia with gonococci is rare.
- ❖ [Note: Gonococcal infection is the most common cause of **septic arthritis** in sexually active adults.]

[Note :**In contrast**, meningococci multiply rapidly in blood]

Laboratory identification:

- In male, finding of numerous neutrophils containing gram-negative diplococci **in a smear of urethral exudate indicates gonococcal infection.**
- In contrast, a positive culture is needed to diagnose gonococcal infection in the female, or at other sites in the male.

Treatment and prevention:

- A single intramuscular dose of ceftriaxone is recommended therapy for uncomplicated gonococcal infections of the urethra, endocervix, or rectum.
- Intramuscular spectinomycin is indicated in patients who are **allergic** to cephalosporins.

Neisseria meningitides:

- ***N. meningitidis*** is one of the most frequent causes of **meningitis**.
- Infection with ***N. meningitidis*** can also take the form of a fulminant **meningococemia**, with intravascular coagulation, circulatory collapse, and potentially fatal shock, but without meningitis.

Structure:

- Like ***N. gonorrhoeae***, ***N. meningitidis*** is a nonmotile, gram-negative diplococcus, shaped like a kidney bean.
- Piliated.
- encapsulated.
- The meningococcal **polysaccharide capsule** is **antiphagocytic** and, therefore, the most important **virulence factor**.

Epidemiology:

- **Transmission** occurs through **inhalation** of respiratory **droplets** from a carrier or a patient in the early stages of the disease.
- **Risk factors :**
 - Recent viral or mycoplasma upper respiratory tract infection.
 - Active or passive smoking.
 - Immunodeficiency.

❖ **Humans are the only natural host.**

Pathogenesis:

- **Antiphagocytic properties** of the meningococcal **capsule** aid in the maintenance of infection.
- gonococci and meningococci make an **IgA protease that cleaves IgA₁** and, thus, helps the pathogens to evade immunoglobulins of this subclass.

❖ [Note: Nonpathogenic neisseriae do not make this protease.]

Clinical significance:

- *N. meningitidis* initially colonizes the **nasopharynx** , resulting in a largely asymptomatic **meningococcal pharyngitis**.
- In young children and other susceptible individuals, the organism can cause
 - -meningitis.
 - -fulminating septicemia.

❖ *N. meningitidis* is currently a leading cause of **meningitis**.

Laboratory identification:

The gold standard for diagnosis of systemic meningococcal infection is the isolation of *N. meningitidis* from a usually sterile body fluid, such as blood or cerebrospinal fluid (CSF).

N. meningitidis obtained from **CSF** and **skin lesion** appear as **gram-negative diplococci**.

Culture conditions:

- Cultured on **chocolate agar** with increased **CO₂**.
- The sample must be plated **promptly**.
- meningococci cultured from **CSF** or **blood** on **plain chocolate agar**
- a selective medium **is not required**

[Note: **Thayer-Martin medium** is required for samples obtained from a **skin lesion** or **nasopharyngeal swab**, to eliminate contaminating organisms.]

Treatment:

- Bacterial meningitis is a medical emergency. Accordingly, antibiotic treatment **cannot await a definitive bacteriologic diagnosis**.
- meningococcal infection are **treated immediately** to prevent **septicemia** in which the mortality rate is high.
 - cefotaxime or ceftriaxone.

Prevention:

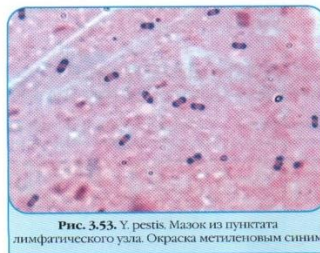
Vaccines: A conjugate meningococcal vaccine (MCV4).

Prophylaxis: **Rifampin** is usually used to treat family members of an infected individual, oral ciprofloxacin and intramuscular ceftriaxone.

***Yersinia*:**

- The genus *Yersinia* is a member of the family enterobacteriaceae.
- The genus *Yersinia* includes **three** species of medical importance.
 1. *Yersinia pseudotuberculosis*.
 2. *Yersinia enterocolitica*.
 3. *Yersinia pestis*.
- The most notorious member of this genus is *Y.pestis*.
- **Cause plague.**
- Is a small rod that stains bipolarly.
- Produce V and W antigens (virulence factors).
 - **Endotoxins and antiphagocytic capsule.**

Yersinia pestis



Transmission:

- Plague is characteristically **transmitted by fleas**, which serve to **maintain the infection within the animal reservoir**.
- Plague can also be transmitted by **ingestion** of contaminated animal **tissues**.
- via **respiratory** route (pneumonic plague).

Human *Y.pestis* infection:

- Human infection takes **three** main form.
 - Pneumonic plague.
 - Septicemic (Bubonic) plague.
 - Plagues meningitis (less common).

Treatment:

- **Streptomycin** is the drug of choice.
- **Tetracyclines** and **gentamicin** are acceptable alternatives.
- **Chloramphenicol** for plague meningitis.

Shigella:

- **Shigella species cause shigellosis (bacillary dysentery).**
- A human intestinal disease that occurs commonly among young children.

Characteristics of Shigella Species:

- Non-motile.
- Generally non-lactose fermenting.
- Unencapsulated.
- Most strain do not produce gas in a mixed acid fermentation of glucose.

Pathogenesis and Clinical Infection of Shigella:

- **Low inoculum (fewer than 200 viable organisms are sufficient to cause disease).**
 - Spread by fecal-oral route or by flies.
 - Higher risk , Daycare centers, crowded populations, and poor sanitation.

Pathogenesis:

- Shigellae invade and **destroy the mucosa of the large intestine.**
- Infection rarely penetrates to deeper layer of the intestine and **does not** lead to shigella bacteremia.
 - Produce exotoxin (**Shiga toxin**) with enterotoxic and cytotoxic properties.
- Shigellae cause classic **bacillary dysentery.**
- **Bacillary dysentery characterized by diarrhea with blood ,mucus , and painful abdominal cramping .**
- The disease more severe in **very young** and **elderly** , and **malnourished** individuals.

Among uncompromised populations ,untreated dysentery commonly resolve in a week .

Laboratory identification:

- Organisms culture from stools , using differential ,selective **Hekton agar** or other media specific for intestinal pathogens.

Treatment and prevention:

- **Ciprofloxacin or azithromycin can reduce the duration of illness and the period of shedding organisms.**
 - Protection of the water and food supply.

Personal hygiene are crucial for preventing *shigella* infections.

***Vibrio*:**

General Characteristics:

- Closely related to the family **Enterobacteriaceae**.
- Short curved gram-negative rods.
- Facultative anaerobes.
- Motile by means of a single polar flagellum.
- **O and H antigens are both present.**
- **O antigens are useful in distinguishing strains of *Vibrios* that cause epidemics.**
- The **growth** of many *vibrio* strains either requires or stimulated by **NaCl**.



Pathogenic *Vibrio*:

- ***V. cholerae*** , serogroup O1 strains that associated with epidemic cholera.
- ***Non-O1 V.cholera*** and related strains cause **cholera like** and other illness.
- ***V. parahaemolyticus*** which cause gastroenteritis and extra-intestinal infections.

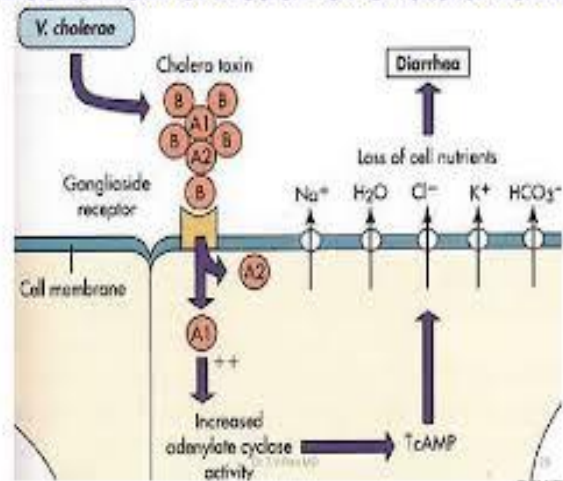
Epidemiology of *V. cholera*:

- *V.cholera* is transmitted by contaminated water and food.
- Raw or under cooked sea food harvested from contaminated water.
- There are two biotypes (subdivisions) of the species *V.cholera*: **classical** and **El Tor**.

