

RESPIRATORY SYSTEM

MICROBIOLOGY



Title: Microbiology sheet 6

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Miscellaneous respiratory tract infections:

Note: The underlined sentences were not mentioned by the doctor.

Atypical Pneumonia

Atypical pneumonia is called so because they do NOT present as classical pneumonia (which is characterized by being confined to one lobe of the lung (lobar pneumonia), high fever, productive cough, dyspnea, malaise, loss of appetite, etc.). Instead, they have mild, low grade fever, dry cough, shortness of breath (dyspnea), and extra-pulmonary symptoms (sore throat, headache), hence atypical! It is also called "Walking Pneumonia" since the patients are still able to walk, function, and do daily life activities regardless of the symptoms they are describing. Also, their treatment differs from the classical pneumonia.

So, it causes milder form of pneumonia characterized by slow development of symptoms, unlike other forms of pneumonia which can develop more quickly with more severe early symptoms.

Atypical pneumonia is caused by *Mycoplasma*, *Chlamydia*, and *Legionella*. These related Gram-ve bacteria are attached to respiratory mucosa but they are not a common part of the respiratory flora, so they are opportunistic pathogens. However, some mycoplasma species **might be** part of the respiratory flora, while *Chlamydia* and *Legionella* are **not**. Also, they can be part of the normal flora in other places in the body.

1-Mycoplasma

Mycoplasma pneumoniae:



- The smallest size bacteria.
- Aerobic growth and associated with diseases in humans, animals, and birds.
- They lack a cell wall → so antibiotics like penicillin (which works on the bacterial cell wall) will not work on them (unique). They have a lipid bi-layer membrane.
- Mode of transmission is via droplets.
- We have 4 species that are important for us as doctors 😊 which are:
 - 1- **Mycoplasma pneumoniae: their target are the lungs.**
 - 2- **Mycoplasma hominis**
 - 3- **Mycoplasma parvum**
 - 4- **Ureaplasma urealyticum**

The target of the last 3 species is the genitourinary tract. As a result, mycoplasma **might be** part of the normal flora of the **respiratory mucosa**, as well as the genitourinary tract.

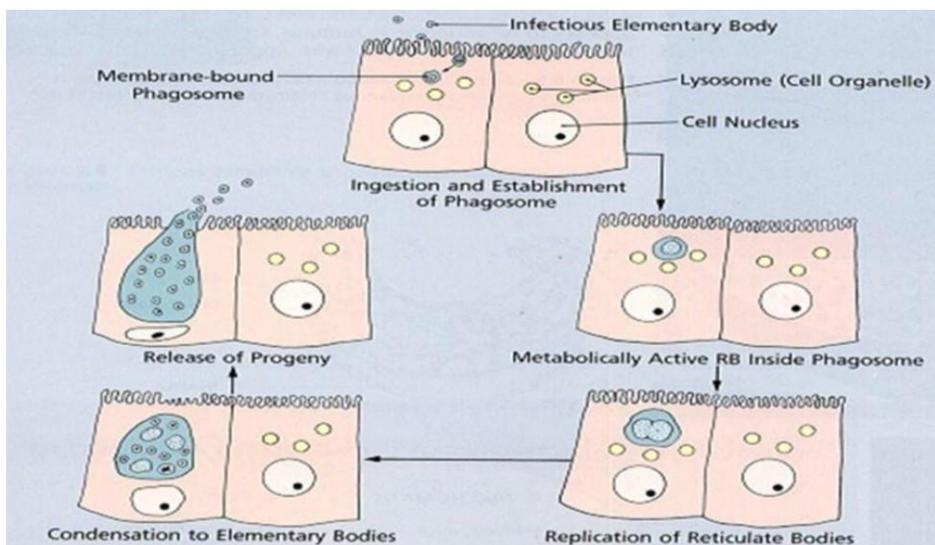
- It affects old children and young adults (**school age children, as well as teens [>5 and <20 years old]**). Severe forms of pneumonia have been described in all age groups.
- **Lab Diagnosis:**
 - 1- Culture is not used for diagnosis, because it takes about a month, mycoplasma is almost the size of large viruses (very small) and pleomorphic, often are contaminants in other cultures, and it requires a special culture medium.
 - 2- PCR (Polymerase Chain Reaction) and cold agglutination test [the human body starts to produce autoantibodies against RBCs, and they clump the RBCs when they are exposed to cold temperature]. These methods are faster. They report positive in 70% of patients, so there is 30% of patients that have the organism but are negative to the test. Thus, these tests are **not** highly specific nor sensitive.
 - 3- The most specific test is **microimmunofluorescence (MIF)** [done by comparing diluted antibody titers (of IgG or IgM) from a sick patient and a healthy individual], but it is a sophisticated test and is not available in Jordan.
- **Treatment:**

