Viral infections
Childhood infections

- fever
- fever with a rash
- fever with a localised site of infection
- serious infection

Many infections lack:
- localisation
- rash
- severe complications

...but these may evolve
Plan:

- **Exanthems**
  - Measles
  - Rubella
  - Mumps
  - Parvovirus

- **Herpesviridae**
  - EBV
  - CMV
  - HHV6
  - VZV
  - HSV

- **Enteroviruses**
  - Echo
  - coxsackie

- **Retroviruses**
  - HIV
  - HTLV

- **Miscellaneous**
  - Molluscum
  - HPV
  - adeno
Fever with a blotchy or spotty rash

- measles
- rubella
- erythema infectiosum (parvo)
- roseola infantum (HHV6)
- scarlet fever
- erythema multiforme
- Kawasaki disease
- systemic JCA (Still’s)
- allergy
Virus classification

DNA VIRUSES
- Double stranded
  - Enveloped
    - Circular
    - Linear
  - Non-enveloped
- Single stranded
- Complex
  - Enveloped
  - Non-enveloped

RNA VIRUSES
- Single strand positive
  - Enveloped
  - Non-enveloped
  - Togaviridae
  - Coronaviridae
  - Retroviridae
  - Picornaviridae
  - Caliciviridae
- Single strand negative
  - Enveloped
  - Non-enveloped
  - Orthomyxoviridae
  - Paramyxoviridae
  - Rhabdoviridae
  - Bunyaviridae
  - Arenaviridae
  - Filoviridae
- Double strand
  - Reoviridae
Common viral pathogens in childhood

(1) DNA viruses

- **Pox viruses**
  - molluscum contagiosum: benign skin nodules

- **Herpes viruses**
  - HSV 1: stomatitis
  - HHV 6: roseola infantum
  - varicella zoster: chickenpox
  - cytomegalovirus: congenital infection
  - Epstein-Barr virus: infectious mononucleosis

- **Adenoviruses**
  - many serotypes: URTI

- **Small DNA viruses**
  - parvovirus: erythema infectiosum
Common viral pathogens (2)
RNA viruses

<table>
<thead>
<tr>
<th>‘childhood fevers’</th>
<th>rubeola (measles)</th>
<th>rubella (German measles)</th>
<th>mumps</th>
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<tbody>
<tr>
<td>respiratory infection</td>
<td>rhino</td>
<td>respiratory syncytial virus</td>
<td>influenza</td>
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<td>diarrhoea</td>
<td>rotavirus</td>
<td>Norovirus</td>
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<tr>
<td>enteroviruses</td>
<td>coxsackie</td>
<td>echo</td>
<td>polio</td>
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<tr>
<td>other important viruses</td>
<td>human immunodeficiency virus</td>
<td>dengue</td>
<td></td>
</tr>
</tbody>
</table>
7 year old boy
- cough
- fever
- sore eyes
Measles

Highly contagious acute viral illness due to a paramyxovirus and characterised by the classic triad:

- Cough
- Coryza
- Conjunctivitis
Measles: epidemiology

- Endemic worldwide
- Kills ~1 million each year
- 2-3 yearly epidemics in non-vaccinated populations
- Temperate climates max late winter-early spring
- Peak susceptibility infants and young children
  - 40% < 16m
Measles: aetiology

- Paramyxovirus
- ssRNA
- Minor antigenic shifts only seen
- External proteins:
  - H- haemagglutinin
  - F- fusion
  - Envelope proteins
Measles: pathogenesis

Transmission - aerosolised respiratory secretions
- Max infectivity prodrome to d4 of rash
  - from 7-10 days after contact
- Stable for at least 1hr fomites
- Invades/replicates nasopharynx
  - → spreads to regional lymphatics
  - 2º viraemia d5-7 after exposure (esp PBMCs)
  - Dissem replication d7-14
  - Immunity 15-17 d after exposure
Measles:
common features

3-4 days of URTI-like symptoms
- fever, coryza, cough
- conjunctivitis
- lymphadenopathy
- Koplik’s spots

followed by rash
- florid, blotchy
- starts on head & neck, spreads to whole body

incubation
10 - 14 days
Measles: clinical picture

Typical:

- Incubate 8-12d
- Prodrome
  - Fever, cough, non-purulent conjunctivitis, coryza
- Koplik’s spots within 2-3d
  - Anywhere buccal mucosa
    - Classically opposite lower premolars 12-72hrs
    - Coalesce
- Rash ~14 days after exposure
  - Forehead/post occipital
    - Spreads over 3 days to trunk & extremities
    - Confluent higher up
Measles
Measles: exanthematous phase

- high fever peaks 2-3 d after rash appears
  - If persisting think 2° bacterial infection
- Occas GI Sx- diarrhoea major Cx in developing countries
- Severe haemorrhagic measles
  - Pneumonia, seizures, DIC, mucosal bleeds
- Can get milder modified measles post exposure if given Ig (longer incub)
Measles: Cx

- 1 in 1000 †
  - Usually LRTI (60%) or encephalitis
- stomatitis
- AOM 7-9%
- LRTI – viral extension or bacterial 1-6%
- Developing: mastoiditis, pneumonia, diarrhoea
- Thrombocytopenia, hepatitis, appendicitis etc
Measles is a major cause of childhood mortality in developing countries. In some parts of Africa the case fatality rate is as high as 30%.
Measles: complications in the malnourished child

- stomatitis
- desquamating rash
- corneal ulceration
- diarrhoea
- immunosuppression

- cancrum oris
- pyoderma
- blindness
- malnutrition
- secondary infection
Measles encephalitis

Acute:
- 0.1-0.01%
- 2-6 days after rash starts
  - Mild in most, 15% severe, 25% sequelae
- Pleocytosis

SSPE
- If wild infection b4 2yo, M>F
- Sx usually ~10 years after infection
- Slow behav and intellectual deterioration
  - Then myoclonic seizures, 6-9 months to death
- EEG: burst suppression
Measles Mx:

- Vaccine may be protective if within 72 hrs
- Resp isolation until 5 days after rash
- Vitamin A
  - Decreases diarrhoea and pneumonia
Rubella

togavirus, ssRNA
Only one antigenic type
resp transmission (n-p)
  - Day 3-8 after exposure, lasts 11-14 days
Active replication throughout body d8-14
Rare in vaccinated populations
  - Immigrants increased risk incl SEA
Immunity lifelong- Ab and CMI
  - Reinfection rarely causes cong rubella
Rubella:
common features

- incubation 14 - 21 days

- generally a mild illness
  - fever
  - pink macular rash
  - generalised lymphadenopathy (suboccipital nodes)
  - URTI
Rubella complications

These are rare in children:

- thrombocytopenia
- encephalitis
- arthritis

Main risks are in first 3 months of pregnancy:

- abortion
- severe birth defects

CONGENITAL RUBELLA

- deafness
- heart defects
- mental retardation
- cataracts / retinopathy
- thrombocytopenia
- hepatosplenomegaly
- bony lesions
Acquired Rubella

- ‘Rash and suboccipital lymphadenopathy’
- Prodrome d10-20: fever, eye pain, sore throat, arthralgia
- Rash d14-21: start face, cephalocaudal spread over 24h, fades over 2-3d (m-p, but can vary)
  - Can be pruritic in adults
- Adenopathy- up to 1w before rash
  - Suboccipital and post auricular
Congenital rubella

- Risk inversely related to gestation
  - 80% exposed in TM1 have defects
  - Almost none after 16/40

- Transient:
  - Thrombocytopaenia, hepatosplenomegaly, IUGR, bone lesions
    - Lymphadenopathy, hepatitis, haemolytic anaemia, pneumonitis, cloudy corneas,

- Permanent:
  - Deafness, pulmonary stenosis, PDA, VSD, retinopathy, cataract, microphthalmia, UDT, inguinal hernia, IDDM

- Delayed:
  - SNHL, periph PS, MR, language defects, IDDM, immune complex disease, hypogammaglobulinaemia
    - hypothyroidism
Congenital rubella

