USMLE

Step 1 lecture Notes

2019 Edition

Microbiology and Immunology

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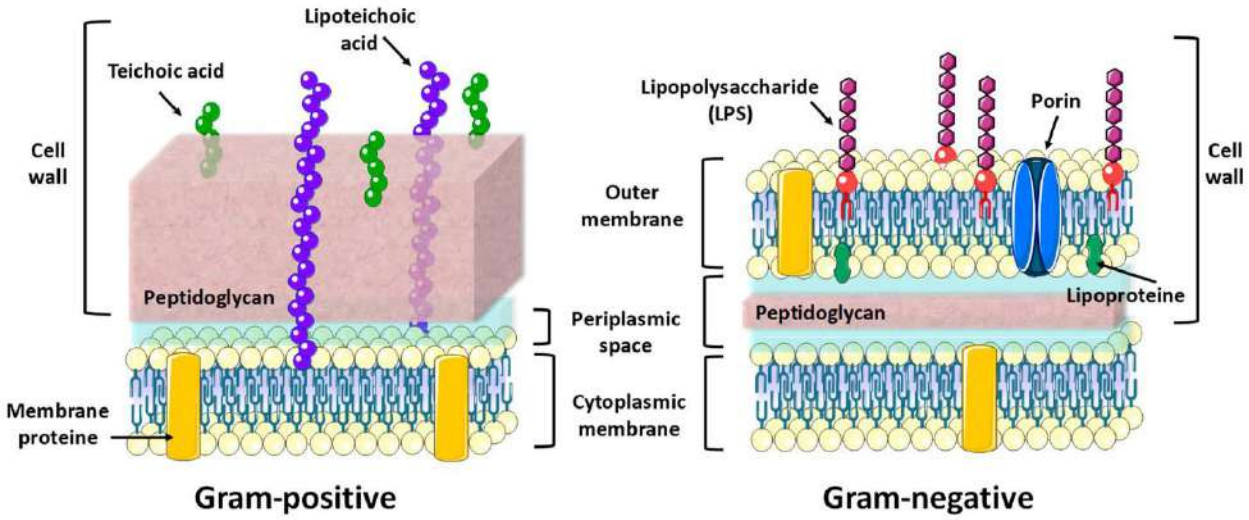
Microbiology Notes

Bacterial cell wall

Outline:

- Gram positive VS gram negative cell wall
- Peptidoglycan
- Lipoteichoic acid
- Periplasm
- Lipopolysaccharide
- Bacterial capsule
- Pilus and fimbriae
- Flagellum
- Plasmids

Gram positive VS gram negative cell wall



Structure	Gram positive	Gram negative
Lipoteichoic acid	Present	Absent
Peptidoglycan layer	Thick multilayer	Thin (single layer)
Periplasmic membrane	Absent (rarely seen)	Obvious
Outer membrane	Absent	Present

Porins	Absent	Present
Lipopolysaccharide	Absent	Abundant
Flagella	Present	Present
Toxins	Exotoxin	Endotoxin and Exotoxins
Capsule	Present	Present

Peptidoglycan

- Composed of amino acids and glucose
- Involved in binary fission during bacterial cell reproduction
- Transpeptidase enzyme that cross-links the peptidoglycan chains to form rigid cell walls
- Protects again osmotic pressure damage

Lipoteichoic acid

- Found in gram positive bacteria
- Help maintain cell wall rigidity
- Has antigenic properties being able to stimulate specific immune response.
- Produce IL1 and tumor necrosis factor (TNF)
- IL1 causes release of endogenous pyrogen
- Increase functional chemokine secretion
- Inhibits lipopolysaccharide-induced adhesion molecule expression

Periplasm

- The space between the inner and outer membrane in Gram-negative bacteria
- Extremely small in gram positive bacteria in comparison of gram negative
- Play several roles regarding transport, degradation and motility
- β-lactamases are located in the periplasmic space

  Note: β-lactamases cleave the amide bond in the β-lactam ring, rendering β-lactam antibiotics harmless to bacteria

Lipopolysaccharide (LPS)

- The major component of the outer layer of gram negative bacteria such as Neisseria and Haemophilus species
- Composed of O antigen, oligosaccharide and Lipid A
- Lipid A responsible for the toxic effects of the bacteria
- In cases of bacterial infection, bacterial cells are lysed by host immune system leading to release of lipid A into the circulation causing fever, diarrhea and eventually fatal endotoxic shock (septic shock)

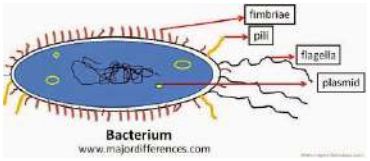
- LPS binds to several immune cells especially monocytes, dendritic cells and macrophages which promote the release of inflammatory mediators such as cytokines, Il4

Bacterial capsule

- Polysaccharide layer outside cell envelope
- When it's neatly arranged called Glycocalyx, however when it loses its integrity called Slim layer
- Quellung reaction used to visualize capsule under the microscope (anti-capsular serum)
- Considered one of the virulence factors of the bacteria, it prevents phagocytosis and inhibit bacterial engulfment by macrophages
- Examples:
- Even- E. coli
- Some- Strep Pneumonia
- Pretty- Pseudomonas aeruginosa,
- Nasty- Neisseria meningitis
- Killers- Klebsiella pneumonia
- Have- Haemophilus influenza
- Shiny- Salmonella typhi
- Bodies- Group B Strep

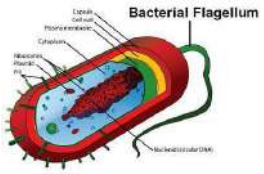
Pilus and fimbriae

- Required for bacterial conjugation
- Bacteria attach to the pili to start the reproduction cycles
- Fimbriae is required by the bacterial to produce biofilm



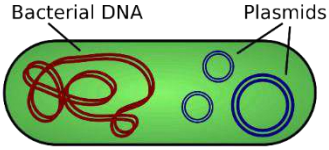
Flagellum

- Protein structure used for bacterial motility



Plasmid

- Circular DNA found in bacterial cytoplasm
- Carry genes which are essential for bacterial resistance against antibiotics



References:

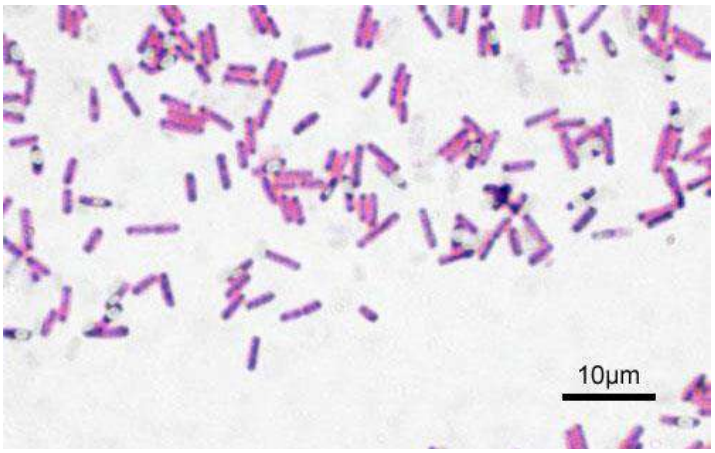
- Mesoporous Silica Materials as Drug Delivery: "The Nightmare" of Bacterial Infection. Review. Journal of Pharmaceutics 2018

- The Bacterial Cell Envelope. Cold spring harbor perspective in biology. 2010

Bacterial Morphology

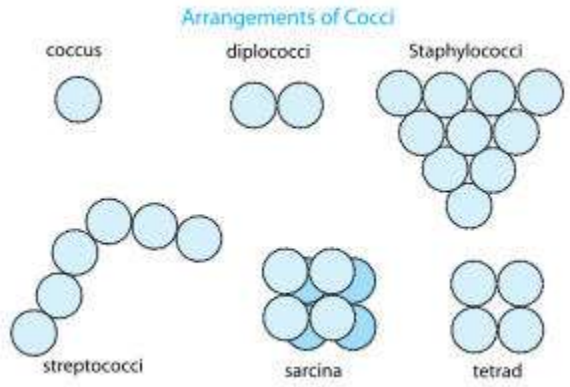
Bacilli:

Gram Positive	Gram Negative
Clostridium	E. Coli
Bacillus	Enterobacter
Listeria	Proteus
Mycobacterium	Salmonella
	Pseudomonas
	Yersinia
	Legionella
	Shigella
	Klebsiella
	Helicobacter
	Vibrio
	Pseudomonas



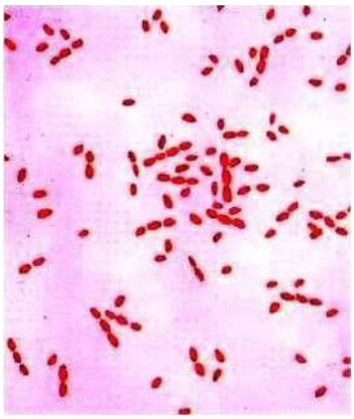
Cocci:

- Diplococci (e.g. Streptococcus pneumoniae and Neisseria gonorrhoeae*)*
- Streptococci (e.g. Streptococcus pyogenes).
- Staphylococci irregular (grape-like) clusters of cocci (e.g. Staphylococcus aureus).



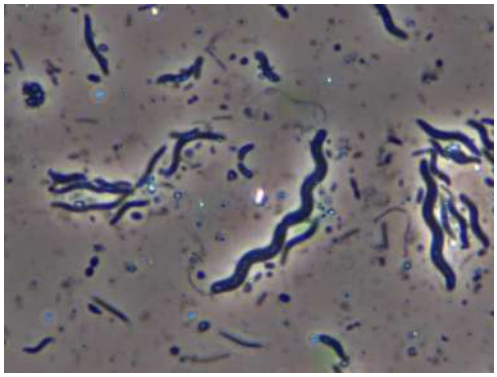
Coccobacilli:

- A type of bacterium with a shape intermediate between cocci (spherical bacteria) and bacilli (rod-shaped bacteria).
- Examples: Haemophilus influenzae, Gardnerella vaginalis, and Chlamydia trachomatis



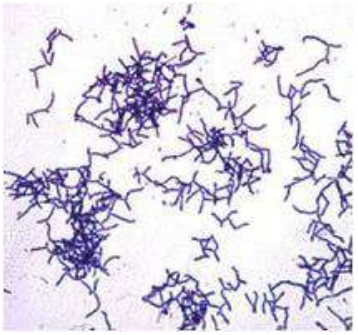
Spirilla:

- large, elongate, spiral shaped, rigid cells
- Gram-negative, curved and spiral-shaped bacteria found in stagnant, freshwater environments
- Some species cause rat bite fever
- Examples: Borrelia, Treponema, Leptospira, Spirillum



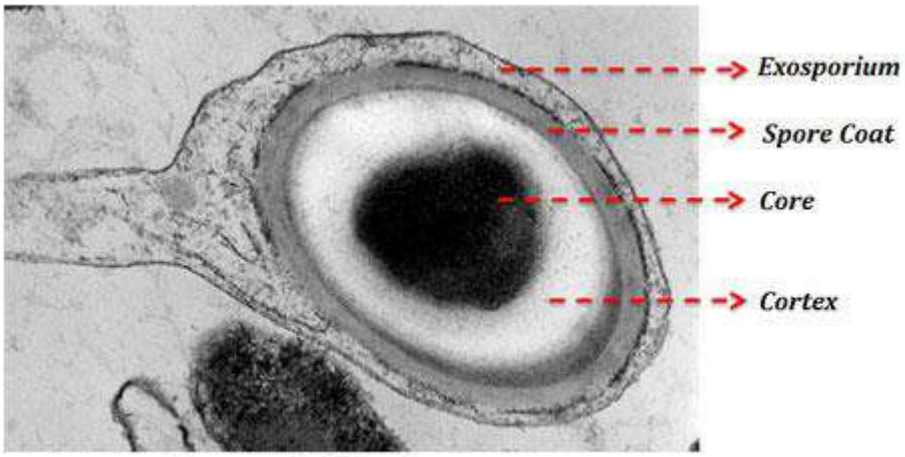
Branching filaments:

- Called filament form the appearance of branching when two filaments attach to one another.
- Actinomycetes, Norcardia



Endospore producing bacteria:

Examples: Bacillus anthrax and clostridium perfringes



Bacterial Endospore

Stains and special culture requirements

Outline:

- Principle of bacterial staining
- Gram stain
- Giemsa stain
- Periodic acid Schiff stain Treatment
- Ziehl nelson staining (carbol fuchsin)
- India ink
- Silver Ink

Principle of bacterial staining:

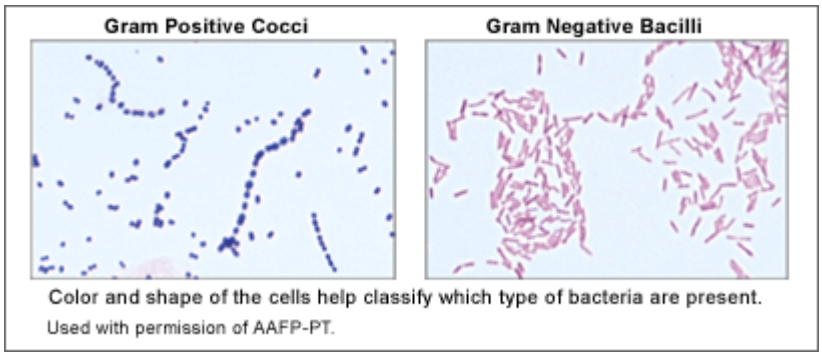
- Basic stain: stain -**ve** charged molecules in the bacterial **cell surface**
- Acidic stain: stain **+ve** charged molecules in the bacterial **Capsule**

Gram stain

- Method used to differentiate between gram positive and gram-negative bacteria
- Depends on the composition of the cell wall

Principle:

- By addition of crystal violet, all bacteria appear violet
- Addition of iodine form crystal violet iodine complex (crystals)
- Addition of acetone/alcohol: Bacteria with **thick peptidoglycan cell wall** become dehydrated and retain the crystal violet iodine complex (violet), however, bacteria with **thin peptidoglycan layer** unable to retain these crystals (appear pink)
- Safranin (counterstain) stain gram negative bacteria (red)



Poor staining bacteria:

- Treponema (thin to be detected)
- Mycobacteria (high lipid cell wall content)
- Mycoplasma (without cell wall)

- Legionella, Rickettsia, Bartonella, Anaplasma and Ehrlichia (intracellular bacteria)
- Chlamydia atypical cell wall due to decrease muramic acid (intracellular)

Giemsa stain

- Method used to detect phosphor group on the DNA
  Help to identify intracellular parasites plasmodium,trapanosoma, histoplasma, chlamydia

Periodic acid Schiff stain (PAS):

- Method used to detect polysaccharide (**sugar**) such as glycogen, glycoprotein and Proteoglycan (signaling molecules at surface)
- Used to stain macrophages in whipple's disease
- Whipples's disease: Bacterial infection caused by Tropheryma whipplei

Ziehl nelson staining (carbol fuchsin)

- Known as acid fast stain
- Used to differentiate between acid fast (Mycobacterium) and non-acid fast (Norcardia)
- Acid-fast bacteria retain carbol fuchsin, so they appear red.

India ink

- Used for negative staining and encapsulated organisms
- Visualize in dark background
- Used for identification of Cryptococcus neoformans (Large polysaccharide capsule)

Silver ink (Gomori's Methenamine silver stain GMS)

- Method used to stain fungi and bacteria.
- The fungi and bacteria are turned black, while everything else is stained green with Light green SF solution.
- Chromic acid oxidation forms aldehydes from fungal cell wall mucopolysaccharide components
- Fungi (Coccidioides E , Pneumocystis jirovecii)
- Bacteria (Legionella, Helicobacter pylori)

References:

- Microbial life educational resources
- First aid 2018
- Crush Step 1- The ultimate USMLE step 1 Review

Bacterial growth curves

Outline:

- Bacterial growth phases
- Special culture requirements

Bacterial growth phases:

Lag phase:

- The number of bacterial cells remain constant but start preparing for cell division
- Phase of metabolic activity
- Last from 0-5 hours

Exponential (log) phase:

- The number of bacterial cells increased significantly
- From 5-10 hours

Stationary phase

- Bacterial growth reaches steady state, the number of new cells produced balances the number of cells that die
- Most of culture nutrients are consumed resulting in accumulation of metabolites
- Lasts more than 10 hours

Death phase

- Occur when incubation period exceeds stationary phase
- The culture medium lacks nutrients hence bacteria die
- Viable count: the number of actively growing/dividing cells in a sample

Special culture requirements:

- **Chocolate blood agar**:
  - ❖ contain red blood cells which have been lysed at 80 C
  - ❖ Contain also factor V NAD and factor X hemin
  - ❖ Used to isolate Haemophilus influenza and Neisseria meningitis

- **Thayer Martin Media (VPN):**
  - ❖ Entails 3 different antibiotics
  - ❖ Vancomycin: to cover gram positive bacteria
  - ❖ Polymyxin: to cover gram negative bacteria
  - ❖ Nystatin: to kill fungi
  - ❖ Used to isolate Neisseria gonorrhea and meningitis

- **Bordet-Gengou agar:**
  - ❖ Contain blood, potato extract, and glycerol, with an antibiotic such as cephalexin or penicillin
  - ❖ Used to isolate Bordetella Pertussis

Tellurite plate, Loffler's media:

- Used to isolate Diphtheria and Clostridium

Lowenstein Jensen Agar:

- Used to isolate mycobacterium Tuberculosis

Eaton's Agar:

- Used to isolate Mycoplasma Pneumonia

Charcoal yeast agar:

- Used to isolate Legionella

Sabouraud agar:

- Used to isolate Fungi

MacConkey agar

- Used to isolate gram negative and enteric bacilli based on lactose fermentation
- Used to isolate detection of E. coli 157:H7.

Type of culture	Uses
• Chocolate blood agar	• Haemophilus influenza and Neisseria meningitis
• Thayer Martin Media	• Neisseria gonorrhea and meningitis
• Bordet-Gengou agar	• Bordetella Pertussis
• Tellurite plate, Loffler's media	• Diphtheria and Clostridium
• Lowenstein Jensen Agar	• Mycobacterium Tuberculosis
• Eaton's Agar	• Mycoplasma Pneumonia
• Charcoal yeast agar	• Legionella
• Sabouraud agar	• Fungi
• MacConkey agar	• E. coli 157:H7

References:

- Current and Past Strategies for Bacterial Culture in Clinical Microbiology. Journal of Clinical microbiology reviews, 2015
- First aid 2018

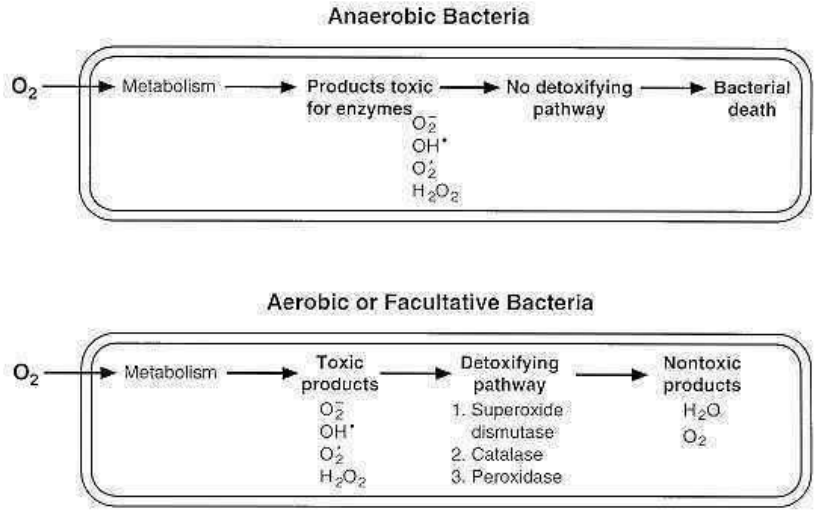
Obligate Aerobes and Anaerobes

Outline:

- Overview
- Aerobes
- Anaerobes

Overview:

- Bacterial metabolism of oxygen yields superoxide radicals which are toxic to the cells, only bacteria containing enzymes (**catalase, peroxidase, superoxide dismutase**) can survive in the presence of oxygen



- Based on bacterial **oxygen requirements**, bacteria could be **divided** into:

1. Aerobes:

- Could survive in ambient air and can't grow in its absence

1.1. Obligate aerobes:

- Absolute dependent on oxygen for survival (ATP production)
- Lack of fermentation process
- Nocardia - pulmonary infection in immunosuppressed patients
- Pseudomonas- common in burns, diabetic wounds, pneumonia (cystic fibrosis)
- Mycobacterium tuberculosis causes fever, weight loss, cough
- Bacillus

2. Anaerobes

2.1. Obligate anaerobes:

- Can't survive in the presence of oxygen (oxygen is toxic for them)
- Lack catalase and superoxide dismutase
- Clostridium, Actinomyces and Treponema

2.2. Facultative anaerobes

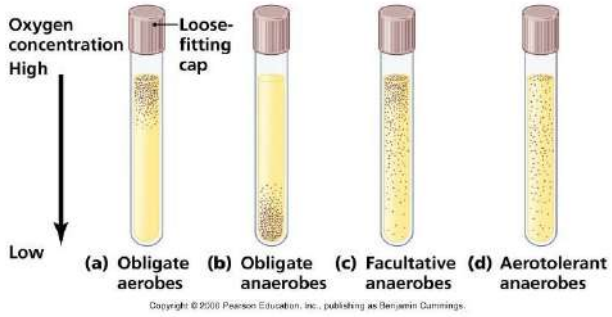
- Versatile bacteria which could grow under both aerobic and anaerobic conditions.
- Energy production through aerobic respiration or fermentation process
- Staph, E.coli, Listeria vibrio, Salmonella, Shigella, Klabsella

3. Microaerophiles:

- Could grow under reduced oxygen concentration, prefer fermentation for energy production
- Jars or bags might be a possible environment for these bacteria.
- Streptococcus pyogenes, H. Pylori, Borrelia and Campylobacter.

4. Aerotolerance bacteria:

- Anaerobic bacteria that could survive in presence of oxygen but can't use oxygen for energy production



Classification	Characteristics	Examples
Obligate aerobes	• Require oxygen • Produce superoxide dismutase	• Nocardia • Pseudomonas • M.Tuberculosis • Bacillus
Obligate anaerobes	• Cannot survive in oxygen • Lack catalase and superoxide dismutase	• Clostridium • Actinomyces • Treponema
Facultative anaerobes	• Could grow under both aerobic and anaerobic conditions.	• Staph • E.coli • Listeria vibrio • Salmonella • Shigella • Klebsiella
Microaerophilic	• Could grow under reduced oxygen concentration	• Streptococcus pyogenes • H. Pylori, Borrelia • Campylobacter
Aerotolerance	• Anaerobic bacteria survive but can't use oxygen	

References:

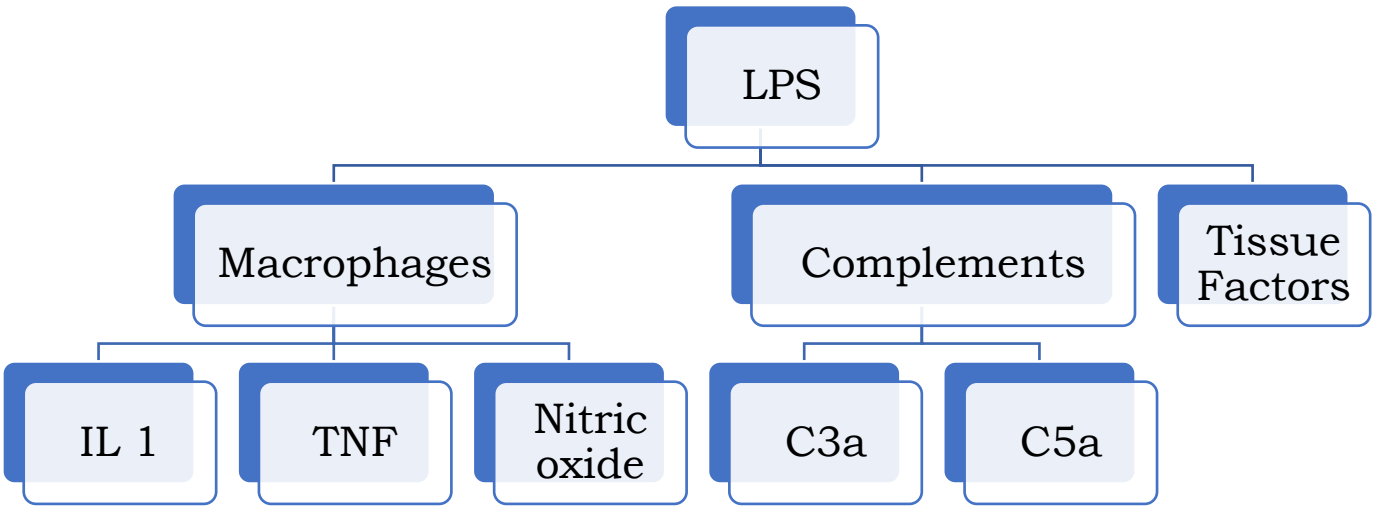
- First aid 2018
- Medical microbiology 4th edition, Chapter 17Anaerobes: General Characteristic

Bacterial Endotoxin

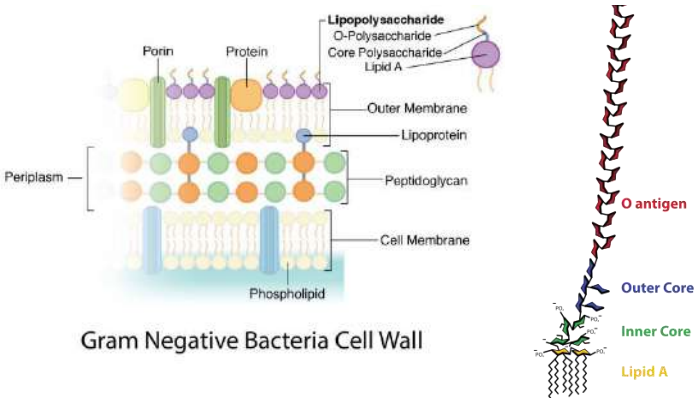
Outline:

- Overview
- Effects of endotoxins

Overview:



- Produce by gram negative bacteria
- Endotoxin upregulates TNF-α, IL-1 and IL-6, complement and coagulation pathways
- Lipopolysaccharide (LPS): The major component of the outer layer of gram negative bacteria such as Neisseria and Haemophilus species
- Composed of O antigen, oligosaccharide and Lipid A
- Lipid A responsible for the toxic effects of the bacteria
- In cases of bacterial infection, bacterial cells are lysed by host immune system leading to release of lipid A into the circulation causing fever, diarrhea and eventually fatal endotoxic shock (septic shock)
- LPS binds to several immune cells especially monocytes, dendritic cells and macrophages which promote the release of inflammatory mediators such as cytokines, Il4

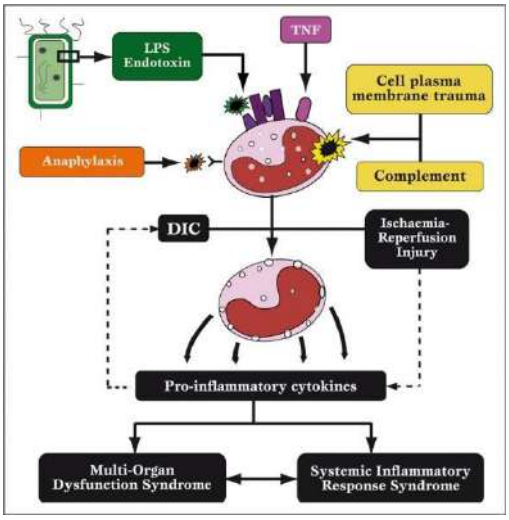


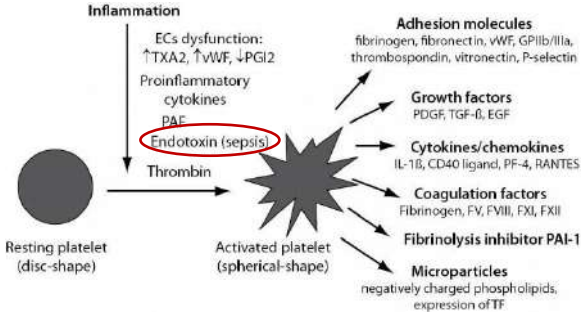
Effects of Endotoxins:

- Endotoxin initiate liver released Il4 which causes fever
- TNF is one of the main cytokines responsible for septic shock
- TNF induces vasodilation and loss of vascular permeability and eventually leads to hypotension
- Nitric oxide a potent vasodilator -hypotension
- Hypotension is usually associated with reflex tachycardia
- Reflex tachycardia ↓Co= ↑HR X SV↓

Note: During septic shock the heart attempts to compensate by working harder, increasing the heart rate and the amount of blood pumped. Eventually, the bacterial toxins and the increased work of pumping weaken the heart. As a result, the heart pumps less blood, and vital organs receive even less blood.

- Endotoxins activates the complement system (Anaphylatoxins C3a,5a) which lead to increase vascular permeability, swelling and neutrophil chemotaxis.
- LPS acts on platelets and causes disseminated intravascular coagulation (DIC) leading to ischemic damage to various organs e.g brain (encephalopathy), Kidney (renal failure), Heart (cardiac arrest).





E-Endotoxin

N-Nitric oxide

D-DIC/death

O-Outer membrane

T-TNF-alpha

O-O antigen

E-Extremely heat stable

I-Il-1

N-Neutrophil chemotaxis

References:

- Complexity of complement activation in sepsis. Journal of Cellular and Molecular medicine 2008.
- Cytokines in the systemic inflammatory response syndrome: A review.2010

Bacterial Exotoxin part 1

Outline:

- Overview
- Category of Exotoxins
- Superantigen
- Bacteria produces Superantigen
- Different toxins produced by Staphylococcus aureus
- Different toxins produced by Streptococcus pyogenes

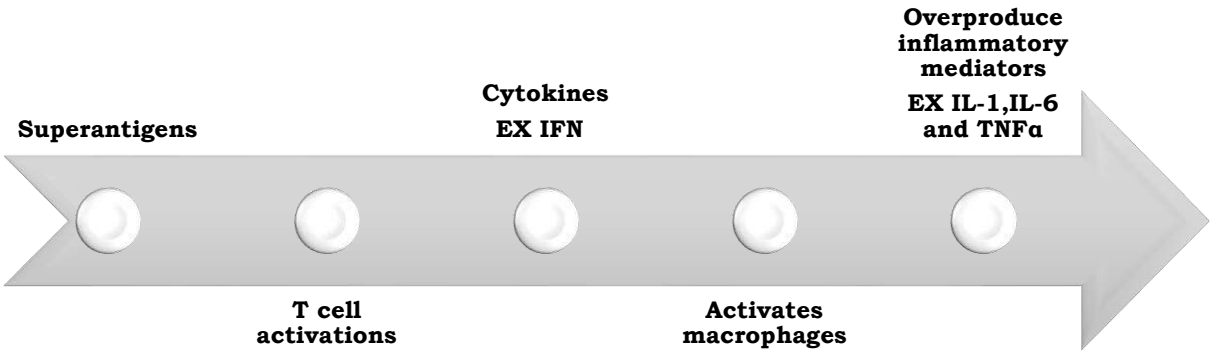
Overview

- Exotoxins are produced inside most of gram positive bacteria
- Exotoxins are secreted and causing severe damage to the tissues
- The genes of most of exotoxins are carried inside plasmids
- Highly immunogenic

Categories of Exotoxins:

Superantigen

- Group of antigens which induce continuous T-cell activation leading to massive cytokine release
- Superantigens bind first to the MHC Class II on antigen presenting cells then T cell receptors
- These cascades of inflammation eventually lead to severe toxic shock



Bacteria produces Superantigen

Staphylococcus aureus:

- Produce Superantigen that causes toxic-shock-like syndrome (TSLS)
- The most common toxin is TSS toxin type-1 (TSST-1)
- Signs and symptoms:
- Fever
- Rash
- Hypotension
- Skin peeling
- Desquamation, typically of the palms and soles

Mechanism of shock:

- The patient first subjected to Staph infection
- Untreated infection progresses to systemic infection especially in patients lacks protective antitoxin antibody
- Once the infection reached the blood circulation, the toxin will trigger cytokines release (IL-1) and TNFα

Streptococcus pyogenes (Erythrogenic toxin):

- Named as streptococcal pyrogenic exotoxin **SPE**
- When injected intradermal into susceptible individuals produced erythematous reaction (Dick test)

- Three types of SPE (A, B, C)
- Symptoms include:
- Fever
- Shock
- Desquamation
- Rash
- Hypotension

Different toxins produced by Staphylococcus aureus:

Alpha toxin

- Pore-forming toxin
- Has cytotoxic effect
- Create unregulated pores in the membrane of targeted cells

Beta toxin

- Produce an enzyme called sphingomyelinase C which is toxic to many cell types including macrophages, leukocytes, fibroblasts and erythrocytes

Gamma toxin

- Comprises two non-associated protein
- Damage leukocytes

Panton-Valentine leucocidin

- Cytotoxin
- Associated with increased virulence of certain strains
- Associated with community-associated Methicillin-resistant staphylococcus aureus (CA-MRSA)
- Causes necrotic hemorrhagic pneumonia

Enterotoxin

- Heat stable toxin
- Associated with food poisoning and traveler's diarrhea

Exfoliative toxins (Disambiguation)

- Associated with staphylococcus skin scalded syndrome (SSSS)

Different toxins produced by Streptococcus pyogenes

Streptolysin O

- **Immunogenic**
- Oxygen labile
- Hemolytic (hemolysis of red blood cells)
- Anti-streptolysin O titer used to measure streptolysin O antibodies levels for the diagnosis of scarlet fever and rheumatic fever

Streptolysin S

- **NOT Immunogenic**
- Cardiotoxic

Pyogenic exotoxin A, B, C

- Causative agent of scarlet fever and toxic shock syndrome

References:

- Superantigens, an verview

https://www.sciencedirect.com/topics/immunology-and-microbiology/superantigen

- Neutrophils in innate host defense against Staphylococcus aureus infections. 2011
- First aid 2018

References:

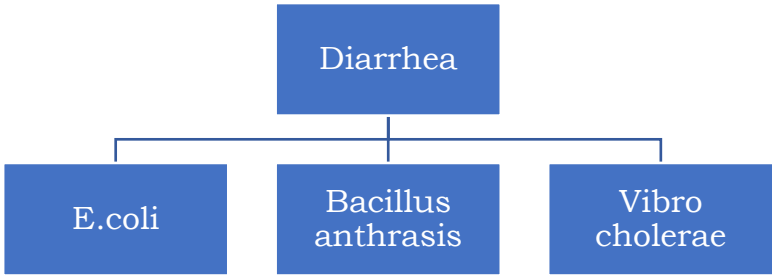
- Crush Step 1- The ultimate USMLE step 1 Review

Bacterial Exotoxin part II

Outline:

- Toxins increase fluid secretion in the gut
- Protein synthesis inhibition toxins
- Neurotransmitter release inhibitors toxins

Toxins increase fluid secretion in the gut:



E coli:

- **Enterotoxigenic E. coli** causes Traveler's diarrhea
- Enterotoxins produced by ETEC include heat-labile enterotoxin (LT) and heat-stable enterotoxin (ST).

Heat stable enterotoxin

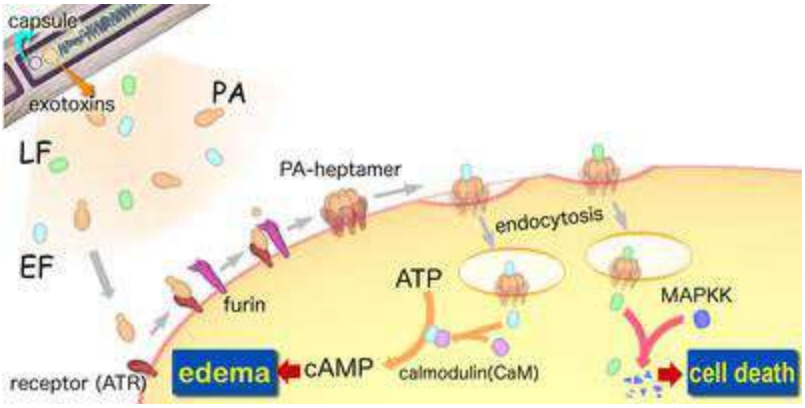
- Heat labile toxin (AB toxin) similar to cholera toxin
- The toxin activates adenylate cyclase-↑ cAMP-Increased chloride secretion (Secretory or watery diarrhea)
- LT composed of A and B components
- The A component is enzymatically active, and the B component is the cell binding component.

Heat labile Enterotoxin

ADP-ribosylation of the alpha-subunit of a Gs protein → Activate adenylcyclase → ↑cGMP → Secretion of chloride ions and water from the enterocyte into the gut lumen.

Bacillus Anthracis (Anthrax)

- Causes Anthrax (Cutaneous anthrax)
- Cutaneous anthrax characterized by necrotic, black eschar
- Produce **Edema Toxin** which increase fluid secretion and lead to neutrophils dysfunction
- Edema toxin is a lethal toxin leads to cell death



Vibrio Cholerae:

- Produce **Cholera Toxin** that causes ↑cAMP (Increase NaCl secretion and H_2O efflux)
- Characterized by watery diarrhea named as rice-water stool
- Hypersecretion of electrolytes and water

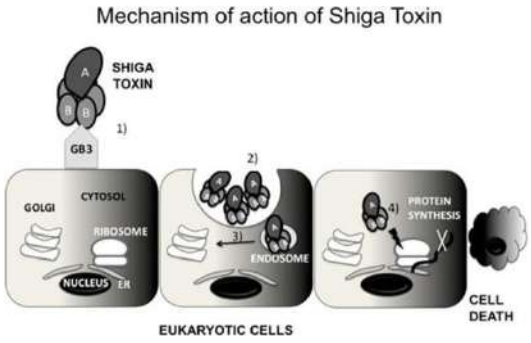
Yersinia Enterocolitica

- Causes diarrhea, enterocolitis
- Acute terminal ileitis (Pseudo corhn disese)
- Right quadrant pain RLQ (**pseudo appendicitis**)
- Yersinia stable toxin -↑ CAMP that lead to diarrhea
- Invade mucosal wall causing bloody diarrhea

Protein synthesis inhibition toxins:

Shigella species:

- Penetrate through mucosal surface of colon and invade intestinal epithelium releasing shiga toxin
- Shiga toxin inhibits protein synthesis (inactivate 60S ribosome) which lead to GI mucosal damage-**dysentery**
- Shiga toxin enhances cytokine release causing hemolytic uremic syndrome (HUS)
- Associated with diarrhea and severe dehydration

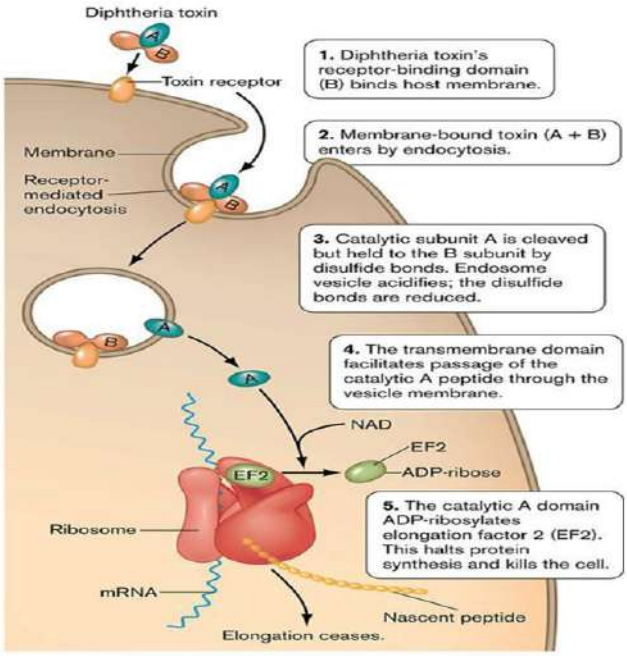


Enterohemorrhagic E. coli 0157:H7:

- Produce shiga like toxin
- Causes hemorrhagic colitis
- **Bloody diarrhea**
- Bind to epithelial cells and produce shiga like toxin that block protein synthesis causing cell death
- Considered as foodborne infection (undercooked or contaminated food commonly associated with **Burger**)
- Associated with Hemolytic uremic syndrome **HUS characterized by** progressive renal failure, hypotension, hemolytic anemia, ↑ LDH and uremia

Corynebacterium Diphtheria:

- Causes **Pseudomembranous pharyngitis** (grayish white membrane)
- Produce Shigella toxin
- Shigella toxin composed of 2 fragments:
    1. Toxin A: which is responsible for toxin activity
    2. Toxin B: Receptor binding domain which binds to Epidermal growth factor (EF-2) leading to cardiac and cranial nerve deficits
- Mechanism of action depend on releasing an exotoxin (Toxin A) which inhibit adenosine diphosphate (ADP) ribosylation of EF-2 which eventually inhibit protein synthesis



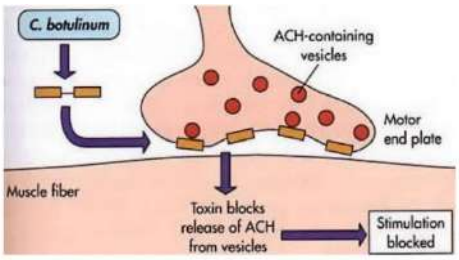
Pseudomonas aeruginosa

- **Exotoxin A** is responsible of tissue necrosis. Inhibit protein synthesis by inhibition of elongation factor-2 through ADP-ribosylation of EF2.
  - Exotoxin A composed of A and B components
  - The A component is enzymatically active, and the B component is the cell binding component.

Neurotransmitter release inhibitors:

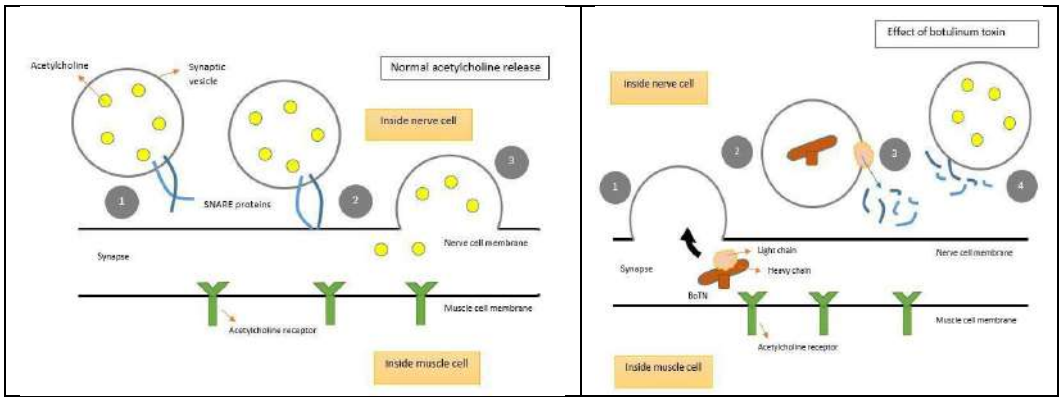
Clostridium Tetani:

- Clostridium tetani infect the patient at the wound site and release tetanus toxin
- Tetanus toxin induce tetanic paralysis
- **MOA**: Inhibits the release of Inhibitory neurotransmitters such as GABA and glycine from interneurons leading to lack of inhibition (continuous activation or muscle contraction)
- The patient suffers from sustained muscle contraction in the jaw (trismus) and facial muscles (risus sardonicus)
- Opisthotonus or arching of the back



Clostridium Botulinum:

- Heat labile toxin which prevent release of acetyl choline release at neuromuscular junctions that leads to termination of paralysis causing rapid flaccid paralysis
- In adult associated with spore ingestion though canned or jarred food
- In babies associated with floppy baby syndrome through jarred honey
- Symptoms are urinary retention and constipation, dyspnea, dysarthria, dysphagia



Clostridium Perfringes:

- Attack soft tissues and wound, associated with Gas gangrene by producing enterotoxins (α toxin)
- α-toxin hydrolyses and cleaves phospholipid C and diacylglycerol leads to myonecrosis
- Could survive in undercooked food leads to food poisoning
- Diagnosis through blood culture (**double zone of hemolysis**)

Bordetella Pertussis:

- Primary cause of whooping cough
- Pertussis toxin inhibit G protein coupled receptor
- Has one A subunit (toxic part) ↑cAMP and B subunit (involved in binding)

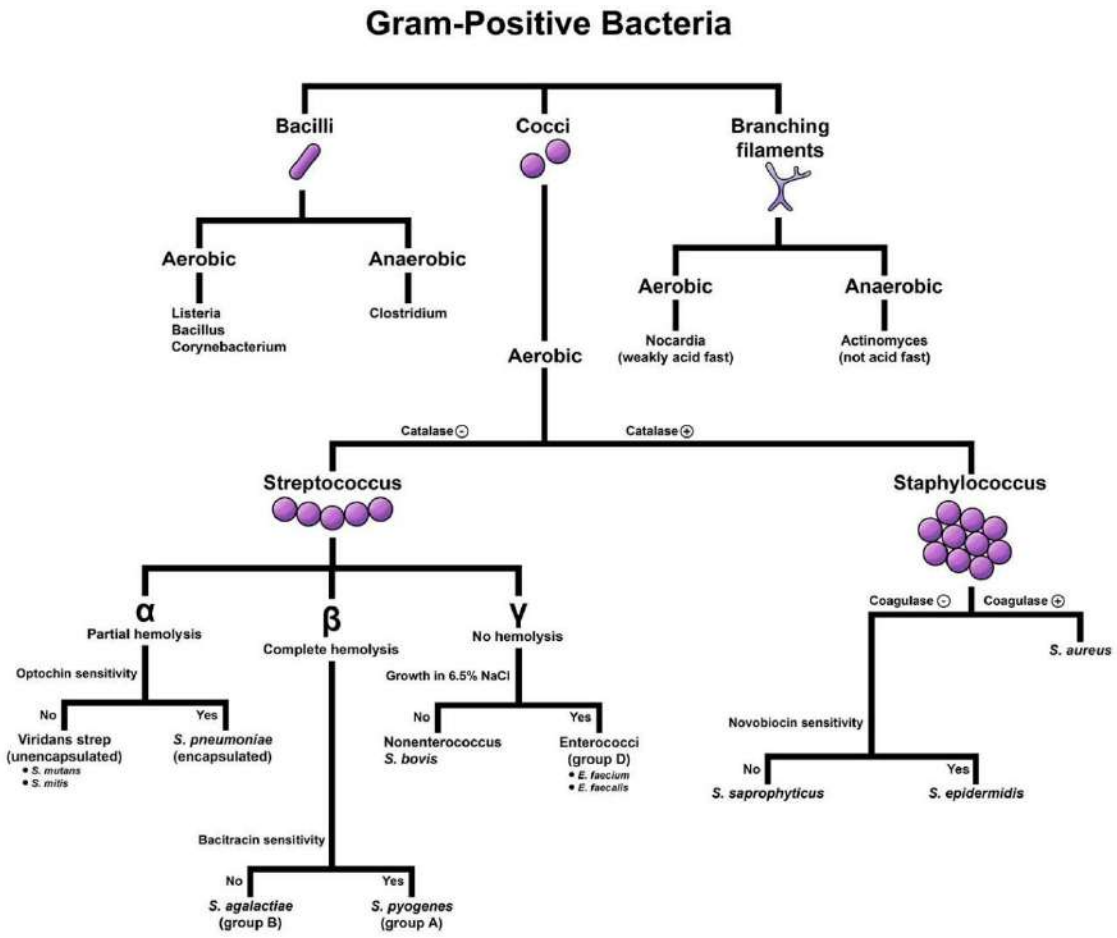
Increased cAMP associated with:

- ↑ insulin release leading to hypoglycemia
- ↑ histamine sensitization, cough and vascular permeability
- Interfere with phagocytosis of neutrophils which increase the survival of the microbe and prolong the disease.

References:

- First aid 2018
- Centers for Disease Control and Prevention [CDC]. (2014). Botulism. Retrieved from http://www.cdc.gov/nczved/divisions/dfbmd/diseases/botulism/#treat
- Crush Step 1- The ultimate USMLE step 1 Review.

Clinical bacteriology:



Catalase test:

- Used to test the presence of catalase enzyme in the bacteria
- It's an essential test to differentiate between streptococcus and staphylococcus

Coagulase test:

- Used to differentiate staph. Aureus from another coagulase negative staph such as staph. Epidermis and staph. Saprophyticus
- Coagulase is an enzyme like protein which causes plasma to clot by converting fibrinogen to fibrin.

Novobiocin sensitivity test:

- Novobiocin resistance is intrinsic to staph. Saprophyticus ONLY
- Used to differentiate between coagulase negative Staphylococci

Hemolysis test:

- Differentiated test for hemolytic reaction
- Blood agar is used for this test
- Alpha α hemolysis means partially breakdown of hemoglobin (Greenish color)
- Beta is complete lysis of red blood cells
- Gamma means NO hemolysis

Optochin sensitivity test:

- Used to differentiate between Strep. Pneumonia from other alpha hemolytic streptococci
- Strepto. Pneumoniae is the only streptococcus susceptible to small concentration of the antibiotic

Bacitracin susceptibility test:

- Bacitracin is a polypeptide antibiotic derived from B. subtilis that functions to block cell wall formation by interfering with the dephosphorylation of the lipid compound that carries peptidoglycans to the growing microbial cell wall.
- Used for identification of Group A staphylococci (S. Pyogenes).

Salt tolerance test for enterococcus species:

- The ability of the bacteria to grow in high salty medium
- This test is used to identify enterococcal group D

References:

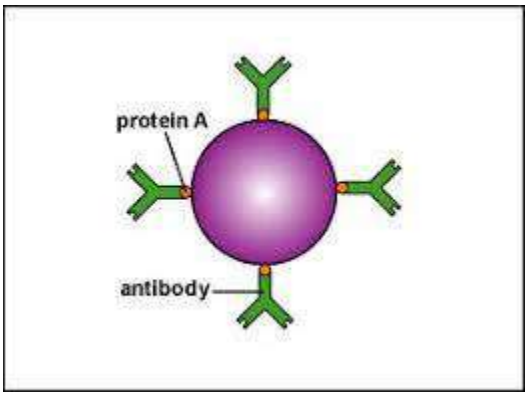
- Pharmacology and Therapeutics for Dentistry (Seventh Edition), 2017

Gram positive staphylococcus:

- Staphylococcus aureus
- Staphylococcus epidermis
- Staphylococcus saprophyticus

Staphylococcus aureus:

- Frequently found in the skin, nose and respiratory system
- Catalase and Coagulase positive
- Virulence factor (Protein A) binds to FC complex of the antibody hence prevent bacterial engulfment by macrophages (Inhibit phagocytosis)



Diseases caused by S. aureus:

- Skin infections:
  - Folliculitis (carbuncle)
  - Impetigo (baby honey crusted vesicles)
  - Wound infection-abscesses
- Pneumonia: initially started by flu, fever, coughing, shortness of breath (after influenza infection)
- Kidney: Urinary tract infection in the bladder
- Heart: Endocarditis
- Brain: meningitis
- Bones: osteomyelitis, septic arthritis
- GIT: S. aureus food poisoning diarrhea and emesis (short incubation period 2-6 hours)
- Eye: Blepharitis

MRSA: Methicillin resistant S. aureus which is responsible for nosocomial infection

Acquired resistance through **Penicillin binding protein 2A (PBP2A)** (new form created by MRSA capable of cell wall synthesis

Note: Linezolid, Daptomycin and vancomycin are common used antibiotic for more resistant strains

S. aureus toxic mediated diseases such as

- Toxic shock syndrome TSST-1 (Fever, shock, hypotension, ↑ALT, AST) Associated with prolonged used of vaginal tampons or nasal packing
- Rapid onset food poisoning (Enterotoxins)
- Exfoliative Toxin A or B scalded skin syndrome in babies (Impetigo) honey crusted vesicles
- MRSA is usually associated with Panton-Valentine leucocidin (cytotoxin)
- Panton-Valentine leucocidin is an aggressive toxin which increase bacteria's ability to infect skin

  Staphyloxanthin considered as a new virulence factor created by S. aureus to develop resistance against the immune system

Staphylococcus Epidermis:

- Found in the skin also contaminate blood clutures
- Coagulase negative and catalase positive
- Infect prosthetic devices such as hip plant, IV catheter and foley catheter through biofilm adherence
- Intravascular devices such as prosthetic heart valves and shunts
- Treatment with Vancomycin with or without Rifampin, Gentamycin

Staphylococcus Saprophyticus:

- Coagulase negative and catalase positive
- Common to appear in female genital tract (UTI)

References:

- An acquired and a native penicillin-binding protein cooperate in building the cell wall of drug-resistant staphylococci. PNAS 2001

- Panton-Valentine Leukocidin Genes in Staphylococcus aureus. Journal of emerging infectious disease 2006

Gram positive Streptococcus:

- S. Pneumoniae
- S. Virdans
- S.Pyogenes (Group A streptococci)
- S.agalactiae (Group B streptococci)
- Group D streptococci

S. Pneumoniae:

- Catalase negative
- Optochin sensitive organism
- Encapsulated cocci (quelling test)
- Alpha hemolytic
- Secrete IGA protease

Diseases caused by S. Pneumoniae:

- Meningitis (fever, headache)
- Otitis media
- Pneumonia
- Sinusitis
- Septic arthritis
- Endocarditis
- Patients without a spleen, HIV and immunocompromised patients are susceptible for overwhelming sepsis with Streptococcus pneumoniae. Prophylaxis by (Prevnar vaccine)

S. Virdans:

- Found in the oral flora and saliva
- Alpha hemolytic positive and catalase negative
- Optochin sensitivity used to differentiate between S. Pneumoniae and S.Virdans (resistant to optochin)
- Negative quelling test
- strep mutans and mitis cause dental cares
- Strep Sanguinis could cause subacute endocarditis following a dental procedure especially for damaged prosthetic heart valve

NOTE: Quelling reaction (test the presence of polysaccharide capsule) and optochin sensitivity test are used to differentiate between S. Pneumonia and S. Virdans

S.Pyogenes (Group A streptococci)

- β hemolytic positive and catalase negative

Diseases caused by S. Pyogenes:

- Skin infection like Staph. Aureus (Folliculitis, cellulitis, impetigo)
- Pharyngitis (sore throat)
- Necrotizing fascitis causes gas gangrene
- Toxic shock syndrome

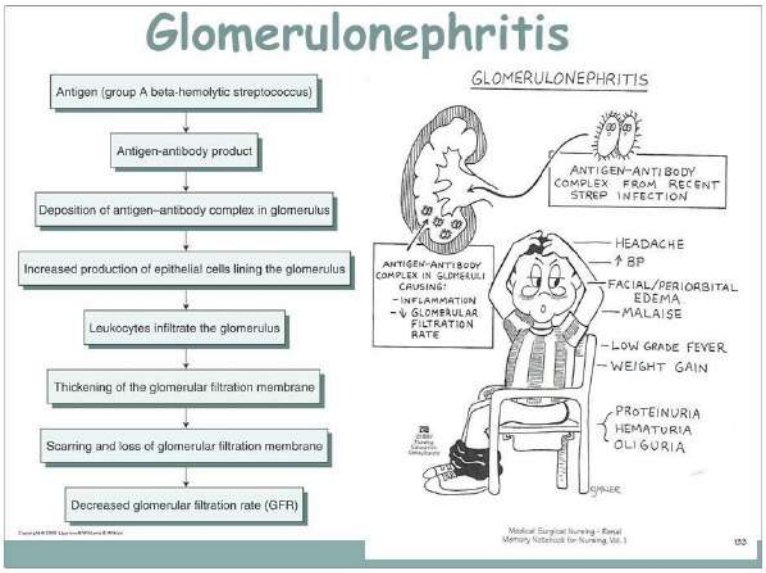
- Auto immune disorders:

Rheumatic fever:

- Common to occur in developing countries
- Cross reactivity (heart failure-Edema-myocarditis-chest pain) common children 5-15 years old
- Occurs 2-3 weeks after the patient experienced pharyngitis
- Fever
- Valvular damage
- Elevated ESR or C-reactive protein
- Red rash
- Subcutaneous nodules aschoff bodies
- Sydenham chorea
- Type II hypersensitivity reaction

Acute glomerulonephritis (Acute post streptococcal nephritis)

- Appear after a week of infection
- Tea colored urine
- Treatment by Penicillin
- Type III hypersensitivity reaction
- Hematuria (tea colored)
- Hypertension
- Edema
- Antibody–antigen complexes deposit in the glomerular basement membrane.



Virulence factors:

- ✓ Streptolysin O
- ✓ M protein (anti phagocytic)
- ✓ Anti C5a peptidase
- ✓ Streptolysin S
- ✓ Hyaluronidase
- ✓ Exotoxin
- ✓ DNase B
- ✓ Pyogenic exotoxin

- Streptolysin S & O: could rupture RBCs and WBCs
- Antibodies for streptolysin O (ASO) or anti-DNase B indicate a recent infection

Key words: Strep. Pyogenes- rheumatic fever (Type II sensitivity)-acute glomerulonephritis (Type III sensitivity)- Virulence factors

S.Pyogenes (Group B streptococci):

Streptococcus agalactiae

- Common to live in female's vagina
- Associated with infection of new born (neonatal meningitis, pneumonia and sepsis)
- Catalase negative- β hemolytic
- pregnant woman with (35-37 gestation) are tested for infection, and if positive Penicillin is given for prophylaxis

Key words: Strep. Agalactiae – inside the vagina- babes infection

Group D streptococci:

- Catalase negative-
- 4 types
- 2 are Enterococci (Enterococcus faecalis and Enterococcus faecium)
- 2 of which are not (Streptococcus bovis and Streptococcus equinus)
- Streptococcus bovis is associated with colon cancer, bacteremia and subacute endocarditis
- Enterococci:
- More resilient than streptococci, can grow in bile, NaCl 6.5%

✓ usually grow inside colon flora
✓ These species are resistant to many antibiotics
✓ Associated with nosocomial infection VRE Vancomycin resistant enterococci
✓ Associated with UTI, endocarditis and bacteremia

Keywords: Strept.bovis Colon cancer- Enterococci (nosocomial infection VRE-colon flora)

References:

- Enhanced vulnerability for Streptococcus pneumoniae sepsis during asplenia is determined by the bacterial capsule. Journal of immunobiology 2011.

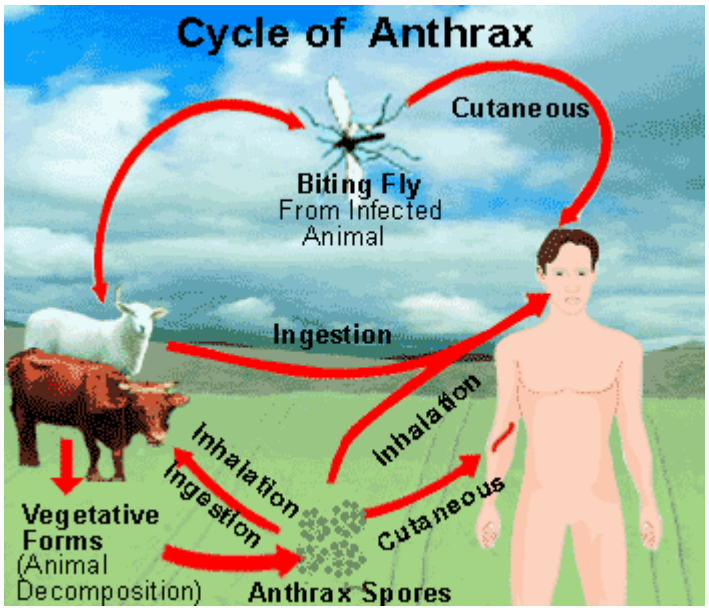
Bacillus Anthracis

Outline

- Overview
- Cutaneous anthrax
- Inhalation anthrax
- Diagnosis
- Treatment

Overview:

- Rod shape
- Gram positive encapsulated bacteria
- Only organism which has a protein capsule D-glutamate



Cutaneous anthrax:

- Anthrax is considered a disease of herbivores such as sheep, goat, horses
- Lives dormant in soil with the spores
- Human become infected when in contact with infected animals
- Mechanism of infection usually acquired by the entry of the spores through injured skin (cutaneous anthrax)
- Named as woolsorter's disease
- Associated with painless necrotic ulcer with black eschar
- Mechanism of pathogenesis: through delivery of Exotoxin called edema toxin which increase fluid secretion and lead to neutrophils dysfunction

- Edema toxin is a lethal toxin leads to cell death

Inhalation Anthrax:

- Inhalation of the spores lead to fever, flu like symptoms, myalgias, pulmonary hemorrhage, mediastinitis
- widening mediastinum in chest x- ray
- chest pain
- septic shock
- lung crackles due to hemorrhage
- Positive exudates

Diagnosis:

- Blood culture
- hemorrhagic CSF
- widening mediastinum in chest x- ray
- lung crackles
- Positive exudates

Treatment

- Antibiotics
- Monoclonal antibody called raxibacumab

References:

- Anthrax lethal and edema toxins in anthrax pathogenesis. Journal of Trends in Microbiology 2014
- https://www.medindia.net/patients/patientinfo/anthrax.htm

Bacillus Cereus

Overview:

- Causes food poisoning
- The spore survives high temperature in cooking rice known as Reheated type syndrome
- The Spore survive the cooking process and germinate enterotoxin
- Treatment with antibiotic isn't recommended since the causal agent is toxins
- Infection with Bacillus Cereus divided into 2 types:
    1. Nausea and Vomiting which usually occur within 1-5 hours caused by cereulide (performed toxin)
    2. Diarrhea type characterized by non-bloody diarrhea within 8-15 hours

References:

- First aid 2018

Clostridium species

Clostridium tetani;

- Often found in rusty places
- Clostridium tetani infect the patient at the wound site and release tetanus toxin
- Tetanus toxin is tetanic paralysis
- Inhibits the release of Inhibitory neurotransmitters such as GABA and glycine from interneurons leading to lack of inhibition (continuous activation or muscle contraction)
- The patient suffers from sustained muscle contraction in the jaw (trismus) and facial muscles (risus sardonicus)
- Opisthotonus or arching of the back
- Prophylaxis through tetanus vaccine
- Treatment by administration of tetanus toxin immunoglobulin (tetanus vaccine booster), antibiotics, muscle relaxant (Diazepam) and wound debridement

Clostridium botulinum;

- Heat labile toxin which prevent release of acetyl choline release at neuromuscular junctions that leads to termination of paralysis causing rapid flaccid paralysis
- In adult associated with spore ingestion though canned or jarred food
- In babies associated with floppy baby syndrome through jarred honey
- Symptoms are urinary retention and constipation, dyspnea, dysarthria, dysphagia
- Treatment by injection of human botulinum immunoglobulin

Clostridium perfringens;

- Attack soft tissues and wound, associated with gas gangrene by producing enterotoxins (α toxin)
- α-toxin hydrolyses and cleaves phospholipid C and diacylglycerol leads to myonecrosis
- Could survive in undercooked food leads to food poisoning
- Diagnosis through blood culture (double zone of hemolysis)

Clostridium difficile;

- Causes pseudomembranous enterocolitis
- Occurs as a result of prolonged antibiotic administration such as Clindamycin and ampicillin, also proton pump inhibitors
- Associated with diarrhea
- Produces 2 toxins:
    1. Toxin A (enterotoxin) which alter fluid secretions
    2. Toxin B (Cytotoxin) which disrupt cytoskeleton
- Treatment by Metronidazole and Vancomycin

- For recurrent cases, use fidaxomicin and fecal microbiota transplant
- Diagnosed by colon spectroscopy, stool analysis and PCR

References:

- First aid 2018

Corynebacterium Diphtheria:

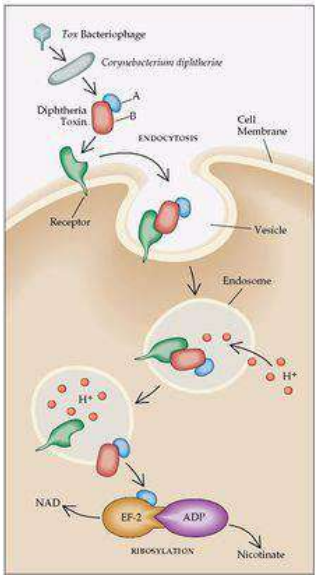
Outline:

- Overview
- Pathogenesis
- Clinical presentations
- Diagnosis
- Treatment

Overview:

- Gram positive bacilli
- Slender rods with clubbing at both ends
- Grow on tellurite agar
- Rare in US due to availability of vaccines (DTAP/DPT)

Pathogenesis



- Causes Diphtheria
- Affect the pharynx of young children less than 12 years old via respiratory droplets
- Composed of 2 fragments:
    1. Toxin A: which is responsible for toxin activity
    2. Toxin B: Receptor binding domain which binds to Epidermal growth factor leading to cardiac and cranial nerve deficits
- Mechanism of action depend on releasing an exotoxin (Toxin A) which inhibit adenosine diphosphate (ADP) ribosylation of elongation factor-2 (EF-2) which eventually inhibit protein synthesis

Clinical presentations:

- Causes fever, sore throat

- Pseudomembranous pharyngitis (grayish white membrane)
- Swelling
- Cervical lymphadenopathy
- Dysphagia and cough
- lymphadenopathy, myocarditis
- arrhythmias

Diagnosis

- Culture on potassium tellurite (forms gray-black cultures)
- Diagnosed by culture metachromatic granules (blue and red) with aniline dye
- Throat swab
- Elek test diphtheria toxin
- Leukocytosis (proteinuria)
- Loeffler coagulated blood serum

Treatment:

- Antibiotics: Erythromycin or Penicillin
- Vaccines: Antitoxin immunoglobulin, TDaP (tetanus, diphtheria and pertussis)

References:

- Microbe Wiki
- First aid 2018

Listeria Monocytogenes:

- The only gram-positive bacteria that produces endotoxin
- Listeria monocytogenes could be found in dairy products, vegetables, fish and meat products
- In healthy patients could cause mild gastroenteritis
- Listeria develops rocket tail structure which allow free motility
- Grows at 4 degrees inside macrophages especially in immunocompromised patients
- In healthy individual CD4T cells kills the bacteria inside the macrophages

Who are at risk with listeriosis:

Immunocompromised patients such as

1. Infants
2. Elderly patients
3. Patient receive chemotherapy
4. HIV/AIDS
5. Patients can develop brain abscesses

Pregnant women are subjected to bacteremia which results in

1. Neonatal death
2. Premature labor
3. Amnionitis
4. Continuous abortion (granulomatosis infantiseptica)
5. Still birth (dead baby)

New born could acquire listeriosis during vaginal infection:

1. Neonatal meningitis
2. Flu like symptoms
3. Headache
4. Diarrhea
5. Fever
6. Cyanosis (Neonatal Listeriosis)

Diagnosis:

- tumbling motility in broth.
- CSF collection by lumbar puncture
- Colonies are surrounded by zone of β-hemolysis

Treatment:

- Ampicillin
- Trimethoprim-sulfamethoxazole (TMP-SMX).

