Viral infections of the respiratory system
Coronaviridae

Microbiology Lecture 5-part 2 RS Module
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RNA VIRUSES

SINGLE STRANDED
positive sense

ENVELOPED
- ICOSAHEDRAL
- HELICAL

NONENVELOPED
- ICOSAHEDRAL

SINGLE STRANDED
negative sense

ENVELOPED
- HELICAL

NONENVELOPED
- ICOSAHEDRAL

DOUBLE STRANDED

ORTHOMYXOVIRIDAE
PARAMYXOVIRIDAE
RHABDOVIRIDAE
FILOVIRIDAE
BUNYAVIRIDAE
ARENAVIRIDAE

CORONAVIRUS

Modified from Volk et al., Essentials of Medical Microbiology, 4th Ed. 1991
Coronavirus structure

The genome

- SS linear non segmented +ve sense RNA

- The largest among RNA viruses 80-160 nm in size and 27-34 kb in length

- Enveloped (ER and Golgi)

- Alphacoronavirus: 229E, NL63
- Betacoronavirus: OC43, HUK1, SARS-CoV, MERS-CoV, SARS-CoV-2

- 1960s: 229E and OC43
- 2003: SARS-CoV
- 2004: NL63
- 2005: HUK1
- 2012: MERS-CoV
- 2019: SARS-CoV-2
The four major antigenic groups of CoV

• Alphacoronavirus: contains bat, canine, feline, porcine coronaviruses and a human corona virus HCoV-229E and HCoV-NL63

• Betacoronavirus: contains bat, bovine, porcine, rat and mouse CoV and the human strains: OC43, HUK1, SARS-CoV, MERS-CoV, SARS-CoV-2

• Deltacoronavirus: no human strains only Avian and porcine CoV

• Gammacoronavirus: no human strains only Avian and porcine CoV
1 With their S-protein, coronaviruses bind on cell surface molecules such as the metalloprotease \( \text{N} \) amino-peptidase. Viruses, which accessoriely have the HE-protein, can also bind on N-acetyl neuraminic acid that serves as a co-receptor.

2 So far, it is not clear whether the virus get into the host cell by fusion of viral and cell membrane or by receptor mediated endocytosis in that the virus is incorporated via an endosome, which is subsequently acidified by proton pumps. In that case, the virus have to escape destruction and transport to the lysosome.

3 Since coronaviruses have a single positive stranded RNA genome, they can directly produce their proteins and new genomes in the cytoplasm. At first, the virus synthesize its RNA polymerase that only recognizes and produces viral RNAs. This enzyme synthesize the minus strand using the positive strand as template.

4 Subsequently, this negative strand serves as template to transcribe smaller subgenomic positive RNAs which are used to synthesize all other proteins. Furthermore, this negative strand serves for replication of new positive stranded RNA genomes.

5 The protein N binds genomic RNA and the protein M is integrated into the membrane of the endoplasmatic reticulum (ER) like the envelope proteins S and HE. After binding, assembled nucleocapsids with helical twisted RNA budd into the ER lumen and are encased with its membrane.

6 These viral progeny are finally transported by golgi vesicles to the cell membrane and are exocytosed into the extracellular space.
Genetic variation and evolution of new strains

Replication of coronaviruses was seen to be associated with high frequency of:

• Deletion mutations

• Recombination during replication which is unusual for an RNA virus with unsegmented genome
Infections caused by coronaviruses

- Respiratory: common cold, sore throat, bronchitis, and pneumonia
  - Incubation period 3 days
  - 15-30% of respiratory illness in adults during winter months but lower respiratory infections were rare.
  - Antibodies appear early in childhood and are found in 90% in adults

- Gastrointestinal: Gastroenteritis

  Most illnesses with coronaviruses are MILD

- Sever infections with coronaviruses were seen with:
  - SARS-CoV: China in 2003 (MR= 9.6%)
  - MERS-CoV: Saudi Arabia in 2012 (MR= 34.4%)
  - SARS-CoV-2: China in 2019 (MR= 3.4%)
Laboratory Diagnosis of Coronavirus

DIRECT DETECTION:
• Antigen detection in cells of respiratory secretions by IF or ELISA
• Detection in respiratory secretions by RT-PCR

ISOLATION:
• CoV are difficult to grow in CC.
• Reliable isolation of the virus is accomplished using human embryonic tracheal organ cultures.
• These methods are not routinely available.

SEROLOGY:
• ELISA
• Passive haemagglutination test
Treatment and prophylaxis

• There is no specific antiviral medication for treatment for coronavirus infections.
• Drink plenty of water.
• Paracetamol may help with symptoms such as pain or fever.
• Antibiotics do not work against coronavirus.
• Supportive treatments, like oxygen therapy, can be given while your own body fights the virus.
• Life support can be used in extreme cases.

• There is currently no vaccine to treat or protect against coronavirus.
• The flu vaccine does not protect against coronavirus.
# SARS MERS and COVID-19

<table>
<thead>
<tr>
<th></th>
<th>SARS</th>
<th>MERS</th>
<th>COVID-19</th>
</tr>
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<tbody>
<tr>
<td>Year</td>
<td>2003</td>
<td>2012</td>
<td>2019</td>
</tr>
<tr>
<td>Country of origin</td>
<td>China</td>
<td>Saudi Arabia</td>
<td>China</td>
</tr>
<tr>
<td>Animal host</td>
<td>Bat, civets</td>
<td>Bat, camels</td>
<td>Bat, pangolin</td>
</tr>
<tr>
<td>Receptor</td>
<td>ACE-2</td>
<td>DPP-4</td>
<td>ACE-2</td>
</tr>
<tr>
<td>Incubation period</td>
<td>2-10</td>
<td>2-14</td>
<td>2-14 (5.1 days)</td>
</tr>
<tr>
<td>Mortality rate</td>
<td>10%</td>
<td>35%</td>
<td>4%</td>
</tr>
</tbody>
</table>
**SARS**

- Age average: 50
- Age range: 18-95
- Male:female ratio: 2.7:1
- Confirmed cases: 206,668
- Case fatality rate: 8,272 (4%)
- Health-care workers: >6,000 (2.9%)
- Detection date: December 2019
- Detection place: Wuhan, China
- Total recovered: 83,000
- 18.03.2020

**MERS**

- Age average: 56
- Age range: 14-94
- Male:female ratio: 3.3:1
- Confirmed cases: 2,494
- Case fatality rate: 858 (37%)
- Health-care workers: %9.8
- Detection date: June 2012
- Detection place: Jeddah, Saudi Arabia

**CORONAVIRUS (COVID-19)**

- Age average: 50
- Age range: 18-95
- Male:female ratio: 2.7:1
- Confirmed cases: 206,668
- Case fatality rate: 8,272 (4%)
- Health-care workers: >6,000 (2.9%)
- Detection date: December 2019
- Detection place: Wuhan, China
- Total recovered: 83,000
- 18.03.2020
Mode of transmission
COVID-19

- Primarily through droplets containing virus during coughing, sneezing (up to 1 meter)
- Also, contact of droplets with eyes, nose, and mouth with contaminated hands/fomites
- Airborne route, Is it an important route???
- Virus is isolated in stool, but fecal-oral route does not seem to be an important route
- Animals: from/to ????

