## Chapter 7
### Microbiology

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Bacteria

- All bacteria are haploid structures; they can trap iron using siderophores, and can also perform fermentation processes.
- Gram-positive bacteria appear violet because they absorb cresyl violet stain.
- Gram-negative bacteria appear red because they absorb safranin stain.
- Cell wall of bacteria is mainly made up of peptidoglycan:
  1. Gram positive: It is thick with extensive cross-linking.
  2. Gram negative: It is thin with minimal cross-linking.

Structure

Gram-Positive Bacteria

- Cell envelope from inside out is formed of two layers:
  1. Cytoplasmic membrane: A lipid bilayer spanned by proteins. This layer, unlike animals’ membranes, contains no sterols.
  2. Cell wall: Formed of 3 P’s—Peptidoglycan, Polysaccharides, Proteins—and an antigenic determinant known as teichoic acid.

Gram-Negative Bacteria

- Cell envelope from inside out is formed of three layers:
  1. Cytoplasmic membrane: Lipid bilayer spanned by proteins
  2. Cell wall: Very thin peptidoglycan layer with no teichoic acid; however, it is rich in murein lipoprotein. Cytoplasmic membrane and cell wall are separated by the periplasmic space, which is rich in enzymes and proteins.
  3. Outer layer: Lipid bilayer containing porin channels and lipopolysaccharides (LPSs). LPS is differentiated into:
     - O antigen: Toward the outside
     - Polysaccharides: Forms the core
     - Lipid A: An endotoxin situated toward the inside

Notes:

1. The only gram-positive bacterium that contains endotoxins is Listeria monocytogenes.
2. Mycoplasma only has a cytoplasmic membrane and no cell wall.

Toxins

- Exotoxins
  1. Neurotoxins: e.g., tetanus and botulism
  2. Enterotoxins: e.g., Escherichia coli. Composition: Action and binding regions. Mechanism: Increases the NaCl content inside the intestine, which causes diarrhea.

- Endotoxins: A component of the gram-negative bacterial cell membrane

- Septic shock: Treating gram-negative bacteria with antibiotics can lead to bacterial destruction and release of huge amounts of endotoxins, causing septic shock. This process is regulated by interleukin-1 (IL-1) and tumor necrosis factor (TNF).

Cocci and Bacilli

- Gram-positive cocci: Staphylococci (clusters), streptococci (chains) or pneumococci (pairs)
- Gram-negative cocci: Meningococci and gonococci (kidney-shaped pairs)
- Gram-positive bacilli: Corynebacterium diphtheriae (Chinese letters appearance), Clostridium tetani (terminal spores), and Clostridium welchii (subterminal spores)
- Gram-negative bacilli: E. coli, Klebsiella, and Vibrio cholera (short curved comma shaped)

Metabolism

- Bacterial DNA is a double-stranded circle, while smaller circles might exist, and are known as plasmids. Plasmids have the ability to resist antibiotics.
- Bacteria release catalase and peroxidase to protect themselves from the destructive effect of hydrogen peroxide (H₂O₂). They also release superoxide dismutase to break down the oxygen free radicals.
- Metabolic types of bacteria:
  1. Obligate aerobe: Needs the presence of oxygen
  2. Obligate anaerobe: Needs the absence of oxygen. They are malodorous. Suspect in cases of aspiration pneumonia, e.g., alcoholics, syncope
  3. Facultative aerobe: Aerobic, but can also work in anaerobic conditions
4. Microaerophilic: Works only in the presence of small amounts of oxygen. These bacteria are deficient in catalase and peroxidase enzymes.
5. Heterotrophs: Bacteria using organic carbons for metabolism
6. Autotrophs: Bacteria using inorganic ammonium and sulfide for metabolism

Notes:
1. Aminoglycosides and Tetracyclines work AT 30S subunit of ribosomes; all other protein synthesis inhibitors work on 50S.
2. Facultative intracellular organisms, e.g., Salmonella, Listeria: They can live and metabolize normally inside macrophages after being phagocytosed.

Flagella
- They bind to the cell membrane by means of a basal body, and are the means of motility. Bacteria could have no flagella (e.g., Shigella), single flagellum (e.g., Vibrio), or multiple flagellae (e.g., E. coli).
- Pili (fimbriae): They are short and not motile, so they are used by the bacteria as means of adhesion to other structures. E. coli, Campylobacter jejuni, and Neisseria gonorrhoeae contain large number of pili.

Capsule
- Composition: Capsules are made of polysaccharides. The only exception is Bacillus anthracis, which is made of amino acids, e.g., glutamate, etc.
- Colonies: Capsulated Streptococcus pneumoniae form smooth colonies, and vice versa.
- India ink: It makes the capsule look like a halo around the capsulated bacteria, thus used to diagnose infection with capsulated organisms, e.g., Cryptococcus neoformans.
- Quellung reaction: Depends on antibody-induced swelling of the capsule
- Opsonization: Depends on binding of the Fc portions of antibodies to the capsule, which in turn allows macrophages to eat the bacteria
- Spores: Composed of three membranes, keratin, and exosporium layer.

Multiplication
- Transformation: Naked DNA of one cell attaches itself into another cell of close species. This is followed by entrance of the DNA into the cell and attaching to its genome, resulting in the transformation of the genetic characters of the recipient cell.
- Conjugation: A sex pilus builds up between two cells like a bridge, to facilitate the transport of fertility (F) plasmid and antibiotic resistance genes.
- Transduction: Bacteriophage (a virus that infects bacteria) transmits a piece of DNA from one bacterial cell into another. A bacteriophage holds on to the cell by its tail fibers and injects the DNA from its head all the way down into the cell. Types of bacteriophages are listed in Table 7.1.
- Transposons: Walking DNA strands that pass from one cell to another

Streptococci
- Characteristics: Arranged in chains, and have no catalase enzyme.
- Hemolytic activity:
  1. Beta-hemolytic: Complete hemolysis
  2. Alpha-hemolytic: Partial hemolysis
  3. Gamma-hemolytic: No hemolysis
- Lancefield classification: Streptococci are classified based on the (C) of the carbohydrate in the cell wall into types A to S.

Group A Beta-Hemolytic Streptococcus pyogenes Virulence Factors
- C of the carbohydrate component (CHO)
- M protein: Virulence factor, which stimulates antibody production
- Streptolysin O: Oxygen labile toxin, which mediates hemolysis. Streptococci carrying this toxin are inhibited by oxygen.
- Streptolysin S: Oxygen stable toxin, which mediates hemolysis. Streptococci carrying this toxin are not inhibited by oxygen. Streptolysin S is not antigenic.

| TABLE 7.1 Types of bacteriophages. |
|-----------------------------------|
| Mechanism | Virulent | Temperate (phage) |
|-----------|---------|-----------------|
| Transduction Errors | Generalized Incorporation errors | Specialized Splicing errors |
| When DNA converts to messenger RNA (mRNA), it ruptures the cell | It acts on lysogenization of bacteria Lysogenic immunity: a phage blocks subsequent infection with a similar phage |
Diseases Caused by Streptococcus pyogenes

- Streptococcus pharyngitis: Clinical picture: Sore throat, fever, cervical lymphadenopathy, exudates and pus on tonsils, and lack of cough. Treatment: Penicillin.
- Streptococcus skin infection: Folliculitis, cellulitis and impetigo, which can also be caused by staphylococci. Treatment: Penicillinase-resistant penicillin, e.g., dicloxacillin.
- Necrotizing fasciitis: It is a flesh-eating infection caused by Streptococcus entering through a break in the skin and causing myositis, redness, and bullae. Treatment: Penicillin G plus clindamycin (used to block toxins).
- Scarlet fever: Scarlet rash (sandpaper erythematous rash sparing the face), fever, circumoral pallor, and strawberry tongue accompanied by erythematous tonsils covered by pus and exudates. Treatment: Penicillin.
- Toxoplastic shock syndrome: Also caused by Staphylococcus. Clinical picture: Vomiting and diarrhea followed by rash. Common with use of cervical contraception, e.g., sponges. Treatment: Penicillin G plus clindamycin.
- Rheumatic fever: Following Streptococcus pharyngitis. Discussed in Chapter 10, Pathophysiology.
- Post-Streptococcus glomerulonephritis: Following Streptococcus pharyngitis or skin infection. Discussed in pathophysiology.

Alpha-Hemolytic Streptococcus (Streptococcus viridans)

- Streptococcus salivarius: Most common cause of subacute bacterial endocarditis. Staphylococci are the most common cause of acute bacterial endocarditis.
- Streptococcus intermedius: Causes abscesses. If Streptococcus Intermedius is isolated in the blood, next best step is computed tomography (CT) with contrast of the abdomen and pelvis to locate any abscesses.
- Streptococcus mutans: Causes dental caries.

