Viral Skin Rashes/Cutaneous Viral Diseases

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Outline

- Morphological classification
- DNA viruses that cause cutaneous disease:
- RNA viruses that cause cutaneous disease

Morphological classification

- **Maculopapular:**
  - Measles
  - Rubella
  - VHFs
  - HHV 6 & 7
  - Parvovirus B19
- **Vesicular**
  - HSV 1
  - HSV 2
  - HHV 3 (VZV)
  - Coxsackie virus A
- Warts – HPV
- Nodules - Poxviruses

Definitions of skin rashes

1. Maculopapular rash

   a. Macules – small flat discoloured spots on skin surface

   b. Papules – small, raised bumps

   - hence: maculopapular rash -> flat, red area on the skin (covered with small confluent bumps

   c. Pustules - small elevation of the skin containing pus

2. Vesicular rash – often fluid-filled (5-10mm)

3. Nodules (poxviruses) – e.g. milkers nodules

DNA viruses

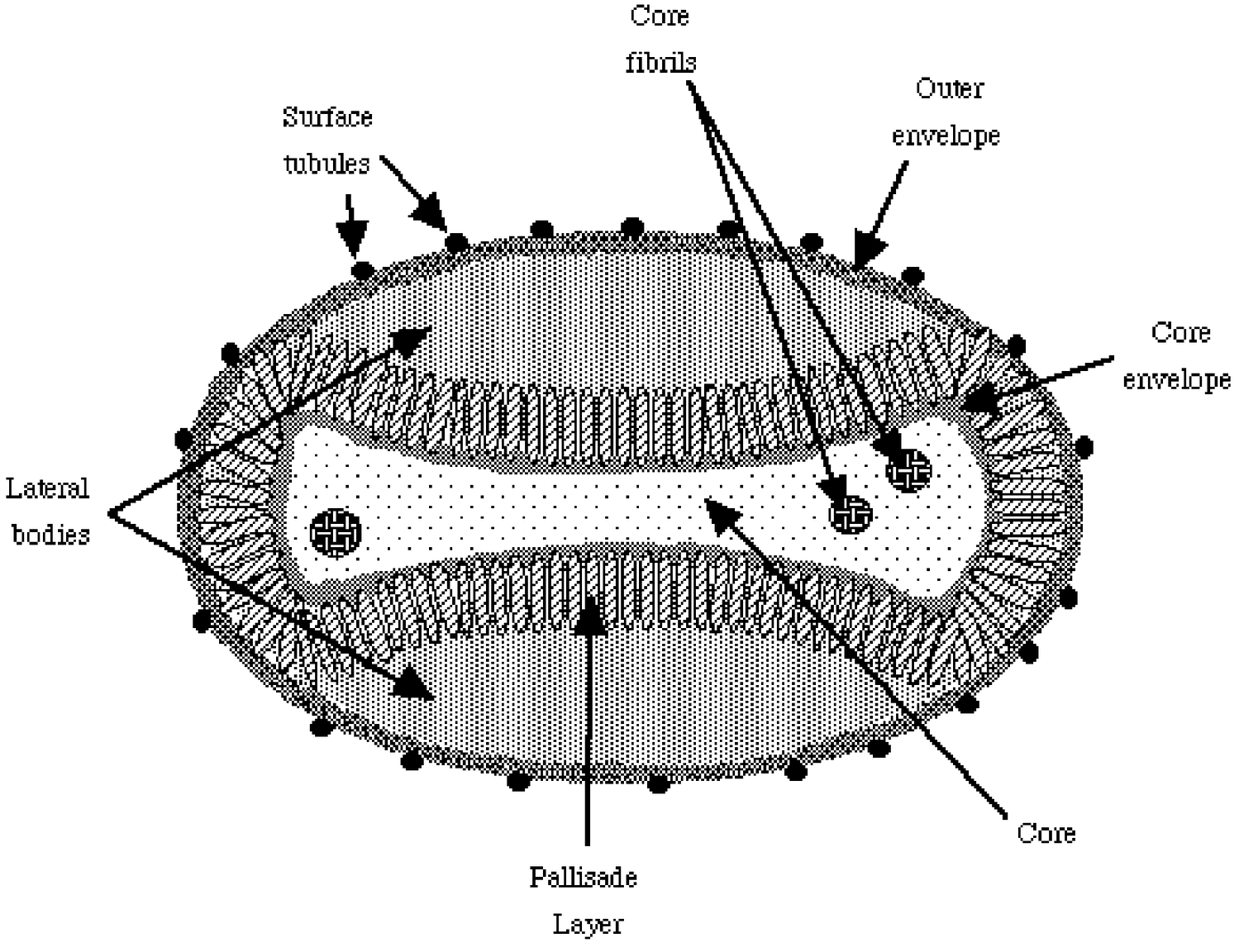
Family	Species
Poxviridae	Variola virus, monkeypox, cowpox, Tanapox, Molluscum contagiosum
Herpesviridae	HHV 1 – 8
Papillomaviridae	HPV (several genotypes) e.g. HPV 1, 2, 4
Parvoviridae	Parvovirus B19
Hepadnaviridae	HBV
Adenoviridae	Adenoviruses