- Virus survives on hands 15-30 minutes, 3 hours airborne and 2-3 days on plastic and stainless-steel surfaces.
Infectivity and pathogenesis

When are the patients infectious?

• Some may shed the virus in the incubation period
• Asymptomatic persons can also shed the virus
• Virus shedding is maximum in patients exhibiting symptoms
• Virus shedding may occur after resolution of symptoms as well

• In the lungs: the virus accesses host cells via the enzyme ACE2, which is most abundant in the type II alveolar cells of the lungs.
• The virus uses a special surface glycoprotein, called "spike", to connect to ACE2 and enter the host cell.
• ACE2 might also be the path for the virus to assault the heart causing acute cardiac injury. People with existing cardiovascular conditions have the worst prognosis.
Diagnosis

• Reverse transcription polymerase chain reaction (rRT-PCR)

Chest X-ray

Lung CT scan
Prevention

- No vaccine available
- Stay home
- Avoid travel and public activities
- Wash hands with soap and hot water often
- Practice good respiratory hygiene
- Avoid touching the eyes, nose, or mouth with unwashed hands
- CDC recommends that those who suspect they carry the virus wear a simple face mask to protect others from becoming infected.
Treatment

• There are no specific antiviral medications for the virus.
• People are managed with supportive care such as fluid and oxygen support if needed
• Steroids such as methylprednisolone are not recommended unless the disease is complicated by acute respiratory distress syndrome.
• Ibuprofen increases ACE2 enzymes at cell level which could worsen COVID-19 infections, WHO warns against its use.
• Mechanical ventilation: reserved for severe cases
• Experimental drugs:
  • Remdesivir: Nucleotide analogue
  • Lopinavir/Ritonavir: Protease inhibitors
  • Chloroquine: Antimalarial
Prognosis

COVID-19 fatality rate by age

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Fatality Rate</th>
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<tbody>
<tr>
<td>10-19</td>
<td>0.2%</td>
</tr>
<tr>
<td>20-29</td>
<td>0.2%</td>
</tr>
<tr>
<td>30-39</td>
<td>0.2%</td>
</tr>
<tr>
<td>40-49</td>
<td>0.4%</td>
</tr>
<tr>
<td>50-59</td>
<td>1.3%</td>
</tr>
<tr>
<td>60-69</td>
<td>3.6%</td>
</tr>
<tr>
<td>70-79</td>
<td>8.0%</td>
</tr>
<tr>
<td>80+</td>
<td>14.8%</td>
</tr>
</tbody>
</table>

Case fatality rate depending on other health problems

- Hypertension: 6.0%
- Diabetes: 7.3%
- Cardiovascular disease: 10.5%
- Chronic respiratory disease: 6.3%
- Cancer (any): 5.6%
- No comorbidity condition: 0.9%
Prognosis in CHINA

New Cases vs. New Recoveries

(Number of newly infected vs. number of recovered and discharged patients each day)
What is the possible outcome of COVID-19?

- The pandemic may infect most of the population (60-70%) until herd immunity develops, before dying out.

- Mortality will be seen in a small proportion.

- If a vaccine/treatment becomes available, mortality will decline dramatically.
Summary

• COVID-19 is a disease with high transmission, but relatively low mortality
• Spreads by droplet and contact route
• Patients primarily develop fever and respiratory symptoms
• Most recover on their own, and few require special care
• Masks are advised for sick patients and close contacts/care givers only
• Frequent hand hygiene and cough etiquette should be practiced by everyone
• Close contact with cases, and gatherings should be avoided, especially by the vulnerable population (elderly and with underlying conditions)
• Vaccines and treatment may be available in a few months
Infections of the respiratory system
*Pseudomonas, Mycoplasma, Legionella*

Microbiology Lecture 6 RS Module
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Pseudomonas aeruginosa
Pseudomonas aeruginosa

- Motile (by single or multiple polar flagella) gram-negative rods
- Obligate (strict) aerobes (most strains)
- Oxidase (usually) and catalase positive
- Grows on wide range of culture media: minimal growth requirements
- Some strains produce diffusible pigments:
  - Pyocyanin (blue): reactive oxygen species >>> oxidative damage >> cell death
  - fluorescein (yellow); pyorubin (red); pyoverdine (green): Iron chelator
- *P. aeruginosa* produces characteristic grape-like odor and blue-green pus & colonies
- Broad antibiotic resistance
Structural Components

- Adherence to host cells mediated by pili and nonpilus adhesins.

- LPS (lipopolysaccharide) inhibiting antibiotic killing and suppress neutrophile and lymphocyte activity.

- Alginate – mucoid exopolysaccharide that forms a shiny biofilm protecting from antibodies, complement, phagocytosis, and antibiotics.