Most patients resolve spontaneously, but they remain infectious to others (household contact results in a 50-90% transmission rate to the individuals living with the patient). Treatment with macrolides (Azithromycin) and fluoroquinolones (Levofloxacin, Moxifloxacin).
- Mycoplasma is an **extracellular infection** (attachment to ciliated and non-ciliated respiratory cells using a protein called PI). Although there is documented cases of intracellular event, but we describe the mycoplasma as an extracellular infection.
- No vaccine
- Common infection in Fall-Winter.
- Often develop low fever and dry cough symptoms. Lasts for a few days to weeks. Other symptoms include anemia, rashes, neurological syndromes, meningitis, encephalitis, acute/subacute pharyngitis, and bronchitis.

2-Chlamydia

- 3 important species that cause atypical pneumonia are Chlamydia pneumonia, Chlamydia trachomatis, and Chlamydia Psittaci.
- Chlamydial pneumonia accounts for more than 15% of all pneumonia cases.
- **Obligate intracellular** infection (VIP).
- Characterized by attached human mucosal membrane, intracytoplasmic inclusions. They are rapidly killed outside the body, in dryness, and high temperature > 4 C.

- **Chlamydia trachomatis (Serotypes C, K):** Common cause of sexually transmitted diseases (STDs), nonspecific urethritis, mother to newborn babies, maternal fluid, atypical pneumonia, eye infection, and ophthalmia neonatorum. A and C serotypes of endemic Ch. trachomatis cause **Trachoma**, which is characterized by conjunctival scarring, damage to eyelids, cornea, and blindness. In fact, it is one of the most common infective agents resulting in preventable blindness.
- **Chlamydia Life Cycle:**



As you can see, Chlamydia has biphasic morphology:

- 1- **Elementary bodies:** extracellular and infectious form.
- 2- **Reticulate body (RB):** intracellular and reproductive form. It's metabolically active (unable to survive extracellularly). They also form intracellular granules (cytoplasmic inclusions) that can be stained.

[Life cycle (according to the above picture): First, C. trachomatis attaches to the host mucosa as **infectious elementary body** and promotes its entry → elementary body is surrounded by a cytoplasm phagosome → C. trachomatis transforms into the **metabolically active RB** → replication of RB takes place forming many intracellular bacteria → these bacteria will transform back to **elementary bodies** → the cell will rupture and elementary bodies are released, which will eventually reinitiate the cycle].

A- Chlamydia pneumoniae:

- **Mode of transmission is by droplets.**
- **Also called Chlamydophila to distinguish it from chlamydia trachomatis, which causes STDs.**
- **Tend to infect children.**

☺ In infants/children, it often develops gradually. Several weeks of mild respiratory symptoms, dry irritating prolonged cough, nasal congestion, and with/without fever. No blood sepsis.

☺ C. pneumoniae infections in adults are often asymptomatic, mild, and may include sore throat, headache, fever, and dry cough.