References:

- First aid 2018
- Crush Step 1- The ultimate USMLE step 1 review

Actinomyces

Outline:

- Overview
- Pathogenesis
- Clinical presentations
- Diagnosis
- Treatment

Overview:

- Actinomyces are gram positive anaerobe, beaded filamentous bacilli (Not acid fast)
- Lives in oral bacterial flora

Pathogenesis:

- Occurred usually post-surgical operation
- prevalent in periodontal pockets, dental plaques, and on carious teeth

Clinical presentations:

- Cervicofacial actinomycosis characterized by abscess formation, draining sinus tracts, fistulae, and tissue fibrosis
- Oral facial nodules
- Sulfur granules (small yellow bodies found in the pus of actinomycotic abscesses and consisting of clumps of the causative actinomycete.
- Lock Jaw

Diagnosis

- Microscopic examination of the pus, which usually contain yellow sulfur granules
- Increased inflammatory markers (↑ESR, ↑CRP, ↑WBC)

Treatment

- Abscess drainage through surgical therapy and excision of sinus tracts and recalcitrant fibrotic lesions, decompression of closed-space infections
- Penicillin is considered the drug of choice for treatment of actinomycosis

Nocardia

Outline:

- Overview
- Pathogenesis
- Clinical presentations
- Diagnosis
- Treatment

Overview:

- Nocardia are gram positive aerobe (Weak acid fast)
- Lives in the soil
- Differentiated from actinomyces by acid-fast staining, as Nocardia typically exhibit varying degrees of acid fastness due to the mycolic acid content of the cell wall

Pathogenesis:

- Causes Nocardiosis (opportunistic infection)
- Associated with immunocompromised patients causing pulmonary and cutaneous infection
- Nocardia infection characterized by its ability to disseminate to any organ, particularly CNS, and its tendency to relapse

Clinical presentations:

- lung abscesses and cavitations
- Fever
- Productive cough

Diagnosis

- Microscopic examination of the pus,
- Blood culture- Gram positive and weak acid fast
- Radiographic findings such as:

1. Irregular nodules (which may cavitate),
2. Reticulonodular or diffuse alveolar pulmonary infiltrates,
3. Lung abscess formation
4. Pleural effusion

Treatment

- Surgical removal of the abscess
- TMP-SMX

References:

- Actinomycosis: etiology, clinical features, diagnosis, treatment, and management. Journal of infection drug resistance, 2014
- https://emedicine.medscape.com/article/224123-workup
- Pulmonary nocardiosis: Under-diagnosed respiratory opportunistic infection – A case report

Mycobacterium Tuberculosis

Outline:

- Overview
- Pathogenesis
- Pathogenesis life cycle
- Comparison between Primary and secondary TB
- Clinical diagnosis of TB
- Treatment of TB
- References

Overview:

- Infectious contagious disease
- Gram positive acid-fast bacteria
- Heating is needed to melt the outer cell wall in order to allow penetration and staining with carbolfuchsin (resist depolarization by acid)
- Hydrophobic aerobic bacilli (obligate aerobic) require high level of oxygen for survival
- Grow slowly
- Mycobacterium Tuberculosis cell wall characterized waxy lipid content such as mycolic acid
- This thick lipid cell wall allows to survive within the macrophages for years
- Mycobacterium entail 2 virulence factors:
- 1-Cord factor allow mycobacterium to form long and slender formation

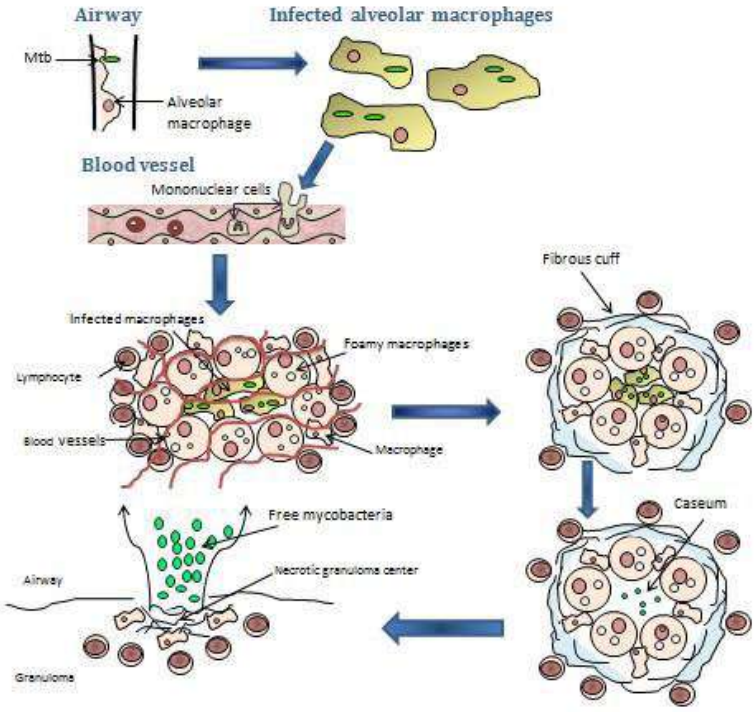
  - The cord factor inhibits neutrophils migration and damage mitochondria
  - Cord factor causes elevation in the levels of TNF interfere with lipid metabolism, causing a severe weight loss.
  - Intracellular growth of M. tuberculosis causes increased activation of macrophages, and subsequent production of multiple cytokines.

  2- Sulfatides- inhibit the phagosome lysosome fusion which is important for intercellular survival

Pathogenesis:

- Mycobacterium spread from person to person through the air
- Common in older adults and immunocompromised patients (e.g., AIDS patients, who lack the cellular immunity necessary to combat this bug).
- Lower immunity leads to secondary TB
- Primary TB starts with idiopathic symptoms
- Probability of TB transmission depend on:

- The immune system status of the exposed person
- Length of exposure
- Virulence or strength of TB



Pathogenesis life cycle:

Mostly Primary TB

1- Primary exposure of bacteria from active host
2- Neutrophils and macrophages release name as facultative intracellular growth
3- Bacteria starts to multiply inside the macrophages
4- Then diffuse from macrophages to lymphatics (facultative intracellular growth)
5- Initiation of cell mediated immunity
6- Macrophages migrate to lymph node for protection
7- More macrophages are being activated by Gamma interferons and IL-12
8- Lung necrosis associated with formation of granuloma around dead macrophages (calcified structure from fibroblast and collagen) **caseous necrosis**

Comparison between Primary and Secondary tuberculosis

	Primary TB	**Secondary TB**
Incidence	Affect 5-10% of patients which develop active TB	Reactivation during immunocompromised state
Infection site		Affect upper lobe (most oxygenated part)
Symptoms	Asymptomatic BUT can lead to exudative plural effusion	• Miliary TB (hazy glass appearance) • Fever • Night sweat • Weight loss • Malaise • Dry cough progressed to purulent sputum • Hemolysis • Apical rales (lung exam)

Extrapulmonary TB:

Usually occur in case of reactivated TB or Secondary TB

- Lymph node infection (lymphadenopathy): called scrofula and manifests as large, matted lymph nodes.
- Pleural and pericardial infection presents (pleural effusion)
- Kidney infection (WBS without bacteria) sterile Pyuria
- Brain infection: Subacute meningitis
- Pott's disease
- Choroidal tubercles

Clinical Diagnosis of TB:

1. Chest X-ray upper lobe infiltrate with cavitation characterized by:

- Pleural diffusion
- Ghon complex calcified primary focus
- Ranke's complex- calcified primary focus plus calcified lymph node

2. Sputum sampling, the definitive diagnosis is identified TB with acid staining
- 3 morning samples and cultures takes 4-8 weeks

3. PCR DNA of TB

4. Tuberculin skin test (PPD) purified protein derivative used to test latent TB

- Purified protein derivative (PPD): used to test whether the patient has already developed immunity towards TB

- It is positive for active, latent, and past infections, demonstrating only the presence of a type IV hypersensitivity (cell-mediated response) to TB antigens
- A subdermal injection of proteins is read 48 to 72 hours later
- acid-fast bacteria in sputum is the only test to diagnose active infections
- In healthy patients PPD >15 mm
- Homeless and high prevalence exposure, prisoners, health care workers are vulnerable to TB
- If PDD with 10mm means that the patient develops reactivated TB
- For HIV patients who under close with TB patients, chest x-ray showed positive Ghon complex with > 5mm.

Treatment of Tuberculosis:

2 months regimens by the following drugs then switch for 4 months (INH +Rifampin)

Isoniazid (INH):

Side effect:

- Peripheral neuropathy –overcome by giving (Vitamin B6-Pyrodoxin
- Hepatotoxicity monitor AST, ALT levels

Rifampin

Side effects:

- Red orange urine
- induced CYT P-450 (double the dose)

Pyrazinamide

Ethambutol

Side effects: Optic neuritis

References:

- Crush step 1-The ultimate USMLE step 1 Review
- MYCOBACTERIAL PERSISTENCE AND IMMUNITY. Frontiers in Bioscience 7, d458-469, Feburary 1, 2002
- Bilateral choroidal tuberculoma in miliary tuberculosis - report of a case. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4384973/
- Spinal tuberculosis: A review https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3184481/

Leprosy

Outline:

- Overview
- Types of Leprosy
- Treatment
- Signs and Symptoms
- Clinical diagnosis

Overview:

- Chronic mycobacterium disease
- Caused by Mycobacterium Leprae (acid fast bacillus)
- Bacteria prefer to grow in cooler conditions such as skin, nose, eyes
- Affects peripheral nerves causing glove and stocking “loss of sensation”
- Like TB, Mycobacterium Leprae develops resistance against macrophages
- The protection mechanism depends on innate immune system

Types:

Lepromatous Leprosy:

- Affects the entire body
- Depend on the immune system of the host (low cell mediated immunity)
- Highly contagious
- Leonine like face (lion-like face)
- Lethal
- Nasal cartilage (saddlenose deformity), testes (infertility), and eyes (blindness).

Lepromatous Tuberculoid:

- Occurs in response high immune response humoral Th1-type immune response
- Non-contagious
- Low bacterial load

Treatment:

	Lepromatous Leprosy	**Lepromatous Tuberculoid**
Treatment	Dapsone+ Rifampin+ Clofazimine	Dapsone+ Rifampin

Signs and symptoms:

- ❖ Occurs slowly through the year
- First symptoms: Numbness and loss of temperature sensation
- With disease progression: Loss of pain, touch sensation
- ❖ Reddish skin patch

Clinical diagnosis:

- Can't grow in culture (grow in mouse footpad)
- Skin biopsy, PCR
- Lepromin skin test

References:

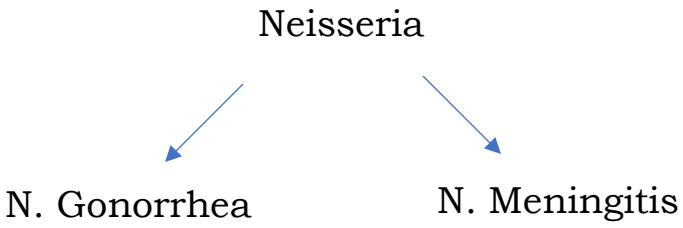
- Crush step 1-The ultimate USMLE step 1 Review

Neisseria

Outline:

- Overview
- Pathogenesis
- Clinical presentations
- Diagnosis
- Treatment

Overview:



- Both N. Gonorrhea and N. Meningitis are Gram-negative, diplococci

Neisseria Gonorrhea

- NO poly saccharide capsule
- The second-most common sexually transmitted disease (STD) after chlamydia.
- Catalase and Oxidase positive
- Glucose fermenter

Pathogenesis

- The term gonorrhea refers to urethritis and/or cervicitis in a sexually active person.
- N. Gonorrhea spread during sexual contact, also could be transmitted from the mother to the newborn during birth
- Gonorrhea can also spread throughout the body to cause localized and disseminated disease

Clinical presentations:

Males	Females
• Urethritis (yellowish white discharge) • Acute epididymitis • Renal infection • Burning upon urination • Urethral exudate • Prostatitis	• Vaginal discharge • Vaginitis Inflammation of vaginal wall) • Dysuria • Dyspareunia (painful intercourse) • Endometritis (infection of the uterus) • Mild lower abdominal pain

- Vaginal discharge: The most common presenting symptom of gonorrhea, vaginal discharge from endocervicitis is usually described as thin, purulent, and mildly odorous; however, many patients have minimal or no symptoms from gonococcal cervicitis
- 80% of infected women are asymptomatic (endometritis)
- Most of the cases of endometritis progress to salpingitis (inflammation of the fallopian tubes) or oophoritis (inflammation of the ovaries) called pelvic inflammatory disease (PID) which characterized by
  - Abdominal pain
  - Fever
  - Discharge
  - Irregular bleeding
  - Fibroid tissue deposition which might cause sterility
  - Progress to abscesses, Peritonitis
  - Scarring of the fallopian tube lead to fallopian ectopic pregnancy
  - Infection and inflammation may spread to the liver capsule causing acute gonococcal perihepatitis (Fitz-Hugh-Curtis syndrome)

Fitz-Hugh-Curtis syndrome associated with Violin-string (adhesions of parietal peritoneum to liver)

- N. Gonorrhea BUT NOT Chlamydia can cause oropharyngeal infection through oral sex
- N. Gonorrhea could develop septicemia or disseminated gonococcal infection manifested by arthritis-dermatitis syndrome then progress to septic arthritis Characterized by fever, joint pain

  NOTE: Examination of synovial fluid reveal gram- negative diplococci within white blood cells (WBCs)

- Affects neonates causing neonatal conjunctivitis (ophthalmia neonatorum) from the birth canal treated by silver nitrate eye drops
- Symptoms include eye pain, redness and purulent discharge

- Treatment by application of silver nitrate or erythromycin eye drops to prevent ophthalmic infection

Diagnosis:

- Culture from female or male discharge exudate on Thayer- martin medium (chocolate agar)
- Thayer-martin medium entails mixture of different antibiotic called VCN inhibitors such as
    1. Vancomycin to kill Gram positive organisms
    2. Colistin or Polymyxin to kill Gram negative organisms
    3. Nystatin as antifungal
- A positive culture will indicate infection with N. Gonorrhea

NOTE very important:

❖ A negative culture on Thayer-Martin in a patient exhibiting symptoms of pelvic inflammatory disease most likely indicates an infection with Chlamydia trachomatis.

- Gram stain (kidney shaped diplococci)

Treatment

- Ceftriaxone is the antibiotic of choice for Gonorrhea
- In case of sexually transmitted gonorrhea (Ceftriaxone+ azithromycin) or doxycycline to cover Chlamydia (common coinfection)
- Administration of condoms to decrease sexual transmitted disease
- No vaccine available BUT a recent vaccine produced in 2018 called MeNZB vaccine is shown to have efficacy, albeit relatively low, against N. gonorrhoeae

Virulence factors:

- Pili help in attachment of gonococci to mucosal surfaces and contribute to resistance by preventing ingestion and destruction by neutrophils.
- Neisseria LPS is referred to as lipooligosaccharide (LOS) to protect against phagocytosis
- Porin channels (porA, porB) form pores in the outer membrane help invading epithelial cells
- Opacity-associated (Opa) proteins increase adherence between gonococci and phagocyte

Neisseria Meningitis

- Gram negative diplococcus
- Catalase and oxidase positive
- Thick polysaccharide capsule
- Glucose positive maltose fermentation

Pathogenesis

- Meningococcal meningitis primarily affects infants, children, and young adults
- Meningococcal meningitis can occur as an epidemic in subgroups in closed quarters such as people in the military services or students in dormitories
- Transmitted by Inhaled droplets/ oral secretions
- There are at least 13 serogroups of the bacterium, with the most important being serogroups A, B, C, and W-135

Clinical presentations:

- Meningococcemia (meningitis or sepsis) affect central nervous system but usually proceeded by sore throat or respiratory infection
- The neurologic damage associated with meningitis is a consequence of the following 3 main processes:

1. Direct bacterial toxicity
2. Indirect inflammatory processes, such as cytokine release, ischemia, vasculitis, and edema
3. Systemic effects, including shock, seizures, and cerebral hypoperfusion

- Initially the symptoms started by fever, headache, a stiff neck, nausea, vomiting and altered mental state such as confusion or coma
- The bacteria release endotoxin (LPS), causing vascular hemorrhage (seen as a petechial rash) and an acute inflammatory response (seen as spiking fever, chills, arthralgia, and muscle pain)
- Meningococcal infection may spread through the bloodstream and localize in other parts of the body causing Septic arthritis, purulent pericarditis

- Systemic meningococcal infection causes adrenal hemorrhage and insufficiency Known as fulminant meningococcemia or Waterhouse-Friderichsen syndrome

Waterhouse-Friderichsen syndrome:

- Defined as adrenal gland failure due to bleeding into the adrenal gland. Characterized by hypotension, vasomotor collapse, septic shock, disseminated intravascular coagulation (DIC), adrenal insufficiency followed by cardiovascular dysfunction and multiple organ failure
- Skin rash is one its characteristic features with pink macules or papules progress to large purpuric plaques
- Treatment: Antibiotic and glucocorticoids to increase blood pressure levels

Diagnosis

- Retrieval of meningococci from Blood, CSF, joint fluid
- Culture on Thayer-Martin VCN media
- Quellung reaction

Virulence factors:

- Thick polysaccharide capsule protects against phagocytosis
- Lipo-oligosaccharide endotoxin (LOS)
- Immunoglobulin A1 (IgA1)

Treatment:

- Ceftriaxone and Penicillin are drugs of choice for treatment
- Ciprofloxacin and rifampin for prophylaxis
- Serogroup A, B, C, Y and W-135 meningococcal infections can be prevented by vaccines

References:

- Neisseria gonorrhoeae vaccine development: hope on the horizon? Journal of current opinion infection disease, 2018
- Vyas JM, Zieve D, Black B. Waterhouse-Friderichsen syndrome. *MedlinePlus*. September 1, 2013
  http://www.nlm.nih.gov/medlineplus/ency/article/000609.htm.

Haemophilus Influenzae

Outline:

- Overview
- Types of Haemophilus Influenzae
- Epiglottitis
- Diagnosis
- Virulence factors
- Hib vaccine
- Treatment

Overview:

- Small, pleomorphic, gram negative coccobacillus
- Some strains possess polysaccharide capsule and subdivide into 6 different types (a-f), the most virulent strain is H influenzae type b (Hib)

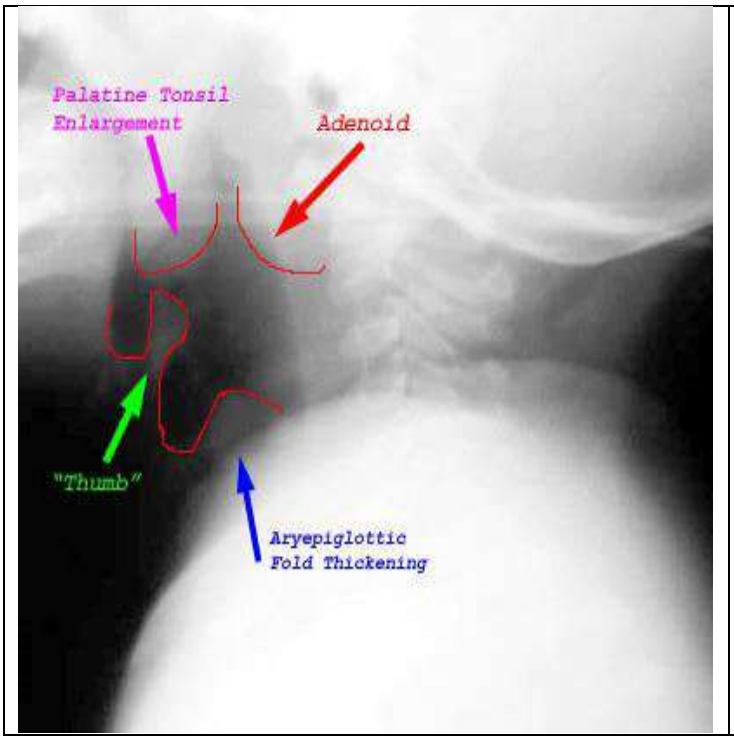
Types of Haemophilus Influenzae

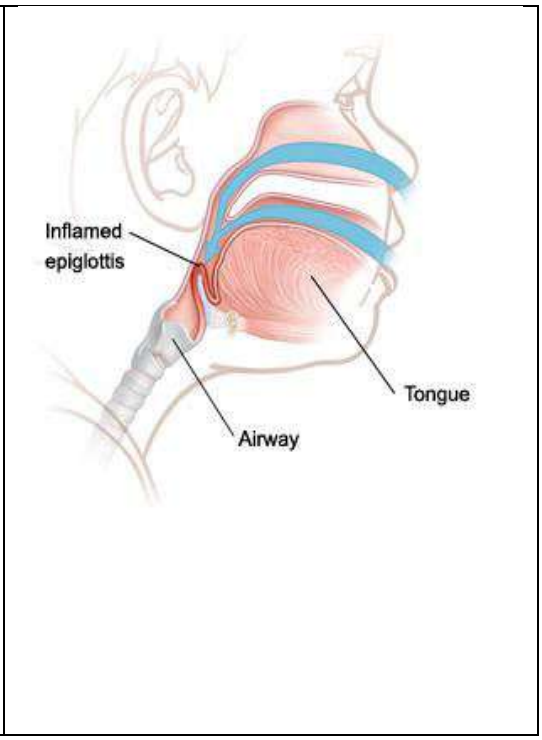
	Typeable	Non typeable
	Haemophilus type B (Hib)	Nontypeable H influenzae (NTHi)
Capsule	Encapsulated	Nonencapsulated
Causative agent of	• Epiglottitis Common in children from 6 months to 3 years • Infantile meningitis • Neonatal infection such as bacteremia in kids	• Mucosal Infection ❖ Otitis media ❖ Pneumonia ❖ Conjunctivitis ❖ Bronchitis
Vaccine	Available	Not available

- Infants are more susceptible to Hib due to lack of immune globulin to Hib

Epiglottitis

- Upper airway obstruction with acute onset of inflammatory edema
- Swelling significantly reduces the airway aperture
- Associated with dysphagia, respiratory distress
- The thickening of the epiglottis results in the "thumb sign".
- Most commonly in children with 1-5years old
- Availability of Hib vaccine significantly reduced its incidence





Diagnosis

- Lumbar puncture for CSF analysis (gram negative rods)
- Culture through chocolate agar
- Growth requirement, Factor X (hematin), factor V (NAD)
- Satellite phenomena, Hib grows around colonies of Staph. Aureus on unheated blood agar
- Staph. Aureus lysis blood cells releasing Factors X and V, hence, Hib feed on them
- Quelling reaction for detection of polysaccharide capsule

Virulence factors:

- Thick polysaccharide capsule (polyribosylribitol phosphate) protects against phagocytosis
- Lipo-oligosaccharide endotoxin (LOS)
- Immunoglobulin A1 (IgA1) allow to stick to upper airways
- B-lactamase

Vaccines

- A conjugate vaccine such as (DPT vaccine)
- This vaccine contains type b capsular polysaccharide (polyribosylribitol phosphate) conjugated to diphtheria toxoid or other protein.
- Given at 2 months, 4 months and six months

Treatment:

- Ceftriaxone is the drug of choice for treatment of meningitis
- Glucocorticoids to decrease inflammation and swelling associated with Epiglottitis
- Amoxicillin / Clavulanic Acid for treatment of mucosal infection
- Rifampin for prophylaxis

References:

- Pediatric radiology, school of medicine, University of Virginia

- Acute epiglottitis due to Haemophilus influenzae b: A severe consequence of increased skepticism about vaccination. Journal of Archives de Pédiatrie, 2017

Bordetella Pertussis

Outline:

- Overview
- Pathogenesis
- Clinical stages of Pertussis
- Complications associated with Pertussis
- Diagnosis
- Virulence factors
- Treatment

Overview:

- Pleomorphic gram negative aerobic coccobacillus

Pathogenesis:

- Causes whooping cough
- Pertussis is a toxin-mediated disease.
- Pertussis is a very contagious disease, spreads from person to person by coughing or sneezing
- The bacteria attach to the cilia of the respiratory epithelial cells, produce toxins that paralyze the cilia, and cause inflammation of the respiratory tract, which interferes with the clearing of pulmonary secretions
- whooping cough affects mostly unimmunized infants and young adults

Clinical stages of Pertussis:

- Pertussis is a 6-week disease divided into incubation, catarrhal, paroxysmal, and convalescent stages

Incubation Period:

- Patient gets inoculated
- Last for 7-10 days with mild respiratory symptoms

Catarrhal Period:

- It includes nasal congestion, rhinorrhea, and sneezing, low-grade fever, tearing.
- Pertussis is most infectious when patients are in the catarrhal phase
- Last for 1-2 weeks
- At this point, culture analysis could be done.

Paroxysmal Period:

- Patients present with paroxysms of intense coughing lasting up to several minutes.
- This stage lasts cough 2-4 weeks
- Initially dry, intermittent evolved into inexorable paroxysms
- These episodes of violent coughing followed by an inspiratory “whoop” (gasp

of air through a narrowed epiglottis).

- people with Pertussis cough up (expectorate) large amounts of thick mucus, which may cause vomiting (post-pertussis emesis)
- Lymphocytosis

Convalescent stage:

- Begins 4 weeks after onset of the disease.
- Coughing become less frequent and not intense
- Gradual recovery during this phase

Complications associated with pertussis:

- Aspiration of mucous into the lungs may cause bacterial pneumonia
- Increase in the blood pressure at the nose (epistaxis) and eyes (scleral hemorrhage)
- Seizures
- Inguinal hernia

Diagnosis:

- Culture isolation on Bordet-Gengou medium or PCR
- The culture specimen should be obtained during the first 2 weeks of cough by using deep nasopharyngeal aspiration
- For PCR testing, nasopharyngeal specimens should be taken at 0-3 weeks following cough onset

Virulence factors:

Pertussis toxin:

- Has one A subunit (toxic part) ↑cAMP and B subunit (involved in binding)

Increased cAMP associated with:

1. ↑ insulin release leading to hypoglycemia
2. ↑ histamine sensitization, cough and vascular permeability
3. Interfere with phagocytosis of neutrophils
4. Prevent chemotaxis
5. Lymphocytosis
6. ↑ IL4 production

Adenylate cyclase/hemolysin toxin

- Impair alveolar macrophage inhibition

Treatment:

- Supportive treatment (hospitalization especially to infants).
- Azithromycin or erythromycin, recommended at catarrhal stage so it could decrease the coughing exacerbation at the paroxysmal stage

DTaP vaccine: Recommended at the ages of 2, 4, 6, and 15-18 months
Tdap vaccine (booster shot): Recommended at preschool age (7-10 years)

References:

- Pink Book's chapter on pertussis

- Pertussis toxin and adenylate cyclase toxin: key virulence factors of Bordetella pertussis and cell biology tools. Journal of Future Microbiology, 2010

Legionella Pneumophila

Outline:

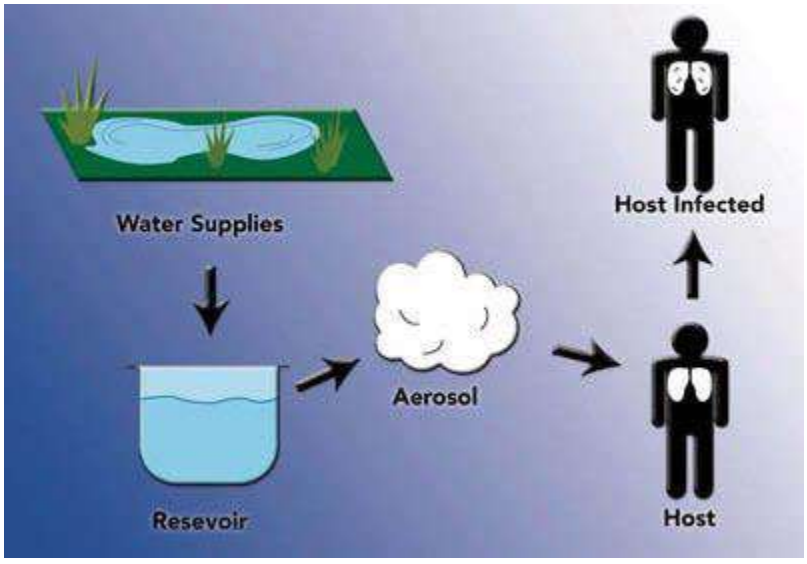
- Overview
- Pathogenesis
- Clinical Presentations
- Risk factors
- Diagnosis
- Virulence factors
- Bacteria causes atypical pneumonia
- Treatment

Overview:

- Gram negative aerobic waterborne bacilli
- The Legionella bacterium was first identified in the summer of 1976 during the 58th annual convention of the American Legion in Philadelphia

Pathogenesis

- Legionella is an obligate or facultative intracellular parasite.
- Water is the major environmental reservoir for Legionella
- Contaminate water systems, air conditioning units and transmitted through aerosolized droplets
- Could replicate and grow inside lung's macrophages and neutrophils



Clinical Presentations

- Main cause of Legionnaire's disease (sever pneumonia) with high fever, cough, headache and muscle aches
- The Bacteria enters through the alveoli, multiply inside the macrophages and neutrophils
- Causes Pontiac fever- self limiting

Risk factors:

- Smocking
- Compromised immune system
- Chronic lung disease

Diagnosis

- Urine antigen test: detection of Legionella pneumophila in the urine and if the patient has pneumonia so he considered to have Legionnaire's disease
- Transtracheal aspiration of bronchioalveolar lavage
- Cultured on charcoal yeast extract with iron and cysteine

Virulence Factors

- Legionella Pneumophila could multiply inside the phagocytes
- Inhibit phagosome-lysosome fusion which allow intracellular growth
- Catalase positive (peroxide) hence, inhibit generation of bactericidal substances in phagocytic cells
- Dot/icm type IV secretion system (defective organelle trafficking)
- Coiling phagocytosis
- Unique lipid cell wall which allow thermoresistance
- Degrades FC portion of antibodies and compliments
- Beta lactamase resistant
- Metalloprotease dampens the cytokine secretion from infected macrophages and limits the levels of cytokine transcripts in infected macrophages.

Bacteria causes atypical pneumonia:

- Legionella Pneumophila
- Mycoplasma
- Chlamydia

Treatment:

- Macrolides (Erythromycin, Azithromycin)
- Drug of choice for atypical pneumonia

References:

- Legionella: virulence factors and host response. Journal of current opinion in infectious disease, 2016

Pseudomonas aeruginosa

Outline:

- Overview
- Diagnosis
- Virulence factors
- Treatment

Overview:

- Gram negative rode, strict aerobe
- Oxidase positive and lactose nonfermenters.
- Characteristic sweet grape like odour
- This pathogen is widespread in nature soil, water and plants

Pathogenesis:

- Pseudomonas aeruginosa is an opportunistic pathogen common with immunocompromised patients
- common in immunocompromised patients with diabetes.
- It's a frequent cause of nosocomial infection such as pneumonia, bacteremia

Clinical Presentations

- Pseudomonas aeruginosa could affect several organs such as:
- Urinary tract- UTI
- Respiratory tract-Pneumonia, Cystic fibrosis
- Heart-Endocarditis
- Ear-Otitis Externa (swimmer's ear)
- Blood stream-Bacteremia/Sepsis
- Eye-Conjunctivitis, Keratitis (contact lens)
- Hair- Hot tub folliculitis
- A common type of folliculitis, a condition which causes inflammation of hair follicles with papulopustular lesions
- Bones and joints (osteomyelitis)
- Skin Ecthyma gangrenosum

Ecthyma gangrenosum: are hemorrhagic (bloody) pustules that evolve into necrotic (black) ulcers.

Diagnosis

- Urine culture, blood cultures (oxidase, Catalase positive, β-hemolytic)
- Sputum in case of patient with cystic fibrosis
- Surface swab from burned patient
- The blue-green pigment due to pyocyanin
- Isolation of thick sputum from patient lungs due to alginate production

Virulence factors:

- Pyocyanin impair ciliary function, and produce toxic free radicals
- The pili allow adherence to the epithelium.
- Exotoxin A is responsible of tissue necrosis. Inhibit protein synthesis by inhibition of elongation factor-2 through ADP-ribosylation of EF2
- Exotoxin S: Inhibit protein synthesis
- Elastase: Destruction of elastin containing tissue (blood vessels, skin, cornea)
- Phospholipase C is a thermolabile haemolysin.
- P. aeruginosa produces at least four proteases causing bleeding and tissue necrosis

Treatment:

- Aminoglycosides plus extended spectrum Penicillin (Piperacillin, Ticarcillin)
- Steroids are used in conjunction with these antibiotic
- Proper hygiene regarding medical devices like catheters is important to prevent opportunistic infection in a patient
- Severe burn victims should be put into strict isolation to prevent unnecessary contact with potential pathogens

References:

- Ecthyma gangrenosum, a skin manifestation of Pseudomonas aeruginosasepsis in a previously healthy child. Journal of Medicine 2017
- [Virulence factors in Pseudomonas aeruginosa: mechanisms and modes of regulation]. Journal of Annales de Biologie Clinique, 2011

Salmonella

Outline:

- Overview
- Pathogenesis
- Clinical presentations
- Diagnosis
- Treatment

Overview:

- Gram-negative, rod-shaped bacilli that can cause salmonellosis
- It has flagella
- Only about 3.4% of Salmonella infections in the United States are laboratory-confirmed (self-limiting)
- Salmonella might be life threating when it didn't handle properly

Pathogenesis

- It is the most common cause of foodborne illness. Salmonella occurs in raw poultry, eggs, beef, vegetables, dairy products and shellfish
- Salmonella typhi induce typhoid fever
- Salmonella osteomyelitis is predominantly seen in patients with haemoglobinopathies such as sickle cell anemia

Clinical presentations of typhoid fever:

- Bloody diarrhea
- Fever
- Abdominal cramps
- Headache
- Dehydration
- Myalgia
- Rose spot on chest and abdomen (critical sign in typhoid fever)
- Symptoms usually last 4 - 7 days
- Typhoid carrier state

❖ Salmonella typhi lives only in human. Persons with typhoid fever can carry the bacterial in their blood stream and intestine for long period

❖ Persons who recovered from typhoid fever called Carriers since they continue to carry the bacteria

❖ Both ill and carrier persons have salmonella in their stools

Diagnosis

- Bone marrow aspiration
- Stool culture

- Blood analysis, associated with leucopenia, anemia, neutropenia
- Urine culture

Treatment:

- Supportive care (oral rehydration)

References:

- Salmonella Osteomyelitis. Journal of Ulster Medical Society, 2015
- First aid 2018

Shigella

Outline:

- Overview
- Pathogenesis
- Clinical Presentations
- Diagnosis
- Treatment

Overview

- Enterobacteriaceae
- Gram negative bacilli
- Non-motile, non-sporing and non-capsulate
- Lactose negative
- Four subgroups: S. dysenteriae, flexneri, sonnei and boydii

Pathogenesis

- Spread by fecal-oral transmission or ingestion of contaminated food or drinks
- Commonly in developing countries where poor sanitation and water supplies are polluted
- Leading cause of infant diarrhea in developing countries
- Mechanism of pathogenesis: penetrate through mucosal surface of colon and invade intestinal epithelium releasing shiga toxin (Similar to Enterohemorrhagic E. Coli)
- Shiga toxin inhibits protein synthesis (inactivate 60S ribosome) which lead to GI mucosal damage-dysentery

NOTE: Shiga toxin enhances cytokine release causing hemolytic uremic syndrome (HUS)

- Like Salmonella, invades the GI tract via M cells of Peyer patches.
- Very low infectious dose ID_{50}

Clinical Presentations

- Causes bacillary dysentery or shigellosis
- Shigellosis starts with acute gastroenteritis associated with abdominal pain and diarrhea
- Progress to mucus with pus and blood
- Severe dehydration
- Bloody diarrhea
- Causes reactive arthritis

Diagnosis

- Stool specimen with fecal blood
- Appearance of neutrophils in fecal smear
- Culture in selective medium to isolate shigella from faeces e.g. XLD agar: shigella produce red pink colonies

Treatment

- Beta-Lactamase Ampicillin
- Trimethoprim TMP-SMX
- Because shigellosis is self-limiting, its recommend withholding antibiotic therapy since antibiotic prolong bacterial excretion
- Anti-diarrheal compounds shouldn't have given. It might worsen the situation
- Fluid and electrolytes replacement
- Zinc supplements especially for infants

References:

- Cellular Aspects of Shigella Pathogenesis: Focus on the Manipulation of Host Cell Processes. Journal of frontiers in cellular and infection microbiology, 2016
- Recent insights into Shigella. Current opinion in infectious diseases, 2018

Yersinia enterocolitica

Outline:

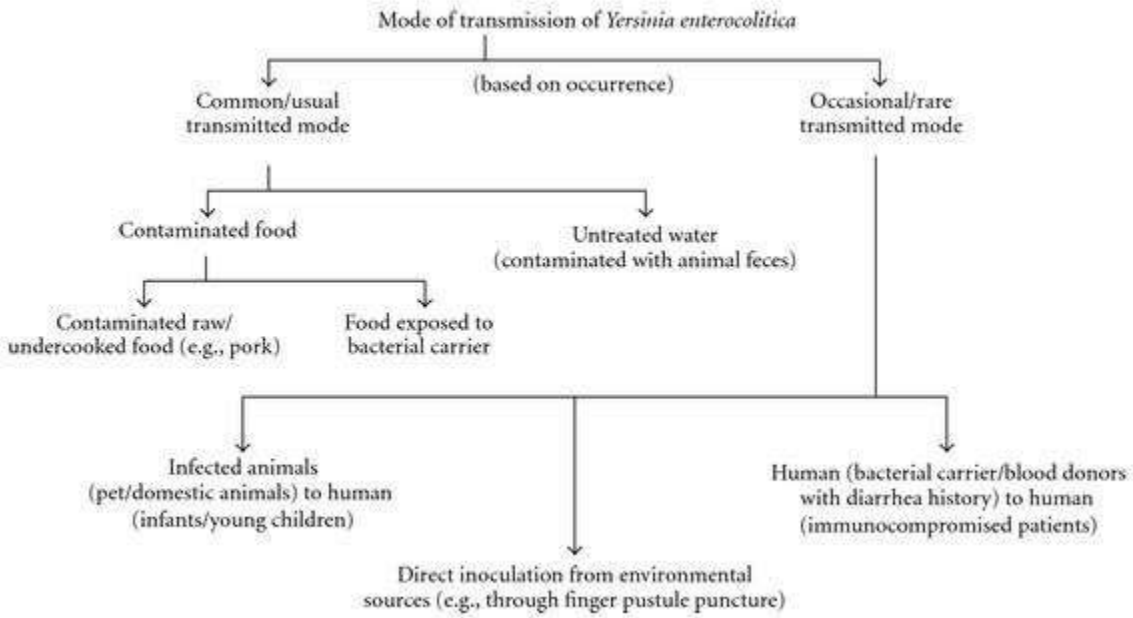
- Overview
- Pathogenesis
- Clinical Presentations
- Diagnosis
- Virulence Factors

Overview:

- Gram negative coccobacillus-shaped
- Facultative anaerobe that is motile at temperatures ranging from 22 to 30°C

Pathogenesis:

- Transmitted through eating contaminated food, especially raw or undercooked pork, or infected pet faeces.



Clinical Presentations

- Starts with diarrhea, fever, abdominal pain
- The patient may also develop erythema nodosum
- Enterocolitis
- Acute terminal ileitis (Pseudo corhn disese)
- Acute mesenteric lymphadenitis (pseudo appendicitis) in children 5-15 years
- Acute diarrhea in children < 5 years

- Adult diarrhea
- Might progress to spondyloarthropathies (inflammatory arthritis of the spine and joints)
- HLA-B27 is a positive for spondyloarthropathies or reactive arthritis

Acute mesenteric lymphadenitis:

- Inflammation of the mesenteric lymph node
- Difficult to differentiate from acute appendicitis
- Yersinia enterocolitica spread through the intestinal lymphatics to reach the lymph node

Diagnosis

- Culture of faeces and joint fluid (↑HLA-B27)
- Culture on broth medium at 28 degrees.

Virulence Factors

- Yersinia adherence proteins (Ail, YadA and invasion)
- M cells: Antigen-sampling intestinal epithelial cells
- Enterotoxin -↑ CAMP that lead to diarrhea

References:

- Yersinia enterocolitica: Pathogenesis, virulence and antimicrobial resistance. 2011
- Medscape http://emedicine.medscape.com/article/232343-overview
- CDC. http://www.cdc.gov/ncidod/dbmd/diseaseinfo/yersiniag.htm

Escherichia Coli

Outline:

- Overview
- E. coli strains
- Hemolytic uremic syndrome (HUS)
- Diagnosis
- Virulence factors

Overview:

- Gram negative rod
- Normally live in the intestines of people and animals.
- E. coli can be transmitted through contaminated water or food, or through contact with animals or persons.
- Leading cause of urinary tract infection which can lead to acute cystitis and polynephritis
- Causes gastroenteritis, neonatal menegitis and nosocomial pneumonia

E. coli strains:

1. Enteropathogenic E coli (EPEC):

- Main cause of childhood diarrhea.
- Pathogenic
- Characterized by loose stool, tenesmus, GIT symptoms
- Adhere to apical surface
- Blocks absorption by attaching to the apical surfaces causing the villi to flatten
- No Toxin is produced
- Frequent in summer months
- Treatment by administration of oral rehydration solution

2. Enterotoxigenic E. coli (ETEC):

- Causes traveler's diarrhea
- Heat labile toxin (AB toxin) similar to cholera toxin
- The toxin activates adenylate cyclase-↑ cAMP-Increased chloride secretion (Secretory or watery diarrhea)
- Toxigenic

Note:

- There are 2 types of enterotoxins LT (labile toxin) and ST (stable toxin):
- LT, heat labile bind to Gm1 gangliosides in the small intestine, hence increase cAMP production (Increase fluid transport into the bowel)
- LT composed of A and B components
- A active and B for binding

3. Enteroinvasive E. coli (EIEC):

- Causes dysentery (diarrhea with mucus)
- Invade intestinal epithelia and release Shiga like toxin, resulting in an inflammation and necrosis
- Invasive
- No toxin is produced

4. Enterohemorrhagic E. coli (EHEC):

- Causes hemorrhagic colitis
- Bloody diarrhea
- Bind to epithelial cells and produce shiga like toxin that block protein synthesis causing cell death
- Considered as foodborne infection (undercooked or contaminated food)
- 0157:H7 strain of EHEC causing hemolytic uremic syndrome

Hemolytic uremic syndrome:

Progressive renal failure associated with:

- Thrombocytopenia and hemolytic anemia
- Damage to the lining of blood vessel walls
- Destruction of red blood cells (hemolysis)
- Schistocytes (Fragment part of red blood cells) common in hemolytic anemia
- Elevated lactate dehydrogenase (LDH)
- Destruction of blood platelets (involved in clotting)
- Disseminated intravascular coagulopathy (DIC)
- Septic shock

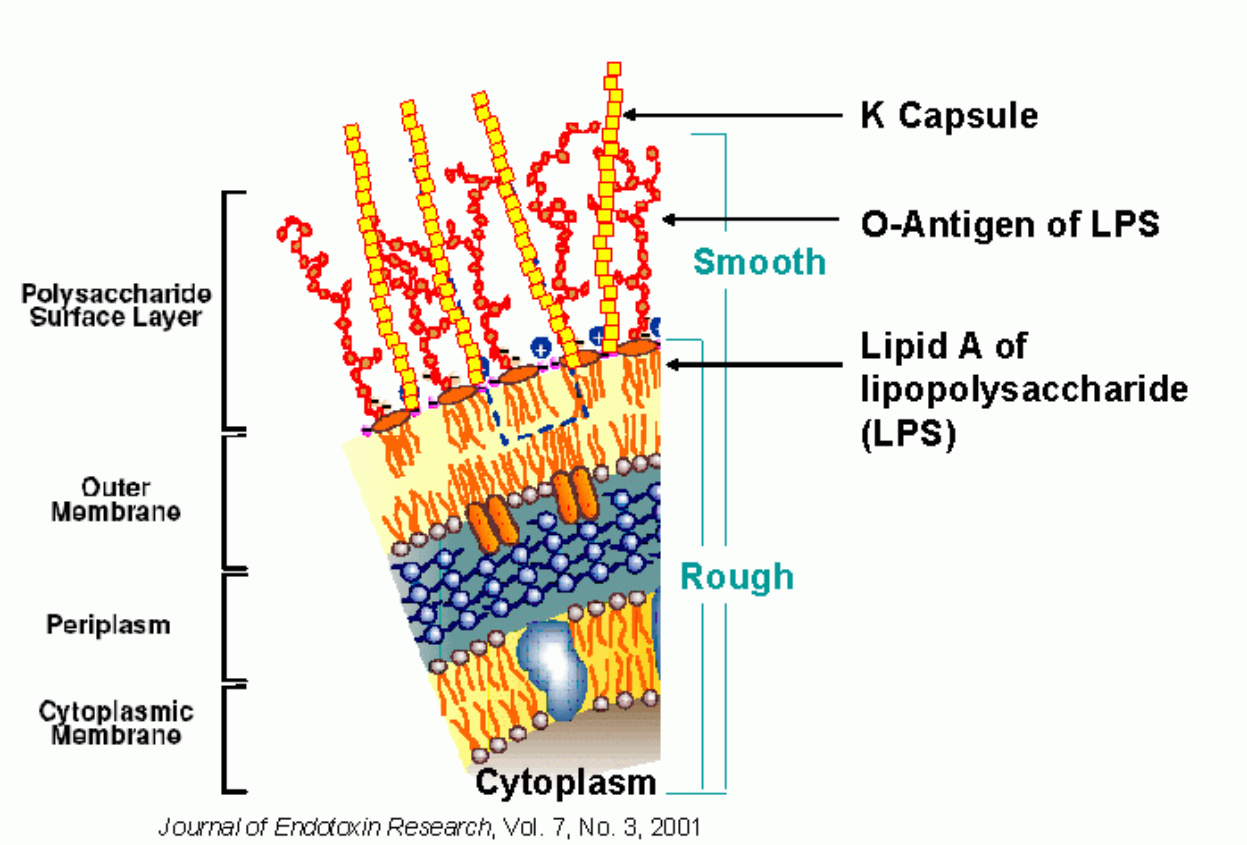
Pathophysiology:

- Glomeruli become clogged with platelets and damaged red blood cells, hence, the kidney's ability to filter and eliminate waste products.

Diagnosis:

- Large pink colonies on Mac Conkey agar
- Lactose fermenters

Virulence factors (E coli antigenic structure):



- K antigen (Capsular K): Protect against phagocytosis
- H antigen (Flagella): Help in motility and chemotaxis
- O antigen: Lipopolysaccharide (LPS)
- Fimbriae promote virulence (especially in UTI)

References:

- Review on pathogenicity mechanism of enterotoxigenic Escherichia coli and vaccines against it. Journal of microbial pathogen, 2018

Klebsiella Pneumoniae

Outline:

- Overview
- Pathogenesis
- Clinical presentations
- Virulence factors
- Diagnosis
- Treatment

Overview:

- Gram-negative bacteria with polysaccharide capsule
- The organisms are named after Edwin Krebs, a 19th century German microbiologist

Pathogenesis

- Infection with Klebsiella pneumonia occurs in the lungs, where they cause destructive changes
- Major cause of nosocomial pneumonia
- Affects alcoholics, diabetics and malnutrition, intubated and debilitated patients
- Also associated with Foley catheter-associated UTIs
- Pneumonia occurred because of aspiration of stomach contents

Clinical presentations:

- Pneumonia
- Focal lung infection
- Productive cough
- Necrosis
- Inflammation
- Hemorrhage occur within lung tissue, sometimes producing a thick, bloody, mucoid sputum described as currant jelly sputum
- Wound infection
- Nosocomial sepsis

Virulence factors:

- Poly saccharide capsule
    1. protect against phagocytosis and antibiotics
    2. Makes the colonies moist and mucoid
- B-lactamase

Diagnosis

- Mucoid colonies due to polysaccharide capsule
- Grows on MacConkey and blood agar media

Treatment:

- Third-generation cephalosporins (eg, cefotaxime, ceftriaxone)
- Broad spectrum antibiotics

References:

- Chronic Klebsiella pneumonia: a rare manifestation of Klebsiella pneumonia, case report, Journal of thoracic disease, 2015.

- Virulence Factors and Antibiotic Resistance of *Klebsiella pneumoniae* Strains Isolated from Neonates with Sepsis. Journal of Frontiers in Medicine, 2018

Campylobacter Jejuni

Outline:

- Overview
- Pathogenesis
- Clinical Presentations
- Diagnosis
- Virulence Factors

Overview:

- Microaerophilic curved negative rods
- Comma S or gull-wing shaped spiral rods
- Thermophilic growing well at 42 C
- Oxidase, Catalase and Nitrate reduction positive
- Part of the normal intestine flora of domestic animals

Pathogenesis:

- Source of infection: food of animal origin, especially raw milk, poultry and meat
- Transmission through fecal-oral route
- The most common cause of community-acquired inflammatory enteritis.
- Campylobacter Jejuni may cause bacteremia in individuals with AIDS.
- Multiply in the small intestine, penetrate the gut epithelium and disrupt fluid absorption

Clinical presentations:

1. Gastroenteritis and characterized by:

   - Bloody diarrhea
   - Dysentery
   - Abdominal pain
   - Crypt abscesses
   - Gastric ulceration

2. **Guillain Barre syndrome**: Acute inflammatory polyradiculoneuropathy with resultant weakness and diminished reflexes.
3. Reactive arthritis

Diagnosis:

- Stool specimen
- Culture: Campy agar grows at 42 C

Virulence factors

- Antigenic diversity
- Flagellum – Used for bacterial motility and chemotaxis
- Adhesion and invasion through lipopolysaccharide and flagella

- Produce enterotoxin which ↑ cAMP. Destroyed upon boiling (heat labile toxin)
- Cytotoxins which stop cell growth
- Superoxide dismutase

References:

- Postinfectious irritable bowel syndrome: Mechanisms related to pathogens, Journal of neurogastroentology and Motility, 2014

Vibrio

Outline:

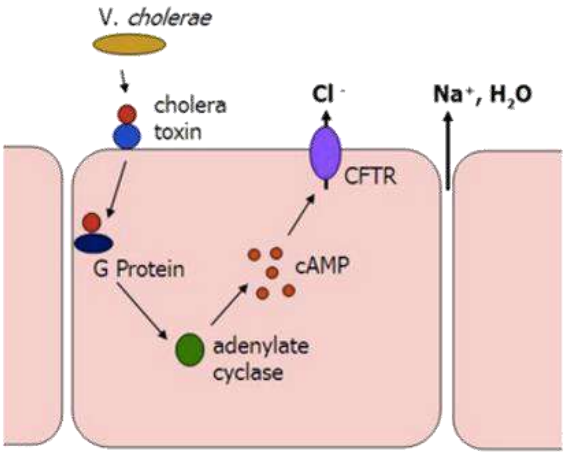
- Overview
- Diagnosis
- Virulence factors
- Vibrio parahaemolyticus:
- Treatment

- Vibrio has two important species Vibrio Cholera and Vibrio parahaemolyticus

Vibrio Cholera:

Overview

- Halophilic (salt loving)
- Grow in alkaline medium
- Gram negative halophilic bacteria
- Non-lactose fermenting
- Facultative anaerobe
- Oxidase positive
- Cholera is common in developing country (endemic) due to poor sanitation
- Mechanism of pathogenesis: The bacteria binds to the epithelium which release cholera toxin that causes ↑cAMP (Increase NaCl secretion and H_2O efflux)



Clinical Presentations

- Profuse watery diarrhea known as rice-water stool
- Occasional vomiting and abdominal cramps
- Diarrhea dehydration which leads to hypotension, tachycardia, oliguria and finally renal failure
- Decrease intravascular volume

- Massive fluid loss
- Decrease renal perfusion
- Less renal output

Virulence factors:

- Enterotoxin (Cholera toxin): Hypersecretion of electrolytes and water
- Pili: Adhesion to mucosal cells
- Mucinase (protease): induce intestinal inflammation
- Serotype 01 is the most common

Treatment:

- Rehydration
- Glucose IV fluids

Vibrio parahaemolyticus:

- Gram negative bacteria
- Found in salt water
- Halophilic

Pathogenesis:

- Transmitted by Fecal-oral route or ingestion of undercooked sea food specially shellfish and sushi
- Causes gastroenteritis, self-limiting diarrhea, abdominal pain
- Causes skin infection when the wound exposed to warm seawater

Diagnosis

- B- hemolysis in high salt blood agar known as kanagawa phenomena

Virulence factors:

- Has two hemolysins virulence factors, thermostable direct hemolysin (tdh) contributes to the invasiveness of the bacterium in humans,
- TDH-related hemolysin (trh)
- Type III secretion systems (T3SS1 and T3SS2) codes for adhesion

References:

- https://www.khanacademy.org/test-prep/mcat/biological-sciences-practice/biological-sciences-practice-tut/e/virulence-factors-in-outbreak-strain-cholera

- Vibrio parahaemolyticus: a review on the pathogenesis, prevalence, and advance molecular identification techniques

Helicobacter Pylori

Outline:

- Overview
- Pathogenesis
- Clinical Presentations
- Diagnosis
- Virulence Factors
- Treatment

Overview:

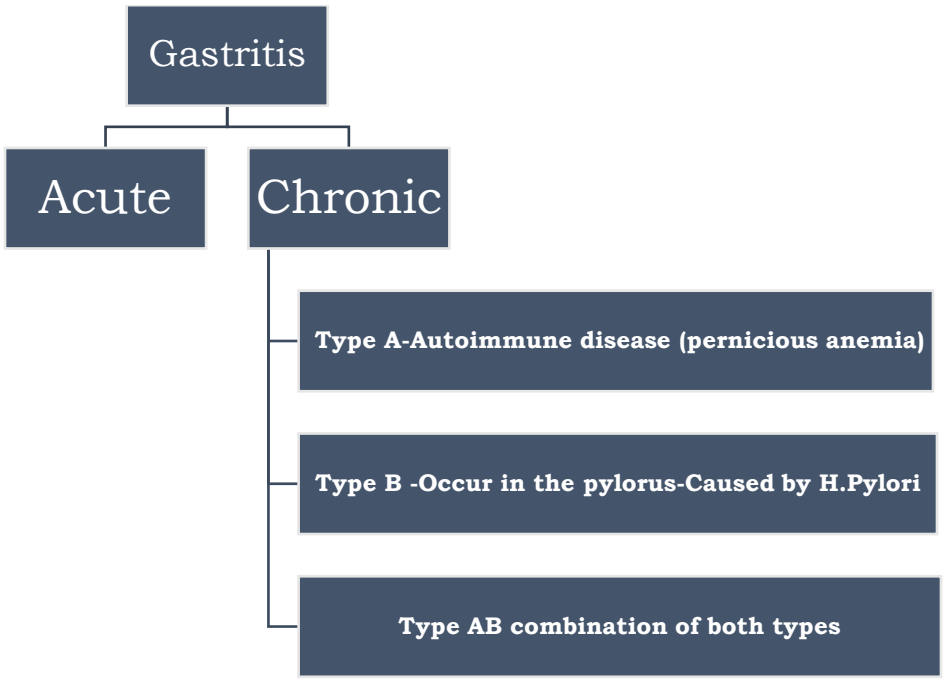
- Gram negative rod
- Catalase, urease and oxidase positive
- Wavy shaped
- Highly motile microorganism

Pathogenesis:

- Common route of H. pylori infection is either oral-to-oral or fecal-to-oral contact
- Infect human stomach
- Associated with inflammatory responses

Clinical Presentations:

- Causes gastritis and peptic ulcer disease (90%
- Considered risk factor for:
- Gastric adenocarcinoma, lymphoma
- Mucosa-associated lymphoid tissue lymphomas (MALTomas)
- Gastroesophageal reflux disease (GERD)



Diagnosis

- Carbon-13 urea breath test (urease breath test): Concentration of the labeled carbon is high in breath only when urease is present in the stomach, a positive reaction indicates H pylori infection
- H pylori fecal antigen test
- Catalase, urease and oxidase positive

Virulence Factors:

- Flagella: Used for bacterial motility to invade gastric mucosa
- The body's natural defenses cannot reach the bacterium in the mucus lining of the stomach
- Once H. pylori is safely landed in the mucus, it is able to fight the stomach acid that does reach it with an enzyme it possesses called urease.
- Urease converts urea from saliva and gastric juices into bicarbonate and ammonia, which are strong bases (neutralize gastric acid)
- Mucinase to break mucous layer
- Catalase enzyme, helps survive within the neutrophils
- Lipopolysaccharide for host cell adherence
- Type IV secretion system

Treatment

- Triple antibiotic therapy (Clarithromycin+ Amoxicillin+ Metronidazole)
- Proton Pump inhibitors (Omeprazole)
- Bismuth Salicylate (coating stomach lining)

References:

- Helicobacter pylori urease for diagnosis of Helicobacter pylori infection: A mini review. Journal of advanced research ,2018
- The Helicobacter Foundation

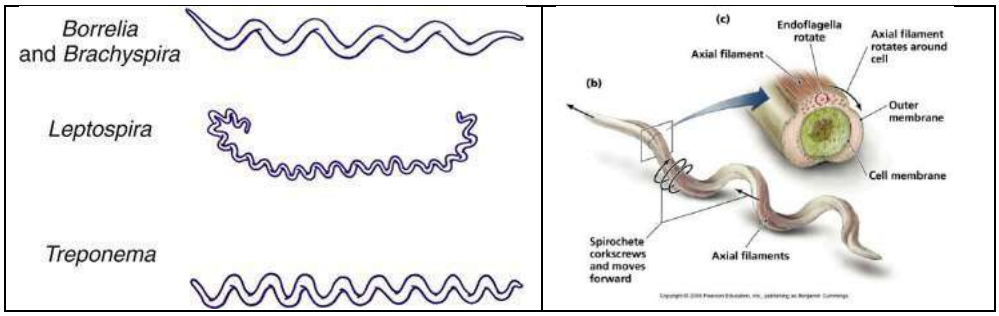
Spirochetes

Outline:

- Overview
- Pathogenesis
- Treponema Pallidum
- Borrelia burgdorferi
- Leptospira interrogans

Overview:

- Elongated motile spiral shaped bacteria with axial filaments
- Spin to achieve propulsion
- Contains endoflagella
- Extremely small detected only by dark field microscope



Pathogenesis:

- Spirochetes associated human diseases

Species	Disease
Treponema Pallidum	Syphilis
Borrelia burgdorferi	Lyme disease
Leptospira interrogans	Leptospirosis (Weil's disease)

Treponema Pallidum:

- Primary cause of Syphilis (STD)
- Could be detected in fresh primary or secondary lesions by dark filed microscope or fluorescent antibody technique
- Can't cultivated in culture media
- Transmission through:

1. sexual contact of an infected person
2. Mother to fetus in utero (Treponema Pallidum crosses the placenta)

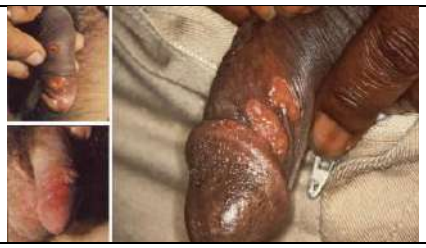
Clinical presentations of Syphilis:

Syphilis progresses in three stages:

Primary stage:

- painless chancre with incubation period (3 to 6 weeks)
- Chancre:
  - A lesion has a punched-out base and rolled edges
  - Highly infectious
  - Appear on the cervix, vaginal wall and anal canal
  - Characterized by mononuclear leukocytic infiltration, macrophages, and lymphocytes
- The spirochetes could be isolated from the exudate of the chancre
- Diagnosis: Dark field microscope, VDRL test, FTA-ABS, RPR

- Venereal Disease Research Laboratory (VDRL test)
- Rapid Plasma Reagin (RPR)
- Fluorescent Treponemal Antibody Absorption Test (FTA-ABS)



These photographs depict the characteristic chancre observed in primary syphilis. Used with permission from Wisdom (Left) A. Color Atlas of Sexually Transmitted Diseases. Year Book Medical Publishers Inc; 1989. (Right) Centers for Disease Control and Prevention

Medscape

Secondary stage:

- Develops about 4-10 weeks after primary syphilis
- The spirochetes spread throughout the body causing dissemination
- Systemic signs include fever, malaise and lymphadenopathy
- Widespread mucocutaneous rash (global red macular rash) all over the body involve palms and soles
- condylomata lata and patchy alopecia
- All such lesions and aggregations contain treponemes.
- Patients at this stage develops moth-eaten appearance
- Latent syphilis is one of the characteristics of this phase, where the features of secondary syphilis have resolved but the patient considered seroreactive positive
- Diagnosis: Dark field microscope, (VDRL test, RPR) nonspecific then FTA-ABS

Condylomata lata: painless, highly infectious gray-white aggregations that develop in warm, moist sites such as genital areas

Patchy alopecia: hair loss of the scalp and facial hair, including the eyebrows

Tertiary Syphilis

- Composed of three categories:

1. Gummatous syphilis:
   - Localized granulomatous dermal lesions called Gummas
   - Characterized by necrotic center on the skin (painless) yet painful for bones
   - Associated with release of macrophages and fibroblast which reflect the immunogenic response of the host to the infection
   - Appear 3-10 years after primary infection

2. Cardiovascular syphilis:
   - Caused by chronic inflammation destruction of the vasa vasorum leading to aneurysm formation in the ascending aorta (Aortitis)
   - As a result, aortic valve insufficiency may also occur
   - Appear 10 years after primary infection

N.B: Vasa vasorum: the penetrating vessels that nourish the walls of large arteries.

3. Neurosyphilis:
   - Could be developed in several forms;

A. Syphilis meningitis:
   - when spirochetes invade CNS
   - Usually occur 6 months post primary infection
   - Characterized by fever, stiff neck, headache and CSF showed high protein, high lymphocytes and low glucose.
   - Positive syphilis test

B. Meningovascular syphilis:
   - Occur because of damage to blood vessels of meninges, brain and spinal cord
   - Cause sever neurological damage

C. Parenchymal Syphilis
   - Causes tabes dorsalis and general paresis
   - Both conditions characterized by Argyll-Robertson pupil (The pupil accommodates but not react) called also prostitute's pupil
   - Tabes dorsalis is also associated with Positive Romberg's test and Charcot joint

Diagnosis: VDRL test RPR then FTA-ABS

Tabes dorsalis: is severe damage at the posterior column and dorsal root ganglia leading to ataxia, loss of reflexes and impaired proprioceptive sensation, leading to a wide-based gait

Romberg's test: A test used evaluate neurological function for balance sensation (proprioception), vestibular function and vision

Charcot joint: progressive degeneration of weight bearing joint and eventually lead to bone deformity due to loss of sensation.

Congenital syphilis:

- Treponema Pallidum crosses the placenta
- Congenital syphilis can be prevented if the mother is treated in the first trimester
- Early congenital syphilis mimics secondary syphilis (rash, condyloma lata)
- Late congenital syphilis mimics tertiary syphilis and characterized by:
  - Saddle nose (changes in the cartilage of the nasal septum)
  - Saber shins (inflammation and bowing of the tibia)
  - Clutton's joints (inflammation of knee joints)
  - Hutchinson's teeth (the upper incisors are widely spaced and notched)
  - Mulberry molars (the molars have too many cusps)
  - CN VIII deafness, optic nerve atrophy and corneal inflammation might lead to blindness

Diagnosis:

- Dark light microscope: detection of spirochetes in active lesions (chancre, condyloma lata, macules)
- VDRL and RPR are nonspecific tests depend on the presence of antibodies against cardiolipin and lecithin (present in the blood stream after infection)
- FTA-ABS is a confirmatory, accurate and specific test for Treponema Pallidum

Cases of false positive VDRL test:

- Pregnancy
- Viral infection (eg, EBV, hepatitis)
- Drugs
- Rheumatic fever
- Lupus and leprosy

Treatment:

- Benzathine penicillin G
- Jarisch-Herxheimer reaction; Flu-like symptoms (headache, fever, myalgia) after Penicillin treatment due to release of pyogenic toxins

Borrelia burgdorferi:

- Primary cause of Lyme's disease
- Transmitted to humans via tick bites from infected Ixodes tick
- Mouth is the natural reservoir of lyme's disease
- Common in the northeast cost of USA
- Could be detected by light microscopy with Giemsa, Aniline or Wright stains.

