

Before you start:

You must read the slides! The Dr. did not bother to explain them all

Mycobacteria and fungal infections of the respiratory tract

- TB is a global problem that the WHO is trying to combat. WHO officials thought that they could decrease the number of TB cases to clinically insignificant numbers; however, TB proved to be very hard to eradicate especially in the developing countries. What has been lately observed is the emergence of new cases in industrialized countries like the United States and European countries. According to the statistics, there are, at least, 10 million cases annually with a death toll of two to three million patients.
- One of the important points about TB is the emergence of new types of bacteria that are resistant to multiple drugs (multi-resistant strains) and the emergence of many cases among immune-deficient patients (suffer from high incidence rate).
- The classical causative agent is *Mycobacterium tuberculosis*; it is responsible for more than 95% of the cases. The remaining cases are caused by other types of bacteria that either cause localized or pulmonary infections.
- Typical and atypical causative agents have the same clinical manifestations. The atypical, however, might establish infections in those who have immunodeficiency in the presence of lung fibrosis or malignancies or other forms of underlying diseases.
- It is not a disease restricted to those who belong to a low socio-economical class; it can be found in people from other social classes in the presence of underlying diseases like AIDS.
- The identification test is simple and accurate:
 - o Aspirate from nose (sputum sample)
 - o Identify causative agent using acid fast bacilli stain (Ziehl-Neelsen stain)
 - o Culture bacteria
 - o Sensitivity tests
- Despite the simplicity of the process, this test might fail to identify certain cases.
- Infection is caused by a few numbers of cells. The route of transmission is usually through inhalation. After that, they disseminate to reach the lung where they form a granulomatous lesion. This lesion might be associated with clinical symptoms; however, it can be asymptomatic. Both can be demonstrated using the tuberculin test.
- The reactivation of an old lesion is usually associated with the formation of a cavity in the lung. Moreover, it is associated with necrosis of lungs and other internal organs. It can produce meningitis in children (rare in adults).
- **Tuberculin test:**
 - o Many children are positive by the age of 12 (especially in developing countries)
 - o We always have a number of positive asymptomatic cases that spread the infectious agent.
 - o The infectious agent of TB survives under harsh conditions for long periods of time. They can resist extremes of heat and dryness; however, when it comes to sunlight, they are sensitive (especially to UV light). In darkness, they can survive for years.

- In our community, we do not have many cases. In fact, many of the cases are restricted to children. Others are asymptomatic carriers (tuberculin positive, as well)
- Primary infections are associated with an immune response that can be detected through the tuberculin test.
- This test is important to distinguish those who had previous contact with TB causative agents from those who did not.
- A positive tuberculin test result is when the patient shows an erythematous skin lesion at the site of infection.
- In the case of a true infection, the lesion is more than one centimeter in diameter. However, if it were not a true infection, the lesion would be small.
- **How do we perform the test:**
 - Culture *M. bovis* 50 times (**sub-culture**) in order to reduce its pathogenicity (virulence factors).
 - Cultured cells are purified extracting cell wall components (mycolic acids and lipoproteins)
 - Inject purified components at a concentration of 0.5 IU (international units) on the forearm of the patient
 - If there is a positive reaction after 48 hours, then it is considered a positive test. If there was no reaction, and you still suspect an infection, repeat the test with higher doses.
- A positive tuberculin test is not pathognomonic for TB; other tests are used to confirm the findings. These include:
 - Isolation of the microorganism via culture (sputum or other bodily fluids)
 - X-ray
 - Clinical features (they vary from one person to the other; thus, it is hard to decide based upon them)
- **Atypical mycobacteria:**
 - **M. bovis:**
 - It is related to animals but might infect humans producing the same clinical features.
 - The true human form cannot infect animals, but the animal form can infect humans.
 - The infection usually starts in the GIT. This is due to the fact that this organism is mostly transmitted by contaminated food products (mainly milk).
 - Its growth pattern is similar to typical mycobacteria tuberculosis.
 - **M. kansasii:**
 - First discovered in the state of Kansas, hence the name.
 - It is related to contamination of soil.
 - In the presence of light, it produces a yellow pigment (transparent under dark conditions).
 - Other species cannot produce pigmentation. The culture is kept in well-lit and dim environments to test for the presence of this bacterium.