Poxviruses

- Large complex viruses
- dsDNA
- Enveloped
- Code for over 100 polypeptides
  - Many target the immune system
- Replicate in the cytoplasm
- Diverse host-range: vertebrates and invertebrates
- Used as vectors for vaccines and gene therapy (experimental)

Subfamilies	Genera	Members
Chordopoxvirinae (vertebrates)	**Orthopoxvirus**	**Variola, vaccinia, cowpox, monkeypox, camelpox**
	Molluscipoxvirus	**Molluscum contagium**
	Yatapoxvirus	**Tanapox**
	Capripoxvirus	Goatpox, sheeppox
	Leporipoxvirus	Hare fibroma, myoma, rabbit fibroma, squirrel fibroma
	Suipoxvirus	Swinepox
	Parapoxvirus	Sealpox, parapox of deer, pseudocowpox
	Avipoxvirus	Canarypox, fowlpox, pigeonpox, turkeypox, penguinpox
Entomopoxvirinae (insects)	Capripoxvirus A	
	Capripoxvirus B	
	Capripoxvirus C	

Poxvirus



Brick-shaped
Dumb-bell core
Lateral bodies

9 ORTHOPOXVIRUS GENUS

Smallpox (Variola)

- Variola major and variola minor (20% & 2 % fatality)
- Killed 300 million people in the 20th century
- Used as a biological weapon by the British
- Global eradication began in 1967, achieved by 1980

Smallpox - Pathogenesis

- Transmission: Droplet/respiratory system
- Incubation period: 10-14 days
- Spreads to local lymph nodes
- Primary viremia
- Multiplication in reticuloendothelial system (RES) >> secondary viremia
- Enters endothelial cells in skin & oropharyngeal mucosa >> enanthem & exanthem

Clinical Features

- Fever
- Malaise
- Rash
  - macules
  - papules
  - pustules

Smallpox progression

Smallpox pustules

Smallpox lesions

Molluscipoxvirus GENUS

Molluscum contagiosum

- **Molluscivirus** genus of poxviridae
- Benign
- Single or multiple lesions
- Painless papules
- Anywhere on the body
  - ✓ Children: face, trunk, extremities
  - ✓ Adult: Groin/genitalia

PARAPOXVIRUS GENUS

Pseudocowpox

Common in cattle
Pseudocowpox (paravaccinia) in cattle
Characteristic "horseshoe" scabs
Milker's nodules in humans

Milkers Nodule

- Localized, cutaneous, and mostly benign infection
- Caused by poxvirus (genus *Parapoxvirus)*

