MSS System
Viral Infections

Mahmoud Alkawareek, PhD

Measles

- Caused by measles virus which is an **enveloped** (-) sense ssRNA virus from **paramyxovirus** family
- Measles is a **relatively severe illness** which is characterized by **high fever**, widespread **maculopapular rash** and **transient immunosuppression**
- The disease is also called rubeola, **5-day measles** and hard measles
- Mainly affects **children** more than 6 months old
  - It still represents a **major cause of mortality** among children in **developing countries** (with **mortality** rate of **15-25%** recorded in **some** developing countries)

Measles

- Epidemics tend to occur during the **winter** and **spring**
- Measles is a **highly contagious** disease; **infection rate** among exposed susceptible subjects in crowded settings is estimated at **85%**
  - It is usually contagious **3 to 5 days before** appearance of the rash to **4 days afterwards**
- It also has **high morbidity**; more than **95%** of infected subjects become ill

Measles

- Measles virus-specific **cell-mediated immunity** develops **early** in infection and is necessary to **promote recovery** from the illness
  - It plays a role in **mediating some of the features** of disease
  - However, cell-mediated immune responses **to other antigens** may be acutely **depressed** during measles infection and persist for **several months**
- **Antibodies** appear in the **first few days**, **peak** in **2 to 3 weeks**, and then persist at lower levels
  - **Immunity** to reinfection is **lifelong** with the presence of neutralizing antibodies

Measles

- The **incubation period** is around **1-2 weeks**
- Typical illness usually **begins 9 to 11 days** after exposure, starting with **cough**, **rhinitis**, **conjunctivitis**, and **fever**.
- **1-3 days after onset**, characteristic gray–white spots (**Koplik's spots**) appear on the buccal mucosa and persist for **1 to 2 days**
- **Within a day** of Koplik's spots, the typical semi-confluent **maculopapular rash begins**,
  - **First on the head**, then on the **trunk** and **extremities**.
  - It **persists for ~5 days** before fading.
  - **Fever** and severe systemic symptoms **gradually diminish** as the rash progresses to the extremities
- **Lymphadenopathy** is also common, with particularly involvement of the cervical nodes

Measles

Measles

- Complications:
  - The **most common** complication is **secondary bacterial infections** (5-15% of all cases)
    - including acute **otitis media**, **sinusitis**, **pneumonia**, and **sepsis**
  - **Acute thrombocytopenic purpura** may also develop leading to bleeding episodes
  - **Abdominal pain** and **acute appendicitis** can occur secondary to inflammation and swelling of lymphoid tissue
  - **Post-infection acute encephalitis** develop in 1 of 1000 cases
  - A rare complication called **Subacute sclerosing panencephalitis (SSPE)** can occur in 1 of 10,000 of cases
    - It is a progressive neurologic disease that usually **begins 6 to 15 years** after a measles infection
    - Caused by a **persistent infection** with measles virus where the virus directly invade and infect brain tissue
    - Very high mortality rate (>90% die within 3 years)

Measles

- Diagnosis:
  - Usually diagnosed on the basis of **clinical findings**
  - Isolation of **viral RNA** from **respiratory specimens** (most productive in the **first 5 days** of illness)
  - Rapid **serological tests** are also available
    - Testing for measles-specific **IgM or IgA**
- Treatment:
  - **No specific antiviral therapy** is available
  - Usually by **symptomatic treatment** and close **observation** for the development of **complications** such as bacterial infections

Measles

- Prevention:
  - **Live attenuated vaccine** is available for measles
    - Highly protective
    - Most commonly administered as part of **MMR vaccine**
  - This live attenuated vaccine is **contraindicated** in **pregnant** and **immunocompromised** individuals
    - **Passive immunization** can be used for the immunocompromised if given within **6 days**

Active Immunization in Jordan

	Age (months)					
Vaccine	<1	2	3	4	9	18
BCG						
DTaP						
HBV						
Hib						
Polio		IPV	IPV+OPV	OPV	OPV	OPV
Measles						
MMR						