Pathogenesis:

- Borrelia burgdorferi infection involves 3 stages:

1. Early stage:
   - Flu-like symptoms.
   - Erythema chromicum migrans – Rash at the site of infection
   - Lymphadenopathy
   - Bulls-eye lesion that develops around the site of a lone star tick bite
   - These signs start 10 days after tick bite

2. Second stage:

- Early disseminated disease
- Characterized by high immune response manifested by ECM with multiple skin lesions
- Nervous system (facial nerve (bell) palsy, peripheral neuropathy)
- Heart (AV node block, require peace maker replacement)
- Joints (Migratory arthritis)

3. Late stage:

- Encephalopathy
- Chronic arthritis
- Knee pain
- Migratory polyarthritis
- Polyneuropathy

Diagnosis:

- Depend on the appearance of ECM rash
- Could be detected by light microscopy with Giemsa, Aniline or Wright stains.
- ELISA or western blot

Treatment:

- Doxycycline
- Ceftriaxone

Leptospira interrogans:

- Primary cause of Leptospirosis
- Found in water contaminated with animal urine
- Most common among surfers in Hawaii

Clinical presentations:

- Symptoms start when bacteria invade blood and CSF causing flu-like symptoms
- Hepatocellular dysfunction (Jaundice)
- Conjunctivitis (photophobia)
- vasculitis of capillaries
- Advanced stage of Leptospirosis manifests icteric leptospirosis (Weil disease):
  - Jaundice
  - Renal failure with oliguria, azotemia (↑Bilirubin/creatinine ratio)
  - Hemorrhage
  - Systemic inflammatory syndrome or shock
  - Anemia

Diagnosis:

- Culture of blood or CSF
- PCR of urine, blood or CSF
- ELISA
- Liver function tests
- CSF analysis
- Coagulation studies
- Renal function studies

Treatment:

- Doxycycline
- Ampicillin or amoxicillin
- Azithromycin or clarithromycin
- Fluoroquinolone such as ciprofloxacin or levofloxacin

References:

- https://emedicine.medscape.com/article/229461-overview
- First aid 2018
- Crush Step 1 - The Ultimate USMLE Step 1 Review, 1E (2014)

Gardnerella Vaginalis

Outline:

- Overview
- Signs and Symptoms
- Diagnosis
- Treatment

Overview:

- Pleomorphic
- Facultative anaerobic gram rod
- Associated with sexual activity
- Causes bacterial vaginosis due to bacterial overgrowth (disruption of normal bacterial flora) NOT STD infection

Signs and Symptoms:

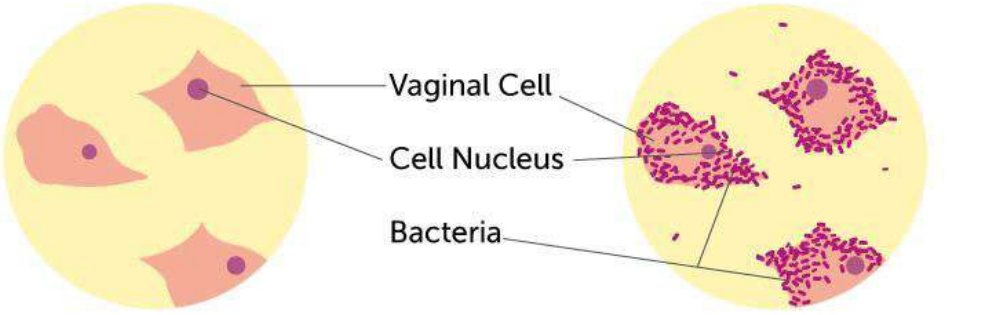
- Fishy smell
- Itching
- Burning of the labia
- Gray/off-white vaginal discharge

Diagnosis:

- Detection of Clue cells in vaginal smear

Treatment:

- Metronidazole



Normal vaginal cells seen under a microscope.

"Clue Cells", vaginal cells with bacteria stuck to them.

References:

- https://youngwomenshealth.org/2012/09/21/bacterial-vaginosis/
- Crush Step 1- The ultimate USMLE step 1 Review.

Chlamydia

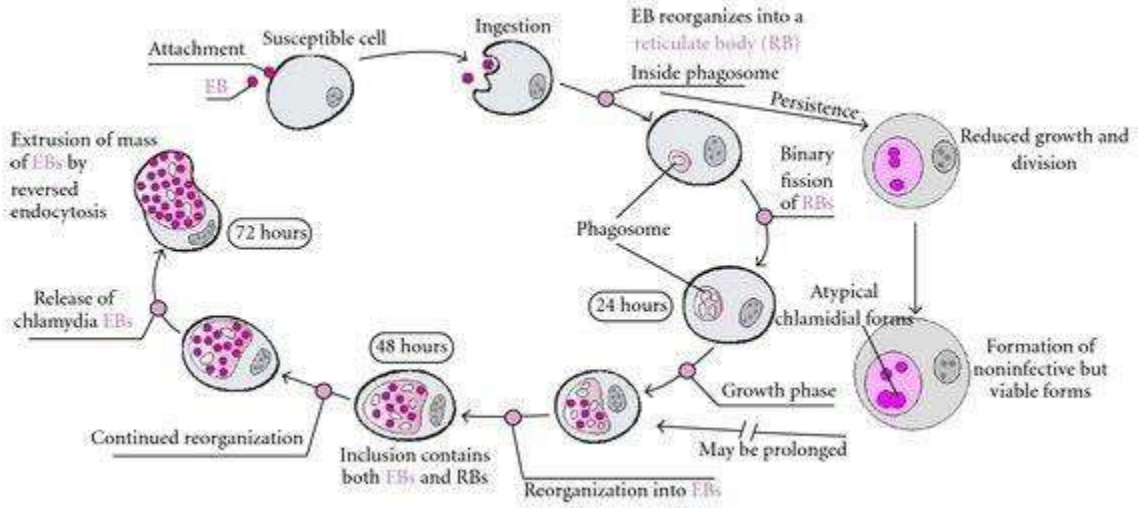
Outline:

- Overview
- Pathogenesis
- Chlamydia subtypes
- Diagnosis
- Treatment

Overview:

- Obligate intracellular bacteria
- Lacks peptidoglycan cell wall due to reduced muramic acid
- Lack ATP, require ATP from the host cell
- Multiply in the cytoplasm of host cell
- Extremely small
- The chlamydial growth cycle involves transformation between distinct forms: the elementary body (EB) and the reticulate body (RB)

Elementary body	Reticulate body
• Extremely small • Enter via endocytosis • Released from ruptured infected cell	• Intracytoplasmic form • Replicate and grow inside the cell by fission



Life cycle of Chlamydia

Pathogenesis:

- Chlamydia targets mucous membranes such as (Eyes, GIT and Lungs)

Chlamydia subtypes

1. Chlamydia Trachomatis:
    - Divided into different serological strains
    - Serotype (A-C)/more common in developing countries causes Trachoma characterized by sever conjunctivitis and might lead to blindness.
    - Serotype (L1-L3) causes Lymphogranuloma venerum STD/painless
    - Serotype (D-K) causes

    1. Urethritis characterized by dysuria and white discharge
    2. Epididymitis in men
    3. Pelvic inflammatory disease (PID) characterized by lower abdominal pain, cervical discharge, fever and dyspareunia
    4. Ectopic pregnancy
    5. Neonatal pneumonia from birth canal infection (staccato cough)
    6. Neonatal conjunctivitis or inclusion conjunctivitis from birth canal infection characterized by yellow discharge and swelling of eyelids

    N.B Chlamydia trachomatis infection might progress to reactive arthritis known as Reiter syndrome (inflammatory arthritis, urethritis, and conjunctivitis)

2. Chlamydia Pneumonia:
    - Cause atypical pneumonia with characterized staccato cough. Spread from human to human

3. Chlamydia Psittaci:
    - Transmitted through exposure of bird faeces
    - Common among bird breeders and pet shop workers
    - Caused atypical pneumonia

Diagnosis:

- Identification of cytoplasmic inclusions (RB) on Giemsa or Fluorescent antibody
- In case of neonatal conjunctivitis diagnosis is made by observing inclusion bodies in cells scraped from the eyelids.
- In case of urethritis PCR or urine sample is required

Treatment:

- Azithromycin
- Doxycycline

References:

- Chlamydia cell biology and pathogenesis. Nature reviews microbiology 2016.
- Antichlamydial Antibodies, Human Fertility, and Pregnancy Wastage. Journal of obstetrics and gynecology 2011.

Rickettsia infection

Outline:

- Overview of Rickettsia species
- Pathogenesis
- Classification of Rickettsia infection
- Rash group
- No Rash group

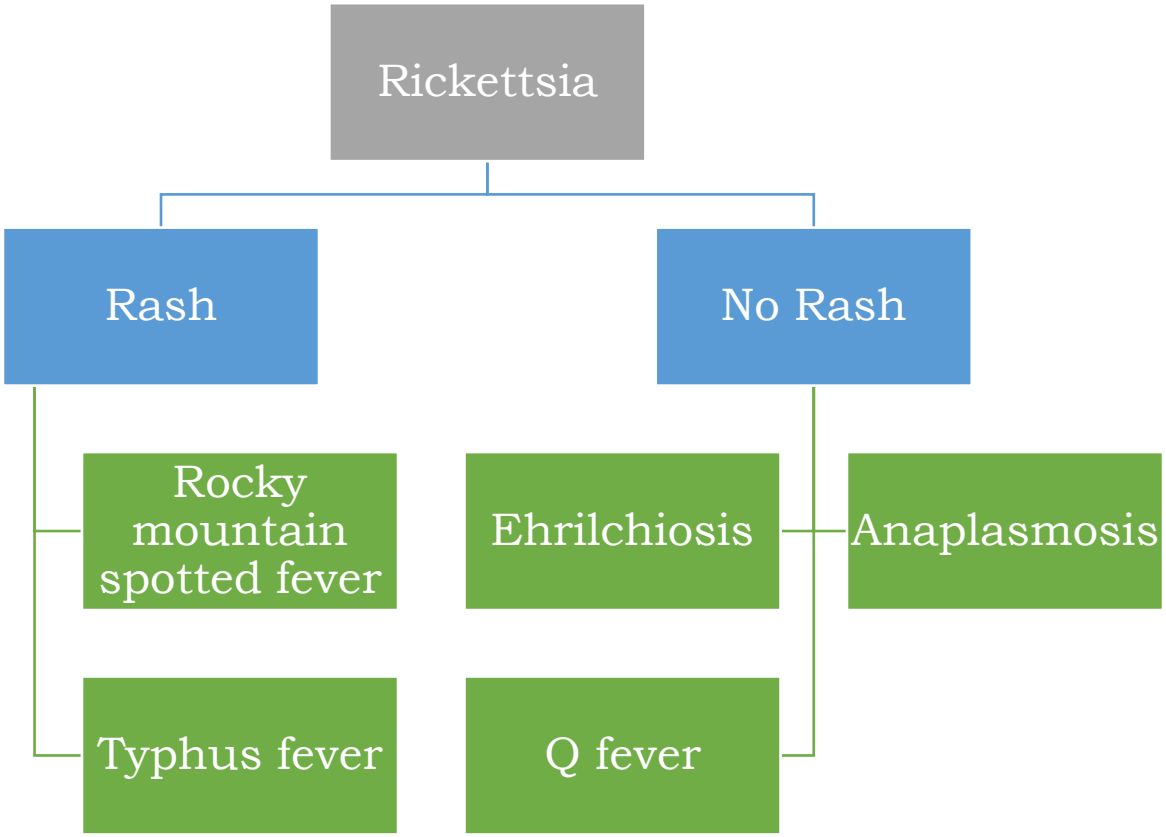
Overview:

- Obligate intracellular parasite (rely on ATP)
- Gram negative pleomorphic rod
- Require tick vector
- Mammals and arthropods are natural hosts for Rickettsia species
- Doxycycline is the drug of choice for tick bites

Pathogenesis:

- Rickettsia infection is transmitted through a bite f infected tick
- Infection starts by invading the endothelial lining of blood vessels
- Adhesins protein help the rickettsia to be phagocytosed into the host cells

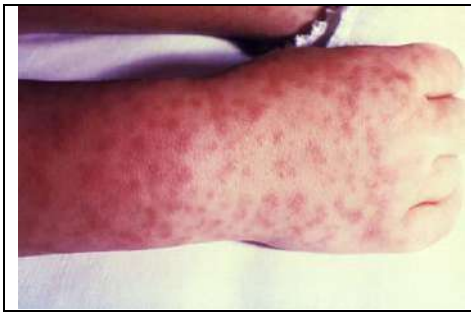
Classification of Rickettsia infection



Rash group:

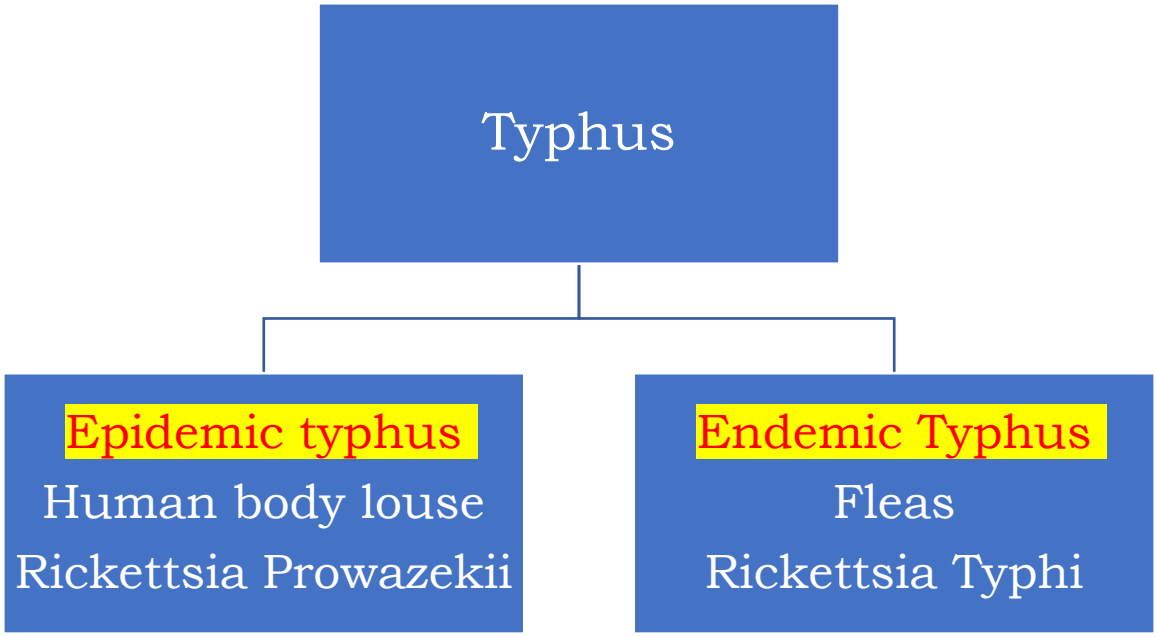
Rocky mountain fever:

- Causes by Rickettsia Rickettsii
- Symptoms start after a week of tick bite
- Patient suffers from vasculitis (fever, headache and ascending rash) (starts from wrists-palms and soles -ankles then spread to the trunk)
- Mechanism of pathogenies: Invasion of endothelium wall of blood vessels which causes wide spread rash, conjunctival redness, edema and hypotension

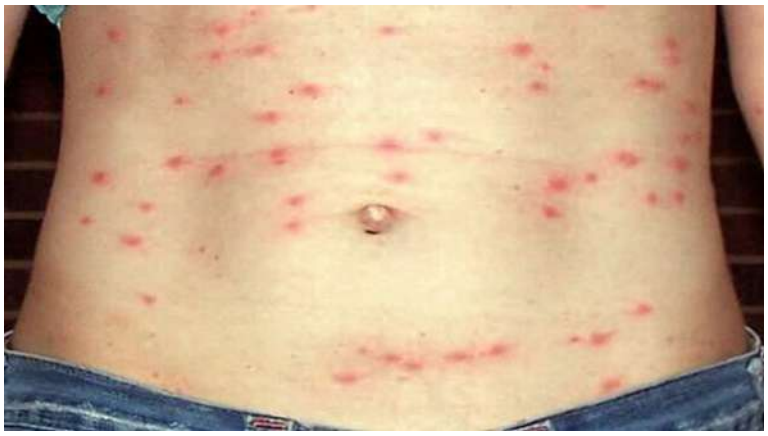


The patient's rash is a major diagnostic sign of Rocky Mountain spotted fever (RMSF). Image courtesy of the Centers for Disease Control and Prevention (CDC).

Typhus fever:



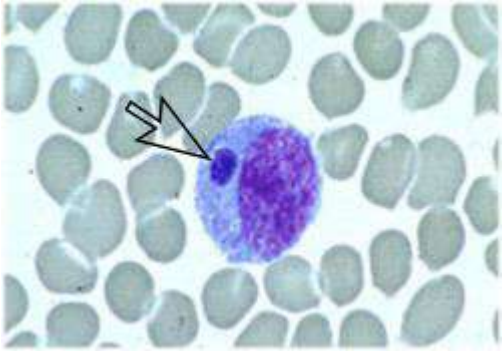
- Rash starts with small pink macules appear on the trunk then spread-out



NO rash Group:

Ehrlichiosis:

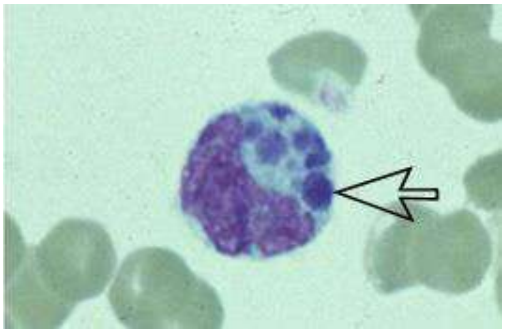
- Caused by Ehrlichia chaffeensis
- Transmitted by dog tick
- Monocytes with morulae in cytoplasm (mulberry-like inclusions)



Ehrlichia chaffeensis morula in a monocyte.
http://www.cdc.gov/anaplasmosis/symptoms/index.html.

Anaplasmosis:

- Caused by Anaplasma
- Granulocytes with morulae in cytoplasm



Anaplasma phagocytophilum morula in an immature granulocyte.
http://www.cdc.gov/anaplasmosis/symptoms/index.html.

Q fever:

- Caused by Coxiella burnetiid
- Does NOT require a vector
- Transmitted by transmission by aerosolized tic/cow feces
- Form endospores that provide it the ability to surivive outside host cell
- Causes Pneumonia, granulomatous hepatitis and culture-negative endocarditis

References:

- Crush Step 1- The ultimate USMLE step 1 Review

Mycoplasma Pneumoniae

Outline:

- Overview
- Pathogenesis
- Clinical Presentations
- Diagnosis
- Treatment

Overview:

- Pleomorphic bacteria which lacks cell wall
- Penicillin are not effective due to absence of cell wall
- More common in closed environments such as prisons and Military

Pathogenesis:

- Transmission through inhalation of respiratory infected droplets
- Mechanism of Pathogenesis: Target respiratory epithelial cells with the advantage of H_2O_2 release that responsible for ciliary movement inhibition

Clinical Presentations:

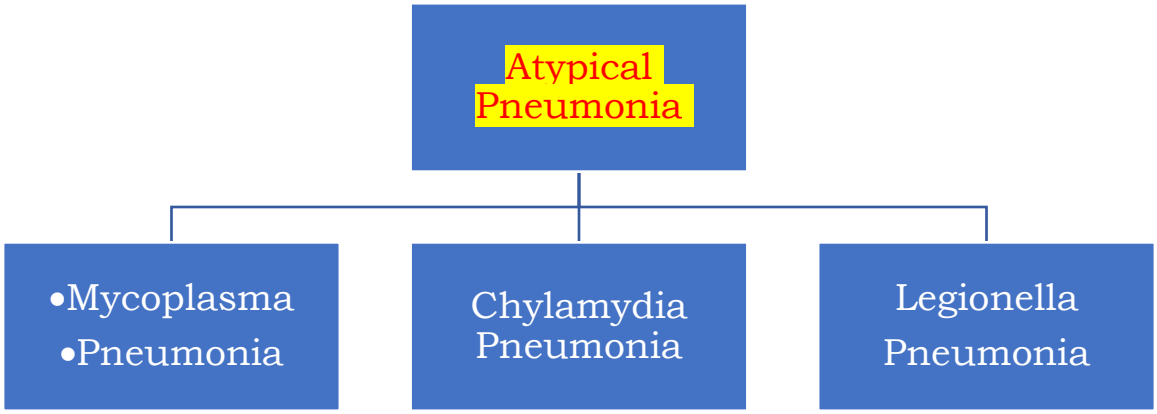
- Cause Atypical Pneumonia (walking pneumonia)- nonproductive Cough, fever-malaise
- Diffuse Interstitial infiltrate

Diagnosis:

- X-ray showed diffuse interstitial infiltrate
- Positive cold agglutinin test: blood clumping on ice (due to formation of anti-RBC antibodies)
- PCR
- Culture on Eaton agar (Fried egg shaped)

Treatment:

- Macrolides (Azithromycin, Clarithromycin and Erythromycin



References:

- Crush Step 1- The ultimate USMLE step 1 Review

Types of Systemic Mycoses:

- Fungi that switch between the yeast and mold forms are termed dimorphic
- Dimorphic fungi are the main source of systemic infection
- Mold usually grow at 20 C, while yeast grow at 37 C.
- Coccidioides, which is a spherule (not yeast) in tissue.
- Inhalation of mold spores from the soil is the primary route of infection
- Whenever these spores reach the lung (high temperature), the dimorphic fungi transform into yeast
- Four types of systemic mycoses:
    1. Blastomycosis
    2. Histoplasmosis
    3. Coccidiomycosis
    4. Paracoccidiomycosis
- Considered endemic infections in the United States
- All types could predispose patient to Pneumonia and disseminate into the body leading to systemic infection (Immunocompromised patients)
- Systemic mycoses can form granulomas (like TB)

Histoplasmosis:

- Caused by Histoplasma capsulatum
- More common in Mississippi and Ohio states
- Histoplasma commonly found in soil (bird or bat droppings)
- Named as caves disease or spelunker's lung disease

Clinical presentations:

- Usually the patient is asymptomatic but might develop pneumonia with flu-like symptoms (cough, fever, malaise, body ache)
- Inhalation of bat/bird stools associated with invasion of lung alveoli and macrophages
- The macrophages in lymph node engulf the spores and form granuloma
- Severe Histoplasmosis might lead:
    - Acute respiratory distress syndrome
    - Pericarditis
    - Fibrosing mediastinitis
    - Pruritic chest pain

Diagnosis:

- Appearance of yeast forms in macrophages and giant cells
- Usually the macrophages are filled with Histoplasma
- Urine or skin antigen test
- Chest x-ray
- Pancytopenia
- Elevated alkaline phosphatase
- Blood culture

Treatment

- Fluconazole or itraconazole for local infection
- Amphotericin B for systemic infection
- Amphotericin B could cause renal insufficiency and ototoxicity

Note: Amphotericin B might lead to ototoxicity and nephrotoxicity

Blastomycosis

- Caused by Blastomyces dermatitidis
- More common in eastern (Mississippi) and central USA
- Blastomyces dermatitidis lives in soil or rotten roads near lakes and rivers

Clinical presentations:

- The patient develops primary pneumonia with symptoms of high fever, chills, a productive cough, and pleuritic chest pain.
- Skin infection is considered the primary pathogenesis (skin lesions)
- Skin infection might progress to verrucous (wart-like) or granuloma
- Blastomycosis usually disseminate and invade many organs in case of immunocompromised patients
- Blastomycosis causes bone infection and joint pain

Diagnosis:

- Detection of Blastomyces yeast forms with broad-based buds in in sputum, skin scrapings, or pus.
- Elevated leukocytosis
- Hypoxemia due to inflammation and decrease oxygen in blood stream
- Positive KoH test
- Positive blood culture

Treatment:

- Fluconazole or itraconazole for skin infection
- Amphotericin B for systemic infection

Coccidioidomycosis:

- Caused by Coccidioides immitis
- More common in the southwestern United States (southern California, Arizona, Nevada, New Mexico).
- Known as Valley fever or California fever
- In the air appear as spores while in the lung appear as spheres

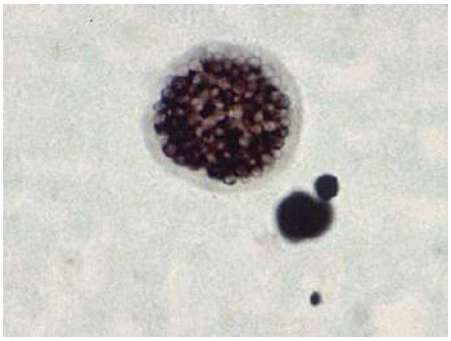
Clinical presentations:

- Usually patients are asymptomatic, but the symptoms might develop to pneumonia. In chronic causes develops into disseminate infection (meningitis).
- The patient might also develop pulmonary fibrosis
- Coccidioidomycosis characterized by triad of "desert rheumatism" include fever, arthralgia, and erythema nodosum and may occur in acute infection
- Erythema nodosum: palpable painful nodules on anterior tibia.

- In case of disseminate infection (meningitis) the patient develops headache, blurry vision, photophobia, decline in cognition, hearing changes, and focal neurologic deficit

Diagnosis:

- A lumbar puncture with analysis of cerebrospinal fluid (CSF)
- Chest x-ray
- Serologic analysis detecting fungal antigen or host IgM or IgG antibody produced against the fungus
- Microscopic detection of spherules
- Positive fungal culture



A Coccidioides immitis spherule containing endospores.

Treatment:

- Amphotericin B for systemic infection

Para-coccidioidomycosis:

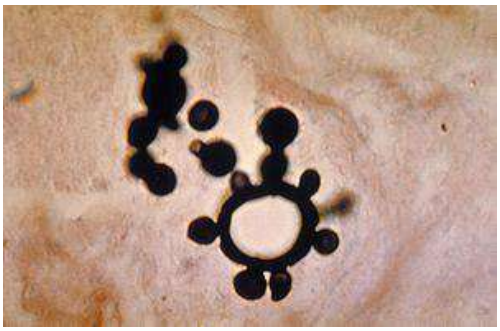
- Caused by Paracoccidiodies brasiliensis
- More common in latin America
- Men are more predisposed than females

Clinical presentations:

- Usually patients are asymptomatic, but the symptoms might develop to pneumonia and pulmonary fibrosis.
- Dissemination- lungs- dry productive cough, malaise, fever, shortness of breath, oral lesions
- Cervical lymphadenopathy

Diagnosis:

- Captain's wheel formation



Captain's wheel

References:

- First aid 2018
- Crush Step 1- The ultimate USMLE step 1 Review.

Types of cutaneous Mycoses:

Tinea

- Caused by dermatophytes (cutaneous fungal infection)
- Types of dermatophytes Trichophyton, Microsporum, Epidermophyton
- These fungi feed on keratin of hair, nails and skin
- Usually associated with Purities
- Diagnosis: Skin scraping with KOH prep shows branched hyphae.

Tinea capitis (barber's itch/folliculitis):

- Infection of head and scalp
- Characterized by alopecia and scaling and associated with lymphadenopathy

Tinea Corporis:

- Infection of body /torso
- Known as ringworm because its erythematous scaling ring and central clearing

Tinea Cruris (Jock itch):

- Infection of inguinal area
- Characterized by scaly patches of skin

Tinea Pedis (Athlete's foot)

3 subtypes:

- Interdigital
- Moccasin distribution
- Vesicular type

Tinea unguium (onychomycosis)

- Infection of nails
- Characterized by brittle, thickened, yellowish nails

Tinea versicolor and tinea nigra

- Considered as superficial infection
- Caused by Malassezia species
- Produces acids which have bleaching effect, degradation of lipids and discoloration of the skin
- Characterized by hyperpigmentation and pink patches
- Associated with hot and humid weather
- Diagnosed microscopically as spaghetti and meat balls
- Treatment by antifungal and **selenium sulfide**

References:

- First aid 2018
- Crush Step 1- The ultimate USMLE step 1 Review.

Opportunistic Fungal infection

Outline:

- Overview
- Candida albicans
- Aspergillus fumigatus
- Cryptococcus Neoformans
- Mucor and Rhizopus spp.
- Pneumocystis jirovecii
- Sporothrix schenckii

Overview:

- Opportunistic fungal infection is more common in immunocompromised patients such as AIDS with CD4< 200.
- Also, neonates and diabetic patients are more prone to these infection

Candida albicans

- Dimorphic yeast
- Pseudo hyphae with budding yeast

Clinical presentations:

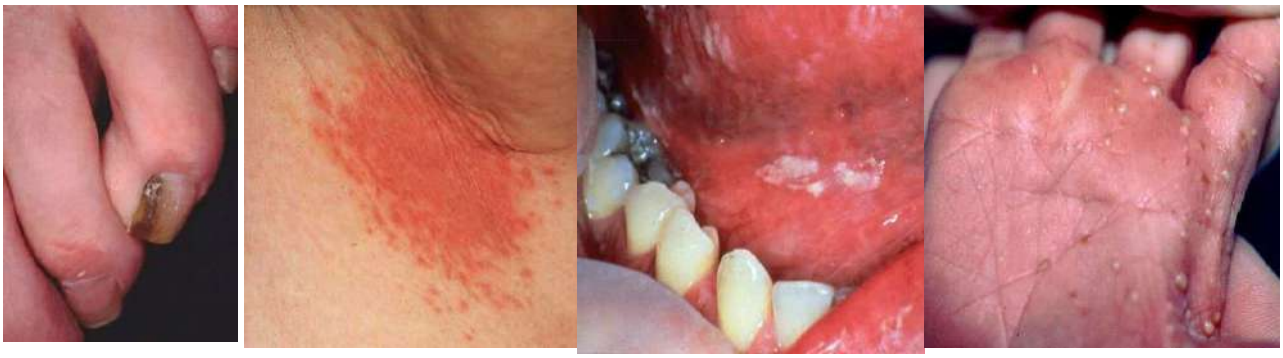
- Can cause systemic or superficial infection
- Local infection such as oral and esophageal thrush especially in immunocompromised patients such as (AIDS, diabetes, steroids and neonates)

Note: Oral candidiasis could overlap with oral hairy leukoplakia. The difference is leukoplakia cannot be scraped off easily and tends to occur on the sides of the tongue, while mucosal or esophageal candidiasis could be scraped off

- Diaper rash in newborns (satellite lesions)
- Vulvovaginitis
- Diabetic patients are more prone to fungal infection due to the high glucose level (opportunistic medium for fungi)
- Systemic disseminated infection (Fungemias or Candidemia) such as endocarditis (IV drug abusers)

Treatment:

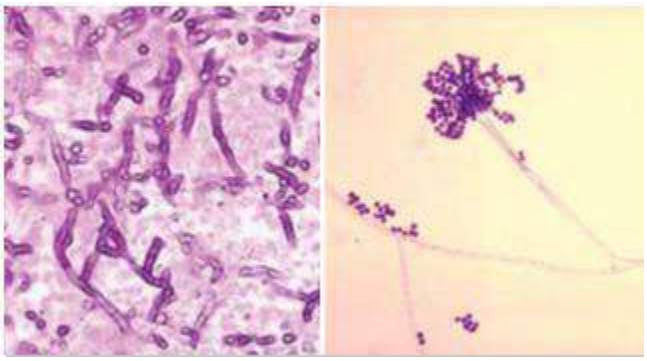
- Oral fluconazole or topical azole for vaginal infection
- Fluconazole or echinocandins for oral thrush
- Amphotericin B or caspofungin for systemic infection
- Consider prophylactic fluconazole in HIV patients with recurrent candidiasis



Source: https://emedicine.medscape.com/article/213853-overview

Aspergillus fumigatus:

- Monomorphic septate hyphae which branch at 45 angle
- Transmitted through inhalation of spores
- Aspergillus produce aflatoxin (Associated with hepatocellular carcinoma)



Septate hyphae that branch at 45 angle

Clinical presentations:

- Causes invasive aspergilloses in immunocompromised patients (Patients with chronic granulomatous disease)
- Invasive aspergilloses start with invasive fungal sinusitis and rapidly begin to disseminate and spread to the brain
- Associated with post-TB infection. Aspergillus might invade lung cavities and reside for years leaving lesions and granulomas
- Cause allergic bronchopulmonary aspergillosis (ABPA)

ABPA:

- Hypersensitivity reaction due to inhaled Aspergillus causing release of peripheral eosinophilia and bronchospasm
- Usually associated with asthma and cystic fibrosis

Treatment:

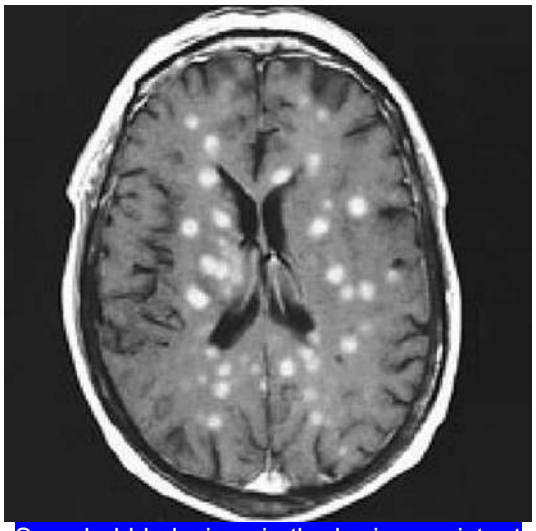
- Systemic aspergillosis treated by voriconazole, caspofungin, or amphotericin B

Cryptococcus Neoformans:

- 5–20 µm yeast with white capsule halos
- Unequal body- **NOT** dimorphic
- Could be found in Soil and transmitted through inhalation of yeast from (pigeons and bird droppings)

Clinical presentations:

- Associated with meningitis manifested by fever, headache and confusion
- Also associated with lung and skin infection
- Pruritic chest pain, lymphadenopathy
- Systemic disseminated infection includes cryptococcosis, cryptococcal encephalitis ("soap bubble" lesions in brain), primarily in immunocompromised.



Soap bubble lesions in the brain consistent with Cryptococcus neoformans infection

Diagnosis:

- CSF lumbar analysis and stain for encapsulated yeast (Indian Ink stain)
- Measurement of cryptococcal antigen level
- Latex agglutination test detects polysaccharide capsular antigen
- Culture on Sabouraud agar
- Detection of soap bubble in the brain

Treatment:

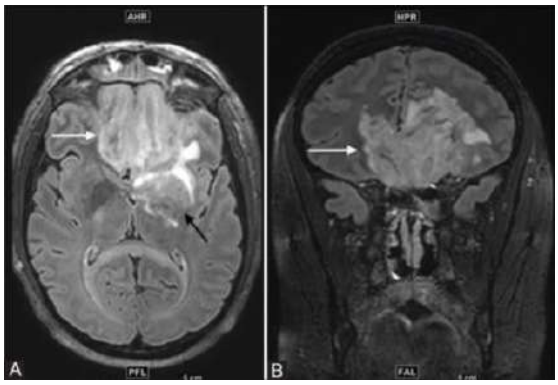
- Oral fluconazole for mild infection
- Amphotericin B + flucytosine followed by fluconazole for cryptococcal meningitis.

Mucor and Rhizopus spp:

- Irregular non-septate hyphae branching at wide angles (>90°).

Clinical presentations:

- Rhinocerebral mucormycosis commonly affects individuals with diabetes and those in immunocompromised states
- Fungi start grow in the blood vessels then spread into the brain frontal lobe and start forming abscesses rhinocerebral mucormycosis
- Symptoms include cavernous sinus thrombosis, headache, facial pain, black necrotic eschar in the face, facial cellulitis, diplopia and vision loss
- Diabetic patients (Ketoacidotic patients) are prone to these infections due to increase blood glucose levels
- Associated with high mortality 60-70% while disseminated infection with 100% mortality.



Rhinocerebral mucormycosis

Diagnosis:

- Right angle hyphae on plate culture
- Tissue biopsy of necrotic tissue

Treatment:

- Amphotericin B
- Posaconazole
- Surgical debridement of necrotic tissue

Pneumocystis jirovecii

Transmitted through inhalation

Clinical presentations:

- Causes Pneumocystis pneumonia (diffuse interstitial pneumonia) especially among AIDS patients CD4 count< 200
- Pneumocystis pneumonia linked to AIDS patients especially when CD4 count< 100

Diagnosis:

- Chest x-ray and hypoxemia in an immunocompromised patient
- Diffuse, bilateral ground-glass opacities on CXR/CT, with pneumatoceles B
- lung biopsy or bronchoalveolar lavage.
- Disc-shaped yeast seen on methenamine silver stain of lung tissue

Treatment:

- TMP-SMX is the drug of choice. Pentamidine and dapsone for prophylaxis only
- Prophylaxis should begin with a CD4 count <200 in all AIDS patients

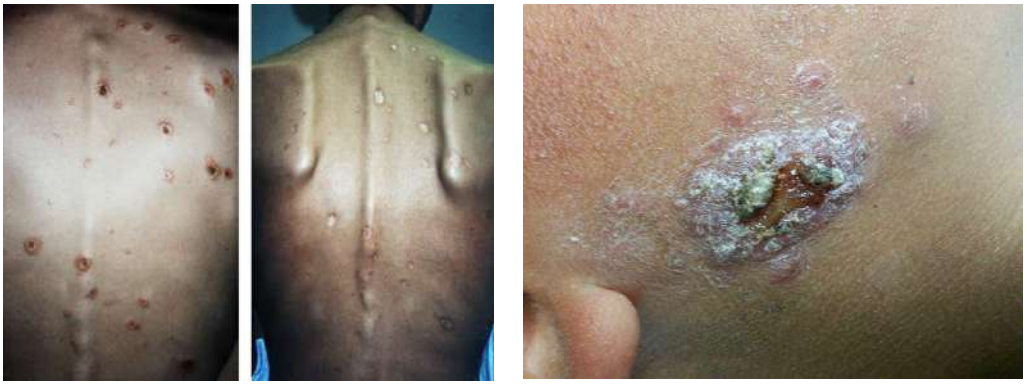
Sporothrix schenckii

- Dimorphic with cigar shaped budding yeast
- Transmitted through a cut or puncture wound in the skin

Photomicrograph that shows the conidiophores and conidia of the fungus Sporothrix schenckii
Source: Medscape

Clinical presentations:

- The causative agent of sporotrichosis, commonly known as "rose gardener's disease"
- Cutaneous sporotrichosis is a small skin lesion characterized by ulceration and/or erythema
- Infection spreads through the lymph node and causes lymphocutaneous sporotrichosis.



Source: Medscape

Treatment:

- Antifungal such as Itraconazole
- Potassium Iodide

References:

- First aid 2018
- Diagnosis and treatment of mucormycosis in patients with hematological malignancies: guidelines from the 3rd European Conference on Infections in Leukemia (ECIL 3). Journal of Hematologica 2013

GIT protozoa infection

Outline:

- Giardia Lamblia
- Entamoeba histolytica
- Trypanosoma spp.
- Acanthamoeba

Giardia Lamblia

- Transmitted through oral -fecal route by ingestion of contaminated water with Giardia cyst
- Common among hikers and campers (drinking from untreated river/spring water)
- Infection starts when Giardia trophozoites attack intestinal enterocytes causing injury and atrophy followed by alteration in fat absorption (Foul-smelling, fatty diarrhea)
- Causes Giardiasis

Clinical Presentations:

- Associated with flatulence, bloating, abdominal pain and foul smell odour

Diagnosis:

- Entero-test: detection of Trophozoites / cysteine in stool
- IgA deficiency in an individual with recurrent giardiasis.
- Multinucleated trophozoites

Treatment:

- Metronidazole

Entamoeba histolytica

- Transmitted through ingestion of contaminated water with Entamoeba cyst
- Causes amebiasis- Amebic dysentery
- Could disseminate to other organs, leading to abscess formation in the lung, liver, colon, and brain (rarely)

Clinical Presentations:

- Abdominal pain, bloody diarrhea
- (Dysentery) liver abscess characterized Anchovy paste exudate, RUQ pain and ulceration of intestinal epithelium

Diagnosis:

- Blood test, detection of trophozoite with RBC in cytoplasm
- Detection of cyst with multiple nuclei
- Colon biopsy- flask shaped ulcers
- Antigen testing against Entamoeba histolytica

Treatment:

- Metronidazole for invasive disease
- Iodoquinol/paromomycin colonization

Cryptosporidium parvum:

- Can be found in unfiltered water
- Characterized by sever watery diarrhea in AIDS patients
- Mild diarrhea/ self-limiting diarrhea in immunocompetent individuals

Diagnosis:

- Detection of oocysts on acid fast stain (like TB)

Treatment:

- Supportive treatment: filtering drinking water
- Nitazoxanide in immunocompetent patients

	Giardia Lamblia	Entamoeba histolytica	Cryptosporidium parvum
Clinical presentations	Foul-smelling, fatty diarrhea	Bloody diarrhea	Severe watery diarrhea (AIDS)
	Giardiasis	amebiasis- Amebic dysentery	
Treatment	Metronidazole	Metronidazole-Iodoquinol	Nitazoxanide
Diagnosis	Multinucleated trophozoites	detection of trophozoite with RBC in cytoplasm	Detection of oocysts on acid fast stain

References:

- https://www.medscape.com/viewarticle/421533_3
- Five facts about Giardia lamblia. Journal of Plos pathogens 2018
- Review: Facts Concerning Entamoeba histolytica Induced Amoebiasis. 2017

CNS protozoa infection

Outline:

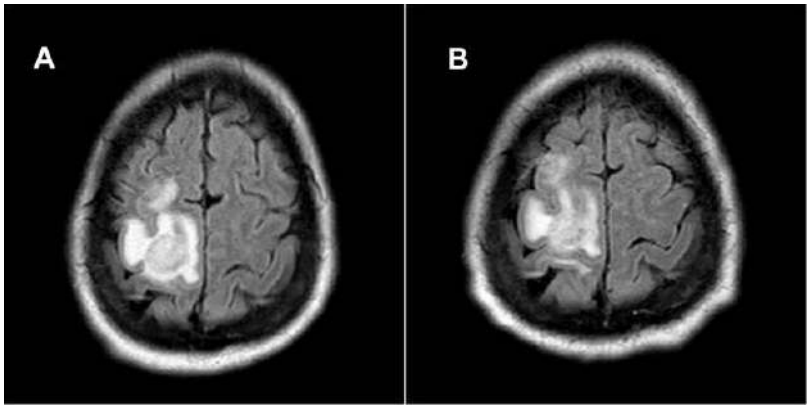
- Toxoplasma gondii
- Naegleria fowleri
- Trypanosoma spp.
- Acanthamoeba

Toxoplasma gondii

- Protozoa found in most animals. Common in cat faeces (oocysts)
- Transmitted through ingestion of cysts in infected undercooked meat (e.g., pork or lamb)
- The infection starts when the cyst reached GIT where it decyst and eventually the sporozoites released attacking macrophages
- The infected macrophages burst allowing the sporozoites to circulate in the blood where it invades other host cells including nerve cells

Clinical presentations:

- Flu like illness (Runny nose, cough and fever)
- Immunocompromised HIV or AIDS present with altered mental status or encephalitis – brain abscess
- Systemic infection is usually associated with ring-enhancing lesions on CT or magnetic resonance imaging



Brain MRI with contrast showing multiple ring-enhancing lesions

Congenital toxoplasmosis:

- Transmitted to pregnant woman when become in close contact to oocyst in cat faeces

Congenital toxoplasmosis is associated with:

- Intrauterine infection (still birth)
- Chorioretinitis
- Hydrocephalus

    - Intracranial calcifications
- Pregnant woman should avoid cats to avoid congenital problems

Diagnosis:

- CT/MRI showing ring enhancing lesions (caused also by CNS lymphoma)
- Diagnose by antibodies against T. gondii or biopsy of brain lesions

Treatment

- In case of immunocompromised /AIDS patients (CD4 count<100) recommended for prophylaxis TMP-SMX or sulfadiazine
- For systemic or congenital toxoplasmosis sulfadiazine and pyrimethamine

Naegleria fowleri:

- Ameba in fresh water
- Transmitted through ingestion of Trophozoite via the olfactory mucosa and cribriform plate of the swimmer

Clinical presentations:

- Get access to the brain rapid onset of acute mengioencephalites (1-14d later)
- Very low survival rate

Diagnosis

- lumper puncture of CSF

Treatment:

- Amphotericin B

Trypanosoma brucei and cruzi:

Trypanosoma brucei

- Named as African trypanosomiasis caused by Trypanosoma brucei Gambiens (East Africa) and Trypanosoma brucei rhodesiense
- Transmitted by tsetse fly

Clinical presentations:

- Infection started when Trypomastigotes are disseminated through the body and replicate in the blood, lymphatics, and spinal fluid. Symptoms are:

- Large painful chancre (Tsetse fly bites leaves an itchy chancre)
- Recurrent fever, lymph node swelling
- CNS changes manifested by headache, changes in behavior, focal neurological deficits
- Eventually excessive somnolence leading to eventual coma and death.

Diagnosis:

- Detection of Trypomastigote in blood smear

Treatment:

- Suramin for bloodborne disease or melarsoprol for CNS penetration

Trypanosoma cruzi

- More common in south America
- Causes Chagas disease and caused by reduviid bug or kissing bug
- Enter the blood through the bite wound or through mucous membranes
- Associated with dilated cardiomyopathy, apical atrophy, megacolon and megaesophagus

Diagnosis:

- Detection of trypanosomes in the blood during acute infection.

Treatment:

- Benznidazole or nifurtimox.

Acanthamoeba:

- Free-living amoebae
- Transmitted through skin inhalation or the blood
- Causes Keratitis in contact lens users
- Causes chronic meningoencephalitis in immunocompromised patients

References:

- Paradoxical immune reconstitution inflammatory syndrome due to toxoplasmic encephalitis: Two cases and review of initiation of antiretroviral timing in toxoplasmic encephalitis IRIS. 2013

Babesia microti/Leishmania

Outline:

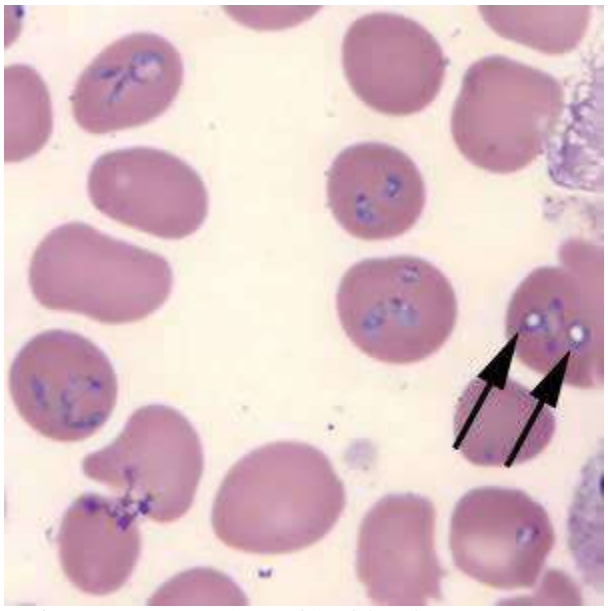
- Babesia microti
- Leishmania

Babesia microti:

- Transmitted by the bite of the infected Ixodes tick (also cause Lyme disease)
- Also, could be transmitted through blood transfusion
- Causes babesiosis and associated with fever, fatigue, myalgia and hemolytic anemia

Diagnosis:

- Visualization of Babesia trophozoites (ring forms) and merozoites (Maltese crosses



Babesia microti in a thin blood smear stained with Giemsa. Note the intra-erythrocytic vacuolated forms indicated by the black arrows.

Treatment:

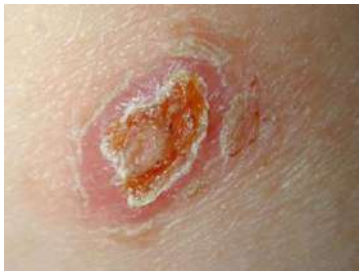
- Quinine and clindamycin.

Leishmania donovani and Leishmania species (leishmaniasis)

- Most common in tropical regions (Mexico, South America, southern Europe, Asia, Middle East, and North and East Africa)
- Transmitted through bite of infected sandfly.

Types of Leishmania infection:

- Cutaneous Leishmaniasis caused by L. Tropica characterized by skin ulcer at site of sandfly bite



Localized cutaneous leishmaniasis

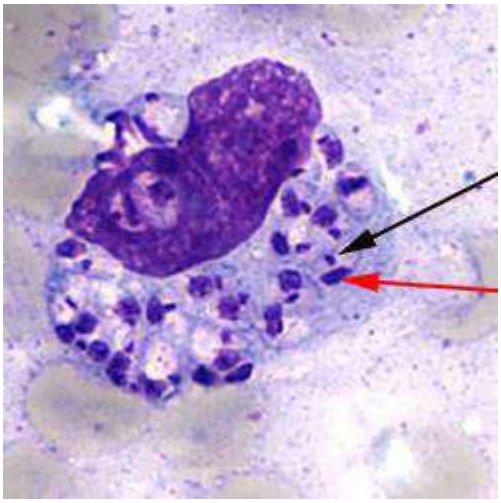
- Diffuse Leishmaniasis: Disseminated subcutaneous infections which may last longer in immunocompromised patients

- Mucocutaneous Leishmaniasis: Caused by L. L. braziliensis, L. Mexicana and associated with ulcer in the skin and mucous membrane.

- Visceral Leishmaniasis (L. donovani): Known as Kala-azar and characterized by hyperpigmented skin lesions disseminated to liver, spleen and lymph nodes causing spleno and hepatomegaly. Pancytopenia, fever, weight loss

Diagnosis:

- Visualization of amastigotes within macrophages and tissues



specimen from a patient with visceral leishmaniasis—showing a macrophage (a special type of white blood cell) containing multiple Leishmania amastigotes

Treatment:

- Sodium Stibogluconate

References:

- https://www.cdc.gov/parasites/leishmaniasis/diagnosis.html

Chagas disease drugs

Outline:

- Chagas disease
- African sleeping sickness

Chagas disease

- Known as known as American trypanosomiasis. It is caused by the parasite Trypanosoma cruzi, which is transmitted to animals and people by insect vectors (**Reduviid bugs**) and is found only in the Americas (mainly, in rural areas of **Latin America** where poverty is widespread).
- Reduviid bug known as kissing bug or **Triatomine**
- The infection starts when the bug deposited feces in a painless bite

Clinical presentations

- Acute infection characterized by ever or swelling around the site of inoculation
- **Romaña's sign**, which includes swelling of the eyelids on the side of the face near the bite wound is one of the recognized signs of acute infection
- Complications of chronic infection (10-20 years after infection) includes:

Heart

- Dilated cardiomyopathy leads to congestive heart failure
- Heart rhythm abnormalities that can cause sudden death;

Esophagus

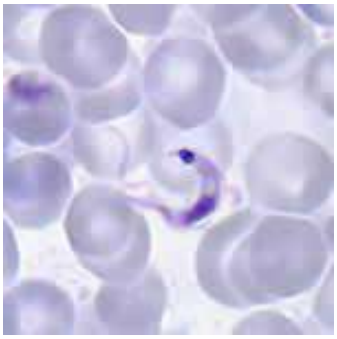
- Dilation of the esophagus
- Weight loss
- Swallowing difficulties
- Achalasia lead to malnutrition

Colon

- Megacolon leading to difficulty with passing stool

Diagnosis

- Microscopic examination of Peripheral smear (During the acute phase of infection, parasites may be seen circulating in the blood)



Treatment

- Nifurtimox drug of choice

African sleeping sickness

- Known as **African trypanosomiasis**
- Caused by Trypanosoma brucei/ gambiense

- Treatment: Pentamidine, Suramin, melarsoprol

References:

- First aid 2018
- Current Topics in Tropical Emerging Diseases and Travel Medicine. 2018
- Chagas Heart Disease an Emerging Concern in the United States. 2016

Anti-Leishmaniasis
Leishmaniasis

- Leishmania is responsible for the disease **Leishmaniasis**
- Transmitted by sandflies

Visceral leishmaniasis

- Leishmania donovani responsible for visceral leishmaniasis known as kala-azar disease
- Characterized by:

1. Spiking fevers,
2. hepatosplenomegaly
3. pancytopenia

- Diagnosed by amastigotes in macrophages in bone marrow, liver, spleen
- Treatment: **sodium stibogluconate**

Cutaneous leishmaniasis

- Characterized by amastigotes in macrophages in cutaneous lesions
- Treatment: **sodium stibogluconate**

References:

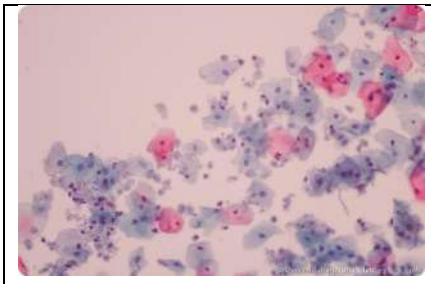
- First aid 2018

Trichomonas Vaginalis:

- Causes trichomoniasis
- Acquired by sexual transmission ONLY since cannot form cysts
- Causes vaginitis characterized by foul-smelling, greenish discharge; itching and burning
- In women cause inflammation of the cervix (Cervicitis)
- In men causes urethritis

Diagnosis

- Microscopic detection of motile trophozoites on wet mount
- Strawberry cervix

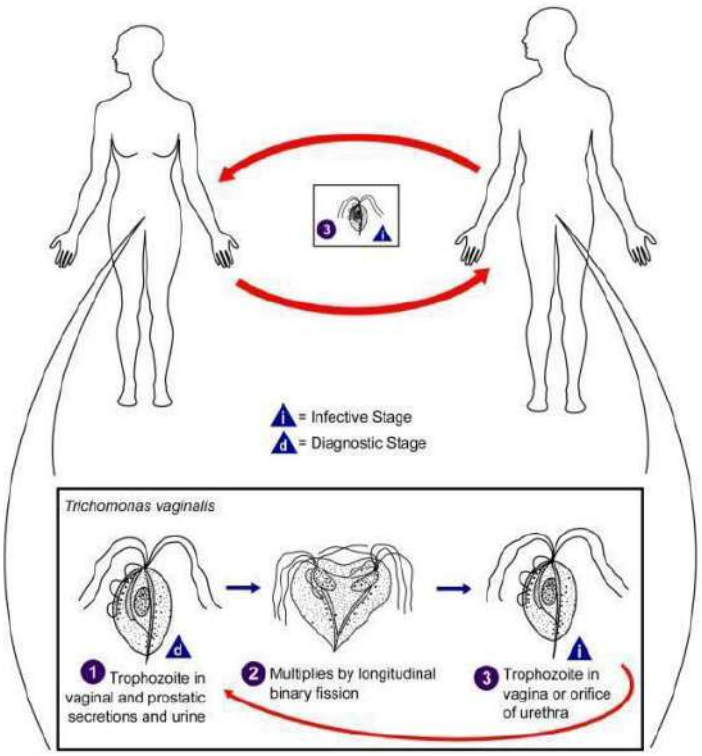
	
Trichomonas vaginalis infected pap smear test.	Endoscopic image showing frothy discharge and vaginitis associated with Trichomonas vaginalis

Treatment:

Metronidazole for both partners

Type of vaginal discharge:

- White/thick discharge usually at the end of menstrual cycle (Yeast or candida infection)
- Gray/fishy smell (bacterial infection)
- Greenish/itchy/burning (trichomoniasis)



Life cycle of *Trichomonas vaginalis (image source: CDC)*

References:

- CDC
- Crush step1- The ultimate USMLE step 1 review

Nematodes (roundworms)

Outline:

- Nematodes infect intestine
- Nematodes infect tissue

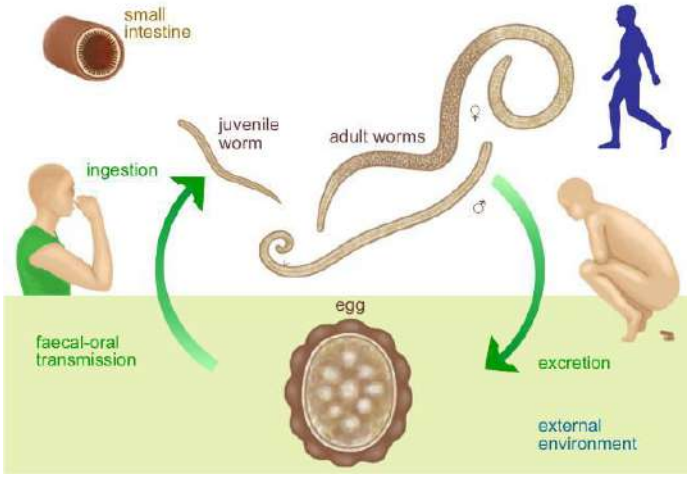
Nematodes infect intestine

Pinworm (Enterobius vermicularis)

- Transmitted through infected food with pinworm eggs
- Mature pinworms hatch and live in the large intestine.
- Pinworms are more active at night around anus where it lays their eggs
- Cause **anal pruritis**
- Diagnosis:
- **Scotch tape test**, detection of the eggs on adhesive tape when applied to preanal area
- Treatment:
- Bendazoles

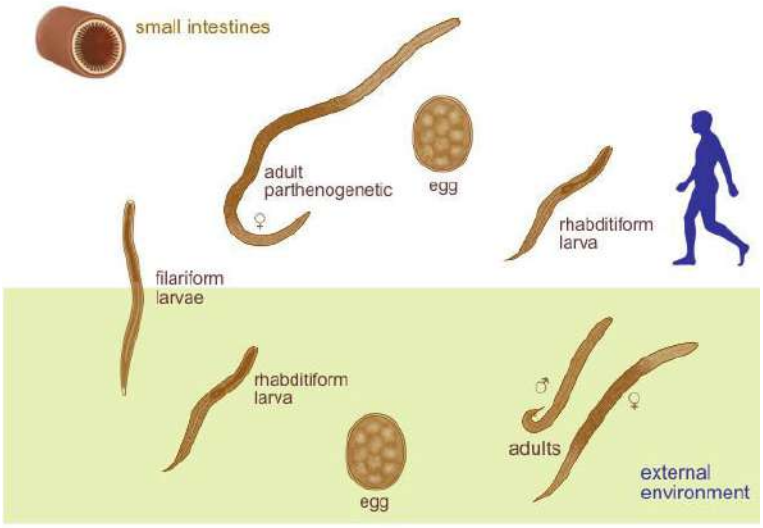
Ascaris lumbricoides (giant roundworm):

- Found on soil
- Transmitted through ingestion of Ascaris eggs
- The infection starts when it migrates to the intestine and penetrate intestinal mucosa reaching blood stream
- Symptoms include malnutrition or bowel obstruction, biliary obstruction, intestinal perforation.
- The patient might progress into pneumonitis
- Diagnosis:
- Microscopic detection of oval eggs in faeces
- Treatment:
- Bendazoles or pyrantel pamoate



Strongyloides stercoralis (threadworm)

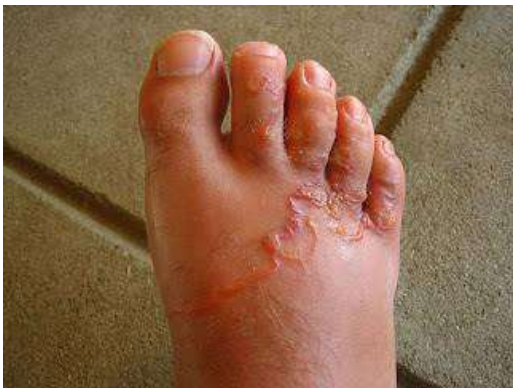
- Strongyloides found in the soil where it penetrates the skin reaching lung and intestine
- It invades intestinal mucosal wall and spread into blood stream and stay forever
- Diagnosis:
- Detection of rhabditiform larvae in faeces
- Treatment:
- Bendazoles



Hookworms (Ancylostoma duodenale, Necator americanus)

- Warm climate and poor sanitation are risk factors for hookworm's infection
- Hookworm eggs found in the soil where it penetrates the soles of bare feet.

- It migrates to the lung through blood stream then reaches the intestine during coughing.
- The symptoms start by allergic reaction from skin penetration includes pruritic rash and itching.
- The symptom might progress to pneumonitis, iron deficiency anemia since hookworm is sucking blood from intestinal wall.
- Treatment:
- Bendazoles or pyrantel pamoate



Trichinella spiralis:

- Transmitted to human through eating undercooked meat (especially pork)
- Initially larvae excyst in the stomach then migrate to the muscle (inflammation) through blood circulation
- The symptoms include muscle pain and weakness and periorbital edema
- Diagnosis:
- Detection of Trichinella cyst on muscle biopsy
- Treatment:
- Bendazoles

Whipworm (Trichuris trichiura):

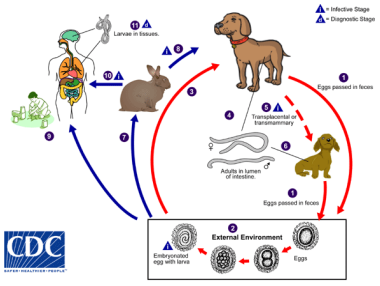
- Transmitted through oral-fecal route
- The infection starts in the intestine then spread to large intestine

- The symptoms include bloody diarrhea and rectal prolapse
- Treatment:
- Bendazoles

Nematodes infect tissue:

Toxocara canis:

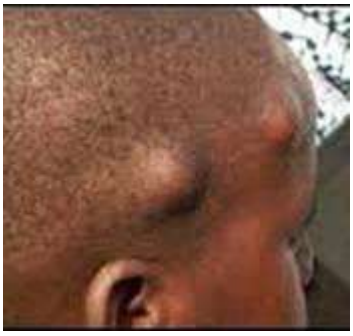
- Usually found in dogs
- Transmitted through fecal-oral route
- Causes **visceral larva migrans**
- Initially the infection starts when the larvae penetrate the intestinal mucosa then find its way to blood stream
- The symptoms include:
  - Hepatitis
  - Myocarditis
  - Seizures, coma
  - Retinal lesions of the eye.
- Treatment:
- Bendazoles



Onchocerca volvulus:

- Transmitted by female black fly
- Skin is considered the main site of infection
- The symptoms include initial pruritis followed by subcutaneous nodules, hyperpigmented skin lesions in chronic conditions
- Severely affect retina causing river blindness

- Treatment:
- Ivermectin



Loa loa:

- Transmitted by biting flies such as Deer fly, horse fly, mango fly
- Characterized by calabar swellings and appear in the conjunctivae of the eye
- Treatment:
- Diethylcarbamazine.

Wuchereria bancrofti:

- Transmitted by female mosquito
- More common in tropical and subtropical regions
- Causes lymphedema and elephantiasis
- Treatment:
- Diethylcarbamazine.

References:

- A review of methods for nematode identification. Journal of microbiol methods, 2017
- https://www.cdc.gov/parasites/about.html
- Crush step 1- The ultimate USMLE step 1 Review, 2014

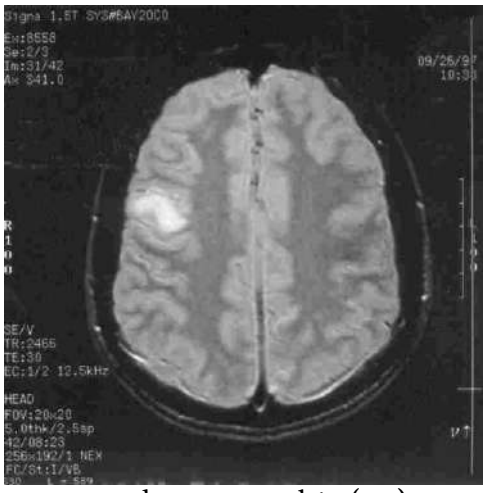
Cestodes (Tapeworms)

Outline:

- Taenia species
- Diphyllobothrium latum
- Echinococcus graulosus

Taenia Solium

- Transmitted by Ingestion of larvae encysted in **undercooked pork**
- Ingestion of contaminated food with Taenia eggs
- The patient initially suffers from abdominal pain and if the larvae migrate to the brain it might cause cysticercosis or neurocysticercosis
- Neurocysticercosis characterized by cystic CNS lesions and seizures
- Diagnosis:
- MRI brain scan shows Cerebral cysticercosis showing a cyst containing developing larva.



Computed tomographic (CT) scan of the brain in a patient who presented with an episode of generalized tonic-clonic seizure. Note the calcified lesion in the left parieto-occipital region. Source: Medscape

- Treatment:
- First line of treatment (intestinal symptoms) Praziquantel, while progressive cysticercosis should be treated with Albendazole

Diphyllobothrium latum (fish tapeworm):

- Transmitted through consumption of raw fish or seafood
- Fish tapeworm live on intestinal B12
- Causes Vitamin B12 deficiency features:
  - Megaloblastic anemia
  - Increased MCV
  - Hyper segmented neutrophils
  - Increased homocysteine
  - Increase methylmalonic acid levels
- Treatment:
- Praziquantel

Echinococcus granulosus (dog tapeworm)

- Transmitted through dog faeces and sheep (intermediate host)
- The infection starts in the intestine then migrate to the liver showing cystic cavity (hydatid cyst).
- Rupture of the cyst might cause anaphylaxis and treated by injection of ethanol before surgical removal
- Diagnosis:
- Liver CT scan shows eggshell calcification
- Treatment:
- Albendazole

References:

- https://www.cdc.gov/parasites/taeniasis/biology.html

Trematodes

Outline:

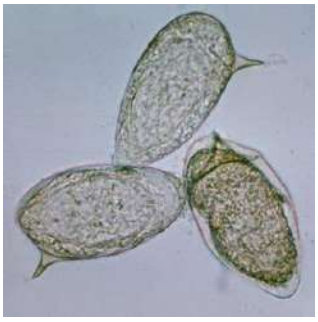
- Overview
- Schistosomiasis
- Echinococcus graulosus

Overview:

- Infection of trematodes are carried out through two intermediate host
- First snails are infected with nematodes then fish or shellfish transmit the infection to human

Schistosomiasis (blood flukes)

- S mansoni with lateral spine shape
- Migrate to the liver causing portal hypertension-Liver and spleen enlargement - Liver fibrosis



- S. haematobium with terminal shape
- Migrate to the lung causing pulmonary hypertension
- Can cause squamous cell carcinoma of the bladder (painless hematuria)

Clonorchis sinensis (Chinese liver fluke)

- More common in Asia
- Transmitted through undercooked fish

- Associated with cholangiocarcinoma
- Cause Portal hypertension and hepatic cancer
- Infect gall bladder causing pigmented gallstones

Treatment for all trematodes is **praziquantel**

References:

- https://www.cdc.gov/parasites/liver_flukes/index.html
- https://emedicine.medscape.com/article/219662-overview

Ectoparasites

Outline:

- Sarcoptes scabiei
- Pediculus humanus

Sarcoptes scabiei

- Ectoparasites means outside hence it usually infects the outer layer of the skin (startum corneum)
- Causes scabies
- Characterized by severe itching (pruritis) and burrows in hands and feet
- Mites burrow under the skin and lay eggs
- Very common among children and overcrowded population such as prisons, nursing homes
- Transmitted through skin to skin contact
- Treatment
- Permethrin
- Wash clothes and bedding

Pediculus humanus (lice)

Phthirus pubis (pubic louse)

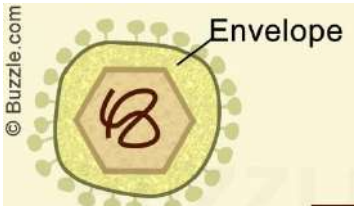
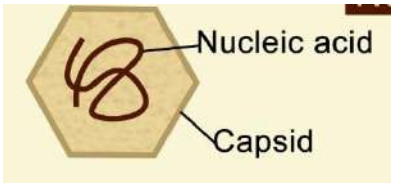
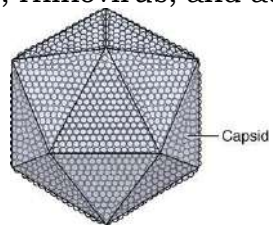
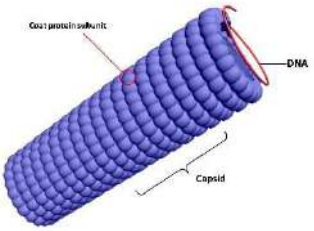
- Scalp and neck (head lice) or waistband and axilla (body lice).
- Feed on human blood
- Can transmit Rickettsia prowazekii (epidemic typhus), Borrelia recurrentis (relapsing fever), Bartonella quintana (trench fever).
- Treatment:
- Permethrin
- Ivermectin lotion
- Malathion
- Nit combing

References:

- Centers for disease control and prevention (CDC)
- The unusual reproductive system of head and body lice (Pediculus humanus). Journal of Medical and Veterinary entomology, 2018.