PARVOVIRUS INFECTIONS

Properties of Parvoviruses

- Structure
  - Icosahedral
  - 18-26 nm diameter
  - Single-stranded DNA, 5.6 kb
  - Two proteins
  - Nonenveloped (naked viruses)
- ssDNA (Baltimore class????)
- Family Parvoviridae
- Subfamilies

  – Parvovirinae (vertebrate host)

  - Densovirinae (invertebrate)
- Parvovirinae – 5 genera

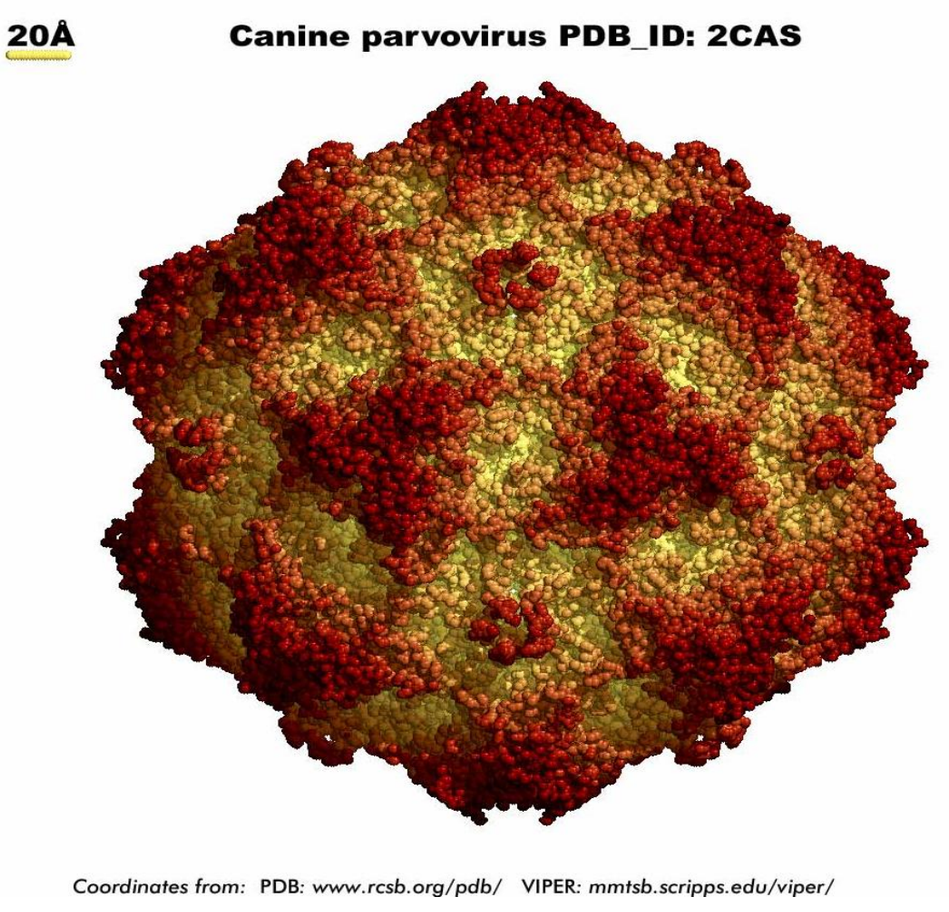
  a. Amdovirus

  b. Bocavirus

  c. Dependovirus

  d. Erythrovirus

  e. Parvovirus



Properties of Parvoviruses

- Replication
  - Attachment and entry
  - Translocation of viral DNA into nucleus
  - Transcription and translation of viral nonstructural protein and nucleocapsid
  - DNA replication
  - Virus assembly (nucleus)
  - Release from the cell through lysis

- B19 (Human parvovirus)

- life cycle is supported only in rapidly dividing erythroid cells.

- Hence belongs to the genus Erythrovirus (prototype).

