The Royal Women’s and
The Royal Children’s Hospitals
Melbourne
Department of Microbiology and Infectious
Diseases

Congenital Infections and
Rashes in Pregnancy

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A rash diagnosis …

- Varicella zoster virus
- Human parvovirus
- Enteroviruses
- Cytomegalovirus
- Rubella virus
- Herpes simplex virus
- Lyme disease
- Epstein-Barr virus

- Listeria
- Toxoplasmosis
- Meningococcus
- Syphilis
- Hepatitis B
- Hepatitis C
- H.I.V.
- Others …
A rash diagnosis …

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- Hepatitis B
- Hepatitis C
- H.I.V.
- Others …
Effects on the fetus

- Non-specific effects of maternal infection
  - Fetal death
  - Premature delivery

- Specific effects of viral replication
  - Benign / self-limiting
  - End-organ damage
  - Chronic infection – Hepatitis B/C, HIV
Varicella Zoster Virus
Varicella Zoster Virus (VZV)

- Herpesviridae family
- Large 120nm
- Icosahedral
- dsDNA
- Enveloped
- Latent infection - dorsal root ganglia
- Chickenpox and herpes zoster
Chickenpox

- IP 10-20 days (median 14 days)
- Respiratory / direct contact
- Fever, lethargy, pruritic vesicular rash
- Face, trunk → centripetal spread
- Clear vesicle → cloudy → rupture
- 2-6 days
Chickenpox - Complications

- Secondary bacterial infection
  - commonly *Streptocococcus pyogenes*
  - *Staphylococcus aureus* (bullous varicella)

- Pneumonitis
  - Immunocompromised
  - Adults – 25x more common
  - tachypnoea, cough, haemoptysis

- Acute cerebellar ataxia
  - 1/4000, complete recovery 2-4 weeks
Chickenpox - Complications 2

- Encephalitis & meningitis
  - 2-15/100,000, mortality 5-20%
- Hepatitis
  - mild in otherwise healthy patients
  - immunocompromised patients, progressive
- Reye’s Syndrome
  - 3/100,000, association with aspirin
- Neurological complications
  - Guillain-Barre, peripheral & optic neuritis
Maternal varicella

- More severe in pregnant adults

- Deaths most common in 3rd trimester
  - ~ 2% mortality
Congenital Varicella Syndrome

- First trimester primary infection
- Limb hypoplasia
- Cicatricial scarring (dermatomal)
- Microcephaly, cataracts
- Gastrointestinal & genitourinary abnormalities
Congenital Varicella Syndrome

• Risk varies with gestation:
  0-12 weeks gestation 0.4%
  13-20 weeks gestation 2%

• 1-3 cases per year in Australia

• Increased risk of herpes zoster in infancy:
  – exposure 25-36 weeks: 0.8-1.7%
Perinatal Varicella

- Primary maternal varicella
  - -7 to +2 days from delivery
  - lack specific antibody
- 30-50% transmission to neonate
- Disseminated infection
- Mortality 25-30%
- Varicella zoster immunoglobulin (VZIG)
- Acyclovir
Acyclovir

- Prophylaxis for significant exposure
  - ZIG not given (eg. >96 hours)
  - 3rd trimester / 2nd half of pregnancy
  - Chronic lung disease
  - Immunosuppression
  - Cigarette smoking
Acyclovir

- Treatment of acute varicella
  - Intravenous if pneumonitis, neurological symptoms, organ involvement, haemorrhagic rash
  - Oral if <24 hours of rash and no systemic symptoms
Prophylactic VZIG

• Given post-exposure (<72-96 hours)
  – susceptible pregnant women
  – Infants whose mothers develop varicella <7 days prior to delivery and in first month of life
  – immunocompromised
    – transplant, malignancy
  – premature babies (<28/40, 1000g)

• Prolongs IP to 30 days
Varicella Vaccine

- Live attenuated virus (OKA strain)
- Seroconversion >90%
- Given at 12 months of age
  - ? MMR-V
- 2 doses for >12-year-olds
- Non-immune adults in ‘high risk’ occupations
- ? booster
Parvovirus
Parvovirus B19