- Pyocyanin – impairs ciliary function, mediates tissue damage through production of oxygen radicals.
Epidemiology

- Primary habitat is the environment (water and soil)
- Normal flora 2-10% of healthy individuals
- Infections mostly in hospitalized patients with illnesses, such as CF, leukemia and burns.
- Minimal nutritional requirements and can tolerate broad temperature spectrum (20-42°C) and thus contaminate respirator humidifiers, medications and contact lens solutions.
- Can transiently colonize the respiratory and GI tract of hospitalized patients
- Respiratory colonization of CF patients become chronic leading to high morbidity and mortality rates.
- No seasonal incidence
Pathogenesis

- Require break of first-line defenses (wound or contaminated solution)
- Attachment by pili, flagella and extracellular polysaccharide
- Virulence Factors (toxins and enzymes):
  - **Exotoxin A**
    - Similar in structure to Diptheria toxin
    - Inhibits protein synthesis by ADP-ribosylating EF-2 (G-protein)
    - Causes Dermatonecrosis in burn wounds, corneal damage in ocular infections, and tissue damage in chronic pulmonary infections.
    - Also this toxin is immunosuppressive
    - Its presence is associated with fatal outcome and Ab against it is with survival.
  - **Exoenzyme S**
    - ADP-ribosylates G-proteins including p21 RAS interfering with host cell growth
    - Cellular destruction and spread from burn wounds
  - **Elastase**
    - Destruction of elastin-containing tissues (blood vessels, lung tissue, skin), collagen, immunoglobulins (IgA and IgG), and complement factors
    - Can produce hemorrhagic lesions (ecthyma gangrenosum) associated with disseminated infection
  - **Endotoxins:** Illicit strong immune response >>> extensive damage to host cell
  - **Phospholipase C**
    - Breaks down lipids and lecithin causing tissue destruction
Clinical Disease

- Folliculitis: hot tubs
- Pulmonary Infections
- Burn Wound Infections and other skin and soft tissue infections (life threatening)
- UTI’s (especially catheterized)
- External Otitis (malignant OE, swimmer’s ear)
- Eye Infections (conjunctivitis) and corneal ulceration via contaminated contact lens cleaning fluids
- Pseudomonal Endocarditis
Pulmonary Infections

- Can range from asymptomatic colonization to severe necrotizing bronchopneumonia

- Colonization is seen in patients with cystic fibrosis, chronic lung disease, and neutropenia

- Mucoid strains are commonly isolated from chronic pulmonary patients and are more difficult to eradicate

- Predisposing conditions include previous therapy with broad spectrum abx (disrupts normal protective bacteria population and use of respiratory therapy equipment (can introduce the organism to lower airways)

- Mortality rate can be as high as 70% for invasive bronchopneumonia
Ecthyma Gangrenosum

• Ecthyma gangrenosum is a well recognized cutaneous manifestation of severe, invasive infection by *Pseudomonas aeruginosa* that is usually seen in immunocompromised, burn patients, and other critically ill patients
• Start as blisters >>>> tissue necrosis

Black necrotic ulcer
Malignant Otitis Externa

Diabetic pts
Pseudomonas Keratitis and Corneal Ulceration

In 24-48 hrs
Endocarditis

- Tricuspid valve endocarditis: IV drug users
Diagnosis and treatment

Dx
• Oxidase positive colonies, pyocyanin production and ability to grow at 42C are diagnostic
• Culture and sensitivity tests
• CBC

Rx
• Inherently resistant to many antibiotics (penicillin, ampicillin, tetracycline, earlier aminoglycosides and sulfonamides)
• Can mutate to more resistant strains during therapy
• Production of B-lactamases
• 3rd generation cephalosporins, carbapenems and monobactams drugs of choice
• Combination of active antibiotics generally required for successful therapy:
  – Anti-β-lactam and aminoglycoside
  – Carbapenem, fluoroquinolones, and aminoglycoside
• No vaccine
Moraxella catarrhalis

GENERAL OVERVIEW
• Formerly classified as Neisseria & more recently Branhamella
• Gram negative, aerobic coccobacilli, nonmotile
• Grows on blood or chocolate agar

CLINICAL SYNDROMES
• In Elderly Patients with Chronic Pulmonary Disease
  • Bronchitis
  • Bronchopneumonia
• In Previously Healthy People (normal flora)
  • Sinusitis
  • Otitis

TREATMENT, PREVENTION, AND CONTROL
• Most strains produce β-lactamase; Penicillin Resistant
• Amoxicillin-clavulanate, second and third generation cephalosporin, fluoroquinolones, erythromycin
Colony morphology

Catalase positive

B. catarrhalis

24 h

48 h

1 cm

1 cm

GC II base medium + 1% IsoVitalex

Slide

Oxidase positive

Penicillin resistant

B. catarrhalis: Oxidase-positive

B. catarrhalis

24 h

48 h

1 cm

1 cm

GC II base medium + 1% IsoVitalex

Slide

B. catarrhalis: Oxidase-positive

B. catarrhalis

24 h

48 h

1 cm

1 cm

GC II base medium + 1% IsoVitalex

Slide
Mycoplasma

• Classification – order Mycoplasmatales; family Mycoplasmataceae; 2 medically important genera
  – *Mycoplasma*
  – *Ureoplasma*
  – Three common clinical isolates – *M. pneumoniae*, *M. hominis*, *M. genitalium* and *U. urealyticum*

• Morphology and cultural characteristics
  – Do not possess the distinctive cell wall of bacteria
Mycoplasma

- Plasma membrane is the outermost part of the organism and is unique among bacteria in that it has a high content of sterols (acquired from medium or tissue living in) that act to prevent osmotic lysis
- Very small in size (too small to be seen with an ordinary light microscope) and highly pleomorphic
- Don’t stain with a Gram stain
- Non-motile
- May possess a capsule
- Although some are free living, most are closely adapted parasites
Mycoplasma

– Grow on media enriched with serum (need cholesterol)
– Grow best at 35-37°C either aerobically or anaerobically
– *M. pneumoniae* grows in 5-14 days, *M. hominis* in 2-4 days, and *U. urealyticum* in 24-28 hours.
– *M. pneumoniae* colonies resemble fried eggs and can be stained with Dienes stain (they stain blue)
Mycoplasma colonies with Diene’s stain

**Figure 21-16**
Diene's stain of *Mycoplasma* spp. colonies demonstrating typical “fried egg” appearance.

**Figure 21-17**
Typical mixed sizes of *Mycoplasma* organisms on primary isolation media: *Mycoplasma salivarium*. (Courtesy Bionique Testing Laboratories, Saranac Lake, N.Y.)
Mycoplasma

• Virulence factors
  – Not invasive and simply colonize cell surfaces through specific binding
  – It binds to cilia in the bronchus via surface mycoplasmal cytadhesin (P1 protein) to sialic acid leading to interference with the ciliary action resulting in its desquamation.
  – Damage to host tissues may be due to immune response rather than invasion by the organism.
  – Organism shed in UR secretions for 2-8 days before onset of symptoms and shedding continue up to 14 weeks
Clinical significance

- Tracheobronchitis in children 60%
- M. pneumonia – the major cause of primary, atypical pneumonia (walking pneumonia). 10% of all pneumonia
  - Transmitted by droplet infection
  - Age range: 5-15 yrs old, more severe in older children
  - After a 2-3-week incubation, the disease begins as a mild, upper respiratory tract infection and progresses to fever, sore throat, headache, malaise, and a dry cough which is usually mild and self-limited.