Discovery of B19

- Accidental – serum of an asymptomatic blood donor (1974)
- Name – from ID of the tested sample: number 19 of panel B.
- EM – 23-nm virus particle (similar to animal parvoviruses)

Parvovirus B19 Transmission

1. **Contact with secretions of the nose and lungs**
2. **Blood – favoured by 2 viral characteristics**:

   a. Persistent infection of asymptomatic individuals (bone marrow)

   b. Prolonged replication (several yrs) after initial infection/reinfection
3. **Blood transfusion-based-> serious consequences.**

   High-risk patients

   a. Persons with shortened RBC survival (chronic hemolytic conditions)

   b. Pregnant women

   c. Immunocompromised patients

   -> chronic anemia (inability to clear the persistent B19V replication

Pathogenesis & clinical aspects

- Transmission

  - Mainly respiratory droplets

  - Contaminated blood, organ transplant

  - Vertical (MTCT)

- Replication in nasopharyngeal lymphoid tissue -> viremia
- Disseminated throughout the body
- Virus enters the bone marrow microenvironment

  -> generalized erythroblast infection

- Acute viremic phase

Parvovirus Infections in Humans

- Diseases
  - Fifth disease (cutaneous rash)
  - Transient aplastic crisis (severe acute anemia)
  - Pure red cell aplasia (chronic anemia)
  - Hydrops fetalis (fatal fetal anemia)
  - B19 virus most common

Fifth Disease (parvovirus B19)

WHAT IS FIFTH DISEASE?

1. Erythema infectiosum ('fifth disease')

- Major manifestation (B19 in children)
- Targets red blood cell progenitors
- Symptoms: mild fever, headace, sore throat, & flu-like symptoms
  – incubation period: 4-14days
  - Children: bright red rash (face) = "slapped cheeks"
- Pain in joints (more in adults than children)
- Result: lysis of cells -> depleting source of mature red cells
- Anemia ensues
- Rash involves cheeks (slapped-cheek disease/syndrome)
- Contagious
- Rarely fatal and without complications (self-limiting)

2. Transient Aplastic Crisis (TAC)

i. Drop in hemoglobin due to cessation of reticulocyte production

ii. Temporary

iii. Potentially life-threatening (patients with chronic hemolytic anemia – e.g. iron deficiency)

iv. Presentation – severe anemia associated with weakness & lethargy

v. Sudden drop of Hb values – due to disappearance of erythroid progenitors (bone marrow)

vi. Recovery – within 1 wk (maintained by intensive blood transfusion)

3. Primary Infection in pregnancy

- 33% chance of MTCT

- Only 10% babies have complications

Complications:

a. Heart inflammation (myocarditis)

b. Bone marrrow damage (RBCs not made)

-> anemia) = aplastic crisis. Fetuses with mild anemia – generally recover

c. Rare cases: severe heart damage & anemia

-> excess fluid in fetal tissue (hydrops fetalis) can lead to fetal death

d. Babies with hydrops may also have severe breathing problems at birth.

Fetal Risk

1) 20% risk of fetal death in the 1st trimester
2) Causes up to 3% of miscarriages
3) Risk of hydrops is greatest in the second trimester
   - Fetal death rate of about 15%
   - Babies with hydrops -> severe breathing problems at birth.

4. Chronic anemia [pure red cell aplasia (PRCA)]

- Immunosuppressed persons – unable to clear B19 virus effectively
- Result – persistent low-titer viremia, PRCA, & chronic anemia
- PRCA – normally seen in patients with disturbed CMI & infected with B19 (e.g. HIV+ve patients, bone marrow transplants, children with congenital immune deficiencies
  - Patients develop persistent anemia due to uncontrolled B19 replication & constant involvement of erythroid progenitors

5. Arthropathy

a) Development of arthritis

b) Major symptom in adults

c) Abs against B19 deposited in synovial fluid (joints)