Pathogenesis of *V. cholerae*:

- Following ingestion *V. cholerae* colonize the small intestine and release toxin.
- Diarrhea.
 - Caused by cholera toxin (also called **cholera toxin**).
 - A subunits and five multiple binding B subunits.
 - B subunits bind to GM1 ganglioside receptor the cells lining the intestine.
 - A2 subunit allows A1 subunit to enter.
 - A1 subunit stimulates adenylate cyclase by inactivating a G_s protein which in turn activates cAMP.
 - Leads to outflowing of ions and water to the lumen of the intestine.

Mechanism of Action of Cholera Toxin



Clinical significance:

- Full-blown cholera characterized by massive loss of fluid and electrolytes from the body.
- Profuse watery diarrhea (**rice –water stools**) after incubation period ranging from hours to a few days.
- Untreated , the death from severe dehydration causing **hypo-volemic shock** may occur in hours to days.
- Death rate may exceed 50% .

Laboratory identification:

- *V.cholera* grow on standard media such as blood and MacConkey agars.
- Thiosulfate –citrate-bile salts-sucrose (TCBS)medium can enhance growth.
- The organism is oxidase positive.
- Further **biochemical identification testing** is necessary for specific identification.

Treatment:

- **Replacement of fluids and electrolytes is crucial** in preventing shock and does not require bacteriologic diagnosis.
- Tetracycline is the drug of choice.

Prevention:

- Reduce fecal **contamination of water supplies and food**.
- Adequate cooking of foods can minimize transmission of *V.cholera* .

Rickettsiae:

The group of organisms known as rickettsiae (**family Rickettsiaceae**) consists of **three** genera:

- Rickettsia.
- Ehrlichia.
- Coxiella.

Rickettsiaceae:

Rickettsia, **Ehrlichia**, and **Coxiella** have a number of features in common:

- They grow **only** inside living host cells (**obligately intracellular parasites**).
- Most rickettsial infections are transmitted by **infected arthropods**.
- Rickettsial diseases are generalized infections.

General characteristics:

- They are small, rod like or **coccobacillary** shaped.
- Have a typical **double-layered gram-negative cell wall**.
- Visualized under the light microscope with one of the **polychrome stains**, such as **Giemsa**.

Pathogenesis:

- **Parasitized endothelial cells through out the circulatory system.**
- Transmitted to human by **arthropods (fleas, ticks, mites, or lice)**.
- Reservoirs are rodents, humans, or arthropods.
- Following a **bite** the organisms are taken into cells by a process similar to phagocytosis.
- The organism produce **phospholipase** that damage host cell membrane ,and facilitate cell entry.
- The organisms multiply in both the **nucleus** and **cytoplasm** of host cells.
- host cells are killed, and rickettsia spread throughout the body.
- Focal thrombi are formed in various organs including the skin.
- **Variety of small hemorrhages and hemodynamic disturbances created the symptoms of the illness.**

Clinical significance:

1-Rocky Mountain spotted fever:

- Caused by *Rickettsia rickettsii*
- Human infection is initiated by the bite of an infected **wood or dog tick**



Symptoms:

- High fever.
- Malaise.
- Prominent rash.
- In untreated cases, vascular disturbances and myocardial or renal failure may ensue.

Rocky mountain spotted fever rash



Clinical significance:

2-Other spotted fevers:

Tick-borne spotted fevers similar to Rocky Mountain spotted fever.

- They vary in severity.
- Caused by *R. conorii*, *R. canada*, and *R. sibirica*.

3-Louseborne (epidemic) typhus.

- Is caused by *Rickettsia prowazekii*.
- ❖ [Note: Epidemic typhus is a different disease from salmonella-induced typhoid fever.

4-Other forms of typhus-like fever: Murine (endemic) typhus.

- Caused by *R. typhi*, is a clinically similar, but usually milder disease than that caused by *R. prowazekii*.

Laboratory identification:

- Serological tests.
- Infected cells detection by immunofluorescence or histochemical procedures on some clinical samples, such as punch biopsies from areas of rash.

Treatment:

- Doxycycline is the drug of choice for the treatment of Rocky Mountain spotted fever in both adults and children, except for pregnant women who should be treated with chloramphenicol.

Prevention of infection:

- Prevention depends on vector control.
- Personal protection.
- Vaccines are not currently licensed for use in the United States.

Coxiella:

- *Coxiella burnetii*, the causal agent of **Q fever**.

Transmission to human:

- Inhalation of infected dust.
- Via other mucous membranes, abrasions.
- **Gastrointestinal** tract through consumption of milk from infected animals.

Clinical significance:

- *C. burnetii* reproduces in the respiratory tract and then (in the absence of treatment) is disseminated to other organs.
- **Classic Q fever** is an **interstitial pneumonitis**.

Laboratory identification:

- Serologic assays are the principal means of specific diagnosis.

Treatment and prevention:

- Doxycycline is the drug of choice for treatment.
- A vaccine has been reported to be of limited use in occupationally exposed individuals.

Antimicrobial drugs:

- Antimicrobial drugs are effective in the treatment of infections because of their **selective toxicity** (that is, they have the ability to kill or injure an invading microorganism without harming the cells of the host).

Definitions:

- **Antibiotics:** Substances produced by some microorganisms and inhibit or kill other microorganisms.
- **Broad spectrum antimicrobial agents :** act against many different types of bacteria both Gram-positive and Gram-negative.
- **Narrow spectrum antimicrobial agents :** selective and limited in their activity. For example they act against either Gram-positive or Gram-negative bacteria but not both.

Agents Used in Bacterial Infections:

The clinically useful antibacterial drugs are organized into six families:

- **Penicillins.**
- **Cephalosporins.**
- **Tetracyclines.**
- **Aminoglycosides.**
- **Macrolides.**
- **Fluoroquinolones.**

plus a group labeled **Other** that is used to represent any drug not included in one of the other six drug families.

A. Penicillins:

- **Penicillins are β -lactam antibiotics**, named after the β -lactam ring that is essential to their activity.
- Penicillins selectively interfere with the **synthesis** of the bacterial **cell wall** (a structure not found in mammalian cells).
- To be **maximally** effective, penicillins require **actively proliferating bacteria**; they have little or no effect on bacteria that are not dividing.
- Their action is usually **bactericidal**.

B-Cephalosporins:

- **Cephalosporins are β -lactam antibiotics** that are closely related both **structurally** and **functionally** to the **penicillins**.
- **They are also bactericidal**. Cephalosporins have the **same mode of action** as the penicillins.
- Cephalosporins are classified as **first, second, third, or fourth** generation, largely on the basis of:
 - Bacterial susceptibility patterns.
 - Resistance to β -lactamases.
 - **First-generation agents** are active primarily against **gram-positive organisms**, including **methicillin-sensitive *Staph.aureus*** , and have **limited activity** against **gram-negative bacilli**.
 - **Second-generation agents** have increased activity against **gram-negative bacilli** and **variable activity** against **gram-positive cocci**.
 - **Third-generation agents** have significantly increased activity against **gram-negative bacilli**, with some of these agents active against ***Pseudomonas aeruginosa***.

[Note: **Cefepime** has been classified by some as **fourth-generation** because of its extended spectrum of activity against **both gram-positive and gram-negative** organisms that include ***P. aeruginosa***.].

C- Tetracyclines:

- A number of antibiotics, including **tetracyclines**, **aminoglycosides**, and **macrolides**, exert antimicrobial effects by targeting the **bacterial ribosome**, which has components that differ structurally from those of the mammalian cytoplasmic ribosomes.
- **inhibiting bacterial protein synthesis.**
- Tetracyclines are **broad-spectrum antibiotics** (that is, many bacteria are sensitive to these drugs).
- **Tetracyclines** are generally **bacteriostatic** (the bacteria are prevented from multiplying, but are not killed by the drug).