Viral structure and genetics

- Viral structure

Envelope Virus	Non-Envelope Virus (Naked)
Sensitive to heat	Heat resistant
Enclosed within a lipid membrane	Lacks bilayer lipid membrane
Transmitted by direct contact (blood – Sexual- respiratory)	Oral-fecal transmission
	
Icosahedral	**Helical**
Capsid and nucleic acid just like naked Icosehedral	The capsid shaped into a filamentous, or rod-shaped structure
The genetic material is fully enclosed inside of the capsid	Central cavity that encloses its nucleic acid
poliovirus, rhinovirus, and adenovirus.	The plant tobacco mosaic virus
	

Note: All viruses are single stranded (Haploid) except HIV is DS

- Interaction between viruses

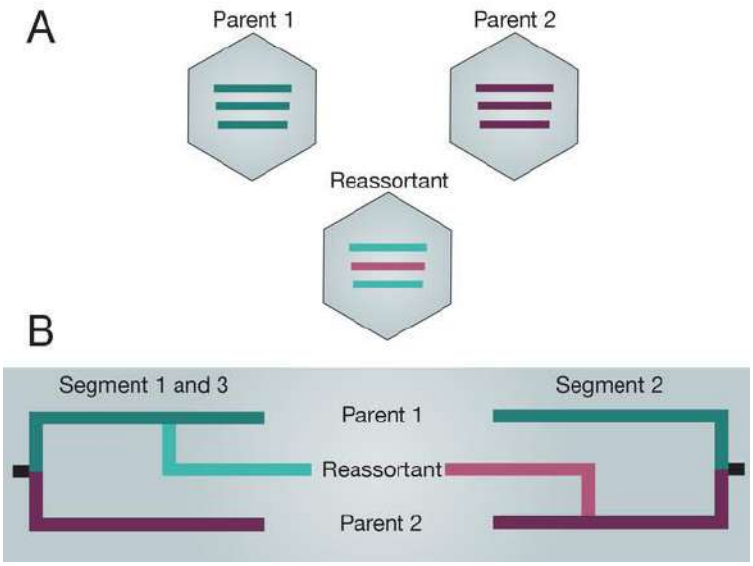
Recombination:

- Produced by recombining pieces of DNA from different virus strains resulting in new progeny not present in the original infecting viruses
- Occurs by homologs crossing over

Reassortment:

- When two viruses infect the same cell and during this process genetic material is being exchange

- Reassortment occur among influenza virus (segmented genome)



Complementation:

- Interaction at a functional level NOT at the nucleic acid level.
- This process allows defective viruses to replicate and spread
- If the cell is coinfected with 2 viruses and one of them is not functional (defective) so both viruses help each other's to complement the missing part. However, the defect virus will die in the next cell due to absence of the complement protein

Phenotypic mixing:

- The cell is being attacked by two viruses each of which holds its own unique genetic material.
- Both viruses share capsid or coat protein
- Viral genome of one virus may be encapsulated in the capsids or the other virus Pseudovirion

- The infectious power will be determined based on the parental genome is packed

References:

- RNA Virus Reassortment: An Evolutionary Mechanism for Host Jumps and Immune Evasion. Journal of PLOS, 2015

DNA Viruses

Outline:

- Herpes simplex Viruses
- Herpes simplex type-2
- Varicella Zoster Virus (HHV3)
- Epstein Barr Virus (HHV4)
- Cytomegalovirus (HHV-5)
- Human Herpes Virus 6 (HHV6)
- Human Herpes Virus 7 (HHV7)
- Human Herpes Virus 8 (HHV8)
- Human Papillomavirus
- Adenovirus
- Polyomavirus
- Pox virus
- Hepadna virus
- Parvovirus B19

Herpes Simplex Viruses:

Herpes simplex type-1:

- Associated with orofacial infection

Mechanism of transmission:

- Saliva and respiratory system

Clinical Presentations:

- Blister in the lips
- Gingivostomatitis
- Keratoconjunctivitis
- Temporal lobe encephalitis

Treatment:

- Acyclovir

Herpes simples type-2:

- Associated with genital infection
- Affects Sacral nerve root ganglia (S2-S5)

Mechanism of transmission:

- Sexual contact and perinatal

Clinical Presentations:

- Genital herpes
- Viral meningitis (neurovirulence)
- Newborn infection (birth defects, neonatal encephalitis, intrauterine death) if the mother displayed HSV II infection (through Herpes Labialis)

Varicella Zoster Virus (HHV3):

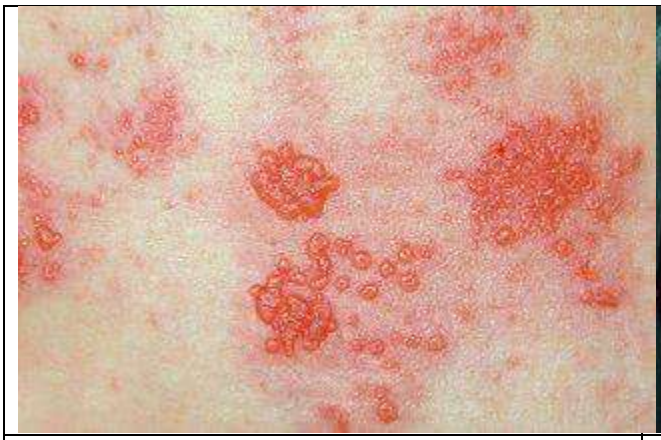
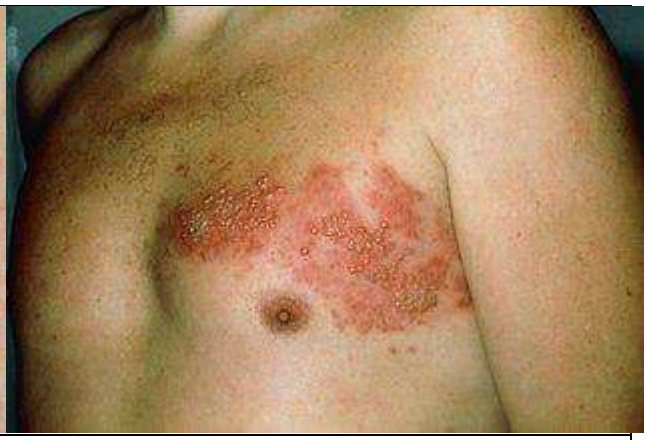
- Dormant in dorsal ganglia and reactivation during stress or immunocompromise patients

Mechanism of transmission:

- Respiratory transmission and skin contact
- Two weeks incubation period followed fever, malaise and pharyngitis then by vesicular rash in face and trunk.
- After a week of lesion rupture, the patient is no longer contagious

Clinical Presentations:

- Causes Chicken box and Shingles (Reactivated infection)
- Immunocompromised patients might develop severe conditions of pneumonia and encephalitis.

	
The blotches become itchy blisters that ooze fluid. A few days later, the blisters dry out and scab	The rash can form a band that only appears on one side of your body. The skin remains painful until after the rash has gone

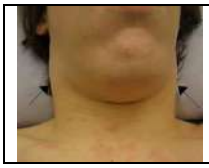
Epstein Barr Virus (HHV4):

Mechanism of transmission: Oral saliva (from kissing) and genital secretions – Common in teens

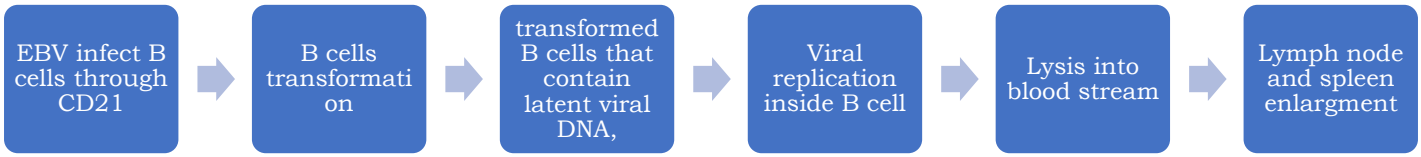
Clinical Presentations:

- Causes active Mononucleosis

- Lymph node and spleen enlargement, flu-like symptoms and painful pharyngitis
- Patients with active mononucleosis should avoid sport due to high risk of splenic rupture.

	Swollen lymph nodes in the neck of a person with infectious mononucleosis

Mechanism of infection:



Diagnosis:

- Monospot test for heterophile antibody (not specific)
- Confirmation is done by anti-EBV immunoglobulin M
- Atypical lymphocytes on peripheral blood smear

Cancer associated with EBV:

- Hodgkin's Lymphoma
- Burkitt's Lymphoma
- Diffuse Large Cell Lymphoma
- Nasopharyngeal carcinoma in Asian adults
- Oral Hairy Leukoplakia

The transformed B cells are not controlled by the immune system that result in massive proliferation eventually leading to cancer

Cytomegalovirus (HHV-5):

Mechanism of transmission:

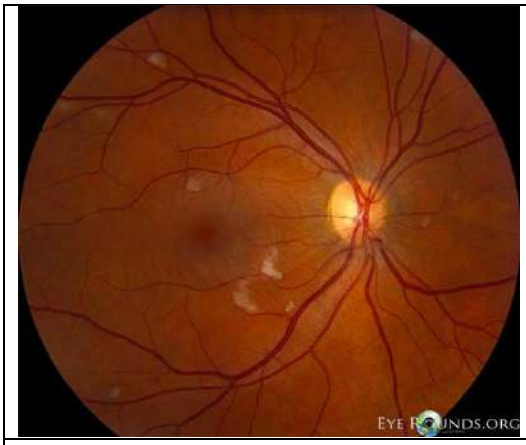
- Transmitted though close contact such as sexual intercourse, transplacental, organ transplant

Clinical Presentations:

- Typically occurred in immunocompromised patients
- AIDS patients with immunocompromised immunity develop CMV retinitis, colitis, and viremia.

CMV retinitis: Cotton wood exudate, hemorrhage and vision loss

- Patients undergo bone marrow transplant develop CMV pneumonitis
- CMV cross the placenta leading congenital CMV such as microcephaly, birth defects, hepatomegaly and blueberry muffin baby
- Causes false positive Monospot test (Mononucleosis-like disease)

	
Right eye-Multiple cotton wool spots adjacent to the nerve and throughout the macula, consistent with HIV retinopathy	**Left eye** - broad retinal whitening and intraretinally hemorrhages along the superior arcades, with cotton wool spots adjacent to the nerve consistent with CMV retinitis and HIV retinopathy

Diagnosis:

- Intranuclear inclusion bodies "Owl's eye"

Human Herpes Virus 6 (HHV6):

- Causes roseola, or exanthem subitem
- Known as sixth disease and occur mostly in infants
- consisting of several days with high fever followed by macular rash on the trunk
- High fever might develop to seizures

Human Herpes Virus 7 (HHV7):

- Causes roseola, but less common
- Reactivate later in life

Human Herpes Virus 8 (HHV8):

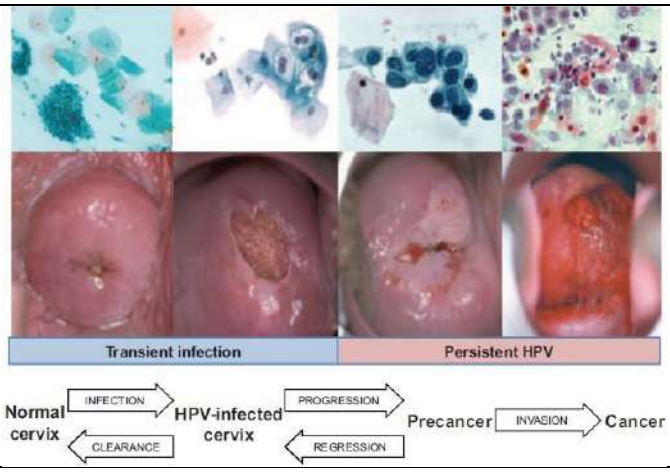
- Transmitted sexually and transplant patients
- Causes Kaposi sarcoma in AIDS patients

Kaposi sarcoma: nodules or blotches that may be red, purple, brown, or black

Human Papillomavirus:

- Most common sexually transmitted infection in United states
- Composed of several **serotypes** but most importantly (**1&2&6&11)**

- Associated with genital warts usually appear as a small bump or group of bumps in the genital area
- Infection could progress to cancer such as **cervical cancer (serotype 16,18)** or cancer of the vulva, vagina, penis, or anus.
- Vaccination is recommended for prophylaxis.



Reprinted with permission from Schiffman M, Wentzensen N. From human papillomavirus to cervical cancer. *Obstetrics and Gynecology* 2010;116(1):177–185.

Adenovirus:

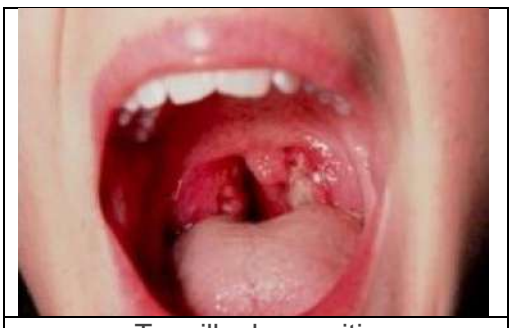
Mechanism of transmission

1. close contacts touching or shaking hands
2. Coughing or sneezing
3. Oral fecal

- Most common cause of febrile illness in children.

Clinical Presentations:

- Conjunctivitis- Pink eye
- Respiratory tract infection: Pneumonia, Febrile pharyngitis and rhinitis
- Gastroenteritis
- Myocarditis
- Acute hemorrhagic cystitis
- Diarrhea



Tonsillopharyngitis

Pox viruses

- Envelope DNA virus from pox viridae family
- Small pox variola virus
- Cowpox caused by vaccinia milk made blisters
- Molluscum contagiosum (water warts), characterized by flash colored domed lesion with a dimple in the center

Polyomavirus:

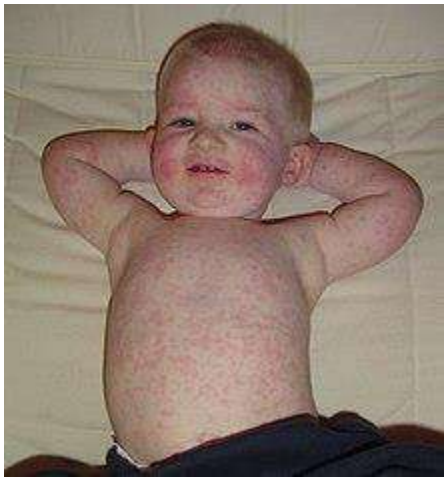
- The JC virus or John Cunningham virus is a type of human polyomavirus
- Associated with immunocompromised patients
- Associated with progressive multifocal leuko-encephalopathy

Hepadnavirus:

- Known as Hepatitis E virus (Enteric)
- Spread by fecal-oral route
- Associated with hepatitis, hepatocellular carcinoma and hepatic cirrhosis
- Symptoms similar to Hepatitis A virus

Parvovirus B19:

- Small, nonenvelope ,Single strand DNA virus
- Causes childhood rash named fifth disease or erythema infectiosum or slapped cheek syndrome
- Causes transit aplastic anema crisis in patients with hemolytic anemia (sickle cell anemia, thalathemia)
- Can cause hydrops fetalis in pregnant women



Erythema infectiosum

References:

- https://www.nhs.uk/conditions/shingles/
- https://webeye.ophth.uiowa.edu/eyeforum/atlas/pages/CMV-Retinitis/index.htm

Herpes Viruses

Outline:

- Cytomegalovirus CMV
- Herpes simplex type 1& 2
- Varicella Zoster virus
- Epstein Barr virus

Cytomegalovirus (HHV-5):

- Transmitted though close contact such as sexual intercourse, transplacental, organ transplant
- Typically occurred in immunocompromised patients
- AIDS patients with immunocompromised immunity develop CMV retinitis, colitis, and viremia.
- Causes false positive Monospot test (Mononucleosis-like disease)
- Diagnosed by Intranuclear inclusion bodies "Owl's eye"

Herpes Simplex Virus:

Herpes simplex type-1:

- Associated with orofacial infection
- Transmitted through Saliva and respiratory system
- Characterized by Blister in the lips, Gingivostomatitis, Keratoconjunctivitis and Temporal lobe encephalitis

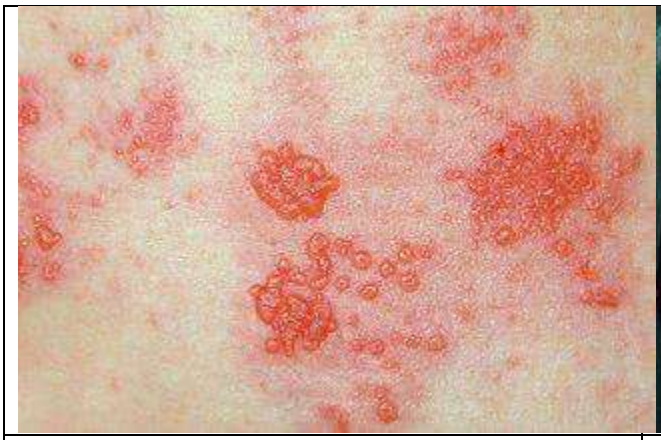
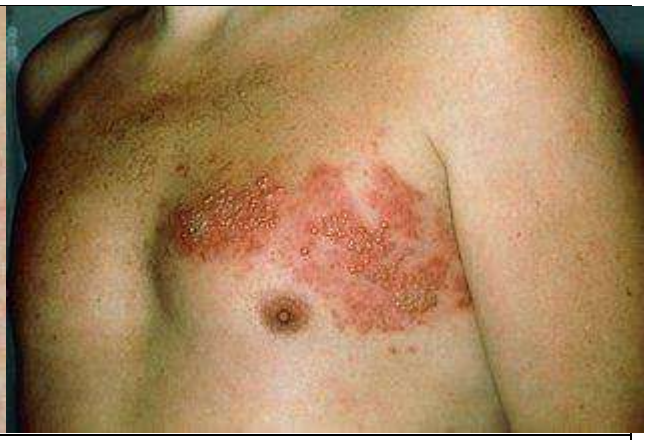
Herpes simples type-2:

- Associated with genital infection
- Sacral nerve root ganglia (S2-S5)
- Transmitted through Sexual contact and perinatal
- Characterized by genital herpes
- Diagnosed by PCR, tzanck smear test, detection of intranuclear Cowdray A inclusion

Tzanck smear: Used to determine whether skin lesions are caused by a herpes virus, a blister is scraped and its contents are smeared on a slide for detection of multinucleated giant cells

Varicella Zoster Virus (HHV3):

- Dormant in dorsal ganglia and reactivation during stress or immunocompromise patients
- Causes Chicken box and Shingles (Reactivated infection)
- Immunocompromised patients might develop severe conditions of pneumonia and encephalitis.
- Characterized by vestibular rash which is painful and itchy

	
The blotches become itchy blisters that ooze fluid. A few days later, the blisters dry out and scab	The rash can form a band that only appears on one side of your body. The skin remains painful until after the rash has gone

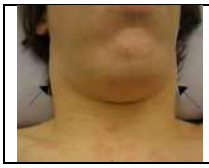
Epstein Barr Virus (HHV4):

- Causes active Mononucleosis
- Infect B cells
- Common among teenagers (15-20 years old) kissing disease
- Spleen and hepatomegaly, flu-like symptoms and painful pharyngitis
- Diagnosed by
    1. Monospot test for heterophile antibody (not specific)
    2. Confirmation is done by anti-EBV immunoglobulin M
    3. Atypical lymphocytes on peripheral blood smear

Cancer associated with EBV:

- Hodgkin's Lymphoma
- Burkitt's Lymphoma
- Diffuse Large Cell Lymphoma
- Nasopharyngeal carcinoma in Asian adults
- Oral Hairy Leukoplakia

The transformed B cells are not controlled by the immune system that result in massive proliferation eventually leading to cancer

	Swollen lymph nodes in the neck of a person with infectious mononucleosis

References:

- Herpesviruses: Harmonious Pathogens but Relevant Cofactors in Other Diseases. Journal of frontiers in cellular and infection microbiology 2018

RNA viruses

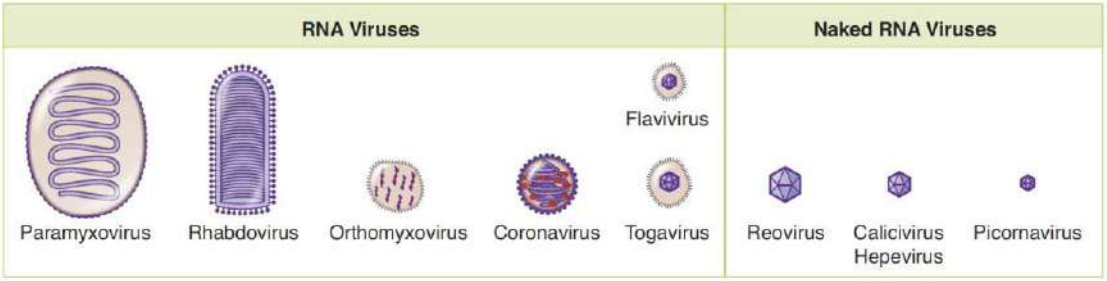
Outline:

- Overview
- Reoviridae
- Picornaviridae
- Calicviridae
- Flaviviridae
- Togaviridae
- Orthomyxoviridae
- Paramyxoviridae
- Rhabdoviridae
- Bunyonviridae
- Retroviridae

Overview

- All RNA viruses are single-stranded (ss) except Reovirus
- ss (-) RNA viruses require RNA polymerases contained in the complete virion.
- It should be transcribed first from negative to positive strand which include Arenaviruses, Bunyaviruses, Paramyxoviruses, Orthomyxoviruses, Filoviruses, and Rhabdoviruses.
- Most RNA are enveloped; the only naked ones are Picornavirus, Calicivirus and Hepevirus, and Reovirus.
- Segmented viruses: different genes on different pieces of RNA such as:

1. Reovirus
2. Orthomyxovirus
3. Bunyavirus
4. Arenavirus



Reoviridae

- Naked-ds RNA

Rotavirus

- Most common in daycare kinder garden
- Associated with fecal-oral gastroenteritis (infantile diarrhea)

Signs and symptoms

- Anorexia
- Low-grade fever
- Watery, bloodless diarrhea
- Vomiting
- Abdominal cramps

Coltivirus

- Colorado fever tick
- Transmitted by wood tick

Picornaviridae

- Naked
- + sense SSRNA
- Usually common in summer time

- **Enteroviruses (acid-stable):** Include polio virus; coxsackie virus A; coxsackie virus B; D68; echoviruses
- **Rhinoviruses** (acid labile)
- **Heparnaviruses:** HAV

Heparnaviruses (Hepatitis A virus-HAV)

- Associated with acute virus hepatitis
- Fecal-oral transmission
- Self -limiting infection
- Not required a carrier

- **Symptoms usually last less than 2 months:**

1. Fatigue
2. Fever
3. Appetite loss
4. Jaundice
5. Nausea
6. Abdominal discomfort

Echovirus

- Associated with aseptic meningitis, myocarditis and URT infection
- Transmitted by fecal-oral
- Diagnosed by CSF analysis revealed:

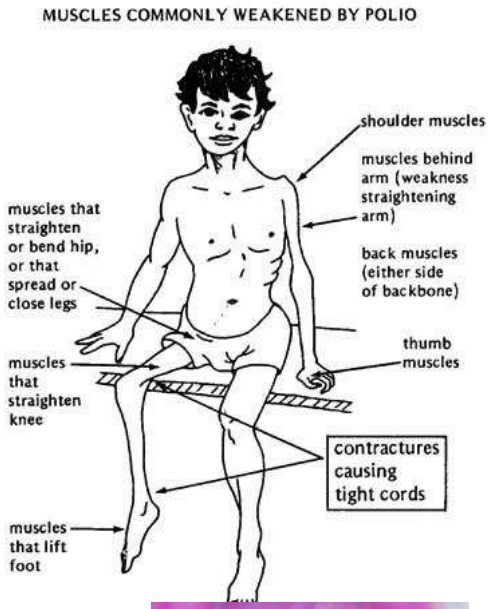
1. High lymphatic count
2. Normal glucose level
3. Low number of WBC

Poliovirus

- Transmitted by fecal-oral
- Fecal-oral Virus targets anterior horn motor neurons
- Initial symptoms include

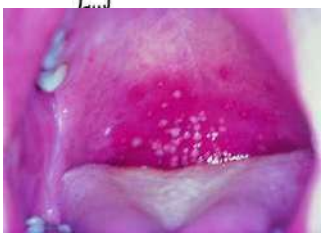
1. headache, fatigue, fever
2. Neck pain or stiffness
3. Pain or stiffness in the arms or legs
4. Muscle weakness or tenderness

- Advanced stage includes paralytic polio (flaccid asymmetric paralysis, no sensory loss)
- Prophylaxis through polio vaccine: Live vaccine (**Sabin**); killed vaccine (**Salk**)



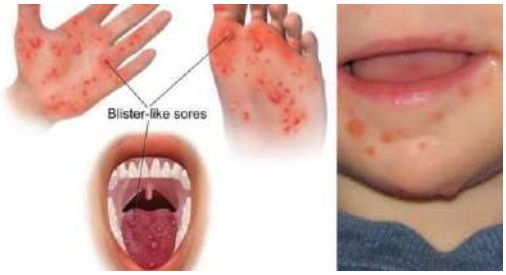
Rhinovirus

- Most common virus that cause common cold
- Congested and runny nose



Coxsackie virus

- Transmitted though fecal-oral
- Associated with aseptic meningitis, myocarditis, pericarditis
- Herpangina known as **Mouth blisters (painful mouth infection)**
- Hand, foot and mouth disease (Vesicular and Papular rash)
- Acute lymphoglandular pharyngitis



Calicviridae

- Naked, +ssRNA

Norwalk Virus

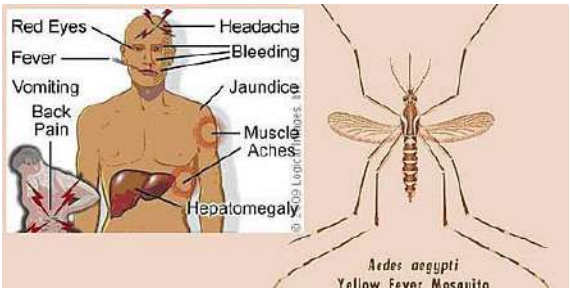
- Transmitted though Fecal-oral route
- Common among school aged child to adult
- Cause acute gastroenteritis especially related to **cruise ships**
- Characterized by nausea, vomiting, diarrhea, pus in stools
- Self-limiting

Flaviviridae

- Envelope virus, +ssRNA
- Arthropod-borne virus

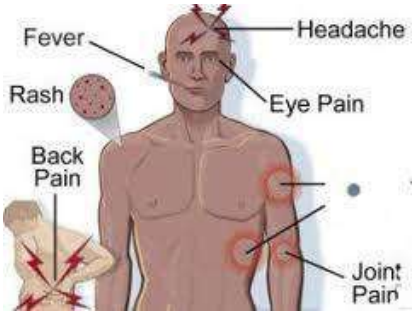
Yellow fever virus

- Transmitted through **Ades mosquitoes** and the reservoir might be human or monkeys
- Characterized by high fever, black vomit (GIT hemorrhage)
- Jaundice
- Liver inflammation (inclusion bodies)
- High mortality rate more than 50%
- Most common in south Africa



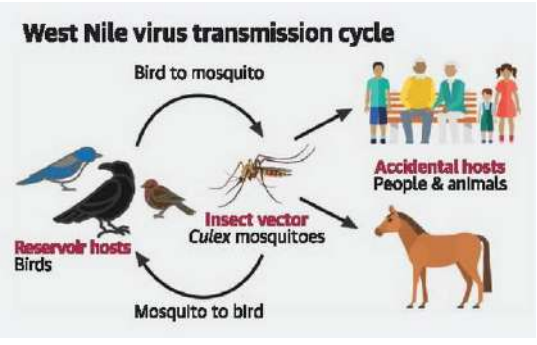
Dengue virus

- Most common mosquito born infection due to poor sanitation and stagnant water
- Characterized by Severe headache (retroorbital), Myalgias, Arthralgias
- Hemorrhagic fever
- Thrombocytopenia
- **Backbone fever** (rash, muscle and joint pain)



West Nile encephalitis virus

- Usually spread by infected mosquitoes. Mosquitoes become infected when they feed on infected birds
- The virus is hard to transmitted by human contact
- **Signs and Symptoms:**
- Fever
- Malaise
- Backpain
- Anorexia



- In rare care develop paralysis, muscle weakness and encephalitis
- **Diagnosis:**

1. Lymphocytic pleocytosis
2. Increased protein, lactic acid
3. Detection of virus-specific antibody IgM and neutralizing antibodies (**detection of IgG is not specific**)

- **Treatment:**
- Supportive care (antipyretics, fluids)

St. Louis encephalitis virus

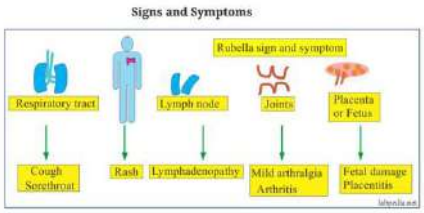
- Related to Japanese encephalitis virus
- **Signs and symptoms include**

1. Flu like symptoms (Fever, headache, malaise)
2. In advanced situation the patient might experience neck stiffness, disorientation, coma, tremors, occasional convulsions

- Diagnosed by Lumbar puncture and detection of SLEV

Togaviridae

- Envelope virus, +ssRNA

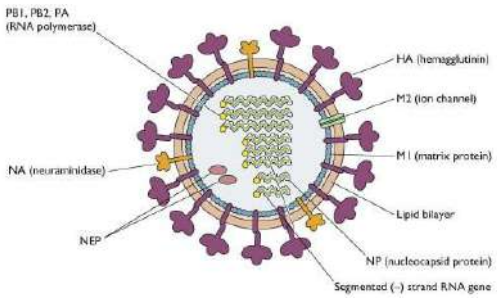


Rubella

- German measles or 3-days **measles**
- Rubella is one **TORCH infection**: toxoplasmosis, rubella, cytomegaly virus and herpes or HIV
- Characterized by:
- Erythematous rash begins on face, progresses to torso)
- Fever
- Posterior auricular/ occipital lymphadenopathy
- Fine truncal rash

Congenital rubella syndrome

- Infection during the first 16 weeks of pregnancy presents major risks for the unborn baby.
- patent ductus arteriosis
- Pulmonary stenosis
- Cataracts
- Microcephaly
- Sensorineural deafness (VIII)
- Blue berry muffin baby
- Mental retardation



Treatment

- MMR vaccine to mother before pregnancy
- Child given vaccine 12 to 15 months

Orthomyxoviridae

- Envelope virus, (-) ssRNA

Influenza virus

- Transmitted through direct contact
- The reservoir for influenza A is (birds, pigs and humans)
- The reservoir of influenza B are human only
- H5N1 strain from birds to humans
- H1N1 strain— swine flu
- Envelope contains two glycoproteins, Hemagglutinin and Neuraminidase
- Viral neuraminidase enables the virus to be released from the host cell.
- Neuraminidases are enzymes that cleave sialic acid groups from glycoproteins and are required for influenza virus replication.
- Influenza virus bind through hemagglutinin into **sialic acid** sugars on the surfaces of epithelial cells in nose, throat, lungs and mammals

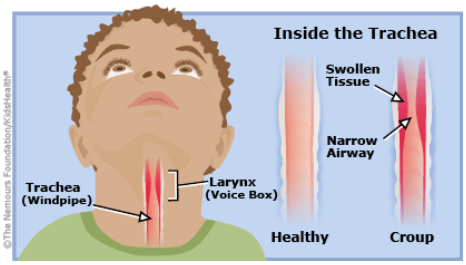
Signs and symptoms

- Headache and malaise
- Fever, chills, myalgias, anorexia
- Bronchiolitis, croup, otitis media, vomiting (younger children)
- Super infection by staph aureus
- Pneumonia/secondary bacterial infections
- Can lead to Reye syndrome or Guillain-Barré syndrome

Genetic shift	Genetic drift
Responsible for **pandemics**	Causes **epidemics**
Rare genetic reassortment Coinfection of cells with two different strains of influenza A (H5N1 and H3N2)	Due to virus mutation
Influenza A only	Influenza A and B
Deadly and sudden	slow

Prevention:

- Killed vaccine
- Zanamivir- Neuraminidase inhibitor (inhalation) for H1N1
- Oseltamivir- Neuraminidase inhibitors (orally) for H5N1

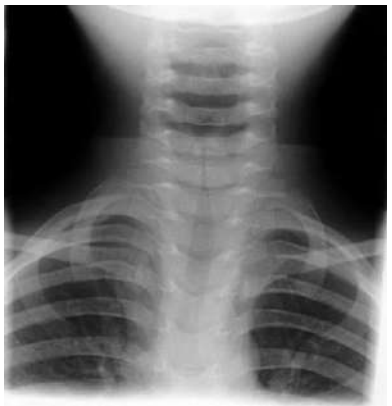


Paramyxoviridae

- Envelope virus, (-) ssRNA

Human parainfluenza virus type 1-

- Cause croup infection ((laryngotracheobronchitis): hoarseness, seal-like barking cough, stridor, subglottal swelling)
- **Pathophysiology:**
- Narrowing of the larynx and trachea below the level of the glottis causing the characteristic **audible inspiratory stridor**
- The steeple or pencil sign of trachea
- **Treatment in mild cases:**
- Cool mist



- Coughing can be treated with warm, clear fluids to loosen mucus in the oropharynx
- Frozen juice popsicles also can be given to ease throat soreness
- **Treatment in severe cases:**
- Corticosteroids
- Nebulized epinephrine
- Steroids
- **Other infectious causes for croup-like illnesses include the following:**

1. Adenovirus
2. Respiratory syncytial virus (RSV)
3. Influenza virus

Respiratory Syncytial Virus (RSV)

- Most common during winter
- **F protein** cause formation of synctitium
- **Signs and symptoms**

1. In adults: colds
2. infants/preemies: bronchiolitis, and necrosis of bronchioles, atypical pneumonia (low fever, tachypnea, tachycardia, expiratory wheeze)

Treatment:

- supportive treatment
- Bronchodilators (Albuterol)
- Chest physiotherapy
- Epinephrine
- Excessive nasal suction of secretion
- Nebulized hypertonic saline
- Systemic or inhaled corticosteroids
- palivizumab (monoclonal antibody)

Rubeola (Measles)

- Characterized by **3Cs**:

1. Cough
2. Coryza
3. Conjunctivitis
4. Photophobia
5. **Koplik spots** → maculopapular rash from ears down (red spots with a bluish white center)
6. Giant cell pneumonia (Warthin-Finkeldey cells) in immunocompromised patients
7. Maculopapular rash

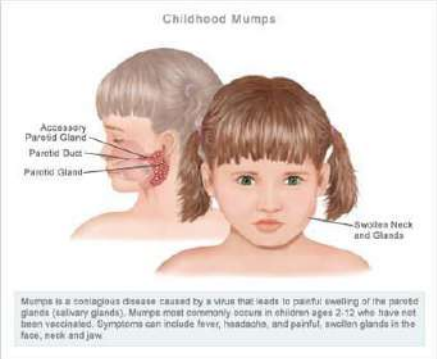
- **Chronic symptoms include:**
- Subacute sclerosing panencephalitis (SSPE): progressive brain inflammation caused by measles virus characterized by:

1. Behavior change
2. Intellectual problems
3. Myoclonic seizures
4. Blindness
5. Ataxia

- **Diagnosis:**
- Detection of oligoclonal bands of antibodies in CSF

Mumps virus

- Transmitted through respiratory droplets
- Lytic infection of epithelial cells of upper respiratory tract and parotid glands → spread throughout body
- **Signs and symptoms:**
- The symptoms start with headache and malaise and might progress to
- Parotitis
- Orchitis (lead to sterility in males)
- Meningoencephalitis
- **Treatment and prevention:**
- live, attenuated vaccine, MMR



Rhabdoviridae

Rabies virus

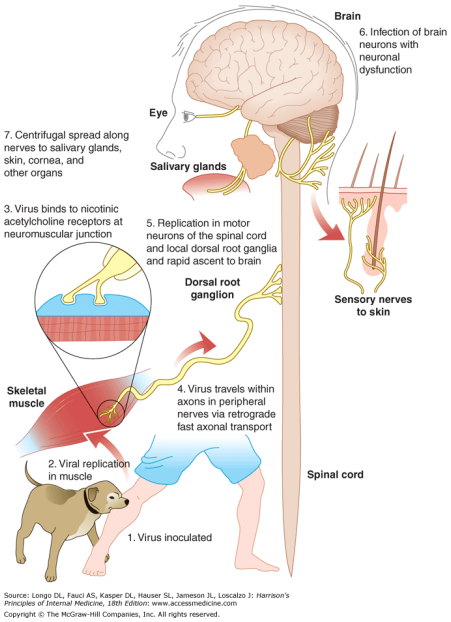
- The reservoir are bats, raccoons, foxes, shunks and dogs
- Transmitted through an animal bite that carry rabies virus
- **Pathophysiology:**

1. After contact, virus binds to peripheral nerves by binding to nicotinic acetylcholine receptor or indirectly into the muscle at site of inoculation
2. virus travels by retrograde axoplasmic transport to dorsal root ganglia and spinal cord
3. once virus gains access to spinal cord, brain becomes rapidly infected

- **Signs and symptoms:**
- The symptoms start with flu like symptoms followed by neurological symptoms include:

1. Hydrophobia
2. Seizures
3. Disorientation
4. Hallucination
5. Pharyngeal spasm
6. Hypersalivation

- **Diagnosis**
- Negri bodies
- Intracytoplasmic inclusion bodies (brain biopsy)
- DFA (impression smears of corneal epithelial cells)
- **Treatment:**
- Long incubation period allows immunization opportunity
- vaccine for high-risk individuals



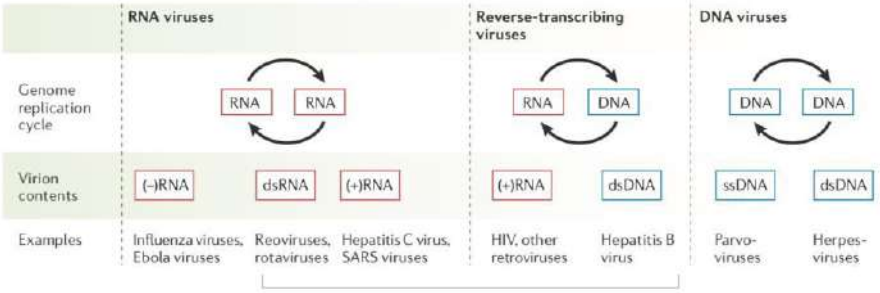
Bunyonviridae

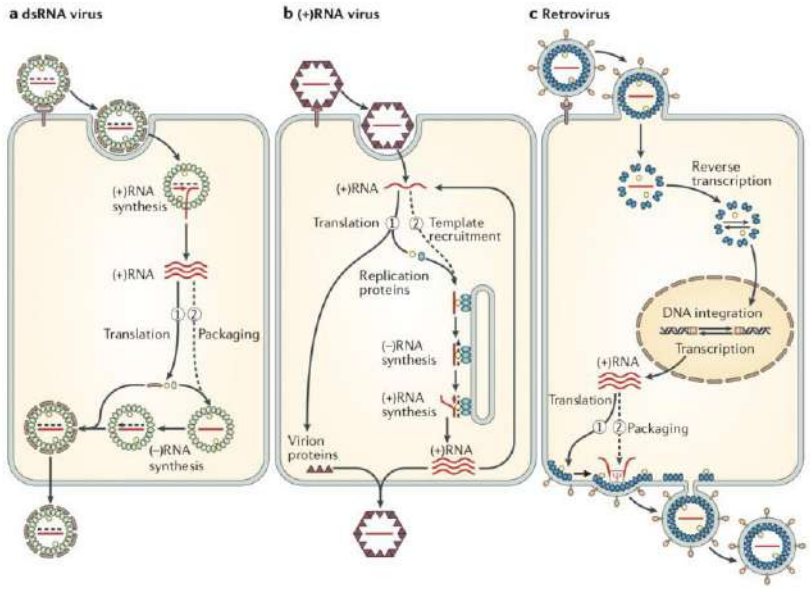
Hantavirus

- Infection caused by aerosolized mouse urine- deer mouse with high incidence in summer and spring
- **Hantavirus pulmonary syndrome/ hemorrhagic fever** (cough, myalgia, dyspnea, tachycardia, pulmonary edema and effusion, and hypotension

Retroviridae

- dsRNA
- HIV
- Human T cell leukemia virus
- In most viruses, DNA is transcribed into RNA, and then RNA is translated into protein
- **In retrovirus**, RNA is reverse-transcribed into DNA, which is integrated into the host cell's genome (when it becomes a provirus), and then undergoes the usual transcription and translational processes to express the genes carried by the virus





References:

- First aid 2018
- Kaplan medical 2017
- Parallels among positive-strand RNA viruses, reverse-transcribing viruses and double-stranded RNA viruses. Nature reviews 2006

Hepatitis A, C, E and D

Outline:

- Hepatitis A& E
- Hepatitis C
- Hepatitis D

Hepatitis A&E

- Transmitted though oral/fecal route
- Acute infection with short incubation period
- No carrier states
- Caused by picornavirus
- Asymptomatic
- Self-limited acute hepatitis with hepatocyte swelling
- **Hepatitis E** caused by RNA Hepevirus
- Causing **fulminant hepatic failure** in pregnant women
- With Bad prognosis especially pregnant women
- Diagnosed with patchy necrosis

Hepatitis C:

- Caused by RNA flavivirus
- Transmitted through blood and post-transfusion
- Chronic disease, may progress to hepatic cirrhosis and carcinoma
- Require long incubation period
- Require carrier state
- Diagnosed by lymphoid aggregates with asteatosis
- Lacks endonuclease enzyme hence no proofreading ability

Hepatitis D:

- Caused by RNA delta virus
- Transmitted sexually, perinatal and parentally
- Defective virus, virus that requires the presence of HBV to replicate
- Hepatitis D can occur simultaneously with HBV (coinfection) or displayed later after chronic Hepatitis B infection (Superinfection)
- The HBsAg coat provided to HDV by HBV enable the defective virus to invade the hepatocytes

References:

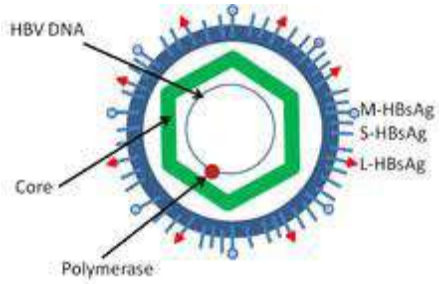
- Division of viral hepatitis. Centers for disease control and prevention(CDC)

Hepatitis B

Outline:

- Structure-Components
- Mechanism of transmission
- Pathogenesis

Structure:



- Hepatitis B is a member of Hepadnavirus family
- The virus particle called virion composed of outer lipid envelope and an icosahedral nucleocapsid core composed of protein

Components:

- HBsAg mushroom looking structure
- Chain of HBsAg (core antigen)
- HBeAg (early antigen)
- Hepatitis B virus DNA polymerase

Mechanism of transmission:

- Transmitted by bloody/body fluid
- Blood transfusion
- Needles IV drug abuse
- Sex

Pathogenesis:

- The virus gains entry into the cell by binding to receptors on the surface of the cell (Unknown) and entering it by endocytosis.
- Following endocytosis, the virus membrane fuses with the host cell's membrane, releasing the nucleocapsid into the cytoplasm
- Note: HBV is a noncytopathic virus. This means that the virus itself does not cause direct damage to liver cells. Instead, it is the immune system's aggressive response (recruitment of cytokines and lymphatic T cells)to the virus that usually leads to inflammation and damage to the liver (hepatitis).

- HBV can cause acute hepatitis, until the immune system is able to clear the virus from the body, usually within six months of becoming infected with the virus.
- HBV can become a chronic infection. This means that the immune system is not able to get rid of the virus within six months after infection
- In response to acute hepatic infection, ALT and AST enzymes concentration significant increased.

Serology course:

- 70% asymptomatic "silent disease)
- 20% Sever symptoms "Icteric hepatitis)
- 5% chronic hepatitis B carriers

Signs and symptoms

- The first symptoms are flu like symptoms such as fever, chills, myalgia, joint pain
- Loss of appetite, headache
- Nausea
- Icteric RUQ pain,
- Yellowing of the skin, whites of the eyes and under the fingernails (jaundice)

Acute hepatitis B virus infection:

- An acute hepatitis B infection follows a relatively long incubation period - from 60 to 150 days with an average of 90 days.
- HBsAg (hepatitis B surface antigen) is the first serologic marker to appear in a new acute infection/ chronic, which can be detected during the first two weeks of infection
- The presence of HBsAg indicates that the person is infectious.
- The body normally produces antibodies to HBsAg as part of the normal immune response to infection.
- HBsAg is the antigen used to make hepatitis B vaccine
- In response to infection, the body starts to produce IgM antibody to hepatitis B core antigen (IgM anti-HBc)
- HBsAg will start to drop then IgM anti-HBc will decline also
- IgG anti-HBc – this blood test remains positive indefinitely as a marker of past HBV infection.

Note: Patient who recovered from acute infection will be negative for HBsAg

- HBeAg (hepatitis B e-antigen) is detectable in patients with a new acute infection; the presence of HBeAg is associated with higher HBV DNA levels, thus, increased infectiousness.

- In response to increase HBe Ag, the body will start produce IgG anti-HBe

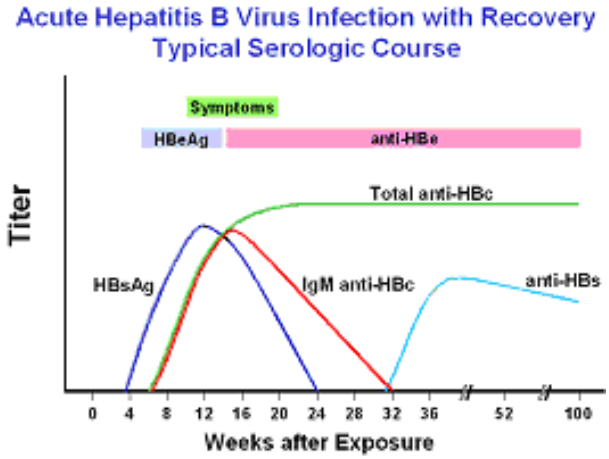
- Once HBeAg started to be cleared out of the body, the system is going to produce IgG anti-HBs to acquire immunity

The window period of HBV:

- The short period when the body system gets cleared from the virus i.e. between the disappearance of surface antigen (HBsAg) from serum and the appearance of HBsAb (anti-HBs)

- During this period, IgM anti-HBc is the only detectable antibody

- After 6 months (IgG anti-HBs +) means the patient become a chronic carrier

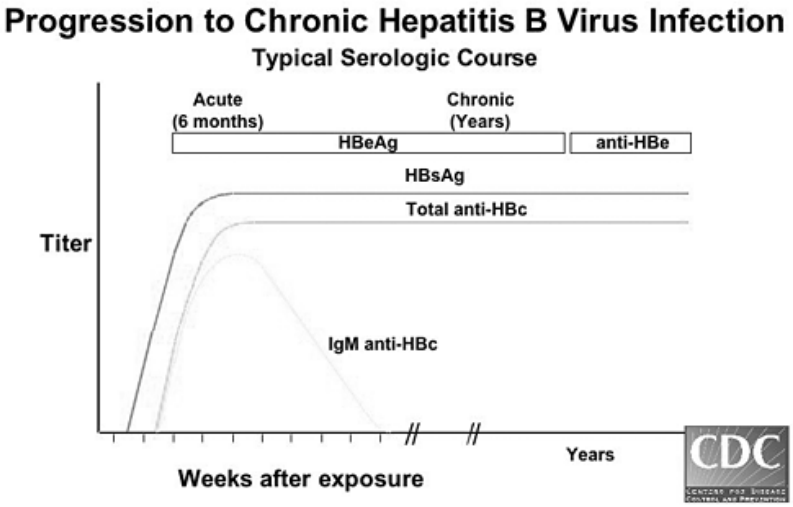


Lab serology:

- Initial blood tests to diagnose HBV infection look for one antigen, HBsAg (the hepatitis B surface antigen), and two antibodies, anti-HBs (antibodies to the HBV surface antigen) and anti-HBc (antibodies to the HBV core antigen).
- There are two types of anti-HBc antibodies produced: IgM antibodies and IgG antibodies.
- IgM antibodies are produced early during infection. IgG antibodies are produced later while infection and replace IgM antibodies.

- HBsAg+, HBeAg+ and IgG anti-HBs (negative) REFER to acute hepatitis B infection
- HBsAg (negative), IgG anti-HBs (Positive) REFER to patient receive vaccine
- IgG anti-HBc (Positive), HBsAg (negative), IgG anti-HBs (Positive) REFER to past infection of Hepatitis B and recovered
- IgG anti-HBc (Positive), HBsAg (negative), IgG anti-HBs (negative) the patient in **window period**
- If the patient has positive IgM anti-HBc, HBsAg (negative), IgG anti-HBs (negative) REFER to **window period**

Chronic hepatitis B virus infection:



- During chronic infection, the system will continually produce HBsAg
- In response to chronic infection, IgG anti-HBe and IgG anti-HBe will be produced.
- Although IgM anti-HBc is produced during the first weeks of exposure but its effect will be diminished throughout chronic infection
- Complications of chronic HBV infection include primary hepatocellular carcinoma and cirrhosis.

Treatment:

- Alpha interferon
- A defovir
- Lamivudine
- Entercavir
- Tenofovir/Telbivudine
- Post- exposure prophylaxis
- Hepatitis B vaccine
- Hepatitis B Immunoglobulin (HBIG)

HBeAg, which is a marker for active disease

(anti-HBsAg) confer immunity to the virus

References:

- Division of viral hepatitis. Centers for disease control and prevention (CDC)

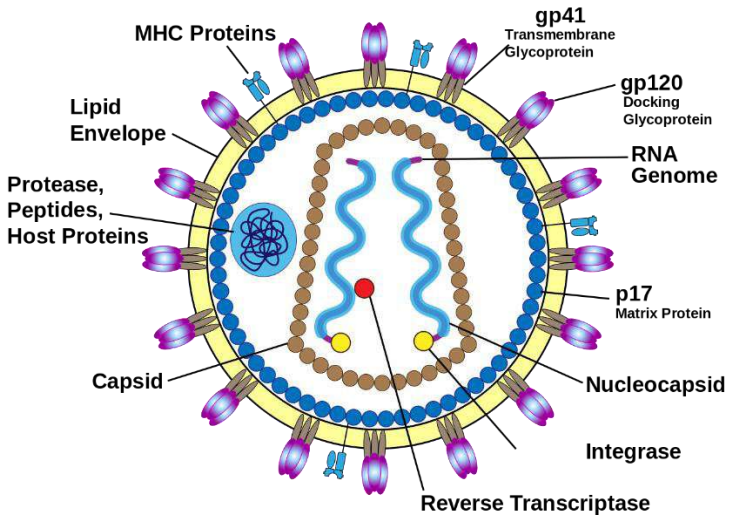
HIV/AIDS

Outline:

- Virus structure
- HIV life cycle
- Stages of HIV infection

Virus structure:

- Composed of nucleic acid (DNA or RNA) and Capsid (protein coat)
- Entails diploid genome (2 RNA copies)
- Envelope glycoprotein (Glycoprotein 120 & Glycoprotein 41)
- Glycoprotein 120 attach to host CD4 T cells
- Glycoprotein 41 responsible for fusion and entry
- Matrix protein P17
- Capsid protein 24



HIV life cycle:

- HIV targets the immune system through CD4 cells
- HIV uses CD4 cells to multiply and replicate

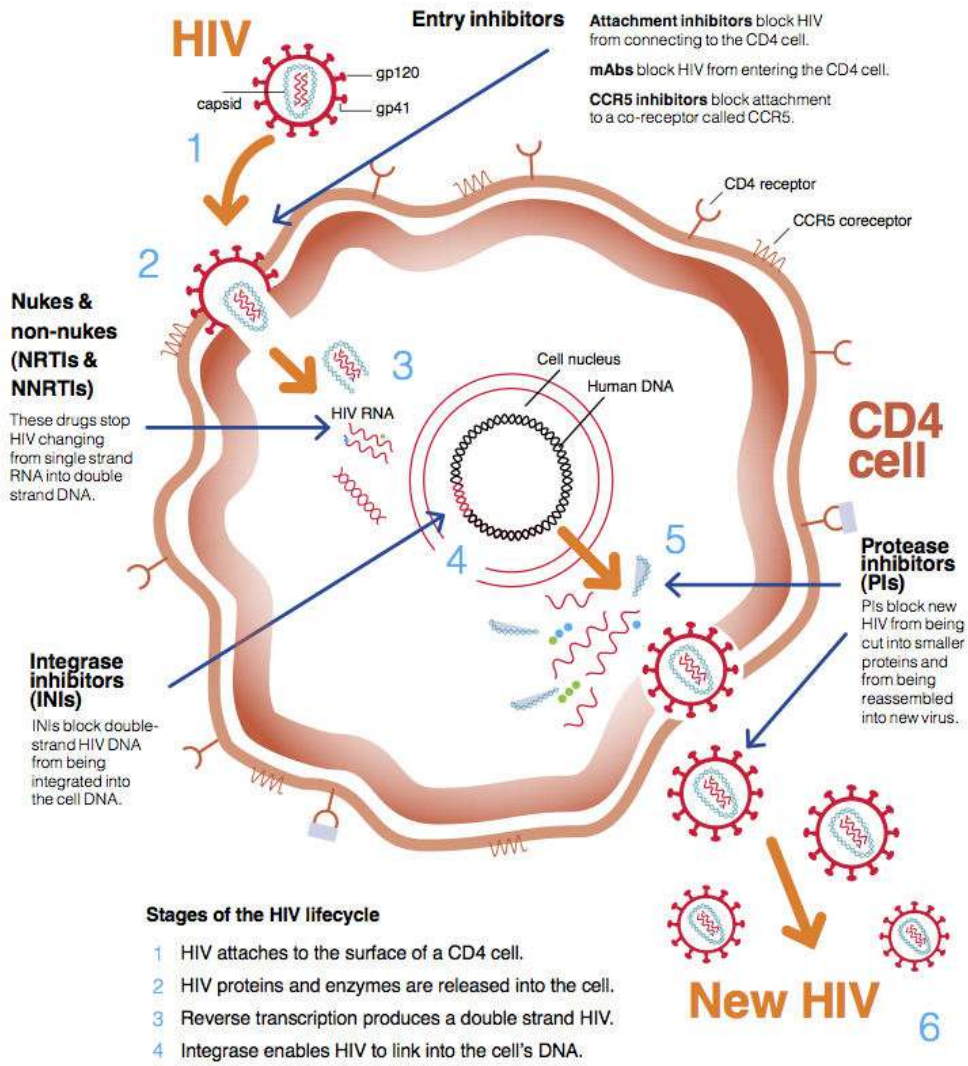
The HIV cycle involves several stages:

- Binding: HIC virus attach CD4, the virus binds itself to the surface of the CD4 receptor either CCR5 (late infection) or CXR4 (Early infection)

CCR5 are expressed on macrophages, dendritic cells, eosinophils and microglia

- After this attachment, gp120 attaches to CCR5 or CXC).

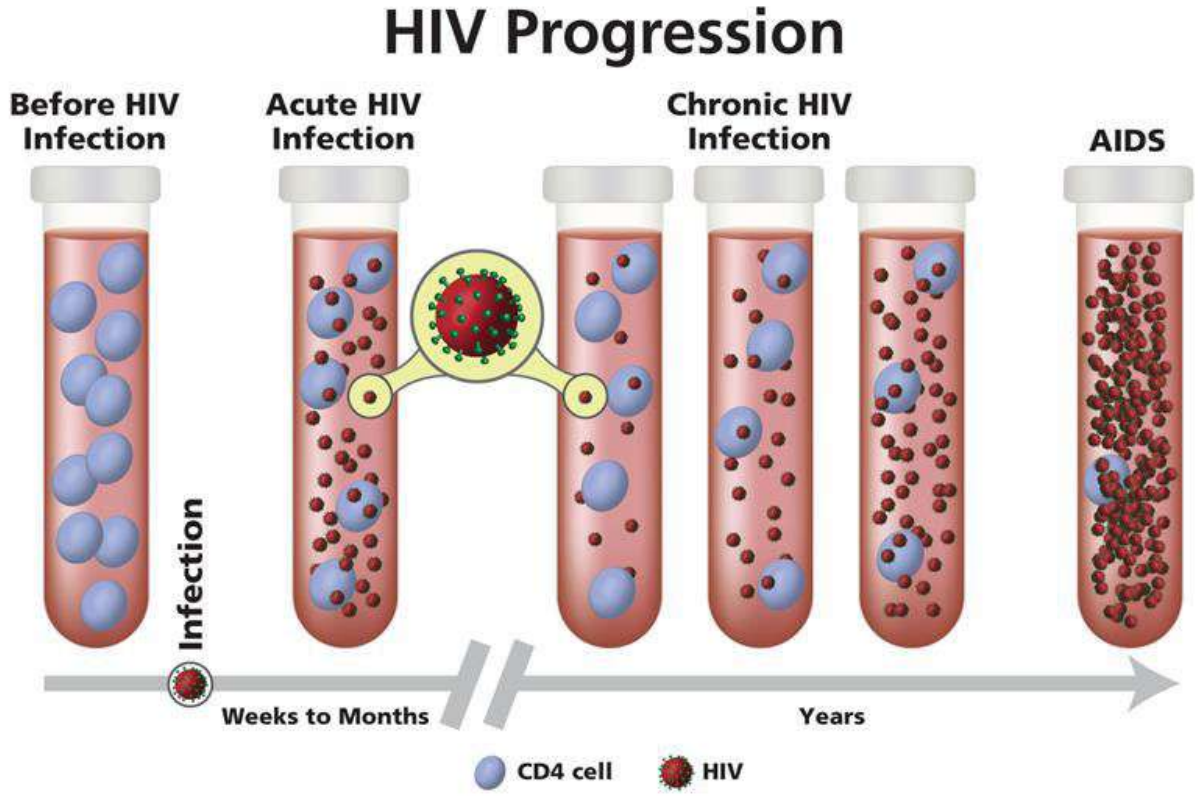
- The attached gp120 and co-receptor undergo a conformational change.
- After the conformational change of gp120, gp41 has the ability to make a structural change.
- CCR5 receptors are subjected to mutations, patients with homozygous mutations are resistant to HIV infection while heterozygous mutations are associated with lower pre-AIDS viral loads and delayed progression to AIDS
- Inside the CD4 cells, HIV uses reverse transcriptase enzyme to convert RNA to DNA HIV, this conversion help HIV to enter the nucleus and combine with cell genetic material
- Inside CD4 nucleus, HIV release integrase enzyme to allow insertion its viral DNA into DNA of CD4 cells.
- Once HIV integrated into CD4 cell DNA, HIV uses CD4 machinery to replicate and produce more HIV protein.
- HIV RNA moves to the surface getting out from the host CD4 cells and releasing protease enzyme (cut out the large protein chains into smaller ones)



Stages of the HIV lifecycle

1. HIV attaches to the surface of a CD4 cell.
2. HIV proteins and enzymes are released into the cell.
3. Reverse transcription produces a double strand HIV.
4. Integrase enables HIV to link into the cell's DNA.
5. Protease cuts and reassembles new HIV.
6. Each cell produces hundreds of new virions.

Stages of HIV infection:



Acute HIV infection:

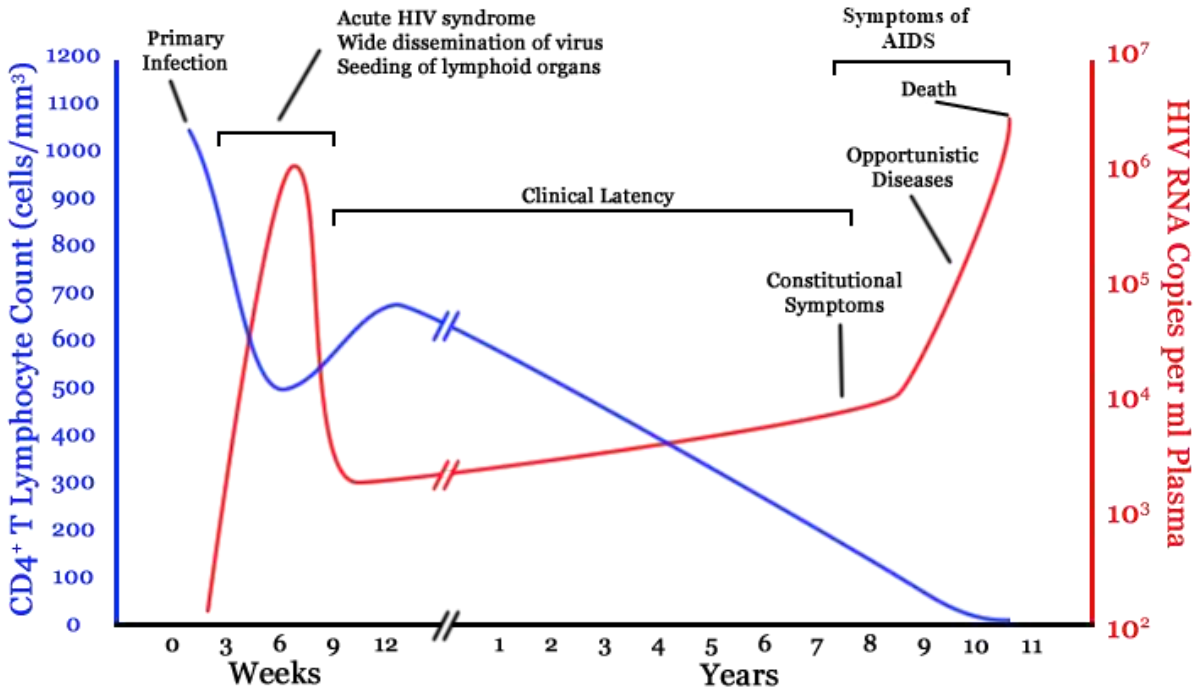
- Starts with flu-like symptoms (fever, fatigue, pharyngitis and headache)
- During this phase HIV virus multiply rapidly and destroys CD4 cells
- The virus load is extremely high and that increases the risk of HIV transmission
- During this time the immune systems fight back and decrease the viral load but the virus itself continue replicating inside the lymph node

Latency period (clinical latency):

- Last for 7 years
- Asymptomatic
- The virus continues to replicate and CD4 count decreases
- When the CD4 counts reached <400 the patients will be susceptible to several infections including skin (athlete's foot, oral thrush and shingles) bacterial (Mycobacterium tuberculosis)

AIDS:

- AIDS will develop when the CD4 counts reached < 200
- The patient is subjected to opportunistic infections
- In cases of lack of treatment, the patient dies within 2 years
- NOTE: CD4 count refers to the risk status of the patient, while Viral load refers to how quickly the patient progressing to death



Diagnosis of HIV:

- Elisa screening test to detect HIV antibodies
- Western blot analysis for confirmation (No longer used by CDC)
- Viral load tests determine the amount of viral RNA in the plasma. For newborn babies
- High viral load associated with poor prognosis.
- Viral load is used to monitor the progress of drug administration

Diagnosis of AIDS:

- CD cell count < 200 cells/microliter. Normal cell count (500-1500 cells/mm3)
- CD4 percentage in T lymphocytes < 14 %. Normal 40%
- Progression of opportunistic infection. Constant candida infection and PCP pneumonia

Opportunistic infection in AIDs:

- CD4+ cell count< 400
- Reactivation of past infection like syphilis, shingles
- Dissemination of bacterial infection
- Fungal infection such as coccidioidomycosis and non-Hodgkin lymphomas

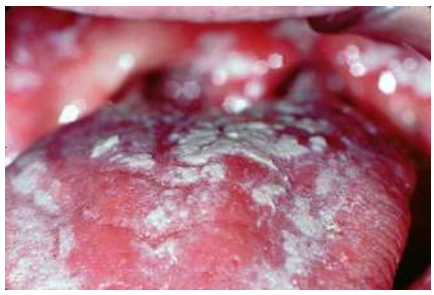
Systemic infection:

- Involved in Histoplasma capsulatum
- Target macrophages

- CD4 T cell < 100
- Fever, weight loss, fatigue, cough, dyspnea, nausea, tongue ulcer, diarrhea

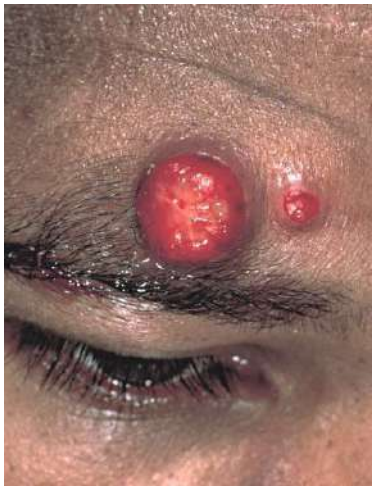
Skin:

- Yeast infection such as Candida Albicans characterized by fluffy white cottage Cheese Lesions on the skin (Oral thrush)
- Involved in Esophagitis and vaginal yeast infection
- CD cells <400



Bacillary angiomatosis:

- Caused by Bartonella henselae
- Characterized by lesions on and under the skin (non-neoplastic vascular lesions)



GIT tract

- Cryptosporidium it's a parasite disease
- Affect distal small intestine
- Characterized by chronic watery diarrhea when CD4 < than 200
- Diagnosed by Acid-fast oocysts in stool

Neurological manifestations:

- Encephalopathy
- Caused by JC virus reactivation
- Progressive multifocal leukoencephalopathy DMC
- Demyelination of the brain

- Brain abscess
- Caused by Toxoplasma Gondie -Multiple ring enhancing lesions
- CD4 <100

- Meningitis
- Caused by Cryptococcus Neoformens
- lumbar puncture for CSF analysis or stain with India ink
- CD4 count <50

- Dementia

Eyes

- Retinitis: Caused by cytomegalovirus
- Diagnosed by Cotton cool spots on funduscopic exams
- CD4 <50
- CMV also causes Esophagitis

Oncological manifistations:

- Kaposi sarcoma:
- Caused HHV-8
- Neoplastic vascular lesions
- Purple cutaneous lesions in internal organs or skin

Oral hairy leukoplakia:

- Caused by Epstein-Barr virus EBV
- Characterized by Unscrapable white plaque on lateral tongue

Note: In case of Candida albicans, scraping the tongue yield white materials with bleeding

Non-Hodgkin's lymphoma:

- Caused by Epstein-Barr virus EBV
- Appear in the back of the Pharynx

Squamous cell carcinoma

- Due to HPV infection
- Cervical or anal

primary CNS lymphoma

- Caused by Epstein-Barr virus EBV

Lung

Interstitial pneumonia

- Caused by CMV
- Diagnosed by Intranuclear inclusion bodies “Owl’s eye”

- Aspergillosis:
- Caused by Aspergillos Fumugatous
- Characterized by pleuritic pain and hemoptysis

- Pneumocystis pneumonia
- Caused by Pneumocystis jirovecii
- CD4 count < 200

- Tuberculosis like disease
- Caused by Mycobacterium avium intracellular
- CD4 <50

References:

- http://i-base.info/guides/starting/hiv-life-cycle

Neonatal Infection

Outline:

- Congenital Toxoplasmosis
- Congenital Rubella
- Congenital Cytomegalovirus
- Congenital HIV
- Congenital herpes simplex infection
- Congenital Syphilis

Congenital Toxoplasmosis

- Caused by transplacental acquisition of Toxoplasma gondii.
- Source of infection: Ingestion of inadequately cooked meat containing cysts or food, or water contaminated with cat feces.

