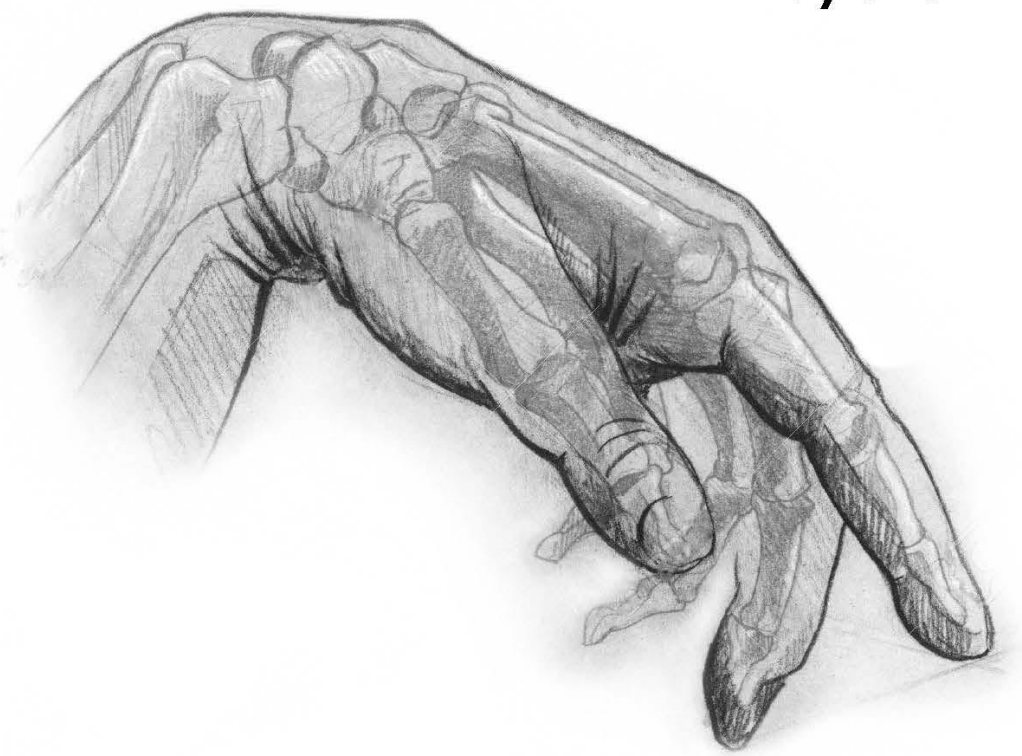
The

Musculoskeletal

System



Virology

☑ Sheet ☐ Slide ☐ Handout

Number:	3
Subject:	Childhood Exanthems
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Childhood Exanthems (introduction)

The major viruses described in this lecture are **mumps**, **measles**, **rubella**, **roseola infantum (caused by HHV6 &HH7)**, and the **Erythema infectiosum (caused by human parvovirus B19)**, which are from different virus families and genetically unrelated, but share several common epidemiologic and clinical characteristics, including:(1) *worldwide distribution, with a high incidence of infection in nonimmune individuals*;(2) *humans as sole reservoir of infection*; and (3) *person-to-person spread primarily by the respiratory (aerosol) route*.

Most of these viruses are characterized by the presence of rash, here we have to differentiate between two types of rash :

Exanthemes (Childhood Exanthemes):means external rash on the skin. ***enanthemes***: means internal rash that appears on mucus membranes.

3.1 Measles -الحصبة-

Measles (aka *Rubeola* or *five-day measles*) belongs to *paramyxovirus* family, genus *Morbillivirus*. *It contains a linear, negative-sense, single-stranded RNA genome* surrounded by a helical nucleocapsid protein and a lipid bilayer envelope containing two glycoprotein projections; *hemagglutinin (H)* that mediates virus adsorption to the cell surfaces, and *fusion (F)* protein that mediates cell fusion, hemolysis, and viral entry into the cell. Unlike the mumps virus, the measles virus lacks neuraminidase (N) activity. The receptor for measles virus is *CD46*.

Note: the terms *five-day* and *three-day measles* are used to differentiate between measles and rubella. If the rash lasts for 3 days, its rubella. And If lasts for 5 days it's measles.

Measles have only one serotype restricted to human infection , so one infection is sufficient to develop life-long immunity. However, subtle antigenic and genetic variations among wild-type measles strains do occur.