- Pharyngitis with fever and sore throat
- Myringitis or otitis media
- Encephalitis: occur in children following atypical pneumonia
  - Fever
  - Change in mental status
  - Neck stiffness
Mycoplasma DX

– M. pneumoniae

• Isolation in culture: incubation for more 2-3 weeks on Eaton’s agar (fried egg colony)
• 4-fold rise in specific antibody titer
• Cold agglutinin test – a **nonspecific** test in which the patient produces cold reacting antibodies that agglutinate type O human RBCs at 4°C, but not at 37°C
• Chest X-ray
Mycoplasma

- **Treatment**
  - *M. pneumonia* – Tetracyclin, Macrolides (Clarythromycin and *Azithromycin*) and quinolones
  - Genital infections – **Tetracycline**, azithromycin and quinolones
Legionella

• Classification – family Legionellaceae with more than 21 species. We will only discuss *L. pneumophila*

• Morphology/cultural characteristics
  – Small, G- pleomorphic rods that stain very poorly alternative Dieterle stain
  – Motile
  – Requires cysteine, ferric ions and PH 6.9 for growth and, therefore, won’t grow on ordinary lab media
  – The best media for primary isolation is buffered charcoal yeast extract with alpha keto glutarate (BCYEα).
    • This can be made selective by the addition of cefamandole, anisomycin, and polymyxin B.
Legionella in BCYEα
Legionella

- Growth is enhanced by incubation in a candle jar or in 2.5% CO$_2$
- Growth might take 2-10 days
- Colonies are pinpoint with a ground-glass appearance
Legionella

• Virulence factors
  – Inhibit phagosome-lysosome fusion which allows for intracellular growth
  – Endotoxin (LPS) less toxic than other G-ve
  – Inhibit generation of bactericidal substances in phagocytic cells (hydrogen peroxide)
Legionella

• Clinical significance
  – Acute pneumonia – Legionnaire’s disease
    • Airborne transmission with an incubation of 2-10 days
    • Symptoms include fever, chills, malaise, myalgia, headache, dry cough, vomiting, diarrhea, and abdominal and chest pain. Hospitalization is usually required in 3-5 days.
    • Without antibiotics, the fatality rate is as high as 15%
    • The disease occurs more in males over 60 years of age and in the immunocompromised
    • No person to person transmission
    • Disease rate after exposure is low
    • The reservoir of infection is often in the cooling towers of air conditioning systems and in hot water lines as well as in soil and water
Legionella

– Pontiac fever – an acute, self-limited febrile illness with an incubation of 24-36 hours. Symptoms include a high fever, chills, malaise, myalgia, and headache which lasts 2-5 days

– Reaction to endotoxin or hypersensitivity to *Legionella* components
Diagnosis

- Urinary antigen for *L. pneumophila* serogroup 1
- Inoculate BCYEα and CBA and look for growth versus no growth
- Catalase +
- Direct fluorescent antibody testing (positive in 25-50%)
- PCR

Treatment

- **Macrolides** (clarithromycin or azithromycin)
- Flouroquinolones (ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin, trovofloxacin)

Prevention

- Minimize production of aerosols in public places
- Resistant to chlorine and heat
Infections of the respiratory system
Fungal and parasitic infections

Microbiology Lecture 7 RS Module
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Histoplasma capsulatum

- Dimorphic fungus
- Yeast form in tissue and cultures 37°C
  - Reproduce by budding (blastoconidia)
- Mold form cultures incubated 22-25°C; saprophyte in soil.
  - Mycelia are septate, produce microconidia and macroconidia.
  - Diagnostic structure: tuberculate macroconidia (thick wall with finger projections)
- Grows on Blood agar, Chocolate agar and Sabouraud’s agar (dextrose and peptone; PH5.6). Takes few weeks to grow
- It is not encapsulated
HISTOPLASMOSIS

(Histoplasma capsulatum)

• This is one of the most common fungal infections.
• The ecological niche of *H. capsulatum* is in blackbird roosts, chicken houses and bat guano.
• Inhalation of the mold microconidia reaching the alveoli is the mode of transmission.
• Histoplasmosis is a significant **occupational disease** in bat caves in Mexico when workers harvest the guano for fertilizer.
• In the endemic area the majority of patients who develop histoplasmosis (95%) are asymptomatic.
• Not transmitted from person to person
• More common in men
• The diagnosis is made from their history, serologic testing or skin test.
Histoplasma capsulatum

periodic acid–Schiff (PAS) stain

FIGURE 44-2 Schematic illustration of the natural history of the saprobic and parasitic cycles of Histoplasma capsulatum.
Histoplasmosis is a systemic disease, mostly of the reticulo-endothel, manifesting itself in the bone marrow, lungs, liver, and the spleen.

- Attach to integrin and fibronectin receptors and taken by phagocytes.

- In dendritic cells: yeast cells are killed

- In neutrophiles and macrophages: survive by modifying (raising) PH to 6-6.5 where an acidic PH is needed for optimal killing.

- Most lesions remain confined to the lungs, but lymphatic spread is possible, and reactivation is possible in immune compromised pts.

- Lesions: granulomatous inflammation with necrosis in lungs, hepatosplenomegaly.

- In fact, hepatosplenomegaly is the primary sign in children, while in adults, histoplasmosis more commonly appears as pulmonary disease.

- Immunity is Th1 mediated. Macrophages activated by T-lymphocyte cytokines can inhibit intracellular growth and control disease. Defective cellular immunity leads to disease dissemination.
Histoplasma manifestations

• Immunocompetent individuals are subclinical (majority)
• In the patients who are clinically ill
• occurs in one of three forms:
  • **Acute pulmonary disease**: "flu-like" illness (fever and cough), few days- weeks.
  • **Progressive pulmonary disease**: Chronic, shortness of breath and a cough which becomes productive. The sputum may be purulent or bloody, weight loss and night sweats. Last months- years.
  • **Disseminated**: febrile illness with enlargement of the RES. CNS, skin, GI and adrenals may be involved. Painless ulcer on mucus membranes is common.

**Diagnosis**

• Blood and bone marrow cultures
• H&E and Wright stained bone marrow
• Detection of polysaccharide antigen in serum and urine by ELISA or PCR
Treatment and prevention

• Primary infections and localized lesion resolve without treatment.
• Mild disease: Itraconazole
• Severe or disseminated: Amphotericin B followed by itraconazole.