Rubella

- Caused by rubella virus which is an **enveloped** (+) sense ssRNA virus from **togavirus** family
- Also called **German measles** or **3-day measles**
- Infections by rubella virus are often **mild**, or even **asymptomatic**. The major concerns are the profound effects on **developing fetuses** (**congenital rubella syndrome**)
  - So the major concern is susceptible women of **childbearing age**, who carry a risk of exposure during pregnancy
- Infections are usually in **winter and spring**
- In contrast to measles, **only 30 to 60%** of rubella-infected susceptible persons **develop clinically apparent disease**

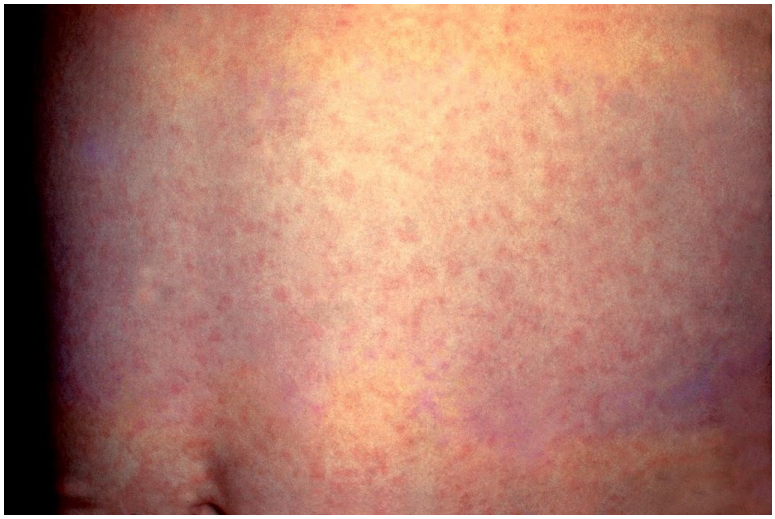
Rubella

- Patients with **primary acquired infections** are **contagious** from **7 days before to 7 days after** the onset of rash
- **Congenitally infected infants** may **spread** the virus to others for **6 months after birth**
- After infection the **serum antibody** titer rises, reaching a **peak** within **2 to 3 weeks of onset**
- Natural infection also results in the production of specific **secretory IgA antibodies**
- **Immunity** to disease is nearly always **lifelong**; however, **re-exposure** can lead to **transient respiratory tract infection**

Rubella

- The **incubation period** for acquired infection is **2-3 weeks**
- primary acquired infection is **generally very mild**, consisting primarily of **low-grade fever**, **upper respiratory symptoms (rhinitis)**, and **lymphadenopathy** (mainly cervical and postauricular areas)
- **Maculopapular rash** appears **first on the face** and **spreads** to the **trunk and limbs** and usually **fades after three days**
- **Arthralgia** and **arthritis** is common in **women**

Rubella



Rubella

- **Congenital rubella syndrome**:
  - Occurs in the newborn following **intrauterine infection** by the rubella virus
  - Causes **multiple congenital malformations** including cardiac, cerebral, ophthalmic and auditory defects
  - It may also cause prematurity, low birth weight, **miscarriage** or **stillbirth**
  - The **risk** of major defects is **highest** for infection in the **first trimester**

Rubella

- Diagnosis:
  - Diagnosis **cannot be made on clinical grounds alone**, confirmation of the diagnosis **requires laboratory studies**:
    - **Serologic tests**: raised virus-specific **IgM** antibodies usually indicates **recent infection**
      - However, these antibodies can **persist for over a year** so for a confirmed diagnosis the raised titer should be coupled by the **previous appearance of the characteristic rash**
      - Or instead, **comparison between acute and convalescent samples** collected 10-21 days apart is used
    - **Viral isolation** from respiratory secretions in the acute phase followed by inoculation into **cell culture** can also be used