D-Aminoglycosides:

- **Aminoglycosides** inhibit bacterial **protein synthesis**.
- **All aminoglycosides** are **bactericidal** (that is, the bacteria are killed).
- They are effective only **against aerobic organisms**.
- **Gentamicin** is used to treat a variety of infectious diseases including those caused by many of the **Enterobacteriaceae** and, in **combination** with **penicillin**, endocarditis caused by **viridans group streptococci**.

E-Macrolides:

- **Erythromycin** was the first of these to find clinical application, both as the drug of first choice, and as an **alternative to penicillin** in individuals who are **allergic to β -lactam antibiotics**.
- **Newer macrolides**, such **clarithromycin** and **azithromycin**, offer extended activity against some organisms and less severe adverse reactions.
- **Inhibit the protein synthesis.**
- Generally considered to be **bacteriostatic** they may be **bactericidal** at higher doses .

F-Fluoroquinolones:

- Fluoroquinolones uniquely **inhibit the replication of bacterial DNA**.
- All of the fluoroquinolones are **bactericidal**.
- e.g-ciprofloxacin

Other important antibacterial agents:

- **Vancomycin**: effectiveness against multiple drug-resistant organisms, such as **methicillin-resistant staphylococci**.
- Vancomycin inhibits synthesis of **bacterial cell wall**.
- Vancomycin is useful in patients with serious **allergic reactions to β -lactam antibiotics** and who have **gram-positive infections**.
- **Vancomycin** is also used for potentially life-threatening antibiotic-associated colitis caused by ***Clostridium difficile*** or **staphylococci**.
- **Trimethoprim-sulfamethoxazole**, a combination called co-trimoxazole, shows greater antimicrobial activity than equivalent quantities of either drug used alone.
- The **synergistic** antimicrobial activity of co-trimoxazole results from its **inhibition** of two sequential steps in the synthesis of **tetrahydrofolic acid**.

Agents Used in Viral Infections:

- When viruses reproduce, they use much of the host's own metabolic machinery. Therefore, few drugs are selective enough to prevent viral replication without injury to the host.
- ❑ **Treatment of herpesvirus infections:**
 - e.g acyclovir, cidofovir.
 - **Inhibit viral DNA synthesis.**

Treatment of acquired immunodeficiency syndrome (AIDS):

Divided into **four main** classes based on their mode of inhibition of viral replication.

- **The first class** nucleoside analogs reverse transcriptase inhibitors.
- **A second class** non-nucleoside analogs reverse transcriptase inhibitors.
- **The third class** is protease inhibitors.
- **The fourth class** prevents HIV from entering the host cell.
- ❖ Therapy with these antiretroviral agents, usually given in **combination**.

Treatment of viral hepatitis;

- Prolonged (months) treatment with **interferon- α** has succeeded in reducing or eliminating indicators of hepatitis **B virus replication** in about one third of patients.
- **Lamivudine**, an oral nucleoside analogue, is an effective treatment in patients with previously untreated chronic hepatitis B.
- The therapy of choice for hepatitis C is **interferon- α** in combination with **ribavirin**.

Treatment of influenza:

- First-generation antiviral agents effective against influenza A include two related drugs, **amantadine** and **rimantidine** , both stop **viral uncoatin**

Medically Important Of Fungi

OBJECTIVES:

- Cutaneous Mycosis.
- Subcutaneous mycoses.
- Systemic Mycoses.

Cutaneous Mycosis:

- Also called **dermatophytoses**.
- The dermatophytes fall into **three genera** ,each with many species :
 - ***Trichophyton***.
 - ***Epidermatophyton***.
 - ***Microsporum***.
- The causative organisms of the **dermatophytoses** are often distinguished according to their natural habitats:
 - **Anthrophilic**-residing on human skin.
 - **Zoophilic** –residing on the skin of domestic and farm animals.
 - **Geophilic**-residing in the soil.
- **Most** human infections are by **anthrophilic** and **zoophilic** organisms.
- Transmission from human to human ,or animal to human ,is by infected skin scales.

Pathology:

- A defining characteristic of the **dermatophytes** is their ability to use **keratin** as a source of nutrition.
- This ability allows them to infect **keratinized tissues** such as **skin ,hair** and **nails**.
- All three organisms attack the skin ,***Microsporum*** does not infect **nails** ,and ***Epidermophyton*** does not infect **hair**.
- They do not invade underlying , nonkeratinized tissues.

Clinical Significance:

- **Dermatophytoses** are characterized by itching ,scaling skin patches that can become inflamed and weeping.
- Specific diseases are usually identified according to affected tissues.
- A given disease can be caused by any one of several organism, and some organisms can cause more than one disease depending on the **site of infection , condition of the skin ,etc.**

Dermatophytoses:

- The most common encounter **dermatophytoses**:

Tinea pedis (athlete's foot):

- Organisms most often isolated from infected tissues are:
- ***Trichophyton rubrum*.**
- ***Trichophyton mentagrophytes*.**
- ***Epidermatophyton floccosum*.**
- The infected tissue is initially **between the toes**, but can spread to the nails , which become yellow and brittle.
- **Id reaction** :is an allergic rash caused by an inflammatory fungal infection (tinea) at a distant site. ****

Tinea corporis (ring worm):

- Organisms most often isolated are :
- ***Epidermatophyton floccosum***, and several species of ***Trichophyton*** and ***Microsporum*.**
- Lesions appear as advancing annular rings with scaly centers.
- The periphery of the ring ,which is the site of active fungal growth , is usually inflamed and vesiculated.
- Lesions most often occur on nonhairy areas of the trunk ,but any site on the body can be affected.

Tinea corporis (ring worm):



Tinea capitis (scalp ringworm):

- A number of species of **Trichophyton** and **Microsporum** have been isolated from scalp ringworm lesions.
- Disease manifestations range from small , scaling patches ,to involvement of the entire scalp with the extensive hair loss.
- The shafts can become invaded by ***Microsporum hyphae***.

Tinea capitis (scalp ringworm)

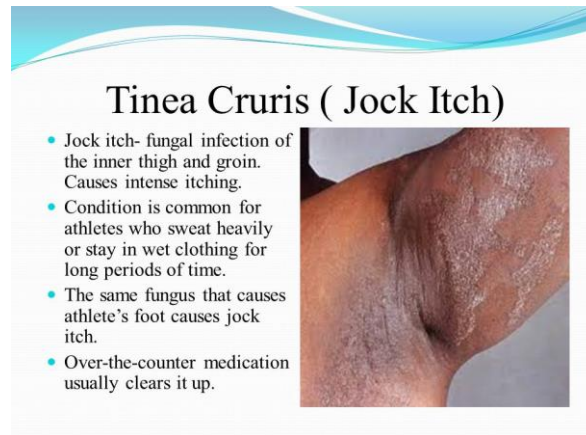


Tinea cruris (“jock itch”):

- Caused by *Epidermatophyton floccosum* and *Trichophyton rubrum*.
- Disease manifestations are similar to **ringworm** except that lesions occur in the moist groin area, where can spread from the upper thighs to the genitals.

Tinea unguium (onychomycosis).

- Caused by *Trichophyton rubrum*.
- Nails are thickened , discolored , and brittle.
- Treatment must be continued for three to four months until all infected portions of the nail grow out and are trimmed off.



Tinea unguium (onychomycosis)



Treatment:

- Removal of the skin.
- Followed by **topical application** of antifungal antibiotics such as **miconazole** or **clotrimazole**.
- Refractory infections usually respond well to oral **griseofulvin** and **itraconazole**.
- Infection of the **hair** and **nails** usually require **systemic (oral) therapy**.