Measles infections often produce severe illness in children, it is characterized by many serious complications: *(fever and 3Cs)*

1- **high fever,** the patient temperature may reach 40°C/105 F.
2- **Cough**
3- **Coryza (runny nose)**
4- **Conjunctivitis**
5- This virus is also associated with **transient immunosuppression** since it attack T and B lymphocytes once it reaches the blood.

Epidemiology

The highest attack rates of measles have been in children, usually sparing infants less than 6 months of age, *why??*

1. Because of passively acquired antibody.
2. This virus is one of the most contagious agents among humans, The infection rate among exposed susceptible subjects in a classroom or household setting is estimated at 85%, and more than 95% of those infected become ill. So if we have a class with 30 students, at least 29 student will be infected.

Epidemics tend to occur during the winter and spring. The period of communicability is estimated to be 3 to 5 days before appearance of the rash to 4 days afterward.

Pathogenesis

1- Measles is transmitted through respiratory inhalation (by aerosols or direct contact with contaminated fluids like saliva) and, after implantation of the virus in the upper respiratory tract, viral replication proceeds in the respiratory mucosal epithelium.

2- Susceptible cells are damaged or destroyed by virtue of the intense viral replicative activity and the promotion of cell fusion with formation of syncytia. This results in disruption of the cellular cytoskeleton, and the appearance of inclusion bodies within the nucleus and cytoplasm.

3- Replication is followed by viremia and lymphatic dissemination throughout the host to distant sites, including lymphoid tissues, bone marrow, abdominal viscera, skin, conjunctiva, urinary tract and CNS.

4- During the viremic phase, measles virus infects T and B lymphocytes and polymorphonuclear leukocytes so a depression of cell-mediated immunity occurs during the acute phase of illness and persists for several weeks thereafter, this may lead to the development of many bacterial superinfections.

5- The lymphoid tissues show hyperplastic changes, and large multinucleated giant cells are often observed (Warthin-Finkeldey cells). *Some of the giant cells contain intracytoplasmic and intranuclear inclusions.*

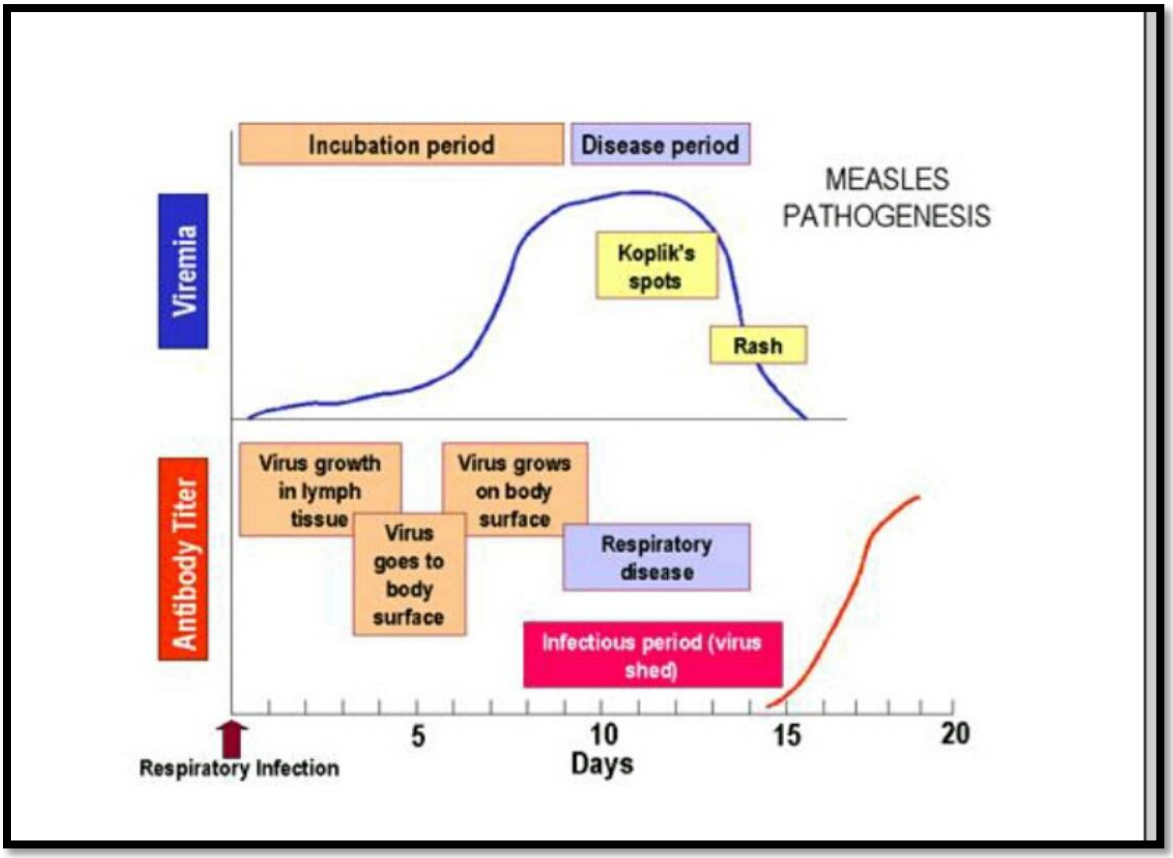
6- skin lesions show vasculitis and skin rash.