–> contribute to pathogenesis of arthralgia

a) Self-limiting condition (may recur, may involve different joints)

B19 Infection in Malaria Patients

- Malaria endemic regions - Africa, Latin America, South and South-East Asia
- Dual infection (co-infection) with malaria parasites

  –> synergistic effects
- Differential diagnosis

Virological Diagnosis

1. Cytological methods

- Cytoplasmic vacuolization, viral inclusion bodies
- Useful for evaluation of suspected hydrops fetalis

2. Electron Microscopy (EM)

- Plasma & fetal tissues (especially acute phase)

3. Immunohistochemistry (IHC)

- Visualization of B19 VP1/VP2 proteins
- Pathologic exam of different tissue mtls from hyropic fetuses (lungs, thymus, heart, placenta)

Virological Diagnosis

4. Serological methods

- Recent vs past infection with B19
- EIA (detection IgM & IgG – plasma)
- Commercial assays: VP1 & VP2 (baculovirus-expressed)

5. Polymerase-Chain Reaction (PCR) - Sensitive

- Most useful during viremia
- B19 detection (serum & fetal tissues)
- Several primers (different genome targets)
- Several genotypes of B19 – types 1-3 differentiation (key)

Treatment of Intrauterine Parvovirus Infection

- No vaccines/medications available
- Regular ultrasound – detect hydrops

  -> 2nd & 3rd trimester

Epidemiology

- B19 virus is common and widespread
- Most adults have been infected
  - Most infections are subclinical
  - IgG is detectable in most healthy people
- Sporadic outbreaks, usually among children, occur each year
- Transmission from patient to health care staff is not uncommon
  - Role in nosocomial transmission to other patients
- Treatment
  - Address symptoms
  - Transfusions for serious anemic crises
  - Commercially-available neutralizing IgG (passive immunization)
- Prevention and control
  - No vaccine available for human parvoviruses
  - Good hygienic practices mitigate transmission

Parvovirus B19 (Summary)

- ssDNA, Non-enveloped
- Infects RBC precursors
- Infection leads to life-long immunity
- Disease:
  - Rash – ***Erythema infectiosum***
  - Arthritis
  - Aplastic crisis

  Rash is commoner in children than adults, arthritis is commoner in Adults

39

PAPILLOMAVIRIDAE

Papillomaviridae

- dsDNA virus
- Non-enveloped
- Over 120 HPV genotypes
- Several cause mucocutaneous lesions
- HPV 1,2,3,4 – Cutaneous warts
- HPV 6,11 – Genital warts

Cutaneous Warts (HPV)

Genital Warts (HPV)

Epidermodysplasia verruciformis (HPV Infection)

1. Eruption of wart-like lesions
2. Occur anywhere in the body
3. Caused by HPV

Herpesviridae

Species	Disease
HSV 1	
HSV 2	
HHV 3 (VZV)	
HHV 4 (EBV)	
HHV 5 (CMV)	
HHV 6	
HHV 7	
HHV 8	

Herpes Labialis

Herpetic whitlow

Herpes gladiotorum

Herpes zoster

Herpes zoster ophthalmicus

Ramsay Hunt Syndrome – Herpes Zoster Oticus

-Following HZ virus infection of inner, middle, & outer ear
-Manifestation - severe otalgia and associated cutaneous vesicular eruption (usually of the external canal and pinna)
-Called Ramsay Hunt Syndrome when associated with facial paralysis

KS (HHV-8)

RNA Viruses

Family	Species
Paramyxoviridae	Measles, Mumps, RSV
Retroviruses	HIV
Picornavirus	Coxsackie virus, enterovirus, echovirus
Togaviridae	Rubella, alphaviruses (e.g. Chikungunya)
Flaviviruses	Yellow fever virus, Dengue, Zika, etc.
Other VHFs	Arenaviruses, Filoviruses, Bunyaviridae