- Clusters of infection have been reported more common in children than in adults.
- About half of all newborns with Chlamydial pneumonia develop inclusion conjunctivitis. 1-2 weeks starts mild and then severe eye redness, swollen eyelids, inflammation, and yellow thick discharge eyes.
- **Diagnosis:**
Sputum, throat-nasal swab, MaCoy Cell Culture, ELSA specific antibodies, PCR and Microimmunofluorescence (MIF). So, we can culture them, but PCR, MIF, and ELISA are better. **(MIF is the gold standard)**. Also, its culture is easier than mycoplasma.
- **Treatment:**
Tetracyclines, Macrolides, levofloxacin, moxifloxacin. Again, penicillins don't work, so we use macrolides, fluoroquinolones and tetracyclines.
- **No vaccine**

B- Chlamydophila Psittaci:

- **C. psittaci causes zoonotic diseases. It causes a rare human disease called psittacosis (ornithosis).**
- **Transmission:** Human infection followed contact with birds (parrots, pigeons, turkeys, and ducks), usually from people who work with them or work in slaughterhouses). It is NOT via droplets. Humans respiratory tract can be infected via inhalation of bacteria shed from feathers, secretions, and droppings. However, person to person transmission has never been documented.
- **Localized inflammation in bronchi and lung tissues.**
- **Signs Symptoms:** Starts mild and flu-like, and ends with severe disease, including fatal pneumonia, associated high fever, dry cough, and headache.
- **Diagnosis and treatment are similar to other Chlamydia (specifically C. pneumoniae).**

3- Legionella pneumophila:

- **Legionella are gram negative bacteria and include pathogenic and nonpathogenic species.**
- **It causes two diseases:**
 - 1) **Pontiac fever** is very mild and has flu-like symptoms. So, no treatment is needed.

2) **Legionnaires** presents with **atypical pneumonia as well as GI symptoms** (ex. diarrhea). Another characteristic of Legionnaires is **hyponatremia** due to fluid and electrolyte imbalance.

- **Tends to affect children and elderly with risk factors** [these risk factors include heavy cigarette smoking, old age, underlying diseases such as renal failure, cancer, diabetes, or chronic obstructive pulmonary, suppressed immune system and corticosteroids].
- **Often found in natural aquatic bodies and wet soil** (aquatic bacteria living in water systems), and cause outbreak of disease. **Facultative anaerobes that grow in cold/hot (4-80C) water.**
- **Transmission: they are water transmitted by inhalation of infected water droplets from natural water systems, and air condition (AC), AC is the most common mode of transmission. Transmission is NOT from an infected patient, thus person to person transmission is very rare. Legionnaires disease is not contagious.**
- Lung mucosa. Multiply intracellular within the macrophages.
- Incubation period: 2-10 days.
- **Present as high fever, nonproductive/ productive dry cough, shortness of breath, chest pain, muscle aches, joint pain, diarrhea, renal failure, with high mortality rate.**
- **Diagnosis:** Special culture media (using a selective media → charcoal yeast extract (CYE)) and their culture is easier than mycoplasma and chlamydia. Also, blood/urine specimen for detection of specific antibodies or antigens by PCR or ELSA. Urine sample is the most common used test for diagnosis.
- **Treatment:** Macrolides (azithromycin), fluoroquinolones (levofloxacin, moxifloxacin).
- **No Vaccine.**

4- OPPORTUNISTIC MYCOSES:

- **Opportunistic: causes significant disease in immunocompromised patients. However, they can also cause disease in healthy people, but it is not significant . Patients at risk include those with hematologic dyscrasias (e.g., leukemia, neutropenia), patients with HIV/AIDS with CD4 counts less than 100 cells/ μ L, as well as those treated with immunosuppressive drugs (e.g., corticosteroids and post-transplantation therapy), and cytotoxic drugs.**
- Opportunistic mycoses are caused by globally distributed fungi that are either members of the human microbiota, such a Candida species, or environmental yeasts and molds.
- They can produce disease ranging from superficial skin or mucous membrane infections to systemic involvement of multiple organs.

Cryptococcus neoformans:

- Cryptococcus neoformans causes **cryptococcosis**.
- A widespread **encapsulated yeast** (capsule is antiphagocytic); thus, the capsule plays a major role in the pathogenesis. It inhabits soil around pigeon roosts. Reservoir is birds, whose droppings infect soil, and are then inhaled.
- Common infection of AIDS, cancer, or diabetic patients (immunocompromised). Also, pregnant women are considered to be at risk.
- C. neoformans are characterized by being **neurotropic**. After infecting lungs, they try to get to the CNS and cause meningitis. Infection of lungs leads to cough, fever, and lung nodules. Dissemination to meninges and brain can cause severe neurological disturbance and death.
- **Diagnosis:**
 - 1) **Microscopic:** India Ink for capsule stain (50-80% + CSF). It shows the capsule (the capsule is **diagnostic** of C. neoformans).
 - 2) **Culture:** **Bird seed agar** is selective for C. neoformans (gold standard). Also, routine blood culture can be used.
 - 3) **PCR (Polymerase Chain Reaction)**