• ssDNA virus; IP 4-21 days
• Shortens lifespan of RBC progenitors
• Erythema infectiosum; Fifth disease
  • fever, rash (‘slapped cheek’) and generalised maculopapular, lace-like rash on body
  • common cause of febrile convulsions
• Arthralgia + rash in adults
• Acute aplastic crisis
  • chronic haemolytic anaemia (eg. sicklers)
Congenital Parvovirus Infection

- 60-70% pregnant women immune
- Hydrops foetalis (anaemia)
- Foetal loss:
  - <10/40 10%
  - 9-20/40 3%
- Vaccine in development
- Intrauterine transfusions

Parvovirus inclusions, erythroid precursors (spleen)
Parvovirus Diagnosis

• Serology
  – IgG  past infection; immunity
  – IgM  present at time of rash; positive for 2-4 months

• Nucleic acid detection
  – Persistent infections in immunocompromised hosts
Parvovirus Diagnosis

- Ultrasound at 1-2 weekly intervals for 6-12 weeks
- Fetal blood sampling
- Intrauterine transfusion
Neonatal Enteroviral Sepsis

Hand, foot and mouth disease

Enterovirus, immuno-EM
Enteroviruses

- Picornaviridae
  - Coxsackievirus (A1-24, B1-6)
  - Echovirus (1-34)
  - Poliovirus (1-3)
  - Enterovirus ..

- ssRNA
- Icosahedral
Epidemiology

• Transmission
  – Faecal-oral, respiratory
  – Hands, water, fomites
  – Flies

• Intrauterine infection
  – Uncommon, stillbirth

• Perinatal infection
  – Contact with secretions / faeces
Septic Twins & Summer Bugs

Case 1
Presenting history

- 36/40 gestation
- Emergency LUSCS
- Twin I - 2815g
  - initial respiratory distress
  - penicillin + gentamicin 48 hours
- Twin II - 2910g
  - well
Progress - days 3 & 4

• Lethargy and poor feeding
• Temperature instability
• Frequent desaturations
• Thrombocytopenia (30x10^9/L)
• Hyponatraemia (125 mmol/L)
• Abdominal distension & loose green stools

? Bacterial sepsis
? Rotavirus
Initial management

- Blood culture
- Stool culture & antigens
- Penicillin + gentamicin
- Mechanical ventilation
Progress - day 5

- Hepatosplenomegaly
- Abdominal distension
- Stools + blood, rotavirus Ag negative
- ↑ bilious aspirates
- Hypotonic & poorly responsive
- Thrombocytopenia (17x10⁹/L)
- Coagulopathy (PT 75, APTT 120, INR 7.9, +D-dimers)
Investigations

- Bili 120, GGT 104, ALP 180, ALT 40
- Hb 15.8, WCC 21.7 (Nº 8.7)
- Film: left shift, reactive L⁰, M⁰ vacuolation
- AXR: dilated loops, ? intramural gas
- CXR: NAD
- Blood cultures: NG
Further management

- ? Bacterial sepsis
- ? N.E.C.
- ? CMV

- Vancomycin + gentamicin + metronidazole
- ‘TORCH titres’
- Urine viral culture
Progress - day 6

• Maternal history

  – 34 years, G₄P₃, uncomplicated pregnancy
  – 6 days prior to delivery:
    - fever (38.5°C), cough, rhinorrhea
    - mucus stools 48 hours post-partum
Diagnosis & Investigations

Congenital enteroviral sepsis
? Herpes simplex virus infection

• Stool & NPA IF + viral culture
• Enteroviral serology on babies/mother
• Enteroviral RT-PCR blood, stool, ETT aspirate
• CXR, ECG, troponin, CK-MB

→ Continue antibiotics + acyclovir
Progress - day 8

Enteroviral RNA detected in blood
Echovirus 33 isolated from faeces

– Pleconaril commenced
  – 5mg/kg/dose 8 hourly via NGT

– Oliguria - frusemide, fluid restriction
– Coagulopathy - FFP, cryoppte, Plts, Vit K
– Intravenous immunoglobulin x2
– Antibiotics ceased
Progress - twin II