Clinical presentations

- Usually infected pregnant women are **asymptomatic,** but the neonates may suffer from:

1. Jaundice
2. Myocarditis
3. Intracranial calcifications
4. Hydrocephalus
5. Chorioretinitis
6. Seizures
7. Hepatosplenomegaly
8. Prematurity

Diagnosis

- PCR

Treatment

- pyrimethamine, sulfadiazine, and leucovorin.

Congenital Rubella

- Congenital rubella typically results from a primary maternal infection

Clinical presentations

- Usually infected pregnant women are **asymptomatic, but** it may suffer from upper respiratory infection including fever, conjunctivitis, maculopapular and joint symptoms
- The fetus might develop the following symptoms:

1. Microcephaly
2. Cataracts
3. Hearing loss
4. Patent duct arteriosus
5. thrombocytopenia with purpura
6. Dermal erythropoiesis resulting in bluish red skin lesions

Cytomegalovirus

- Acquired by exposure to infected cervical secretions, breast milk, or blood products.
- Neonates known to protective against CMV infection through maternal antibody, however, preterm infants who lacks these antibodies are subjected to serious infection

Clinical presentations at birth:

- Sensorineural hearing loss
- Jaundice
- Periventricular calcifications
- Sepsis-like syndrome
- Microcephaly
- Hepatitis

Diagnosis

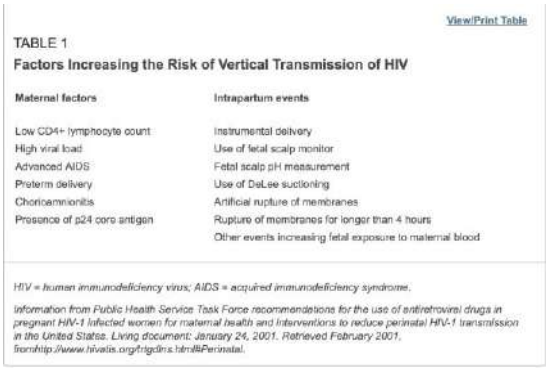
- Culture detection or PCR

Treatment

- Parenteral antiviral Ganciclovir or oral Valganciclovir

HIV

- Neonates are exposed to HIV infection in utero, during labor or after delivery



View/Print Table

TABLE 1

Factors Increasing the Risk of Vertical Transmission of HIV

Maternal factors	Intrapartum events
Low CD4+ lymphocyte count	Instrumental delivery
High viral load	Use of fetal scalp monitor
Advanced AIDS	Fetal scalp pH measurement
Preterm delivery	Use of DeLee suctioning
Chorioamnionitis	Artificial rupture of membranes
Presence of p24 core antigen	Rupture of membranes for longer than 4 hours
	Other events increasing fetal exposure to maternal blood

HIV = human immunodeficiency virus; AIDS = acquired immunodeficiency syndrome.

Information from Public Health Service Task Force recommendations for the use of antiretroviral drugs in pregnant HIV-1 infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States. Living document: January 24, 2001. Retrieved February 2001, fromhttp://www.hivatis.org/trtgdlns.html#Perinatal.

- **According to WHO**, giving antiretroviral drugs (ARVs) to either the HIV-infected mother or HIV-exposed infant can significantly reduce the risk of transmitting HIV through breastfeeding

Neonatal herpes simplex infection

- Transmission during delivery through an infected maternal genital tract

Clinical presentations

- Skin vesicles
- Encephalitis

- Might progress to **disseminated disease** that include hepatitis, disseminated intravascular coagulation

Diagnosis

- HSV culture or PCR
- Immunofluorescent testing of lesions or electron microscopy

Treatment

- High-dose parenteral acyclovir

Congenital Syphilis

- Acquired through exposure of Treponema pallidum and transmitted to fetus via placenta
- Untreated syphilis in pregnancy is also associated with a significant risk of stillbirth and neonatal death

Clinical presentations

Early signs:

- Copper-colored rash on the palms and soles
- Papular lesions around the nose and mouth and in the diaper area, as well as petechial lesions
- Blood-stained nasal discharge causing snuffles
- Failure to gain weight or failure to thrive

Late signs:

- Abnormal notched and peg-shaped teeth, called Hutchinson teeth
- Blindness
- Clouding of the cornea (the covering of the eyeball)
- Decreased hearing or deafness
- Deformity of the nose with flattened nasal bridge (saddle nose)
- Gray, mucus-like patches around the anus and vagina
- Joint swelling
- Saber shins (bone problem of the lower leg)
- Scarring of the skin around the mouth, genitals, and anus

Diagnosis

- Darkfield microscopy of lesions, placenta, or umbilical cord
- Serologic testing of mother and neonate; possibly CSF analysis

Treatment

- Penicillin

References:

- First aid 2018

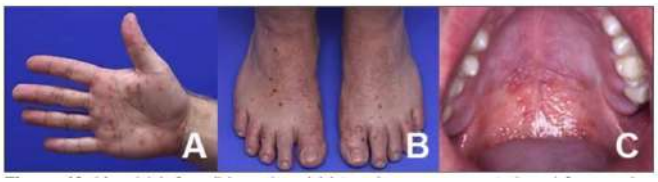
- Management of Newborns Exposed to Maternal HIV Infection

Red rash in childhood

Outline:

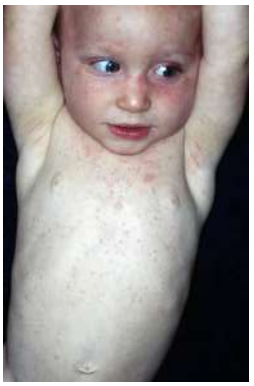
- Coxsackievirus
- Roseola
- Measles
- Rubella
- Slapped Checked syndrome
- Chicken box

Coxsackievirus



- Involved in hand, foot, mouth disease
- Signs and Symptoms:
- Causes painful red blisters in the throat and on the tongue, gums, hard palate, inside of the cheeks, and the palms of hands and soles of the feet.

Roseola



- Due to exposure to virus infection HHV6
- Named as roseola infantum" or "sixth disease".

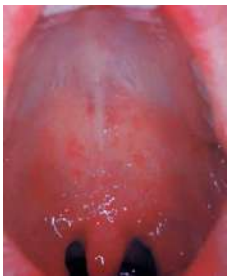
- Signs and Symptoms:
- The presentation in roseola classically is that a child with a high fever develops a rash after the fever abates
- **The rash can be characterized by:**

1. Pinkish-red spots, patches or bumps start on the chest before spreading to the face, neck and arms
2. isn't usually itchy or uncomfortable
3. normally fades and disappears within two days

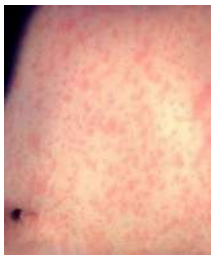
Measles

- The rash usually begins on the face and then moves down the neck and the rest of the body over the course of a few days (Head down and confluent).
- Signs and Symptoms:

1. Cough
2. Conjunctivitis
3. Coryza
4. Koplic spots (gray-white papules)
5. The measles rash is red-brown blotches.

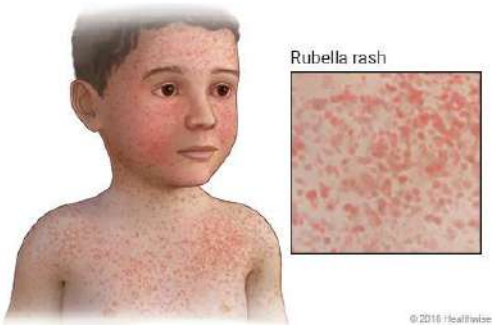


Mouth of a patient with Koplik spots, an early sign of measles infection.



Skin of a patient after 3 days of measles infection.

Rubella



- A fine, pink rash that begins on the face and quickly spreads to the trunk and then the arms and legs, before disappearing in the same sequence
- Signs and Symptoms:
- Fever
- Headache
- Stuffy or runny nose
- Inflamed, red eyes
- Enlarged, tender lymph nodes at the base of the skull, the back of the neck and behind the ears
- Aching joints

Slapped cheek syndrome

- Signs and Symptoms

1. Fever
2. Runny nose
3. Sore throat
4. Headache
5. GIT upset

- After a few days, a distinctive bright red rash on both cheeks (the so-called "**slapped cheeks**")
- After another few days, a light pink rash may also appear on the chest, stomach, arms and thighs. This often has a raised, lace-like appearance and may be itchy.

Chicken box

- It causes a rash of red, itchy spots that turn into fluid-filled blisters.

- They then crust over to form scabs, which eventually drop off.
- The spots normally appear in clusters and tend to be:

1. behind the ears
2. on the face
3. over the scalp
4. on the chest and belly
5. on the arms and legs

References:

- First aid 2018
- CDC

Nosocomial Infection

Outline:

- Overview
- Sources of nosocomial microbes

Overview

- Infection developing in patients after admission to the hospital. The infection can originate from the outside environment, another infected patient, staff that may be infected
- Signs and symptoms might appear during patient stay or after their discharge
- Microorganisms involved in these infections are able to survive in hospital environment and develop resistance to antibiotics and disinfectants

Sources of nosocomial microbes

- Cross infection from patient to patient
- Transmitted through medical personnel
- Patient´s own flora
- Hospital environment such as:

Aspiration

- In Unconscious patients and pulmonary ventilation may lead to pulmonary infection caused by gram negative bacteria especially anaerobes
- Signs and Symptoms:

1. Right lower lobe infiltrate
2. purulent malodorous sputum
3. Might progress to alter mental status in elderly patients

Surgical wound infection

- S aureus (including MRSA), gram negative anaerobes
- Signs and Symptoms:

1. Erythema
2. Tenderness
3. Induration
4. Purulent discharge around wounds

IV catheters

- Suspected organism: S aureus (including MRSA), S epidermidis (long term), Enterobacter
- Signs and Symptoms:

1. Erythema

2. Induration
3. Tenderness
4. Drainage from access sites

Mechanical ventilation, endotracheal intubation

- Suspected organism: P aeruginosa, Klebsiella, Acinetobacter, S aureus
- Usually associated with patients in intensive care units
- Signs and Symptoms:

1. New infiltrate on chest X ray
2. Increase sputum production;
3. Sweet odor (Pseudomonas)

Urinary catheterization

- Suspected organism Proteus spp, E coli, Klebsiella
- Signs and Symptoms:

1. Dysuria,
2. leukocytosis
3. Costovertebral angle tenderness

Water aerosols

- Suspected organism: Legionella
- Signs and Symptoms:

1. CNS abnormalities
2. GIT symptoms (Diarrhea, nausea, Vomiting)
3. Signs of pneumonia

Antibiotic

- Suspected organism: Clostridium Difficile
- Signs and Symptoms:
    1. Fever
    2. Diarrhea
    3. Leukocytosis

Needle sticks

- Hepatitis B, C

References:

- First aid 2018

Antiviral drugs

Outline:

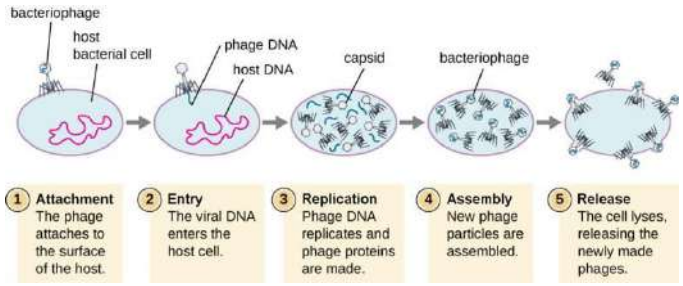
- Overview
- Steps of viral replication
- Characteristics of Antiviral drugs
- Mechanism of actions of antiviral drugs

Overview

- Obligate intracellular parasite
- Viruses have no cell wall and made of nucleic acid components
- Depend on host cell
- It then uses the host cell's energy to synthesize protein, DNA, and RNA
- A virus cannot replicate on its own
- Viruses are hard to target because they live inside the cells
- **Antiviral drugs** usually have several side effects since any drug that kills a virus may also kill cells
- Many antiviral drugs are purine or pyrimidine analogs
- Some Antiviral drugs entail the characteristics of prodrugs (need to be activated to become active)

Steps of viral replication

1. Cell entry
2. Penetration
3. Uncoating
4. Transcription of viral genome
5. Translation
6. Assembly
7. Release

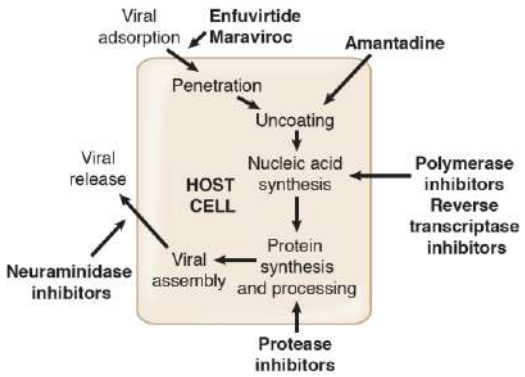


Characteristics of Antiviral drugs

- Interfere with viral nucleic acid synthesis or regulation
- Interfere with the ability of virus to bind to cells
- Stimulate body`s immune system

Mechanism of actions of antiviral drugs

Mechanism of Actions	Major drugs
• **Block viral penetration/uncoating**	• Amantadine, enfuvirtide, maraviroc
• **Inhibit viral DNA polymerase**	• Acyclovir, Foscarnet, ganciclovir
• **Inhibit viral RNA polymerase**	• Foscarnet, ribavirin
• **Inhibit viral transcriptase**	• Zidovudine, didanosine, zalcitabine, lamivudine, stavudine, nevirapine, efavirenz
• **Inhibit viral aspartate protease**	• Indinavir, ritonavir, saquinavir
• **Inhibit viral neuraminidase**	• Zanamivir, oseltamivir



References:

- First aid 2018
- Kaplan medical 2017

Zanamivir/Oseltamivir

Signs and Symptoms of influenza:

1. Fever* or feeling feverish/chills
2. Cough
3. Sore throat
4. Runny or stuffy nose
5. Muscle or body aches
6. Headaches
7. Fatigue (tiredness)

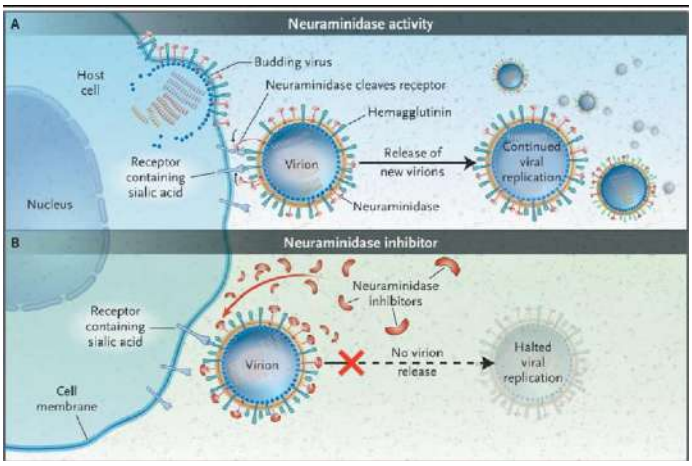
Adapted from center for disease control and prevention (CDC)

Cold vs Flu

Signs and Symptoms	Cold	Influenza (Flu)
Symptom onset	Gradual	Abrupt
Fever	Rare	Usual; lasts 3-4 days
Aches	Slight	Usual; often severe
Chills	Uncommon	Fairly common
Fatigue, weakness	Sometimes	Usual
Sneezing	Common	Sometimes
Chest discomfort, cough	Mild to moderate; hacking cough	Common; can be severe
Stuffy nose	Common	Sometimes
Sore throat	Common	Sometimes
Headache	Rare	Common

Mechanism of action:

- Inhibit neuraminidases of influenza A and B
- Oseltamivir reduces shedding of both influenza A and B virus by inhibiting the release of infectious virus from infected cells
- **Viral neuraminidase enzyme activity is important both for:**
- viral entry into uninfected cells and for the release of recently formed virus particles from infected cells
- and for the further spread of the infectious virus in the body



Clinical uses:

- Treatment and prevention of influenza A and B
- When started early: decrease duration of flu symptoms by 2-3 days

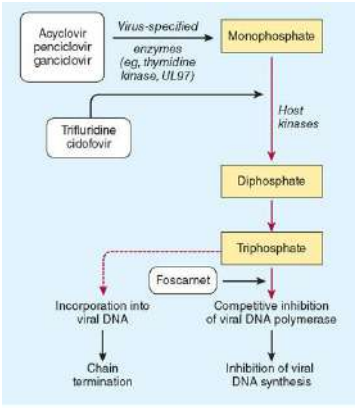
References:

- First aid 2018
- Kaplan medical 2017
- Neuraminidase inhibitors for influenza. Journal of New England journal of medicine 2005

Acyclovir

Outline:

- Mechanism of action
- Clinical uses
- Side effects
- Herpes simplex virus subtypes



Mechanism of action

- Guanosine analogs
- Monophosphorylated by viral thymidine kinase (TK), then further bioactivated by **host-cell kinases** to the triphosphate that terminate DNA polymerase chain replication
- Resistance possibly due to changes in DNA polymerase or to decreased activity of TK
- Most of Herpes simplex virus strains are resistance to **acyclovir** due to lack of thymidine kinase

Clinical uses

- Activity includes herpes simplex virus (HSV) and varicella-zoster virus (VZV)
- Actively using against both forms of HSV I &II and advanced HSV induced encephalitis
- Used as prophylaxis in immunocompromised patients
- **Acyclovir** Reduces viral shedding in genital herpes; ↓ acute neuritis in shingles but has no effect on postherpetic neuralgia
- Acyclovir available as topical, oral and IV form
- **NO effect against CMV**
- Valacyclovir, a prodrug of acyclovir, has better oral bioavailability, can be used in acyclovir resistant strains

Side effects

- Crystalluria (maintain full hydration) and neurotoxicity (agitation, headache, confusion—seizures in OD)

Herpes Simplex Virus subtypes

Herpes simplex type-1:

- Associated with orofacial infection
- Transmitted through Saliva and respiratory system
- Characterized by Blister in the lips, Gingivostomatitis, Keratoconjunctivitis and Temporal lobe encephalitis

Herpes simples type-2:

- Associated with genital infection
- Sacral nerve root ganglia (S2-S5)
- Transmitted through Sexual contact and perinatal
- Characterized by genital herpes

References:

- First aid 2018
- Kaplan medical 2017

Ganciclovir

Outline:

- Mechanism of action
- Clinical uses
- Side effects
- Sources of CMV transmission
- Signs and symptoms in adult

Mechanism of action:

- Similar to that of acyclovir
- Guanosine analog
- First its monophosphorylated by **thymidine kinase** then triphosphate form inhibits viral DNA polymerase and causes chain termination

Clinical uses:

- Used to treat CMV, especially in **immunocompromised patients.**
- Also used for HSV, VZV
- **Valganciclovir**, a prodrug of ganciclovir, has better oral bioavailability
- prophylaxis and treatment of CMV infections, including retinitis, in AIDS and transplant patients— relapses and retinal detachment occur

Side effects:

- Bone marrow suppression (leukopenia, neutropenia, thrombocytopenia)
- Renal toxicity.
- More toxic to host enzymes than acyclovir
- **Crystalluria** (maintain hydration)

Sources of CMV transmission:

- **Congenital**

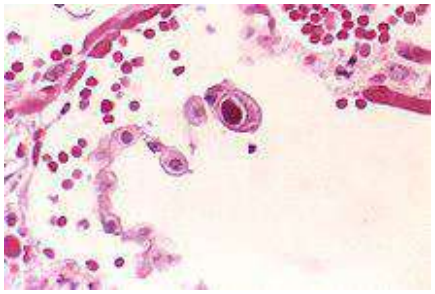
1. Premature birth.
2. Low birth weight.
3. Yellow skin and eyes (jaundice)
4. Enlarged and poorly functioning liver.
5. Purple skin splotches or a rash or both.
6. Abnormally small head (microencephaly)
7. Enlarged spleen.
8. Pneumonia

- Blood transfusion, organ transplantation
- Adult cytomegalovirus infection in the immunocompetent host

Signs and symptoms in adult:

- Viral pneumonia
- Hepatitis
- Encephalitis

- Retinitis
- Diagnosis: Characterized by Owl's eye appearance of inclusion bodies



Owl's eye

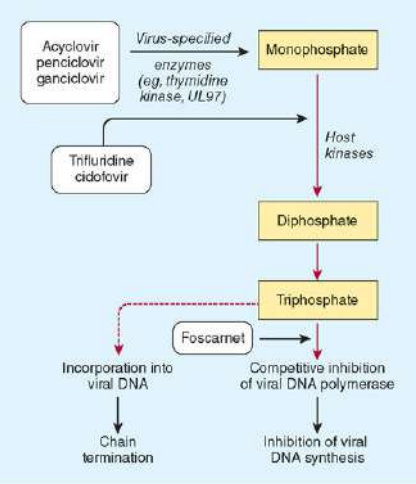
References:

- First aid 2018
- Kaplan medical 2017

Foscarnet

Mechanism of action:

- Pyrophosphate analogue
- Inhibits DNA polymerase
- Different from **Ganciclovir** since it doesn´t require any kinase activation



Clinical uses:

- Drug of choice for Ganciclovir resistance
- Entail high activity versus acyclovir-resistant strains of HSV
- CMV retinitis in immunocompromised patients

Side effects:

- Dose-limiting **nephrotoxicity** with acute tubular necrosis, electrolyte imbalance with hypocalcemia (tremors and seizures)

Mechanism of resistance:

- Mutation of DNA polymerase

Cidofovir

Mechanism of action:

- Selective inhibition of viral DNA synthesis

Clinical uses:

- Treatment of cytomegalovirus (**CMV**) retinitis in patients diagnosed with AIDS

Side effects:

- Nephrotoxicity (Co-administration with **probenecid** and IV saline to decrease toxicity).

Drug of choice for treatment of CMV infection

- Gancyclovir >Foscarnet >Cidofovir

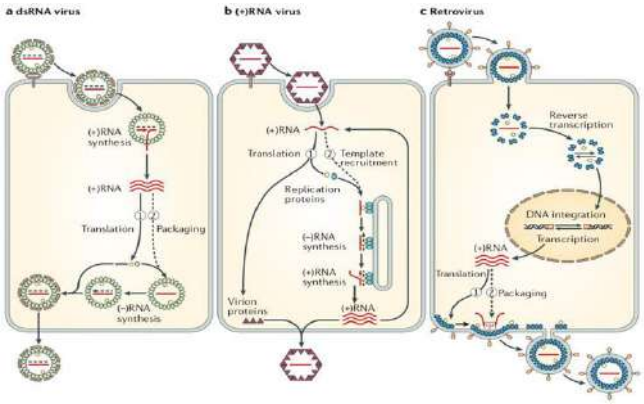
References:

- First aid 2018
- Kaplan medical 2017

HIV/AIDS Drugs

Outline:

- Overview
- AIDS
- Diagnosis of AIDS
- Treatment of HIV
- Reverse transcriptase inhibitors
- Protease inhibitors
- Integrase inhibitors



Overview

- HIV is a retrovirus
- HIV targets the immune system through CD+4 cells
- HIV uses CD+4 cells to multiply and replicate
- Inside the CD+4 cells, HIV uses reverse transcriptase enzyme to convert RNA to DNA HIV, this conversion help HIV to enter the nucleus and combine with cell genetic material
- Inside CD+4 nucleus, HIV release integrase enzyme to allow insertion its viral DNA into
- DNA of CD+4 cells.
- Once HIV integrated into CD+4 cell DNA, HIV uses CD+4 machinery to replicate and produce more HIV protein

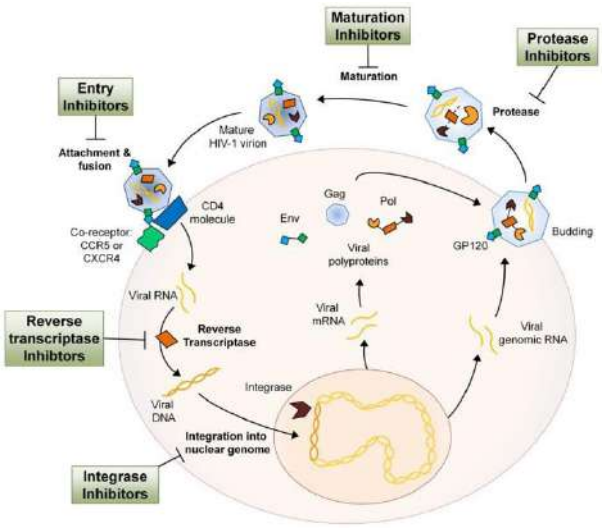
AIDS

- AIDS will develop when the CD+4 counts reached < 400
- The patient is subjected to opportunistic infections
- In cases of lack of treatment, the patient dies within 2 years
- NOTE: CD+4 count refers to the risk status of the patient, while Viral load refers to how quickly the patient progressing to death

Diagnosis of AIDS:

- CD cell count < 400 cells/microliter. Normal cell count (500-1500 cells/mm3)
- CD+4 percentage in T lymphocytes < 14 %. Normal 40%
- Progression of opportunistic infection. Constant candida infection and PCP pneumonia

Treatment of HIV



- An initial antiretroviral regimen generally consists of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) in combination with a third active drug from one of the following classes:

1. nonnucleoside reverse transcriptase inhibitor (NNRTI)
2. protease inhibitor
3. integrase strand transfer inhibitor (INSTI).

Reverse Transcriptase Inhibitors (RTIs)

Nucleoside reverse transcriptase inhibitors (NRTIs):

- They are nucleoside Antimetabolites such as Zidovudine
- Converted to active forms via phosphorylation reactions
- They inhibit the **HIV reverse transcriptase enzyme** competitively and act as a chain terminator of DNA synthesis
- Incorporate into the growing HIV viral DNA strand by reverse transcriptase, then viral DNA synthesis will be terminated
- Tenofovir is the only NtRTI (need to phosphorylate), has a single phosphate on its sugar residue and must be further phosphorylated to the triphosphate form
- Highly active antiretroviral therapy (**HAART**) has often resulted in ↓ viral RNA, reversal of the decline in CD4 cells, and ↓ opportunistic infections
- ZDV can be used for general prophylaxis and during pregnancy to decrease risk of fetal transmission
- NRTIs are used together with **a protease inhibitor (PI)**

Examples

- Abacavir (ABC)
- Didanosine (ddI)
- Emtricitabine (FTC)
- Lamivudine (3TC)
- Stavudine (d4T)
- Tenofovir (TDF)
- **Zidovudine (ZDV, formerly AZT)**

Side effects:

- Bone marrow suppression: Can be reversed by Granulocyte colony stimulating factors or erythropoietin which stimulate new red blood cells

- Peripheral neuropathy
- Lactic acidosis
- Anemia (ZDV)
- Pancreatitis (Didanosine)
- Neutropenia
- Headache
- Fatigue
- Myalgia

Non-Nucleoside reverse transcriptase inhibitors (NRTIs):

- Inhibit reverse transcriptase at a site different from the one NRTIs bind to

- NNRTIs do not require phosphorylation to be active
- Are not myelosuppression
- Additive or synergistic if used in combination with NRTIs and/or PIs

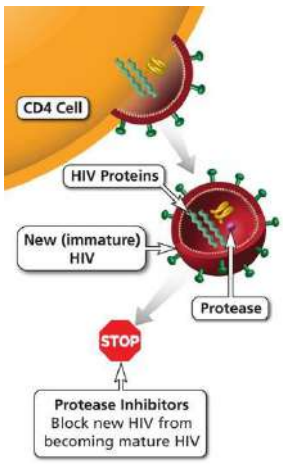
Examples:

- Delavirdine contradicted during pregnancy
- Efavirenz contradicted during preganacy
- Nevirapine

Side effects:

- Delavirdine- Rash
- Efavirenz- Vivid dreams, drowsiness, insomnia, rash, hyperlipidemia
- Nevirapine Rash, hepatotoxicity

Protease inhibitors



- Bind reversibly to the active sites of HIV Aspartate protease enzyme and interfere with its cleaving function
- Aspartate protease (pol gene encoded) is a viral enzyme that cleaves precursor polypeptides in HIV buds to form the proteins of the mature virus core.
- The advantage of protease inhibitors, since its working in the last step of viral cycle, its effective against new and chronically infected cells
- Resistance occurs via specific point mutations in the pol gene
- **Ritonavir** is the most commonly used protease inhibitor

Examples:

- Atazanavir
- Darunavir
- Fosamprenavir
- Indinavir
- Lopinavir
- Ritonavir
- Saquinavir

Side effects

- Nephrotoxicity (**Crystalluria**)
- Hematuria
- Hyperglycemia

Integrase inhibitors

Raltegravir

- Raltegravir inhibits HIV integrase to prevent the viral genome being incorporated into the human genome

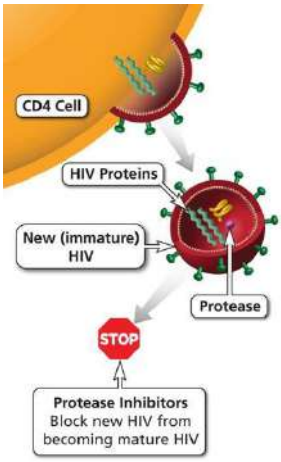
References:

- First aid 2018
- Kaplan medical 2017
- Parallels among positive-strand RNA viruses, reverse-transcribing viruses and double-stranded RNA viruses. Nature reviews 2006

Protease and Fusion inhibitors

Protease inhibitors

Mechanism of action:



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- Resistance occurs via specific point mutations in the pol gene
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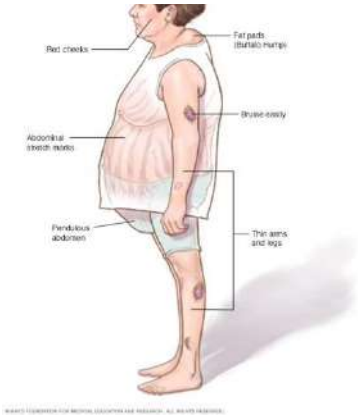
Side effects:

- General side effects:
- Hyperglycemia, GI intolerance (nausea, diarrhea), lipodystrophy (Cushing-like syndrome).

Indinavir



- Nephropathy
- Hematuria
- Thrombocytopenia

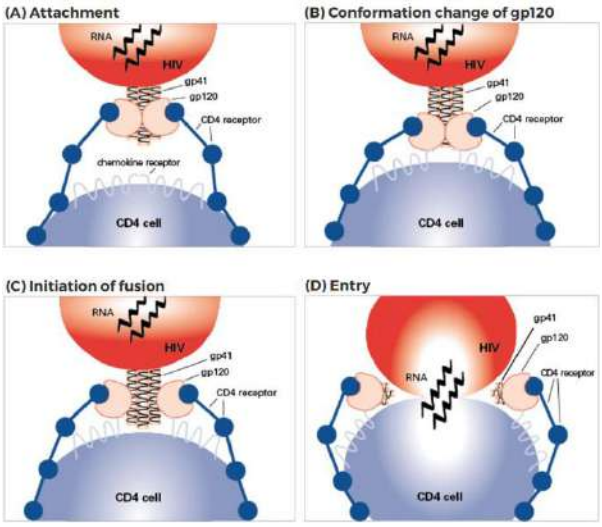
Ritonavir

- Major drug interactions induce CYP 1A2 and inhibits the major P450 isoforms (3A4 and 2D6)

Rifampin

- Rifampin (potent CYP/UGT inducer) reduces protease inhibitor concentrations; use rifabutin instead.

Fusion inhibitors

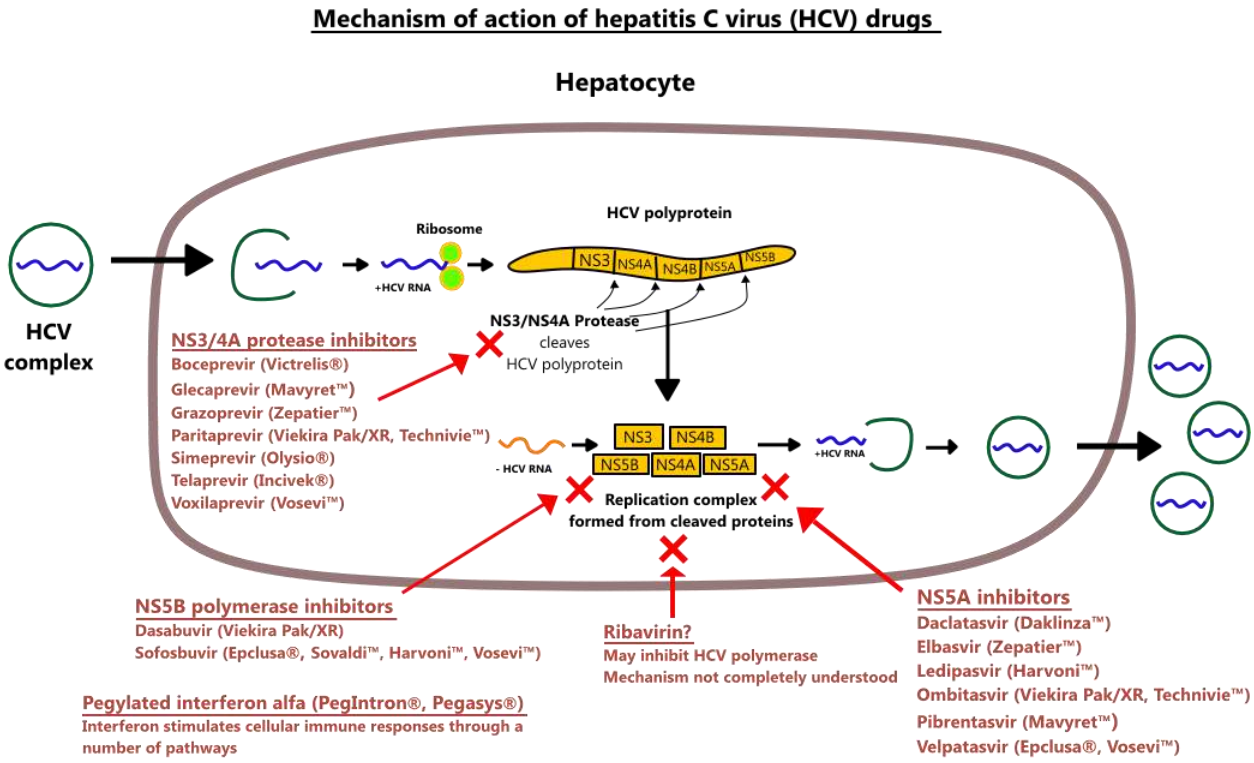


- Bind to GP41, GP 120 and prevent HIV entry into the cell (Inhibits fusion HiV1 to CD4+)
- Enfuvirtide: binds to pg41 and inhibits the fusion HIV-1 to CD4+ cells
- Maraviroc: blocks the binding of the gp120 HIV protein to CCR5 on macrophage surface to prevent viral entry
- Enfuvirtide and maraviroc block the entry of HIV into cells. Side effects: Skin reaction at injection sites.

References:

- First aid 2018
- Kaplan medical 2017

Hepatitis C therapy



Ledipasvir

- Inhibitor of the Hepatitis C Virus (HCV) Non-Structural Protein 5A (**NS5A**), which is required for viral RNA replication and assembly of HCV virions
- prevent hyperphosphorylation of **NS5A** which is required for viral protein production

Ribavirin

- It's a guanosine analog used to stop viral RNA synthesis
- It's a prodrug when metabolized resembles purine RNA nucleotides
- Inhibits synthesis of guanine nucleotides by competitively inhibiting inosine monophosphate dehydrogenase.
- Depletes intracellular GTP pools
- Ribavirin induces mutations in the virus that lead to viral death or production of virus with diminished infectivity
- Ribavirin alters T-cell profiles in favor of T-helper 1 cells that are more antiviral

Side effects:

- Hemolytic anemia-increase uric acid levels
- Causes birth defects, and pregnant women or women hoping to become pregnant should not take ribavirin
- Hair loss
- Pancytopenia

Simeprevir

- Hepatitis C virus (HCV) NS3/4A protease inhibitor
- viral protease NS3/4A complex is essential for cleaving the HCV encoded polyprotein into individual viral proteins facilitating replication, the drug blocks the viral replication process.

Side effects:

- Photosensitivity reactions, rash.

Sofosbuvir

- **Sofosbuvir** is an inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is essential for viral replication.
- Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203), which can be incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator

Side effects:

- Fatigue
- Headache
- Nausea

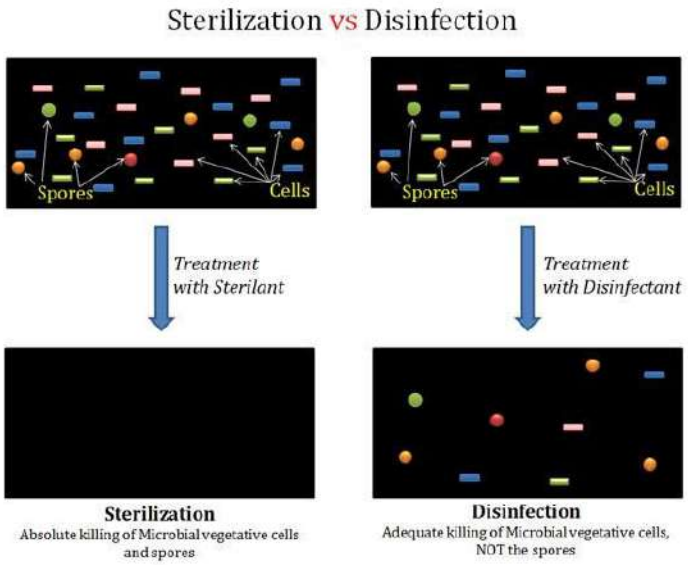
References:

- First aid 2018
- https://www.straighthealthcare.com/hepatitis-c-drug-moa.html

Sterilization and Disinfection

- **Sterilization**: complete removal or killing of all viable organisms (vegetative and sporing states).
- Spore: reproductive structure that can adapted surviving for extended periods in unfavorable conditions

- **Disinfection:** the removal or killing of disease-causing organisms. Compounds for use on skin: antiseptics.



Sporicidal:

- **Autoclaving** (steam under pressure): → (130°C for 3 mins or 120 °C for 15 mins) (sterilizing)
- May not reliably inactivate prions.
- Dry heat might be used 180°C for 2hr
- **Chlorine/bleach** Oxidizes and denatures proteins (oxidizing agent inactivating sulfhydryl-containing enzymes)
- **Hydrogen peroxide** Oxidizes and denatures proteins through free radical generation

Not Sporicidal:

- Denature proteins and disrupt cell membranes.
- **Alcohol**
- **Chlorhexidine**
- **Quaternary amine**

May be Sporicidal:

- Halogenation of DNA, RNA, and proteins
- Iodine
- Iodophors

References:

- First aid 2018

Introduction to Antimicrobials

Outline:

- Overview
- Mechanism of Action of Antibiotics
- Antibiotic Selection Criteria
- Definitions
- References

Overview:

- Bacteria are eukaryotic organisms
- They have DNA, mRNA, protein machinery, and a cell wall for protection
- These are the targets of antibiotics
- Antibiotics are

N.B Bacterial proteins composed of **30S** and **50S** subunits

Mechanism of Action of Antibiotics (possible targets):

Cell-wall synthesis:

- β-Lactam Antibiotics inhibiting the synthesis of the **peptidoglycan** layer of bacterial cell walls (Penicillin)
- Vancomycin

Cell-membrane integrity:

- Daptomycin

DNA gyrase:

- Fluoroquinolones (ciprofloxacin and levofloxacin)
- Nalidixic acids

mRNA synthesis (RNA polymerase):

- Rifampin

Protein Synthesis (**30S** and **50S** subunits)

- Inhibitors of 30S are Aminoglycosides and Tetracyclins
- Inhibitors of 50S are Chloramphenicol and Macrolides

Folic acid synthesis

- Sulfonamides
- Trimethoprim

Sulfa antibiotics inhibit the pathway that bacteria use to synthesize folic acid, which is considered a major metabolite used to produce DNA, RNA or most proteins inside the cell

Antibiotic selection criteria:

- ✓ Organism identification
- ✓ Understand drug safety profile
- ✓ Recognition of the site of infection.
  - ➢ Example: Drugs that could pass the blood brain barrier are ideal to treat meningitis
- ✓ Understand the patient antibiotic history (in terms of immune system, renal or hepatic function)
  - ➢ Development of Anaphylaxis shock due to penicillin administration
  - ➢ Patient with Renal insufficiency could accumulate toxins of the drug used
  - ➢ Caution should be taken in case of pregnant or lactating women to avoid drug crossing into the placenta or the milk respectively.

Definitions:

Bacteriostatic VS Bactericidal:

Bacteriostatic: Inhibit bacterial growth and replication to allow the immune system to recover and attach the bacteria

Bactericidal: Kill bacteria immediately

Bacteriostatic	Bactericidal
Macrolides	Aminoglycosides
Clindamycin	Vancomycin
Sulfonamides	Penicillins
Trimethoprim	Cephalosporins
Tetracyclines	Carbapenems
Chloramphenicol	Monobactams
Spectinomycin	Fluoroquinolones
	Metronidazole

N.B: in some case both bacteriostatic and bactericidal drugs might use in combination to broaden its efficacy

Drug Resistance:

The ability of bacteria to survive and grow in the presence of a drug that normally kills or inhibits the microbe's growth. That could be achieved through either making changes in the cell wall, RNA, DNA or by insertion of certain mutations

Empiric therapy (early intervention):

Applied before the confirmation of the causing pathogen. Fighting the infection sooner decreases the risk of complications. Usually, empiric antibiotics are broad-spectrum to enhance the magnitude of treatment towards either Gram-Positive or Gram-negative bacteria.

Once the diagnosis is confirmed for example (Blood culture test), treatment might change to more specific antibiotic (narrow-spectrum antibiotic)

Antimicrobial prophylaxis:

Prevention the spread of microbial infection before it begins, especially if the infected patient is in close contact with others

References:

- Action and resistance mechanisms of antibiotics: A guide for clinicians
- A clinician's guide to the appropriate and accurate use of antibiotics: the Council for Appropriate and Rational Antibiotic Therapy (CARAT) criteria. https://doi.org/10.1016/j.amjmed.2005.05.007

Penicillin (β-Lactams)

Outline:

- Overview
- Classification of Penicillin antibiotics
- Cephalosporins
- References

Overview:

- Bacterial cells are surrounded by a cell wall made of peptidoglycan.
- Peptidoglycan is linked together to provide protection for the cell
- Bacterial cells entail penicillin binding protein inside the cell which is involved in cell wall synthesis.
- Transpeptidase: bacterial **enzyme** that cross-links the peptidoglycan chains to form rigid cell walls
- β-Lactam Antibiotics inhibiting the synthesis of the peptidoglycan layer of bacterial cell walls (Penicillin)

Classification of Penicillin antibiotics:

- Natural penicillin
- Anti-staphylococcus penicillin
- Anti-pseudomonal penicillin
- Extended spectrum

Natural Penicillin:

Examples:

- Penicillin G, V Penicillin G (IV and IM form)
- penicillin V (oral).
- Penicillin G benzathine (I/M) For syphilis

Mechanism of Action (MOA):

- Bind penicillin-binding proteins (transpeptidases) therefore inhibit secretion of peptidoglycan.
- Without peptidoglycan, the cell wall will be vulnerable for invasion and disruption
- Penicillin is considered Bacteriocidal due its powerful disruption of Bacterial cell wall

Clinical Use of Penicillin:

1. Streptococcal pneumonia,

2. Streptococcal pyogenes which causes Pharyngitis

3. Actinomyces,

4. Neisseria meningitis,

5. Treponema pallidum,

6. Syphilis,

7. Listeria monocytogenes.

8. Gram positive.

Adverse Effects:

- Hypersensitivity reaction such as anaphylaxis reaction characterized by urticaria, swollen and skin itching, hypotension, bronchospasm, fever, purities.
- Diarrhea
- Hemolytic anemia (lysis of red blood cells)

Resistance:

- Bacteria which have β-lactamase will be resistance to Penicillin
- β-lactamase cleaves the β-lactam ring therefore the antibiotic won't be effective anymore.

Anti-staphylococcal penicillin (penicillin resistant drugs):

- Staphylococcal bacteria developed β-lactamase by time
- New group of Penicillin's which are resistant to β-lactamase (Penicillinase-resistant Penicillins).
- Coverage for methicillin-sensitive Staphylococcus aureus (MSSA).

Examples:

- Methicillin.
- Nafcillin.
- Oxacillin.
- Dicloxacillin.

Mechanism of action:

The same mechanism of penicillin (prevents the peptidoglycan synthesis and cross linking of the peptidoglycan)

Clinical use:

- Staphylococcus aureus except Methicillin-resistant Staphylococcus aureus (MRSA)
- Skin infection such as folliculitis

Adverse Effects:

- Hypersensitivity reaction such as anaphylaxis reaction leads to urticaria, swollen and skin itching, hypotension, bronchospasm, fever, purities.
- Methicillin causes **Interstitial nephritis** (inflammation of the kidney) diagnosed by increased levels of **eosinophils**

Aminopenicillin:

- Extended coverage (wide spectrum)
- (Penicillinase-sensitive Penicillins).

Examples:

- Amoxicillin. (Greater Oral bioavailability than ampicillin)
- Ampicillin.

Clinical use:

- Gram- positive and Gram-negative
- **Gram-negative** rods including such as

1. Hemophilus influenza.
2. E.coli/enterococci. Involved in UTI and food infection.
3. Listeria monocytogenes. Common in pregnant women when they eat cheese products
4. Proteus mirabilis.
5. Salmonella. Associated with Diary product and raw milk

Adverse Effects:

- Hypersensitivity reaction.
- Rash (Jerisch Herxheimer reaction). Diagnosed as Runny nose, flu, coughing, pharyngitis.
- Pseudomembranous colitis (clostridium difficile). Patient suffers from persistent diarrhea.

Anti-pseudomonal penicillin:

Examples:

- Ticarcillin.
- Carbenicillin.
- Pipracillin

Note: β-Lactamase inhibitors (clavulanic acid, sulbactam, tazobactam) are used in combination with β-lactam antibiotics to extend their coverage by inhibiting β-lactamases. Combinations include (Trade names)

- amoxicillin + clavulanic acid = Augmentin
- ticarcillin + clavulanic acid = Timentin
- ampicillin + sulbactam = Unasyn
- piperacillin + tazobactam = Zosyn

Mechanism of action:

same as that of penicillin but with beta lactamase inhibitors so considered as broad-spectrum antibiotics

Clinical use:

- Pseudomonas.
- Gram negative rods.

Cephalosporins:

	1St Generation	2nd Generation	3rd Generation	4th Generation
Examples	cefazolin, cephalexin	cefaclor, cefoxitin, cefuroxime, cefotetan	ceftriaxone, cefotaxime, cefpodoxime, ceftazidime	cefepime
Organisms	Gram positive Proteus mirabilis E coli Klebsiella pneumoniae	Gram positive H influenzae Enterobacter aerogenes Neisseria spp Serratia Marcescens Proteus mirabilis	Ceftriaxone for meningitis, gonorrhea, Ceftazidime for Pseudomonas. Cefotaxime for **spontaneous bacterial peritonitis** (cirrhotic patients due to excessive alcohol usage)	Broad gram-positive and gram-negative coverage Pseudomonas aeruginosa

		E coli Klebsiella pneumoniae.		

Mechanism of action:

- Cephalosporin inhibits the bacterial cell wall synthesis.
- Cephalosporins are considered Bacteriocidal antibiotics
- Cephalosporins are β-Lactam ring modified to be resistant to penicillinases

Adverse Effects:

- Hypersensitivity.
- Vitamin K deficiency
- Disulfiram like reaction (nausea, vomiting due to excessive alcohol consumption
- Increases nephrotoxicity of aminoglycosides
- Low cross reactivity with penicillins.

References:

First Aid 18

Carbapenem

Outline:

- Drug names
- Mechanism of Action
- Clinical use
- Adverse effects

Drug names:

- Doripenem
- Imipenem
- Meropenem
- Ertapenem

Mechanism of Action (MOA):

- Inhibit Cell wall like penicillin
- Highly resistance to B-lactamase
- Imipenem rapidly inhibited by Dehydropeptidase I
- Imipenem should be given with Cilastatin
- Cilastatin is a peptidase inhibitor that block renal degradation of Imipenem (decrease renal toxicity of Imipenem)

Clinical Use of Carbapenems:

- Life threating conditions
- Gram positice cocci, gram negative rodes and anaerobic bacteria

Adverse Effects:

- GIT distress
- CNC toxicity seizures at high plasma levels (Meropenam less seizures)
- Skin rash
- Imipenem rapidly inhibited by Dehydropeptidase I (increased renal toxicity)

Aztreonam (Monobactams)

Outline:

- Mechanism of Action
- Clinical use
- Adverse effects

Mechanism of Action (MOA):

- Inhibit peptidoglycan cross linking by binding to penicillin binding protein 3
- Highly resistance to B-lactamase
- Bactericidal
- Synergistic with aminoglycosides

Clinical Use of Aztreonam:

- Aerobic Bacteria
- Gram negative rodes
- NO actvity aneorobic bacteria
- Used for penicillin allergic patients

Adverse Effects:

- GIT distress

Vancomycin

Outline:

- Mechanism of Action
- Route of Administration
- Clinical use
- Adverse effects
- Mechanism of Resistance
- References

Mechanism of Action (MOA):

- Inhibit Call wall synthesis through binding to D-alanyl-D alanine the precursor of the cell wall
- Prevent polymerization of peptidoglycan causing lysis of Cell wall
- Considered as a Bacteriocidal antibiotic.

Route of Administration:

1. Intravenous Injection (IV): Most common route of administration since it is NOT absorbed from the intestine.
2. Oral: The only approved indication for oral vancomycin therapy is in the treatment of pseudomembranous colitis, where it must be given orally to reach the site of infection in the colon.

Clinical Use of Vancomycin:

1. Serious Gram-negative infection such as **MRSA** (Methicillin resistance Staphylococcus aureus)
2. Pseudomonas colitis (Clostridium difficile) characterized foul-smelling, and watery stools
3. Prophylaxis before surgery

Adverse Effects:

Although Vancomycin is considered a well-tolerated antibiotic but it might have sever toxicity such as:

- Nephrotoxicity due to IV administration
  N.B: Vancomycin excreted through the Kidney
- Ototoxicity
- Thrombophlebitis at infusion site (vein Inflammation)
- Red man syndrome: Due to high infusion rate that leads to massive release of histamine (vasodilation) and transit hearing loss
  N.B Red man syndrome could be overcome by pre-treatment with antihistaminic (Diphenhydramine) and by slow injections.

- Dress Syndrome: Vancomycin is involved in **vancomycin** in drug rash with eosinophilia and systemic symptoms

Mechanism of resistance:

vancomycin-resistant enterococci (VRE)

References:

- First Aid 18
- Clinical characteristics of *Clostridium difficile*-associated diarrhea among patients in a tertiary care center in China
- Resistance Mechanisms, Epidemiology, and Approaches to Screening for Vancomycin-Resistant Enterococcus in the Health Care Setting

Protein synthesis inhibitors

Outline:

- Overview
- Mechanism of Action
- Examples

Overview

- Eukaryotic ribosomes are larger. They consist of a 60S large subunit and a 40S small subunit, which come together to form an 80S
- Antibiotic that target bacteria usually attack 70S (prokaryotes) leaving 80S unaffected
- Bacterial ribosomes are composed of 3 active sites
- A site: The point of entry for the aminoacyl tRNA
- P site: where the peptidyl tRNA is formed in the ribosome
- E site: the exit site of an empty tRNA after it gives its amino acid to the growing peptide chain.

Mechanism of action:

1. Protein synthesis inhibitor are ALL Bacteriostatic except Aminoglycosides are Bactericidal
2. Divided according to which ribosomal subunit is being targeted

Examples

Protein Synthesis inhibitors	30 S inhibitors	50 S inhibitors
	Aminoglycosides	Linezolid
	Tetracyclines	Macrolides
		Clindamycin
		Chloramphenicol

Aminoglycosides

Outline:

- Overview
- Mechanism of protein synthesis in Bacteria
- Mechanism of Action
- Different forms of Aminoglycosides
- Clinical use
- Adverse effects
- References

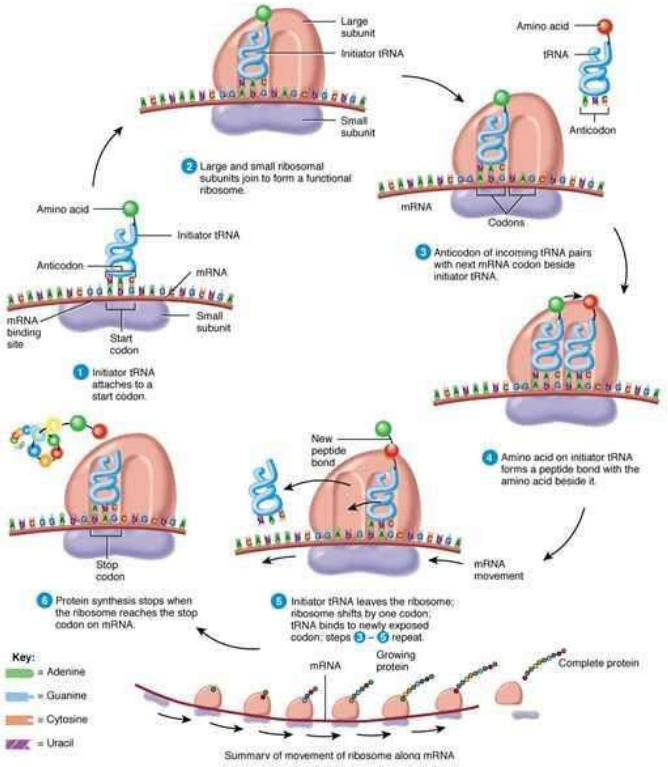
Overview

- Aminoglycosides are protein synthesis inhibitors which bind to 30 S subunit
- Eukaryotic ribosomes are larger. They consist of a 60S large subunit and a 40S small subunit, which come together to form an 80S

Mechanism of protein synthesis in Bacteria:

Protein synthesis composed of 3 major steps:

1. Initiation: Aassembly of ribosome on mRNA molecule
2. Elongation Repeated cycles of amino acid edition
3. Termination Release of protein chain



Mechanism of Action (MOA):

- Protein synthesis inhibitors
- Irreversibly bind to 30S subunit and inhibit formation of initiation complex
- Misreading of mRNA
- Prevent tRNA translocation and consequently there is No protein synthesis
- Require oxygen for uptake into bacterial cell wall (oxygen dependent mechanism) therefore efficient for aerobic bacteria NOT anaerobic
- Aminoglycosides penetrate body fluid Except CSF

Different forms of Aminoglycosides:

1. Neomycin
2. Tobramycin
3. Amikacin
4. Gentamycin
5. Streptomycin

Clinical Use of Aminoglycosides:

- Target aerobic bacteria such as gram-negative Bacteria which are oxygen dependent: E. Coli, Pseudomonas, klebsiella, Enterobacter
- Used in combination with B-lactams inhibitor for synergistic effect

Adverse Effects:

- Nephrotoxicity (manifested by elevated creatinine and albumin levels)
- Ototoxicity might lead to deafness
- Neuromuscular blockade

References:

- First Aid 18
- Section 29.5Eukaryotic Protein Synthesis Differs from Prokaryotic Protein Synthesis Primarily in Translation Initiation.
- Selimoglu E (2007): Aminoglycoside-induced ototoxicity. Curr Pharm Des 13(1):119-126.
- Taber HW et al (1987): Bacterial uptake of aminoglycoside antibiotics. Microbiological Reviews 51(4):439-457.

Tetracyclines

Outline:

- Examples
- Mechanism of Action
- Clinical use
- Adverse effects
- Mechanisms of resistance
- References

Examples:

- Tetracycline
- Doxycycline
- Minocycline
- Demeclocycline

Mechanism of Action (MOA):

- Protein synthesis inhibitors
- Bind to 30S subunit and inhibit aminoacyl-tRNA binding to the ribosome–RNA complex
- Actively transported (concentrated) into bacterial cells.

Clinical Use of Tetracyclines:

- Broad spectrum bacteriostatic
- Limited use due to its toxicity
- Minocycline for Acne
- Doxycycline is widely used to treat:
  - Borrelia burgdorferi (Lyme disease)
  - Atypical Mycoplasma pneumonia
  - Chlamydia infection (STD)
  - Rickettsia
- Doxycycline excreted fecally so could be used for renal failure patients
- Demeclocycline is used as ADH antagonist
  - Demeclocycline inhibit the renal antidiuretic hormone
  - Used to treat hyponatremia due to the syndrome of inappropriate antidiuretic hormone (SIADH)

Adverse Effects:

- Staining of teeth (yellow teeth)
- Photosensitivity (increased risk of sunburn)
- Retardation of fatal bone growth in children
- Contraindicated in pregnancy

- Contraindicated to use with:
  - Calcium (milk or dairy products)
  - Antacids
    Tetracyclines form chelates with these products and interfere with their absorption

Mechanism of resistance:

- Through inhibition of drug accumulation inside bacterial cell
- Decrease bacterial uptake of antibiotic
- Increased influx out through plasmid encoded pump

References:

- Klein, Natalie C.; Cunha, Burke A. (1995). "Tetracyclines". Medical Clinics of North America. 79 (4): 789–801. doi:10.1016/S0025-7125(16)30039-6.

- Miell, J.; Dhanjal, P.; Jamookeeah, C. (2015). "Evidence for the use of demeclocycline in the treatment of hyponatraemia secondary to SIADH: a systematic review". Int. J. Clin. Pract. 69 (12): 1396–1417. doi:10.1111/ijcp.12713. PMID 26289137.

Chloramphenicol

Outline:

- Mechanism of Action
- Clinical use
- Adverse effects
- Mechanism of Resistance
- References

Mechanism of Action (MOA):

- Bind to 50S ribosomal unit and inhibit peptidyltransferase activity.
- Prevent the formation of peptide bond and block protein synthesis.
- Considered as a Bacteriostatic antibiotic.
- Not used anymore in developed countries due its toxicity
- Cheap antibiotic so it's used in developing countries

Clinical Use of Chloramphenicol:

1. Drug of choice for treatment of Meningitis (Developing countries) while Ceftriaxone is commonly used in Developed countries
   N.B: Lipid soluble, with excellent tissue penetration including the CNS
   N.B: Sources of Meningitis are:
   - Streptococcus pneumoniae
   - Neisseria meningitidis
   - Haemophilus influenzae type b

2. Rickettsial diseases: In children and pregnant women, where tetracyclines should be avoided
3. Brain abscesses

Adverse Effects:

- Anemia (dose dependent) and Pancytopenia
  N.B: Pancytopenia: deficiency of blood components (red cells, white cells, and platelets).
- Aplastic anemia ((dose independent)
- Gray baby syndrome: Occurred in premature infants

Gray baby syndrome in premature infants due to lack of liver UDP-glucuronyl transferase. Characterized by ashen gray skin discoloration, cyanosis, vomiting, vasomotor
collapse

N.B: UDP-glucuronyl transferase play a major role in transferring Bilirubin to soluble forum which get easily metabolized.

N.B: Chloramphenicol is Metabolized and completely inactivated by glucuronidation in liver

Mechanism of resistance:

Through enzymatic inactivation by acetyltransferases which metabolize chloramphenicol to inactive form

References:

- First Aid 18
- Multi-antibiotic resistant brain abscess sensitive only to chloramphenicol: a case report.
- Crush Step 1 the ultimate USMILE step review 1

Clindamycin

Outline:

- Mechanism of Action
- Clinical use
- Adverse effects

Mechanism of Action (MOA):

- 50S subunit inhibitors-Inhibit protein synthesis by blocking polypeptide transfer eventually block peptide chain prolongation

Clinical Use of Clindamycin:

- Anaerobic infections (Bacteroides fragilis, clostridium perfringens
- Clindamycin to kill anaerobic bacteria Above the diaphragm such as aspiration pneumonia, lung/dental/skin abscesses
- Metronidazole to kill anaerobic bacteria Below the diaphragm such as pseudomembranous colitis, bacterial vaginosis, abdominal penetrating wounds).

Adverse Effects:

- Pseudomembranous colitis (clostridium difficile)
- Clindamycin associated with overgrowth
- Fever
- Diarrhea

Macrolides

Outline:

- Examples
- Mechanism of Action
- Clinical use
- Adverse effects
- Mechanism of Resistance

Examples:

1. Azithromycin
2. Erythromycin
3. Clarithromycin

Mechanism of Action (MOA):

- Protein synthesis inhibitors by blocking peptide chain elongation
- Binds to the 23s rRNA (50s) ribosome and prevents the translocation of the tRNA on the mRNA
- Bacteriostatic
- Potent inhibitors of CYP450 system, leading to many drug–drug interactions.

Clinical Use of Macrolides:

- Chlamydia (STDs)
- Atypical Pneumonia such as (Mycoplasma, Chlamydia, legionella)
- Gram positive cocci specially for patient allergic to penicillin
- Upper respiratory infection such as sore throat, pharyngitis, tonsillitis
- Otitis media specially for patient who are allergic to penicillin

Adverse Effects:

- Mortality
- Arrhythmia (QT interval prolongation)
- Acute cholestatic hepatitis
- Skin rashes and eosinophilia
- Drug-Drug interaction due to its CYP450 inhibition (increases serum (Theophyllines, warfarin, clopidogrel)

Mechanism of Resistance:

Methylation of 23 RNA (50S ribosome) which alter drug affinity

References:

- Crush Step 1- The ultimate USMILE step1 review

Sulfonamides

Outline:

- Common sulfonamide drugs
- Bacterial synthesis of DNA and RNA
- Mechanism of Action
- Clinical use
- Adverse effects
- Mechanism of Resistance
- References

Common sulfonamide drugs:

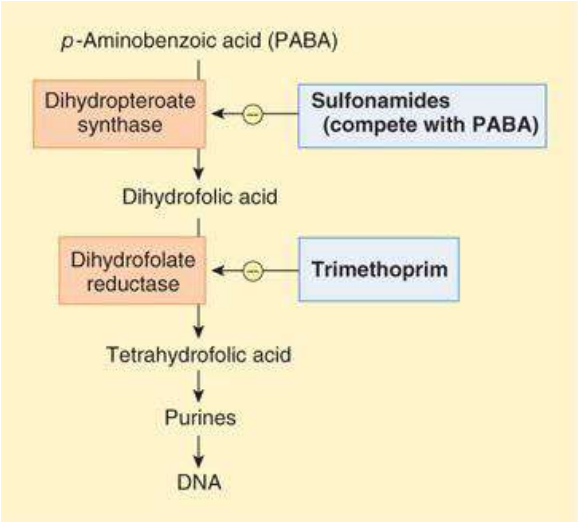
- Sulfamethoxazole
- Sulfadiazines
- Sulfisoxazole.

Bacterial synthesis of DNA and RNA:

- Bacteria make its own Folic acid from a constitutive production of P-aminobenzoic acid
- Dihydropteroate is an important enzyme which transfer PABA to Dihydrofolic acid (DHF)
- Dihydrofolate reductase (DHFR) next convert Dihydrofolic acid (DHF) to Tetrahydrofolic acid (THF) which eventually used to produce DNA, protein.