Measles virus

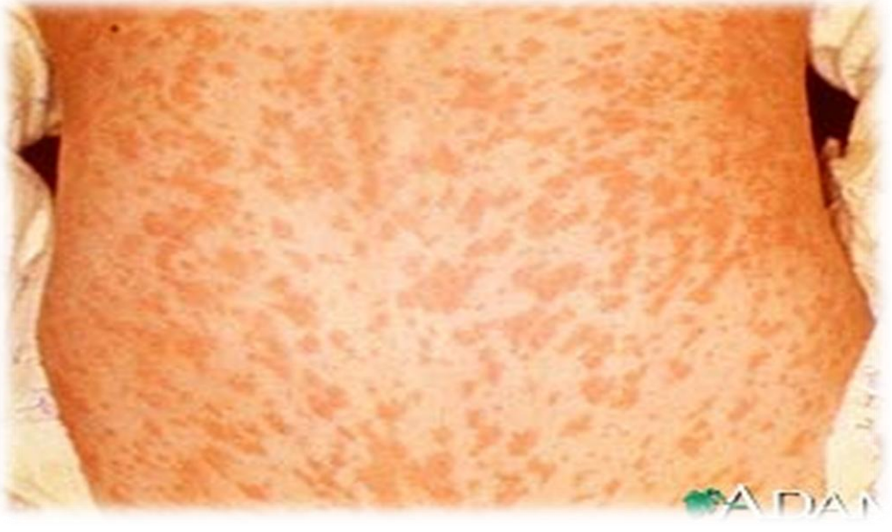
- Genus Morbilivirus; Family: Paramyxoviridae
- (-)ssRNA, linear, enveloped
- Used to infect nearly everyone before vaccine was available (1963)
- Transmission through aerosol, direct contact
- Affects humans only
- Infection leads to life-long immunity

Clinical Features:

- Fever
- Respiratory symptoms: Coryza, cough, conjunctivitis
- Koplik's spots on mucosae
- Maculopapular rash extending from face to extremities
- Complications: Pneumonia, Encephalitis, Blindness

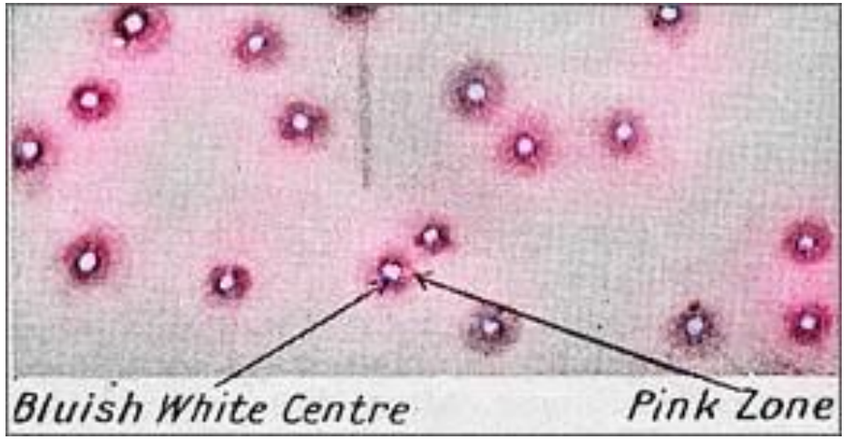
Morbilliform rash

aka Maculopapular rash



Measles

Koplik's spots (Buccal mucosa)



Rubella

- A.k.a German Measles, or 3-day measles
- Rubella virus>> Togaviridae family, Genus Rubivirus
- A (+) ssRNA virus, enveloped
- Transmission: droplet (respiratory)
- Generally causes a mild disease
- Congenital Rubella syndrome can be quite severe