Group D Streptococcus (Alpha-Hemolytic)

- Enterococci: Most common is Enterococcus faecalis, which is a cause of nosocomial infections. Treatment: Pristinomycins. It resists penicillin and vancomycin.
- Non-enterococci: Most common is Streptococcus bovis, a risk factor for colon cancer

Streptococcus pneumoniae

- Morphology: Alpha-hemolytic lancet–shaped diplococci with a thick capsule
- Diagnosis:
  1. Culture: Streptococcus pneumoniae is Optochin sensitive, i.e., cannot grow in the presence of Optochin. Note: Streptococcus viridans is Optochin resistant, and Streptococcus pyogenes is bacitracin sensitive.
  2. Positive Quellung reaction
- Prevention: Vaccine (Pneumovax) is formed of 23 polysaccharide capsular antigens.
- Clinical picture and treatment: It is the most common cause of:
  1. Community-acquired pneumonia: Treatment: macrolides (e.g., azithromycin) plus a third-generation cephalosporin
  2. Otitis media and mastoiditis in children: Treatment: amoxicillin
  3. Meningitis in the elderly: Treatment: penicillin

Staphylococci

- Characteristics: Arranged in clusters; release catalase enzyme
- Staphylococcus aureus: It releases the following:
  1. Coagulase: Works on fibrin
  2. Protein A: Binds Fc portion of immunoglobulin
  3. Penicillinase: Destroys penicillin
  4. Hemolysin: Against red blood cells (RBCs) and neutrophils
  5. Leukocidin: Against white blood cells (WBCs)
  6. Hyaluronidase: A spreading factor
  7. Exfoliatin: Exotoxin causing scalded skin syndrome
  8. Enterotoxin: Heat stable exotoxin causing food poisoning
  9. TSST-1: Exotoxin causing toxic shock syndrome, by binding to class II major histocompatibility complex (MHC)
- S. aureus is the most common cause of postinfluenza pneumonia. Pneumonia caused by S. aureus is characterized by lung cavitation, hemoptysis, empyema, and pneumatoceles.
**S. aureus** is the most common cause of *septic arthritis* and *osteomyelitis*. *Salmonella* is a common cause of osteomyelitis in patients with sickle cell disease; however, *S. aureus* is still the most common cause.

Food poisoning due to *S. aureus* is contracted through ingestion of dairy products, e.g., yoghurt, pudding. It starts 1–2 hours after ingestion and resolves quickly without complications.

Methicillin-resistant *S. aureus* (MRSA) is treated with *vancomycin*. Recently, new strains exist that are resistant to vancomycin, such as vancomycin-Indeterminate *S. aureus* (VISA).

*Staphylococcus epidermidis*: Normal skin flora that can contaminate prosthetic devices. So, when you see a patient on the USMLE with sepsis or endocarditis that developed shortly after insertion of any mechanical object into the body, e.g., valve or catheter, you know what to think!

*Staphylococcus saprophyticus*: The second most common cause of urinary tract infection (UTI) in sexually active women after *E. coli*.

**Bacillus anthracis**

*Spore-forming, gram-positive* bacillus. It is the only encapsulated bacteria with a *protein capsule*.

**Mechanism**: *Bacillus anthracis* exotoxin is formed of three parts:

1. *Edema factor*: An extracellular adenylate cyclase
2. *Lethal factor*: Can cause pulmonary edema
3. *Protective antigen*: Facilitates invasion of edema factor into the cells

**Clinical picture**: Anthrax, which has different forms:

1. *Respiratory*: Exotoxins released in the lungs, causing pneumonia known as *woolsorter’s disease*
2. *Cutaneous*: Black round lesion, also called a *malignant pustule*
3. *Gastrointestinal (GI) tract*: Intestinal necrosis

**Prevention**: Vaccine, made from the *protective antigen* portion of the exotoxin

**Treatment**: Penicillin

**Clostridium tetani**

*Spore-forming, gram-positive anaerobic* bacillus with terminal spores (*C. tetani* has terminal spores).

**Mechanism**: *Tetanospsamin* toxin causes tetany by inhibiting the release of gamma-aminobutyric acid (GABA) from cerebellum, and glycine from Renshaw cells of spinal cord.

**Clinical picture**: Muscle spasms, lockjaw, and risus sardonicus. The latter is a fixed smile due to muscle spasm, and is a sign of advanced disease.

**Prevention**: Vaccination, and tetanus toxoid is given every 10 years.

**After exposure**: Example: patient injured his foot by stepping on a rusty nail:

1. If last toxoid dose was within the last 5 years, no toxoid is needed.
2. If last toxoid dose was more than 5 years ago, give a new dose of toxoid.
3. If patient has never been immunized, give tetanus toxoid and immunoglobulin.

**Treatment of tetanus**:

1. Airway protection, and clean wound
2. Medications: Vaccine, immunoglobulin, and muscle relaxants

**Clostridium botulinum**

*Spore-forming, gram-positive anaerobic* bacillus

**Mechanism**: The toxin prevents acetylcholine release at the level of the neuromuscular junction.

**Source**: Canned foods and honey. A typical case on the USMLE is for an infant whose parents put honey in his milk bottle.

**Clinical picture**: Botulism:

1. *Flaccid paralysis*: Descending march from head to toe ("floppy baby")
2. Five D’s: Dilated pupils, diplopia, dysphagia, dysarthria, and diminished gag reflex

**Diagnosis**: Detection of toxins in stools (*Best specimen*) or serum

**Treatment**:

1. First step is to secure an airway by intubating the patient
2. Botulinum antitoxin: Even before confirming the diagnosis

**Clostridium difficile**

*Spore-forming, gram-positive anaerobic* bacillus

**Mechanism**: Exotoxins. Toxin A causes diarrhea. Toxin B is cytotoxic.
Clinical picture: Pseudo-membranous colitis. Usually follows the use of broad-spectrum antibiotics, e.g., ampicillin, clindamycin. Patient presents with severe watery malodorous diarrhea and abdominal pain.

Diagnosis: Detecting C. difficile toxins in the stools

Treatment: Oral metronidazole or vancomycin. They have to be given orally as they act locally inside the intestine.

**Clostridium perfringens**

- Spore-forming, gram-positive anaerobic bacillus
- Clinical picture: Gas gangrene; presents as severe cellulites and myonecrosis
- On exam:
  1. Crepitus on palpation of the lesions, indicating the presence of gas
  2. Black fluid oozing from the lesion upon pressure
- Treatment: Hyperbaric O₂ and antibiotics, e.g., penicillin G plus clindamycin

**Corynebacterium diphtheria**

- Non–spore-forming, gram-positive bacillus, with a unique Chinese letter appearance
- Mechanism: Colonizes in pharynx, and releases exotoxins targeting the cardiovascular system (CVS) and the central nervous system (CNS).
- Clinical picture: Fever, chills, sore throat, and bark-ing cough; often confused with croup
- On exam: Grayish pseudomembrane on pharynx. Histologically, it is formed of C. diphtheria, necrotic tissue, WBCs, and fibrin.
- Diagnosis: Culture on Loeffler or Tellurite media
- Complications: Respiratory failure, myocarditis, bulbar palsy, or even lower motor neuron lesion (LMNL) (combined motor and sensory loss)
- Treatment: Helpful to remember: “Treat diphtheria with DAD”:
  1. Diphtheria antitoxin
  2. Antibiotics: Penicillin (PCN) is the drug of choice. If PCN allergy exists, erythromycin is a good alternative.
  3. DPT (diphtheria, pertussis, tetanus) vaccination: As there is no postinfectious immunity
- Notes:
  1. Diphtheria toxins can only be produced in patients with iron deficiency.
  2. Exotoxin of diphtheria works through its A portion by inhibiting elongation factor 2 (EF2) and protein synthesis. This is achieved by adenosine diphosphate (ADP) ribosylation.