Mechanism of Action (MOA):

- Sulfonamides are structural analogues to PAPA the main precursor for bacterial folic acid. (Antimetabolite)
- Sulfonamides inhibit folate synthetase through inhibiting Dihydropteroate enzyme
- Trimethoprim—inhibits dihydrofolate reductase (DHFR) to block conversion of DHF to tetrahydrofolate (THF)



Clinical Use of Sulfonamides:

1. Gram-negative and positive

bacteria such as S. pneumoniae, H. influenzae, Shigella, Salmonella, Neisseria gonorrhoeae, Chlamydia, Nocardia

2. E.Coli
    - Main source of Urinary tract infection (UTI)
    - Bactrim is a combination of sulfamethaxazol (sulfanomides) SMX and Trimethoprime TMP for treatment of mild UTI
3. Toxoplasma gondii main source of Toxoplasmosis

    Toxoplasmosis:
    - Appeared as flu like symptoms
    - spread by eating poorly cooked food that contains cysts or exposure to infected cat feces
    - If infected during pregnancy, a condition known as congenital toxoplasmosis may affect the child
    - Cutaneous toxoplasmosis appeared in immunodeficient patients such as HIV/AIDS who are subjected to Toxoplasmosis
    - Might damage Eye causing Toxoplasma chorioretinitis
    - Effected treatment is a combination of Pyrimethamine, sulfadiazine

Adverse Effects:

- Hypersensitivity reactions
- Hemolytic anemia especially in patient with Glucose-6-phosphate dehydrogenase deficiency (G6PD)
    - Absence of this enzyme causes red blood cells to break down prematurely. This destruction of red blood cells is called hemolysis.
    - G6PD protects red blood cells from the effects of potentially harmful molecules called reactive oxygen species (Free radical scavenger)
- Tubulointerstitial nephritis
- Photosensitivity
- kernicterus/hyperbilirubinemia in infants due to increased bilirubin production
    - Usually appeared in newborn infants with Jaundice (yellow pale skin)
- Interfere with drug metabolism such as Warfarin, phenytoin and methotrexate due to bilirubin drug displacement
- skin rash including severe reactions (Stevens-Johnson syndrome

Mechanism of resistance:

Through induction of certain mutations which overproduce PABA or adopt alternative ways for folate synthesis.

References:

- First Aid 18
- Chapter 46: Sulfonamides, Trimethoprim, & Fluoroquinolones, Katzung & Trevor's Pharmacology: Examination & Board Review, 11e
- Trimethoprim-sulfamethoxazole: An overview https://www.uptodate.com/contents/trimethoprim-sulfamethoxazole-an-overview

Trimethoprim

Outline:

- Mechanism of Action
- Clinical use
- Adverse effects

Mechanism of Action (MOA):

- Trimethoprim—inhibits dihydrofolate reductase (DHFR) to block conversion of DHF to tetrahydrofolate (THF)
- Bacteriostatic

Clinical Use of Trimethoprim:

- Trimethoprim used as synergistic drug with sulfonamides to treat UTI infection (trimethoprim-sulfamethoxazole(SMX+TMP)
- Shigella, Salmonella, Pneumocystis jirovecii pneumonia
- Prophylaxis

Adverse Effects:

- Megaloblastic anemia due to deficiency in folic acids affect red blood cell production (MCV greater than 100 Macrocytic anemia)
- Bone marrow suppression (Leukopenia, granulocytopenia)
- Folinic acid (leucovorin) is commonly used to minimize bone marrow suppression

Fluoroquinolones

Outline:

- Examples
- Mechanism of Action
- Clinical use
- Adverse effects
- Mechanism of Resistance

Examples:

1. Ciprofloxacin
2. Norfloxacin
3. Levofloxacin
4. Moxifloxacin
5. Gatifloxacin
6. Nalidixic acid

Mechanism of Action (MOA):

- Inhibit DNA gyrase (bacterial topoisomerase II) & topoisomerase IV (the enzymes that cause DNA to rewind after copying)
- Bactericidal

Clinical Use of Fluoroquinolones:

- Gram negative rods
- UTI (E. Coli)
- GI infection (Pseudomonas)
- Neisseria
- Otitis externa

Adverse Effects:

- Tender rupture in elderly (65 years) +prednisone
- Arrhythmia QT interval prolongation)
- Tendonitis
- GIT upset
- Headache
- Dizziness
- Skin rash
- Contraindicated to pregnant women and children below 18 years old due to possible damage to the cartilage
- CYP450 inhibition (Ciprofloxacin)

Mechanism of Resistance:

- Chromosome encoded mutation in DNA Gyrase
- Drug efflux pump
- Plasmid mediated resistance

Anti-Tuberculosis drugs

Outline:

- Rifamycins
- Isoniazid
- Pyrazinamide
- Ethambutol
- Streptomycin

Rifamycins:

Mechanism of Action:

- Inhibits DNA-dependent RNA polymerase

Clinical uses:

- M. Tuberculosis
- Prophylaxis against meningitis
- Chemoprophylaxis against Influenza Type B
- Serious staph infection, used in combination therapy with B-lactam antibiotics to decrease the probability of resistance such as MRSA infection

Side effects:

- Orange red color of body fluids (urine, tears and sweat)
- Hepatotoxicity
  - Rifamycin is excreted through the liver with high incidence of induction of P-450 isozymes (increase metabolism of itself or the combined drug)
  - Decrease half-life of several drugs such as warfarin, corticosteroids, oral contraceptives, oral hypoglycemic, digoxin, methadone
  - Rifabutin is the drug of choice for HIV patients since its avoid induction of P-450 isozymes

Mechanism of resistance

- Structural changes to RNA polymerase
- Rifamycin treatment alone are vulnerable for resistance, used in combination therapy

Isoniazid:

Mechanism of Action:

- Inhibits mycolic acid synthesis which is crucial for mycobacterial cell wall
- Requires bacterial catalase-peroxidase (KatG) to convert INH to active metabolite.

Clinical uses:

- M. Tuberculosis

- Drug of choice for treatment for all Tuberculosis cases

Side effects:

- Isoniazid (INH) induces Injures, Neurons& Hepatocytes
- Hepatotoxicity
- Peripheral neuropathy overcome by administration of Vit B6 (pyridoxine)
- Causes drug-induced lupus erythematosus (diagnosed by Anti histone antibodies)
- Sideroblastic anemia
- Anion gap metabolic acidosis leads to neurotoxicity and seizures

Mechanism of resistance

- Alteration in bacterial catalase-peroxidase

Pyrazinamide:

Mechanism of Action:

- The exact mechanism of action isn't known yet
- Prodrug need to be activated first by pyrazinamidase to inhibit fatty acid synthase I (involved in mycolic acid biosynthesis)
- Metabolite active only in acid pH (inside phagolysosomes)

Clinical uses:

- M. Tuberculosis

Side effects:

- Uricemia (gout)
- Hepatic toxicity

Mechanism of resistance

- Mutations in gene coding pyrazinamides

Ethambutol:

Mechanism of Action:

- Inhibit synthesis arabinosyl transferase required for mycobacterial cell wall.

Clinical uses:

- M. Tuberculosis

Side effects:

- Optic neuropathy

Streptomycin

Mechanism of Action:

- Inhibit protein synthesis (interfere with 30s component)

Clinical uses:

- Considered as a second line of treatment of M. Tuberculosis

Side effects:

- Ataxia, Tinnitus, vertigo, nephrotoxicity

References:

- Crush step 1-The ultimate USMLE step 1 Review
- Severe isoniazid related sideroblastic anemia. Hematology report. 2011

Metronidazole

Outline:

- Mechanism of Action
- Clinical use
- Adverse effects

Mechanism of Action (MOA):

- Generation of toxic metabolites (Nitro reductase) that disrupt bacterial DNA
- Free radical generations that damage DNA
- Bactericidal

Clinical Use of Metronidazole:

- Protozoa such as:
  - Giardia lamblia (Giardiasis) smelling diarrhea
  - Entamoeba histolytica (Amebiasis) diarrhea
  - Trichomonas Vaginalis (STD)
- Anaerobic bacteria (BELOW diaphragm) such as:
  - Clostidium difficile
  - Bacteroides fragilis
  - Helicobacter pylori (Gastric ulcer)

Triple therapy: Metronidazole+ Clarithromycin (Macrolide)+PPI (Omeprazole)

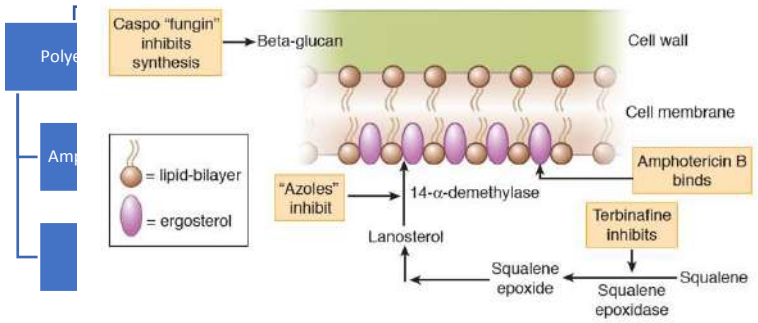
Adverse Effects:

- Disulfiram reaction (Alcohol with metronidazole develops nausea and vomiting)
- Metallic taste
- Hemolytic anemia if they have G6PD deficiency

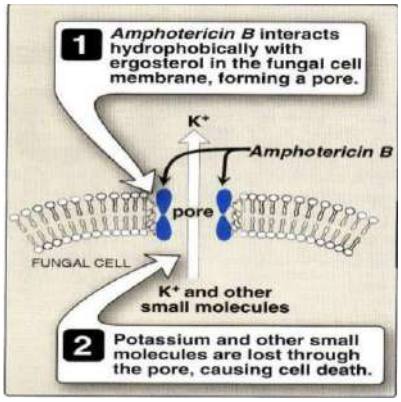
Antifungal

Classification of antifungal drugs

- Fungal infection is either systemic or superficial mycoses



Amphotericin B



Mechanism of action

- Interact with ergosterol in fungal membranes to form artificial "pores," which disrupt membrane permeability
- The pores disrupt membrane function allowing **electrolytes** (Particularly) and small molecules to leak from the cell, resulting in cell death

Clinical applications

- Drug of choice for sever systemic mycoses infection
- Treatment of cryptococcus infection, preferably in combination with flucytosine (synergistic effect)
- Blastomyces
- Coccidioides
- Histoplasma
- Candida
- Mucor
- In case of fungal meningitis applied intrathecally

Side effects

- Nephrotoxicity that include decrease GFR, Elevated BUN, Decrease K and Mg
- Fever
- Chills

- Muscle rigor
- Hypotension due to histamine release
- Anemia
- Arrhythmia
- IV phlebitis

- **Note:** Patient should be supplied with K and Mg to avoid hypokalemia and hypomagnesemia
- Amphotericin B toxicity can be avoided by using liposomal amphotericin B, or by drug
- combinations (e.g., + flucytosine), permitting ↓ in amphotericin B dose
- Resistant fungal strains appear to have low ergosterol content in their cell membranes

Nystatin

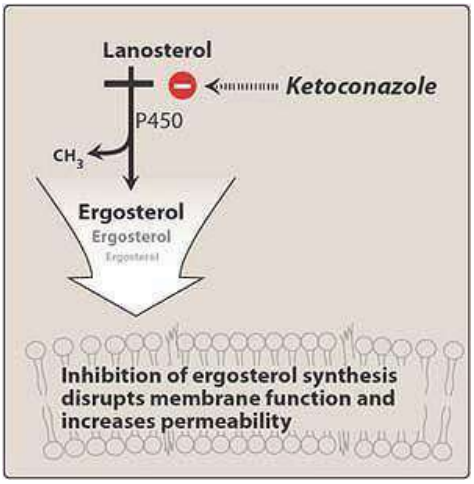
Mechanism of action

- Interact with ergosterol in fungal membranes to form artificial "pores," which disrupt membrane permeability
- The pores disrupt membrane function allowing **electrolytes** (Particularly) and small molecules to leak from the cell, resulting in cell death

Clinical applications

- Nystatin (too toxic for systemic use)—used as "Swish and swallow" for oral candidiasis (thrush); topical for diaper rash or vaginal candidiasis.

Azoles



- Interfere with the synthesis of ergosterol by inhibiting 14-a-demethylase, a fungal P450 enzyme, which converts lanosterol to ergosterol

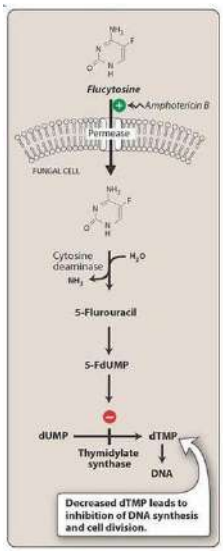
Clinical applications

- Used in cases local and less serious systemic mycoses
- Fluconazole: Prophylaxis and suppression of cryptococcal meningitis in AIDS patients and candidal infections of all types- Penetrates CSF hence can be used in meningeal infection
- Ketoconazole: Paracoccidioides and backup for Blastomyces and Histoplasma
- Clotrimazole and miconazole: Used topically for candidal and dermatophytic infections
- Itraconazole and Voriconazole: Blastomycoses, Sporotrichoses, Aspergillosis
- Isavuconazole: For serious Aspergillus and Mucor infections

Side effects:

- Decrease synthesis of steroids leads to decrease libido, gynecomastia and menstrual irregularities
- Hepatotoxicity
- Ketoconazole and itraconazole are metabolized by liver enzymes (Inhibition of hepatic P450s)

Flucytosine



Mechanism of action

- Flucytosine enters fungal cells a cytosine-specific permease enzyme
- Activated by fungal cytosine deaminase to 5-fluorouracil (5-FU), which after triphosphorylation is incorporated into fungal RNA
- It inhibits thymidylate synthase that decreases dTMP production and inhibit DNA synthesis and cell division

Clinical applications

- Use in combination with amphotericin B in severe candidal and cryptococcal infections—enters CSF
- Note: Fungal resistance might increase in case of using Flucytosine alone

Side effects

- Bone marrow suppression

Caspofungin/Fungins/ Anidulafungin

- Inhibit the synthesis of beta-1,2 glucan, a critical component of fungal cell walls

Clinical applications

- Invasive aspergillosis/ candida infection

Side effects

- GIT upset
- Flushing due to histamine release

Terbinafine

- Active only against dermatophytes by inhibiting squalene epoxidase →↓ Ergosterol

Clinical applications

- Onychomycosis—fungal infection of finger or toe nails

Side effects

- GI distress
- Rash
- Headache
- Taste disturbance
- ↑ liver function tests

Griseofulvin

- Active only against dermatophytes (orally, not topically) by depositing in newly formed keratin and disrupting microtubule structure

Clinical applications

- Oral treatment of superficial infections; inhibits growth of dermatophytes (tinea, ringworm).

Side effects

- Disulfiram-like reaction

- Teratogenic
- Carcinogenic
- Increase Cytochrome P-450 and warfarin metabolism

References:

- First aid 2018
- Kaplan medical 2017

Introduction to antiprotozoal drugs

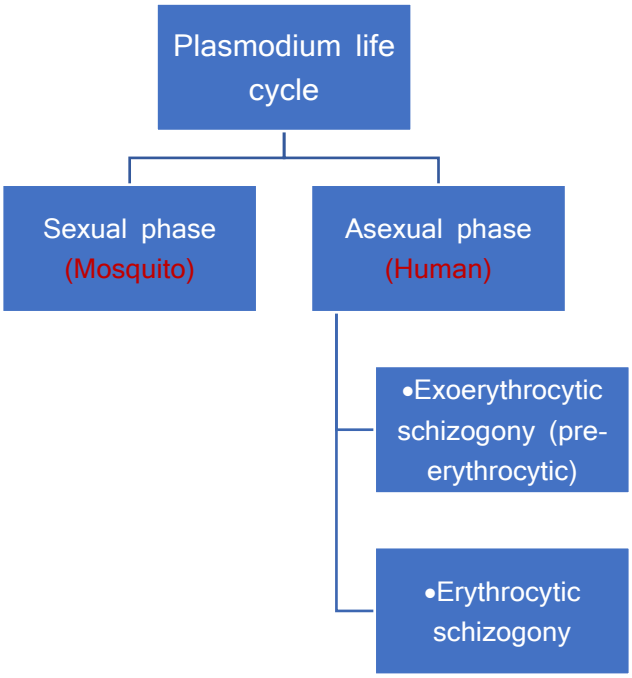
Outline:

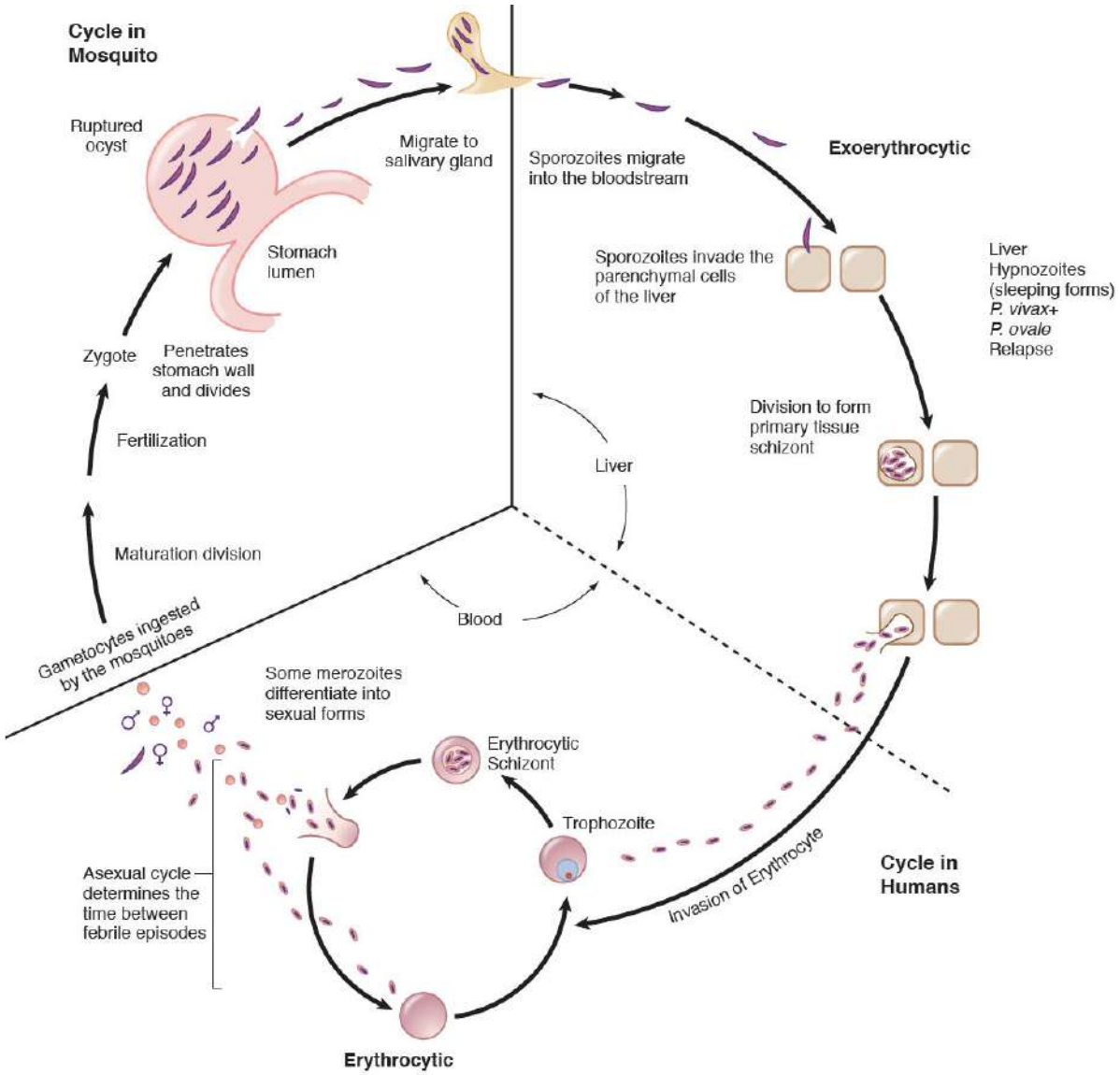
- Overview
- Plasmodium life cycle
- Signs and Symptoms of Malaria
- Diagnosis
- Anti-malarial drugs

Overview

- Malaria is a mosquito-borne infectious disease caused by plasmodium
- Transmitted by infective bite of **female Anopheles mosquitos**
- Malaria Is unicelular

Plasmodium life cycle:





- Sporozoite found in salivary glands of female mosquitoes
- Infected mosquito bites the skin releasing sporozoites into blood stream infecting liver cells
- Once it reaches hepatocytes in turn into merozoites which quickly invade red blood cells
- Within red blood cells, merozoites release enzymes that trigger red cell lysis
- Some parasites develop into Gametocytes and released into blood stream

Signs and Symptoms of Malaria

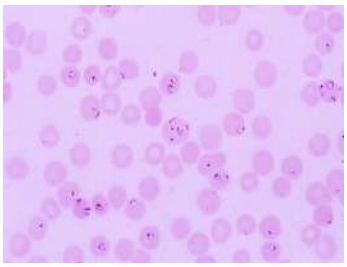
- Headache (noted in virtually all patients with malaria)
- Cough
- Fatigue
- Malaise
- Shaking chills
- Arthralgia
- Myalgia

- Paroxysm of fever, shaking chills, and sweats (every 48 or 72 hours, depending on species)
- Anemia in severe cases

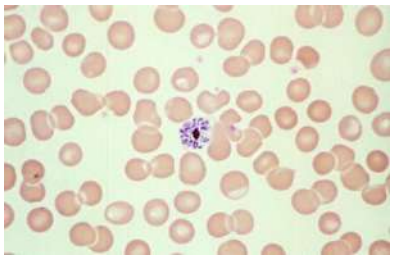
Malaria species	**Signs**
Plasmodium Vivax/ovale	48 hours after spikes
Plasmodium Malaria	72 hours after spikes
Plasmodium falciparum	Irregular fever spikes causes cerebral malaria

Diagnosis

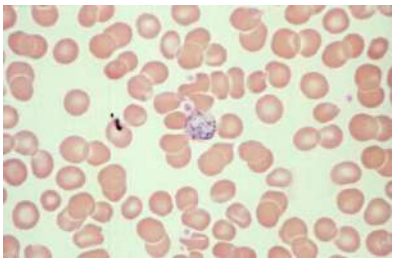
- Thick and thin blood smear



immature-ring form, of the malarial parasite within peripheral erythrocytes



An erythrocyte filled with merozoites



A mature schizont within an erythrocyte

Anti-malarial drugs

Chloroquine

- For sensitive species
- MOA: Block plasmodium heme polymerase

Mefloquine atovaquone/proguanil are used in case of resistance

Quinine might be used in serious condition, but with caution especially in case of G6PD patients (Hemolytic anemia)

- **Note:** In G6PDH deficiency, the ability of erythrocytes to detoxify oxygen radicals is impaired. Ironically, the accumulation of the radicals in erythrocytes in G6PDH deficiency gives protection against malaria
- Female heterozygous for G6PDH deficiency have increased resistance to malaria

References:

- First aid 2018
- Kaplan medical 2017
- Medscape

Anti-mite/ louse

Permethrin

- Consider as neurotoxin Inhibit Na channel which lead to neuronal membrane depolarization
- Available as 5% cream or 1% liquid

Malathion:

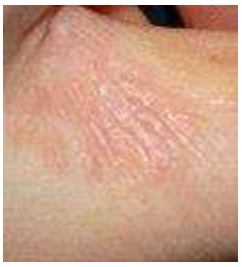
- Acetylcholinesterase inhibitors
- Available as 5% lotion

Lindane

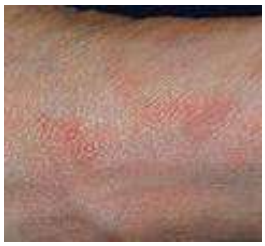
- Block GABA channels lead to neurotoxicity
- Available as 1% lotion or shampoo

Clinical uses:

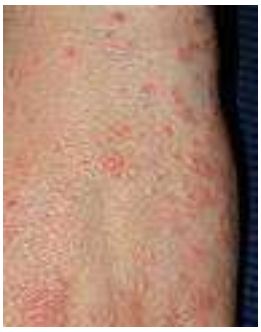
- used to treat head lice, tiny insects that infest and irritate your scalp
- Scabies (Sarcoptes scabiei)



Scabies of the finger



Scabies of the foot



Scabies of the hand

Head lice

References:

- First aid 2018
- Kaplan medical 2017

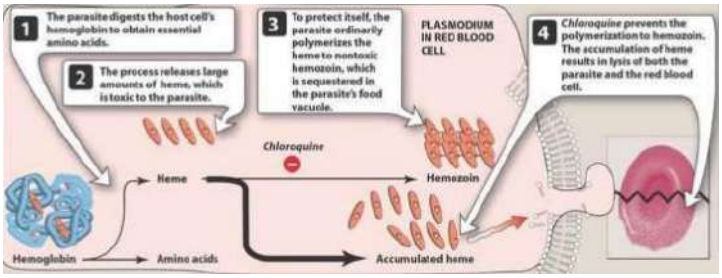
Chloroquine

Outline:

- Mechanism of action
- Chloroquine resistance
- Chloroquine Toxicity

Mechanism of action:

- Block plasmodium heme polymerase leading to accumulation of toxic hemoglobin to the parasite
- Prevent heme polymerization into hemozoin causing heme accumulation
- Chloroquine increase pH inside parasite vacuole
- Heme damage plasmodium membrane
- Interfere with DNA synthesis



- Effective against all plasmodium species EXCEPT **Falciparum**

Chloroquine resistance

- Due to enhanced efflux of parasite vesicle (increased expression of human multi drug resistance transporter P-glycoprotein) leads to decrease intracellular concentration in the blood

Drugs used to overcome Chloroquine resistance

- Artemether+ Lumefantrine
- Artesunate+ Mefloquine
- Atovaquone+ Proguanil
- Recommended to take these drugs as prophylaxis before visiting endemic africans countries where Malaria exist

Chloroquine Toxicity

- Retinopathy

References:

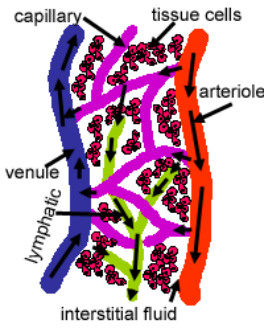
- First aid 2018

Immunology Notes

Lymphoid structures

Outline:

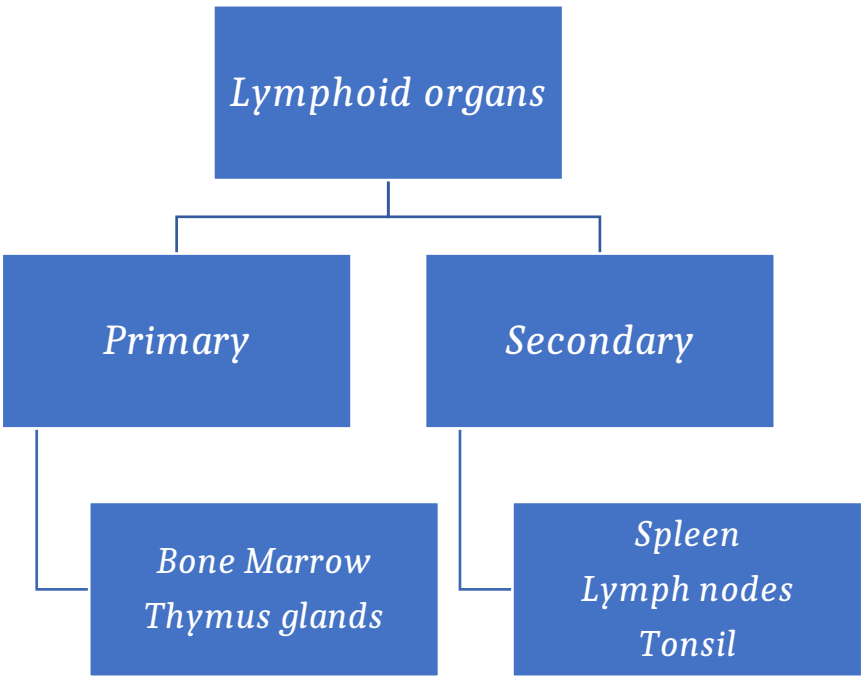
- What's lymphoid tissue
- Primary& Secondary lymphoid organs
- Bone marrow
- Thymus (Cortex, Medulla)



What's lymphoid tissue?

- Lymph means clear fluid
- This fluid flows in in lymphatic vessels, lymphatic tissue and red bone marrow.
- The main function is to filter out of capillaries and drains into lymphatic vessels to become lymph.
- Lymph eventually drains into venous blood.
- Lymph drains interstitial fluid, transports dietary lipids and facilitates immune responses.

Primary& Secondary lymphoid organs:



- Provide the right environment for immature progenitor cells to generate, mature
- Function as the house for stem cells to divide and mature into B- and T- cells
- Both T-cell and B-cells are 'born' in the bone marrow.

Bone marrow:

- Red marrow is the bone marrow parenchyma and contains the hematopoietic stem cells, which function in the formation of all blood cell lines, including B and T cells.
- Yellow marrow is the bone marrow stroma (supportive tissue) and contains mostly fat.
- Note: Orthopedic injuries especially fractures of the long bones are the most common cause of fat embolism syndrome, characterized by rapid breathing and shortness of breath. Following trauma, fat is released directly from the bone marrow into the circulation.
- This is because after trauma, an elevated pressure in the medullary cavity of the bone causes the release of fat globules into venous system supplying the bone.
- This explains the obstruction of the fat emboli in the lung capillaries.

Thymus

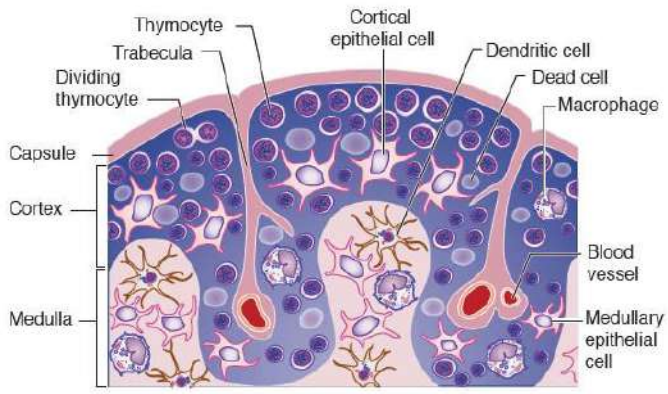
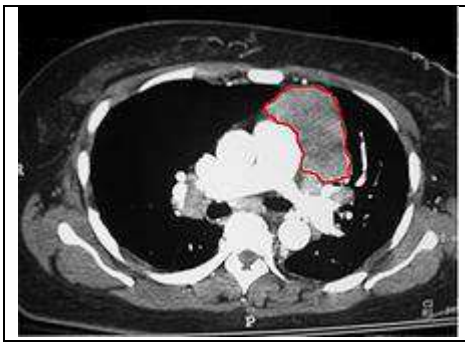


Figure I-3-9. Structure of the Thymus

- Encapsulated, bilobed organ, located in the anterior mediastinum
- Derived from the third pharyngeal pouch
- Morphologically thymus changes during development, during early childhood, the thymus is large and is easily seen on a chest radiograph. However, during adulthood it becomes invisible on a chest film.
- Provide an adequate condition for T cell differentiation and maturation
- They are called T cells because they mature in the thymus from thymocytes

	CT scan of the chest revealing a large necrotic mass in the left anterior mediastinum (indicated by the red line). Histology later established the diagnosis of a thymoma.

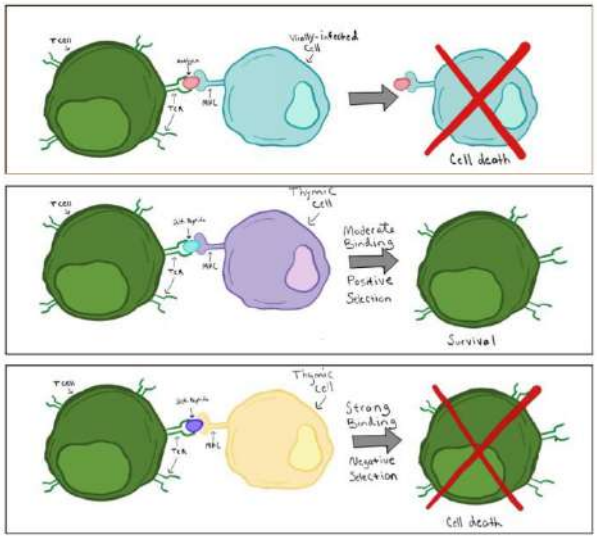
- Thymoma is considered the most common tumor associated with the thymus
- Thymoma is usually **associated with <u>myasthenia gravis</u>**
- Removal of thymus glands in myasthenia gravis associated with better prognosis

Thalamus composed of 2 areas:

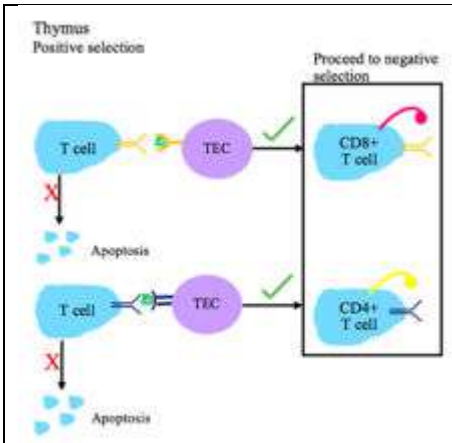
Cortex

- High cellular density with packed immature T cells awaiting positive (functional) selection.

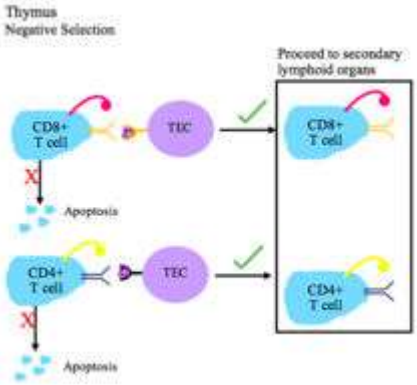
- The immature T cells undergo positive selection where it binds (reversibly/Not strong binding) to the cell surface proteins major histocompatibility complex class I (MHC I) or II.



- T cells which bind strongly to MCH I/II will undergo apoptosis.
- The majority of developing thymocytes will die during this process.
- Thymocytes that interact well with MHC I mature into $CD8^+$ cells.
- Thymocytes that interact well with MHC II mature into $CD4^+$ cells.
- Thymocytes that survive positive selection migrate towards the boundary of the cortex and medulla in the thymus.
- Don't bind to human body antigens
- Some immature T cells mange to pass through the periphery
- If the peripheral system didn't recognize the escaped T cells, the patient is going to progress to autoimmune disease
- The autoimmune cells are removed by the process of negative selection, which occurs in the corticomedullary junction
- Negative selection destroys cells that see the body's own normal antigens as foreign invaders.



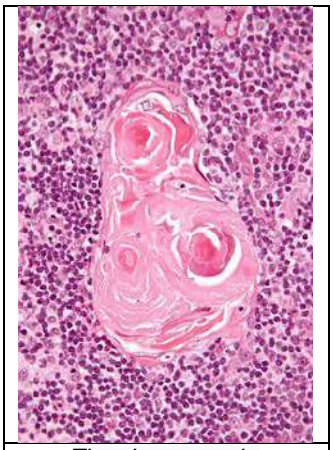
This figure depicts the process of positive selection for T cells.



This figure depicts the process of negative selection for T cells.

Medulla:

- low cellular density with mature T cells having already gone through positive and negative selection.
- This area also contains *Hassall corpuscles*, which are remnants of apoptosed T cells seen on histology.

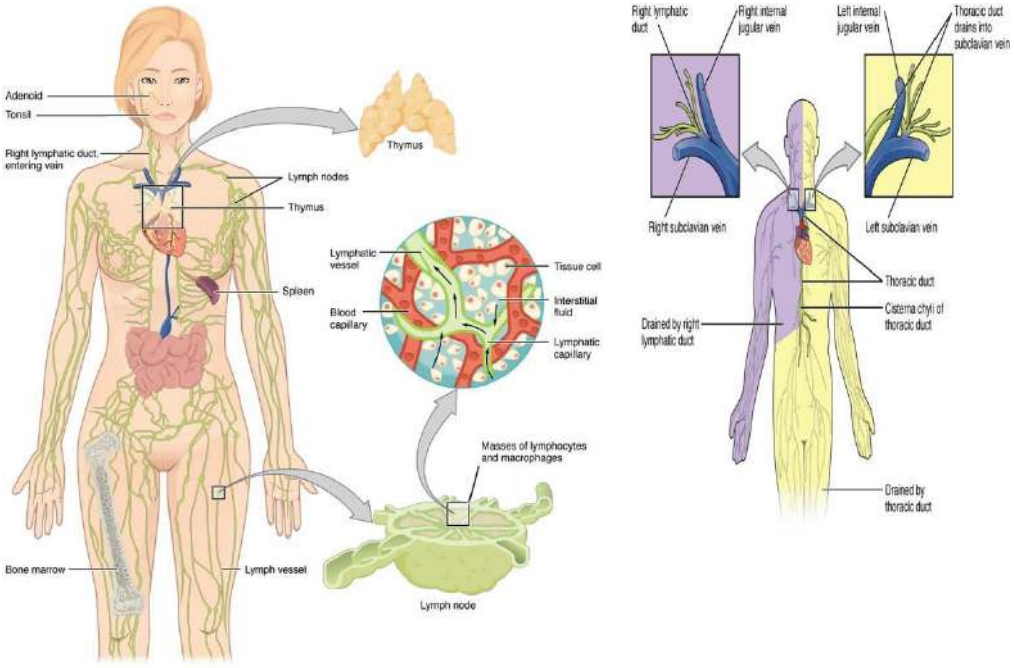


Thymic corpuscle

References:

Lymphatic drainage

Overview:



- The overall drainage system of the body is **asymmetrical**
- **The** right lymphatic duct receives lymph from only the upper right side of the body (right arm, chest, half of head)
- The lymph from the rest of the body enters the bloodstream through **the thoracic duct** via all the remaining lymphatic trunks.

- The thoracic duct drains a much larger portion of the body than does the right lymphatic duct

Lymph node	Area of body drained
Upper limb and lateral breast	Axillary
Stomach	Celiac
superior mesentery	Duodenum
Inferior mesenteric	Sigmoid colon
Internal iliac	Lower rectum to anal canal (above pectinate line), bladder, vagina (middle third), cervix, prostate
Superficial inguinal	Anal canal (below pectinate line), skin below umbilicus (except popliteal area), scrotum, vulva
Popliteal	Dorsolateral foot, posterior calf
Para-aortic	Testes, ovaries, kidneys, uterus

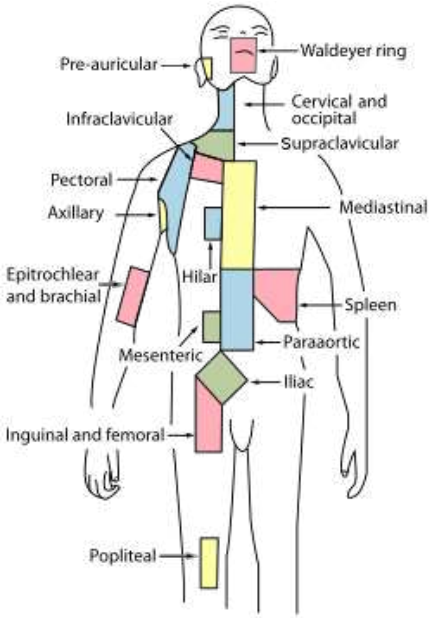
References:

- First aid 2018

Lymphatic drainage and associations

Outline:

- Cervical lymph node
- Mediastinal lymph nodes
- Hilar lymph nodes
- Axillary lymph nodes
- Celiac lymph nodes
- Paraaortic lymph nodes
- Internal iliac and Superficial inguinal
- Popliteal



Cervical lymph node:

- Located in the neck region and divided into two groups:
- Anterior superficial and deep nodes include submental and submaxillary (tonsillar) nodes located under the chin and jawline.
- Posterior lymph nodes are located along the back of the neck.

Associated pathology:

- Bronchitis
- Tonsillitis
- Sore throat
- Infectious mononucleosis
- Kawasaki disease

Mediastinal lymph nodes:

- Glands that are located in the part of the chest that lies between the sternum and the spinal column
- Mediastinal lymphadenopathy generally suggests a problem related to lungs, whether benign or malignant.
- **Associated pathology:**
- Anthracosis (Miner`s lung)
- Cystic fibrosis
- Lung cancer
- Tuberculosis
- Chronic obstructive pulmonary disease
- Acute Lymphoblastic Leukemia
- Granulomatous disease

Hilar lymph nodes:

- located in the retrotracheal region or the area posterior to the trachea.

- **Associated pathology:**
- Enlargement of the hilum may occur due to:
- Tumors (such as lung cancer)
- pulmonary hypertension
- Enlarged hilar lymph nodes due to conditions such as infections (especially tuberculosis and fungal infections)
- Cancer (either local or metastatic)
- Sarcoidosis

Axillary

- Lymph nodes located in the armpits.
- Drain lymph vessels from the lateral quadrants of the breast

- **Associated pathology:**

- A local infection of the arm or breast, including skin and wound infections and cellulitis. The bacteria are carried in the lymph to the axillary lymph nodes, causing a reaction there.
- An infection that is affecting your whole body, such as strep throat, measles, mononucleosis, herpes or AIDS.
- Cancers, including lymphomas, leukemias, and breast cancer.
- **Immune disorders** such as lupus or rheumatoid arthritis.

Celiac

- The celiac lymph nodes are grouped into three sets: the gastric, hepatic and splenic lymph nodes.

Associated pathology:

- Mesenteric lymphadenitis
- Typhoid fever
- Ulcerative colitis
- Celiac disease

Paraaortic lymph nodes

- Group of lymph nodes that lie in front of the lumbar vertebrae near the aorta. These lymph nodes receive drainage from the gastrointestinal tract and the abdominal organs

Associated pathology:

- Metastasis especially colorectal cancer

Internal iliac and Superficial inguinal:

- Inguinal lymph nodes are the lymph nodes in the inguinal region

Associated pathology:

- Sexually transmitted infections
- The presence of swollen inguinal lymph nodes is an important clinical sign because lymphadenopathy (swelling) may indicate an infection, or spread as a metastasis from cancers, such as anal cancer and vulvar cancer.

Popliteal:

Dorsolateral foot/ posterior calf Foot

Associated pathology:

- leg cellulitis
- Popliteal artery entrapment syndrome

References:

- First aid 2018

Secondary lymphoid structures

Outline:

- Overview
- Lymph nodes
- Medulla
- Cortex
- Paracortex
- Spleen
- Cases of splenic dysfunction

Overview:

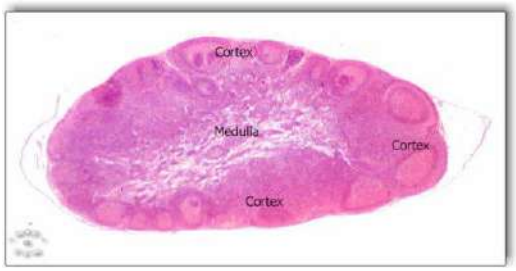
- Sites where lymphocytes undergo differentiation (increase specificity) and clonal expansion (increase number) in antigen- dependent manner.
- Examples of secondary lymphoid organs
- lymph nodes, spleen, tonsils, adenoids, and mucosa-associated lymphoid tissue (MALT).

Lymph nodes:

- T cells undergo maturation in the thalamus then through the circulation to lymph nodes and other organs
- Lymph nodes are spread throughout the body and present in group where lymphatic vessels come together to form larger vessels such as in the groins, neck and axilla.
- Lymph nodes are also part of the lymphatic system that includes the lymphatic vessels, lymphoid tissue and lymphoid organs.
- Lymph nodes filter and purify the lymph before it flows into the venous system.
- Encapsulated and trabeculated secondary lymphoid organs with many afferent vessels (Many ways in and one way out)

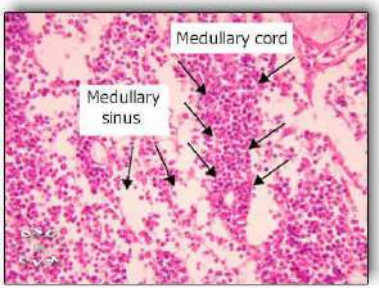
Functions of lymph nodes:

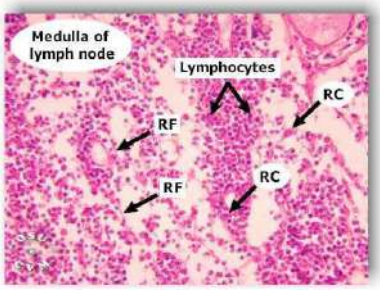
- Filtration of debris and microorganisms via phagocytosis
- facilitate the interaction between antigen presenting cells and circulating lymphocytes to initiate an immune response
- Activation and proliferation of B lymphocytes
- Activation of T lymphocytes to become T helper and T cytotoxic cells



Medulla

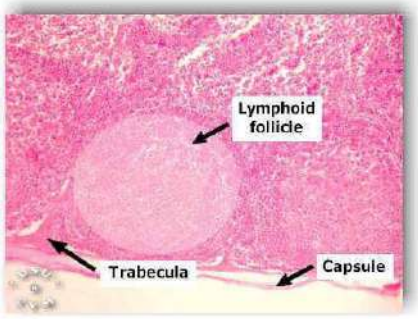
- The medulla of a lymph node is composed of medullary cords (densely packed lymphocytes) interspersed between medullary sinuses. The medullary sinuses are composed primarily of reticular fibers, reticular cells and macrophages.





Cortex:

- The cortex is composed of the cortical sinuses surrounded by dense accumulations of lymphocytes.
- Arranged into spherical follicles, lymphoid follicles.
- Where that B lymphocytes are activated and undergo proliferation.

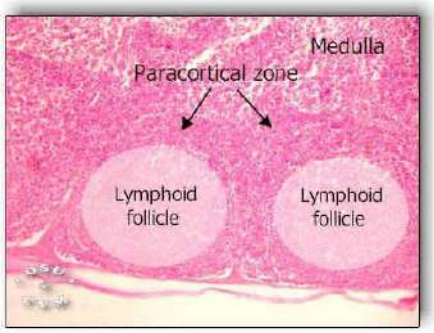


Paracortex

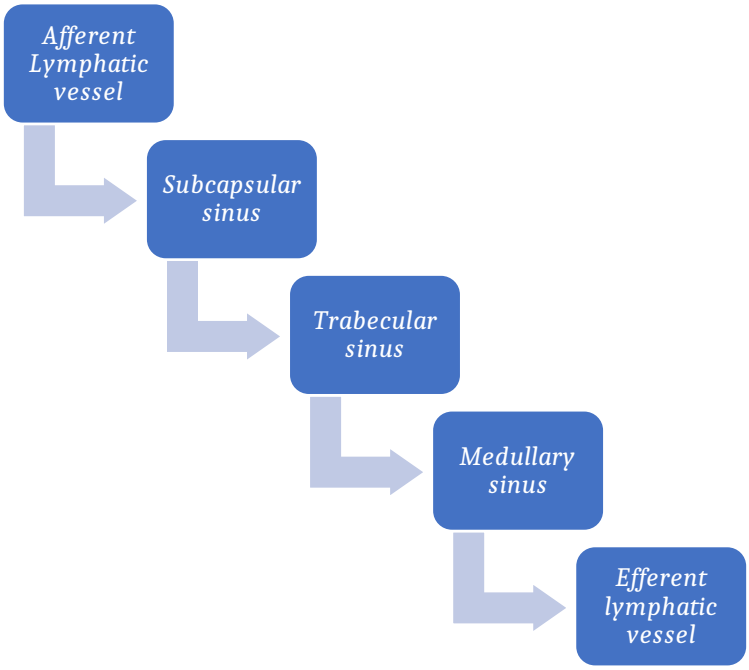
- Contains high endothelial venules
- T cells are concentrated within the paracortex
- Paracortex enlarges in an extreme cellular immune response (eg, viral infection).

Thymic hypoplasia (DiGeorge syndrome):

- Lymphoid follicles are usually present, but lymph node paracortical areas and thymus-dependent regions of the spleen show variable degrees of depletion.



Flow Through a Lymph Node:



Spleen:

- Located between the stomach, left kidney and diaphragm, the spleen is the largest lymphoid organ in the body

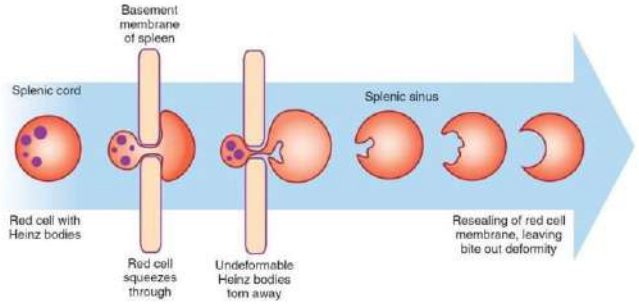
The spleen is divided into two pulps:

- Red pulps: Filtration of red blood cells.

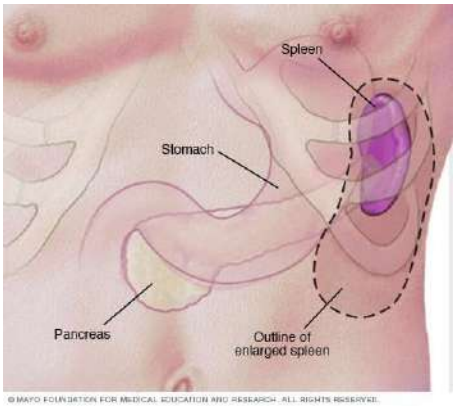
- Composed of macrophages and the rest of the red pulp is occupied by numerous venous sinuses (VS).
- RBCs undergo phagocytosis by splenic macrophages
- Also encapsulated bacteria are removed by splenic macrophages
- White pulps: Reservoir for T cells
- Contains the periarterial lymphatic sheath (PALS), which contains T cells and follicles that contain B cells.
- B cells are found in the marginal zone between red pulp and white pulp

Cases of splenic dysfunction:

- Splenic macrophages remove Heinz bodies from RBC leading to characteristic bite cells
- In case of patients with G6PD deficiency, large number of Heinz bodies are produced



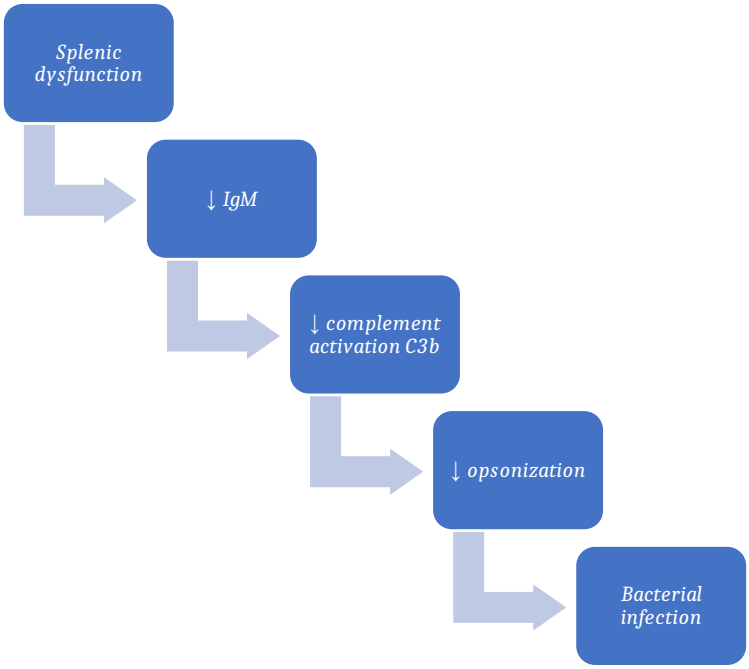
- Patients with infectious mononucleosis (EBV infection) develops splenomegaly increase risk of splenic rupture



Enlarged spleen

- The spleen contains macrophage
- These macrophages are activated when bacteria bound by IgG antibodies or the complement component C3b.
  Note: IgM is produced by plasma cells in the spleen and lymph nodes
- These types of antibodies and complement are immune substances called opsonizes, molecules that bind to the surface of bacteria to facilitate phagocytosis

- In cases of splenic dysfunction, IgG and C3b are still bound to bacteria, but they cannot be removed from the blood circulation due to the loss of the splenic macrophages. Hence the bacteria are free to cause infection (encapsulated bacteria) such as:
    - Streptococcus pneumonia
    - Haemophilus influenza type B
    - Neisseria meningitidis
    - Salmonella
    - Klebsiella pneumonia
    - Group B streptococcus



References:

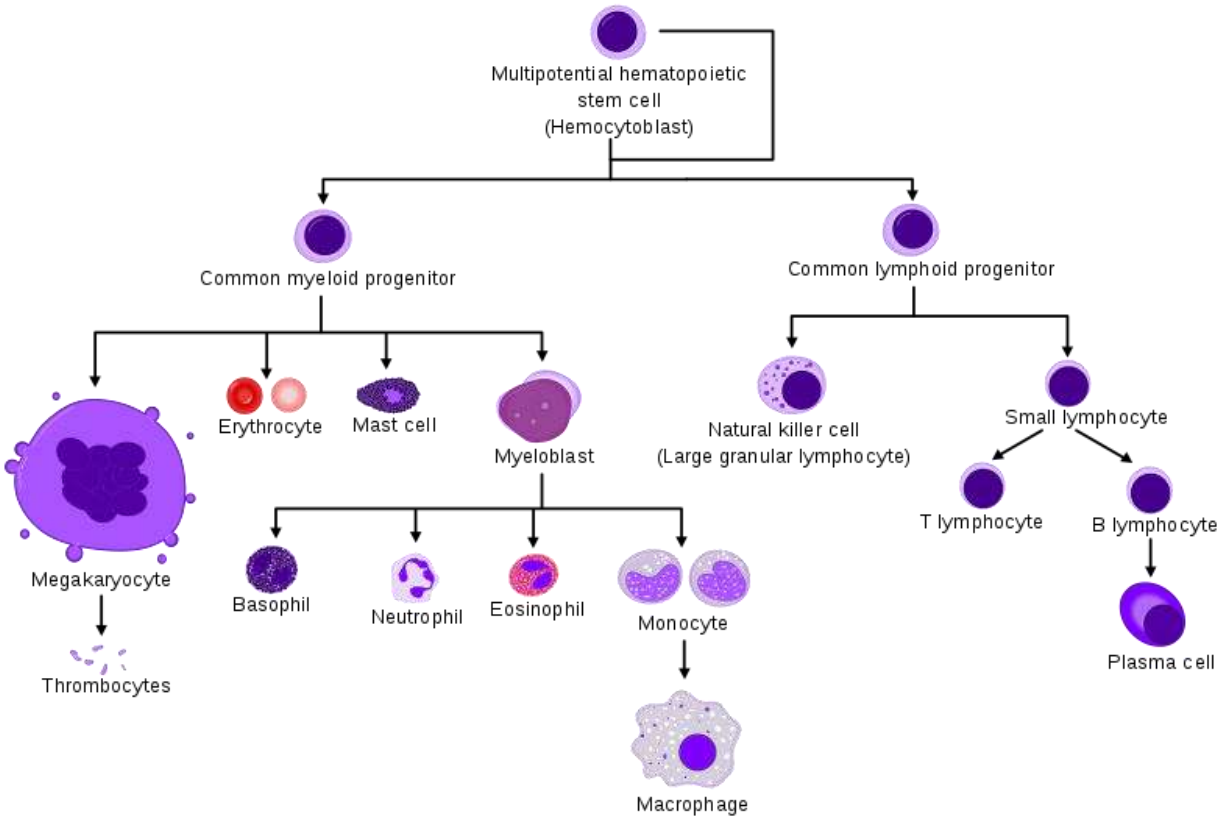
- Crush step 1 The ultimate step 1 review 2014

Cells of the immune system

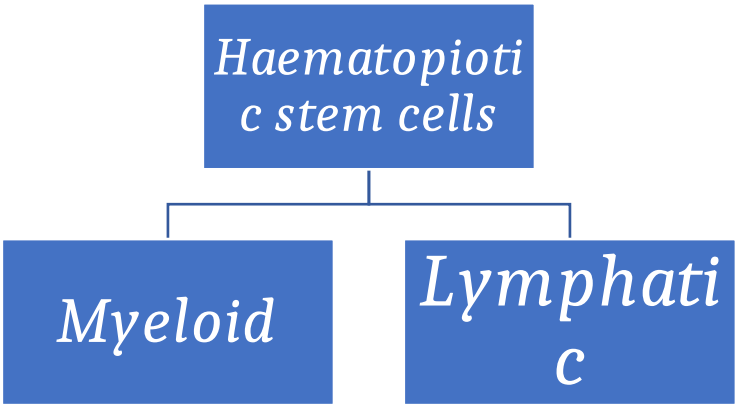
Outline:

- Overview
- Myeloid linage
- Lymphoid linage

Overview:



- Hematopoietic stem cells located in the bone marrow and capable of differentiating into all different mature blood cells types and tissues which considered the immune cells
- Multipotent and self-renewal



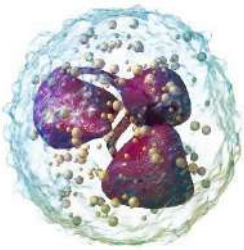
Myeloid linage:

- Monocytes:
  - Circulate in the blood, differentiate to macrophages in the tissues
  - Phagocytose pathogens
  - Produce cytokines that initiate inflammation (Il-1, IL8, IL-12, IL-6 and TNF α)
  - Play an important role in tissue repair
  - Large, kidney-shaped nucleus with frosted glass cytoplasm

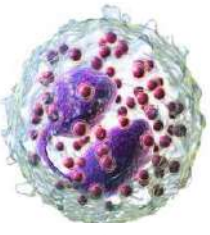
- Dendritic cells:
  - Cells with long cytoplasmic arms, found in all tissues
  - Express MHC II and Fc receptors on the surface
  - Three major functions:

1. Efficient antigen presentation to lymphocytes (professional antigen- presenting cell (APC)
2. Stimulate adaptive immune response
3. Initiate inflammatory response

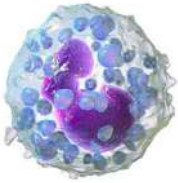
- Neutrophils:
  - Mature cells with multilobed nucleus
  - Contains toxic cytoplasmic granules
  - Number increases in bacterial infection
  - Main function: Circulating phagocytes



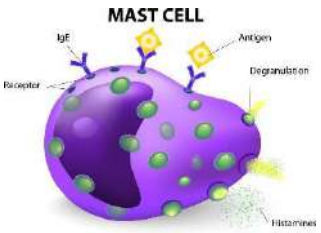
- Eosinophils:
  - Mature cells with a bilobed nucleus
  - Contain the major basic proteins
  - Packed with large eosinophilic granules of uniform size
  - Main function: Protect against parasitic and helminthic infections



- Basophils:
  - Mature cells with large blue granules



- Mast cells:
  - These cells release histamine in response to antigen exposure
  - Concentrated within the respiratory and gastrointestinal tracts
  - Like Basophil (contain large cytoplasmic granules) with small nucleus
  - Cromolyn sulphate is used as mast cells stabilizer (used for asthma prophylaxis)



Lymphoid linage:

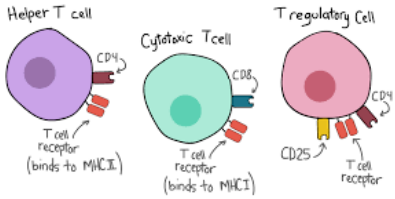
- Lymphocytes:

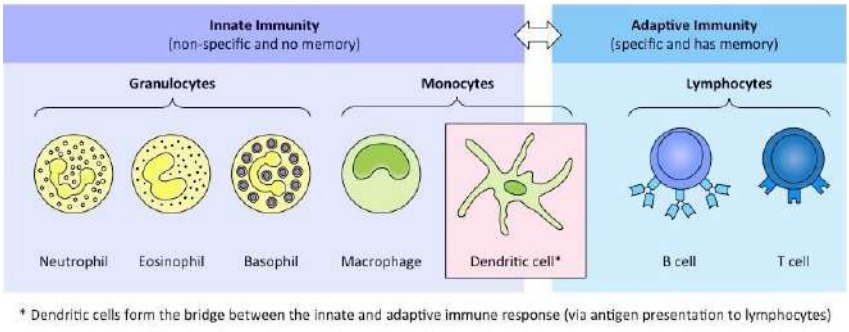
Divided into 3 classes:

A. B cells
- Belongs to adaptive immune system (Humoral immune response)
- Differentiate into either memory B cells or plasma cells (circulating antibodies)

B. T cells
- Belongs to white blood cells and plays a role in cell mediated immunity
- T cells differentiate into either CD4+, helper T cells, CD8+ cytotoxic T cells, regulatory T cells or memory T cells

C. Natural killer cells
- Named like this because they don't require activation to kill cells that lack MHC
- CD56+ lymphocyte that contains cytoplasmic toxic granules (such as granzymes)
- Activity enhanced by Il-2, Il-12, IFN-β, IFN-α
- Able to recognize stressed cells in the absence of antibodies and MHC allowing for faster immune response
- Able to kill malignant cells, virus-infected cells, or antibody-coated (opsonized) cells





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- USMLE- Step 1 Lecture Notes, 2017

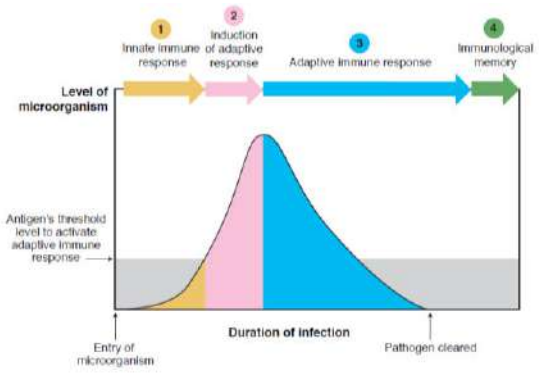
Innate and adaptive immunity

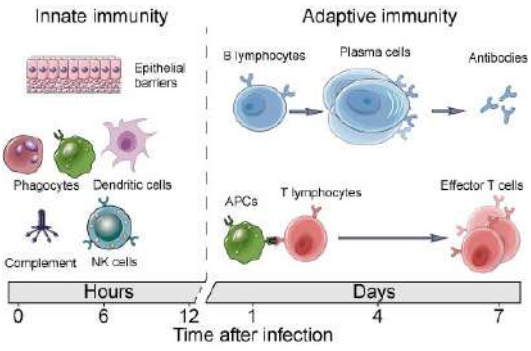
Outline:

- Overview
- Innate immunity
- Mechanism of Pathogen recognition
- Adaptive immunity
- Cross link between innate and adaptive immune response
- Innate versus Adaptive immunity

Overview:

- The innate and adaptive immune response work together to stop an infection.
- Initially, once a pathogen has broken through the anatomic and physiologic barriers, the innate immune response is immediately activated, oftentimes it is able to contain and eliminate the infection.
- BUT, when the innate immune response is unable to handle an infection, the adaptive immune response is engaged and activated by the innate immune response in an antigen-specific manner.
- Typically, it takes 1-2 weeks after the primary infection for the adaptive immune response to begin clearance of the infection through the action of effector cells and antibodies.
- Once an infection has been cleared, both the innate and adaptive immune responses cease.
- Antibodies and residual effector cells continue to provide protective immunity, while memory cells provide long-term immunologic protection from subsequent infection.





Innate immunity:

- Innate immunity provides the body's first line of defense against infectious agents.

Characterized by:

- Fast (Minutes to hours)
- nonspecific response to infection
- Lack of immune memory.
- Does not improve after exposure to antigen
- Always present
- Available on short notice to protect
- It allows for an individual to have basic immunity

Functions:

- Fight against microbes
- Activation of adaptive immunity

Components:

1. Anatomical barrier:
   Physical barrier (skin, cilia, mucosal tissue and normal flora), chemical barrier (enzymes, antimicrobial peptides)
2. Cell response
   Recognize pathogen by **receptors**
3. Soluble proteins
   - Such as Natural killer cells (in case of viral infection and malignancy)
   - Phagocytic cells (Macrophages, Neutrophil)
   - Dendritic cell **activates adaptive immune response**

Specificity:

- Has limited specificity. Different microbes could be recognized by the identical mannose receptor

Receptors:

- Included in germline with limited diversity

Receptor distribution:

- Non- clonal: Identical receptors are found at cells of the same lineage such as Neutrophils

Mechanisms of pathogen recognition:

- Phagocytic cells (monocytes/macrophages, neutrophils and dendritic cells) are considered the first line of defense mechanism against infection
- They recognize pathogens via shared molecules that are not expressed on host cells.
- Receptors of the innate immune system are referred to as pattern recognition receptors (PRRs).
- PRRs recognize pathogen-associated molecular patterns (PAMPs), such as LPS, flagellin (bacteria), nucleic acids (viruses).
- PPRs could also recognize damage-associated molecular patterns (DAMPs) released from dying or damaged cells.
- Receptors of innate immune system examples: Toll like receptors (TLR), Nod like receptors (NLR), Rig like receptors (RLR)
- These receptors are present intrinsically, encoded in the germline genes, and are not generated through somatic recombination as the lymphocyte receptors are generated.