Rubella

- Treatment:
  - **No specific antiviral therapy** is available for acquired or congenital infection
  - Usually **symptomatic treatment** for acquired infection
  - Treatment of **newborn** babies is focused on **management of the complications**
- Prevention:
  - Live attenuated vaccine is available (usually part of **MMR** vaccine)
  - Vaccine-induced immunity can be **lifelong**
  - In addition to **children**, the vaccine is recommended for **hospital workers**, and **female adolescents**.
  - **Pregnant women** are usually **tested** for immunity to rubella **early** in pregnancy. But women found to be susceptible are **not vaccinated until after the baby is born** because the vaccine contains live virus

Herpesviruses

- **Herpesviridae** (Herpesviruses) is a large family of **enveloped dsDNA** viruses
- They are **ubiquitous**, found in both animals and humans, and produce infections ranging from painful **skin ulcers** to **chickenpox** to **encephalitis**
- Members that infect humans include two **herpes simplex viruses** (HSV-1 and HSV-2), cytomegalovirus (CMV), **varicella–zoster virus** (VZV), Epstein-Barr virus (EBV) and **human herpesviruses 6, 7** & 8

Herpesviruses

- Characteristic to this family, all of these viruses produce an **initial infection** followed by a period of **latent infection**
  - In latent infection, the genome of the virus is present in cells as an **episome** (not integrated), but infectious virus particles are not released.
  - **Limited expression** of specific virus genes required for the maintenance of latency also occurs.
- **Reactivation** of virus due to certain factors may then result in **recurrent disease**.

Herpes Simplex Viruses

- Herpes simplex viruses (HSV) are the best known of all viruses, given their **frequency** of infection and their tendency to **cause recurrent ulcers** in areas of **skin** and **mucous membranes**
- There are two types which differ in their tendency for causing lesions **"above the waist" (HSV-1)** or **"below the waist" (HSV-2)**.
- As with all herpesviruses, HSV persist in a **latent** form and reactivates to cause viral release and/or disease

Herpes Simplex Viruses

- **Humans** are the only known natural **reservoir**
- Mainly transmitted by **direct contact** with infected secretions
- Their prevalence varies according to the **age and socioeconomic status** of the population
  - HSV-1: **~90% in developing countries** and ~60% in developed contries
  - HSV-2:~**15 to 30% of sexually active adults** (in the West). Its detection is not usual before puberty since it is **sexually transmitted**
- Can be **asymptomatic** in many cases but **still can be transmitted**

Herpes Simplex Viruses

- **Acute infections** produce **inflammation** and **multi-nucleated giant cells**.
- Virus can infect and spread in **axons & ganglia** and can therefore be unaffected by circulating antibodies
- **Latent infection** of nervous tissue by HSV **doesn't** result in cell death
- **Reactivation** can be precipitated by stress, sun exposure, fever or trauma
- Prior infection with **HSV-1** may **protect against** or shorten the duration of symptoms and lesions from subsequent infection with **HSV-2** due to some degree of **cross protection**

Herpes Simplex Viruses

- Clinical manifestation (HSV-1):
  - Infection with HSV-1 is usually "above the waist".
  - Primary infection consists of grouped or single **vesicular lesions** that become **pustular** and **coalesce** to form single or multiple **painful ulcers** in the **buccal mucosa, tongue, gums,** and **pharynx**
  - **Fever** may also occur
  - Lesions usually **recur** on a specific area of the **lip and adjacent skin** and are commonly called "**cold sores**" or "**fever blisters**"
  - Because **reactivation** is usually from a **single latent source**, these lesions are typically **unilateral**

Herpes Simplex Viruses

- Clinical manifestation (HSV-1):
  - **Primary infection** usually lasts for **5 to 12 days**, and **recurrent infection** usually lasts for **7 days**
  - Complications:
    - Herpetic **corneal and conjunctival infection**: can cause corneal damage and **blindness**
    - **Encephalitis** may also occur (very rare)

