

Viral Skin Infections

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Terminology

- **Macule:** a change in the surface color without elevation or depression, usually less than either 5 or 10 mm in diameter, mostly it is erythematous (redness of skin).
- **Papule:** circumscribed reddish, solid elevation in skin with no visible fluid, less than either 5 or 10 mm in diameter. (Most of the rash we will talk about later lies within maculopapular).
- **Nodule:** similar to the papule (solid) but greater in size (greater than either 5 or 10 mm).
- **Pustule:** small elevation of the skin contains cloudy or purulent material.
- **Vesicle:** circumscribed, fluid containing epidermal elevation, generally less than either 5 or 10 mm in diameter.
- **Bulla:** large vesicle, rounded or irregular shaped cluster, greater than 10 mm.
- **Ulcer:** discontinuity of the skin, exhibiting complete loss of epidermis and portion of the dermis and subcutaneous.
- **Crust:** dry serum puss or blood, usually mixed with epithelial or bacterial debris.
- **Lichenification:** epidermal thickening characterized by visible and palpable and thickening of the skin, with accentuated skin markings.

***Note:** the most important ones are the macule, papule, crust, vesicle and ulcer because they will be repeated later, so you should know the sizes.

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Viruses causing skin lesions

They are distributed worldwide, especially among non-immune individuals.

Humans are the sole reservoirs of these viruses.

The primary route of infection is through the respiratory tract.

- Mumps, Measles, Rubella.

(Although mumps is not considered as childhood exanthema and does not involve any skin lesion, this is the best place to cover the topic of mumps together with measles and rubella.)

- Erythema infectiosum, which is caused by parvovirus B19.

-Roseola infantum also called exanthema subitum which is caused by HHV6 and HHV7.

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Measles (Rubeola)

- Belongs to paramyxovirus family (includes Parainfluenza, measles and mumps), Morbillivirus genus.
- -ve sense, ssRNA enveloped virus.
- Replication strategy:
 - starts by attachment to the cellular receptor CD46.
 - Two glycoproteins mediate this process: the hemagglutinin (H) and fusion (F) protein.
 - (H) is used for attachment, while (F) for fusion (measles virus lacks neuraminidase).
 - After the attachment the virus is internalized. Since it is RNA virus the replication will take place in the cytoplasm, and it is a negative sense so it carries its own RNA dependent RNA polymerase. In order for the virus to make its own protein; RNA dependent RNA polymerase transcribes the -ve sense into +ve sense → the +ve sense goes and binds to the ribosomes → in the ribosome the protein is made and the +ve sense intermediate acts as a template for the replication and production of new copies of -ve sense which all together are assembled and exit the cell by acquiring the membrane from the cellular membrane since it is an enveloped virus.
- Has single serotype, which means that infection for one time is enough to give lifelong immunity. It's prone for antigenic variation –not so frequent- and this is seen in form of epidemics every couple of years, maybe 4, 7 or 10.
- Associated with severe illness in children, fever, rash and immune-suppression.
- Epidemiology:
 - The infection can be seen in all ages, but it was found to spare those who are less than 6 months of age, maybe due to immunity acquired from the mother.
 - Seasonal preference: late winter and early spring (though it can be seen in other times of the year).
 - Exposure to measles is associated with 95% infectivity; if you were –especially children- exposed to someone who is infected with measles, the chance of getting the infection and developing the disease (symptoms) is 95% (very high, with rubella and mumps the percentage will drop). So, measles has a high rate of both; infection and developing symptoms when infected.
 - Communicability: it is contagious or infectious 3-5 days before the appearance of rash, and up to 4 days after the appearance of rash (or till the disappearance of rash).

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- It is associated with exanthemes and enanthemes.
 - Exantheme: rash or lesion on the skin.
 - Enantheme: rash or lesion on the mucosa (especially the buccal mucosa).



Koplik's spot

- In measles, we can see –above- **Koplik's spot** (it is diagnostic for measles infection which is seen in the buccal musoca).