**Listeria monocytogenes**

- Non–spore-forming, gram-positive bacillus, with unique features:
  1. It is a facultative intracellular organism.
  2. It is the only gram-positive organism capable of releasing endotoxins.
  3. End-over-end motility (“tumbling”)
- Clinical picture: Meningitis and sepsis. It is the third most common cause of meningitis in neonates (after Streptococcus agalactiae and E. coli). It also causes meningitis in immunocompromised patients (also see Chapter 3, Neuroanatomy).
- Treatment: Ampicillin + sulbactam or sulfamethoxazole/trimethoprim (SMX/TMP)

**Neisseria meningitidis (Meningococci)**

- Kidney-shaped, gram-negative diplococci; 5% of the population are carriers for this bacterium; occurs in the nasopharynx
- Virulence factors:
  1. Endotoxin: Can cause adrenal hemorrhage and petechiae
  2. Capsule, immunoglobulin A (IgA) protease, the ability to extract iron from human blood
- Risk groups: Army recruits and children younger than 2 years of age
- Clinical picture:
  1. Meningitis: Discussed in Chapter 3, Neuroanatomy
  2. Disseminated meningococcemia: Fever, rash, arthritis, and petechial rash
  3. Fulminant meningococcemia (Waterhouse-Friederichsen syndrome): Bilateral adrenal hemorrhage, and purpura fulminans. So when you see a patient on the USMLE with meningitis, hypotension, hypoglycemia, and purpura, you know what to think!
- Diagnosis:
  1. Culture: Grows on Thayer Martin medium
  2. Meningococci can ferment maltose and glucose into acid (Note: Gonococci can ferment glucose only, but not maltose).
- Treatment: Third-generation cephalosporin
- Prophylaxis for contacts: Rifampicin.
**Neisseria gonorrhea (Gonococci)**
- **Kidney-shaped, gram-negative diplococci**
- **Virulence factors (2 P’s)**: Pili and Protein II
- **Clinical picture**:
  1. *Greenish* penile or vaginal discharge
  2. Newborns: *Ophthalmia neonatorum*. That’s why all newborns receive prophylactic erythromycin eyedrops after birth.
- **Complications**:
  1. Disseminated gonococcalia: *Pustular rash*, arthritis, *tenosynovitis*, and fever
  2. Urethritis, prostatitis, epididymitis, pelvic inflammatory disease, and even ectopic pregnancy *(due to adhesions)*
  3. *Fitz-Hugh–Curtis syndrome*: Perihepatitis, which is also caused by *Chlamydia*. Patient presents with right upper quadrant (RUQ) abdominal pain and elevated transaminases.
- **Treatment**: Drug of choice is *third-generation cephalosporins*. If patient is allergic to cephalosporin, the drug of choice is *ciprofloxacin*.
- **Note**: *Neisseria (Branhamella) catarrhalis* is a respiratory tract flora that *resists penicillin*.

**Escherichia coli**
- **Gram-negative bacillus**
- **Mechanism**: Acts by means of pili, endo-, and exotoxins. Also has flagellar (H) antigen, capsular (K) antigen, and O antigen (LPS).
- **Diarrhea**:
  1. Traveler’s diarrhea (“Montezuma’s revenge”), a severe diarrhea causing dehydration. Treatment: Ciprofloxacin or SMX/TMP. Prophylaxis: Norfloxacin.
  2. *Enterotoxigenic E. coli*: It causes watery diarrhea
  3. Enterohemorrhagic *E. coli* (*E. coli 0157-H7*): Bloody diarrhea due to hemorrhagic colitis, caused by *Shiga-like toxin*, also called *verotoxin*. Complication: Hemolytic uremic syndrome (HUS) *(see Chapter 10, Pathophysiology)*.
  4. *Enteroinvasive E. coli*: Bloody diarrhea high in WBC content
- **UTI**: *E. coli* is the most common cause of UTI in sexually active women. Treatment: Ciprofloxacin or SMX/TMP

**Salmonella**
- A motile *H₂S*-releasing bacterium, with *Vi antigen*
- **Source**: Food or water contaminated with animal feces. A famous source is *undercooked eggs*. *Salmonella typhi* is carried only by humans in the gallbladder; it is not carried by animals.
- S. typhi: A facultative intracellular organism, causing *typhoid* (*enteric*) fever, where patient presents with *stepladder fever*, *rosy spots on the abdomen*, and right lower quadrant (RLQ) abdominal pain often confused with appendicitis. Treatment: ciprofloxacin or ceftriaxone.
- S. cholera-suis: Causes bacteremia, which targets lungs, liver, or even the brain
- S. enteritidis: Causes mucous or watery diarrhea. Treatment: Self-resolving. *Antibiotics will prolong bacterial shedding*.

**Pseudomonas aeruginosa**
- **Gram-negative bacillus**, which produces green pigment (*fluorescin*) and blue pigment (*pyocyanin*) and *exotoxin A*
- **Mechanism**: Exotoxin A functions just like diphtheria’s toxin (*inhibits EF2*)
- **Clinical picture**:
  1. Pneumonia: Mainly in immunocompromised and *cystic fibrosis patients*
  2. Endocarditis: Mainly in *IV drug abusers*, targeting the *tricuspid valve*. However, *S. aureus* is still the most common cause of acute bacterial endocarditis in *IV drug abusers*.
  3. Skin ulcers and osteomyelitis: Mainly in *diabetics* and *IV drug abusers*
  4. Corneal infections: Mainly in patients using contact lenses

**Meningitis**: The second most common cause of neonatal meningitis.

**Klebsiella pneumoniae**
- **Gram-negative bacillus**
- **Mechanism**: It has no *Flagella*, hence no flagellar (H) antigen.
- **Clinical picture**:
  1. Apical (*Friedlander*) pneumonia: *Red current jelly sputum*
  2. Sepsis and UTI
- **Treatment**: *Third-generation cephalosporin*
5. Malignant otitis externa, swimmer’s ear, and hot-tub folliculitis

- **Treatment:** Anti-Pseudomonas penicillin, e.g., carbenicillin, ticarcillin, or piperacillin.

**Vibrio cholera**
- Gram-negative, short, curved, fast-darting bacilli
- **Mechanism:** Cholera toxin (choleragen) acts by ribosylation of adenyl cyclase via activating Gs protein.
- **Clinical picture:** Rice water diarrhea
- **Treatment:**
  1. Supportive for dehydration and electrolyte imbalance
  2. Doxycycline: It only shortens the duration of illness.

**Notes:**
1. *Vibrio parahaemolyticus:* Fever, abdominal colic, and watery diarrhea in a healthy person, 12–48 hours after ingestion of a seafood meal. Treatment: Supportive.
2. *Vibrio vulnificus:* Fever, abdominal colic, watery diarrhea and vesiculobullous skin eruption in a patient with chronic liver disease, 12–48 hours after ingestion of a seafood meal. Treatment: Doxycycline or tetracycline.

**Miscellaneous Enterics**
- *Proteus mirabilis:* Three strains exist, with cross-reacting antigens, namely OX-2, OX-19, and OX-K. This bacterium can split urea to produce ammonia, which leads to UTI with alkaline urine. Association: Magnesium-ammonium-phosphate (MAP) (struvite) nephrolithiasis.
- *Helicobacter pylori:* A urea-splitting, gram-negative bacillus. A common cause of duodenal ulcers. Diagnosis: Clo test (A medium changes its color when urease from H. Pylori converts urea to ammonia), urease breath test, and checking for stool antigens. Treatment:
  1. *Amoxicillin + clarithromycin + proton pump inhibitor for 2 weeks*
  2. If allergic to penicillin: *Metronidazole + tetracycline + bismuth for 2 weeks*
- *Enterobacter:* It is a normal GI tract flora.
- *Serratia:* An enteric that produces bright red pigment.
- *Shigella:* A pathogen transmitted by contaminated hands and water. Releases verotoxin, which causes bloody diarrhea; rich in WBC count.
- *Campylobacter jejuni:* It causes bloody loose diarrhea. Treatment: Erythromycin. Association: Guillain-Barré syndrome.
- *Yersinia enterocolitica:* Causes appendicitis-like pain, mucosal ulceration, and diarrhea. Mechanism: Release of enterotoxins and direct intestinal cells invasion.
- *Bacteroides fragilis:* An intestinal flora that causes abscesses
- *Bacteroides melaninogenicus:* Releases a black pigment, and is famous for causing necrotizing pneumonia and periodontal diseases

**Haemophilus influenzae**
- Polymorphic gram-negative bacillus
- **Requirements:** nicotinamide adenine dinucleotide (NAD) and hematin of blood (factors V and X)
- **Classification:** It is classified according to the type of capsule from A to F.
- **Clinical picture:** *H. influenza B* (HiB) is the most pathogenic type and it causes the following:
  1. **Meningitis:** Common in children between 6 months and 3 years of age. Antibiotics cause lysis of bacteria and release of antigens, inducing an immune reaction. This could be prevented by giving steroids 15 minutes prior to starting the antibiotics.
  2. **Epiglottitis:** Fever, hyperextended neck (dog-sniffing position), copious drooling of saliva and stridor. Do not attempt to examine pharynx (might cause laryngeal spasm). Diagnosis: Neck x-ray shows swollen epiglottis, also called thumbs-up sign. Examine airway in the operation room using a direct laryngoscope, to visualize the swollen cherry red epiglottis.
  3. **Septic arthritis:** Mostly in children and usually affects a single joint
- **Prevention:** HiB capsule vaccine (2, 4, 6, and 12 months) given in combination with DPT. The mechanism depends on stimulation of the T cells by the diphtheria toxin against the HiB capsule.
- **Treatment:** Third-generation cephalosporins (cefotaxime or ceftriaxone). HiB is resistant to penicillin.