Adaptive immunity:

Characterized by:

- Increased with each repeat exposure— immunologic memory

- Capable of distinguishing self from non-self
- Self-limiting

Functions:

- Protect against persistent or recurrent challenge (immunologic memory-specificity)
- Protect against several pathogens
- Protect against auto immune reaction. Ability to distinguish between self (host cells) and non-self (pathogens)

Components:

- T cells, B cells and circulating antibody

Specificity:

- Different microbes could be recognized by different antibody molecules

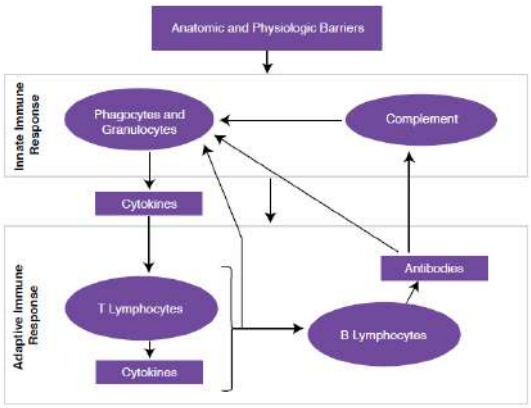
Receptors:

- Encoded by genes produced by somatic recombination of gene segments; greater diversity

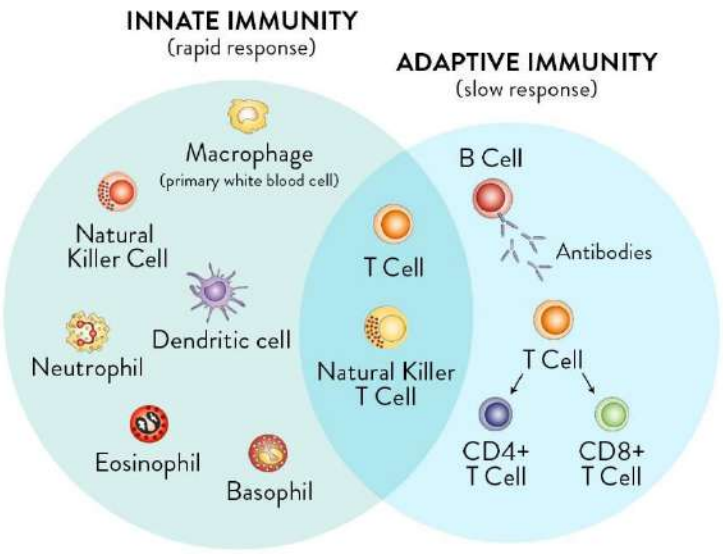
Receptor distribution:

- Variation through V(D)J recombination during lymphocyte development

Crosslink between innate and adaptive immune response



- The responses of both innate and adaptive are overlapped in a positive feedback mechanism
- Phagocytic cells recognize pathogens by binding PAMPs leading to phagocytosis.
- Phagocytic cells present antigen to facilitate stimulation of specific T lymphocytes with subsequent release of cytokines that trigger initiation of specific immune responses.
- T lymphocytes produce cytokines that enhance phagocytosis
- Cytokines will drive differentiation of B lymphocytes into plasma cells and isotype switching.
- Antibodies will aid in the destruction of pathogen through opsonization, complement activation and antibody-dependent cellular cytotoxicity.



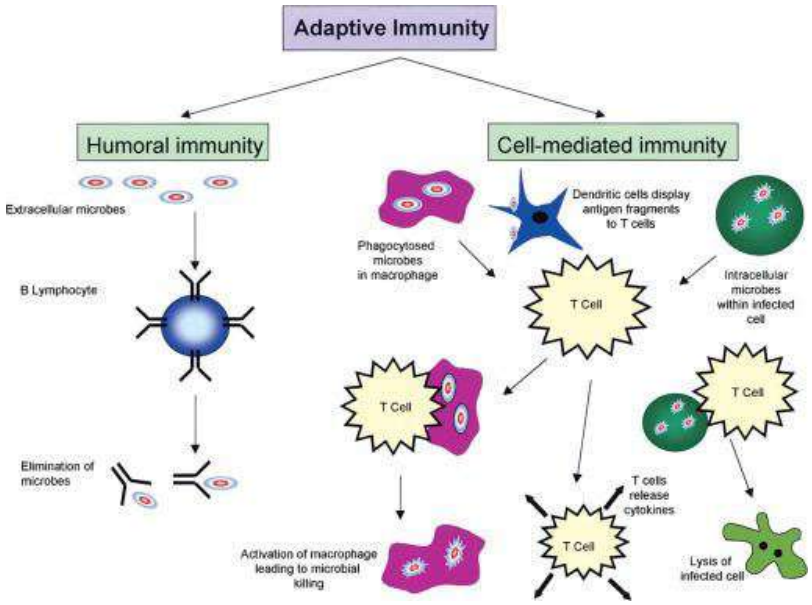
Types of adaptive immunity:

1. Humoral immunity is mediated by antibodies that are produced by B lymphocytes.

- It is the principal defense mechanism against extracellular microbes and their toxins, with secreted antibodies binding to microbes and toxins to assist in their elimination.

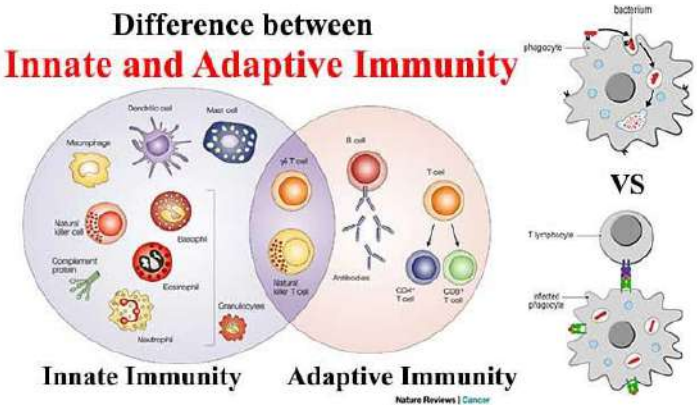
2. Cell mediated immunity is mediated by T cells, with dendritic cells playing important roles in antigen presentation.
   T cells can function by various methods:

A. Activating macrophages to kill phagocytosed microbes
B. Directly destroy infected cells
C. Releasing cytokines and alter the milieu around them.



Innate versus Adaptive immunity:

Innate Immunity	Adaptive Immunity
Antigen independent	Antigen dependent
No time lag	A lag period
Not antigen specific	Antigen specific
No immunologic memory	Development of memory
Present at birth	Developed after birth



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MHC class I and II

Outline:

- Overview
- Class I and Class II gene products
- MHC I
- MHC II
- Previously discussed

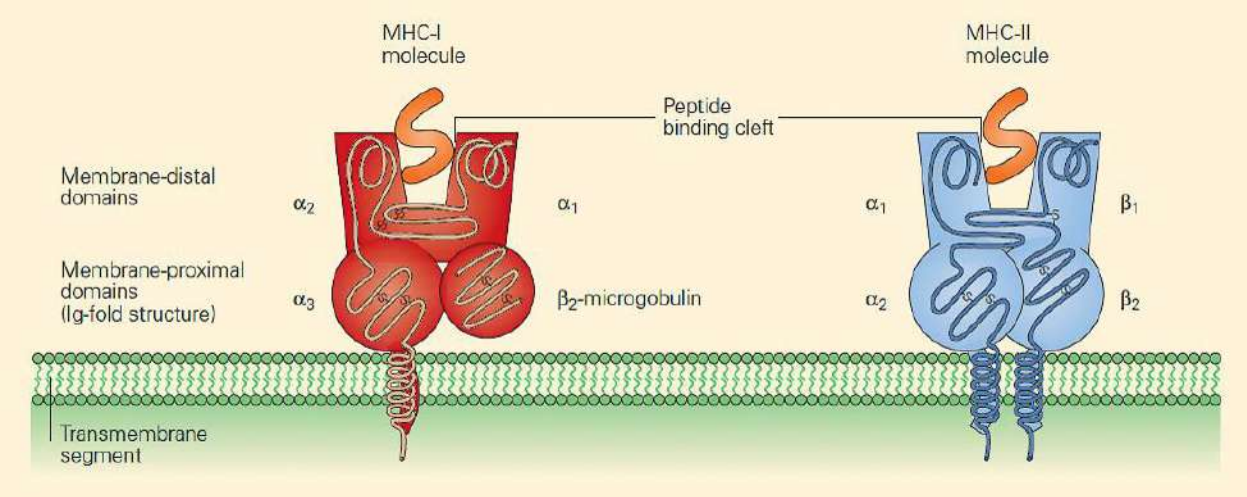
Overview:

T lymphocyte development (origin of MHC):

- Immature lymphocytes leave the **bone marrow** and proceed to the **thymus**, the second primary lymphoid organ dedicated to the maturation of T cells (double negative T lymphocytes since they do not express CD4 or CD8 on their surface
- Within the thalamus, cortex packed with immature T cells, while the inner medulla receives ONLY mature T cells.
- As the developing thymocytes begin to express their T cells receptors (TCRs), they are subjected to a rigorous 2-step selection process (positive and negative selection)
- TCRs designed to bind to antigen presenting cells (APCs)
- **Major histocompatibility complex (MHC) antigens** is necessary to remove those cells that would bind to normal self-antigens and cause autoimmunity.
- MHC is a cell surface protein which is essential for acquired immune system
- Binds to antigens derived from pathogens and display them on the cell surface to be recognized by T cells
- Able to differentiate between self and non-self-antigens
- Detects when the body's own cells are either infected or subjected to malignancy
- There are 2 major classes of cell-bound MHC gene products: I and II.
- Both class I and class II molecules are structurally and functionally distinct from one another
- MHC gene products are also called human leukocyte antigens (HLA).

Class I and Class II gene products:

Class I gene products			Class II gene products			
HLA-A	HLA-B	HLA-C	HLA-DM	HLA-DP	HLA-DQ	HLA-DR

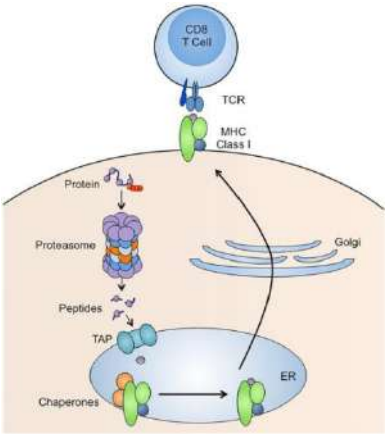


MHC I

- Class I molecules are expressed on all nucleated cells in the body, as well as platelets EXCEPT RBCs

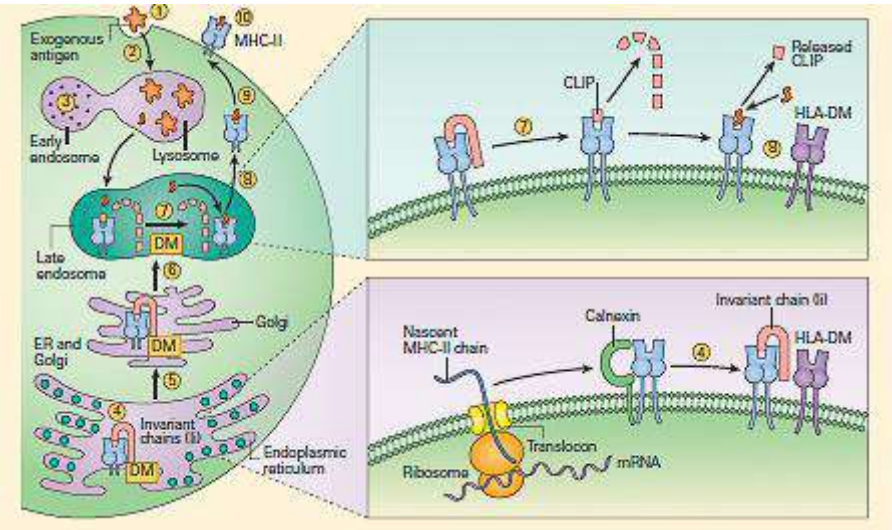
Note: Pathogens within red blood cells can go undetected by cytotoxic T cells, e.g., malaria.

- Functionally, antigen is loaded into the MHC I in the endoplasmic reticulum before the MHC I is inserted into the cell membrane.
- Normally the antigen that is loaded onto MHC I is self-antigen, and cytotoxic T cells (CD8+ T cells) will not react to it.
- In case of viral infection, viral proteins will also be loaded onto MHC I. This is how cytotoxic T cells confer immunity to viral infection.
- They recognize MHC I with loaded viral antigen and targets it for **cytotoxic destruction**



MHC II

- Class II MHC molecules are expressed on the professional antigen-presenting cells of the body (primarily the macrophages, B lymphocytes, and dendritic cells).
- After APCs phagocytose microbes, they process and load these antigens onto MHC II. Then the MHC II is inserted into the cell membrane for binding and recognition by helper T cells (CD4+ T cells).
- Helper T cells can then activate B cells and/or trigger local inflammation.



Previously discussed:

- TCRs capable of binding with low affinity will receive a **positive selection signal** to divide and migrate into medulla
- TCRs that bind too strongly to self MHC molecules will be induced to undergo apoptosis (negative selection) because these cells would have the potential to cause **autoimmune disease**.
- Double positive thymocytes co-express CD4 and CD8
- If TCR binds MHC class I named as CD8 positive
- If TCR binds MHC class II named as CD4 positive
- CD4+ cells that recognize class II MHC are destined to become "helper T cells (Th)
- CD8+ cells that recognize class I MHC are destined to become cytotoxic T lymphocytes (CTLs).

References:

- Crush step 1 The ultimate step 1 review 2014

Outline:

Overview

HLA and disease associations

Overview (previously discussed):

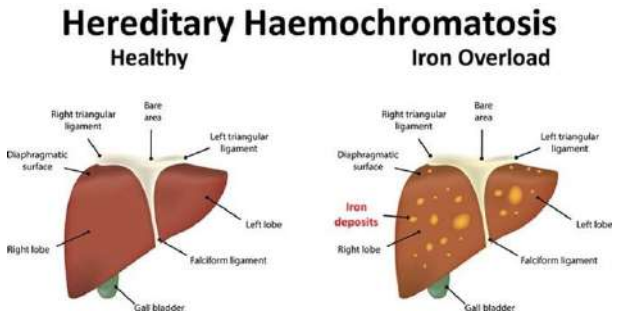
- There are 2 major classes of cell-bound MHC gene products: I and II.
- Both class I and class II molecules are structurally and functionally distinct from one another
- MHC gene products are also called human leukocyte antigens (HLA).

HLA and disease associations

HLA subtypes	Disease
A3	Hemochromatosis
B8	Addison disease, myasthenia gravis, Graves's disease
B27	Psoriatic arthritis, Ankylosing spondylitis, IBD-associated arthritis, Reactive arthritis
DQ2, DQ8	Celiac disease
DR2	Multiple sclerosis, hay fever, SLE, Goodpasture syndrome
DR3	Diabetes mellitus type 1, SLE, Graves' disease, Hashimoto thyroiditis, Addison disease
DR4	Rheumatoid arthritis, diabetes mellitus type 1, Addison disease
DR5	Hashimoto thyroiditis

Hemochromatosis:

- Hemochromatosis is the abnormal accumulation of iron in parenchymal organs, leading to organ toxicity.
- It is the most common autosomal recessive genetic disorder and the most common cause of severe iron overload
- Mutations in human leukocyte antigen A3 (HLA-A3) and human leukocyte antigen B7 (HLA-B7) were linked to Hemochromatosis

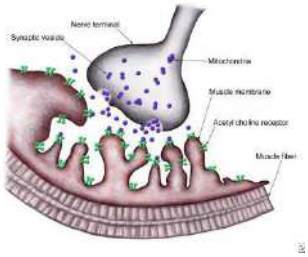


Addison disease:

- Is adrenocortical insufficiency due to the destruction or dysfunction of the entire adrenal cortex.
- It affects glucocorticoid and mineralocorticoid function

- Highest genetic risk is associated with the Major Histocompatibility region (MHC), specifically human leukocyte antigen (HLA)-DR3 haplotypes (containing HLA-B8)
- Addison disease is also associated with HLA- DR3&4

Myasthenia Gravis:

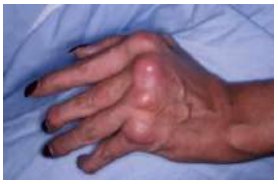


- Myasthenia gravis (MG) is a relatively rare acquired, autoimmune disorder caused by an antibody-mediated blockade of neuromuscular transmission resulting in skeletal muscle weakness.
- The autoimmune attack occurs when autoantibodies form against the nicotinic acetylcholine postsynaptic receptors at the neuromuscular junction of skeletal muscle
- People with certain human leukocyte antigen (HLA) types have a genetic predisposition to autoimmune diseases.
- The histocompatibility complex profile includes HLA-B8.

Graves's disease:

- Graves' disease is an immune system disorder that results in the overproduction of thyroid hormones (hyperthyroidism).
- Although a number of disorders may result in hyperthyroidism, Graves' disease (GD) is a common cause.
- HLA-B8 was reported to be associated with GD in many studies

Psoriatic Arthritis:



- Psoriatic arthritis is most commonly a seronegative oligoarthritic found in patients with psoriasis,
- Characterized by differentiating features of distal joint involvement and arthritis mutilans
- Human leukocyte antigen (HLA)-B27 associated, psoriatic arthritis has also been classified among the seronegative spondyloarthropathies.

Celiac disease:

- Celiac disease is a chronic disorder of the digestive tract that results in an inability to tolerate gliadin
- When patients with celiac disease ingest gliadin, an immunologically mediated inflammatory response occurs that damages the mucosa of their intestines, resulting in maldigestion and malabsorption of food nutrients.
- A strong association exists between celiac disease and two human leukocyte antigen (HLA) haplotypes (DQ2 and DQ8).

- Damage to the small intestinal mucosa occurs with the presentation of gluten-derived peptide gliadin, consisting of 33 amino acids, by the HLA molecules to helper T cells that mediates the inflammatory response.

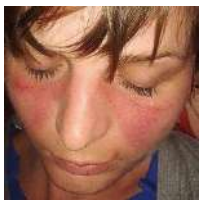
Multiple sclerosis:

- Multiple sclerosis (MS) is a potentially disabling disease of the brain and spinal cord (central nervous system)
- The immune system attacks the protective sheath (myelin) that covers nerve fibers and causes communication problems between your brain and the rest of your body.
- Characterized by Numbness, Slurred speech, Fatigue and Dizziness
- It has been shown that, T cells infiltrating the central nervous system and of myelin basic protein-reactive T cells found in HLA-DR2 MS patients.

Hay fever:

- Hay fever, also known as allergic rhinitis, is a type of inflammation in the nose which occurs when the immune system overreacts to allergens in the air.
- Signs and symptoms include a runny or stuffy nose, sneezing, red, itchy, and watery eyes, and swelling around the eye.

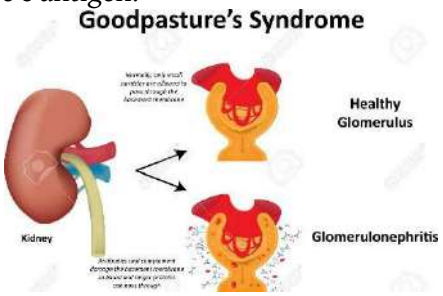
Systemic lupus erythematosus (SLE)



- Is an autoimmune disease in which the body's immune system mistakenly attacks healthy tissue in many parts of the body.
- Symptoms vary between people and may be mild to severe.
- Common symptoms include painful and swollen joints, fever, chest pain, hair loss, mouth ulcers, swollen lymph nodes, feeling tired, and a red rash which is most commonly on the face

Goodpasture syndrome (GPS):

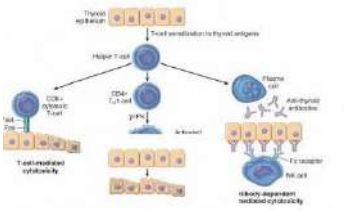
- Known as anti-glomerular basement membrane disease, is a rare autoimmune disease in which antibodies attack the basement membrane in lungs and kidneys, leading to bleeding from the lungs and kidney failure.
- It is thought to attack the alpha-3 subunit of type IV collagen, which has therefore been referred to as Goodpasture's antigen.



Hashimotos Thyroiditis

- Hashimotos Thyroiditis is an autoimmune disorder whereby the body produces antibodies against itself that leads to the destruction of the thyroid gland thereby causing a Thyroid

Disease known as Thyrotoxicosis in the early phase of Hashimotos Thyroiditis or Hypothyroidism in the late phase.



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T cells activation and immunity

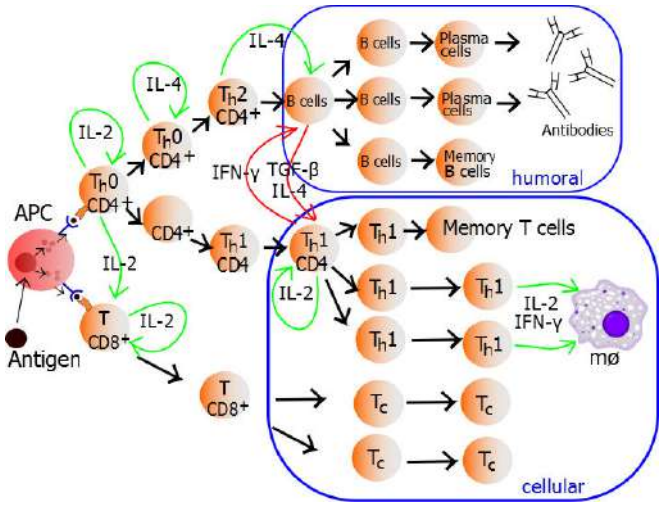
Outline:

- Overview
- Comparison between B and T cells
- Helper T cells
- Activation of T cells
- B cell activation and class switching

Overview:

Characteristics	T cells	B cells
Origin of undifferentiated cells	Red bone marrow	Red bone marrow
Site of differentiation	Thymus	Red bone marrow
Primary Locations	Lymphatic tissues 70-80% of the circulating lymphocytes in blood	Lymphatic tissues 20-30% of the circulating lymphocytes in blood
Primary functions	• Provide cellular immune response in which T cells interact with the antigens to destroy them • CD4+ T cells help B cells make antibodies and produce cytokines to recruit phagocytes and activate other leukocytes. • CD8+ T cells directly kill virus-infected cells.	• Provide humoral immune response in which B cells interact indirectly, producing antibodies that destroy the antigens • Maintain immunologic memory

- T-cell precursors move from the bone marrow (born) to the thymus (maturate) where they are selected for self-tolerance by exposure to **major histocompatibility complex (MHC)**
- Most T-cell precursors entering the thymus are destined to die there (apoptosis).
- Only those with TCRs appropriate to protect the host from foreign invaders will be permitted to exit to the periphery.
- CD4+ cells that recognize class II MHC are destined to become **"helper" T cells (Th)**.
- CD8+ cells that recognize class I MHC are destined to become **cytotoxic T lymphocytes (CTLs)**.



CD4+ T cells known as Helper T cells

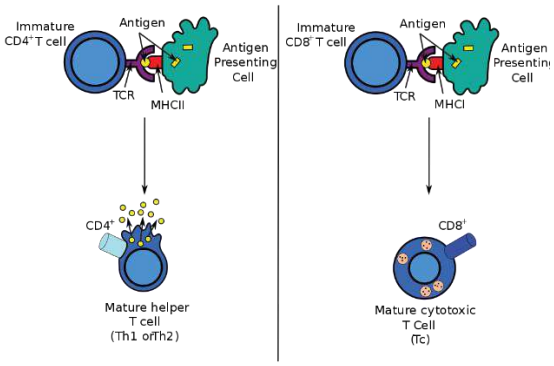
- Helper T cells release cytokines into bloodstream to warn the immune system of the presence of a dangerous cell or virus
- when an antigen-presenting (APC) cells expresses an antigen on MHC class II, a $CD4^+$ cell will aid those cells through a combination of cell to cell
- Stimulation of helper T cells by interleukins become either Th1 or Th2 cells with specific functions to help regulate both the humoral and cell-mediated immune system
- **Note:**
- In the advanced stages of **HIV infection**, loss of functional $CD4^+$ T cells leads to the symptomatic stage of infection known as the acquired immunodeficiency syndrome AIDS.

Subtypes

- **T_h1 helper cells** lead to an increased cell-mediated response, typically against intracellular bacteria and protozoa.
- They are triggered by IL-12 and their effector cytokines are IFN-γ and IL-2.
- They also secrete IL-2, which activates CD8+ (cytotoxic T cells) to kill virally infected cells.
- Main partner cell types: include Macrophage, CD8+ T cell
- **Th2 helper cells** lead to a humoral immune response, typically against extracellular parasites including helminths.
- They are triggered by IL-4 and IL-2, and their effector cytokines are IL-4, IL-5, IL-9, IL-10, IL-13 and IL-25.
- Main partner cell types: include eosinophils, mast and B cells

CD8+ T cells

- A type of cells that kills cancer cells, cells that are infected (particularly with viruses), or cells that are damaged in other ways.
- Cytotoxic T cells have CD8, which binds to MHC I on virus-infected cells.
- Destruction mechanism either by forcing the cell to commit suicide, or
- Secret enzymes that kill the cells (**perforin, granzyme B**)



Activations of T cells

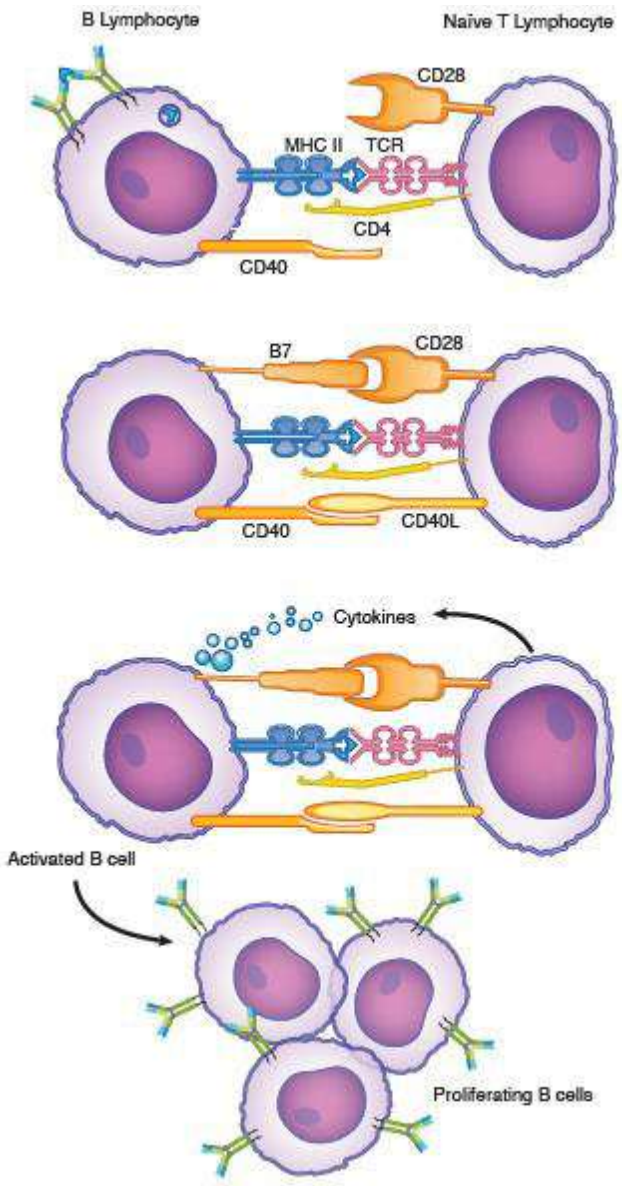


Figure I-6-5. Steps in T-Cell-Dependent B-Cell Activation

- Several surface molecules are involved in the activation of mature, naive T lymphocytes:
- **First (primary) signal**: recognition of the MHC: peptide complex by the T cell receptor and coreceptors (CD4 and CD8)
- **Second (costimulatory) signal**: recognition of B7 by CD28

1. Once T cells leave the thymus, they circulate throughout the body until they recognize their antigen on the surface of **antigen presenting cells (APCs)**.

2. The T cell receptor (TCR) on both CD4+ helper T cells and CD8+ cytotoxic T cells binds to the antigen as it is held in a structure called the MHC complex, on the surface of the APC. This trigger initial activation of the T cells

3. Besides T cells, both CD4 and CD8 molecules then bind to the MHC molecule too

4. This normally takes place in the secondary lymphoid organs.

5. In addition to TCR binding to antigen-loaded MHC, both helper T cells and cytotoxic T cells require several secondary signals to become activated and respond to the threat.

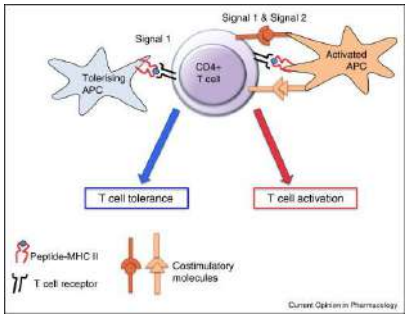
6. The costimulatory molecules B7-1 (CD80) and B7-2 (CD86) on APCs bind to CD28 on the mature, naïve T cells, providing the second signal necessary for successful activation.

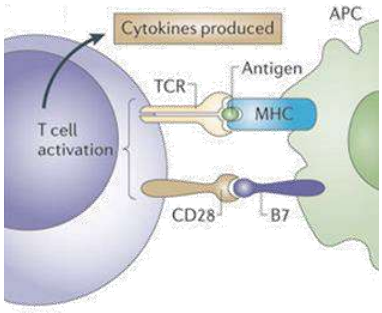
7. The activated CD4+ (helper) T lymphocytes will begin to produce and secrete cytokines and increase surface expression of cytokine receptors.

- The CD4+ T cell will also release IL-2 which lead to:

A. activation and proliferation of CD8+ cytotoxic T cells to kill virally infected host cells

B. Cause CD4+ T cell proliferation and differentiation in an autocrine manner





B cell activation and class switching

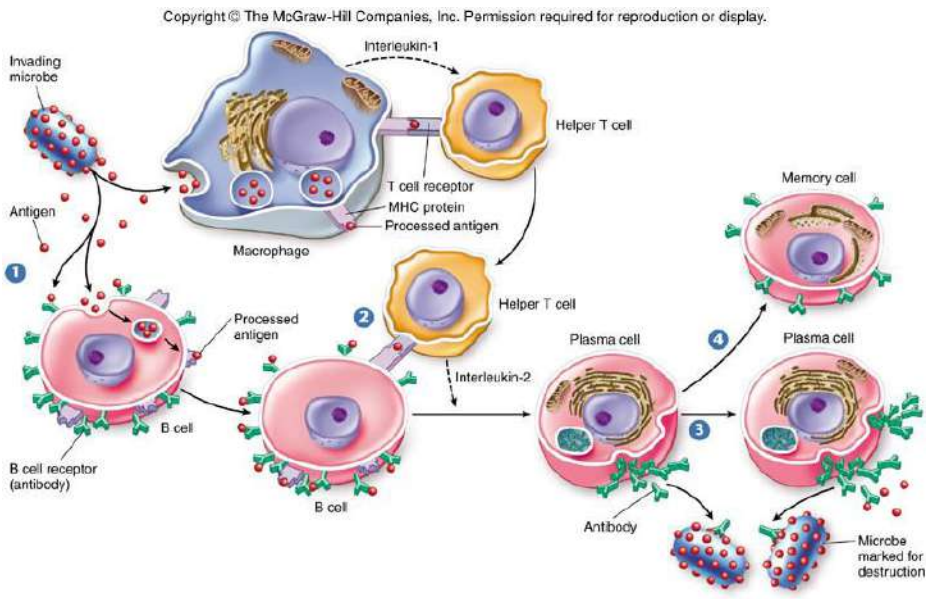
- A helper T cell subtype 2 (Th2 cell) can then recognize the antigen on the MHC II with its T cell receptor (TCR).

- The Th2 cell will then secrete specific cytokines (IL-4, IL-5, and IL-6) to stimulate B cell proliferation, hypermutation, and isotype switching.

- Once a B cell becomes a plasma cell, it is no longer able to proliferate because it is designed for maximal immunoglobulin secretion.

- Two signals to make a Th2 cell secrete B cell activating cytokines:

A. The TCR–MHC II antigen interaction
B. CD40–CD40 ligand interaction.



B cell immune response

References:

- USMLE- Step 1 Lecture Notes, Kaplan 2017
- Key concepts in immunology. 2010
- Antigen-based immunotherapy (AIT) for autoimmune and allergic disease.2015
- The role of interleukin-2 during homeostasis and activation of the immune system. Nature reviews immunology 2012

B cells, antibodies and Humoral immunity

Outline:

- Overview
- Antibody structure and function
- Generation of antibody diversity
- Isotype switching
- Mechanism of Isotype switching
- Types of antibodies
- Biological functions of antibody isotypes

Overview:

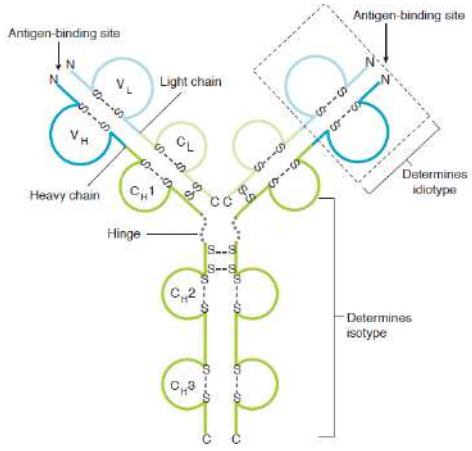
- Antibody formation is accomplished by mature plasma B cells, which synthesize and release antibodies
- Antibody is a large protein, constitutes γ-globulin produced by plasma cells.
- It is used by the immune system to identify and neutralize pathogens such as bacteria and viruses
- Antibodies are also called Immunoglobulins

Humoral immunity antibodies synthesis (immunoglobulins)

Antibody structure and function:

- What is the structure of antibody molecule?
- Each antibody consists of four polypeptides; two heavy chains and two light chains joined to form a "Y" shaped molecule.
- Both heavy and light chains bonded via interchain of di-Sulphide linkages
- Each heavy chain composed of one constant and one variable region
- The trunk of the "Y" is the constant fragment (Fc) and the two branches are antigen-binding fragments (Fab)
- **The Fc region is the constant region:**
- Include the carboxy terminal and various carbohydrate side chains and play an important role in both complement factor binding and determining **the isotype** of the immunoglobulin (IgM, IgA, IgE or IgD).

- **Fab region:**
- Determine **the idiotype** of the immunoglobulin

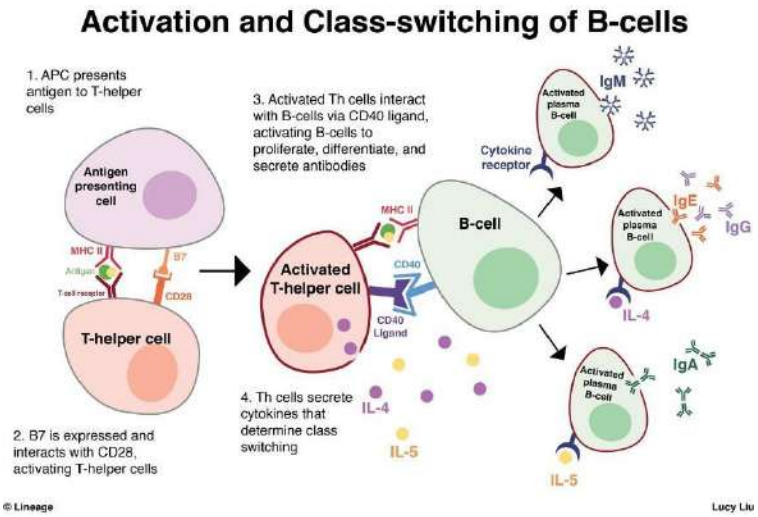


Generation of antibody diversity:

Antigen dependent	Antigen Independent
Somatic hypermutation and affinity maturation (variable region)	Random recombination of VJ (light-chain) or V(D)J (heavy-chain) genes
Isotype switching (constant region)	Random addition of nucleotides to DNA during recombination by terminal deoxynucleotidyl transferase (TdT)
	Random combination of heavy chains with light chains

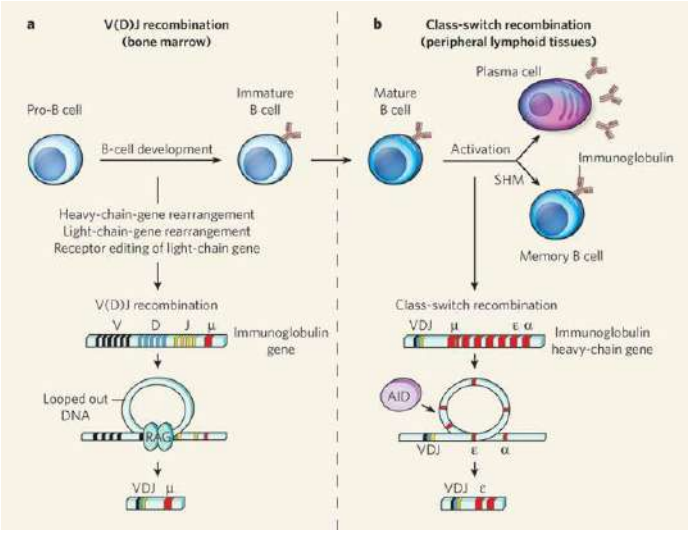
Isotype switching:

- Biological mechanism that changes a B cell's production of immunoglobulin from one type to another.
- During this process, the constant-region portion of the antibody heavy chain is changed, but the variable region of the heavy chain stays the same
- The antibody retains affinity for the same antigens, but can interact with different effector molecules.



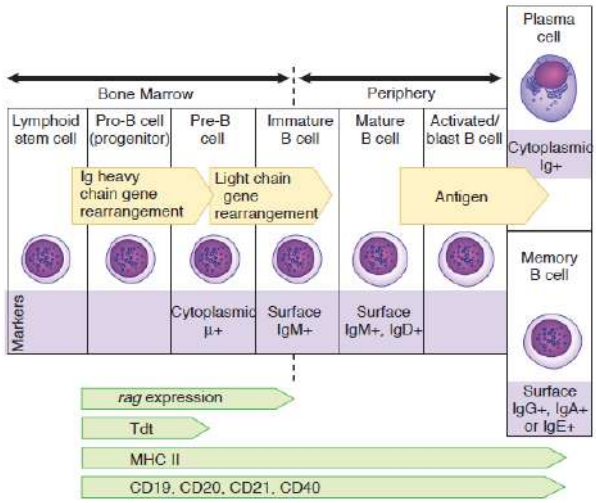
Mechanism of Isotype switching:

- Isotype switching occurs after mature B cell activation
- Generation of different classes of antibodies (with constant variable domains but include changes at the antibody heavy chain)
- mature B cells produce both IgM and IgD, which are the first two heavy chain segments in the immunoglobulin locus
- After activation by antigen, these B cells proliferate.
- If these activated B cells encounter specific signaling molecules via their CD40 and cytokine receptors (both modulated by T helper cells), they undergo antibody class switching to produce IgG, IgA or IgE antibodies



Types of Antibodies

- Antibodies of primary humoral response (IgM)
- Antibodies of secondary immune response
- All isotypes can exist as monomers.
- Mature, naive B cells prior to activation express IgM and IgD on their surfaces.
- They may differentiate in germinal centers of lymph nodes by isotype switching into plasma cells that secrete IgA, IgE, or IgG.



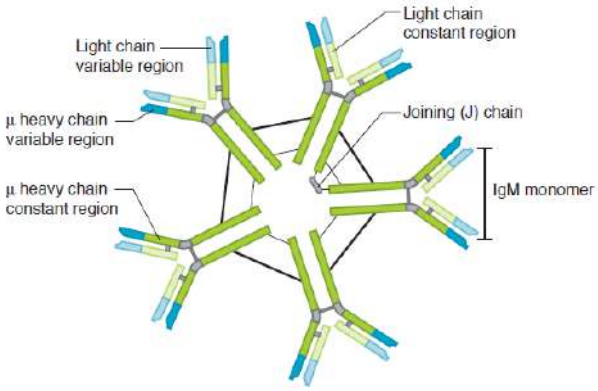
B cell differentiation

IgD (Immunoglobulin D class)

- Expressed on the surface of mature B cells
- Unknown function **BUT**, IgD works with IgM in B cell development.
- IgD is found in very low levels in serum and does not activate the complement pathway

IgM (immunoglobulin M):

- The first isotype of immunoglobulin that can be produced by a B cell **with or without T-cell help**.
- Therefore, considered the fast-antigenic response
- The IgM molecule on the surface of the B cell is a monomer, but the secreted form of this molecule is a **pentamer.**
- The design of the IgM pentamer maximizes its effect critical to the body early during antigenic challenge. Because of its multimeric structure (5 of the Y shaped monomers joined into one unit), plasma IgM has 5 times the capacity for binding antigenic epitopes.
- The multimeric structure of IgM also makes **it the most effective antibody at activating complement**, a set of serum proteases important in mediating inflammation and antigen removal.
- However, the pentamer is very bulky and therefore **does not cross the placenta**



IgG

- The preponderant isotype of immunoglobulin that begins to be produced **after IgM during the primary immune response.**
- Most abundant isotype in serum
- IgG has the following characteristics:
    1. Activates complement
    2. Acts as an opsonin, enhancing phagocytosis
    3. Neutralizes pathogen and toxins
    4. Mediates antibody dependent cellular toxicity (ADCC)
- IgG is also actively transported **across the placenta** and thus plays a crucial role in protection of the fetus during gestation (passive immunity).

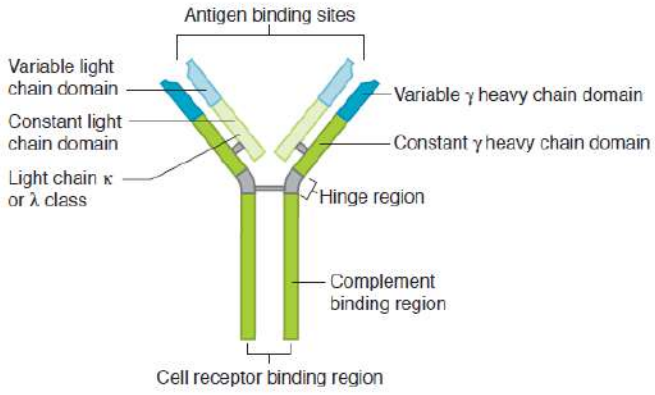


Figure I-7-3. Basic Structure of IgG

IgA

- More commonly produced in the submucosa than in the lymph nodes and spleen
- Prevents attachment of bacteria and viruses to mucous membranes; does not fix complement.
- Occurs as a monomer in the bloodstream and as a dimer when secreted
- Uses transepithelial transport for navigation

- IgA is secreted onto mucosal surfaces (gastrointestinal, genitourinary, and respiratory) to block attachment of pathogens to mucous membranes.
- Most produced antibody overall but has lower serum concentrations.
- Released into secretions **(tears, saliva, mucus) and breast milk**. Picks up secretory component from epithelial cells, which protects the Fc portion from luminal proteases.

Functions of IgA

- Serves as a major protective defense of the mucosal surfaces of the body Any pathogen that infects the mucosa will induce
- Functions as a neutralizing antibody by inhibiting the binding of toxins or pathogens to the mucosa of the digestive, respiratory, and urogenital systems

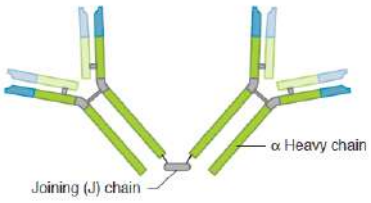


Figure I-7-4. The IgA Dimer

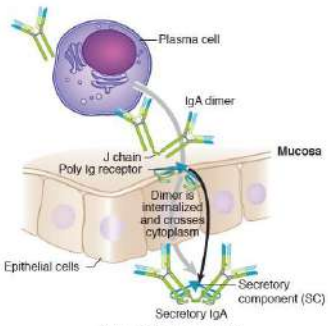
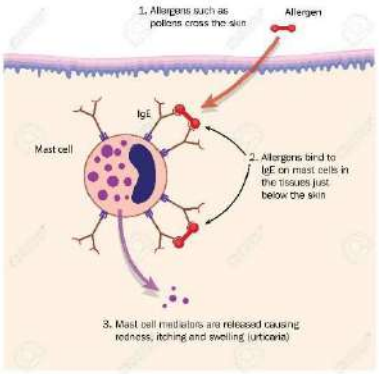


Figure I-7-5. Secretory IgA

IgE

- Binds directly to Fc receptors present on mast cells, eosinophils and basophils
- Involved in elicitation of protective immune responses against parasites and allergens **(Type I hypersensitivity)**
- **It does not activate complement or act as an opsonin.**



Bilogical Functions of the antibody isotypes

Functions	IgM	IgM	IgA	IgD	IgE

Complement activation	+	+	-	-	-
Neutralization	+/-	+	+	-	-
Opsonization	-	+	-	-	-
Antibody-dependent mediated cytotoxicity	-	+	_	_	+/-
Placental transport	-	+	-	-	-
Triger mast cells and granule release	_	_	_	_	+
Naïve B cells antigen receptor	+	_	_	+	_
Memory B cell antigen receptor	_	+	+	-	+

References:

- B cells break the rules, nature immunology, 2009
- USMLE- Step 1 Lecture Notes, 2017

Interleukins Overview

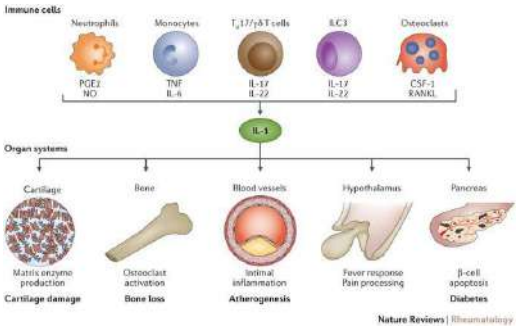
Outline:

- Overview
- Interleukin 1
- Interleukin 2
- Interleukin 3
- Interleukin 4
- Interleukin 5
- Interleukin 6
- Interleukin 8
- Interleukin 10
- Interleukin 12

Overview:

- Interleukins are a group of cytokines (secreted proteins and signaling molecules) that were first seen to be expressed by **white blood cells** (leukocytes).
- The function of the immune system depends in a large part on interleukins.
- Deficiencies of several of them were linked to **autoimmune diseases or immune deficiency**.
- Most interleukins are synthesized by **helper CD4 T lymphocytes**, as well as through monocytes, macrophages, and endothelial cells.
- They promote the development and differentiation of T and B lymphocytes, and hematopoietic cells

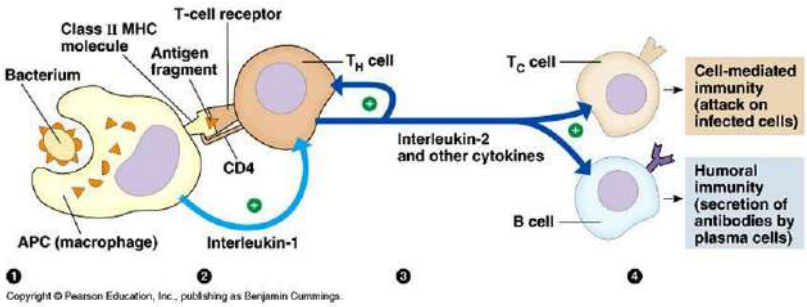
Interleukin 1:



- Produced by activated macrophages- participate in the regulation of immune responses and **inflammatory reactions**
- Enhance corticosteroid release, leukocyte recruitment
- **Induce fever and shivering**
- Induces chemokine secretion to recruit WBCs.

Interleukin 2:

- Stimulates growth of helper, cytotoxic, and regulatory T cells, and NK cells.
- T Lymphocytes regulate the growth and differentiation of **T cells and certain B cells** through the release of secreted protein factors.
- IL2 is a lymphokine that induces the proliferation of responsive T cells.

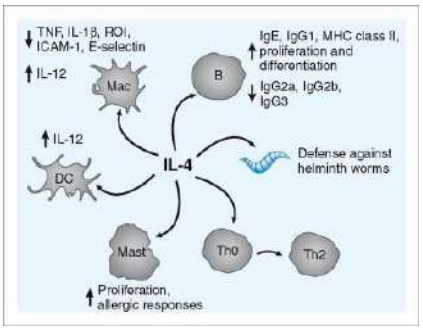


Interleukin 3:

- Interleukin that stimulates **bone marrow**
- regulates blood-cell production by controlling the production, differentiation and function of granulocytes and macrophages

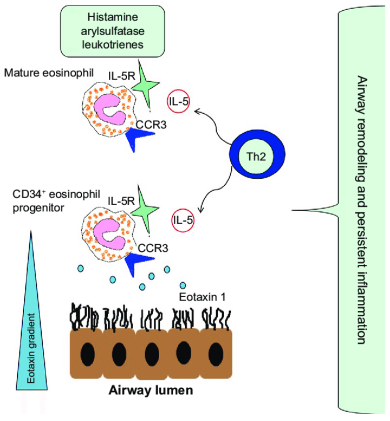
Interleukin 4:

- produced by CD4 T cells specialized in providing help to B cells to proliferate and to undergo class switch recombination (IgE and IgG) and somatic hypermutation.
- IL-4 also promotes **CD8+ Cell growth** and
- promotes TH2 Cell differentiation



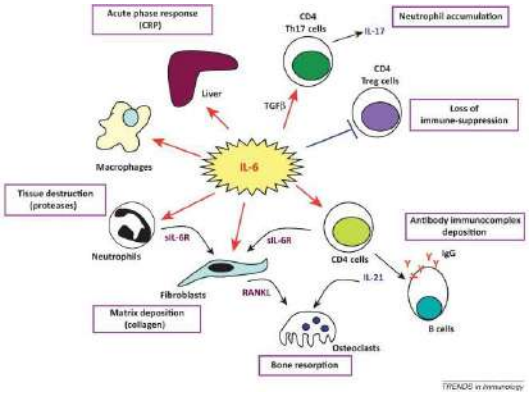
Interleukin 5:

- It regulates eosinophil growth and activation, and thus plays an important role in diseases associated with increased levels of eosinophils, including asthma.
- Secreted by Th2 cells that enhances immunoglobulin class type switching to IgE



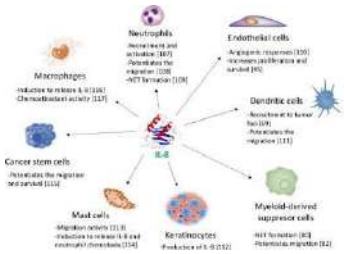
Interleukin 6:

- Is produced by many cell types, including T- Cells, Macrophages, B-Cells, Fibroblasts, and Endothelia Cells.
- IL-6 stimulates several types of Leukocytes, and the production of **acute Phase Proteins in the Liver**.
- IL-6 is particularly important in inducing B- Cells to differentiate into **antibody Forming Cells (Plasma Cells).**



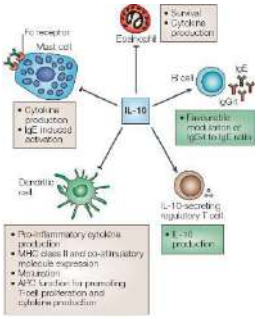
Interleukin 8:

- Produced by most cells of the body, especially Macrophages and Endothelia Cells.
- • IL-8 enhances Inflammation, by enabling Immune Cells to migrate into tissue, & is a powerful inducer of **Chemotaxis for Neutrophil Cells**



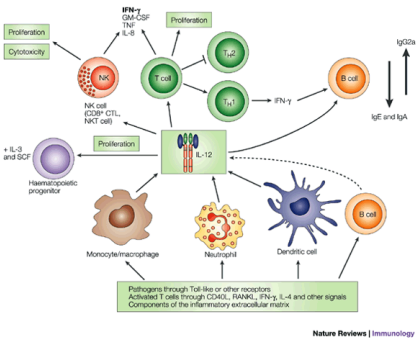
Interleukin 10:

- Secreted by regulatory T cells to **suppress cell-mediated immunity and stimulate humoral immunity**.
- Decreases expression of MHC class II and Th1 cytokines.
- Inhibits activated macrophages and dendritic cells
- Attenuates inflammatory response.



Interleukin 12:

- Secreted by macrophages with functions to enhance **NK cells and T cells**.
- It is involved in the stimulation and maintenance of Th1 cellular immune responses, including the normal host defense against various intracellular pathogens, such as Leishmania, Toxoplasma, Measles virus, and Human immunodeficiency virus 1 (HIV).
- IL-12 also has an important role in pathological Th1 responses, such as in **inflammatory bowel disease and multiple sclerosis**



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- USMLE- Step 1 Lecture Notes, Kaplan 2017
- Interleukin-1 function and role in rheumatic disease. Nature reviews rheumatology 2016
- Interleukin-6: from an inflammatory marker to a target for inflammatory diseases. Trends in immunology 2012.
- Translational Immunotherapy of Brain Tumors, 2017
- Clinical usefulness of mepolizumab in severe eosinophilic asthma. 2016

Oxidative Burst

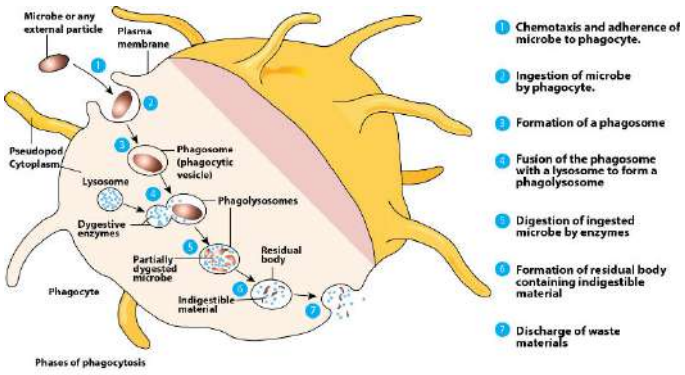
Outline:

- Overview
- Respiratory burst
- Chronic granulomatous disease

Overview:

- When molecular oxygen (O_2) is partially reduced, unstable products called reactive oxygen species (ROS) are formed.
- Reactive oxygen species include:

1. Superoxide (O2-)
2. Hydrogen peroxide (H2O2)
3. Hydroxyl radical (OH)



- The polymorphonuclear neutrophil produces these substances to kill bacteria in the protective space of the phagolysosome during the oxidative burst accompanying **phagocytosis.**

- Phagocytosis is an Innate defense mechanism is ingestion of extracellular particles

- Performed by specialized cells such as Blood Monocytes, Neutrophils and tissue Macrophages

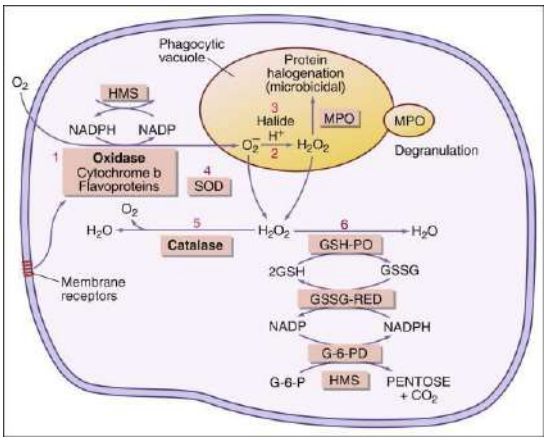
- During phagocytosis, a metabolic process known as the respiratory burst activates a membrane-bound oxidase that generates oxygen metabolites, which are toxic to ingested microorganisms.

- Oxygen uptake increase greatly, undergoes a series of changes **"Respiratory Burst"**

Respiratory Burst

- Respiratory Burst" occurs during:

1. Activation of macrophages during phagocytosis
2. Abrupt rise in Oxygen consumption
3. **Activation of NADPH oxidase/Phagocyte oxidase**



- Respiratory burst Plays an important role in the immune response that initiate the rapid release of reactive oxygen species (ROS).

- Two oxygen-dependent mechanisms of intracellular digestion are activated because of this process.

1. **NADPH oxidase** reduces oxygen to superoxide anion, which generates hydroxyl radicals and hydrogen peroxide, which are microbicidal.
2. **Myeloperoxidase** in the lysosomes acts on hydrogen peroxide and chloride ions to produce hypochlorite (the active ingredient in household bleach), which is microbicidal.

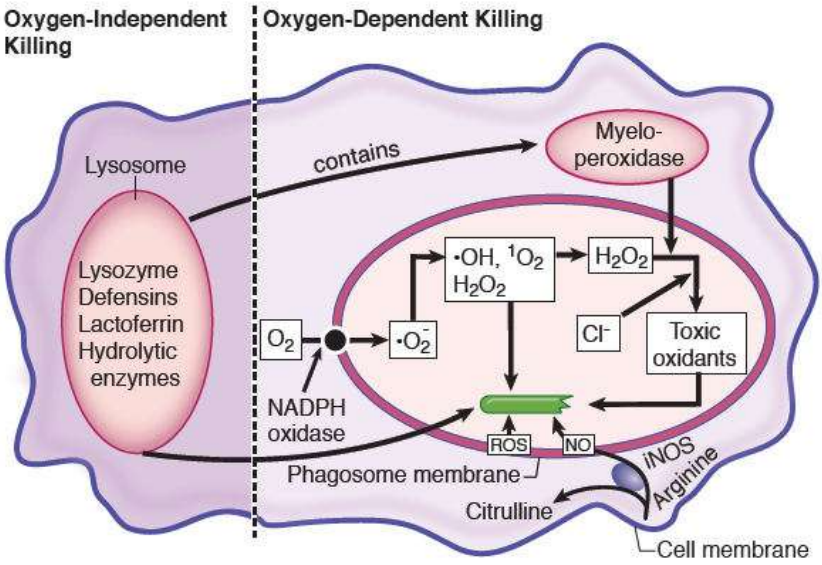


Figure I-4-11. Metabolic Stimulation and Killing Within the Phagocyte

NADPH oxidase

- Present in membrane associated of phagocytic cells
- NADPH oxidase catalyzes the production of a superoxide free radical by transferring one electron to oxygen from NADPH.
- During this process O2 is transported from the extracellular space to the cell interior and the H+ is exported.

Superoxide dismutase

- Catalyzes the dismutation of the superoxide(O_2^-) radical into either molecular oxygen (O_2) or hydrogen peroxide (H_2O_2).

Myeloperoxidase

- Abundantly expressed in **neutrophil granulocytes**
- produces hypochlorous acid (HOCl) from hydrogen peroxide(H2O2) and chloride anion (Cl^-) during the neutrophil's respiratory burst.
- Hypochlorous acid is cytotoxic to bacteria
- Myeloperoxidase contains a blue-green heme-containing pigment that gives sputum its color.

Glutathione peroxidase

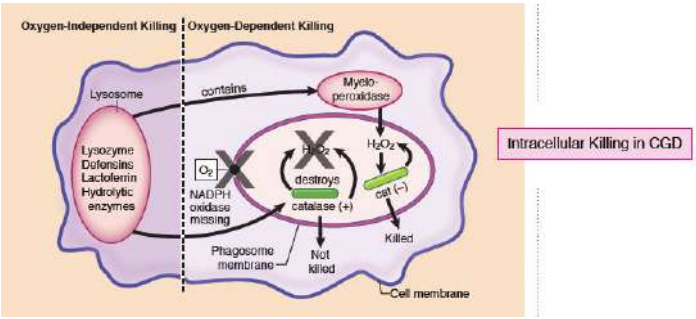
- Glutathione (GSH) is crucial for the detoxification of H_2O_2 that has diffused into the cytosol

Glutathione reductase

- Catalyzes the reduction of glutathione disulfide (GSSG) to the sulfhydryl form glutathione (GSH)

Chronic granulomatous disease

- Chronic granulomatous disease is most frequently caused by genetic deficiency of NADPH oxidase in the polymorphonuclear neutrophils (PMN).
- This defect eliminates the phagocyte's ability to produce many critical oxygen-dependent intracellular metabolites ($\cdot O2^-$, OH, $^1O_2$, and H_2O_2).
- The 2 other intracellular killing mechanisms remain intact (myeloperoxidase + H_2O_2 → HOCl and lysosomal contents).
- If the patient is infected with a catalase-positive organism (e.g., Staphylococcus, Klebsiella, Serratia, Aspergillus), the myeloperoxidase system lacks its substrate (because these organisms destroy H_2O_2),
- Thus, CGD patients suffer from chronic, recurrent infections with catalase-positive organisms. Such as:
- **Staphylococcus aureus, Klebsiella, Escherichia coli, Candida, and Aspergillus**.
- These species neutralizing their own H2O2, leaving phagocytes without ROS for fighting infections
- The patient is subjected to recurrent pulmonary infection
- Skin, lymphatic tissue Hepatic infection
- Fever induced by prostaglandin Il-1, PGE1, TNF alpha
- Diagnosis: Failures of phagocytic cells to generate oxygen radicals are easily detected by the **nitroblue tetrazolium (NBT) reduction test** or neutrophil oxidative index



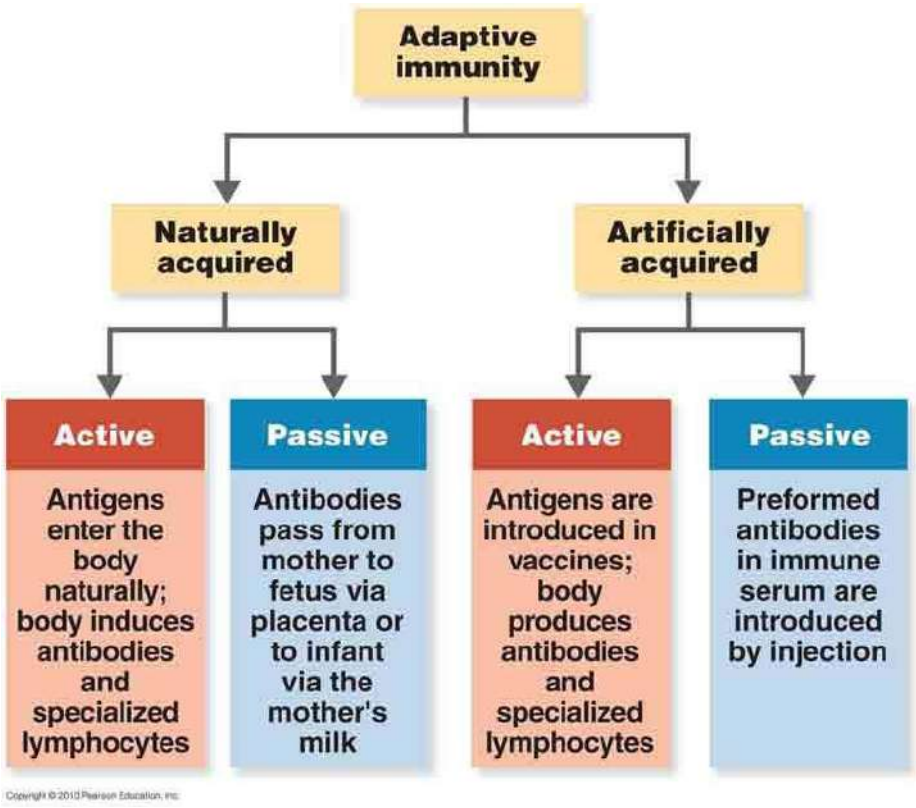
References:

- USMLE- Step 1 Lecture Notes, Kaplan 2017
- The Role of Glutathione Reductase in Neutrophil Respiratory Burst and ERK Signaling. The journal of immunology 2016

Active and passive immunity

Outline:

- Active and passive immunity
- Types of vaccines



		immunity
Duration of immunity	Long lasting immunity	Short lasting immunity half-life 3 weeks
Time taken to achieve immunity	Body needs time to synthesis antibody after exposure to antigen	Ready-made antibodies
Time of injection	Before the person is infected	At the time when the person is infected or at high risk of getting the disease
Type of injection	Vaccines containing dead or weakened antibody	Serum containing specific antibody
Necessity of booster dose	Required because the first injection usually induces a slow & low level of antibody	Not required The first injection usually enough
	• Natural infections • Vaccines • Toxoid	• Antitoxin • Immunoglobulin for intravenous (Kawasaki disease) • Digitalis antibody fragment • Humanized monoclonal antibody • Maternal Ig crossing the placenta
		• After exposure to Tetanus toxin, Botulinum, toxin, HBV, Varicella, Rabies virus, or diphtheria toxin • unvaccinated patients are given preformed antibodies (passive)

Types of vaccines:

Attenuated

- Comprised of live organisms which lose capacity to cause disease but still replicate in the host

- Attenuated vaccines are comprised of live organisms, there is slight potential to revert to a virulent form
- Stimulating both a humoral and cell mediated immune response, as they mimic the natural infection and typically elicit lifelong immunity
- Not safe-dangerous for immunocompromised patients/pregnancy because even attenuated viruses can cause them significant disease.

Examples

- Polio (sabin), Varicella (chickenpox), Smallpox, BCG, Yellow fever, Influenza (intranasal), MMR, Rotavirus

Nonattenuated

- Used by U.S. military against adenovirus types 4 and 7

Killed vaccines

- Utilize organisms that are killed so they can no longer replicate in the host
- Inactivated by chemicals rather than heat, as heat will often denature the immunogenic epitopes
- Typically require several doses to achieve desired response
- Safer but weaker immune response
- Produce humoral immunity

Examples

- Rabies, Influenza, Polio (Salk) and Hepatitis A

References:

- USMLE- Step 1 Lecture Notes, Kaplan 2017
- First aid 2018

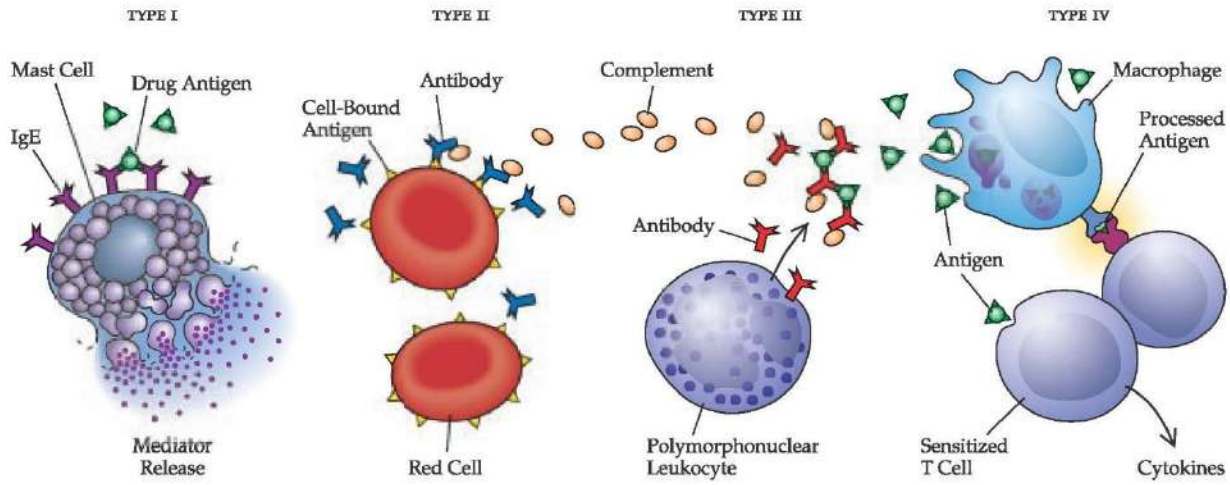
Hypersensitivity response

Outline:

- Overview
- Type I hypersensitivity
- Type II hypersensitivity
- Type III hypersensitivity
- Type IV hypersensitivity

Overview:

- Hypersensitivity diseases are conditions in which tissue damage is caused by immune responses.
- They may result from uncontrolled or excessive responses against foreign antigens or from a failure of self-tolerance, in which case they are called **autoimmune diseases**.