• Itraconazole can be effective prophylaxis for AIDS and immunocompromised pts.
Coccidioides immitis

- Dimorphic fungus
- Mold form in environment and in cultures regardless of incubation temp. (grows in 2-5 days)
  - hyphae are septate, produce thick-walled, parrel shaped arthroconidia in 1 week.
  - Mature arthroconidia separate from hyphae and survive in environment. They are the infectious units when inhaled.

*C. Immitis* arthroconidia
Coccidioides immitis

- spherule form in tissue
  - Spherule development require invagination of fungal membrane, new cell wall production forming multicompartment structure.
  - The compartment differentiates into 200-300 spores

*C. Immitis* spherule

![Life Cycle of Coccidioides](image-url)
Coccidioides immitis life cycle

• **Saprophytic cycle** starts in the *soil* with spores (*arthroconidia*) that develop into mycelium. The *mycelium* then matures and forms alternating spores within itself. The arthroconidia are then released and germinate back into mycelia.
• **Parasitic cycle** involves the *inhalation of the arthroconidia* by animals which then form *spherules* filled with *endospores*. The *ambient temperature* and *availability of oxygen* appear to govern the pathway.
• Grows in alkaline soil of semiarid climates (hot dry summer, mild winter with few freezes and annual rainfall of 10 inches).
• Not transmitted from person to person
• Positive skin test in 50-90% of long-time residents of endemic areas.
• Endemic in Arizona, Nevada, New Mexico, west Texas and central California.
**Coccidioides immitis pathogenesis**

- Inhaled arthroconidia ends up in the terminal bronchi.
- Incubation period 1-3 weeks.
- Human monocytes can ingest and kill some arthroconidia.
- Arthroconidia cell wall has antiphagocytic properties so some develop into spherules.
- Proteases and spherule outer wall are linked to virulence and survival of endospores.
- Life-long immunity usually follows infection with *C. immitis*.
- Macrophages and cellular immunity are important for infection control. Immune deficit spread the disease.
- Humoral response has no role in immunity.
- There is a much greater mortality rate in dark-skinned people (Mexicans, Filipinos, and Blacks).
- They are 25 times more likely to develop progressive disease and death. The reason for this is obscure.
Coccidioides immitis manifestations

- Mild disease: no symptoms (>60%)
- Acute pulmonary disease (valley fever): fever, cough, chest pain, headache, rash, and arthralgia. Last 2-6 weeks, normal CXR. 90% no pulmonary residua.

- Desert rheumatism: It is described as a triad of fever, erythema nodosum, and arthralgias.

- Chronic pulmonary disease: last more than a year, cavity formation and relapses.

- Disseminated: seen in immunosuppressed persons (AIDS). Spread to bones, joints, skin and meninges.
Coccidioides immitis diagnosis

- H&E and Calciflour White stained spherules are difficult to miss
- CSF culture difficult
- Serological tests very useful:
  - IgM antibody in first 3 weeks of illness
  - IgG antibody after 3 weeks. Disappear with resolution and persists with continuing infection.
- CXR
- Chest CT scan

Treatment

- Primary infections and localized lesion resolve without treatment except in immunocompromised and pregnant women to prevent dissemination.
- Severe or disseminated: Amphotericin B followed by itraconazole.
- Fluconazole in meningitis, better CSF penetration.
ASPERGILLOSIS
Aspergillus fumigatus

- Rapidly growing molds with branching septate hyphae with conidia on the conidiphore.
- Fluffy colonies appear in 24-96hrs
- The most common etiologic agents of aspergillosis
  - *Aspergillus fumigatus*
  - *A. Niger*
  - *A. flavus*
- Heat resistant conidia survive in the environment.
- Mode of transmission: Inhaled conidia
- Aspergillus infections are associated with environmental disruptions such as seen in construction works.
- Alveolar macrophages kills inhaled conidia, while PMN attack hyphae.
- Cellular and humoral immunity role?
ASPERGILLOSIS

- **Allergic bronchopulmonary aspergillosis (ABPA):** most commonly affects people with asthma or cystic fibrosis. Inflammation in the lungs and allergy symptoms such as coughing and wheezing, mild fever, and malaise but doesn’t cause an infection.

- **Aspergilloma:** Patients with a previous history of tuberculosis, sarcoidosis, cystic fibrosis or other lung disease are most susceptible. Aspergilloma is also called a “fungus ball.”
  - no specific symptoms, **haemoptysis.**

- **Chronic pulmonary aspergillosis:** Occurs when *Aspergillus* infection causes cavities in the lungs and can be a long-term (3 months or more) condition. One or more fungal balls (aspergillomas) may also be present in the lungs.

- **Invasive aspergillosis:** only occurs in severely immune-compromised patients: organ transplant or a stem cell transplant. Invasive aspergillosis most commonly affects the lungs, but it can also spread to other parts of the body: central nervous system, sinuses, bone, heart, kidney, eye, blood and skin.

- **Fever** and chills.
- A **cough** that brings up blood (hemoptysis)
- **Shortness of breath.**
- Chest or joint pain.
- Headaches or eye symptoms.
- Skin lesions
Aspergillus diagnosis

- **Culture**: Aspergillus require 1-3 weeks for growth. Lung aspirate, biopsy or bronchoalveolar lavage.
- **CXR**: air crescent sign
- **CT**: Halo sign
Treatment

- Voriconazole, itraconazole, caspofungin and Amphotericin B in combination.
- Mortality rate in invasive disease reach 100%.
- Surgical removal in case of fungal ball is helpful.
Pneumocystis jirovecii
Introduction

• The organism has not been grown in culture, and doesn’t infect animals
• It was long considered a parasite based on morphology
• Nowadays classified as a fungi
• *P. carinii* or *P. jiroveci*
• Lives in interstitial tissue of lungs
• Rarely disseminates to spleen, lymph nodes, bone marrow, eyes
Geographic Distribution

• Worldwide
  – Most children exposed by the age of 3-4 years
  – Commonly found in the lungs of healthy individuals, but no disease occurs

• Widespread in mammals
Hosts

- Humans
  - *Pneumocystis jiroveci*(i) alternate names
  - *Pneumocystis carinii hominis*
  - Elderly, malnourished children, primary immunodeficiency disorders, AIDS
  - Patients receiving cytotoxic or immunosuppressive drugs for lymphoreticular cancers or transplants
- Other mammals: rabbits, dogs, goats, swine, cats, chimpanzees, owl monkeys, horses
Transmission