**Haemophilus ducreyi**
- Gram-negative bacillus
- **Clinical picture:** A painful ulcer known as chancroid, which differs from chancre by being painful, and associated with painful lymphadenopathy
- **Treatment:** Erythromycin or SMX/TMP
**Haemophilus (Gardnerella) vaginalis**
- Also called bacterial vaginosis (BV); a gram-negative bacillus
- Clinical picture: Vulvar itching and vaginal whitish discharge with a fishy odor
- Diagnosis:
  1. Whiff test: Adding KOH increases intensity of fishy odor
  2. Clue cells, which are squamous cells with smudged borders.
  3. Vaginal pH > 4.5
- Treatment: Metronidazole

**Legionella pneumophila**
- Gram-negative bacillus
- Source: Shower heads and air conditioners
- Clinical picture:
  1. Pontiac fever: Fever and headache that resolve in a week
  2. Legionnaire pneumonia: Atypical pneumonia, where the x-ray looks much worse than how the patient presents; usually associated with diarrhea and altered mental status
- Diagnosis:
  1. Direct immunofluorescent testing (DIF): Test of choice
  2. Culture: Grows on charcoal agar, rich in iron and cysteine
  3. Legionella antigens in the urine
- Treatment: Erythromycin

**Bordetella pertussis**
- Gram-negative bacillus
- Virulence factors:
  1. Bordetella toxin: Activates cyclic adenosine monophosphate (cAMP) through ADP ribosylation, by inhibiting G protein. This stimulates the release of histamine and insulin, and inhibits phagocytosis.
  2. Adenyl cyclase granules, tracheal cytotoxin, and filamentous hemagglutinin
- Clinical picture:
  1. Catarrhal phase (1–2 weeks): Fever, cough, and expectoration
  2. Paroxysmal phase (4–8 weeks): Paroxysms of cough followed by inspiratory whoop. The pathognomonic feature is vomiting immediately following these paroxysms.
  3. Convalescent phase (months): Mild cough that resolves gradually
- Complication:
  1. Bronchopneumonia: It is the most common complication.
  2. Bronchiectasis: It is the second most common; however, it is very specific.
- Diagnosis: Unique presentation, plus:
  1. Leukocytosis: Namely atypical lymphocytosis
  2. Sputum culture: Bordetella pertussis grows on Bordet Gengou agar
  3. Normal erythrocyte sedimentation rate (ESR)
- Treatment: Erythromycin for 14 days
- Notes:
  1. There is no transplacental immunity against pertussis. Immunity against pertussis is only cell mediated, while the transplacental immunity is humoral.
  2. There is no postinfectious immunity against pertussis.
  3. B. pertussis and C. diphtheria are both extracellular organisms releasing exotoxins.

**Facultative Intracellular Organisms**
- **Yersinia pestis (plague)**
  1. Virulence factors: F1 (antiphagocytic), V and W antigens
  2. Transmitted from rats via flea bites
  3. Clinical picture:
     1. Bubonic plague: Inguinal lymphadenopathy and subcutaneous bleeding
     2. Pneumonic plague: Pneumonia
     3. Septicemic plague: Septicemia
  4. Prevention: Isolation of rats, and DDT for fleas
  5. Note: *Y. pestis’s ends stain darker than its center.*
- **Francisella tularensis (tularemia)**
  1. Transmitted by rabbits and ticks
  2. Clinical picture: Black ulcerating nodule in the skin with enlarged lymph nodes (L.N), plus fever and chills of sudden onset
- **Brucellosis:** Undulant fever (peaks up only at night) and noncaseating granulomas in the liver, due to ingestion or contact with infected meat or milk products
- **Treatment of facultative intracellular organisms:** Aminoglycosides or doxycycline
Chlamydia

• Gram-negative, intracellular organism with ATP/ADP translocator
• Chlamydia cycle:
  1. Elementary body (infectious stage) is endocytosed inside the infected cell to be converted into an initial reticulate body.
  2. Reticulate body then divides into multiple reticulate bodies.
  3. The reticulate bodies undergo a process of conversion into multiple elementary bodies.
  4. Elementary bodies leave the cell to infect other cells.
• Types and clinical picture:
  1. A, B, C: Trachoma: Scarring and traction of eyelid inwards, which leads to irritation of the conjunctiva by the rubbing lashes, and eventually chronic conjunctivitis.
  2. L1, L2, L3: Lymphogranuloma venereum: Genital ulcers, lymphadenitis, lymphangitis, and proctocolitis
  3. D-K:
     • Urethritis: Chlamydia is the most common sexually transmitted disease.
     • Inclusion conjunctivitis: In newborns 3–4 days after birth. Prophylactic erythromycin eyedrops just after birth is now a standard of care.
     • Reiter syndrome: Conjunctivitis, urethritis, and circinate ulcer on glans penis, and big joint migrating arthritis. Associations: Plantar fasciitis, Achilles tendonitis, aortic regurgitation, and lung fibrosis.
     • Fitz-Hugh–Curtis syndrome
     • Infant and atypical pneumonia
• Treatment: Drug of choice is azithromycin
• Notes:
  1. Chlamydia pneumoniae is cultured on HeLa cells of sputum.
  2. Chlamydia Taiwan acute respiratory agent (TWAR) pneumoniae causes mild pneumonia plus cardiac diseases.
  3. Chlamydia psittaci is transmitted from birds, and causes atypical pneumonia as a part of systemic disease, also called psittacosis.

Rickettsia

• Gram-negative, intracellular organism with ATP/ADP translocator
• Characteristics: Same antigens as Proteus mirabilis (OX-2, OX-19, OX-K), which can be distinguished and diagnosed by Weil-Felix test.
• Clinical picture:
  1. Rocky Mountain spotted fever: Caused by Rickettsia rickettsii, transmitted by ticks (Dermacentor). Clinical picture: Fever, and petechial rash that starts in the palms and soles and creeps toward the trunk
  2. Epidemic typhus: Caused by Rickettsia prowazekii, transmitted by ticks. Clinical picture: Fever, and rash that involves the whole body except palms and soles
  3. Endemic typhus: Caused by Rickettsia typhi, transmitted by rats. Clinical picture: Fever, and rash that starts on the fifth day of fever.
  4. Q fever: Caused by Coxiella burnetii, transmitted through contact with animals and animal products. Clinical picture: Fever and pneumonia, due to inhalation of endospores. It is the only rickettsia that does not cause rash.
  5. Bartonella henselae: Causes cat-scratch disease. Clinical picture: Cat scratch, followed by fever, rash, and swollen tender postural lymphadenopathy. Complication: Bacillary angiomatosis, which is proliferation of blood vessels, common in AIDS patients.
  6. Ehrlichia canis: From dog licks, causing fever and rash. Peripheral smear shows numerous morulae inside the monocytes.
• Diagnosis: Complement fixation test (CFT)
• Treatment: Doxycycline plus chloramphenicol.

Treponema pallidum

• A gram-negative organism, also called spirochete
• Incubation period: 6 weeks
• Clinical picture: Syphilis. Congenital syphilis transmits to fetus after the 4th month of gestation.
• At birth:
  1. Atrophied dried nasal mucosa (snuffles)
  2. Hepatosplenomegaly
  3. Maculopapular rash and severe periostitis
• Childhood form: Characterized by multiple pathognomonic findings:
  1. Ear, nose, and throat (ENT): Saddle nose (destroyed nasal bridge), Hutchinson teeth (separated and notched upper central incisors), Mulberry molars (molars with too many cusps), and rhagades.
2. Bone: Sabre shins (inflamed bowed tibiae), Clutton joints (painless effusion), and destruction of medial proximal tibial metaphysis (Wimberger sign)

Adulthood Syphilis

- Primary (6 weeks): Characterized by painless chancre and painless lymphadenopathy. Chancre is a well-demarcated ulcer with indurated base, and it resolves spontaneously without scar formation.
- Secondary:
  1. Rash: All forms except vesicular, i.e., macular, papular, pustular, mixed, but never vesicular. Rash is more prominent in palms and soles.
  2. Condyloma lata: Wart-like lesions on moist surfaces. They are highly contagious lesions.
- Latent: 25% of patients have relapse during that period
- Tertiary:
  1. Gummas: They occur in skin (painless) or bones (painful).
  2. CVS: Injury to Vasa vasora, of aorta, leading to aortic aneurysm and aortic dissection. Also causes coronary obstruction and aortic regurgitation.
  3. Neurosyphilis:
     - Multiple forms ranging from asymptomatic, to meningitis or even infarction
     - *Tabes dorsalis*: As explained in Chapter 3, Neuroanatomy, it targets the dorsal column (causing ataxia), and dorsal roots (causing loss of reflexes, pain, and temperature sensation)
     - General paresis of insane: Aphasias, confusion, and seizures
     - *Argyll-Robertson pupil*: Pupil that accommodates but never reacts to light

Diagnosis:

1. Darkfield microscopy: Corkscrew movement
2. Serology: Veneral Disease Research Laboratory (VDRL) test, rapid plasma reagent (RPR), Treponema pallidum immobilization (TPI) test, or the most specific test, which is the fluorescent treponemal antibody test (FTA)

Treatment: Penicillin is the drug of choice for all patients, as follows:

1. Congenital syphilis: Benzathine penicillin G for 10 days
2. Primary, secondary, and early latent syphilis: Benzathine penicillin G 2.4 million units, only once
3. Late latent syphilis: Benzathine penicillin G 2.4 million units weekly for 3 weeks
4. Neurosyphilis: Procaine penicillin G 2.4 million units daily + probenecid for 14 days

Notes:

1. Patients with penicillin allergy must undergo penicillin desensitization.
2. Jarisch-Herxheimer’s reaction: A few days after starting treatment, patients develop sudden spike in temperature and worsening symptoms. This occurs due to release of pyrogenes from killed bacteria. Treatment: Supportive, and continue treatment.
3. Indication of cure from syphilis: Fourfold decrease in titers
4. *Treponema endemicum*: Causes endemic syphilis, contracted from shared utensils
5. *Treponema pertenue*: Causes yaws, which is disfiguring facial ulcers
6. *Treponema carateum*: Causes pinta, which is colored skin lesions

*Borrelia burgdorferi*

- A gram-negative organism, also called a spirochete, causing Lyme disease
- Transmission: Ixodes tick
- Clinical picture:
  1. Stage 1: *Erythema chronicum migrans* (ECM). It is a ring-shaped lesion with central clearing (Fig. 7.1).
  2. Stage 2:
     - Arthralgias and arthritis
     - CVS injury, e.g., myocarditis, AV block
     - CNS injury, e.g., meningitis, bilateral Bell’s palsy
  3. Stage 3: Chronic arthritis and encephalopathy

Prevention: Vaccination, e.g., Lymerix or Immulyme, before going to infested areas, i.e., northeast, midwest, and West Coast

Diagnosis: Clinical, as antibodies against *Borrelia burgdorferi* cross-react with other organisms

Treatment:

1. Less than 8 years of age: *Oral amoxicillin for 21 days*
2. 8 years of age or older: *Oral doxycycline for 21 days*
3. If CNS or CVS injury: *Parenteral ceftriaxone or penicillin G* for 21 days

   - Note: Do not confuse this with *Borrelia recurrentis*, another spirochete transmitted by ticks and body lice. *Clinical picture*: Relapsing fever. *Diagnosis*: Darkfield microscopy after staining with Wright or Giemsa stain. *Treatment*: Erythromycin or tetracycline.

**Leptospira interrogans**

- A gram-negative organism, also called a spirochete, causing *leptospirosis*
- *Transmission*: Swimming in water contaminated with urine of infected animals
- *Clinical picture*:
  1. *Early stage*: Fever, headache, conjunctivitis, and photophobia
  2. *Late stage*: Meningitis, muscle aches, and rash
  - **Complication**: *Weil disease*: Vasculitis, jaundice, renal failure, and rash
  - **Treatment**: Penicillin

**Mycobacterium leprae**

- An *acid-fast* bacterium, stains red, lives in cold temperature, and causes leprosy (Hansen’s disease)
- *Reservoir*: Armadillo
- *Clinical picture*: Table 7.2 lists types and presentation
- *Diagnosis*: Biopsy of skin or nerve lesions shows acid-fast bacilli. This bacterium cannot be cultured on artificial media.
- *Treatment*: Rifampicin, dapsone, and clofazimine.
  - Note that clofazimine can cause erythema nodosum leprosum, which is treated with thalidomide.
  - Note: Leprosy can cause chronic pneumonitis.

### Table 7.2 Types and clinical picture of leprosy.

|                          | Lepromatous leprosy | Tuberculoid leprosy |
|--------------------------|---------------------|---------------------|
| **Skin and mucous membranes** | Leonine faces: thick skin, saddle nose, no eyebrows | Hypopigmented painless skin lesions, with loss of sensations |
|                          | Nasal mucous membrane involvement, e.g., rhinitis | No mucous membrane involvement |
| **Eyes**                 | Keratitis and iridocyclitis | Unaffected |
| **Testes**               | Atrophy              | Unaffected |
| **Peripheral nerves**    | Late and bilateral  | Early and unilateral |
| **Lepromin test**        | Negative (cell-mediated immunity is destroyed) | Positive (cell-mediated immunity is intact) |
| **Prognosis**            | Bad (contagious)     | Good (not contagious) |
Notes on other acid-fast bacteria:
1. *Mycobacterium tuberculosis*: Causes tuberculosis
2. *Mycobacterium avium* complex (MAC): Causes severe systemic illness in AIDS patients (see below)
3. *Mycobacterium scrofulaceum*: Causes cervical lymphadenopathy in children
4. All acid-fast bacteria have cord factor, which inhibits WBC migration.

**Mycoplasma**
- The only bacteria without a cell wall. It is a very small bacterium, and is covered by a cytoplasmic membrane rich in sterols
- Mycoplasma grows on Eaton agar.
- Types and clinical picture:
  1. *Mycoplasma pneumoniae*
     - Clinical picture: *Atypical pneumonia* (chest x-ray [CXR] looks much worse than the patient’s presentation, along with diarrhea and altered mental status)
     - CXR shows streaky infiltrate.
     - Diagnosis: High serum IgM levels against Mycoplasma
     - Treatment: *Erythromycin* (penicillin-resistant because of absent cell wall)
  2. *Ureaplasma urealyticum* (*T. mycoplasma*)
     - Mechanism: Lyses urea into ammonia and CO₂ (remember Proteus?)
     - Clinical picture: *UTI with alkaline urine*, and magnesium ammonium phosphate (*struvite*) nephrolithiasis.
     - Treatment: *Erythromycin*
   - Note: Autoimmune hemolytic anemia is common with mycoplasma infections.

**Pasteurella multocida**
- Source: Cat and dog bites
- Management: Clean the wound (*do not stitch it tight*) + antibiotics, e.g., penicillin

**Viruses**
- Similarly to bacteria, all viruses are haploid. The only exception is retroviruses.
- The genetic material of viruses is either DNA or RNA (never both).
  1. All DNA viruses are double stranded (ds-DNA), except *parvovirus*.
  2. All RNA viruses are single stranded (ss-RNA), except *reoviruses*, e.g., *rotavirus*.
- Viruses with positive-strand RNA may form proteins.
- Viruses with a negative-strand RNA must convert it first into a positive strand using *RNA polymerase*, then protein synthesis may occur.
- Viruses with DNA undergo *transcription* to positive strand RNA, then protein synthesis.

**Orthomyxovirus**
- Single-stranded (ss) *negative RNA* virus with an envelope
- Characteristics: Two proteins: neuraminidase (NA) and hemagglutinin (HA). They both get attached to cells by means of the M protein to carry on the following missions:
  1. *NA destroys the host cell's mucin.*
  2. *HA attacks the sialic acid of RBCs.*
- *Influenza*: Orthomyxovirus with three serotypes (A, B, C). Influenza A infects humans, causing the flu (fever, rhinitis, tracheobronchitis).
- *Antigenic drift*: During replication, *minor changes* in the antigenic structure of NA and HA of influenza virus takes place. This allows the virus to escape a sensitized host’s immune system.
- *Antigenic shift*: Major viral genome rearrangement, leading to a *major change* in NA and HA, causing worldwide pandemics. Common with influenza *A*.
- Treatment:
  1. *Amantadine* (mechanism: inhibits uncoating of influenza A)
  2. *Zanamivir*: Inhibits neuraminidase; used for both influenza A and B
   - Note: Influenza virus is cultured on monkey kidney cells agar.

**Paramyxovirus**
- Single-stranded negative RNA virus, without an envelope
- Characteristics: *Fusion proteins*, allowing infected cells to fuse forming giant cells
- *Parainfluenza*
  1. Clinical picture: Croup (laryngotracheobronchitis) in children, manifested by hoarseness of voice, retrosternal soreness, a pathognomonic barking cough, fever, and stridor
  2. Diagnosis: X-ray of the neck; showing subglottic narrowing (*steeple sign*), (Fig. 7.2)
  3. Treatment: Racemic epinephrine inhalation
**Respiratory syncytial virus (RSV)**

1. **Clinical picture:** Bronchiolitis in children (4–18 months of age), who present with cough, expectoration, lung wheezes, and crackles
2. **CXR:** Hyperinflated chest
3. **Treatment:** Ribavirin

**Measles**

1. **Clinical picture:** Starts with cough, coryza, conjunctivitis (CCC), and Koplik spots (red lesions with white/blue center on buccal mucosa), followed by a rash
2. **Rash:** Maculopapular and confluent, starts behind the ears and descend downwards. It heals with branny desquamation also from the top downward.
3. **Complications:**
   - Most common: Pneumonia. Early due to measles, or late due to secondary bacterial infection
   - Most specific: Subacute sclerosing panencephalitis (SSPE)
4. **Note:** Measles is a predisposing factor for vitamin A deficiency

**Mumps**

1. **Clinical picture:** Swollen salivary glands, mainly the parotids
2. **Complications:**
   - Most common: Pancreatitis
   - Most dangerous: Endocardial fibroelastosis
   - Orchitis: Might cause testicular atrophy
   - Sensorineural hearing loss