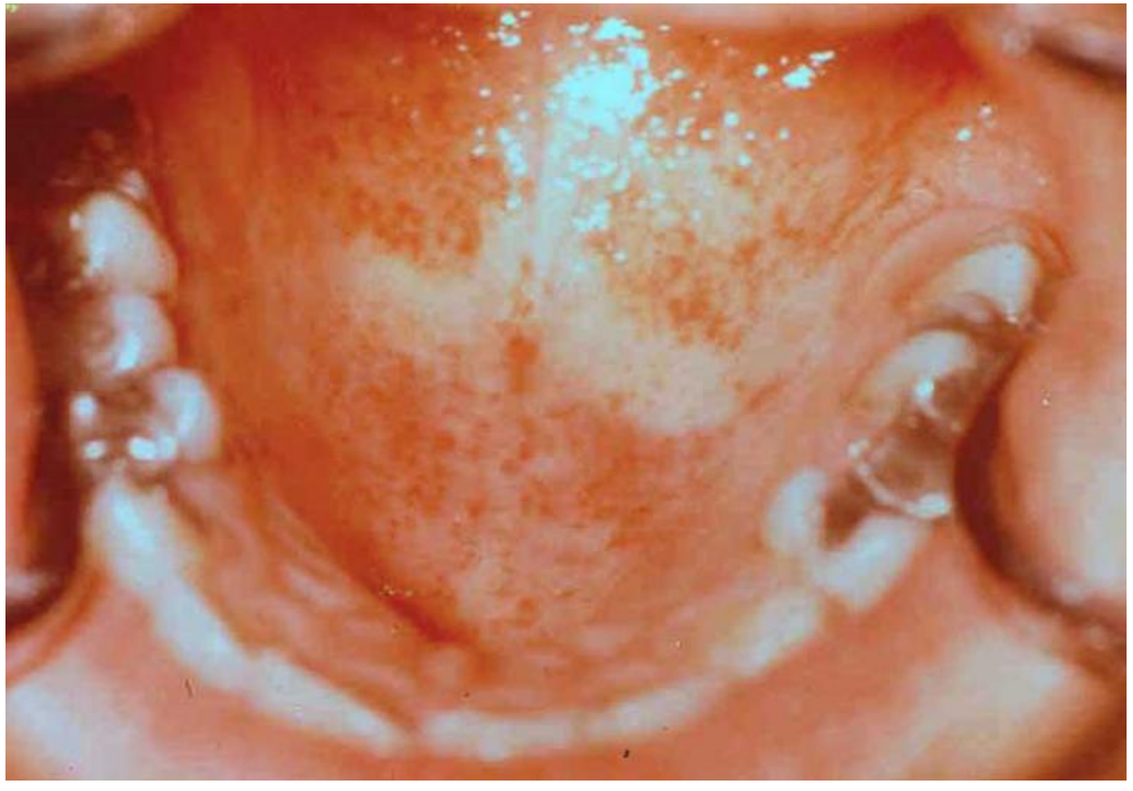
Rubella

Maculopapular rash

Clinical features

- Non-specific signs: Fever, anorexia, headache
- Pharyngitis
- Conjunctivitis
- **Forchheimer sign** (20% of patients)
  - Pin point lesions or petechiae in the soft palate
- Rash:
  - Maculopapular
  - Centrifugal
  - Disappears on day 3