- Ix baby
  - Excretion
    - ceases by 12m in 90%
    - Dx cult from n-p, blood
  - Serol:
    - IgM FPs
      - (Rh factor or maternal IgG)

- Ix: Maternal
  - EIA IgG,A,M
    - Fourfold rise or single IgM
    - IgM may not be detectable until 1-2w after rash
    - May go 3w after rash
Parvovirus B19

- Erythema infectiosum, fifth disease
- ssDNA, resp droplet spread
- 50% 2° infection rate in households
- Single type
- Erythrocyte P antigen is receptor for virus
  - Also found in myocardium, endothelium, placenta, megakaryocyte, foetal liver
- Some effects direct, some immune
- Normal kids:
  - (Direct) Mild fever d8, rash d17-18
    - Slapped cheek, spreads extremities lacy reticular
  - (Immune) arthralgia 3w (asymmetrical)
Parvovirus B19

- **Normal hosts Cx:**
  - HSP, vasculitis
  - Arthropathy
  - Neuropathy, meninigitis
  - Transient anaemia, thrombocytopenia, neutropenia

- **Haemoglobinopathy**
  - Pure red cell aplasia
  - Transient aplastic crisis

- **Immunosuppressed**
  - Can affect all haem cell lines

- **Pregnancy**
  - ~30% foetuses infected
  - ~50% women susceptible
  - ~6% risk of catching in community outbreak
  - Death <10%, mainly TM2
    - Spon abortion
    - Still birth
    - Non-immune hydrops

- **Death <10%, mainly TM2**
<table>
<thead>
<tr>
<th>Herpesviruses</th>
<th>Target cell</th>
<th>Latency</th>
<th>Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herpes simplex-1 (HSV-1)</td>
<td>Mucoepithelia</td>
<td>Neuron</td>
<td>Close contact</td>
</tr>
<tr>
<td>Herpes simplex-2 (HSV-2)</td>
<td>Mucoepithelia</td>
<td>Neuron</td>
<td>Close contact usually sexual</td>
</tr>
<tr>
<td>Varicella Zoster virus (VSV)</td>
<td>Mucoepithelia</td>
<td>Neuron</td>
<td>Contact or respiratory route</td>
</tr>
<tr>
<td>Epstein-Barr Virus (EBV)</td>
<td>B lymphocyte, epithelia</td>
<td>B lymphocytes</td>
<td>Saliva</td>
</tr>
<tr>
<td>Cytomegalovirus (CMV)</td>
<td>Epithelia, monocytes, lymphocytes</td>
<td>Monocytes, lymphocytes and possibly others</td>
<td>Contact, blood transfusions, transplantation, congenital</td>
</tr>
<tr>
<td>Herpes lymphotropic virus</td>
<td>T lymphocytes and others</td>
<td>T lymphocytes and others</td>
<td>Contact, respiratory route</td>
</tr>
<tr>
<td>Human herpes virus-7 (HHV-7)</td>
<td>T lymphocytes and others</td>
<td>T lymphocytes and others</td>
<td>Unknown</td>
</tr>
<tr>
<td>Human herpes virus-8 (HHV-8) Kaposi's sarcoma-associated</td>
<td>Endothelial cells</td>
<td>Unknown</td>
<td>Exchange of body fluids?</td>
</tr>
</tbody>
</table>
5 year old with fever and rash
Fever with vesicles

- chickenpox
- herpes simplex
- hand, foot and mouth
Chickenpox
common features

- incubation 14 - 16 days

- moderate fever
- crops of vesicles
  - macule > papule > vesicle > scab
  - typically trunk and face more than limbs
  - may occur in mouth
  - sometimes become bacterially infected
Chickenpox: complications

- In normal children Cx rare (apart from 2º infection)
  - encephalitis (espec. cerebellar ataxia)
  - pneumonia (leaving calcifications on CXR)
  - haemorrhagic form
- Can be fatal in immunosuppressed patient
  - prophylaxis with zoster immune globuin (ZIG)
  - treatment with intravenous acyclovir
- Congenital infection
  - risk highest if mother is incubating infection just before or after delivery (transmission rate 25%)
  - give ZIG at birth
- Shingles in elderly and immunosuppressed
- Aspirin + VZV = risk factor Reye’s syndrome
CMV