Subcutaneous mycoses:

- Subcutaneous mycoses are fungal infections of the dermis ,subcutaneous tissue ,and bone .
- The causative organisms reside in the **soil** and in **decaying** or **live vegetation**.
- Subcutaneous fungal infections are almost always acquired through **traumatic lacerations** or **puncture** wounds.
- **Sporotrichosis** for example, is often acquired from the prick of a thorn.
- The infections are more common in individuals who have frequent contact with soil and vegetation, and who wear little protective clothing .
- The subcutaneous mycoses are **not transmissible** from human to human under ordinary conditions.

Sporotrichosis:

- Caused by ***Sporothrix schenckii*** ,is a dimorphic fungus that exhibits a yeast form in infected tissue and the mycelial form upon laboratory culture.
- The infection is characterized by granulomatous ulcer at the puncture site , and may produce secondary lesions along the puncture site.
- Oral itraconazole is the standard treatment.

Chromoblastomycosis:

- The infection is characterized by warty nodules that spread slowly along the lymphatics, and develop crusty abscesses caused by several species ,***Phialophora*** and ***Cladosporium***.
- Treatment by Surgical removal is effective.
- Advanced stages treated with oral flucytosine combined with antihelminthic drug ,thiabendazole.



Mycetoma (Madura foot):

- Appears as a localized abscess ,usually on the feet , that discharges pus ,serum, and blood through sinuses (“abnormal channel”).
- The infection can spread to the underlying bone and result in crippling deformities.
- The most common causative pathogen ***Madurella grisea*** and ***Actinomadura madurae***.
- The defining characteristic of mycetoma is the presence of colored grains , composed of compacted hyphae , in the exudate.
- The color of the grains (black ,white ,red , or yellow) is characteristic of the causative organism , and thus useful in identifying the particular pathogen.
- The treatment is usually surgical excision because there no effective chemotherapy.

Systemic Mycoses:

- The organisms responsible for systemic mycoses fall into two general categories.
 - **True pathogens.**
 - **Opportunistic pathogens.**
- The most common **systemic mycotic** infection in the immunocompetent hosts in the united states caused by:
 - **Coccidiomycosis.**
 - **Histoplasmosis.**
 - **Blastomycosis.**
- The clinical manifestations closely resemble those seen in tuberculosis in that asymptomatic primary pulmonary infection is common , whereas chronic pulmonary or disseminated infection is rare.
- Entry into the host is by inhalation of airborne spores, which germinate in the lungs , dissemination can occur to any organ of the body where the fungi can invade and destroy the tissue .
- The fungi causing this diseases are dimorphic.

Clinical Significance:

- Most cases of coccidioidomycosis, histoplasmosis and paracoccidioidomycosis , present mild in healthy patients and self limiting.
- In immunosuppressed patients, the same infections can be life –threatening.

Coccidioidomycosis:

- Caused by ***Coccidioides immitis***.
- In the soil ,the fungus generates spores by septation of hyphal filaments (arthrospores).
- These spores become readily airborne ,and enter the lungs ,where they germinate and develop into large spherules filled with many endospores.
- Rupture of the spherules releases the endospores ,each of which can form new spherule.
- Disseminated disease ,lesion occur most often in the bone and CNS where they result in meningitis.

Histoplasmosis:

- Is caused by ***Histoplasma capsulatum***.
 - In the soil , the fungus generates conidia.
 - Pulmonary infections may be:
 - Acute but relatively benign and self limiting **OR**
 - Chronic ,progressive ,and fatal.
1. AIDS patients who live in or travel through endemic areas are especially at risk.
 2. The clinical manifestation of histoplasmosis often resembling tuberculosis.

Blastomycosis:

- Caused by ***Blastomyces dermatitidis***.
- Like Histoplasma, the fungus produces microconidia ,most often in the soil , which become airborne and enter the lungs where they germinate into thick-walled yeast cells.
- Initial pulmonary infections rarely disseminated to other sites.
- When dissemination occurs, the secondary sites are **skin** (70%) ,**bone** (30%),and **genitourinary** tract (20%).

Paracoccidioidomycosis:

- Also called (South American blastomycosis).
- Caused by ***Paracoccidioides brasiliensis***.
- The clinical manifestations like that of histoplasmosis and blastomycosis except that ,the common secondary site of the infection is the **mucosa of the mouth and nose** ,where painful ,destructive lesions may develop.
- Over 90% of patients with symptomatic disease are mature males.
- It is speculated that female sex hormones may inhibit formation of the yeast form.

Opportunistic pathogens:

- *Absidia corymbifera*.
- *Aspergillus fumigatus*.
- *Candida albicans*.
- *Cryptococcus neoformans*.
- *Pneumocystis carinii*.
- *Rhizomucor pusillus*.
- *Rhizopus oryzae* (*R. arrhizus*).

The opportunistic mycoses:

- Afflict debilitated and/or immunocompromised individuals ,and which are rare in normal individuals.
- The use of **immunosuppressive drugs for organ transplantation** , the use of **chemotherapy** in cancer treatment, and AIDS, resulted in expansion of **immunocompromised** population.
- Fungal infections represent approximately 15% of all nosocomial infections in ICU in the U.S.A with **candida** species being the most commonly occurring fungal pathogen.
- The opportunistic mycoses most commonly encounter today include the following:

Candidiasis(candidosis):

- Caused by yeast ***Candida albicans*** and other candida species which are normal body flora found in the skin ,mouth ,vagina , and intestines.
- Although termed a yeast, ***Candida albicans*** is **dimorphic**.
- Candida infections have various manifestations depending on the site of infection, for example ,oral candidiasis (thrush) presents as raised, white plaques on the oral mucosa ,tongue , or gums.
- **Vaginal candidiasis** presents as itching and burning pain of the vulva and vagina accompanied by a thick or thin white discharge.

Oral thrush



Cryptococcosis:

- Caused by the yeast ***Cryptococcus neoformans***.
- The organism is especially abundant in soil containing bird (especially pigeon) droppings, although the birds themselves are not infected.
- The organism has characteristic thick capsule that surrounds the budding yeast cell and observable on a background of Indian ink.
- The common form of cryptococcosis is a mild ,subclinical lung infection.
- In immunocompromised patients, the infection often disseminates to the brain and meninges , with fatal consequences.
- In AIDS patients, cryptococcosis is the second most common fungal infection (after candidiasis) and is potentially the most serious.

Aspergillosis:

- Is caused by several species of the genus *Aspergillus* , but primarily by ***Aspergillus fumigatus***.
- *Aspergillus* is rarely pathogenic in the normal host , but can produce disease in immunosuppressed individuals , and patients treated with broad - spectrum antibiotics.
- The aspergilli are ubiquitous growing only as filamentous molds and producing prodigious numbers of conidiospores.
- They reside in the soil, decomposing organic matter, and dust.
- Aspergillosis manifested in several forms depend on the immunologic state of health of the patients.

1-acute Aspergillosis Infections:

- The most severe , and often fatal , form of aspergillosis acute invasive infection of the **lung**, from which the infection can be disseminated to the **brain** ,the **GI** ,and **other organs**.
- A less severe ,noninvasive lung infection gives rise to fungus ball (**aspergilloma**) a mass of hyphal tissue that can form in lung cavities derived from prior diseases , such as tuberculosis.
- Although the **lung** is the most common **primary site** of infections , the **eye**, **ear** ,**nasal sinuses**, and **skin** can also be primary sites .

2- Allergic Reaction To Aspergillus:

- A relatively rare condition , termed **allergic aspergillosis**.
- Can rise from the mere inhalation of the spores.
- The allergic reaction results in the formation of mucous that can block the bronchi.

Mucormycosis:

- Caused most often by *Rhizopus oryzae* (*R. arrhizus*).
- Less often caused by members of the order Mucorales, such as *Absidia corymbifera* , and *Rhizomucor pusillus*.
- These organisms are ubiquitous in nature , and their spores are found in great abundance on rotting fruit and old bread.
- Mucor infections occur worldwide , but are almost entirely restricted to individuals with some underlying predisposing condition such as burn ,leukemias ,and diabetes mellitus.
- The most common fatal disease within a week is **rhinocerebral mucormycosis** , in which the infection begins in the nasal mucosa or sinuses ,and progresses to the **orbits**, the **palate**, and **brain**.