- This type only manages to establish infections in immunodeficient patients (other types infect immunocompetent patients). 30% of AIDS patients are infected by this organism.
 - **M. marinum:**
 - It is related to aquatic organisms.
 - It survives in low temperatures and produces skin ulcers known as aquarium granuloma.
 - It often infects fish, and then is transmitted to humans.
 - **M. avium:**
 - It is related to many types of animals (dogs, cats, birds, etc...).
 - It is associated with skin lesions in the form of ulcers.
 - It does not respond to normal antimicrobial drugs, and might require surgical treatment.
 - **Ulcerans:**
 - It is found in tropical and subtropical areas. It produces localized infections.
- **Growth pattern:**
 - Typical and bovis: 2-8 weeks
 - Atypical: 1-3 weeks
- Ulcerans, avium and marinum species cannot disseminate to other parts of the body; they only produce localized infections in the skin of the lower areas of your body.
- All the atypical strains, except for kansasii, produce symptoms related to the skin not to the pulmonary tract.
- There is a rapid growth strain of mycobacterium. This strain is usually found between our skin folds. It is rarely associated with clinical infections. Their rapid growth indicates that they are not human pathogens. They are just contaminants. A patient does not receive treatment unless he/she has a slow growing strain.
- **Stages of detecting a mycobacterium:**
 - Direct smear from skin or sputum followed by staining
 - Culture (report slow or rapid growth)
 - Biochemical tests and resistance tests.
 - PCR is not accurate because it only indicates the presence of an acid fast bacillus without indicating the type.
- **Treatment:**
 - Many multiresistant strains have emerged in the past ten years. These strains are resistant to Rifampin and Isoniazid. However, this depends on the country. In Jordan, we don't have multiresistant bacteria. All multiresistant strains are imported.
- **Duration of treatment:**
 - Normal TB: 3-6 months (200 JD's cost)
 - Multiresistant: 1-3 years. (10,000 JD's cost)
- **Vaccination:**
 - BCG
 - It does not give full protection; it only decreases incidence by 50%.

- **Nocardiosis:**

- Nocardia is a gram positive dimorphic bacillus, but has similar clinical manifestations to TB.
- The only way to distinguish between TB and Nocardiosis is by culture. We use a modified acid fast bacilli culture.
- Nocardia are slow growers and prefer to be grown at room temperature (20-25 degrees Celsius).
- It is widely distributed in nature.
- It can survive in the extremes of temperature.
- It is not only related to respiratory tract; it can spread to the kidneys or any other organ. It is a cause for meningitis and brain abscesses.
- It is associated with an infection during the process of dialysis.
- Nocardiosis is well known for a chronic form of disease.
- It can produce lesions in the skin
- **Treatment:**
 - Cotrimoxazole or aminoglycosides.
 - We do not give typical anti TB agents.

- **Fungal agents:**

- Many people are exposed to fungal spores; these spores are spread all over the world.
- Fungi are usually associated with mild asymptomatic infections or asthma; however, they rarely cause a full-fledge clinical infection.
- People might develop an allergic reaction without developing the symptoms of a clinical infection. The clinical presentation depends on the site of infection.

- **Yeast:**

- There are two types of yeast infections:
 - Endogenous
 - Exogenous
- The endogenous infection is related to the presence of normal fungal flora in our bodily cavities. Their activation produces a clinical infection; they are only activated under certain conditions. This type of yeast is called candida.
- Yeast cells are usually non-filamentous; however, when they become infectious, they transform from the non-filamentous spherical morphology into the filamentous morphology by elongation.
- The tip of the filament attaches itself to certain receptors on the mucosa causing an infection in the form of a biofilm over the infected area.
- We use a wet preparation to demonstrate the presence of filaments. These filaments, in fact, are not true filaments. They are called pseudohyphae. Between the pseudohyphae, we might find blastospores, but this differs from one type of candida to the other.

- The filaments are a proof of the presence of pathogenic yeast. Non-filamentous yeast strains demonstrated in the preparation are of no importance because they do not cause an infection.
- **Candida albicans** and is associated with the majority of clinical infections. It produces pseudohyphae and blastospores.
- **Candida tropicalis** along with other species do not produce spores; they only produce filaments.
- The clinical manifestations are similar; in fact, it is impossible to distinguish between the causative agents on the basis of physical examination.
- **Candidiasis:**
 - It is usually a localized infection.
 - Systemic candidiasis is not common. It is usually related to patients with immunodeficiency. Without the presence of severe immunodeficiency, candida strains do not reach blood. The use of immunosuppressant drugs (especially following organ transplants) produces the same effect of AIDS. Systemic candidiasis is dangerous, and mostly lethal.
 - Treating systemic candidiasis is not easy as it requires a very specific dosing regimen as antifungal drugs (ex. Amphotericin) are highly toxic.
 - For local infections we use ointments such as Nystatin
- **Capsulated yeast:**
 - Cryptococcus family of yeast is the only family of yeast that possess a capsule.
 - Cryptococcus neoformans is representative of all other species. It is the most common infectious agent of its family.
 - The clinical features of all cryptococcoses are similar.
 - It often starts with the inhalation of this form of yeast.
 - The yeast lodges in the sinuses and spreads to the lungs where it forms granulomatous lesions.
 - It can disseminate to the blood causing sepsis.
 - Establishing a clinical case for cryptococci is difficult due to the lack of specific clinical symptoms.
 - They are usually present in small numbers of cells. They are very hard to culture.
 - X-rays and CT scans might give an impression of granuloma, but we cannot get more information.
 - Infection with Cryptococci is associated with a high mortality rate. This sort of infection is usually related to immunocompromised patients.
 - To detect the causative agent, we either use culture or practical tests.
 - Looking for antibodies is useless.
 - A PCR test has been recently developed, but it did not give the expected results.
 - If you have enough cells, you can demonstrate the cells using **India ink**.
 - CSF's biochemical content remains intact. There are no changes in the amount of proteins, sugars, or other substances.
- **Filamentous fungi:**
 - The difference between this type of fungi and yeast is the presence of true hyphae (filaments).
 - They have horizontal (vegetative) and vertical (aerial) filaments.

