

# Rubella Virus

## DETAILED HISTORY OF PRESENTING ILLNESS (HPI)

**RASH** is usually the presenting problem: DISCRETE PINK MACULOPAPULAR LESIONS

**SYMPTOMS IN ORDER OF APPEARANCE (2 week course of illness):**

- Anorexia
- Malaise
- Headache
- ENLARGED NODES: Cervical, post-auricular, occipital
- Viraemia (detectable 9 days before rash)
- FEVER
- RASH ← Presentation therefore, is usually **towards the end of disease progression**
- **RASH APPEARS in the order of FACE → BODY**
- **DISAPPEARS in same pattern -----RASH IS NOT DIAGNOSTIC! Need lab tests**

**PT IS INFECTIVE FOR 1 WEEK BEFORE RASH AND 4 DAYS AFTER!**

## LIST OF DIFFERENTIAL DIAGNOSIS (DDx)

**VIRAL** –

- Scarlet fever,
- Fifth disease,
- Roseola Measles,
- Primary HIV infection,
- Epstein Barr Virus,
- Dengue Fever,
- Viral Exanthems,
- **Rubella**

**ALLERGIC- Allergic Reactions** (Drugs, Contact, Chemicals?)

**BACTERIAL/RICKSETTIA** –

- Meningococemia,
- Bacterial sepsis,
- Rocky Mountain Spotted Fever,
- Typhus

## LIST OF PERTINENT FINDINGS ON HISTORY (HX)

- HISTORY OF TRAVEL TO UN-IMMUNISED REGIONS
- IMMUNISATIONS?

## LIST PERTINENT FINDINGS ON EXAMINATION (EX)

**Physical Examination**

- **Fine rash on trunk extending on to neck and face.**
- **Temperature 38 °C.** (normal 37 °C) = FEVER
- **Lymph nodes behind ears and back of head** enlarged and tender

## EXPECTED AND ACTUAL RESULTS FROM TESTS AND INVESTIGATIONS

**Viral culture for rubella** - specimen should be obtained within 2 weeks of rash onset

**Serology test** by venupuncture

FOR RUBELLA-SPECIFIC ANTIBODIES:

**IgM for existing** infection (>72 hours after onset of rash but < 7-10 days after onset or rash)

**IgG for prior** exposure (or after 2-3 wks of rash onset)

for presence of **rubella specific IgM antibody**

You need a **quantitative pregnancy test** to determine risk to potential infant

## IgG Antibody Titres

No antibodies	0 ut/ml
No significant antibodies	1-20units/ml
Low level of antibodies	20-30 units/ml
Protective	> <b>30 units/ml</b>

## DIAGNOSTIC DECISION / MECHANISM

The initial immune response is marked by the appearance of specific IgM antibodies that rise in titre over 2 to 3 weeks as the rash is fading.

In infected pregnant woman, rubella virus crosses the placenta to infect the embryo. Its greatest effect is on cells rapidly dividing during early gestation. Specific effects vary with time of fetal infection and are likely to be **severe if the fetus is infected within the first 12 weeks.**

As antibody is produced, circulating **virus and antibody form complexes which when deposited in skin** or synovia **induce cytokine production and inflammation, resulting clinically in a rash** (common) or arthropathy (uncommon except in older women). In a significant proportion of cases, however, the **rash may be very mild or completely inapparent.**

THEREFORE: IgM SEROLOGY = DIAGNOSTIC

## MANAGEMENT

GOALS:

- Minimize infectivity (**QUARANTINE**)
- **Vaccination** of relatives with MMR vaccine.
- Vaccination of contacts with MMR.
- Contact, **information** and where necessary vaccination of school contacts.

FOR PREGNANT PATIENT:

- **Counselling** regarding the risks to the fetus if she contracts rubella.
- Follow-up investigation for rubella infection 10 days later

## EXTRA MANAGEMENT

**Treatment of Rubella is symptomatic. Reduce fever and rash.**

Rest, paracetamol, calamine lotion (rash), hydration.