• Aerosol droplets probable.
• Direct contact
• Infants with Congenital immunodeficiencies
• Immunosuppressive therapy
• Household pets
  – Interspecies transmission?
• Reactivation of latent infection when immunocompromised
  – Or, new infection?
Life Cycle

• Life cycle is not fully known
• Asexual and sexual reproduction
• Four general morphological forms in mammals
  – Trophozoite (cell wall, cytoplasmic membrane, nucleus and mitochondria)
  – Precysts
  – Cysts
  – Sporozoites (intracystic bodies)
• Cyst (diagnostic form)
  – chitinous membrane and 8 intracystic bodies
  – Pore in cyst wall used for releasing sporozoites.
  – Can be spherical or collapsed.
Life Cycle
Life Cycle

- Mature, thick-walled cyst
- Sporozoites
- Excystment
- Empty cyst
- Intermediate cyst
- Early, thin-walled cyst
- Trophozoites
Clinical Presentation

• Causes Pneumonitis, Pneumocystis pneumonia (PCP)

• Lung epithelium becomes desquamated
  – alveoli fill with foamy exudate containing parasites

• Fever, nonproductive cough, breathing difficulty on exertion, respiratory failure, cyanosis

• Extrapulmonary lesions occur in a minority (<3%) of patients, involving most frequently the lymph nodes, spleen, liver, and bone marrow

• Death by asphyxia in 3-4 weeks if untreated
Diagnosis

- Clinical symptoms
- Sputum or bronchioalveolar lavage (BAL): Special staining with toluidine blue, methenamine silver, Gram-Weigert stain for cysts
- ELISA, immunofluorescence assay, PCR
Pictures

- Trophozoites in BAL material.
- Cysts in BAL material.
Treatment

- Trimethoprim-sulfamethoxazole (TMP-SMZ) is the treatment of choice with steroids to avoid inflammation.

- Pentamidine isethionate inhalant.

- Treatments can be toxic, and patient must be monitored closely.

- Prophylactic treatment if CD4 count is low (<200), unexplained fever or previous PcP.

- HAART regimen to boost immune system function.
Paragonimus westermani
Introduction

• Agent: Paragonimus westermani also known as the oriental lung fluke.
• Disease: Paragonimiasis
• More than 30 species of trematodes (flukes) of the genus Paragonimus have been reported to infect animals and humans. Among them, more than 10 species are reported to infect humans, the most common is P. westermani.
Transmission

- Eating raw, undercooked or pickled crustaceans such as crab or crayfish
- Spitting, a habit in Asian countries
- Cultures that eat raw crustaceans
  - Drunken Crab in China
  - Raw Crab or Crayfish and alcohol in The Philippines
  - Sushi crab in Japan
Life Cycle

1. Unembryonated eggs
2. Embryonated eggs
3. Miracidia hatch and penetrate snail
4. Sporocysts, Rediae, Cercariae
5. Cercariae invade the crustacean and encyst into metacercariae
6. Humans ingest inadequately cooked or pickled crustaceans containing metacercariae
7. Excyst in duodenum
8. Adults in cystic cavities in lungs lay eggs which are excreted in sputum. Alternately eggs are swallowed and passed with stool.

3-5 months

6-8 weeks
Life cycle

1. Infective stage: Metacercariae
2. Infective mode: eating raw freshwater crabs and crayfish with metacercariae
3. Infective route: by mouth
4. Site of inhabitation: lungs
5. Intermediate hosts: 1\textsuperscript{st} int. host is melania snail. 2\textsuperscript{nd} int. hosts are crab and crayfish.
6. Reservoir hosts: carnivores such as tiger, lion, wolf, fox, dog, leopard, cat and etc
7. Life span: 5-6 years
Morphology

• The living adult worms are a pinkish-brown colour and bean shaped (7 to 15 mm in length to 8 mm in width, and 3 to 5 mm in thickness). It contains a characteristic ovary in the middle of the worm.
• The golden brown colored immature eggs are approximately 45-60 μm by 80-100 μm.
• The metacercariae in the second intermediate host are spherical in shape measuring 220-450 μm.
Morphology of eggs

The egg form leaves the definitive host and hatches in the miracidium that penetrates the snail.

The adult fluke is found in its mammalian host.
Metacercariae and cercaria

The metacercaria is the form ingested by humans.

The cercaria is the form that penetrates the crab.
Pathophysiology

- When humans ingest raw infected crustaceans, larval flukes develop in the small intestine, penetrate the intestinal wall into the peritoneal cavity 30 minutes to 48 hours after excysting. They then migrate into the abdominal wall or liver, where they undergo further development. Approximately 1 week later, adult flukes re-enter from the abdominal cavity and penetrate the diaphragm to reach the pleural space and lungs. Flukes mature, a fibrous cyst wall develops around them, and then egg deposition starts 5-6 weeks after infection.
- The symptoms of the early stages of this disease appear to be few.
- Once the parasite is in the lung or another organ, the worm stimulates an inflammatory response that eventually coats tissue.
- If worms enter the CSF of the spinal cord, it can result in partial or total paralysis.
- There have also been fatal cases of Paragonimiasis by infection of the heart.
- Cerebral cases result in cerebral cysticercosis (condition in which fluid-filled cysts surrounding the worm are present).
Diagnosis

1. Microscopic examination of the characteristic eggs present in sputum, aspired pleural fluid, faeces, and matter of ulcers caused by the parasite.
2. An assay that detects worm antigens with monoclonal antibodies is also available and can be used in conjunction with the intradermal skin test.
3. ELISA serological tests are highly sensitive at >92% detection.
   • The eggs may not be present in these sources until 2 to 3 months after infection.
Treatment

• Praziquantel
  causes severe spasms and paralysis of the worms' muscles
• Bithionol

PREVENTION

• Fully cook shellfish
  – Heat water to 55°C for 5 minutes
• Freeze Fish
  – -20°C for 7 days
  – -35°C for 15 hours
Infections of the respiratory system
Pulmonary Tuberculosis

Microbiology Lecture 8 RS Module

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Pulmonary Tuberculosis is caused by *Mycobacterium tuberculosis*… a species that is included within M.TB complex

- *M. tuberculosis* complex (M.TB complex): contains 4 species:
  1. *M. tuberculosis*
  2. *M. bovis*
  3. *M. africanum*
  4. *M. microti*

- Other species of mycobacteria: so called atypical mycobacteria, MOTT (mycobacteria other than tuberculosis) or NTM (non-tuberculous mycobacteria).
  - These MOTT can cause infection in the lungs, similar to tuberculosis, or outside the lung as skin, soft tissue, and lymph nodes
  - MOTT: *M. avium-intracellulare complex*, *M. cheloni*, *M. scrofulacium*, *M. kansasii*, *M. fortuitum*, and *M. abscessus*.