Herpes Simplex Viruses

- Clinical manifestation (HSV-2):
  - Genital herpes is an important **sexually transmitted disease**
  - Both HSV-1 and HSV-2 can cause genital herpes, but mainly by HSV-2
  - Infection is **asymptomatic** in most cases
  - In symptomatic **primary infection**, lesions begin as small erythematous **papules** that soon form **vesicles** and then **pustules**
  - About **one third** of patients show **systemic symptoms** such as **fever**, **malaise**, and **myalgia**
  - Symptoms **appear after 5 days** and **last for 12 days**
  - Aseptic **meningitis** develops in **~1%** of cases

Herpes Simplex Viruses

- Clinical manifestation (HSV-2):
  - **Recurrent genital herpes** is a disease of **shorter duration**, usually **localized** in the genital region, and **without systemic symptoms**
  - A common symptom is **prodromal paresthesias** in the **perineum, genitalia, or buttocks** that occur 12 to 24 hours **before** the appearance of lesions
  - Recurrent genital herpes usually presents with **vesicular lesions** in the external genital region. Local symptoms such as mild **pain and itching** can occur
  - Symptoms last **2 to 5 days**

Herpes Simplex Viruses

- Neonatal herpes:
  - Neonatal herpes usually results from transmission of virus **during delivery** through infected genital secretions from the mother
  - **In utero** infection is **uncommon**
  - It is an extremely **severe disease** with **disseminated vesicular lesions** with a widespread **internal organ involvement**
  - Overall **mortality of ~60%,** and **neurologic sequelae** are high in those who survive

Herpes Simplex Viruses

- Diagnosis:
  - **Culture**: cell culture inoculated with infected secretions or lesions
  - **Direct smear,** stained by the **Giemsa method**, show **intranuclear inclusions** or **multinucleated giant cells**
  - **Serological tests**: EIA, immunofluorescence assays can be used to **asymptomatic** infection
  - **PCR** can also be used

Herpes Simplex Viruses

- Prevention:
  - **Avoiding contact** with individuals with lesions
  - **Safe sex** practices should reduce transmission
  - **Caesarean section** may be performed to avoid **neonatal infection**
- Treatment:
  - Acyclovir is the drug of choice
    - Decreases the duration of primary infection and has a lesser but definite effect on recurrent infections

Varicella–Zoster Virus

- Varicella–zoster virus (VZV) causes two diseases, **chickenpox** (varicella) and **shingles** (zoster). The former usually occurs in children, the latter in the elderly.
- In the intervening years, the virus remains latent in **neural ganglia** but activates due to **waning cellular immunity**.
- Mainly spread by **respiratory secretions**, but also by direct contact with vesicular lesions
- VZV infection is **ubiquitous**. In temperate climates, nearly all persons contract chickenpox before they reach adulthood, and 90% of cases occur **before the age of 10** years.

Varicella–Zoster Virus

- Varicella occurs most frequently during the **winter and spring months**.
- The **incubation** period is **11 to 21** days.
- **Communicability** is greatest **1-2 days before** the onset of rash and lasts **3 to 4 days afterwards**
- Circulating **antibody** prevents **reinfection**, **cell-mediated immunity** controls **reactivation** (that's why reactivation usually occurs in the elderly)

Varicella–Zoster Virus

- Clinical manifestation (chickenpox):
  - **Vesicular rash** first appear on the back of the **head and ears**, then **spread** centrifugally to the **face, neck, trunk, and proximal extremities**
  - Unlike smallpox, lesions appear in **different stages** of evolution
  - Varicella lesions are **pruritic** (itchy), and the **number** of lesions may vary from **10 to several hundreds**
  - Low-grade **fever** may also occur