## EXTRA DIAGNOSIS

**Hydrops fetalis** due to rubella infection is fatal and will result in either stillbirth or neonatal death.

**Congenital Rubella Syndrome**

- mental retardation,
- hearing loss,
- cardiac defects (patent ductus arteriosus, pulmonary artery stenosis, ventricular septal defects),
- cataract,
- diabetes mellitus (later in life).

## HOW IS THIS DIAGNOSIS MADE

Diagnosis made through **viral culture** using cell lines and detection through RT PCR and **serology of IgM and IgG antibodies specific to Rubella virus.**

Serology is determined through ELISA assay of Rubella antibodies.

## EPIDEMIOLOGY

Congenital Rubella Syndrome Prevalence 20:10,000 (Australia); **MOST AFFECTED ARE 5-9 Yrs old**

## AETIOLOGY

- Caused by RNA Togavirus; MAN IS THE ONLY HOST
  - spreads through air droplet inhalation
  - infects respiratory tract
  - initially replicates in upper respiratory mucosa
  - incubates for ~18 days;
    - **Incubation period = Period in which virus is replicating in host but host is not infectious**
  - Spreads hematogenously
- Transplacental spread across placenta to fetus can occur  
. Ave 18days (12-23days)  
Can be excreted in urine and respiratory tract of congenital rubella infants up to 2yrs.  
Rubella significantly impairs the cell's ability to grow and divide.

## PATHOPHYSIOLOGY

### Rubella infection causes :

#### Direct damage to host cells

- Resulting in cell growth in infected cells being slowed considerably
- Infected cells produce INF-alpha and beta which inhibit viral replication, cell proliferation and increased lytic potential of NK cells.
- **Infected cells are killed by cytolysis.**
- Mechanism of **fetal damage** – **mitotic arrest, tissue necrosis, chromosomal damage**

#### Indirect damage to host tissues

- By **inducing a host immune response** that damages both infected and non infected cells.
- Antibody is produced and forms virus/antibody complexes which are deposited from the circulation into the skin and joints where their presence stimulates the production of cytokines and inflammation.

**Persistent infection**- reactivation of the virus from a latent state can occur months or years after primary infection.

**Transformation of host cell into oncogenes may also occur.**

**Foetal RUBELLA: severe if the fetus is infected within the first 12 weeks.**

## PROGNOSIS

### Time of infection of mother

- <8wks pregnant – 80% chance of fetal damage
- 9-12 wks pregnant – 30% chance of fetal damage
- > 20 wks pregnant – defects rare

## BASIC SCIENCES

### Cellular immunology

- When a virus invades a host cell, **viral DNA is processed**
- **MHC I class** protein binds a portion of the **encoded foreign peptide** and presents this complex extramembranously
- **CD8 T cells recognise the MHC class I protein** and costimulatory molecule CD28
- These two signals **activate the CD8 T cell** and induce a **cytotoxic effect** on the host cell.

**Host response to viral infection**

**Physical barriers:**

- keratinised layers of the skin
- low pH
- mucous secretions that continuously wash over mucosal surfaces
- IgA found in mucous secretions (binds to virus particles and prevents them from binding to infectable host cells)

**Infected cells produce interferon  $\alpha$  and  $\beta$  and IL-1.**

- Interferons  $\alpha$  and  $\beta$  cause neighboring cells to
  - **produce endonuclease** which degrades viral mRNA and
  - **halt all protein synthesis.**
- **IL-1 causes inflammation and recruitment of macrophages, neutrophils, NK cells** to site of infection.
  - NK cells – recognize viral protein expressed on infected cell surface and kill cells through perforins.
- Viral antigen expressed and bound to MHC-I on infected cells are recognized by the immune system CD8 T-cells – this results in the activation and production of cytokines and lymphokines which cause further inflammation and killing.
- Antigen presenting cell (APC) presents viral peptides **via MHC-II to helper T cells**
- Helper T cells clonally activate B Cells which differentiate into memory and plasma cells.
- Plasma Cells begin producing IgM antibodies