Note: the temporal sequence of symptoms in measles is:

- fever.
- After 24 hours the patient will develop Koplik's spots *(red spots with bluish-white centreon the buccal mucosa against the molar teeth)*
- After few days he will develop exantheme. (Starting From head →neck→ the extremities)

Koplik's spots are diagnostic for measles

7- In some patients with measles, an immune-mediated post infectious encephalitis occurs. The pathogenesis is thought to be related to infiltration by cytotoxic (CD8+) T cells, which react with myelin- forming or virus-infected brain cells.



As a summary :

We have an Incubation period which lasts for 7-18 days, then Koplik's spots will appear, then the patient will develop rash (head ,neck, limbs)

Note: Rubella also mimics this distribution, we can differentiate between them by:

Rubella → bale faint rash , pinkish / measles → dark-red rash

Immunity

Cell-mediated immune responses to other antigens may be acutely depressed during measles infection and (*persist from few weeks to several months*), there is evidence that measles virus-specific cell-mediated immunity developing early in infection plays a role in mediating some of the features of disease, such as the rash, and is necessary to promote recovery from the illness. Antibodies to the virus appear in the first few days of illness, peak in 2 to 3 week. Immunity to reinfection is lifelong and is associated with the presence of neutralizing antibody (*since we are talking about one serotype, production of IGg will produce lifelong immunity*)

Clinical Manifestations

Common synonyms for measles is 5-day measles, *because rash remains 5 days* . The incubation period ranges from 7 to 18 days. A typical illness usually begins 9 to 11 days after exposure, with cough, coryza, conjunctivitis,(3 Cs) and high fever. One to three days after onset, Koplik's spots appear on mucous membranes. This sign is usually most noticeable over the buccal mucosa opposite the molar teeth and persists for 1 to 2 days . Within a day of the appearance of Koplik's spots, the typical measles rash begins—first on the head, then on the trunk and extremities. The rash is maculopapular ; it persists for 3 to 5 days before fading .

Lymphadenopathy is also common, with particularly noticeable involvement of the cervical nodes

Infectivity: 3-5 days before and 4 days after rash appearance

Mortality could reach 15-25% especially in immunocompromised and malnourished.

COMPLICATIONS

Bacterial superinfection, the most common complication, occurs in 5% to 15% of all cases, as a result of the transient

immunosuppression. such infections include acute otitis media, mastoiditis, sinusitis, pneumonia, and sepsis sinusitis.

Subacute sclerosing panencephalitis (SSPE) is a rare (1 in 100,000) progressive neurologic disease of children, which usually begins 2 to 10 years after a measles infection. It is characterized by insidious onset of personality change, intellectual deterioration, seizures, myoclonus, spasticity, tremor and ocular abnormalities. We have No treatment for this condition.

Diagnoses

The typical measles infection can often be diagnosed on the basis of clinical finding :

3Cs →cough, coryza (runny nose) and conjunctivitis , maculopapular skin rash (macule→reddens, papule→ elevation) so it's red elevation in the skin without fluid

However, For laboratory conformation we can use:

1-Viral isolation from oropharynx or urine.(virus could be shed in the urine)

2-Multinucleated giant cells.