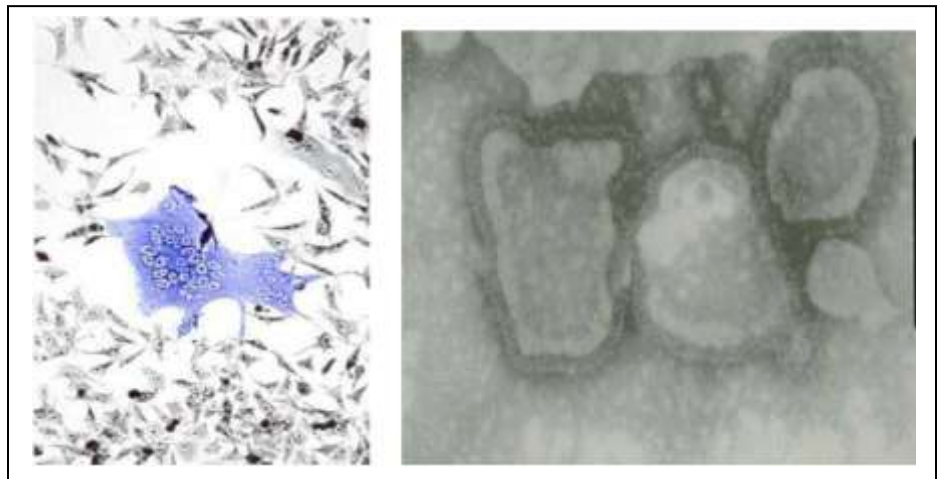
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Pathogenesis

- The infection starts through aerosols or droplets, infecting the upper respiratory tract, and it leads to intense infection as a result of virus replication in the oropharynx.
- Leads to disruption of the cellular cytoskeleton of the infected cells, leading to intracytoplasmic and intranuclear inclusion bodies as well as syncytia formation or multi nucleated giant cell formation, followed by viremia and spread to lymphatic organs (lymphoid tissue, bone marrow) also to the abdomen, skin, conjunctiva, urinary tract and to the CNS.
- In the viremic phase: it infects B and T cells and the polymorphonuclear cells. So, the cellular and the humeral immunity are suppressed.
- In the lymphoid tissue: we can find what is called Warthin-Finkeldey cells, which are multinucleated giant cells or syncytia.
- In the skin lesions: skin rash, vasculitis, exanthemes and enanthemes (Koplik's spots which are red spots with bluish or whitish center on the buccal mucosa).
- In CNS: encephalitis and vasculitis. As a result of the immune cell mediated response of the T cytotoxic cells targeting cells infected by the virus or virus antigens present inside the cell, so it leads to vasculitis and the capillaries become permeable and you see the rash.

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You can see the Warthin-Finkeldey and multinucleated giant cells.



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Immunity

- Cell mediated and humeral immunity are suppressed because of infection of B and T lymphocytes, and it can last for months and this puts the child at the risk of super infection, especially bacterial super infection.
- Cell mediated immunity at early stage mediate rash formation and is necessary for recovery

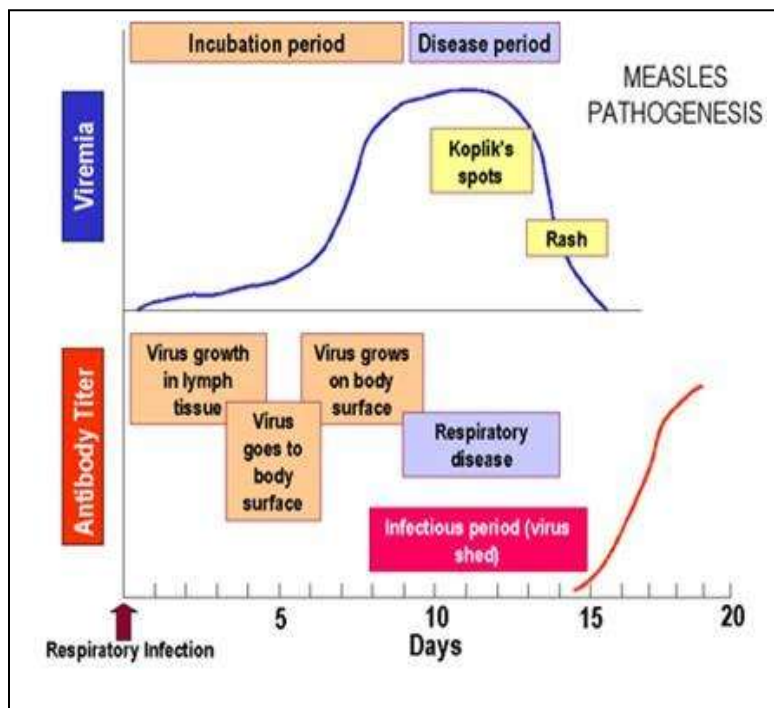
- Humeral immunity (Ab) peaks within 2-3 weeks and persist at a low level.
- Lifelong immunity is acquired through neutralizing antibodies that are formed.