- dsDNA herpes virus
- Latency: viral genome persists as episomal
- Present all human (only) populations
  - There are non-human CMV species
- No seasonal variation
- Early acquisition developing nations & DCC
  - 50-70% children in DCC infected
- Most common cause congenital infection
CMV transmission

- Direct or indirect person-to-person contact
- Close or intimate contact with secretions
CMV transmission

- Direct or indirect person-to-person contact
- No aerosol spread

Close or intimate contact with secretions

- Urine
- Semen
- Tears
- Blood
- Oropharyngeal secretions
- Cervicovaginal secretions
- Breast milk
- Transplanted organs

Excretion starts 4-6 wks after infection

- Persists for months to years
- Intermittent excretion possible at any time

May persist on fomites for hours
CMV risk groups

**Occupational**
- DCC workers x5-10
- Paed health workers no clear increased risk

**Perinatal CMV**
- Perinatal lecture
Acquired CMV: normal host

- >90% asymptomatic
- IM syndrome
  - Fever up to 2w
  - Abn LFTs (bilirubin usually N)
  - malaise, HA, atypical lymphocytosis
  - Rash (esp after ampicillin)
  - EBV >CMV
    - Exudative pharyngitis
    - Hepatomegaly
    - Splenomegaly
    - adenopathy
CMV: immunocompromised host

- Fever
- Malaise
- Leukopenia
- Transaminitis
- Pneumonitis
- Retinitis
- Enterocolitis
- Encephalitis

- Polyradiculopathy
- Graft function deterioration

Primary
- 4-12 w after Tx

Reactivation
CMV Dx

- Viral detection
  - Tissue culture
  - Antigenemia detection (pp65 and others)*
  - DNA PCR- quantitative* vs qualitative
  - Histology

- Serology
  - IgG
  - IgM
    - (FPs in Rh factor, FNs in immunosuppressed)
CMV Mx

Treatment
- Ganciclovir (IV/o)
- Foscarnet
- Cidofovir
- Hyperimmune globulin

Prevention
- Hyperimmune globulin
- GCV
- Hygiene
- Donor screening
- Reduce viable leukocytes in blood product
EBV

dsDNA, herpervirus
Lytic infection in oropharyngeal & salivary cells
Latent infection in B lymphocytes
All human populations
No seasonal variation
Early acquisition developing world and ?DCC
Adolescent seroprevalence 40-50%
EBV pathogenesis

- **B cells**
  - Up to 20% infected
  - Monoclonal and polyclonal proliferation
  - Immortalisation of B cells

- **Atypical LCs are cytotoxic CD8 positive**
  - Kill infected B cells
  - Outnumber B cells 50:1
EBV transmission

- Oropharyngeal secretions
  - Low titre even during acute illness
  - No isolation needed in hosp

- Blood products
  - Less common than CMV
Clinical: acute EBV

- Asymptomatic frequency inverse to age
- IM syndrome
- Neurologic
  - Nerve palsy
  - GBS
  - Meningoencephalitis
  - Transverse myelitis
- ITP
Mononucleosis syndrome

- Incubation 30-50d
- Fever
- Lymphadenopathy
- Pharyngitis
- Splenomegaly
- Hepatitis – mild
- Rash
  - 15% if no antibiotics
  - 60-80% if beta-lactams
- Pneumonitis
- Neurol
- Myocarditis
- Thrombocytopenia
- Anaemia
  - Haemolytic
  - Aplasia
- Neutropenia
EBV: immunosuppressed

- X-linked lymphoproliferative syndrome
- Post Tx B cell lymphoproliferative syndrome
- HIV associated
  - Lymphoma
  - Oral Hairy leukoplakia
EBV cancers

- Burkitt lymphoma - mainly African type
- Nasopharyngeal carcinoma
- Hodgkin’s (some)
EBV Dx