- Moreover, we can find spores (microspores or macrospores) that hold cells ready to be released into the environment to reproduce.
- The arrangement of spores and filaments determines helps in the identification of the fungus.
- There are four clinically important types of **Aspergillus**:
 - **Niger** (black)
 - **Fumigatus**(blue to green)
 - **Flavus** (yellow)
- Aspergillus spores:
 - Widely distributed in nature.
 - They are associated with dead organic material.
 - They are highly resistant to harsh conditions (dryness and extremes of temperature).
 - These spores account for more than 50% of the spores in the environment.
- Diseases related to Aspergillus can be divided into several categories:
 - Mycotoxicosis
 - Allergic bronchopulmonary disease:
 - it is a form of allergic reaction that can end in asthma.
 - It is very common in Jordan and accounts for 5% of allergic reactions.
 - It is associated with an increase in eosinophils
 - Release of aflatoxin:
 - it is released from the flavus species. I
 - t is a fatal toxin (nano amounts are enough).
 - It is associated with milk and nuts.
 - Having a humid environment encourages the growth of spores which release this type of toxin.
 - Respiratory aspergilloma:
 - It is a pulmonary form of the aspergillus infection.
 - As a prerequisite, the lung must have a TB cavity, fibrosis, or malignancy for the fungus to grow.
 - The fungal growth is called a fungus ball.
 - It destroys tissues and affects the pulmonary function.
 - It might disseminate to the sinuses causing rhino-cerebral lesions. They mostly require a surgical intervention.
- **Treatment of aspergillus and other types of filamentous fungi:**
 - Traditional treatment is difficult; therefore, surgical and chemical treatment should be used together.
 - Chemical treatment is not sufficient because you cannot give doses high enough to penetrate the whole fungus ball.
 - In such fungi, you don't recognize the presence of spores with filaments; you recognize short filaments.
 - Spores can only be recognized only in the presence of atmospheric air. Some filaments might give the impression of a spore.

- **Dimorphic fungi:**
 - If we culture them in vitro, we get the typical fungal filaments and spores.
 - Once in tissues, the spores can no longer be recognized.
 - Spores need a high amount of oxygen to develop. Therefore, in tissues, these fungi grow as small segments of filaments that are usually associated with small yeast-like structures.
 - **Causative agents:**
 - *Histoplasma capsulatum*
 - *Coccidioides immitis*
 - *Blastomyces dermatitidis*
 - **Histoplasmosis and related diseases:**
 - Contrary to what the name indicates, *Histoplasma capsulatum* is not capsulated.
 - *Histoplasma*, *coccidioides immitis*, and *blastomyces* are found in the intestinal tract of large birds.
 - They don't produce infections in these birds. They remain viable for a long time in the environment.
 - Once one of these 3 reaches the respiratory tract and lodges in the sinuses or lungs, a form of allergic reaction might ensue.
 - There is a detection test similar to the tuberculin test.
 - A positive result does not mean the presence of the microorganism; it only indicates previous contact with the organism.
 - In immunocompromised patients, the old infection might flare up producing flu like symptoms. These might later develop into pneumonia.
 - The infection might reach different parts of the body including the meninges producing a chronic form of meningitis.
 - Dissemination of hisplasmomosis is difficult to cure and control, but, fortunately, it only happens in immunocompromised patients.
 - This disease is mainly concentrated in the southern areas of the United States.
 - You cannot know that causative agent unless you culture the specimen. All three filamentous fungi produce the same clinical feature, give a positive histoplasma skin test, and have the same antigen
 - *Blastomyces dermatitis:*
 - Infection with this organism might start as a skin infection rather than a pulmonary infection.
 - It can disseminate to other organs, including the meninges, causing a severe infection often leading to the death of the patient.
- **Pneumocystic carinii:**
 - It was first thought of as a parasite; however, they discovered that it is more related to yeasts.
 - The organism is a yeast-like cell that cannot be easily isolated from the animals or humans. A rat origin is suspected.

- **Pneumocystic jirovecii**: a new species discovered ten years ago. It is related to humans not animals.
- The route of infection is unknown, but it is usually a disease of the young. It produces mild clinical symptoms without further complications.
- The infection rate increases with age; by the age 60, 50% of the population is positive for this organism.
- There are no major clinical features associated with this organism
- In immunocompromised patients, it might cause sepsis and meningitis.
- It is not easily isolated in cultures. Most of the identified cases were identified through a lung biopsy.
- It stains with silver stain and Gimsa stain. We test for its antigen; testing for antibodies is useless.
- Treatment:
 - it can be treated with antibacterial drug like cotrimoxazole.