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Clinical manifestation

- 5-day measles. We have another disease; the 3-day measles which is rubella (the German measles).
 - IP around 2 weeks.
 - Initial symptoms: upper respiratory tract symptoms, conjunctivitis, fever.
 - 1-3 days later: appearance of Koplik's spots, which last for 1-2 days
 - After that the Exanthem or skin rash erupts and lasts for 3-5 days.
 - We can see enlarged lymph nodes (lymphadenopathy) in the neck area especially the cervical lymph nodes.
 - Infectivity: 3-5 days before the appearance of rash till the disappearance of the rash.
 - Mortality: high especially in immunocompromised and malnourished children.
 - Complications:
 - Bacterial super infection is the main risk because of the infection of B and T cells. Otitis media, sinusitis, pneumonia, encephalitis, mastoiditis
 - Another serious but rare complication is: SSPE (Subacute sclerosing panencephalitis) can be seen as a single case for every 100,000 cases of measles, it is a chronic measles virus infection to the CNS which occurs 2-10 years after the primary infection and it has no specific treatment.
- Characterized by personality change, intellectual deterioration, seizures, tremors, myoclonus, spasticity, ocular abnormalities, and in very rare cases can lead to blindness.

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This is how the disease starts; first we have the incubation period, followed by respiratory illness then the appearance of fever then koplik's spots. 1-2 days later, the appearance of rash, then by the time of the disappearance of the rash we can see that the patient is no longer infectious.

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Diagnosis and treatment

- Diagnosis based on the clinical picture.
Also on the virus isolation in secretions of oropharynx and the urine.
We can inoculate these secretions into a cell line and look for the formation of syncytia or multinucleated giant cells and we can do PCR or serological test for diagnosis.
- Treatment:
There is no specific antiviral treatment for measles.
Treatment is supportive; if there is fever you can give antipyretics, but never use Aspirin as antipyretic for children because it is associated with Reye's syndrome (CNS symptoms, edema of the brain).
- Prevention:
 - We have a vaccine composed of 3 or 4 different components: MMR or MMRV. (Measles, mumps, rubella and sometimes varicella).
 - Live attenuated vaccine, contraindicated to be given to immunocompromised patients and pregnant women (though a study found that if it was given to a pregnant women, it won't be associated with any complications or side effects, but to be in the safe side it is contraindicated)
 - Exception for measles only: it can be given for AIDS patients; Because the risks of not giving it outweigh the risks of giving it.
- Side effects of the vaccine:
 - Severe: allergic reaction (rarely).
 - Mild: fever, mild rash, swelling of lymph nodes. Most of the time if these mild symptoms occur, they will resolve completely within 1-2 weeks without any sequelae.
 - Moderate: seizure, temporary pain and stiffness in the joints, temporary low platelet count (in this case you should advise the mother to come straight away to the hospital or the PHC center).

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National vaccination program

MMR is given 12-15 months, and then the booster dose is given at 4-6 years.

In Jordan:

- At 9 months → they give measles alone.

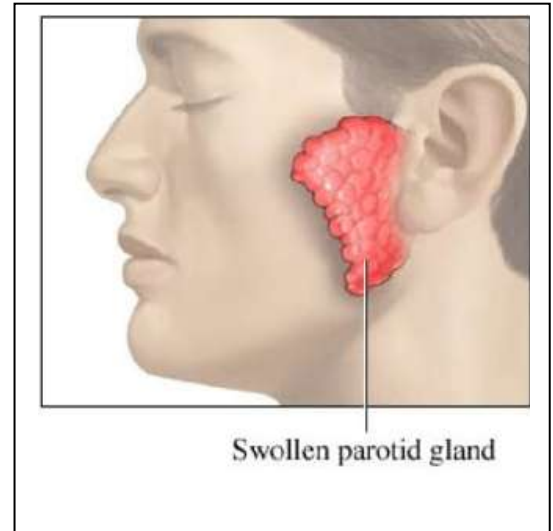
- At 12 months → MMR
- At 18 months → 2nd booster dose of MMR
- And a third booster dose at 4-6 year

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Mumps (أبو دغيم، النكاف)