Aspergillosis: Diseases of the Genus Aspergillus:

- Very common airborne soil fungus.
- **600 species, 8 involved in human disease.** Most commonly, *A. fumigatus*.
- Serious opportunistic threat to AIDS, leukemia, and transplant patients.
- **Mode of infection:** inhalation of the reproduction elements of these fungi.
- Infection usually occurs in lungs, and they can colonize sinuses, ear canals, eyelids, and conjunctiva. In already diseased lungs, spores germinate in lungs and form fungal balls (called aspergilloma). Antifungal medications are not effective against fungal balls, surgery is required.
- Aspergillosis starts in the lung and can present as bronchopulmonary allergies (simplest form). Then, invasive aspergillosis in preformed cavities can happen, which results in the development of necrotic pneumonia, and infection of brain, heart, and other organs.
- **Treatment:** surgery, Amphotericin B, and nystatin.

Zygomycosis (Mucormycosis):

- Zygomycota are extremely abundant saprophytic fungi found in soil, water, organic debris, and food.
- Genera most often involved are *Rhizopus*, *Absidia*, and *Mucor*.
- Usually, harmless air contaminants invade the membranes of the nose, eyes, heart, and brain of people with diabetes (mainly) and malnutrition (*so it's also called Rhinocerebral mucormycosis*). In these patients, it causes severe consequences because it causes huge destruction/ disfigurement of these areas. However, if a

healthy person is infected, he will not have any problems, or only will develop mild problems.

- **Main host defense is phagocytosis.**
- **Diagnosis: It is made by direct smear and by isolation of molds from respiratory secretions or biopsy specimens.**
- **Treatment: Control Diabetes, surgery, and amphotericin B.**
- **Prognosis is very poor because they are immunocompromised , so any simple infection in addition to mucormycosis can be fatal.**

PNEUMOCYSTIS:

- **Pneumocystis jirovecii** is the cause of a lethal pneumonia in immunocompromised persons, **particularly those with AIDS.**
- Initially thought to be parasites, but now classified as fungi.
- Definite diagnosis of pneumocystosis depends on finding organisms of typical morphology in appropriate specimens (Sputum, BAL [Bronchoalveolar Lavage]), because it can **NOT** be cultured in the lab.
- Treatment: TMP-SMX (Trimethoprim/Sulfamethoxazole) is the treatment of choice (the only drug that can treat them). In Jordan, TMP-SMX is called cotrimol or cotrimoxazole.

Endemic mycosis:

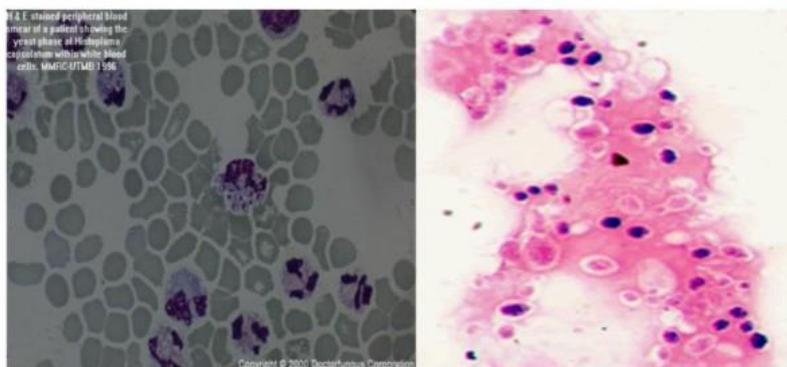
- **Endemic mycosis is caused by a thermally dimorphic fungus, and the infections are initiated in the lungs following inhalation of the respective conidia.**
- **Each of the four primary systemic mycoses—coccidioidomycosis, histoplasmosis, blastomycosis, and paracoccidioidomycosis—is geographically restricted to specific areas of endemicity (not usually seen in Jordan, mainly in south USA and South/Central America).**
- **Common trait among all 4 is that they are dimorphic fungi: which means that they exist as mold/filamentous fungi at room temperature (25C), and they transform into yeast at body temperature (37C).**
- **These are endemic diseases, so they can be seen in healthy people as well as immunocompromised people (more severe with higher fatality rate).**
- **Most infections are asymptomatic or mild and resolve without treatment. However, a small, but significant, number of patients develop pulmonary disease.**
- **Initially, all of them infect the lung.**
- **In healthy people, it is presented as an acute infection. On the other hand, immunocompromised people it is presented as a chronic illness and may disseminate all over the body.**