Pneumocystis carinii pneumonia (PCP):

- Caused by *Pneumocystis carinii*.
- Previously considered a protozoan.
- Lacks the ergosterol ,which is essential component of most fungal membranes.
- The disease was rare before the use of the immunosuppressive drugs and onset of AIDS.
- Currently is one of the most common opportunistic diseases of individuals infected with HIV-1 and 100% fatal if untreated.

Laboratory identification:

- Standard media –Sabouraud's agar , potato dextrose agar , low PH 5.0, inhibits bacterial growth but allows fungal colonies to form cultures can be started from spores or hyphae fragments.
- Specimens :blood , pus, CSF , sputum ,tissue biopsies, skin scrapings , nail clippings.
- Identification by morphology of conidia structure and carbohydrate assimilation tests.

Laboratory Diagnosis of Fungal Infection:

Specimens:

Depend on the site of infection.

- **Systemic:-** Blood culture.
- antigen testing e.g. cryptococcal and histoplasmosis.
- **Pneumonia:-** Bronchoscopy washing or brushings for staining and fungal culture of bronchial biopsy.
- **Meningitis:** Cerebral fluid for methylene blue staining and indian ink and cryptococcal antigen and fungal culture.
- If **skin infection** require skin scrapings.
- If **nail infection** require nail clippings.
- **Galactomannan antigen testing for aspergillus infection.**

Types of Test Carried Out:

- Fungal staining-methylene blue staining or preparation wet using KOH to dissolve tissue material
- Fungal culture on media that encourages fungal growth e . g . PDA
- Antigen Testing i.e. to test for antigen present in the wall of fungus e.g cryptococcal antigens, galactomannan used in serum and CSF samples
- PCR not used on a routine basis on samples

Management of Fungal infections:

- Some such as superficial skin infections require topical therapy only with cream e.g. pessaries for vaginal candidiasis.
- Some require oral therapy for skin and nail infection up to 1 year e.g. terbinafine.
- In the immunocompromised systemic therapy require e.g. voriconazol , fluconazole or amphotericin.
- Important to diagnose fungal infections early in the immunocompromised as there is a high mortality associated with infection.
- Empirical therapy often started in advance of laboratory diagnosis in these patients.

***Candida albicans* and Antifungal**

Objectives:

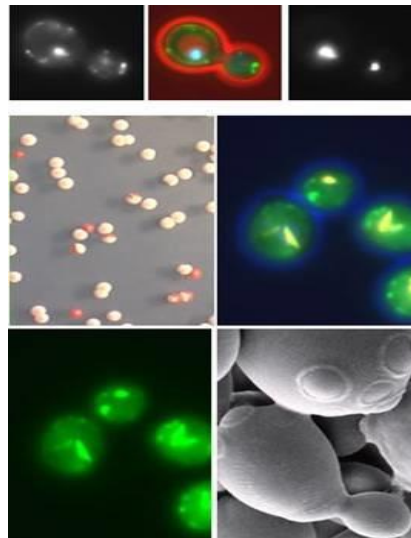
- Mycotoxicoses.
- *Candida albicans*.
- Antifungal.

Mycotoxicoses:

- Some fungi produce **mycotoxins**, the best known of which are the **aflatoxins** produced by the ***Aspergillus* species**.
- These toxins are ingested with the **food stuffs** on which the fungi have been growing.
- **Aflatoxin B₁** may contribute to primary hepatic carcinoma.

Candidiasis:

- At least 70% of all human *Candida* infections are caused by *C. albicans*, the rest by *C. parapsilosis*, *C. tropicalis*, *C. guilliermondii*, *C. kruzei*, and a few other rare *Candida* species.



Morphology and culture:

- 1-Gram staining of primary preparations reveals *C. albicans* to be a **Gram-positive**, budding, oval yeast with a diameter of approximately 5µm.
- 2-Gram-positive **pseudohyphae** are observed frequently and **septate** mycelia occasionally .
- 3-*C. albicans* can be grown on the usual culture mediums.
- 4-After 48 hours of incubation on agar mediums, round, whitish, somewhat rough-surfaced colonies form.

CANDIDIASIS:

Pathogenesis and clinical pictures:

1. Candida is a normal inhabitant of human and animal mucosa (commensal).
2. Candida infections must therefore be considered endogenous.
3. Candidiasis usually develop in persons whose immunity is compromised, most frequently in the presence of disturbed cellular immunity.
4. The mucosa are affected most often, less frequently the outer skin and inner organs (deep candidiasis).
5. In oral cavity infections, a white, adherent coating is seen on the cheek mucosa and tongue.

Frequency:

- The most common fungal pathogen worldwide.
- leading causes of nosocomial infections.
- Significant mortality and morbidity in low birth-weight infants.

Immunocompromised:

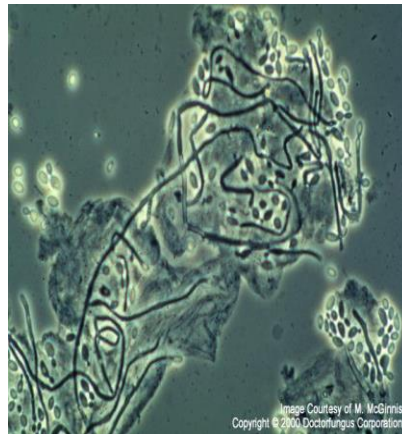
- Most commonly manifested in patients with leukemia, cancer and AIDs patients.
- Oral candidiasis is often a clue to acute primary infection.

Public Concerns:

- increasing resistance to drug therapies due to antibiotics and antifungals.

Candida albicans:

- Commensal Pathogen.
- **Morphogenesis:**
 - yeast form.
 - Filamentous.
- Principal Cell Wall Polymers Glucan and Mannan.
- **Strict aerobe**, favors moist surfaces.
- Commensally found in gut, genitals, and lungs.
- Body Temp 37° C, neutral pH .
- Rapid Multiplication & Spread.

**Yeast in Oral Scraping**

A sample of an oral scraping contains yeast cells and pseudohyphae .(www.doctorfungus.org).

Diseases Caused By *C. albicans*:

- Thrush.
- Esophagitis.
- Cutaneous Candidiasis.
- Genital Yeast Infections.
- Deep Candidiasis

Oral thrush



Angular cheilitis



Pathogenesis:

- Host Recognition: **Adhesins** (surface protein).
- **Enzymes**: hydrolytic enzymes : Phospholipases, Lipases, Proteinases.
- **Morphogenesis**: Yeast form to Filamentous hyphae/pseudohyphae.

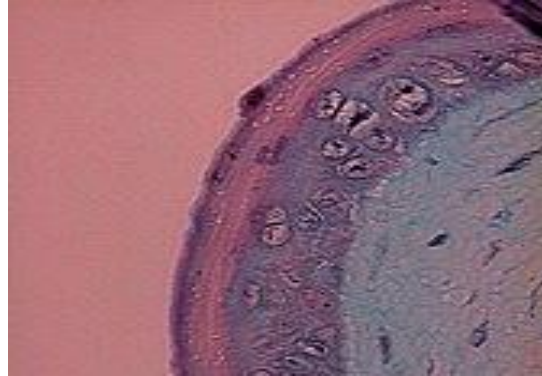


Figure 1. skin equivalent before infection.

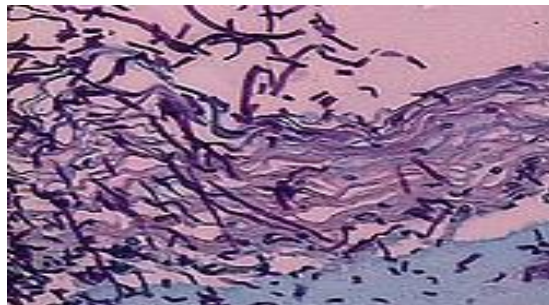


Figure 2. Infection with pathogenic clinical isolate of *C. albicans*. After 48 h the yeast penetrates the skin equivalent and destroys the tissue.