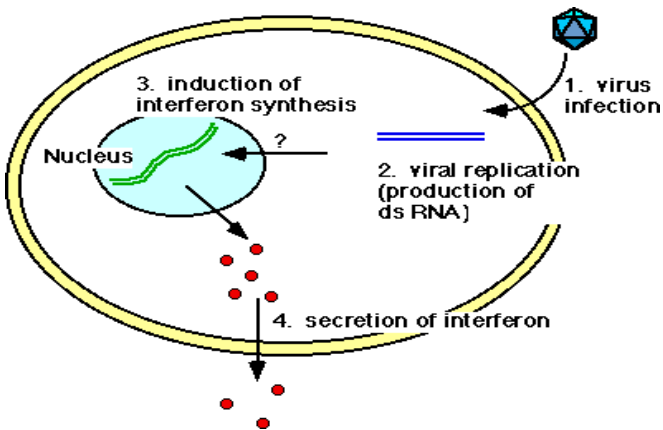
**2 main defense responses by host to a viral infection:**

	(1)	(2)
	<b>Antiviral Interferons (a and b)</b>	<b>Immune System</b>
<b>Virus Specificity</b>	non-specific	strictly virus-specific
<b>Time Frame</b>	short term	long term (including immunological memory)
<b>Range of Effect</b>	localized	systemic
<b>General Mode of Action</b>	induces anti-viral state, affecting protein synthesis (viral and host)	neutralization of virus entry (humoral response) and destruction of virus-infected cells (cell-mediated response)

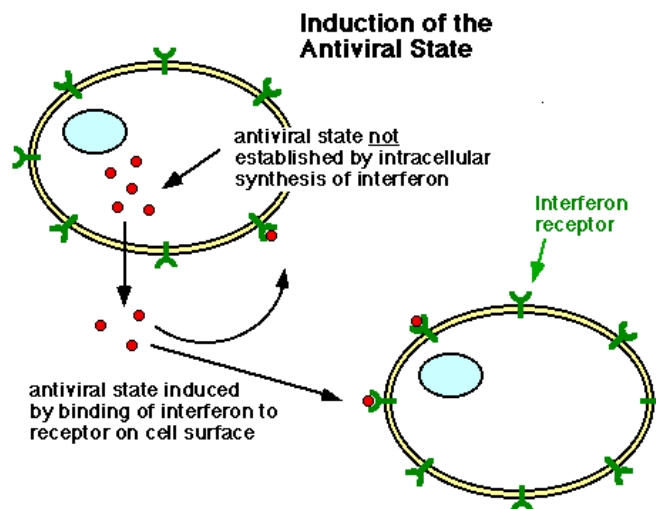
**1)The interferons**

Property	Interferon $\alpha$	Interferon $\beta$	Interferon $\gamma$
Primary Source	leukocytes	fibroblasts	T-lymphocytes, NK cells
Induction	virus infection	virus infection	antigen (mitogen)
Subtypes	20	1	1
Principal Activity	antiviral	antiviral	immunomodulation

- Consider interferons (alpha or beta) synthesized in response to viral infection
- Induction of interferon synthesis (diagram below)



- double stranded RNA is a potent inducer of interferon.
- Induction of the antiviral state
  - antiviral state induced in cell by binding of interferon to cell surface receptor (refer to diagram below)
  - interferon does not induce antiviral state by being in cytoplasm of cell.



## BIOCHEMISTRY

### Biological barriers

#### Host factors

- immune status
- genetic background
- age ( young and old more susceptible )
- gender
- nutritional state
- exercise status
- **smoking (inhibits virus infection)**

#### Virus factors

- Virulence – capacity for virus to cause disease
- Does
- Species specificity
- Stability

#### 1. Initial Infection

- Sites of viral entry  
Mouth, cornea, epidermis, respiratory tract, genitourinary, GIT

#### 2. Tissue Invasion

- Lines of defense – Non specific – granulocytes, macrophages, NK cells  
Specific – Langerhan cells, T/B cells.