Dimorphic Fungus:

☺ Histoplasmosis:

- The name is a misnomer as *histoplasma capsulatum* is NOT encapsulated.
- Dimorphic fungus with conidia and yeast forms at body temperature, and hyphae and macroconidia in vitro culture. Common in soil enriched with excreta of birds.
- Endemic in southern U.S.A, Australia (less in other countries).
- Infection by inhalation of microconidia or macroconidia (the reproduction elements of fungi).
- They are intracellular, living inside immune cells of reticuloendothelial system.
- The primary site of infection is usually pulmonary. Phagocytosed by macrophages, Obligate intracellular parasites. Cause slight inflammatory reaction.
- Most cases of histoplasmosis are asymptomatic /subclinical, benign, and flu-like syndrome. Few may develop chronic progressive lung disease, granuloma and fibrosis, chronic cutaneous or systemic disease involve any internal organ, and fatal systemic disease.
- All infected patients become positive by histoplasmin skin test (test may stimulate humoral antibodies to *histoplasma capsulatum* antigens in histoplasmin-hypersensitive individuals).

Histoplasma capsulatum
in infected White Blood cells



☺ Coccidioidomycosis & Blastomycosis:

- *Coccidioides immitis* and *Blastomyces dermatitidis* cause Coccidioidomycosis and Blastomycosis, respectively. They are soil inhabiting Dimorphic Fungus.
- Endemic in south-western U.S.A., northern Mexico and various parts of South America (found in desert areas).
- They cause infection primarily in the lung.
- Respiratory infection, resulting from the inhalation of microconidia, often resolves rapidly leaving the patient with a strong specific immunity to re-infection. Acute infection in healthy people (not very significant for *C. immitis*, but can be fatal for

B. dermatitidis). Blastomycosis results in severe morbidity and, eventually, mortality.

- In some individuals, the disease may progress to a chronic pulmonary condition or a systemic disease involving the meninges, bones, joints, subcutaneous, and cutaneous tissues.
- Antigen skin test is positive, but, unlike H. capsulatum, is not significant in diagnosis, because these fungi cross-react and can result in false positives.
- Laboratory Diagnosis:
 - Direct microscopy (C. immitis, when viewed microscopically, have an appearance of conidia in a bag, which is unique to it) and culture should be performed on all specimens (sputum, bronchial washings, CSF, pleural fluid tissue biopsies from various visceral organs).
 - Wet mounts in 10% KOH with india ink , Ovoid-budding yeast cells, Gram-stain smear.
 - Cultures on Sabouraud dextrose agar (SDA is used to differentiate based on morphology) should be maintained for one month at 25C.
 - Fungal growths and Wet Mount Identification produce hyphae-like conidiphores and spores. Color of fungal growth.
 - Serological tests are of limited value, not significant.
 - Detection of Histoplasma antigen in blood & urine is significant.

😊 Paracoccidioidomycosis:

- Paracoccidioides brasiliensis is the thermally dimorphic fungal agent of paracoccidioidomycosis (South American blastomycosis), which is confined to endemic regions of Central and South America (can be found in immigrants/tourists in southern USA).
- P. brasiliensis is inhaled, and initial lesions occur in the lung. After a period of dormancy that may last for decades, the pulmonary granulomas may become active, leading to chronic, progressive pulmonary disease or dissemination.
- Typical presentation is similar to Coccidioides immitis.