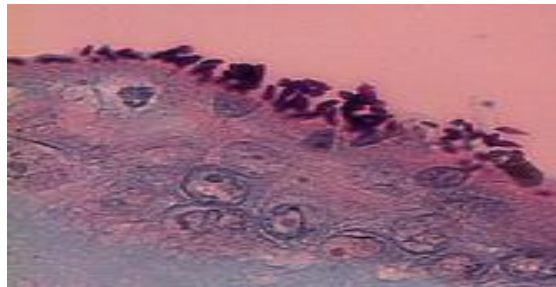


Figure 3. Infection with non-pathogenic *C. albicans*. This strain is not able to penetrate into the tissue.

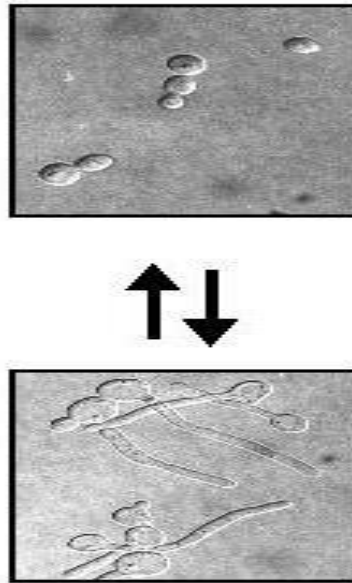


Figure 1. Morphogenesis. Morphogenesis in *C. albicans* is a *pivotal* virulence factor that allows rapid multiplication and subsequent dissemination in host tissue.
(www.kent.ac.uk)

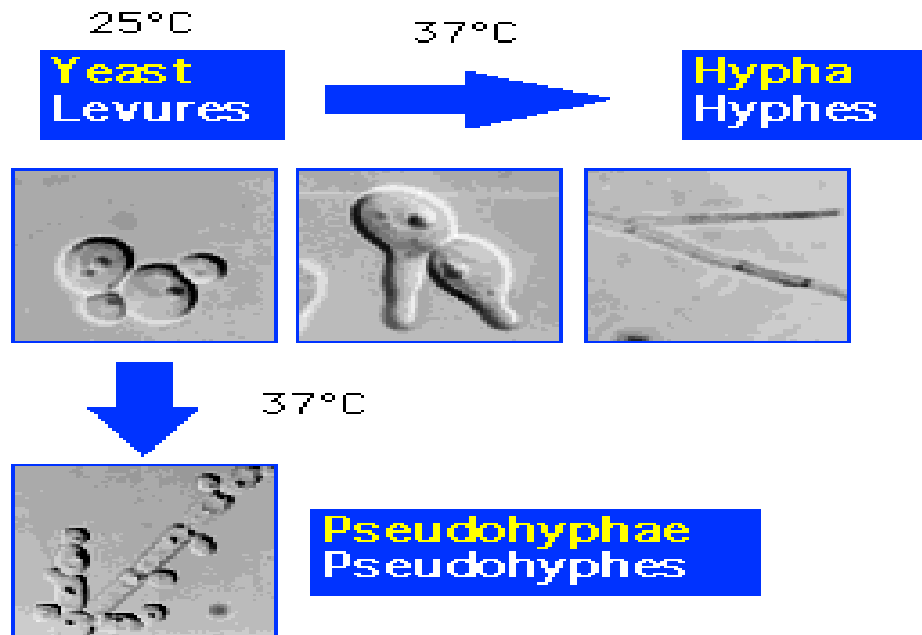


Figure 2. Morphogenic forms of *Candida albicans*
<http://cbrcnrc.gc.ca/thomaslab/candida/caindex.html>.

Tools for Detection & Diagnosis :

Diagnosis:

1. This involves **microscopic** examination.
2. Candida grows on many standard nutrient mediums, particularly well on Sabouraud agar.
3. Typical yeast colonies are identified under the microscope and based on specific metabolic evidence.
4. Detection of Candida-specific antigens in serum (e.g., free mannan) is possible using an agglutination reaction with latex particles to which monoclonal antibodies are bound.
 - PCR Based Molecular Techniques.
 - Fluorescent in situ hybridization.
 - Restriction Enzyme Analysis.

Current methods:

- Culture; biochemical tests, and Serology.

Candidiasis Therapy:

- Nystatin and azoles can be used in topical therapy.
- In cases of deep candidiasis, amphotericin B is the agent of choice, often administered together with 5-fluorocytosine.
- Echinocandins (e.g., caspofungin) can be used in severe oropharyngeal and esophageal candidiasis.

ANTIFUNGAL

A limited number of anti-infective agents are available for specific treatment of fungal infections:

Polyenes:

- These agents bind **to membrane sterols** and destroy the membrane structure.
- Amphotericin B: used in systemic mycoses.
- Fungicidal activity with frequent side effects.
- Nystatin, Natamycin. only for topical use in mucosal mycoses.

Azoles:

- These agents disrupt **ergosterol biosynthesis**.
- Their effect is mainly fungistatic with possible gastrointestinal side effects.
- Hepatic functional parameters should be monitored during therapy.

Ketoconazole:

- One of the first azoles.
- No longer used because of side effects.

Fluconazole:

- Oral or intravenous application.
- For the treatment of surface and systemic mycoses and cryptococcal meningitis in AIDS patients.

Itraconazole:

- Oral and intravenous application.
- Use in systemic and cutaneous mycoses and also for the treatment of aspergillosis.

Voriconazole:

- Oral and intravenous application.
- Good activity against Candida and Aspergillus.

Fluorocytosine:

- Interferes with DNA synthesis (base analog).
- Given by oral application in candidiasis, aspergillosis, and cryptococcosis.
- It is necessary to monitor the course of therapy for the development of resistance.
- The toxicity of **amphotericin B** is reduced in combination with 5-fluorocytosine.

Allylamines:

- Terbinafine.
- By oral and topical application to treat dermatomycoses. Inhibition of ergosterol biosynthesis.

Echinocandins:

- Caspofungin has been approved as a salvage therapy in refractory aspergillosis.
- It is useful also in oropharyngeal and esophageal candidiasis.
- Inhibition of the biosynthesis of **glucan** of the cell wall.

Griseofulvin:

- This is an older antibiotic used in treatment of dermatomycoses.
- By oral application, therapy must often be continued for months.