Rubella



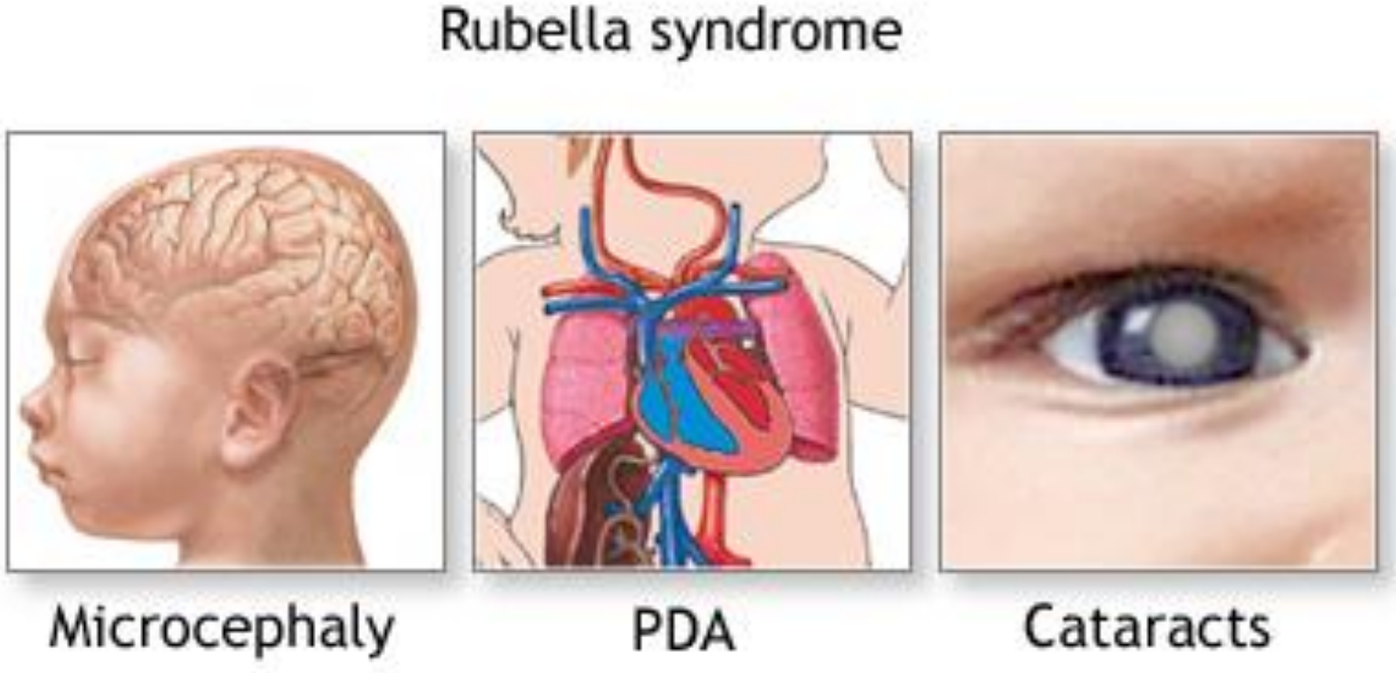
Forchheimer Sign

(Pinpoint lesions on the palate)

Maculopapular rash

Congenital Rubella Syndrome

- Infection occurs during the viremic phase
- Destroys fetal cell
- Infection in first trimester impairs organogenesis > anomalies



Hand, foot and mouth disease

- Caused by **Coxsackie virus A**, an enterovirus
- Palmar and plantar lesions, tend to be elliptical
- The long axis of the lesion oriented along the skin lines
- Painful, start as vesicles then erode into ulcers

HFMD – Coxsackie virus A

PPE (Papular Pruritic Eruption)

Cause: HIV

VHF

- VHFs present with several skin manifestations including: *maculopapular rash, petechiae, echymoses, bullae, etc.*

Family	Some members
Flaviviridae	Yellow fever, Dengue
Togaviridae	Chikungunya, West Nile
Arenaviridae	Lassa, Junin, Machupo
Bunyaviridae	Riftvalley fever, Hantavirus, Crimean-Congo HF
Filoviridae	Ebola, Marburg

Diagnosis of Cutaneous Viral Diseases

- Clinical picture: Most common
- Specimen: Vesicular fluid, blood, urine?
- **Lab tests:**
  - Antibody detection – Enzyme Immunoassays
  - Antigen detection – EIAs
  - Nucleic Acid Detection: PCR
  - Culture (Rarely done)

Deterrence

- Personal Hygiene (e.g. Hand washing)
- Avoid sharing personal items
- Vaccination (for some)
- Health education