**Human Immunodeficiency Virus (HIV)**

- **Enveloped ds-RNA virus** with multiple functional enzymes including reverse transcriptase, protease, and integrase
- The outer shell is formed of capsid protein, gp41 and gp120 capsid proteins, and p24 (early marker)
- Reverse transcriptase (RNA-dependent DNA polymerase) converts the virus’s RNA to DNA
- **HIV genome:** It has long terminal repeat sequences (LTRs) which include:
  1. Sticky ends: Recognized by integrase
  2. Promotor/enhancer region: DNA transcription
  3. gag (group antigens): Code for viral antigenic proteins
  4. pol (protease, integrase, and reverse transcriptase): Protease is the agent that makes HIV contagious.
  5. tat (transactivator): Activates transcription
  6. env (envelope proteins)

- **Transmission:** Infection is mainly through blood or sexual intercourse; more in females and those who engage in anal intercourse
- **Pathology:** HIV targets the following cells:
  1. T lymphocytes: Mainly CD4. If CD4 count drops below 200, the patient requires treatment, even if he does not have any obvious infection.
  2. B lymphocytes: This can trigger other immunologic disease.
  3. Monocytes and macrophages: They act as reservoir for the virus. They can also transport it to the CNS, causing aseptic meningitis and neuropathy.

- **Clinical picture**
  1. Initial viremia followed by a latent period of 5–10 years
  2. AIDS-related complex (ARC): Weight loss, fever, and night sweats

- **Diagnosis:**
  1. Positive enzyme-linked immunosorbent assay (ELISA) test is the first step.
  2. If positive, confirm diagnosis by doing Western blot test.
• **Follow-up:** Best done through the viral RNA load, and CD4 count. They are used for prognostic purposes, early detection of progression of HIV to AIDS, and to assess response to treatment.

• **Complications:**
  1. Kaposi sarcoma (**PURPLE skin nodules**): By *human herpes virus-8 (HHV-8)*. Kaposi sarcoma occurs due to vascular proliferation and hemosiderin deposition.
  2. Oral hairy leukoplaikia: By *Epstein-Barr virus (EBV)*. Can be seen on the lateral borders of the tongue.
  3. Chorioretinitis: By *cytomegalovirus (CMV)*
  4. Esophagitis: By *Candida albicans*
  5. Diarrhea: By *Cryptosporidium parvum*. Treatment: *Azithromycin*.
  6. Meningitis: By *Cryptococcus neoformans*
  7. Seizures: By *Toxoplasma gondii*. They have diffuse intracranial calcifications, and contrast enhancing mass. Treatment: *Sulfadiazine + pyrimethamine*. Drug of choice to treat toxoplasmosis during pregnancy is *spiramycin*.
  8. Leukemia: *Human T-cell leukemia virus 1 (HTLV-1)* causes hairy cell leukemia, while *HTLV-2* causes T-cell leukemia.
  9. Pneumonia:
     - *Pneumocystis jiroveci (formerly P. carinii, which caused P. carinii pneumonia [PCP]).* Suspect when CD4 count is less than 200.

**Diagnosis:** Bronchoalveolar lavage or lung biopsy. **Culture:** Does not grow in vitro, but stains with methenamine silver. **Treatment:** SMX/TMP and/or pentamidine.

• **Mycobacterium-avium Complex (MAC):** An acid-fast bacillus. Suspect when CD4 count is less than 100. **Clinical picture:** Pneumonia. **Diagnosis:** Lung biopsy. **Treatment:** Clarithromycin, ethambutol, and rifabutin.

• **Treatment of HIV:** Discussed in Chapter 9, Pharmacology.

• **Notes:**
  1. Prophylaxis against HIV after a contaminated needle stick injury is a 1-month course of *LIZ* (*Lamivudine, Indinavir, Zidovudine*). The main factor deciding the probability of transmission is the depth of the injury.
  2. Risk of maternofetal transmission of HIV is significantly reduced by treating the mother during pregnancy with *zidovudine*.

## Hepatitis Viruses

- These viruses cause inflammation of the hepatic tissue.
- **Causes:** Hepatitis viruses A, B, C, D, E, F, G, CMV, EBV, alcohol
- Table 7.3 lists hepatitis A, B, and C viruses. Note that hepatitis D and E are weak viruses. Hepatitis D can cause superinfection in a patient *already* infected with hepatitis B.

### Table 7.3 Hepatitis A, B, and C.

| Type | Hepatitis A (HA) | Hepatitis B (HB) | Hepatitis C (HC) |
|------|-----------------|-----------------|-----------------|
| Incubation period | RNA picornavirus 2–6 weeks | DNA hepadnavirus 2–6 months | RNA flavivirus Variable |
| Transmission | Feco-orally | Parenterally | Parenterally |
| Carrier state | No | Yes | Yes |
| Chronicity | No | Yes | Yes |
| Malignancy | No | Yes | Yes |
| Serology | • HA IgM: recent infection | • HBs antigen: active infection | • HC antibodies: not measurable in the serum consistently, even during an active infection |
| | • HA IgG: old infection | • HBs antibodies: old infection or vaccination (patient is immune) | • Polymerase chain reaction (PCR): the best measure to detect hepatitis C |
| Prevention | • Vaccine available | • Vaccine (inactivated HBs antigens) is available (given at 0, 1, and 6 months) | No vaccine or immunoglobulin |
| | • Immunoglobulin can be given within 72 hours after exposure | • Immunoglobulin can be given within 7 days after exposure | |
infected with hepatitis B. Hepatitis E can cause fulminant infection only during pregnancy.

- **Clinical picture:**
  1. Fever, headache, and generalized fatigue
  2. Right upper quadrant pain: Mild tender hepatomegaly on exam
  3. Jaundice: Best seen in sclera and palate. Sclera stays jaundiced for a while after disease resolution, the reason being the high affinity of collagen fibers of the sclera to bilirubin.

- **Complications:**
  1. Chronicity, fulminance, or relapse
  2. Immune mediated due to hepatitis B surface (HBs) antigens: Glomerulonephritis and vasculitis. e.g., polyarteritis nodosa

- **Pathology:** Lymphocytic infiltration of the liver (centrizonal and portal tract)

- **Treatment:**
  1. Hepatitis A: Supportive and bed rest
  2. Hepatitis B: Interferon and lamivudine
  3. Hepatitis C: Interferon and ribavirin

- **Notes on treatment:**
  1. Interferon acts by inhibiting the transcription and translation of the virus. Side effects: Flu-like symptoms and immune disorders, e.g., thyroiditis, bone marrow depression, hemolytic anemia, and Guillain-Barré syndrome.
  2. Sudden rise of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) after starting treatment is a sign of successful therapy. This occurs due to destruction of the virally infected hepatocytes. (Doesn't that remind you of the Jarisch-Herxheimer reaction?)

- **Other forms of hepatitis:**
  1. Chronic active hepatitis: Pathology shows piecemeal and bridging necrosis, and rosette formation in the hepatocytes
  2. Autoimmune hepatitis: Diagnosed by positive ANA and anti-smooth muscle antibodies. Treatment: Steroids; if they fail, add azathioprine.
  3. Alcoholic hepatitis: Pathology shows perivenular ballooning and necrosis along with Mallory bodies. Labs shows AST/ALT ratio of more than 2, elevated IgA, and elevated gamma-glutamyltransferase (GGT).
  4. Acute fatty liver of pregnancy: Severe hepatitis and liver failure during pregnancy, could be caused by hepatitis E virus infection

  5. Cholestasis of pregnancy: Benign condition presenting with pruritus during the third trimester and it resolves spontaneously after delivery. There is high alkaline phosphatase and direct bilirubin.
  6. HELLP: A pregnancy-associated disease. H: Microangiopathic hemolysis. EL: Elevated liver enzymes. LP: Low platelets.

### Herpes Viruses

- It migrates up the nerves to establish a latent infection in the sensory ganglia.
- It has a cytopathic effect.

- **Types and clinical picture:**
  1. **Herpes simplex virus**
     - Type I: Keratitis (branching dendritic ulcer), and gingivostomatitis
     - Type II: Painful genital vesicles, itching, discharge, and dysuria
  2. **Varicella zoster virus**
     - Initial infection: Chicken pox: multiple crops of lesions, in all stages of development, all at the same time, i.e., macules, papules, pustules, vesicles, crusted, and healing lesions
     - Latent stage: Virus dormant in the sensory ganglia and dorsal roots
     - Shingles: Painful vesicular rash following a dermatomal distribution (Fig. 7.3). Reactivation of the virus to cause shingles is common in immunocompromised patients, e.g., diabetes mellitus (DM), malignancy, on chemotherapy.