Medically important of viruses

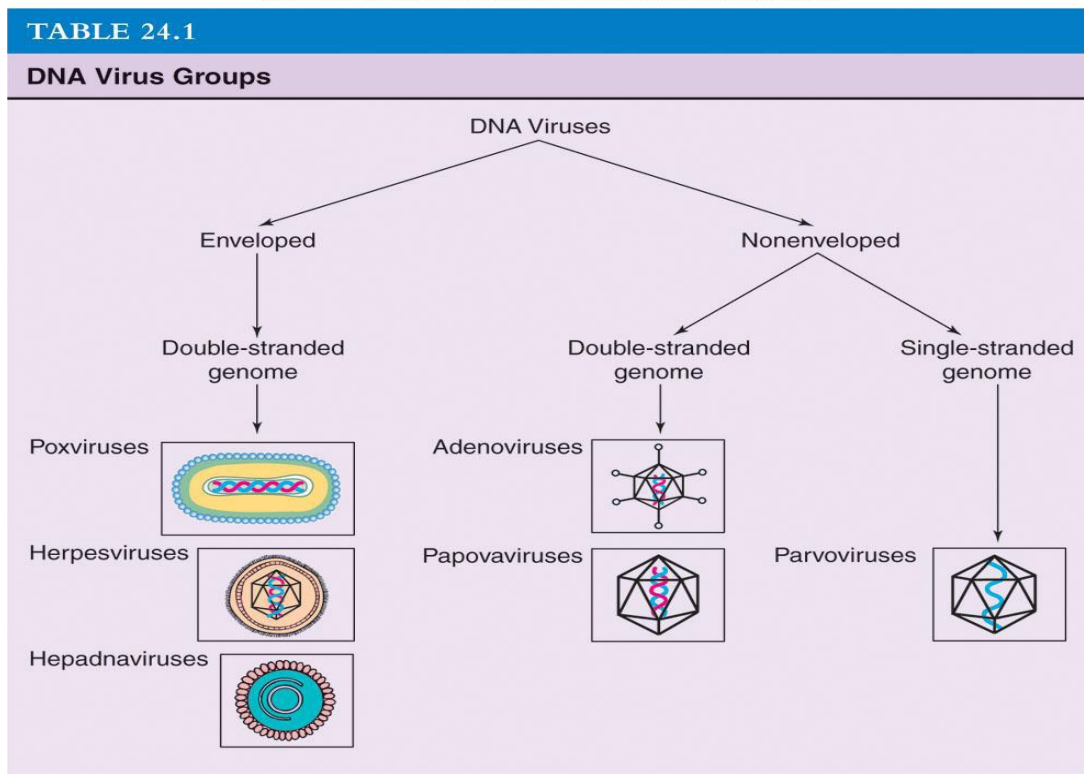
OBJECTIVES:

- Medically important viruses.
- Structure.
- Transmission.
- Treatment & Prevention.

Medically Important Viruses:

- Obligate intracellular parasites.
- Infect animals, plants, & other microbes.
- All DNA viruses are double stranded except for **parvoviruses**, which have ssDNA.
- All RNA viruses are single stranded except for dsRNA **reoviruses**.
- Viruses are limited to a particular host or cell type.

Copyright © The McGraw-Hill Companies, Inc. Permission required for reproduction or display.



Poxviruses (members of the family Poxviridae):

- Produce eruptive skin pustules called pocks or pox, that leave scars.
- Largest & most complex animal viruses.
- Have the **largest genome** of all **viruses dsDNA**.
- Multiply in cytoplasm in factory areas.
- Variola – cause of smallpox.
- Vaccinia – closely related virus used in vaccines.

Smallpox:

- First disease to be eliminated by vaccination.
- Exposure through **inhalation** or **skin contact**.
- Infection associated with fever, malaise, prostration & a rash.
- **Variola major** – highly virulent, caused toxemia, shock, & intravascular coagulation.
- **Variola minor** – less virulent.

Herpesviridae:

- Enveloped, linear double-stranded DNA genome.
- Replication within nucleus.
- Latency & recurrent infections.
- Large family; 8 infect humans.
- Epstein-Barr virus (EBV).
- Herpes simplex virus, type 1 (HSV1).
- Herpes simplex virus, type 2 (HSV2).
- Varicella-zoster virus (VZV).
- Human cytomegalovirus (HCMV).

Herpes simplex virus,type1(HSV1):

- Herpes simplex virus type 1 (HSV-1) has a relatively rapid, cytotoxic growth cycle.
- HSV-1 establishes latency in **trigeminal ganglion** after oropharyngeal infection.
- Transmission of HSV-1 is by direct contact with virus-containing secretions (usually saliva), or with lesions on mucosal surfaces.
- Vesicles or shallow ulcers containing infectious HSV-1 are produced, primarily in the oropharynx. These cause **sore throat, fever, gingivitis, and anorexia**.
- Infection of the eye by HSV-1 can cause severe **keratoconjunctivitis**.
- Treatment: Acycloguanosine (acyclovir) is selectively effective against HSV.

Varicella-zoster virus(VZV):

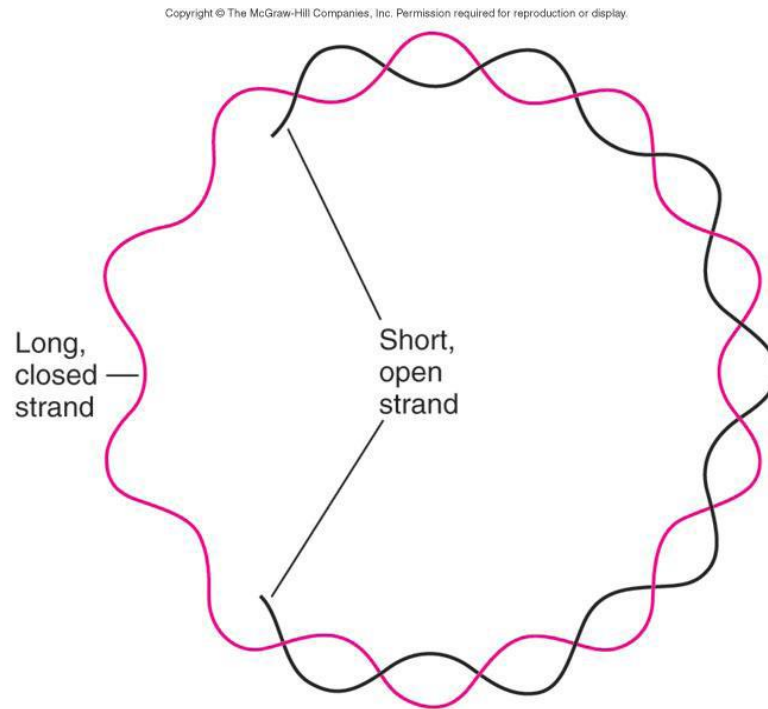
- Transmission of VZV is usually via respiratory droplets.
- Varicella (chickenpox).
- Zoster (shingles).

Shingles



Hepadnaviridae (Hepadnaviruses):

- Enveloped DNA viruses, icosahedral nucleocapsid.
- Never been grown in tissue culture.
- Unusual genome containing both double & single stranded DNA.
- Tropism for liver.
- **Hepatitis B virus** causes hepatitis & can be a factor in liver cancer.



Hepatitis B virus:

- Infectious hepatitis B virus (HBV) is present in all body fluids of an infected individual. Therefore, blood, semen, saliva, breast milk, etc. serve as sources of infection.
- Multiplies exclusively in the liver, which continuously seeds blood with viruses.
- 10^7 virions/mL blood.
- Minute amounts of blood can transmit infection.
- HBV is most frequently contracted by sexual intercourse and by intravenous drug use.
- High incidence among homosexuals & drug addicts.
- Can become a chronic infection.
- Increases risk of liver cancer.
- The primary cause of hepatic cell destruction is the cell-mediated immune response by cytotoxic (CD8) T lymphocytes, which react specifically with fragments of the nucleocapsid proteins expressed on the infected hepatocyte membrane.

Treatment:

- The drug of choice depends on multiple factors, including the antibody and antigen status of the patient.
- Interferon and pegylated interferon, lamivudine, adefovir, entecavir, telbivudine, and tenofovir are treatment options.

Prevention:

- HB immune globulin protects exposed people.
- HBV vaccine – recombinant surface antigen made by yeast; given in 3 doses over 18 months.

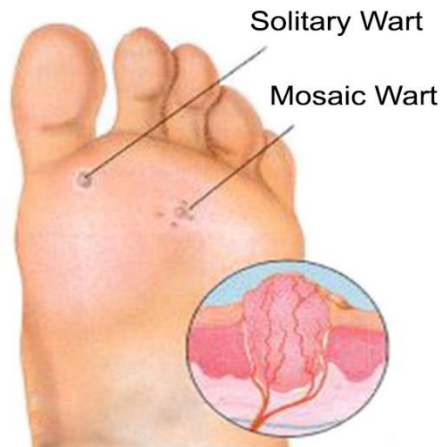
Papovaviridae (Papillomavirus):

- Small non-enveloped , icosahedral nucleocapsids dsDNA.
- Over seventy types of human papilloma viruses currently recognized.
- All human papillomaviruses induce hyperplastic epithelial lesions, infecting either cutaneous (keratinizing) or mucosal (squamous) epithelium.
- The HPVs within each of these tissue-specific groups have varying potentials to cause malignancies.
- Transmissible through direct contact with infected individuals or contaminated surfaces .
- Papilloma – benign, squamous epithelial growth, wart.