- Hepatic failure
- Renal failure
- Disseminated intravascular coagulopathy
- ? Seizures; EEG: encephalopathy; CT: NAD
- CSF (day 17): PMN 3; RBC 549
  - Glucose 1.6 mmol/L
  - Protein 2780 mg/L
  - PCR/Culture negative
Twin II - results

Days

ALT
Bilirubin
Platelets
Creatinine
Progress - twin II

- Day 24 - Death from pulmonary haemorrhage

- Post mortem
  - Pale friable liver with areas of haemorrhagic necrosis
  - Fresh blood in trachea; multiple small pulmonary abscesses
  - Enlarged pale kidneys; adrenal haemorrhage
Progress - twin I

- Hepatic failure
- Renal failure
- Disseminated intravascular coagulopathy

- Extubated day 15
- Discharged day 36
Twin I - results

Days

ALT
Bilirubin
Platelets
Creatinine
Congenital Coxsackievirus Infection

Case 2
Presenting history

- 37/40, 3075g, emergency-LUSCS
- Abdominal pain ? placental abruption
- Apgar: 9↑ 9↑
- Day 3:
  - Fever 38.5°C, ↑ apnoea / bradycardia
  - ↑ lethargy, feed intolerance, diarrhoea
- Ventilation, blood cultures
- Ampicillin + gentamicin
Investigations 1

- Hb 13.2, WCC 6.4, Plt 273
- Creatinine 60 µmol/L
- LFT’s - normal
- Cerebrospinal fluid
  - 161 mononuclear cells
  - protein 3.1, glucose 1.6
  - HSV PCR negative
  - Enterovirus PCR positive
Investigations 2

- Faeces viral culture
  - coxsackievirus B2
- Rectal swab, throat swab, NPA, CSF
  - no growth
- Enteroviral CF titre 32
- Coxsackievirus group IgM negative
Progress

• Ventilated 3 days

• Gradual improvement

• Discharged home day 8
Readmission - day 13

- Sudden onset:
  - floppy, cyanosed, grunting, poorly perfused
  - tachypnoea (100), tachycardia (180)

- CXR: cardiomegaly, congestive changes

- Echo: LV dysfunction (SF 11%) with LV dilatation
Management

Diagnosis: cardiomyopathy

- Digoxin, frusemide, spironolactone, captopril

- Gradual improvement in cardiac function

- Discharged day 17
Congenital Enteroviral Infections

- Echovirus (particularly 11) 50-70%
- Coxsackievirus B 20-30%
- Coxsackievirus A & polio virus <5%

- 75% in spring and summer

- Overall mortality 10% (Echo 80%)
Congenital Enteroviral Infections

• Echovirus
  – Hepatitis and DIC
  – Meningitis (27%)
  – Pneumonia (5%)
  – Rash (5%)
Neonatal Coxsackievirus Infection

• Vertical transmission
  • transplacental
  • maternal secretions

• Horizontal transmission
  • nosocomial outbreaks

• Characteristic maternal syndrome (60%)
  • fever, Abdominal pain, vaginal bleeding
Clinical presentation

• Biphasic illness
  • Initial onset day 3-4: fever, coryza, diarrhoea
  • Recovery: 1-7 days
  • Cardiac failure 2-3 weeks: cyanosis, shock

• Diagnosis
  • Viral culture
  • Nucleic acid amplification
  • Serology
Diagnosis

• **Specimens - culture**
  – faeces (55%)
  – rectal swab (45%)
  – CSF (35%)
  – Throat swab/washings (20%)

• **PCR - blood, CSF**

• **Serology**
  – Complement fixation
  – Coxsackievirus IgM
Treatment

- Supportive
  - inotropes, digoxin

- Immunoglobulin

- ? Anti-enteroviral agents
Enteroviral Chemotherapy

1. Enviroxime & associated compounds
   - Inhibit RNA replication
   - Toxicity & bioavailability problems

2. 3C Protease Inhibitors
   - Block protein synthesis
   - Phase I trials

3. Capsid-binding compounds
   - Prevent viral attachment & uncoating
   - Pleconaril (Picovir®)
Pleconaril in neonatal enteroviral sepsis

- Phase III open-label compassionate use trial
- 14 subjects with proven EV infection
- 12 treated with full 7 day course
- 10 survived