#### 3. Haematogenous spread

- Reticulo-endothelial system – spleen, liver (Kupffer cells)
- Blood brain barrier- fenestrated endothelium, choroid plexus, tight endothelial junctions – astrocyte activity
- Blood retinal barrier
- Placental barrier – Hofbauer cells

### **Barriers to spread**

#### Antiviral effector molecules

- Type I IFNs
- Chemokines
- Reactive nitrogen intermediates
- Reactive oxygen intermediates
- Cytokines of the immune response – Th1 and Th2 spectrum.

## CELL BIOLOGY

### Rubella virus(German measles)

- caused by **spherical enveloped fragile RNA virus** - rubivirus (togavirus family)
- RNA genome produces and single polypeptide which is cleaved into 3 proteins
- **virus is easily killed by heat and UV light**
- disease can occur sporadically, epidemics are not uncommon
- worldwide distribution
- spread by simple contact via droplets
- can produce mild infection (adults and children)
- severe infection – congenital rubella syndrome, hydrops fetalis (fetus, embryo).
- **Maximum infectivity occurs before and during time rash is present**

## EMBRYOLOGY

### **Foetal placental circulation at 21 days gestation.**

#### Function of placenta:

- 1) anchors blastocyst,
- 2) secrete hormones(estrogen and progesterone>20wks???)
- 3) supply of nutrients/exchange of gases, removal of excretory products,
- 4) provides fetal immunity through passive IgG immunity.

Decidua: inner layer of the wall of the uterus, which envelops the embryo, forms a part of the placenta and is discharged with it.

## IMMUNOLOGY

### Fetal Immunity

- **Immunity develops prenatally in the absence of exogenous stimuli**
- Includes the production of immune cells (phagocytes and lymphocytes)
- Specific immune responses are poorly developed but **non-specific mechanisms are relatively mature.**

- Natural Killer (NK) lymphocytes are also present during the fetal period – they are found in the liver by the middle of prenatal life
- Neutrophils in the neonate tend to migrate less rapidly than those in an adult, and the status of mononuclear phagocytes is unclear
- **Primary lymphoid organs – bone marrow, thymus, fetal spleen, fetal liver**
- **Secondary lymphoid organs – lymph nodes, tonsils, spleen**

Features of an ideal antiviral drug might include the following:

- \* Effective inhibition of some essential viral process
- \* Drug-resistant viruses do not appear
- \* Broad spectrum activity (e.g., a single drug effective against any of the 100+ common cold viruses)
- \* No effect on host processes

### Antibodies

#### **2<sup>nd</sup> trimester (>12wks)**

- **Small amounts of IgM produced by fetus** – low affinity, no memory, responds to limited range of antigen
- **Passive immunity** – fetus is protected by infection by its isolation within the uterus and **maternal IgG** which decreases after birth.

#### **Infant at 6 mths – IgG produced by infant**

**IgG antibodies may also be transferred to neonate after birth through breast milk.**

Full immunocompetence achieved at adolescence.

### Lymphocyte development

On the first appearance of lymphocytes the fetus begins to achieve tolerance (immunological non-responsiveness) to 'self' antigens. The extent of fetal damage after an infection such as congenital syphilis, rubella and cytomegalovirus is variable, but **damage is less marked when infection occurs at a later fetal age.**

In humans, **antibodies against the diphtheria toxin, tetanus toxin, erythrogenic toxin, staphylococci, streptolysin, rubeola, rubella, mumps and polio cross the placental wall.** Generally only certain subclasses of the IgG antibodies can cross the placenta. These antibodies give the fetus a small amount of protection up until the end of the first year of life. It is for this reason that such vaccinations such as rubella should generally not be given prior to 1 year of age, as it may react with maternal antibodies.