Type I hypersensitivity:

- When someone is exposed to an allergen, it can lead to a rapid immune response that occurs almost immediately. Such a response is called an allergy and is classified as a type I hypersensitivity.
- The first exposure activates a primary IgE antibody response that sensitizes an individual to type I hypersensitivity reaction upon subsequent exposure.

Immune mechanism:

- Allergen-specific IgE antibodies bind to mast cells via their Fc receptor

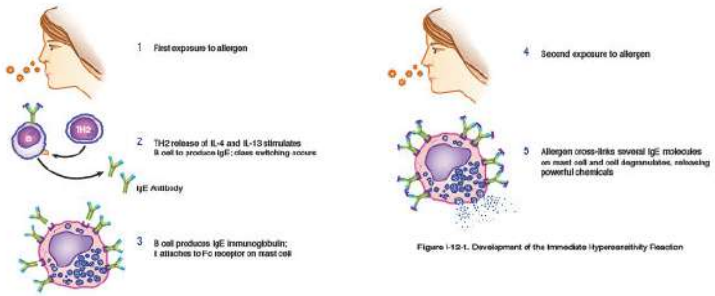
Mechanisms of tissue injury:

Immediate reaction

- Degranulation and release of vasoactive amines (ie. histamine) and proteases
- Degranulation: a reaction in which the contents of the granules in the mast cell are released into the extracellular environment.

Late phase reaction

- Synthesis and secretion of prostaglandins and leukotrienes
- Cytokine-induced inflammation and leukocyte recruitment

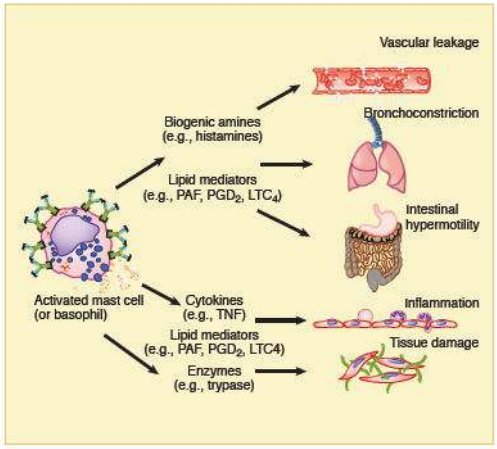


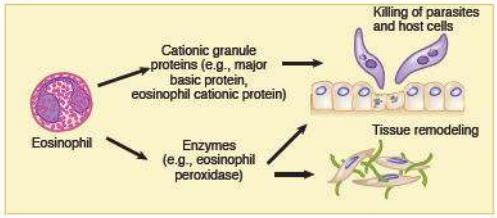
Source of allergy:

- Food allergy milk, egg, fish and peanuts
- Dust, cats, dogs, pet dander, pollen
- Bee stings

Clinical presentations:

- **Allergic rhinitis (hay fever)**: Histamine stimulates mucus secretion in nasal passages and tear formation from lacrimal glands, promoting the runny nose and watery eyes of allergies. Interaction of histamine with nerve endings causes itching and sneezing.
- The vasodilation caused by several of the mediators can result in hives, headaches, angioedema (swelling that often affects the lips, throat, and tongue), and hypotension (low blood pressure).
- **Systemic anaphylaxis** Bronchiole constriction (**Asthma**) caused by some of the chemical mediators leads to wheezing, dyspnea (difficulty breathing),





coughing, and, in more severe cases, cyanosis (bluish color to the skin or mucous membranes).

- **Gastrointestinal problems:** Vomiting can result from stimulation of the vomiting center in the cerebellum by histamine and serotonin. Histamine can also cause relaxation of intestinal smooth muscles and diarrhea

Diagnosis:

- The main test used by allergists is scratch testing in which a positive test result in a wheal and flare reaction of the scratched skin site.

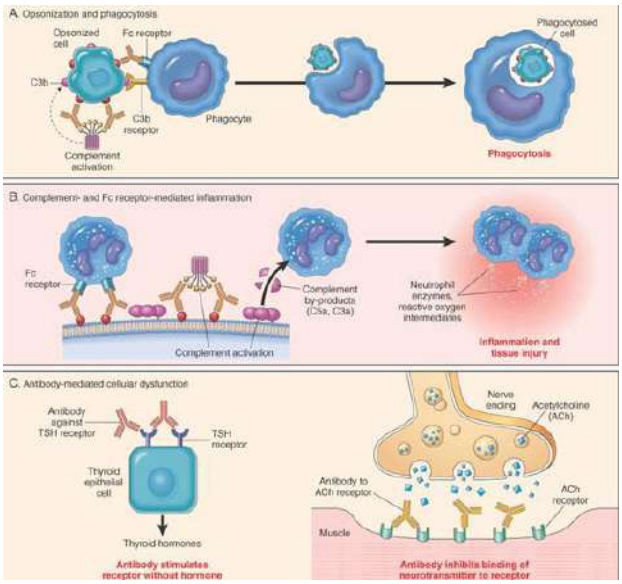
Type II hypersensitivity (cytotoxic hypersensitivity):

- Mediated by IgG and IgM antibodies (**autoantibodies**) binding to cell-surface antigens or matrix-associated antigens on basement membranes.
- These antibodies can either activate complement, resulting in an inflammatory response and lysis of the targeted cells,
- They can be involved in antibody-dependent cell-mediated cytotoxicity (ADCC) with cytotoxic T cells.

- These antibodies can cause tissue destruction by 3 main mechanisms:

1. **Opsonization of cells leading to either phagocytosis/activation of complement system/ NK cell killing**
2. **Activation of the complement system which recruit neutrophils and macrophages that cause tissue damage**
3. **Cellular dysfunction**

- In some types of type II hypersensitivity, complement is activated and/or ADCC is active (hemolytic disease of the newborn).
- In other types, cell function is altered in the absence of complement activation and ADCC (myasthenia gravis).
- During Type II antigen and antibody interaction may cause localized damage, but they do not circulate so the damage is localized to the specific tissue.



Disorders associated with type II hypersensitivity

Cytotoxic	Mechanism	Clinical manifestations
Autoimmune hemolytic anemia	Opsonization, phagocytosis, and complement-mediated destruction of RBCs	Hemolysis, anemia
Acute rheumatic fever	Inflammation, macrophage activation	Myocarditis, arthritis
Goodpasture syndrome	Complement- and Fc receptor– mediated inflammation	Nephritis, lung hemorrhage, linear Ab deposits
Transfusion reaction	opsonization + complement activation	Hemolysis
Autoimmune thrombocytopenic purpura	opsonization and complement activation	Bleeding
Non-cytotoxic		
Myasthenia gravis	Ab inhibits acetylcholine binding, downmodulates receptors	Muscle weakness, paralysis
Graves' disease	Ab-mediated stimulation of TSH receptors	Hyperthyroidism followed by hypothyroidism
pemphigus vulgaris	Autoimmune disease	Oral blisters
Bullous pemphigoid	Formation of anti-hemidesmosome antibodies.	Skin lesions

Other common Type II hypersensitivities:

Hemolytic disease of the newborn (HDN)

- IgG from mother crosses the placenta, targeting the fetus' RBCs for destruction
- Characterized by Anemia, edema, enlarged liver or spleen, hydrops (fluid in body cavity), leading to death of newborn in severe cases

Hemolytic transfusion reaction

- IgG and IgM bind to antigens on transfused RBCs, targeting donor RBCs for destruction
- Characterized by Fever, jaundice, hypotension, disseminated intravascular coagulation, possibly leading to kidney failure and death

Diagnosis:

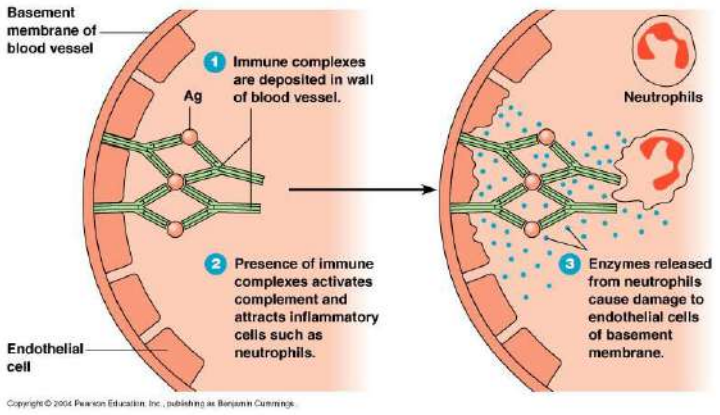
- Direct and indirect coombs test of RBC for hemolytic anemia.
- Direct immunofluorescence of the glomerular basement membrane for Goodpasture syndrome

Type III hypersensitivity (Antigen-Antibody-Complement):

- Antigen-antibody complexes are deposited in tissues lead to:

1. Complement activation with production of pro-inflammatory C3a and C5a
2. IgG binding to antibody receptors on localized mast cells, resulting in **mast-cell degranulation**
3. Increased blood-vessel permeability **(vasculitis)** with chemotactic recruitment of neutrophils and macrophages

   Note: neutrophil degranulation results in the release of lysosomal enzymes that cause extracellular destruction of the immune complex, damaging localized cells in the process.



Clinical presentations:

- Fever, urticaria, arthralgia, proteinuria, lymphadenopathy occur 1–2 weeks after antigen exposure

Serum sickness

- **Systemic type** occurs when immune complexes deposit in various body sites, resulting in a more generalized systemic inflammatory response (within 1-2 weeks)

Examples:

- These immune complexes involve non-self-proteins such as antibodies produced in animals for artificial passive immunity such as **Tetanus vaccine**

- Certain drugs such as haptens, **penicillin**
- Microbial antigens that are continuously released over time during chronic infections:
  - Subacute bacterial **endocarditis**
  - chronic viral **hepatitis**

Arthus reaction

- **Localized type** occurs within 3-10 hours after intradermal injection of antigen into a pre-sanitized person (has circulating IgG) causing necrosis, edema and local pain

Disorders associated with type III hypersensitivity

Disease	Clinical Manifestations
Systemic lupus erythematosus	Nephritis, arthritis, vasculitis, butterfly facial rash
Poststreptococcal glomerulonephritis	Nephritis, "lumpy-bumpy" deposits
Polyarteritis nodosa	Systemic vasculitis

Diagnosis:

- immunofluorescent staining

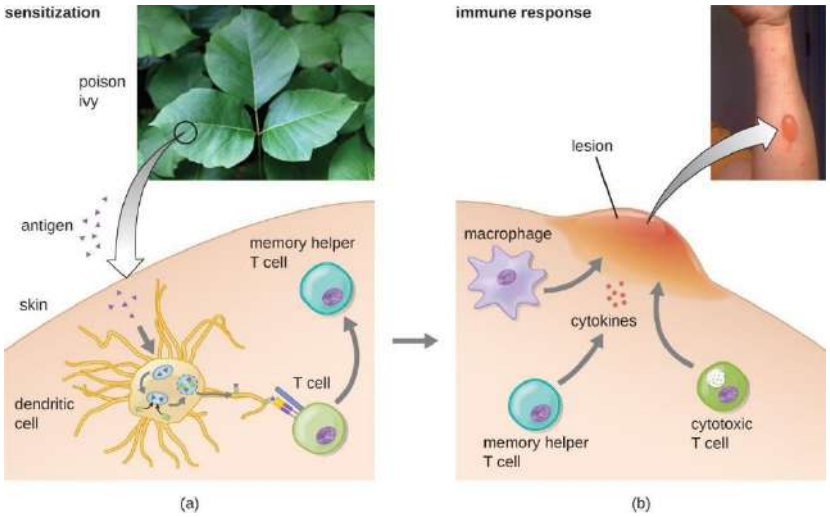
Type IV hypersensitivity

- Known as delayed- type hypersensitivity or antibody-independent cytotoxicity
- Can be organized into three subcategories based on T-cell subtype, type of antigen, and the resulting effector mechanism.

1. The antigen presenting cells activate **helper T cells**, stimulating differentiation into memory **TH1 cells**.
   - These sensitized memory **TH1 cells** release cytokines that activate macrophages
   - Activated macrophages are responsible for much of the tissue damage

2. Effector CD4+ T cells recognize antigen and release inflammation-inducing cytokines
3. Directly killing target cells through CD8+ cytotoxic T cells

- T-cell-mediated tissue injury is common during the protective immune response against persistent intracellular microbes.



Disorders associated with type IV hypersensitivity

Disease	Clinical manifestations
Tuberculin test PPD	Indurated skin lesion (granuloma)
Contact dermatitis	Vesicular skin lesions, pruritus, rash
Multiple sclerosis	Progressive demyelination, blurred vision, Paralysis
Rheumatoid arthritis	Rheumatoid factor (IgM against Fc region of IgG), alpha-cyclic citrullinated peptide (a-CCP) antibodies, chronic arthritis, inflammation, destruction of articular cartilage and bone
Guillain-Barré syndrome	Ascending paralysis, peripheral nerve demyelination
Contact dermatitis	Nickel allergy, exposure to urushiol oil from poison ivy/oak
graft-versus-host disease (GVHD)	Abdominal swelling, yellow discoloration of the skin and/or eyes,
Celiac disease	Gluten-sensitive enteropathy
Corhn disease	Chronic intestinal inflammation due to Th1 and Th17 cells, obstruction

References:

- USMLE- Step 1 Lecture Notes, Kaplan 2017
- First aid 2018
- Crush step 1- The ultimate USMLE lecture notes 2017

Blood transfusion reactions

Outline:

- Allergic reactions
- Anaphylactic reactions
- Febrile non-hemolytic transfusion reactions (FNHR)
- Acute hemolytic transfusion reactions (HTR)

Allergic reactions

- **Type I hypersensitivity reaction** against plasma proteins in transfused blood
- The primary antigen exposure stimulates plasma cells to produce specific IgE.
- This IgE binds to mast cells via its Fc receptor and sensitizes them.
- Causes crosslinking of surface IgE stimulating degranulation of mast cells.

Signs and symptoms:

- Itching, pruritis, fever, wheezing, urticaria

Treatment:

- Antihistaminic

Anaphylactic reactions

- Less common but sever reactions
- IgA-deficient recipient who is transfused with **IgA-containing blood products**

Signs and symptoms:

- Type I hypersensitivity symptoms include:
  - Generalized flushing
  - laryngeal edema
  - bronchospasm and dyspnea
  - profound hypotension, shock and potential cardiopulmonary arrest

Treatment:

- The transfusion should be stopped immediately and adrenaline 1 in 1000 (0.3-0.5 mL) given immediately.
- Supportive therapy for the circulation and respiratory system may be necessary

Diagnosis:

- Diagnosis must be made by demonstrating deficiency of IgA and the detection of an anti-IgA.
- Those patients should receive only IgA-deficient components which are collected from a special panel of IgA-deficient donors.

Febrile non-hemolytic transfusion reactions (FNHR)

- Caused by cytokines from leukocytes in transfused red cell or platelet components, causing fever, chills, or rigors.
- Host antibodies attack donor HLA antigens and leukocytes

Signs and symptoms:

- Type II hypersensitivity symptoms include:
  - Fever
  - Chills
  - Headache

Acute hemolytic transfusion reactions (HTR)

- Intravascular hemolysis due to ABO blood group incompatibility
- Extravascular hemolysis host antibody reacts against foreign antigens

Signs and symptoms:

- Flank pain, hemoglobinuria
- Fever, hypotension
- Tachypnea, jaundice

References:

- First aid 2018
- Crush step 1- The ultimate USMLE lecture notes 2017

B cells immunodeficiency disorders

Outline:

- Selective IgA deficiency
- X-linked (Bruton) agammaglobulinemia
- Common variable immunodeficiency
- Hyper IgM syndrome

Selective IgA deficiency

Molecular defects

- Most common immunodeficiency
- Unknown cause but mostly multiple genetic causes

Clinical presentations

- Mostly asymptomatic
- ↓ IgA levels and **normal** IgM and IgG with ↑ of IgE.
- Repeated sinopulmonary and gastrointestinal infections
- ↑ atopy
- Susceptibility to giardiasis
- Prone to autoimmune disease
- Anaphylaxis to **IgA**-containing products.

Example: Patient with bloody diarrhea and needed blood transfusion BUT few minutes later, the patient develops itching (anaphylaxis) to **IgA containing blood products**

Diagnosis:

- Blood test analysis reveal that IgA <7 mg
- Heterophilic antibodies have been reported in **IgA-deficient individuals**

X-linked (Bruton) agammaglobulinemia

Molecular defects

- Deficiency of the Bruton tyrosine kinase (btk) which promotes pre-B cell expansion
- Lack of B-cell development
- **X linked recessive in boys**

Clinical presentations

- Recurrent bacterial infection after **6 months**
- Increased susceptibility to encapsulated bacteria and bloodborne viruses
- ↓ circulating B-cells, ↓ immunoglobulins of all isotypes
- **↓ Maternal IgG**
- B-cell maturation does not progress past the pre-B cell stage while maintaining cell-mediated immunity.

Common variable immunodeficiency:

Molecular defects

- Several associated genetic defects

Clinical presentations

- Most common form of primary B cell deficiency
- ↓measurable IgG and IgA (occasionally IgM) resulting in immunodeficiency
- **Onsets in late teens, early twenties**
- B cells present in peripheral blood
- Associated with higher rates of lymphomas, gastric cancer and ↑ **autoimmunity**

Hyper IgM syndrome:

Molecular defects

- Deficiency of CD40L on activated T cells with inability for class switching

Clinical presentations

- High serum titers of IgM with diminished levels of IgG and IgA
- Normal level of B cells
- Normal level of B cells but with diminished levels of IgG and IgA and with high levels of IgM
- Associated with higher risk for Pneumocystis infection.

References:

- USMLE- Step 1 Lecture Notes, Kaplan 2017
- First aid 2018
- Crush step 1- The ultimate USMLE lecture notes 2017

T cells disorders

Outline:

- Thymic aplasia (DiGeorge syndrome)
- Il-2 receptor deficiency Hyper IgM syndrome
- Hyper IgE syndrome (Job syndrome)
- Chronic mucocutaneous candidiasis

Thymic aplasia (DiGeorge syndrome)

Molecular defect:

- Heterozygous deletion of chromosome 22q11.
- Failure of formation of **3rd and 4th** pharyngeal pouches
- Lack of thymus and parathyroid development

Clinical presentations

- Characteristic facies and a clinical triad of cardiac malformations, **hypocalcemia** and hypoplastic thymus
- **Tetany** (Hypocalcemia is the primary cause of tetany)
- Low ionized calcium levels in the extracellular fluid increase the permeability of neuronal membranes to sodium ion, causing a progressive depolarization (contraction of peripheral skeletal muscles)
- Tetany is characterized by contraction of distal muscles of the hands (carpal spasm with extension of interphalangeal joints) and feet (pedal spasm) and is associated with tingling around the mouth and distally in the limbs.
- Recurrent fungal and viral infection
- Congenital heart & great vessel defects (**tetralogy of Fallot**, **truncus arteriosus**)
- Thymic aplasia

Diagnosis

- ↓T cells, ↓ PTH, ↓Ca^{2+}
- Thymic shadow absent on CXR.

Il-2 receptor deficiency (severe combined immunodeficiency):

Molecular defect

- IL-2 Is the major cytokine that is produced during the primary response of Th cells
- Upon differentiation into one of the two types of Th effector cells, Th1 and Th2, IL-2 production declines and is replaced by production of Th1-like (IFN-γ) or Th2-like (IL-4) cytokines
- Therefore, deficiency in Il-2 receptor is associated with ↓ Th1 response & ↓IFN-

Clinical presentations

- Characterized by disseminated mycobacterial and fungal infection

Hyper IgE syndrome (Job syndrome):

Molecular defect

- Defects in **JAK-STAT signaling** pathway leading to impaired Th17 function
- Decreased IFN-gamma production
- Unresponsive neutrophils and chemotaxis

Clinical presentations

- Characterized by

1. Coarse facies
2. Cold (noninflamed) staphylococcal abscesses
3. Increased IgE and eosinophils, eczematous rash
4. Pathological bone fractures
5. Retained primary teeth

Chronic mucocutaneous candidiasis

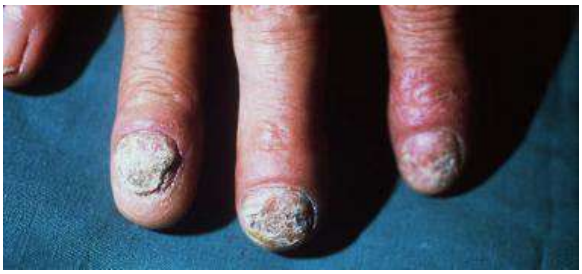
Molecular defect

- A type of T-cell dysfunction.
- Result from congenital genetic defects in IL-17 or IL-17 receptors.

Clinical presentations

- Candida albicans infections of skin and mucous membranes

- Hyperkeratosis, skin ulcer, dyspareunia, endocardium abnormality, vision problems, hepatitis, seizures, hematuria and meningitis.



References:

- First aid 2018
- Crush step 1- The ultimate USMLE lecture notes 2017
- L-2 production in developing Th1 cells is regulated by heterodimerization of RelA and T-bet and requires T-bet serine residue 508. Journal of experimental medicine 2008
- Insights into the Role of STAT3 in Human Lymphocyte Differentiation as Revealed by the Hyper-IgE Syndrome. The journal of immunology 2009
- Severe combined immunodeficiencies and related disorders. Nature reviews 2015

T& B cells disorders

Outline:

- Severe combined immunodeficiency (SCID)
- Ataxia telangiectasia
- Hyper IgM disorder
- Wiskott-Aldrich syndrome

Severe combined immunodeficiency (SCID)

Molecular defect:

- Known as **bubble boy disease** and **bubble baby disease**
- Defects in common γ chain of IL-2 receptor
- Cause widespread defect in interleukin signaling with low or absent T cells and NK cells and non-functional B cells.
- X-linked recessive disorder
- Associated with **adenosine deaminase deficiency**

Clinical presentations:

- Recurrent viral, bacterial, fungal, protozoal infection
- Chronic diarrhea; skin, mouth, and throat lesions; opportunistic (fungal) infections

Diagnosis

- ↓ T cells recombinant excision circles
- Absence of **thymic shadow** (CXR), **germinal centers** (lymph node biopsy), and T cells (flow cytometry).
- low levels of circulating lymphocytes

Treatment

- Bone marrow transplant

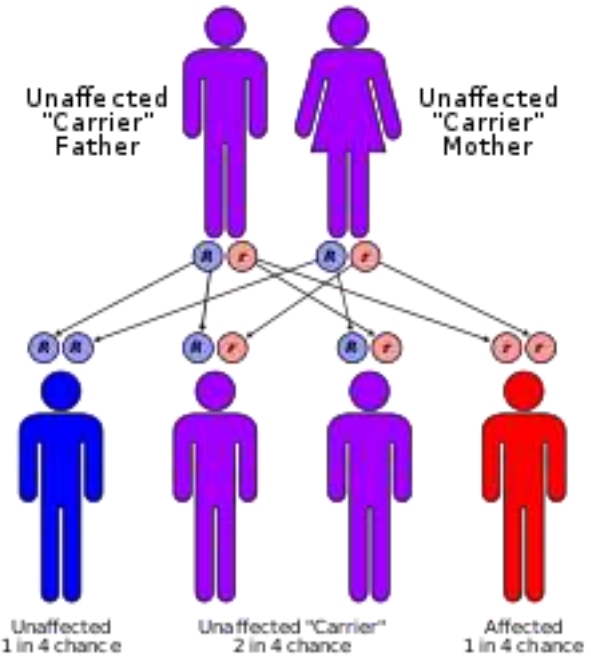
Ataxia telangiectasia

Molecular defect:

- Known as ataxia–telangiectasia syndrome or Louis–Bar syndrome
- ATM gene defects (Defect in the ATM kinase involved in the detection of DNA damage and progression through the cell cycle
- Autosomal recessive disorder

Clinical presentations

- Ataxia (gait abnormalities)
- Telangiectasia (capillary distortions in the eye)
- Deficiency of IgA and IgE production



Diagnosis

- Increased AFP
- Decreased IgA, IgG, and IgE.
- Lymphopenia, cerebellar atrophy
- Increased risk of lymphoma and leukemia

Hyper IgM disorder

Molecular defect

- Defective CD40L on helper T-cell
- Normal level of B cells but with diminished levels of IgG and IgA and with high levels of IgM
- X-linked recessive
- This condition usually results from an inability to undergo isotype class switching secondary to deficiency in **CD40 ligand** on Th2 cells.

Clinical presentations

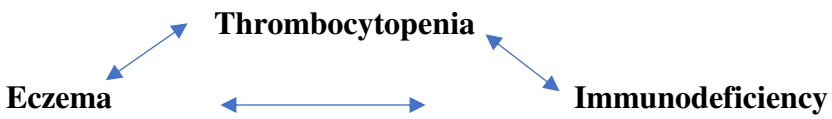
- Associated with higher risk for Pneumocystis infection, CMV and cryptosporidium

Wiskott-Aldrich syndrome:

Molecular defect

- Defect in the WAS protein which plays a critical role in actin cytoskeleton rearrangement
- T cells can NOT recognize actin cytoskeleton

Clinical Presentations



Diagnosis

- ↑IgA and IgE and ↓ IgM
- Low platelets
- Increased risk of autoimmune disorders and cancers

References:

- First aid 2018
- Crush step 1- The ultimate USMLE lecture notes 2017
- L-2 production in developing Th1 cells is regulated by heterodimerization of RelA and T-bet and requires T-bet serine residue 508. Journal of experimental medicine 2008
- Insights into the Role of STAT3 in Human Lymphocyte Differentiation as Revealed by the Hyper-IgE Syndrome. The journal of immunology 2009
- Severe combined immunodeficiencies and related disorders. Nature reviews 2015

Transplant rejections and grafts

Outline:

- Overview
- Types of grafts
- Mechanisms of graft rejection
- Hyper acute graft rejection
- Acute graft rejection
- Chronic graft rejection
- Graft-versus-host disease
- General treatment in graft rejections

Overview

- **Transplantation** is the process of taking cells, tissues, or organs (**a graft**) from one individual (**the donor**) and implanting them into another individual or another site in the same individual (the host or recipient).

Types of grafts:

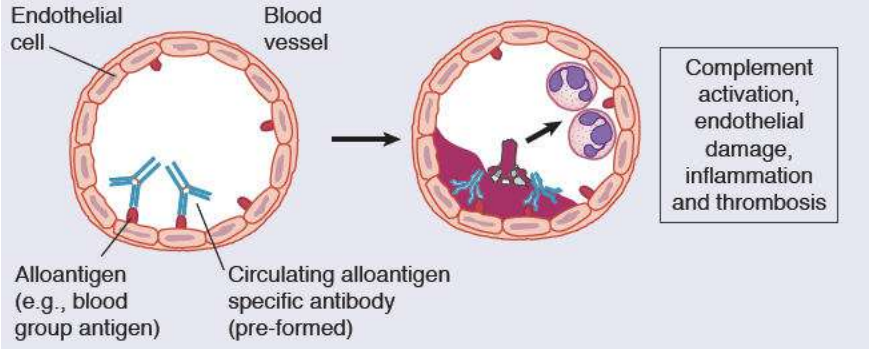
- **Autologous grafts (or autografts)** are those where tissue is moved from one location to another in the same individual (skin grafting in burns or coronary artery replacement with saphenous veins).
- **Isografts (or syngeneic grafts)** are those transplanted between genetically identical individuals (monozygotic twins).
- **Allogeneic grafts** are those transplanted between genetically different members of the same species (kidney transplant).
- **Xenogeneic grafts** are those transplanted between members of different species (pig heart valves into human).

Mechanism of graft rejection:

- As the graft becomes vascularized, **CD4+ and CD8+** cells that migrate into the graft from the host become sensitized and proliferate in response to both major and minor histocompatibility differences
- The cytokines play a critical role in stimulating macrophage, cytotoxic T cell.
- Interferons and TNF-α and -β all increase the expression of **class I MHC** molecules in the graft, **while** IFN-γ increases the expression of **class II MHC** as well
- These processes increase the susceptibility of cells in the graft o MHC-restricted killing.

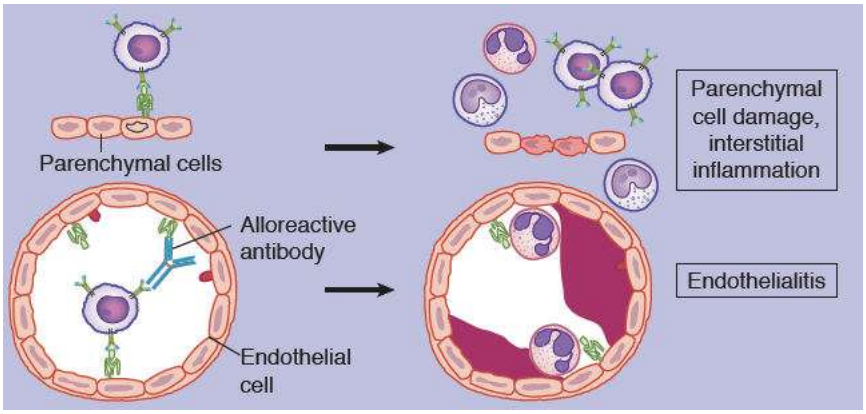
Hyper acute Graft Rejection

- Occurs immediately within minutes to hours
- **Type II cytotoxic hypersensitivity**
- Antibodies bind to the grafted tissue and **activate complement** and the clotting cascade resulting in thrombosis and ischemic necrosis
- Due to pre-formed antibodies
- Graft must be removed.



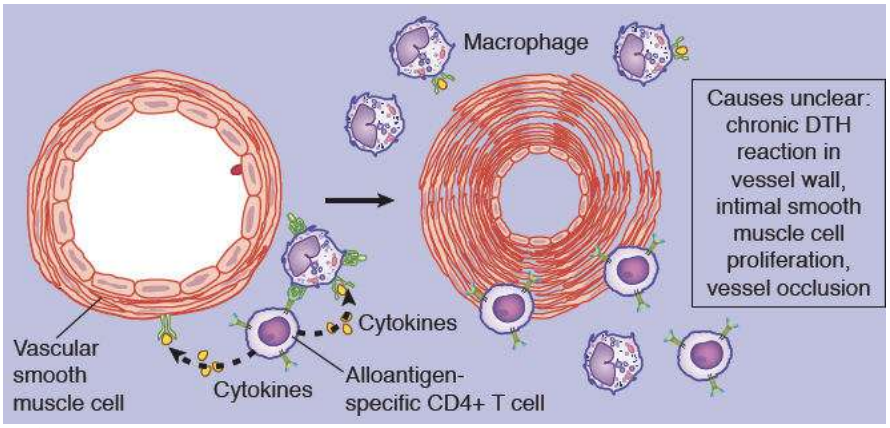
Acute Graft Rejection

- Occurs within days to weeks
- Develop type **IV hypersensitivity** reaction
- Both **CD4 and CD8 T** cells play a role as well as antibodies against donor MHCs
- Reversible by **Immunosuppressive therapy** (Interleukins inhibitors, D-cyclosporine)
- Characterized by **Vasculitis of graft vessels** with dense interstitial lymphocytic infiltrate
- Diagnosis by **graft biopsy**



Chronic Graft Rejection

- Occurs within months to years
- Predominantly **T cell mediated** (CD4+ T cells respond to recipient)
- **Type III and Type IV hypersensitivity** directed against the foreign MHC molecules which look like self-MHC presenting a foreign antigen
- Difficult to treat and usually results in graft rejection
- Chronic rejection appears as fibrosis and scarring in all transplanted organs



- In heart transplants, chronic rejection manifests as **accelerated coronary artery atherosclerosis**. In transplanted lungs, it manifests as bronchiolitis obliterans

Graft-versus-host disease

- Timeline varies
- When the grafted tissue is bone marrow.
- Bone marrow transplantation applicable in cases of cancer patients (leukemia), since **the bone marrow** is the source of pluripotent hematopoietic stem cells, it can be used to reconstitute myeloid, erythroid, and lymphoid cells
- Grafted immune-competent T cells proliferate in the irradiated immunocompromised disease host and reject cells with foreign proteins and cause organ dysfunction
- It is necessary to remove these cells before transplantation to avoid the appearance of graft-versus-host disease in the recipient.
- Type **IV hypersensitivity reaction**.
- **Signs and symptoms** include: Maculopapular rash, jaundice, hepatomegaly, diarrhea, and gastrointestinal hemorrhage.

General treatment in graft rejections:

- Daclizumab, basiliximab (anti-IL-2 receptor antibody)
- Muromonab (anti-CD3)
- Belatacept (CTLA-4-Ig)
- Alemtuzumab (anti-CD52) **CD52** is a marker found on all lymphocytes
- Monoclonal antibodies are used in the treatment and prevention of graft rejection along with the classic therapies (corticiosteroids, cyclosporine A, rapamycin, etc.).

References:

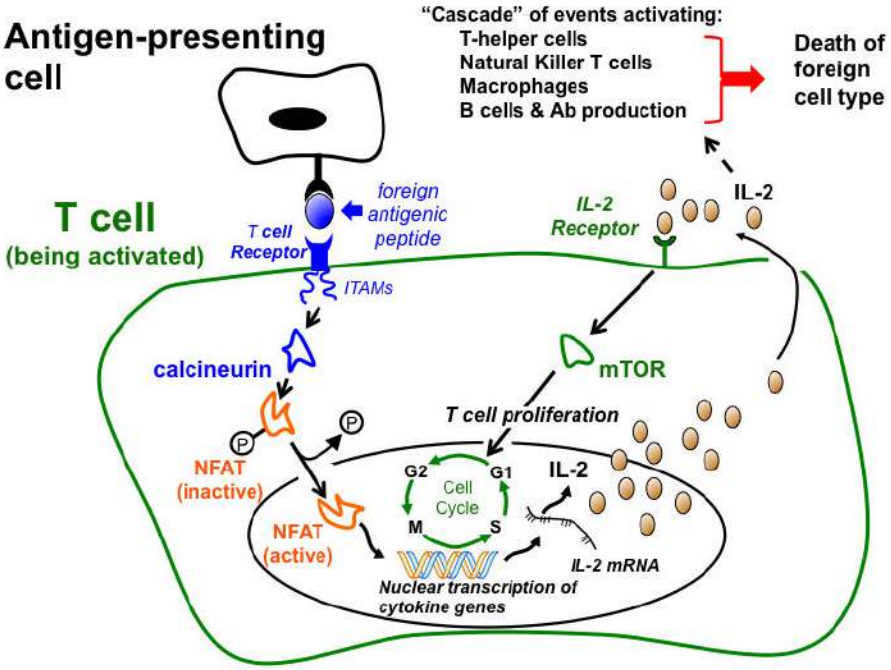
- First aid 2018
- Crush step 1- The ultimate USMLE lecture notes 2017
- Crush step 1- Kaplan, USMLE lecture notes 2017

Cyclosporine

Outline:

- Overview
- Mechanism of action
- Clinical uses
- Toxicity

Overview



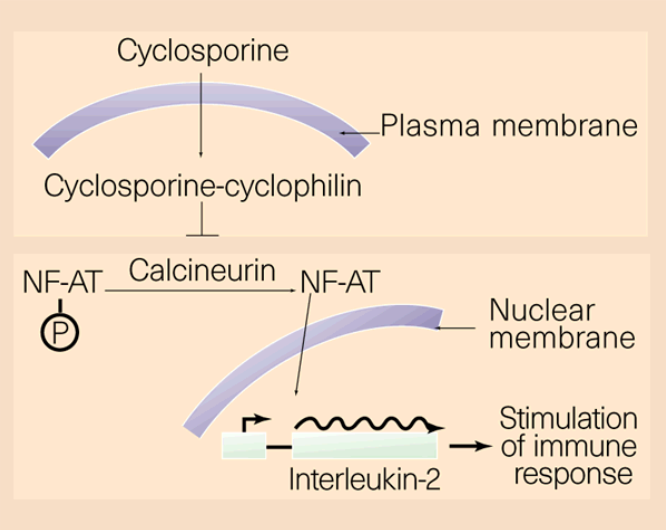
- Activation of T cells in response to a foreign antigen presented by an antigen-presenting cell (which include dendritic cells, macrophages & B lymphocytes).

- This induces "adaptive immune responses" involving multiple cell types that are involved in cell-mediated immunity involving activated **macrophages, natural killer T cells and cytotoxic T cells**, as well as stimulation of humoral immunity involving **B cells & plasma cells** that produce antibodies that bind to foreign antigens and enhance phagocytosis and cellular toxicity of the foreign cells

- Interleukin 2 (IL-2) plays a critical role in the initial activation of T cells

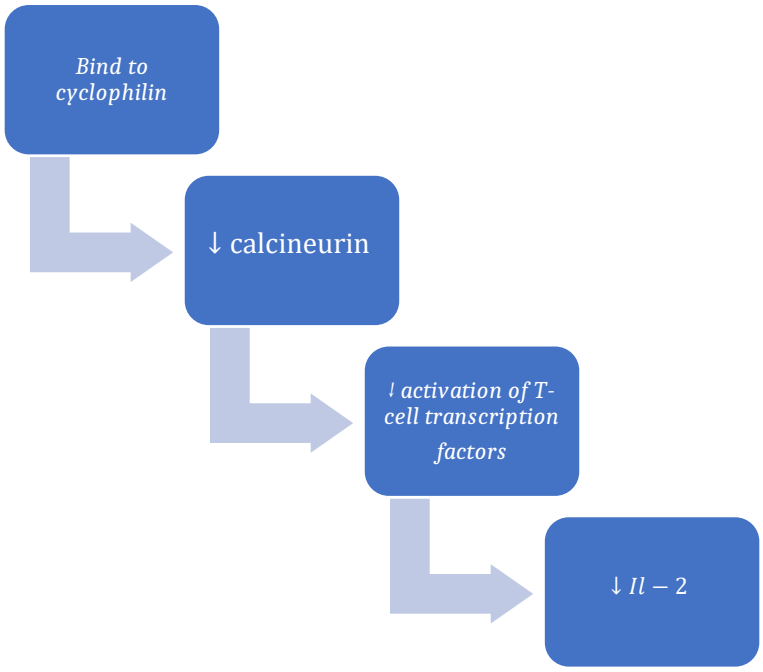
- Many other cytokines (e.g. IFN- γ, TNF-β, IL-4 & IL-5) are involved in later steps in the pathways resulting in activation of other cell types such as **macrophages & B cells**

Cyclosporine:



Cyclosporine (CsA) binds to **cyclophylin** (CpN), forming a complex that binds and blocks the function of the enzyme calcineurin (CaN). As a result, CaN **fails to dephosphorylate** the cytoplasmic component of the nuclear factor of activated T cells (NF-ATc), and the transport of NF-ATc to the nucleus and the binding of NF-ATc to the nuclear component of the nuclear factor of activated T cells (NF-ATn). The NF-ATc–NF-ATn complex binds to the promoter of the interleukin 2 (IL-2) gene and initiates IL-2 production.

Mechanism of action:



Clinical use:

- Cyclosporine is DOC for organ or tissue transplantation (+/– mycophenolate, +/– steroids, +/– cytotoxic drugs)
- Other uses: Psoriasis, rheumatoid arthritis.

Toxicity:

- Nephrotoxicity due to vasoconstriction
- Hyperglycemia: reduce in pancreatic cells
- Hypertension
- Hyperlipidemia
- Neurotoxicity
- Gingival hyperplasia
- Hirsutism

References:

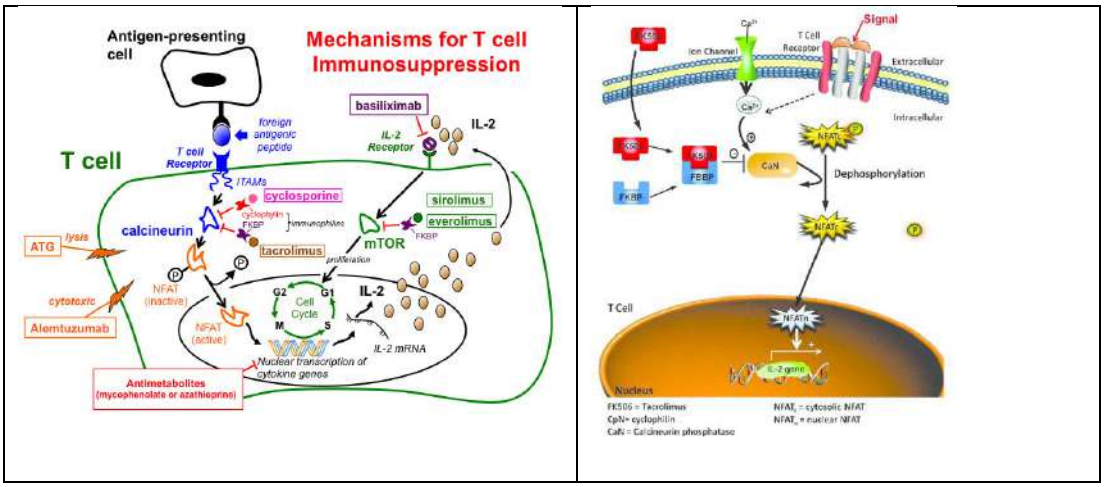
- First aid 2018
- Systemic Cyclosporine in the Treatment of Psoriasis.2012
- A transformed view of cyclosporine. Nature 1999
- Crush step 1- Kaplan, USMLE lecture notes 2017

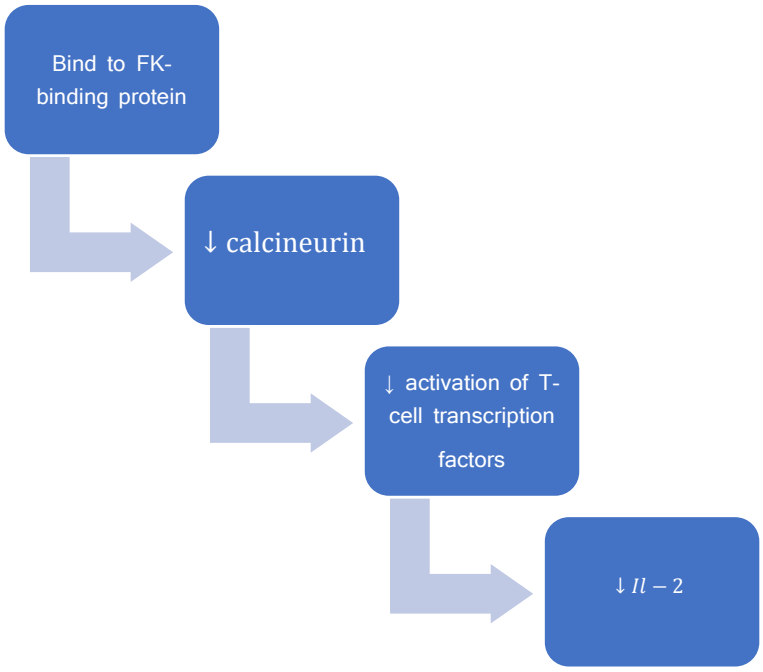
Tacrolimus

Outline:

- Mechanism of action
- Clinical uses
- Toxicity

Mechanism of action:





Clinical use:

- Tacrolimus used alternatively to cyclosporine in renal and liver transplants

Toxicity:

- Nephrotoxicity due to vasoconstriction
- Hyperglycemia: reduce in pancreatic cells
- Hypertension
- Hyperlipidemia
- Neurotoxicity
- Gingival hyperplasia
- Hirsutism

References:

- First aid 2018
- Crush step 1- Kaplan, USMLE lecture notes 2017
- Tacrolimus Modulates TGF-β Signaling to Induce Epithelial-Mesenchymal Transition in Human Renal Proximal Tubule Epithelial Cells. 2016

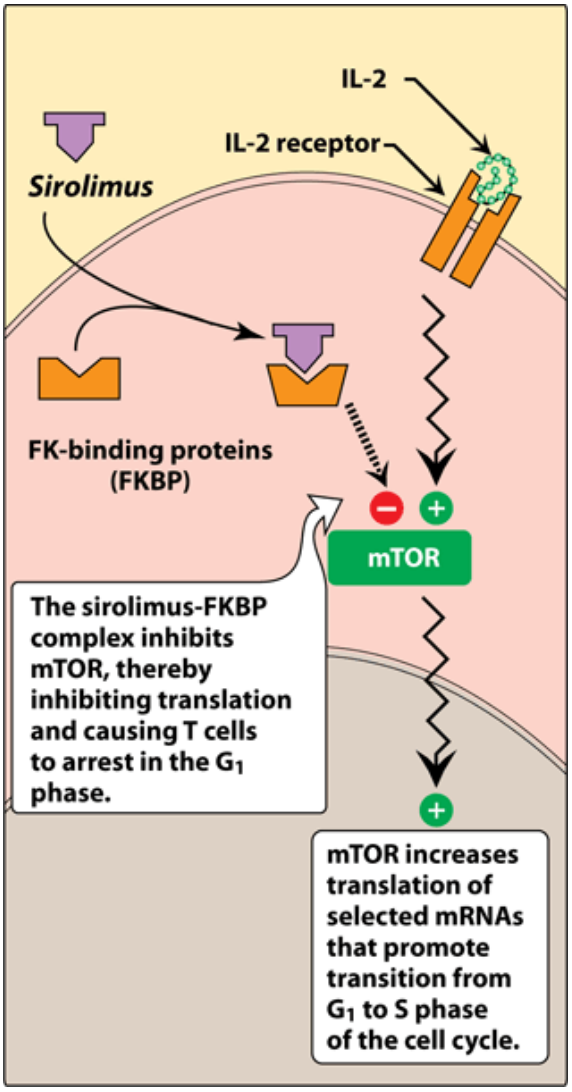
Sirolimus (Rapamycin)

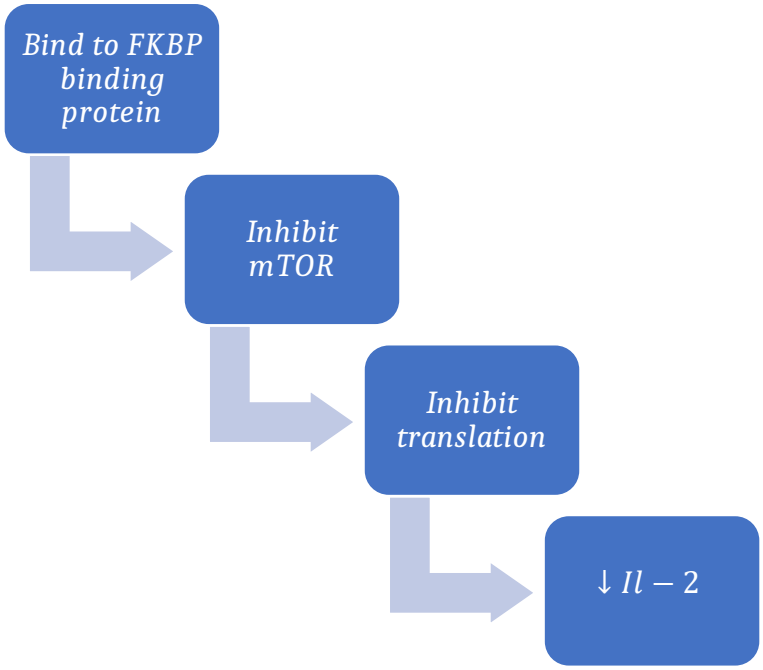
Outline:

- Mechanism of action
- Clinical uses
- Toxicity

Mechanism of action:

- **mTOR inhibitor:** binds to FKBP- Blocks T-cell activation and B-cell differentiation thereby preventing response to IL-2





Clinical use:

- **Immunosuppressant post**- kidney transplant in conjunction with cyclosporine and corticosteroids
- Used with drugs eluting stents to prevent ischemia

Toxicity:

- Pancytopenia
- Insulin resistance
- Hyperlipidemia
- **NOT** nephrotoxic

References:

- First aid 2018
- Crush step 1- Kaplan, USMLE lecture notes 2017
- Long-term effectiveness and safety of sirolimus drug-eluting stents. 2011

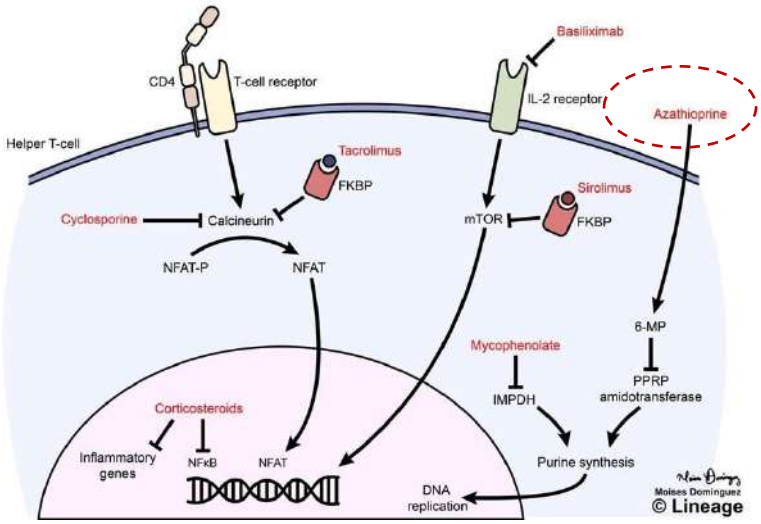
Azathioprine

Outline:

- Mechanism of action
- Clinical uses
- Toxicity

Mechanism of action:

- **Purine antimetabolite**: Azathioprine inhibits DNA and RNA synthesis by preventing interconversion among the precursors of purine synthesis and suppressing de novo purine synthesis
- **Azathioprine** is a prodrug metabolized into 6-mercaptopurine



Clinical use:

- Used in cardiac and kidney transplantations
- Rheumatoid arthritis, Crohn disease, glomerulonephritis, other autoimmune conditions

Toxicity:

- Leukopenia
- Allopurinol and azathioprine should not be co-prescribed unless the combination cannot be avoided.
- Allopurinol interferes with the metabolism of azathioprine, increasing plasma levels of 6-mercaptopurine which may result in potentially fatal blood dyscrasias.
- The dose of azathioprine should be reduced to **25% of the recommended dose** and the patient's blood count should be monitored assiduously

References:

- First aid 2018
- Crush step 1- Kaplan, USMLE lecture notes 2017
- The Autoimmune Diseases (Fifth Edition), 2014

Recombinant cytokines

Outline:

- Aldesleukin
- Epoetin alfa (EPO analog)
- Colony stimulating factors
- Interferon
- Oprelvekin (Interleukin 11)
- Thrombopoietin
- Summary

Aldesleukin:

- Used for treatment of **renal cell carcinoma, metastatic melanoma**
- **MOA**: Aldesleukin binds to the **IL-2 receptor** which leads to stimulate growth and differentiation of T cells.

Epoetin alfa (EPO analog):

- **Erythropoietin**: used to treat anemias due to:

A. Chronic kidney disease
B. Zidovudine in patients with HIV-infection
C. The effects of concomitant myelosuppressive chemotherapy

- **MOA**: Erythropoietin or exogenous epoetin alfa binds to the erythropoietin receptor (EPO-R) and activates intracellular signal transduction pathways

Colony stimulating factors:

- Sargramostim (GM-CSF) granulocyte macrophage colony-stimulating factor
- Filgrastim (G-CSF) granulocyte colony-stimulating factor

Shared the following characteristics:

- Secreted by Macrophages and Th cells Bone marrow
- **Clinical uses**: Induces proliferation; used to counteract neutropenia following ablative chemotherapy
- **MOA**: Sargramostim binds to the Granulocyte-macrophage colony stimulating factor receptor (GM-CSF-R-alpha or CSF2R). This leads to the production of hemopoietic cells and neutrophil

- **MOA**. Filgrastim also stimulates the release of neutrophils from **bone marrow** storage pools and decreases their time to maturation. Filgrastim acts to increase the phagocytic activity of mature neutrophils, thus allowing them to prevent infection.

Interferon:

- **IFN-α** Chronic hepatitis C (not preferred) and B, renal cell carcinoma
- **IFN-β** Multiple sclerosis
- **IFN-γ** Chronic granulomatous disease

Oprelvekin (Interleukin 11):

- Oprelvekin binds to the **interleukin 11 receptor** which leads to a cascade of signal transduction events.
- IL-11 is a thrombopoietic growth factor that directly stimulates the proliferation of hematopoietic stem cells
- **Clinical uses**: Autoimmune thrombocytopenia

Thrombopoietin:

- **Clinical uses:** The procurement of platelets for donation, and recovery of platelet counts after myelosuppressive chemotherapy.

Summary

Cytokine	Clinical uses
Aldesleukin (Interleukin-2)	↑ lymphocyte differentiation and ↑ NKs—used in renal cell cancer and metastatic melanoma
Oprelvekin (Interleukin 11)	↑ platelet formation—used in thrombocytopenia
Filgrastim (G-CSF)	↑ granulocytes—used for marrow recovery
Sargramostim (GM-CSF)	↑ granulocytes and macrophages—used for marrow recovery
Thrombopoietin	Thrombocytopenia
Interferon-α	Hepatitis B and C, leukemias, melanoma
Interferon- β	Multiple sclerosis
Interferon- γ	Chronic granulomatous disease →↑ TNF

References:

- First aid 2018
- Crush step 1- Kaplan, USMLE lecture notes 2017

Therapeutic antibodies

Outline:

A. Cancer therapy
B. Autoimmune disease therapy
C. Other applications

Cancer therapy

Alemtuzumab

- Binds to the **CD52 antigen** present on most B and T lymphocytes. This binding leads to antibody-dependent lysis of leukemic cells.

Clinical uses:

- Chronic leukocytic leukemia
- Multiple sclerosis
- Auto immune hemolytic anemia

Rituximab

- Monoclonal antibody that targets the **CD20 antigen**, which is expressed on the surface of pre-B and mature B-lymphocytes.
- After binding to **CD20**, rituximab mediates B-cell lysis (or breakdown).

Clinical uses:

- Non-Hodgkin's Lymphoma
- Rheumatoid arthritis
- Multiple sclerosis
- Chronic lymphocytic leukemia
- Pemphigus Vulgaris

Trastuzumab

- Trastuzumab is a recombinant humanized IgG1 monoclonal antibody against **the HER-2** receptor, a member of the epidermal growth factor receptors which is a photo-oncogene and over-expressed in breast tumor cells.

Clinical uses:

- Metastatic breast cancer

Cetuximab

- Cetuximab binds to the epidermal growth factor receptor (EGFR) on both normal and tumor cells.
- EGFR is over-expressed in many colorectal cancers.

Clinical uses:

- Treatment of EGFR-expressing, metastatic colorectal carcinoma
- Metastatic squamous cell carcinoma of the head and neck

Bevacizumab

- Bevacizumab is an antineoplastic agent and prevents or reduces the formation of blood vessels (angiogenesis) thereby preventing or reducing metastatic disease progressing.
- Bevacizumab binds VEGF and prevents vascular endothelial growth and endothelial cell proliferation

Clinical uses:

- Glioblastoma
- Colorectal cancer
- Renal cell carcinoma
- Cervical cancer
- Lung cancer

Autoimmune disease therapy

Eculizumab

- Treatment of patients with **paroxysmal nocturnal hemoglobinuria** (PNH) to reduce hemolysis.
- Eculizumab is a monoclonal antibody directed against the complement protein C5.
- This antibody blocks the cleavage of C5

Clinical uses:

- Atypical hemolytic uremic syndrome
- Paroxysmal nocturnal hemoglobinuria

Daclizumab

- Inhibits (anti-CD25) IL-2-mediated activation of lymphocytes, a critical pathway in the cellular immune response involved in allograft rejection.

Clinical uses:

- Relapsing multiple sclerosis

Ustekinumab

- Blocks interleukin IL-12 and IL-23

Clinical uses:

- Psoriasis, psoriatic arthritis

Natalizumab

- Block **α4-integrin** which expressed by inflammatory cells with VCAM-1 on vascular endothelial cells, and with CS-1 and/or osteopontin expressed by parenchymal cells in the brain.

- **α4-integrin** is required for white blood cells to move into organs, therefore, natalizumab prevents these immune cells from crossing blood vessel walls to reach affected organs thereby decreasing inflammation.

Clinical uses: treatment of multiple sclerosis.

Other applications

Abciximab

- Binds to the intact platelet GPIIb/IIIa receptor, which is a member of the integrin family of adhesion receptors and the major platelet surface receptor involved in platelet aggregation

Clinical uses:

The prevention of cardiac ischemic complications

Denosumab

- Designed to target **RANKL** (RANK ligand), a protein that acts as the primary signal to promote bone removal/resorption.
- In many bone loss conditions, RANKL overwhelms the body's natural defense against bone destruction.

Clinical uses:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture

Digoxin immune Fab

- Binds excess digoxin or digitoxin molecules circulating in the blood (making them unavailable for binding at their site of action on cells in the body)

Clinical uses:

- Digitoxin toxicity
- Digitoxin overdose

Omalizumab

- Inhibits the binding of **IgE** to receptors on mast cells and basophils, blocking the IgE-mediated secretion of inflammatory mediators from these cells

Clinical uses:

- Severe Asthma
- Chronic Urticaria

Palivizumab

- Binds to the fusion **glycoprotein of RSV**. This prevents its binding and uptake by host cellular receptors.

Clinical uses:

- Prophylaxis of respiratory diseases caused by respiratory syncytial virus.

References:

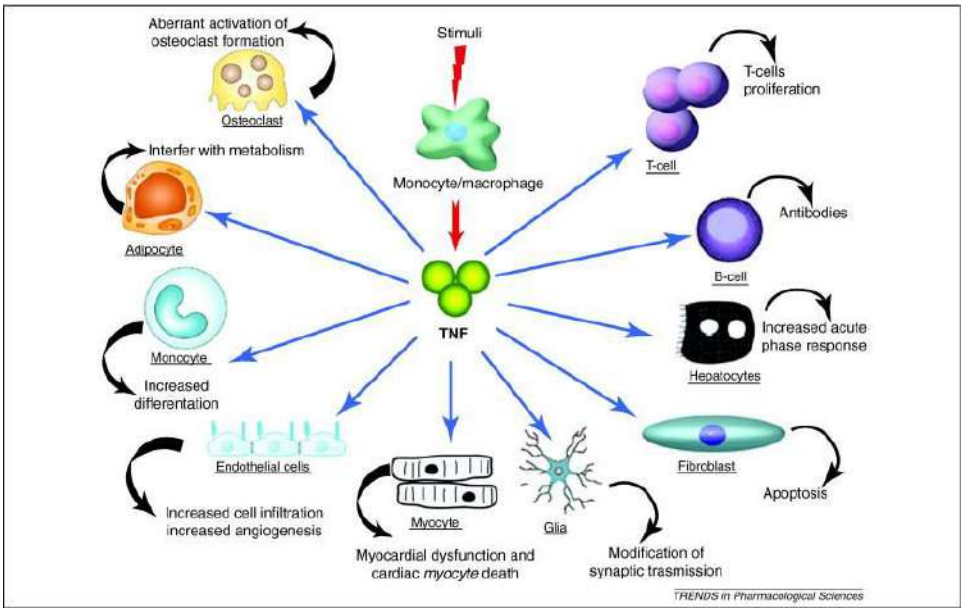
- First aid 2018
- Crush step 1- Kaplan, USMLE lecture notes 2017
- Drug bank

TNF alfa inhibitors

Outline:

- Overview
- Etanercept
- Infliximab, adalimumab, certolizumab, golimumab

Overview:



- Produced by **activated macrophages**, although it can be produced by many other cell types such as
  CD4+ lymphocytes, NK cells, neutrophils, mast cells, eosinophils, and neurons.

- The primary role of TNF is in the regulation of immune cells.

- TNF is able to induce fever, to induce apoptotic cell death, to induce sepsis (through IL1& IL6 production), to induce cachexia, induce inflammation, and to inhibit tumorigenesis and viral replication.

- Dysregulation of TNF production has been implicated in a variety of human diseases, including Alzheimer's disease, cancer, major depression, and inflammatory bowel disease (IBD).

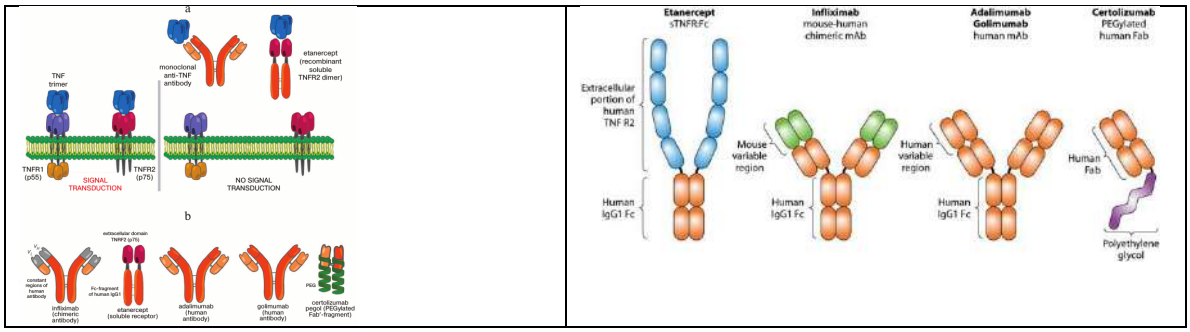
- Anti- TNF-α agents have been successfully introduced into the treatment of inflammatory diseases such as RA, juvenile idiopathic arthritis, psoriatic arthritis, psoriasis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, and Behçet's disease

Etanercept:

- **Etanercept** is made from the combination of two naturally occurring soluble human 75-kilodalton TNF receptors linked to an Fc portion of an **IgG1**

- The effect is an artificially engineered dimeric fusion protein (decoy receptor for TNF-α + IgG1 Fc)

- **Clinical uses:** Rheumatoid arthritis, psoriasis and ankylosing spondylitis



Drug interaction:

- Drug-induced lupus

Infliximab, adalimumab, certolizumab, golimumab

- They are **monoclonal antibodies** and have identical structures and affinities to the target

  - Infliximab, adalimumab and golimumab are full IgG1 monoclonal antibodies against human TNF-α.

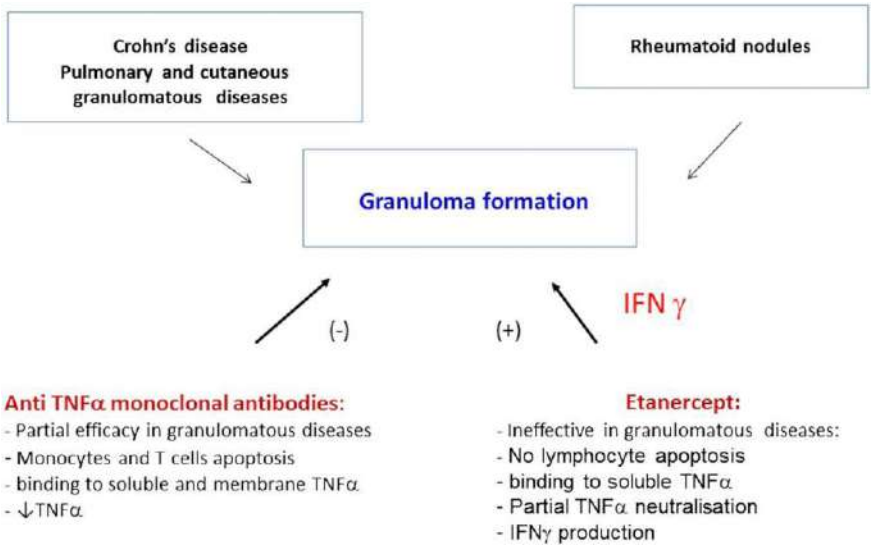
  - **Infliximab** is a chimeric mouse/human anti- TNF-α. monoclonal antibody (mAb) composed of a murine variable region and a human IgG1 constant region.

  - **Adalimumab and golimumab** are fully humanized anti- TNF-α mAbs, which is indistinguishable from the normal human IgG1.

  - **Certolizumab** is a Fab' fragment of an anti- TNF-α mAb and lacks the Fc portion. The hinge region of certolizumab is covalently linked to 2 cross-linked chains of a 20-kDa of poly-ethylene glycol, which is named as certolizumab pegol

- **MOA**: Anti-TNF-α monoclonal antibody

Differences between Etanercept and other Anti-TNF-α monoclonal antibody:



References:

- First aid 2018
- Crush step 1- Kaplan, USMLE lecture notes 2017
- Molecular mechanisms of action of anti- TNF-α. agents – Comparison among therapeutic TNF-α.
  antagonists. 2018
- Anti-TNF therapy in the injured spinal cord. 2011

Muromonab

Outline:

- Mechanism of action
- Clinical uses
- Toxicity

Mechanism of action:

- Blocks function of **CD3** in T lymphocytes (involved in Ag recognition & signal transduction), resulting in a transient activation of T cells, **release of cytokines**, and blocking of T-cell proliferation and differentiation

Clinical use:

- Acute Allograft Rejection or Acute Graft-Vs-Host Disease Treatment
- Cardiac or Hepatic Allograft Rejection, Steroid Resistant

Toxicity:

- Cytokine release syndrome typically 45 min. after injection
- Hypersensitivity reactions

References:

- First aid 2018
- Crush step 1- Kaplan, USMLE lecture notes 2017