3-Serology: ELISA, IF. PCR.. rarely used,

TREATMENT AND PREVENTION

We don't have specific anti-viral drug for measles, but sometimes we use Supportive treatment (anti-pyritic) for fever and some antibiotics (due to transient immunosuppression we will have bacterial superinfection, so we need to treat this infection)

Live attenuated vaccine :

MMR(measles, mump, rubella) vaccine is given in two doses; first (12 to 15 months) second (4-6 years) here we are talking about national vaccination program in case of children, in case of adults

that have not been vaccinated against MMR we give them two doses with 28 days at least between these doses .

In Jordan they give three doses: measles alone at 9 months old , then regular MMR doses.

First dose gives 93% - 94% protection against the virus, second one gives 97% -98% protection. taking these vaccines will almost protect you from being infected. However, in some countries we may have outbreaks of MMR, and some vaccinated individuals may be infected . This outbreaks may occur due to some immunocompromised patients and some religious thoughts that don't accept the vaccination.

In USA measles has been eliminated, because they have not recorded any case in the last 12 months.

MMR vaccine is contraindicated in immunocompromised patients and pregnant women except AIDS patients, because it's live attainted vaccine.

3.2Mumps- النكاف، أبو دغيم-

Mumps virus is a paramyxovirus, and only one major antigenic type is known (*so you will develop lifelong immunity after the first infection*), it contains a single-stranded, negative-sense RNA genome, and a nucleocapsid that is surrounded by a matrix protein followed by a lipid bilayer envelope . Two glycoproteins are on the surface of the envelope; Neuroamemdase-Hemaglutanin glycoproteins for attachment and F glycoproteins for fusion. it's not a Childhood Exanthemes, but it's always discussed with measles and rubella, so we have to discuss it here ..

It causes Parotitis (infection of parotid gland) and aseptic meningitis in children. In adults it causes encephalitis, it may cause also oophoritis (ovarian infection) in females and Acute orchitis (testicular infection)

EPIDEMIOLOGY

Mumps infection is Frequent in 5-15 years old, it isn't highly contagious since 30-40% of contacts do not develop clinical illness.

It's Communicable 7days before to 9 days after parotid gland swelling (parotidites)

highest incidence of infection is usually during the late winter and spring months, but it can occur during any season.

Pathogenesis and immunity

1-entery→ Local replication in RT and local lymph nodes → 1ry viremia →reach salivary glands and CNS →2ry viremia→ spread to organs (kidney).

2-Viruria is common (virus could be isolated from urine)

3-Tissue response characterized by cell necrosis and inflammation.

IMMUNITY

As in most viral infections, the early antibody response in mumps is predominantly with IgM, which is replaced gradually over several weeks by a specific IgG antibody. The latter persists for a lifetime, since we have one serotype . Immunity is associated with the presence of neutralizing antibody. The role of cellular immune responses has also been investigated and found to contribute both to the pathogenesis of the acute disease and to recovery from infection.

Clinical manifestations

After an incubation period of 12 to 29 days (average, 16-18 days), the typical case of mumps is characterized by fever and swelling with tenderness of the salivary glands Fever and parotid swelling, the swelling could be Unilateral or Bilateral (75% unilateral) ,mumps can also infect other salivary glands in 10% of the cases

COMPLICATIONS

The common complications of mumps infection, which can occur 1-3 weeks after disease onset, include the following:

Meningitis 10%, encephalitis, transverse myelitis, Pancreatitis, orchids 10-20%, Oophoritis, Other Rare complications are Myocarditis, nephritis, arthritis, thyroiditis, sensorineural deafness. Most complications resolve without sequale in 2-3 weeks.

Note: although mumps cause gonadal infections (orchids and Oophoritis), *it's not a common cause of sterility.*

Diagnosis and prevention

Mumps virus can be readily isolated early in the illness from the saliva as a result of the primary viremea, and due to it's secondry replication in CNS,it can also be isolated from , CSF, Pharynx and urine

virus grows well in primary monolayer cell cultures derived from monkey kidney, producing syncytial giant cells and viral hemagglutination.

Rapid diagnosis can be made also by PCR and Serology (ELISA, IF and neutralization test)

We don't have specific therapy against mumps. However we can prevent it by two doses of MMR .