- Humans are easily infected with *Mycobacterium tuberculosis* but are resistant to the disease
- Only about 5% of infected people actually develop a clinical case of TB
- MTB infect apparently healthy and immuno-compromised individuals.
M. tuberculosis...the organism

- Non-motile, non-spore-forming, aerobic bacilli.
- Cell wall is rich in lipids (mycolic acids) →
  1. Hydrophobic, not stained by Gram stain
  2. Resist many disinfectants & common antibiotics. Sensitive to heat and UV
  3. Resist acid decolorization of Z-N; i.e.: Acid-Fast.
- Cell division time is 12-24 h compared to 15-20 min in E. coli. Growth enhanced by 10% CO2 and PH 6.5-6.8.
- Peptides in cell wall are biologically important antigens, they stimulate immune response to infection. (Tuberculin)
- MTB replicates in non-activated macrophage (a virulence factor)
- No toxins or enzymes are associated with tissue destruction.
- Disease is primarily due to host response to TB.
  - 1st: Delayed-type hypersensitivity reaction to M. proteins resulting in destruction of nonactivated macrophages.
  - 2nd: Th1 activate macrophages destroying M. within their cytoplasm.
Tuberculosis

1° and 2° tuberculosis

Infection with *Mycobacterium tuberculosis*

- Nonimmune host (usually child) → Primary tuberculosis
  - Hilar nodes
    - Ghon focus (usually in lower to mid zones of lung)
  - Heals by fibrosis
    - Immunity and hypersensitivity
      - Tuberculin (+)

- Partially immune hypersensitized host (usually adult) → Secondary tuberculosis
  - Ghon complex
  - Progressive lung disease (HIV, malnutrition)
  - Severe bacteremia
    - Miliary tuberculosis
    - Death
  - Preallergic lymphatic or hematogenous dissemination
    - Dormant tubercle bacilli in several organs
      - Reactivation tuberculosis of the lungs

- Reinfected
  - Reactivation tuberculosis in adult life

Extrapulmonary tuberculosis
- CNS (parenchymal tuberculoma or meningitis)
- Vertebral body (Pott disease)
- Lymphadenitis
  - Renal
  - GI
  - Adrenals
Pathogenesis of Pulmonary tuberculosis

Stage 1: Droplet nuclei (DN) inhalation

- One DN contains no more than 3 bacilli.
- DN are so small (2-5 µm), can remain air-born for extended time.
- Coughing or 5 min talking generates ~ 3000 DN.
- Sneezing generates most DN; they can spread 3 m away.
- When a person inhales DN, most of the larger ones become lodged in URT, where infection is unlikely to develop.
- However, smaller DN may reach lung alveoli, start infection.
- TB are nonspecifically taken up by alveolar macrophages.
- However, the macrophages are not activated and are unable to destroy the intracellular TB. Interfere with the acidification of the phagosome (↑ PH) rendering the lysosomal enzyme less effective.
Stage 2: intracellular multiplication

- Begins 7-21 days after initial infection.
- MTB multiplies within macrophages which are not activated to kill the bacteria.
- Other macrophages migrate to the site from the peripheral blood, and they begin to engulf the MTB by phagocytosis, but they remain inactivated and are unable to destroy the bacteria. The result is that the macrophages themselves burst.
- MTB-laden macrophages are transported through lymphatic channels to the draining lymph nodes. Bacteremia spread the organism to other tissue (liver, spleen, kidney, bone, brain and meninges).
Stage 3: Immune response to invading MTB

- At this stage, lymphocytes begin to infiltrate.
- T-cells recognize MTB and release cytokines (γ-IFN) that activate the macrophages to become capable of destroying MTB.
- Here, the infected individual becomes tuberculin-positive. This is due to a cell mediated immune response called delayed hypersensitivity.
- If the Th1 process is effective the source of DTH stimulation wanes and the disease resolves.
- Th1 response is responsible for much of TB pathology.
  - Activated macrophages release IL-1 and TNF → pathology.
- Here, the tubercle is formed (granuloma). Its center is characterized by "caseation necrosis" (= cheesy in consistency).
- MTB cannot multiply within “tubercle” because of low pH and ↓O2.
- However, MTB can persist within these tubercles for extended time.
Stage 4: Fate of formed tubercles

➢ Tubercle is a granulomatous lesion resulting from the accumulation of macrophages, lymphocytes, fibroblasts and multinucleated giant cells around MTB, and hypersensitivity to MTB proteins.

➢ Although many activated macrophages surround the tubercles, many remain unactivated → MTB infect & replicate in those, and the tubercle grows.

➢ Tubercle may invade a bronchus, an artery, or vein.

➢ The hematogenous spread of MTB may result in extrapulmonary tuberculosis (milliary tuberculosis).
Stage 5: Progression

- For unknown reasons, the caseous centers of the tubercles liquify.
- This liquid is very conducive to MTB growth and hence it begins to rapidly multiply extracellularly.
- After time, the walls of nearby bronchi become necrotic and rupture.
- This results in cavity formation, and also allows MTB to spill into other airways and rapidly spread to other parts of the lung.
- 1<sup>st</sup> lesion heals by fibrosis and calcifies, referred to as: Ghon complex.
- Small metastatic foci containing low # of MTB may also calcify or may contain viable MTB These are the Simon foci.
- Simon foci are visible by X-ray and are often sites of reactivation. (high O2 in apex of lung, rising load of mycobacterial proteins)
Clinical manifestations

• Primary TB
  – Asymptomatic or mild fever and malaise.
  – CXR: infiltrate in the mid-zones of the lung and enlarged or calcified lymph nodes.
  – 5% primary TB is not controlled and progress into active TB or disseminate to many organs.