**Fig. 7.3 Shingles**
• Diagnosis: Tzanck smear showing intranuclear inclusions (Cowdry A bodies) and multinucleated giant cells

• Treatment: It is helpful only if used within the first 48 hours of rash onset. Treatment does not cure the disease; it only shortens duration of the rash, and decreases risk of complications, e.g., postherpetic neuralgia

  1. Herpes simplex: Acyclovir
  2. Varicella zoster: Famciclovir

• Note:
  1. Acyclovir may cause reversible renal toxicity, due to crystalluria. Accordingly, you must advise your patient to increase fluid intake while taking acyclovir.
  2. Exposure to sunlight and major emotional disturbance may lead to multiple herpes recurrences.
  3. Herpetic lesions ulcerate easily, giving an easy access to more potent infections, e.g., HIV.

Human Herpes Virus-6 (HHV-6)

• It causes Roseola infantum (Exanthem subitum).

• Clinical picture: High-grade fever, followed by rash on the trunk, which spreads outward to the extremities as it fades away.

• Note: Do not confuse this with Erythema infectiosum (fifth disease) caused by parvovirus B19, where the patient presents with a slapped-cheeks appearance and maculopapular rash that starts on the arms and spreads to the trunk and lower extremities. Complication: Aplastic anemia.

Epstein-Barr Virus (EBV)

• It targets B lymphocytes, causing Burkitt’s lymphoma, nasopharyngeal carcinoma, and infectious mononucleosis (IM). IM is discussed in detail below.

• Transmission: Mostly through saliva, hence the name kissing disease

• Clinical picture: Fever, chills, fatigue, sore throat due to pharyngitis, and abdominal pain due to splenomegaly

• On exam:
  1. Petechiae on hard and soft palate
  2. Multiple enlarged and tender cervical lymphadenopathy
  3. Splenomegaly: Lower edge is felt just below the costal margin

• CBC: Atypical lymphocytosis, and anemia due to antibodies against the Li antigen of RBCs

• Diagnosis: Monospot test: Positive heterophil antibodies against sheep RBCs

• Contraindication: Penicillin causes rash in these patients

• Complication: Splenic rupture. So when you see a patient on the USMLE with features of mononucleosis who engages in wrestling, and then comes to the emergency room with excruciating abdominal pain, you know what to think!

• Treatment: Self-resolving

• Note: Cytomegalovirus (CMV) is an important virus, so try to remember:
  1. It lives in the buffy coat of WBCs.
  2. It causes cytomegaly (swollen cells).
  3. Clinical picture: Asymptomatic or infectious mononucleosis, chorioretinitis in AIDS patients, and pneumonitis after bone marrow transplantation.
  4. Treatment: Ganciclovir. If patient is ganciclovir-resistant, use foscarnet.

Rabies

• A rhabdovirus that replicates locally in a wound, and may travel up neuronal axons into the CNS to cause encephalitis

• Source: Multiple, most famous are dogs, cats, bats, and raccoons

• Pathology: Brain tissue shows virions, also called Negri bodies

• Clinical picture: Fever, headache, and hydrophobia due to pharyngeal muscles spasm. This may lead to foaming at the mouth, a classic symptom of rabies.

• Treatment: Immunoglobulins and active immunization, using five injections of a killed virus vaccine

• Note: Washing the wound with soap and water dissolves the lipid envelope of the virus, which leads to prolongation of its incubation period.

Other Viruses

• Rubella (German measles; 3-day measles): Just like measles, it starts with cough, coryza, and conjunctivitis. The key differences are:
  1. Measles is characterized by Koplik spots, while rubella is characterized by posterior auricular and posterior cervical lymphadenopathy.
2. Rash of measles is confluent, while that of rubella is not.

- **Coxsackie virus:** Two types:
  1. **Coxsackie A:** Causes the following:
     - Painful mouth and pharynx vesicles, fever, and sore throat, also called herpangina. If these lesions spread to involve the hands and feet, it is known as hand-foot-mouth syndrome.
     - Acute hemorrhagic conjunctivitis.
  2. **Coxsackie B:** Causes pleurisy, myocarditis (Coxsackie B4), and pericarditis.

- **Poxvirus:** Replicates in the cytoplasm. Clinical picture: Small pox and molluscum contagiosum. The latter are umbilicated, pearly white, hemispherical papules (Fig. 7.4).
- **Papilloma virus:** It causes warts. HPV strains 16, 18, and 31 may cause cervical cancer.
- **Adenovirus:** Cause rhinitis, sinusitis, and conjunctivitis. It is commonly transmitted by swimming pool water in the summer months.
- **Rhinovirus and coronavirus:** Cause common cold (rhinitis, conjunctivitis, and fatigue). Transmitted mainly by fomites.
- **Rotavirus:** Double-stranded RNA virus with double capsid. It is the most common cause of diarrhea in children. Rotavirus cannot be cultured from the stools.
- **Hantavirus:** It causes fever, hemorrhage, and renal failure. Source: Rats. Treatment: Ribavirin.
- **Yellow fever virus:** It causes fever, hepatitis, and jaundice.

- **Poliovirus:** Causes poliomyelitis. Discussed in Chapter 3, Neuroanatomy.

**Fungi**

- The cell membrane of fungi is rich in ergosterol, and is surrounded by a capsule.
- Antifungal medications are discussed in detail in Chapter 9, Pharmacology.

**Tinea Capitis (Fig. 7.5)**

- **Ringworm of the scalp**
- **Cause:** Dermatophyte, microsporum, or trichophyton
- **Clinical picture:** Lesions are well circumscribed, usually multiple in the scalp, oval in shape, of variable sizes, and contain hair stumps. Lesions heal without scar formation.
- **Treatment:** Oral antifungal, such as terbinafine, itraconazole, or griseofulvin for 4–6 weeks
- **Notes:**
  1. Kerion: A subtype of tinea capitis infection. Clinical picture: A painful swelling on the scalp with pustular discharge, often confused with an abscess. Treatment: No incision and drainage is needed, antifungals usually suffice.
  2. Favus: A subtype of tinea capitis infection. Clinical picture: Saucer-shaped, crusty yellow lesions in the scalp, known as scatula. Unlike usual tinea infections, this one heals with a scar, and could cause alopecia.

**Tinea Corporis (Fig. 7.6)**

- **Ringworm of the trunk**
- **Cause:** Dermatophyte, microsporum, or trichophyton
- **Clinical picture:** Lesions are oval or rounded, with red elevated circinate margins and central clearing, hence called tinea circinata.
- **Treatment:** Local antifungal, plus oral antifungal for 3 weeks in severe cases

**Tinea Cruris**

- **Jock itch**
- **Location of lesions:** Groin and buttocks area
- **Clinical picture:** Lesions are bilateral and symmetrical, reddish with raised festooned edges
- **Treatment:** Local antifungal, plus oral antifungal for 3 weeks in severe cases
Tinea Pedis

- **Athlete's foot**
- **Location:** Interdigital spaces of the foot, but can occur anywhere in the foot
- **Clinical picture:** Skin maceration
- **Treatment:** Local antifungal, plus oral antifungal for 3 months in severe cases

Tinea Unguium

- **Onychomycosis**
- **Clinical picture:** White, brittle, and discolored nails
- **Treatment:** Oral terbinafine; 6 weeks for fingernails, and 12 weeks for toenails, plus local antifungal in severe cases

Tinea Versicolor (Fig. 7.7)

- **Pityriasis versicolor**
- **Cause:** Malassezia furfur; a subtype of Pityrosporum orbiculare
- **Location:** Trunk, usually the upper chest, neck, and back
- **Clinical picture:** Lesions are small, well-defined, scaling macules, of various colors
- **Diagnosis:**
  1. Examination of the lesions under Wood’s light shows yellow color.

Fig. 7.5 Tinea capitis

Fig. 7.6 Tinea corporis

Fig. 7.7 Tinea versicolor
2. KOH skin scraping shows the hyphae and yeast in *spaghetti and meatballs appearance*.

- **Treatment:** Local with *imidazole cream*, plus oral ketoconazole in severe cases
- **Note:** Some lesions are hypopigmented due to *aze- laic acid production by the fungus, which inhibits the melanocytes.*

**Candidiasis**

- Candida albicans exists in two forms:
  1. Yeast: It serves as flora.
  2. Mycelia: Pathogenic form

- **Predisposing factors:** Obesity, hyperhidrosis, and DM

- **Clinical picture:**
  1. *Cutaneous candidiasis:* Common in skin folds, e.g., diaper rash. Lesions are red and moist with festooned edges, and are surrounded by papules known as *satellite lesions* (Fig. 7.8).
  2. *Oral candidiasis* (*thrush*): Common in patients using inhaled steroids, and it could involve the tongue and the esophagus. Lesions are multiple white painful plaques. Prevention: *Washing the mouth* after using the steroid inhalers (Fig. 7.9).
  3. *Genital candidiasis:* It is the most common genital infection in females worldwide. Clinical picture: Whitish, milky vaginal discharge and curd-like patches.