3.3Rubella-الحصبة الألمانية-

Rubella (aka German measles and 3-day measles) , it's a mild benign childhood exantheme; causes Malaise, fatigue , faint rash Arthralgia and low graded fever. Unless it infected a pregnant women, it has Profound effects on developing fetuses. If it infect a pregnant women it may cause congenital rubella syndrome , especially in the first trimester.

Rubella virus is classifed as a member of the togavirus family, Rubivirus genus. It is a simple, icosahedral, enveloped virus, and

contains a single-stranded, positive-sense RNA genome. There is a single species of capsid protein, and the lipid bilayer envelope contains two glycoproteins, E1 and E2. The virus can agglutinate some types of red blood cells, such as those obtained from 1-day-old chicks and trypsin-treated human type O cells.

Rubella virus enters target cells via receptor-mediated endocytosis (viropexis). Genomic RNA encodes for nonstructural proteins and subgenomic RNA for structural proteins. Assembly occurs at the golgi or cytoplasmic membrane.

Epidemiology

Rubella infections are usually observed im Winter and spring, only 30-60% develop clinical apparent disease.

Note: *measles is highly infectious and the chance to develop disease is high, in mumps 60% , and here 30% so 70% will not develop any symptoms and will develop a live-long immunity*.

Women of childbearing age, carry a risk of exposure during pregnancy

It's Contagious 7 days before to 7 days after onset of rash.

Q: how can we differentiate between measles and rubella ?

1- **rash**: Rubella → bale faint rash , pinkish / measles → dark-red rash
2- **fever**: measles is associated with higher fever
3- **3Cs**, in measles we have Cough , Coryza and Conjunctivitis. In rubella ,however, we have cold-like symptoms without Conjunctivitis
4- infectious period

Infected babies spread the virus for 6 months after birth.

pathogenesis

1- In acquired infection, the virus enters the host through the upper respiratory tract, replicates, and then spreads by the

bloodstream to distant sites, including lymphoid tissues, skin, and organs.

2- Cellular immune responses and circulating virus– antibody immune complexes are thought to play a role in mediating the inflammatory responses to infection, such as rash and arthritis (*arthritis may be the only symptom in adults)*

3- Congenital infection occurs as a result of maternal viremia that leads to placental infection and then trans placental spread to the fetus, Pathogenesis of congenital defects: 1) vasculitis with impaired fetal oxygenation. 2) chronic viral infection leads to impaired mitosis, cellular necrosis and chromosomal breakage.

4- Shedding of the virus in infected infants is prolonged (up to 30 months)

Note : *observations underscore the fact that such infants are important reservoirs in perpetuating virus transmission. The prolonged virus shedding is somewhat puzzling; it does not represent a typical example of immunologic tolerance. The affected infants are usually able to produce circulating IgM and IgG antibodies to the virus, although antibodies may decrease to undetectable levels after 3 to 4 years*

Pathology and immunity

inflammatory changes can be observed in tissues, In severe cases, *normal calcium deposition in the metaphyses of long bones is delayed*, sometimes referred to as a "*celery stalk*" appearance on a radiograph. Once you do X-ray to infected babies you will notice this .

Natural infection results in the production of *specific secretory IgA antibodies in the respiratory tract.* Immunity to disease is nearly always life- long; however, *reexposure can lead to transient respiratory tract infection*.

Clinical MANIFESTATIONS

Rubella is commonly known as *3-day measles*. The incubation period for acquired infection is 14 to 21 days (average, 16 days). Illness is generally very mild, consisting primarily of low-grade fever, upper respiratory symptoms, and lymphadenopathy , which is most prominent in the posterior cervical and postauricular areas. A macular rash often follows within a day of onset and lasts 1 to 3 days. This rash, *which is often quite faint*, is usually most prominent over the head, neck, and trunk. The most common complication is **arthralgia** or overt **arthritis**, rarer complications include **thrombocytopenic purpura** and **encephalitis.**

The major significance of rubella is not the acute illness but the risk of fetal damage in pregnant women, particularly when they contract either symptomatic or subclinical primary infection **during the first trimester**. The risk of fetal malformation and chronic fetal infection, which is estimated to be as high as 80% if infection occurs in the first 2 weeks of gestation, decreases to 6% to 10% by the 14th week. The overall risk during the first trimester is estimated at 20% to 30%.

Clinical manifestations of congenital rubella syndrome vary, but most common manifestations are : **deafness , cataract, microcephaly ,heart abnormalities, and enlarged Liver and Spleen**.