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- Belongs to paramyxovirus family.
- Have one antigenic type, so infection with this virus will give lifelong immunity.
- -ve sense, ssRNA, enveloped virus.
- The replication strategy is the same as measles, but for the glycoproteins there is a difference; here we can see 2 glycoproteins, (F) fusion protein is the same as measles while the other is the neuraminidase-hemagglutinin tetramer (NH) (as one glycoprotein).
- Associated with parotitis (inflammation in the parotid gland), most of the time it is the presenting symptom of the mumps and it can be associated with aseptic meningitis in children, in adults in can be associated with acute orchitis (inflammation of the testicles) and or encephalitis.
- Epidemiology:
 - Most of the time it occurs in children age 5-15 years of age
 - 30-40% of contacts do **not** develop clinical illness. Leaving 60-70% who develop the illness compared to 95% in measles.
 - Communicable: 7 days before to 9 days after the appearance of the symptoms.
 - Seasonal preference: late winter and spring



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Pathogenesis

- The same as for measles: transmitted by aerosols or droplets, starts by infecting the upper respiratory tract, and the local lymph nodes → then we have primary viremia where the virus reaches the salivary gland and the CNS, replicates there and it is shed into the blood once again → secondary viremia, as a result might spread to distant organs such as the kidney. Presence of the virus in the urine is common.
- Tissue response characterized by cell necrosis and inflammation in the infected tissue. (Because T cells might target the infected cells like what happens in case of measles infection).
- The immunity is characterized by the formation of IgM, followed by IgG which gives lifelong immunity.

- Cell mediated immunity might contribute to pathogenesis and recovery from infection.
- T cells might target the infected cells and lead to cell necrosis and inflammation seen in the infected tissues.
- Permanent immunity through neutralizing antibodies (like measles).

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Clinical manifestation

- IP around 2-4 weeks.
- Characterized by: fever, parotid swelling (might be unilateral or bilateral) and it lasts from 7-10 days.
- Complications:
 - Occur mostly 1-3 weeks after the disease onset (symptoms).
 - There is a wide array of complications that may develop in some patients, however; most of the time it would be present as parotitis alone.
 - Meningitis and orchitis will develop in around 10% of the patients. They are two of the most dangerous or pronounced complications because of meningitis and encephalitis it can infect the spinal cord leading to myelitis, it can also infect the pancreas or cause orchitis.
 - And it could be associated with infertility (sometimes in investigating infertility they would ask about previous infection with mumps and involvement of the testicles). It could also infect the ovaries.
 - Rare complications: myocarditis, nephritis, arthritis, sensorineural deafness, thyroiditis.
 - Most complications resolve without sequelae within 2-3 weeks.
 - Since the virus can spread to various organs it might be associated with some illnesses, and there are some studies that linked diabetes mellitus to infection with mumps virus in the pancreas.

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Diagnosis and prevention

- Isolated in the saliva, CSF, pharynx and the urine.
- Grown in primary monolayer of the monkey kidney cell culture; so we can take samples from saliva or CSF then inoculate them into a culture, observe for cytopathic effect, syncytia formation and it is also capable of hemagglutination.
Can be diagnosed by serology and PCR.
- No specific antiviral treatment.
- Can be prevented by MMR or MMRV.

- Previously they were saying that a single MMR or a single live attenuated mumps vaccine is protective and some countries recommended one dose, but nowadays they all recommend 2 doses because the protection is higher. (1 dose → 80%, 2 doses → 90%)

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Rubella (German measles)

- Mild benign childhood exanthem which is characterized by Malaise, faint rash and arthralgia.
- The risk of infection is among pregnant women because it is associated with congenital anomalies.
- Profound effect on developing fetuses.
- It belongs to Togavirus family, Rubivirus genus.
Togavirus family is divided into two genera: Rubivirus and Alphavirus which belongs to Arboviruses (arthropod-borne virus infections which cause encephalitis).
- Enveloped, icosahedral + ve sense RNA genome.
- Replication strategy:
Attachment by the glycoproteins which are E1 and E2 with the receptors → the virus is internalized in the cytoplasm, it is an RNA virus so it will replicate in the cytoplasm → it is +ve sense so the RNA that enters at the beginning is used for protein synthesis of transcriptases and RNA polymerases and then the genomic RNA is replicated by a –ve sense RNA intermediate which serves as a template for the production of +ve sense subgenomic RNA → this is used in the synthesis of structural proteins → assembly in golgi apparatus or cytoplasmic membrane.
- Has one serotype, so it is associated with lifelong immunity
- Agglutinates chicks RBC's, so as a diagnostic measure we can test for hemagglutination.