Varicella–Zoster Virus

- Clinical manifestation (shingles):
  - Shingles (herpes zoster) is associated with the reactivation of VZV
  - Although zoster is seen in patients of all ages, it increases in frequency with **advancing age**.
  - Starts with **pain** which is followed by **skin vesicular eruptions** within **1-2 weeks** later
  - The vesicular eruption is usually **unilateral**
  - The complications of VZV infection are varied and depend on age and host immune factors
    - **Post-herpetic neuralgia**: persistence of pain months to years
    - **Congenital varicella syndrome**: especially during early pregnancy

Varicella–Zoster Virus

- Diagnosis:
  - Diagnosis is usually **clinical**.
  - Scrapings of lesions may reveal **multi-nucleated giant cells**.
  - For rapid viral diagnosis, the best procedure is to demonstrate varicella–zoster **antigen** in cells from lesions by **immunofluorescent antibody staining**.
  - VZV can be isolated from vesicular fluid or cells inoculated onto **human diploid fibroblasts**
  - **PCR** of CSF may be useful in the diagnosis

Varicella–Zoster Virus

- Prevention:
  - Live attenuated **vaccine** is available: administered at **12 months** old
  - Varicella is a highly contagious disease, and strict **isolation** precautions must be instituted in all hospitalized cases.
- Treatment:
  - **Acyclovir**: recommended in healthy patients **over 18 years** of age (i.e. for **shingles**)
  - Treatment should be started within **3 days of the onset of zoster**
  - **Famciclovir** or **valacyclovir** may be more effective

Roseola

- Also called roseola infantum and exanthem subitum (means sudden rash)
- It is a common illness observed in infants and children **6 months to 4 years** of age
- The most common is human herpesvirus type 6 **(HHV-6)** and, less frequently, human herpesvirus type 7 **(HHV-7)**
- It is characterized by **abrupt onset** of **high fever**, **occasionally** accompanied by brief, generalized **convulsions and leukopenia**.
- After **3 to 5 days**, the **fever diminishes** rapidly, **followed** in a few hours by a **faint, transient, macular rash**.

Roseola

- **No vaccine** available
- Also **No specific antiviral therapy**
- However, the infection is asymptomatic in ~70% of cases and generally the disease is not severe

Human Papillomaviruses

- Human papillomaviruses (HPV) are **small nonenveloped dsDNA** viruses from the family **Papillomaviridae**
- There are **more than 100** different species of HPV
- They can only infect and replicate in the **basal cells** of stratified epithelia (in **both skin and mucous membranes**)
  - Some types are specific for the mucous membranes; others invade the skin
- They can cause **warts/papillomas** on the **soles (plantar warts), other skin areas, larynx and genital area**
- The warts range from **tiny flat inconspicuous bumps** to extensively **branching cauliflower-like masses**

Human Papillomaviruses

- **Cutaneous nongenital warts** are commonly caused by HPV **types 1 and 2** and usually occur in **children and young adults**
- HPV **types 6 and 11** are associated most commonly with **benign genital warts** in males and females and with some cellular **dysplasias** of the cervical epithelium, but these lesions rarely become malignant.
- **Types 16, 18, 31 and 45** may also cause **warty lesions** of the vulva, cervix, and penis. Infections with these viral types, especially 16, may progress to malignancy (i.e. **cervical cancer**)
- **Young women** have the highest rate of genital HPV infections

Human Papillomaviruses

- Diagnosis:
  - HPV **don't grow** in routine tissue culture, and antibody tests are rarely used
  - **Pap smear** can detect abnormal changes caused by HPV infection
  - **PCR** tests can be used in diagnosis
- Prevention:
  - **Gardasil** vaccine:
    - Recombinant **subunit** vaccine
    - Protects against **four sexually transmitted types (6, 11, 16 and 18)**

Human Papillomaviruses

- Treatment:
  - By **cryotherapy** (freezing & excision), **topical cytotoxic agents** or **surgery**.
  - Among the topical cytotoxins are **podophyllin**, **podophyllotoxin**, **5-fluorouracil**, and **trichloroacetic acid**.
  - Treatment is **not fully curable** and recurrences are common even after treatment