Note: Microcephaly means small head, because we have no space for brain development ,other viruses that cause microcephaly is zeka virus .

Diagnosis and treatment

Because of the rather nonspecific nature of the illness, *a diagnosis of rubella cannot be made on clinical grounds alone*. The virus may be isolated from respiratory secretions in the acute phase by inoculation into cell cultures or detected by RT-PCR.
Like other childhood Exanthems, we use Supportive treatment only.

And we have live attenuated vaccines for it like MMR and *MMRV: (measles, mumbs , rubella , vercila)*.

it is strongly recommended that nonpregnant women avoid conception for at least 3 months afar receiving the vaccine.

Now we have finished the most important childhood Exanthems, last two infections are not that important, and the doctor just read the slides. I'll copy the slides here and add some important notes ^^

3.4 Erythema Infectiosum

- It's caused by Parvovirus B19, *this virus is one of the smallest viruses*.
- Naked, icosahedral, SSDNA
- Three capsid proteins VP1-3
- cultured in Bone Marrow cells, fetal liver cells.
- Globoside (P antigen) receptor found on erythroid progenitors, erythroblasts, megakaryocytes and endothelial cells.
- Primary site of replication is the nucleus of immature cell in the erythrocyte lineage.
- Clinical consequence is minimal *unless patient compromised by chronic hemolytic process: sickle cell and thalassemia,* These patient might present with fever only. Then found to have anemia, and aplastic crises.

Note : It's a mild disease in healthy patients, but because it attacks growing RBCs it may cause *aplastic anemia* in chronic hemolytic process: sickle cell and thalassemia.

Manifestations and diagnosis

- Incubation period is 4-21 days
- Symptoms are: Fever, malaise, headache and myalgia and itching Indurated rash on the face (slapped-cheek) " زي الملطوش كف"which spreads in 1-2 days to arms and legs
- It infects lymph nodes, enlarged spleen and liver.

- Illness lasts 1-2 weeks, but rash may recur for 2-4 weeks upon: *exposure to heat or sun light*, on *exercise* or *emotional stress*.

Note: the rash starts as a General rash → slapped-cheek rash →it goes away, but 1 -2 months after recovery there's a chance for occurrence and recovery.

- Some times associated with arthritis and vasculitis.
- Rare complications: hepatitis, Thrombocytopenia, nephritis and encephalitis.
- Transmitted through *respiratory route*
- Spring months
- Viremia last 7-12 days
- Diagnosis: PCR, and serology: IgM-specific anti-bodies
- Treatment: no definitive treatment, immunoglobulin.

3.5 Roseola Infantum

- Also known asvExanthem Subitum and 3 days virus
- Caused by HHV6 and HHV7.
- HHV6 has two variants A and B. 6 is worst, most infections are caused by HHV6
- Replicates in CD4+ T-lymphocytes
- All population has antibodies against it by age 5 years
- HHV6-B associated with Exanthem Subitum. A and B associated with febrile illness with or without seizure and rash.

Note: roseola infantum causes Sudden high grade fever, *that may cause seizures,* So the parents will come to you, telling you that their child suffered from seizures suddenly. You have to take infections in consideration during thinking about differential diagnoses. Here you should measure the body temperature, if it's around 40, these seizures are due to high fever, caused by infections. *It's important also to tell the parents that its normal complication and it won't be associated with any complications in future*.

- It’s Common in 6 months- 2 years
- Exanthem Subitum: Fever (39C°), 3-5 days later Faint macular rash appears that spread from trunk to extremities (no rash on the head).
- EBV, Adenovirus, coxsakieviruses and echoviruses cause similar manifestations.
- Can cause latent infection in T-cells and become reactivated with immunosuppressive status.
- Diagnosis: seroconversion, culture and PCR
- Treatment:no specific but rugs that kill CMV may kill it .. ganciclovir and foscarnet.
- No vaccine.

By that, we have finished common childhood Exanthems, it’s very important to be able to differentiae between different viruses according the symptoms, *especially the rash*.

References :

I. **Dr. Ashraf Khasawneh slides.**
II. **Section 1 record.**
III. **Sherris Medical Microbiology 6th Edition, chapter 10.**

“ You never know how strong you are, until being strong is the only choice you have”

-good luck

-Mohammad Qussay Al-Sabbagh