## **PATHOLOGY**

### Control of Communicable disease

1. **Control of reservoir** – isolation and treatment of infected cases
2. Interruption of transmission
3. **Protection of host** – immunization, quarantine, mask
4. **Control of incidence** – primary prevention
5. **Control of morbidity** - early diagnosis and treatment
6. **Control of mortality** –better treatment for advanced disease

## **PHARMACOLOGY**

### Teratology

Adverse outcomes in pregnancy due to teratogens ('monster' creating chemicals)

- 57% of pregnancies detected by hGC at 8-9 days after fertilization do not develop as clinically detectable pregnancy
- 15-20% end in spontaneous abortion
- 2% end in miscarriage
- 2-3% of newborns have a major malformation severe enough to require hospitalization (including visceral and cardio malformations)

**All congenital malformations occur in first 8wks of embryogenesis( organogenesis period).**

Exception – genitourinary malformations.

### **Therapeutic drugs teratogenic in humans**

- **Anticonvulsants** - phenytoin, carbamazepime
- **Anticancer agents** – alkylating agents eg. Cyclophosphamide. Antimetabolites eg. Methotrexate
- **Androgenic hormones**
- Antithyroid drugs – propylthiouracil
- **Aminoglycoside antibiotics** – **Streptomycin** (deafness)

- Coumarin anticoagulants – **warfarin** (face abnormality defects)
- **Retinoic acids** – acutane
- **ACE inhibitors** – captopril
- **Tetracycline**
- Sleeping tablets – **thalidomide ← !!**

Other human teratogens:  
**Alcohol, cocaine**

### Prevention of rubella through: Vaccination and Immunization

Vaccination : administration of vaccine or toxoid.

Immunization : process of inducing immunity by any means. May be passive, or active.

### **Neonate vaccinations : Hep B, DTP, Polio Hib, MMR**

Live attenuated infection agents may be given (eg. Measles, rubella virus )

- Induces immunologic response more like natural infection.
- Inactivated agents or constituents of products obtained by genetic recombination

Passive immunization is generally used to provide temporary immunity in an unimmunized subject exposed to an infectious disease when active immunization either is unavailable. Used in diphtheria, snake/spider bites, specific immunosuppressant (eg. Rho (D) immunoglobulin.)

The route of administration in part determines the rapidity and nature of the immune responses to vaccines. Vaccines can be administered orally, intranasally, intradermally, subcutaneously, or intramuscularly. Vaccines must be administered by the licensed route to ensure immunogenicity and safety. Use with caution in immunocompromised patients

Because age influences the response to vaccines, schedules for immunization are based on age-dependent responses determined empirically from clinical trials.

**The presence of high levels of maternal antibody and/or the immaturity of the immune system in the early months of life impairs the initial immune response to some vaccines.**

A definable prevalence of immunity in the population above which it becomes difficult for the organism to circulate and reach new susceptibles. This prevalence is called **herd immunity**.

Rubella vaccination ( live attenuated ) available in Aust. since 1971 as a combined vaccination with measles and mumps.

### **Neonate vaccinations: 1<sup>st</sup> at 12-15mths, 2<sup>nd</sup> at 4-12 years**

Use of the vaccine is contraindicated during pregnancy or if there is a likelihood of pregnancy within 3 months of immunization. Inadvertent use of the vaccine during pregnancy has not, however revealed a risk of teratogenicity.

### **HISTOLOGY**

Cytopathic effect (CPE) of virus growth in cell cultures. NOT VERY VISUALLY OBVIOUS – cells get multinucleated  
 Rubella invasion in HELA cell line – multinucleated cells

### **BEHAVIORAL SCIENCES**

Cross cultural communications.

- Language is the main barrier to communication cross culturally and patients who do not speak English as a primary language will have difficulties understanding the questions we ask or answering the questions in a manner that is useful for understanding the presenting medical complaint.
- Modesty is an issue in many cultures and so it is vital to protect and maintain the standards of the culture while examining the patient.
- In all our patient interactions we need to ensure that the patient feels cared for and understood.
- It is important to try to keep our minds open when dealing with patients from different cultural backgrounds.

### **GENETICS (irrelevant drivle)**

Rubella – broke paradigm that congenital malformations are genetic (Gregg's discovery 1940)