- **Diagnosis:** *Pseudohyphae* under microscopy (Fig. 7.10)

- **Treatment:**
  1. Cutaneous and oral candidiasis: Mainly local, with nystatins or imidazole
  2. Genital candidiasis: Single dose of oral fluconazole
Notes:
1. Most fungal infections could be easily treated with a topical antifungal, like imidazole cream or ointment, except for two infections that require systemic therapy: tinea capitis and tinea unguium.
2. Griseofulvin attacks only dermatophytes and it causes GI upset.
3. Ketoconazole and terbinafine are hepatotoxic.

Cryptococcus neoformans
- Polysaccharide encapsulated yeast
- Transmission: Pigeon droppings
- Clinical picture: Meningitis in immunocompromised patients, e.g., AIDS
- Diagnosis:
  1. India ink staining of cerebrospinal fluid (CSF) shows a halo around the yeast cells.
  2. Culture: Grows on Sabouraud’s agar
- Treatment: Combination of amphotericin B and flucytosine
- Notes:
  1. Amphotericin B: Causes phlebitis, nephrotoxicity and febrile reaction. Prevention: Give aspirin or acetaminophen before amphotericin treatment.
  2. Flucytosine: Causes bone marrow depression and GI upset

Coccidiodes immitis
- Thick-walled spherules, causing coccidioidomycosis (San Joaquin valley fever)
- Location: Common in the southwestern United States (desert areas)
- Clinical picture: Atypical pneumonia and erythema nodosum (tender red nodules on tibia)
- Diagnosis: Positive complement fixation test
- Treatment: Fluconazole or itraconazole. Amphotericin B is used only in severe cases.
- Note: So when you see a patient on the USMLE who has been to a desert area in the southwestern U.S. recently, and now has pneumonia and bumps on his legs, you know what to think!

Miscellaneous Fungal Infections
- Sporothrix schenckii: Cigar-shaped budding yeast.
  Transmission: Contact with rose thorns (also called rose-gardener’s disease).
  Clinical picture: Subcutaneous nodules and ulcers.
  Treatment: Potassium iodide (KI) or itraconazole for cutaneous forms, and amphotericin B for extracutaneous forms.
- Aspergillus: Inhalation causes hypersensitivity reactions type I and III, which lead to bronchospasm. May form aspergilloma in lungs. It also releases aflatoxins, which have been linked to liver cancer. Shows branching hyphae under microscope (Candida shows pseudohyphae). Note: Aspergillus is the nightmare of any bone marrow transplant unit.
- Chromoblastomycosis: Causes cauliflower-like masses with copper-colored sclerotic bodies and broad-based budding (BBB) on microscopy. Treatment: Itraconazole
- Histoplasmosis and blastomycosis: Transmitted through birds’ feces and may cause pneumonia
- Actinomycosis: Causes formation of yellow sulfur granules. Treatment: Penicillin

Parasites

Entamoeba histolytica
- A parasite that moves by means of pseudopodia, and it exists in two forms:
  1. Mature cyst: Infective form
  2. Trophozoite: Pathogenic form
- Clinical picture: Severe watery diarrhea, with blood and mucus
- Complication: Liver abscesses, mainly involving the right lobe
- Diagnosis: Stool culture shows trophozoites with intracytoplasmic RBCs
- Treatment: Metronidazole
- Note: Homosexual men are frequent carriers

Giardia lamblia
- A parasite that exists in two forms:
  1. Mature cyst: Infective form
  2. Trophozoite: Pathogenic form. It is pear shaped, with two nuclei and four pairs of flagella.
- Clinical picture: Watery malodorous diarrhea, and abdominal distention and bloating. So when you see a patient on the USMLE who just traveled outside the U.S. recently, and now has abdominal pain, and watery, nonbloody diarrhea, you know what to think!
- Diagnosis: Stool analysis shows cysts or trophozoites.
- Treatment: Metronidazole
• Note: Well water and day care centers are notorious sources of *Giardia lamblia*.

**Trichomonas vaginalis**

- A flagellated protozoon causing a postmenstrual infection
- Clinical picture: Vulvovaginitis and frothy vaginal discharge
- On exam: Punctate hemorrhages in vagina and on the cervix; also called *strawberry cervix*
- Diagnosis: Wet mount prep shows motile flagellated trichomonads.
- Treatment: Metronidazole

**Plasmodium**

- A parasite causing *malaria*, transmitted by the female anopheles
- Clinical picture and causative organism:
  1. Tertian: Attacks of fever and sweats every 48 hours: *Plasmodium vivax* and *Plasmodium ovale*
  2. Quartan: Attacks of fever and sweats every 72 hours: *Plasmodium malariae*
  3. Malignant malaria with variable attack periods: *Plasmodium falciparum*
- Prophylaxis: Chloroquine. If patient is chloroquine-resistant, give mefloquine.
- Treatment
  1. *P. vivax*, *P. ovale*, and *P. malariae*: Chloroquine for blood forms, and primaquine for tissue forms
  2. *P. falciparum*: Chloroquine. If chloroquine-resistant, give quinine, mefloquine, or artemether.
- Notes:
  1. *P. vivax* and *P. ovale* reproduce in the liver to form hypnozoites. These stages can cause multiple relapses (relapsing malaria).
  2. African-Americans resist infection by *P. vivax*, because they do not have *Duffy A* and *Duffy B* antigens in their RBCs.
  3. Sickle cell patients are resistant to infection by *P. falciparum*, due to *HbS*.
  4. Antimalarial medications induce hemolysis in patients with *glucose-6-phosphate dehydrogenase (G-6-PD) deficiency*

**Leishmania donovani**

- Transmission: Sandfly
- Clinical picture:
  1. Visceral form (*kala azar*): Hepatosplenomegaly
  2. Cutaneous form: Depends on the cell-mediated immunity (CMI) of the patient:
     - If CMI is intact: Ulcer heals with a pale scar, also called an *oriental sore*.
     - If CMI is lost: Facial skin nodules, primarily around the nose
- Treatment: Sodium stibogluconate

**Amebas Causing Meningoencephalitis**

- Source: Swimming in lakes or ponds
- Types and clinical picture:
  1. *Naegleria fowleri*: Acute meningoencephalitis
  2. *Acanthamoeba*: Chronic meningoencephalitis, plus keratitis
- Treatment: Amphotericin B
- Note: So when you see a patient on the USMLE who went camping a couple of weeks ago, and swam in a pond, and is now presenting with symptoms of meningitis and encephalopathy, you know what to think!

**Trypanosomas**

- *Trypanosoma brucei* (*Gambiense or Rhodesiense*): Transmitted by *tsetse* fly, and causes *African sleeping sickness*, which can be fatal. Treatment: *Suramin*; however, if there are any signs of CNS involvement, give *melarsoprol*.
- *Trypanosoma cruzi*: Transmitted by *Reduviid* (*kissing*) bug, and causes skin chagoma (nodule or papule), also called *Romana sign*. Late stages might develop *Chagas disease* (toxic megacolon, cardiomyopathy, and achalasia). Treatment: Nifurtimox

**Helminths**

- *Ascaris lumbricoides* (*roundworm*): Life cycle: Ingested in food → intestine → blood → lungs → coughed and swallowed → intestine. This is known as *autoinfection*, which is also done by *strongyloides*. Treatment: *Mebendazole* or *pyrantel pamoate*.
- *Ankylostoma duodenale* and *Necator americanus* (*Hookworm*): Cause iron-deficiency anemia. Treatment: *Mebendazole* or *pyrantel pamoate*.
- *Trichinella*: From raw pork and causes myositis (diagnosed by high serum creatine phosphokinase [CPK]). First sign of trichinosis: *swollen eyelids*. Treatment: *Thiabendazole*. 
- **Enterobius vermicularis** (pinworm): This worm causes perianal pruritus, and is diagnosed by the scotch tape test. Treatment: Mebendazole or pyrantel pamoate.
- **Onchocerca volvulus**: Causes river blindness and intraepithelial granulomas (lizard skin). Treatment: Ivermectin.
- **Wuchereria bancrofti** (filariasis): Causes elephantiasis, and is diagnosed by midnight blood film (nocturnal periodicity). Treatment: Diethylcarbamazine (DEC).
- **Cutaneous larva migrans**: Contracted from dog’s fecal material, and causes pruritic red rash with creeping serpentine eruption. Treatment: Thiabendazole.
- **Tinea (Tapeworm)**
  1. *Tinea saginata*: In beef products, and it leads to malabsorption.
  2. *Tinea solium*: From eating larvae in pork, and it leads to cysticercosis.
  3. Treatment of tinea: Niclosamide + laxatives
  4. Treatment of cysticercosis: Praziquantel
- **Diphyllobothrium latum** (tapeworm): Acquired by eating undercooked fish, and it causes vitamin B₁₂ deficiency. Treatment: Niclosamide + laxatives.
- **Echinococcus granulosus** (tapeworm): From contact with dogs leading to fever, hepatomegaly, and hydatid cyst formation. Treatment: Albendazole.