• Reactivation TB (10%)
  – After 50yrs of age, men> women
  – Precipitated by immunosuppression due to malnutrition, alcoholism, diabetes, old age and AIDS.
  – Symptoms: starts as a dry cough which then become productive (hemoptysis). Fever, fatigue, sweating and weight loss.
  – Reactivation of extrapulmonary TB, most sever is fatal meningitis.
  – Death in 2-5 years if untreated, in AIDS pts rapid course.
Laboratory Diagnosis of Pulmonary Tuberculosis

Sputum sample:

– Spontaneous sputum is the sample of choice.
– To raise sputum, patient must be instructed to take a deep breath, hold it momentarily, and then cough deeply and vigorously.
– He must also be instructed to cover his mouth carefully while coughing and to discard tissues in an appropriate receptacle.
Acid-Fast Staining of Sputum Smear

• Acid-fastness distinguishes TB from other bacteria. However, Nocardia, Rhodococcus, Cryptosporidium and Isospora belli cysts are also AF.
• AF is affected by age of colonies, media of growth, and UV.
• Three types of stains: Ziehl-Neelsen, Kinyoun and Fluorochrome (fluorescent) stain.
• Visualization of AF bacilli in sputum should be considered only presumptive evidence of tuberculosis, since stain doesn’t specifically identify M.tuberculosis.
• Incidence of false-positive smears is very low when good quality control is maintained.
ZN stain:

- This classic Carbolfuchsin stain requires heating the slides for better penetration of stain within the TB cell wall; hence called “Hot stain”.
- At least 100 oil immersion fields should be examined before reporting smear as negative.

Kinyoun stain:

- The method of choice in small labs.
- Similar to ZN, but no heating is required “cold stain”
Acid-Fast bacilli in sputum smear
Interpretation of AF-Stained Smears

➢ Positive ZN smear requires cut-off of at least 5000 bacilli/ml.

➢ Typical AFB appear purple to red, slightly curved, short or long rods (2-8 μ).

For some MOTT (e.g. *M. avium* complex), they appear pleomorphic, usually coccoid.

<table>
<thead>
<tr>
<th>No. of AFB seen</th>
<th>Report as:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-9 per entire smear specimen</td>
<td>Negative; request another specimen.</td>
</tr>
<tr>
<td>10-99 per entire smear</td>
<td>Rare (+)</td>
</tr>
<tr>
<td>1-10 /hpf</td>
<td>Few (2+)</td>
</tr>
<tr>
<td>&gt;10 /hpf</td>
<td>Numerous (3+)</td>
</tr>
</tbody>
</table>
Culture of M. tuberculosis

“CDC has recommended that every effort should be made for labs to use the most rapid methods available for diagnostic mycobacterial testing. These include the use of both a liquid and a solid medium for mycobacterial culture”

Culture is the gold standard above all other diagnostic systems.

Culture is more productive for patients with cavitary TB, with abundant TB in sputum ($>10^8$), but difficult for other organs infection (UT, CSF, Tissue) where True sputum, 3 consecutive days, additional specimens and larger volume of fluid is needed.
Inoculation of culture media:

1. Lowenstein-Jensen medium 4-6 weeks
2. Middlebrook 7H9 (liquid media) ~3 weeks.
Mantoux test or PPD test

• Measure delayed hypersensitivity to tuberculoprotein preparation.
• Intradermal injection (5 units; 0.1 ml) that is read after 48-72 hrs.

• Test readings
  – 5 mm or more is positive in
    • An HIV-positive person
    • Persons with recent contacts with a TB patient
    • Persons with nodular or fibrotic changes on chest X-ray consistent with old healed TB
    • Patients with organ transplants, and other immunosuppressed patients
  – 10 mm or more is positive in
    • Injection drug users
    • Residents and employees of high-risk congregate settings (nursing homes, hospitals)
    • Persons with clinical conditions that place them at high risk (diabetes, prolonged corticosteroid therapy, leukemia and end-stage renal disease)
    • Children less than four years of age, or children and adolescents exposed to adults in high-risk categories
  – 15 mm or more is positive in
    • Persons with no known risk factors for TB

– BCG (Bacillus Calmette–Guérin) vaccinated persons are reactive but less than 10 mm.
Injection of PPD

- Small bleb develops

(a)

- 5–9 mm
  - Positive if person is in category 1

- 10–14 mm
  - Positive if person is in category 2

- ≥15 mm
  - Positive if person is in category 3

(b)
Treatment

Antibacterial chemotherapy:

- Combination of **first** and **second line** drugs for the first 2 months which could include:
  - Isoniazid
  - Rifampicin
  - Pyrazinamide
  - Streptomycin or Ethambutol

- Next 4 months, combination of:
  - Isoniazid
  - Rifampicin

- Early resistance to isoniazid: other first-line drugs such as ethambutol, streptomycin, pyrazinamide and fluoroquinolones can be added to drug arsenal (treatment period also extended).

- These drugs are relatively effective in killing the bacteria, however, they also produce a wide variety of side effects.
Treatment

First line drugs:
- **Bactericidal agents**: kill active bacteria, important in the early stages of infection.
- Isoniazid (INH), rifampicin (RIF), ethambutol (EMB), pyrazinamide (PZA) and streptomycin (SM).

Second line drugs:
• **Fluroquinolones** (oral), kanamycin and amikacin (IV).
• Aminosalicylic acid, Ethionamide, Cycloserine (less effective).
• - **Bacteriostatic**: hinder bacterial growth.
  - Strengthen treatment in the case of resistant bacteria.
  - Less efficient and generally more toxic than first line drugs.

Inappropriate chemotherapy:
- Monotherapy (single drug treatment)
- Decreased treatment period
- Low absorption of drugs
Drug Resistance and Tuberculosis

- *M. tuberculosis*: naturally resistant to certain antibiotics due to presence of:
  - Drug-modifying enzymes
  - Drug-efflux systems
  - Hydrophobic cell wall

- Mycobacteria undergo natural mutations which can lead to development of drug resistance.
  - TB is treated by administration of **combination chemotherapy** decreases probability of development of drug resistance.

- Development of increasingly resistant strains mainly due to: Patient non-compliance
MDR Tuberculosis

MDR: Multidrug-resistant strains:
- Strains of tuberculosis resistant at least to rifampicin and isoniazid.
- Mortality rate: 40-60%
- Estimated that 50 million people are infected with MDR-TB.
- MDR-TB is approximately 125 times more expensive to treat than drug susceptible TB.

prevention

- In case of close exposure to a TB patient and/or conversion of the PPD test from negative to positive.
- Prophylactic treatment with Isoniazid for 6-9 months.
- BCG vaccine given ASAP after delivery. M. bovis strain attenuated with repeated subcultures.
- BCG contraindicated in AIDS pts.