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Epidemiology

- Seasonal preference: Winter and spring.
- Only 30-60% will develop clinical apparent disease.
- Most care should be taken for pregnant women because as we mentioned before the infection might be associated with congenital anomalies (and for women of childbearing ages in general).
- Contagious 7 days before to 7 days after the appearance of the rash.
- Infected babies (born to infected mothers during pregnancy) spread the virus 6 months after birth (they might still shed the virus until 3-4 years after infection).
- Starts by infection in the URT, regional lymph nodes, and then goes to the blood associated with viremia, then to the skin and other organs. (transmission by aerosols/droplets)

- Cell mediated immunity and Immune complexes will lead to the formation of rash and arthritis. Like measles and mumps; T-cytotoxic cells target infected cells and antigen-antibody complexes might deposit in the endothelial cells in the blood vessels leading to vasculitis and the appearance of rash).
- Maternal viremia leads to placental infection and then spread to the fetus and leads to congenital anomalies.
- Pathogenesis of congenital defects (how these anomalies occur):
 - 1) vasculitis of either the placenta or the fetus which leads to impaired fetal oxygenation.
 - 2) Chronic viral infection leads to impaired mitosis, cellular necrosis and chromosomal breakage.
- Shedding of the virus in infected infants is prolonged (up to 30 months or 3-4 yrs.).
 - * Infected babies do produce antibodies against Rubella once they are born, but these antibodies are not able to neutralize the virus present in babies' bodies'; so, they still shed the virus.
- Produce IgM and IgG antibodies to the virus, decrease to undetectable levels in 3-4 yrs.

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- Viremia is noticed 8 days before rash to 2 days after the appearance.
- Virus shedding from oropharynx can be detected up to 8 days after onset of rash

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Pathology

- Mononuclear cell infiltration in tissues (to target the infected cells), Ca⁺⁺ deposition is delayed in the metaphysis of long bones (can be seen in infected babies as **Celery stalk** appearance on X-ray; due to lack of calcium deposition in the bones).
- Antibody titer peaks after 2-3 weeks of onset
- It is associated with IgA immunity in the secretion of the respiratory tract
- Gives Lifelong immunity.
- Reexposure to the Rubella virus is not associated with the full blown picture of the illness and viremia might only present as URT symptoms.

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Clinical manifestation

- Three day measles.

- IP 2-3 weeks.
- Starts as Fever, URT symptoms, LNs (post cervical and post auricular).
- Macular rash 1-3 days later (head, neck and trunk), faint rash.
- Complications: arthralgia, arthritis, encephalitis and TCP (Thrombocytopenic Purpura; is a disorder characterized Bleeding under the skin as a result of vasculitis).
- Risk for fetal damage is up to 80% if the infection occurs in the first 2 weeks in pregnancy, 6 – 10% in 14th week of pregnancy, 20-30% overall risk of congenital abnormalities.
- Congenital abnormalities that can occur to infant:
 - Cardiac: PDA (Patent ductus arteriosus), Pulmonary valvular stenosis.
 - Eye: Cataract, chorioretinitis, Glaucoma, Coloboma, cloudy cornea, microphthalmia.
 - Sensorineural deafness enlarged Liver and Spleen.
 - Thrombocytopenia, intrauterine growth retardation.
 - CNS defects: microcephaly, encephalitis and mental retardation
- Late complications: including DM (diabetes mellitus), chronic thyroiditis, Subacute panencephalitis (SPE).

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Diagnosis and treatment

- Clinical diagnosis is not enough.
- You need to isolate the virus from the respiratory secretions, Urine or feces, and inoculate into
 - Cell culture.
 - RT-PCR.
 - Serological testing is not of great value in infections by Rubella because for some patients (5-10% of patients) IgM might not be detected at all or persists for long period (up to 200 days).
- Supportive treatment.
- Live attenuated vaccine (MMRV)
- Contraindications: IC and pregnant women.
- The lady who plans to get pregnant should avoid conception till 3 months after taking the vaccine.

"هناك فردٌ قد بنى أمره على أن أمةً تحمله فهو يعمل بأضعف ما فيه، و فردٌ آخر بنى أمره على أنه يحمل أمة، فلا يدع في نفسه قوة إلا و ضاعفها.." -الرافعي

ضاعف قواك ☺