Papovaviridae (Papovaviruses):

- Common seed warts – on fingers, etc.
- Plantar warts – on soles of feet.
- Genital warts – prevalent STD.
- Incubation – 2 weeks – more than a year.

Plantar warts



Papovaviridae (Papillomavirus):

Treatment:

- Cutaneous warts generally require surgical removal or destruction of the wart tissue with liquid nitrogen, laser vaporization, or cytotoxic chemicals.
- **Interferon**, given orally, is effective in causing regression of laryngeal papillomas. **When injected directly into genital warts,** interferon is effective in about half of the patients.
- Cidofovir is also effective as a topical application.

Prevention:

- Two vaccines are available to prevent infection with high-risk HPV types.

Adenoviridae:

- Double –stranded ,linear DNA.
- Nonenveloped, Icosahedral .
- Replicates in nucleus, killing host cell.

Adenoviruses causes:

- Respiratory tract diseases.
- Ocular Diseases.
- Gastrointestinal diseases.

Paramyxoviridae:

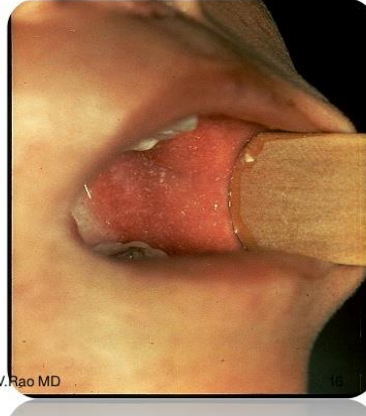
- Negative strand RNA.
- Envelope contain **F** (for fusion)**protein** that allows virus to enter cells via a fusion process, rather than by receptors-mediated endocytosis.
- Measles virus.
- Mumps virus.
- Respiratory syncytial virus.

Measles virus:

- Measles virus is transmitted by sneeze or cough-produced respiratory droplets.
- The virus is extremely infectious, and almost all infected individuals develop a clinical illness.
- Measles virus replicates initially in the respiratory epithelium, and then in various lymphoid organs.
- Classic measles begins with a prodromal period of fever, upper respiratory tract symptoms (cough and coryza), and conjunctivitis.
- Two to three days later, Koplik spots develop in the mouth and throat, and a generalized macular rash appears, beginning at the head and traveling slowly to the lower extremities.

Koplik spots**Koplik Spots leading clue to Measles**

- Within 2-3 days, the pathognomonic Koplik spots typically arise on the buccal, gingival, and labial mucosa



Dr. T.V. Rao MD

Measles virus:

- Soon after the rash appears, the patient is no longer infectious.
- A rare complication occurring within 2 weeks after the onset of the rash is post-infectious encephalomyelitis, an autoimmune disease.
- Children are particularly susceptible, especially those weakened by other diseases or hunger.

Treatment:

- No antiviral drugs are available for measles.

Prevention:

- A live, attenuated measles vaccine is available and is usually administered in the form of the measles-mumps-rubella (MMR) vaccine.

Measles**Mumps****Rhabdoviridae:**

- Single –stranded ,non segmented RNA genome.
- Virus bullet shape.
- Rabies virus.
- Causes Rabies.
- Once an individual has clinical symptoms of rabies there is no effective treatment.

Retroviridae:

- Single –stranded , linear RNA.
- Viral envelope contains glycoprotein that undergoes genetic variation.
- Human immunodeficiency virus (HIV).
- Causes Human immunodeficiency virus infection.

Transmission occurs mainly by one of the three route:

- 1-sexually.
- 2-blood or blood products.
- 3-perinatally (either transplacentally , during passage through the birth canal , or in breast feeding).

Human immunodeficiency virus (HIV):

- HIV enters the cell by fusion of the virus envelope with the plasma membrane.
- The acute phase viremia resolves into a clinically asymptomatic or "latent" period lasting from months to many years. This period is characterized by persistent generalized lymphadenopathy, diarrhea, and weight loss.

Treatment:

- Inhibitors of viral reverse transcriptase.
- Inhibitors of the viral protease delay the production of progeny virus.
- Because administering combinations of these drugs delays the appearance of resistant mutants, 3 or 4 drugs are given at the same time.

Prevention:

- No vaccine is available.
- Perinatal transmission can be reduced with zidovudine (AZT) therapy of the pregnant woman, followed by several weeks of AZT to the newborn.

Prevention:

- Can be achieved by screening blood and tissues prior to transfusion or transplant.
- Using condoms during sexual intercourse, and strict adherence to universal precautions by health care workers.

Flaviviridae:

- Positive-strand ,non-segmented RNA genome.
- Enveloped, icosahedral nucleocapsid.
- Virion do not contain any enzyme.

Hepatitis C Viruses:

- Transmission is via:
 - **blood through transfusion.**
 - **intravenous drug use.**
 - and renal dialysis treatment.**
 - also there is evidence for sexual transmission.**
- Replication occurs in the hepatocyte also in mononuclear cells(lymphocytes and macrophages).
- Causes destruction of liver cells.
- The majority of infections with HCV are subclinical ,but 25%of infected individuals present with acute hepatitis including jaundice.
- A significant proportion of infections progress to **chronic hepatitis** and **cirrhosis** and may go on to develop **hepatocellular carcinoma**.

Orthomyxoviridae:

- Negative stranded RNA genome.
- Spherical ,enveloped ,pleomorphic virus.
- Virion has two types of membrane protein spikes, H protein(hemagglutinin)and N protein (neuraminidase).
- Virion contains RNA polymerase.
- **Influenza** is spread by respiratory droplet , and is an infection solely of the respiratory tract.
- There is rarely viremia ,or spread to other organ systems.

Influenza virus:

- Influenza viruses are classified as types A, B, and C, depending on the antigenicity of their inner proteins (only A and B are of medical importance).

Influenza (the flu):

- Typically, influenza has an acute onset characterized by chills, followed by a high fever, muscle aches, and extreme drowsiness.
- The disease runs its course in 4 to 5 days, after which there is a gradual recovery.
- The most serious problems, such as pneumonia, occur in the very young, older adults, and people with chronic cardiac or pulmonary disease, or who are immunodeficient.
- Reye's syndrome (a rare but serious condition causes swelling in the liver and brain in children).

Treatment:

- Amantidine and Rimantidine prevent the influenza virus from uncoating.

Prevention:

- A vaccine consisting of formalin-inactivated influenza virus is available.
- Given before the onset of symptoms, Amantidine and Rimantidine can also prevent disease, and are useful for treating high-risk groups.

Picornaviridae:

- Positive –strand ,single stranded, nonsegmented RNA genome.
- Nonenveloped, icosahedral.
- Virion do not contain any enzymes.

Coxsackievirus:

- **Hepatitis A virus (HAV)** is a member of the genus hepatovirus.
- **Poliovirus** (member of the genus enterovirus).
- Infection with poliovirus by ingestion of contaminated food or water
- Polioviruses cause poliomyelitis.

Hepatitis A virus (HAV):

- Is a member of the genus Hepatovirus .
- Transmission is by the fecal–oral route, and the virus is shed in the feces.
- Hepatitis A (“infectious hepatitis”).
- The main site of replication is the hepatocyte, where infection results in severe cytopathology, and liver function is severely impaired.
- The prognosis for patients with HAV is generally favorable.

Treatment:

- Immune globulin is used as postexposure prophylaxis.

Togaviridae:

- Positive-stranded, single stranded ,non-segmented RNA genome
- Enveloped ,icosahedral nucleocapsid
- Virion do not contain any enzyme
- Transmission via respiratory secretions from infected individual
- Rubella virus
 - German measles.
 - Congenital rubella.
 - No antiviral drugs are presently in use.