- FBE: platelets (low), WCC (up or down)
  - film: atypical LC

- Heterophile Ab (Paul Bunnel)
  - aggl of sheep/horse RBCs after absorption with guinea pig kidney cells
  - rapid test horse or beef RBCs
  - positivity increases
    - with age (rare<5y)
    - time after Sx onset

- serology IgG/M VCA
  - also EBNA (6-12w) / EA
HHV6

Roseola infantum:
- virus 1st noted in LC of infant 1988
- infects T lymphocytes, esp activated CD4
- latency in macrophages

2 types:
- A- adults- ?role
- B- roseola and other febrile illnesses
HHV6

- Worldwide, no seasonal variation
- peak 6-12 months of age
- 6-12m: causes 20% all ED visits
  - 9.7% all ED visits <3 years
- most adults sero+ve
- shed intermittently, often asymptomatic
  - virus present in saliva of healthy adults
    - ?major source
- transplacental possible, BMilk ?not fd
HHV6 clinically

- Immunosuppressed
  - BM suppression in BMT & HIV
  - interstitial pneumonitis
  - renal dysfunction
  - skin rash

- Neurological manifestations
  - aseptic meningitis
  - FCs
  - meningoencephalitis
  - ?MS flares
HHV6 clinically

- High fever 3-5 days
  - ‘no focus’ often
- Irritable
- Adenopathy: Cx/occ
- Rash: mac-pap
  - 25% during fever
  - most after fever
  - Nagayama’s spots
    - red papules buccal mucosa
- Inflamed TMs
- URI Sx
- GI Sx
- Bulging AF
- Febrile seizures
  - 15-20%
  - incl recurrent FCs
HHV6

Dx:

- Serology
- PCR
  - +ve indicates current or past infection
  - plasma rather than whole blood indicates active

Rx:

- in vitro susceptible to GCV, foscarnet,cidofovir
HHV7

- Frequent
- Older than HHV6
- Mild fever, rash etc
- Found in breast milk and adult saliva
HHV8

- Kaposi’s sarcoma
  - does occur in childhood in Africa
- ?transmission
HSV:

- Latency in neuron DRG episome
  - no role in malignancy/transformation
- Neurovirulent
- HSV thymidine kinase
  - VZV has, CMV does not
- Can affect any organ of body
- Worse if T cell abnormality
- ?Ab only important for neonates
HSV Rx

- Valacyclovir prodrug for ACV
- Famcyclovir also acts TK
- Foscarnet reserved for resistant virus
  - Acts on viral DNA polymerase
Vertically acquired HIV- NHx

- 20% early progression to AIDS and death in infancy
- 40-50% survived to 10 years without ART
Scenario: HIV +ve mother

You are called to counsel an HIV positive mother about vertical transmission of HIV

- What is the transmission risk?
- What are the risk factors?
- What interventions may reduce risk?
- How will you manage and diagnose the baby?
HIV: kids aint adults

- VL much higher, esp early
- CD4 counts age dependent
  - Much higher in infancy
  - Use CD4%
- Lifetime of Rx
  - Resistance/options
  - Toxicity
Vertical Transmission:

- Accounts for >90% paediatric HIV
  - Risk if HIV positive mother
    - Europe ~14%, Africa ~30%
  - *In utero* - from 1st trimester
  - Intrapartum – 50-70% vert t’mission
    - Contact with infected secretion or blood
  - Postpartum – 14-29%*
    - Breastfeeding
Risk factors for vertical infect\textsuperscript{n}:

- Advanced maternal disease/low CD4
- High viral load
- NVD (vs LUSCS)
- ROM > 4 hours
- Bloody delivery
- Prematurity
- Breast feeding- esp long term
What can we do?
Antenatally:

- Maximise maternal status
  - Health, nutrition
- Diminish viral load, raise CD4 %
  - Maximise anti-retroviral regimen by delivery
- Book for elective LUSCS at 37/40
- Don’t breast feed
Vertical Transmission - Antiretroviral treatment:

ACTG 076

- Maternal zidovudine (ZDV) po from 34/40
- ZDV IV during labour
- Oral ZDV to infant for 1st 6 weeks
- Reduced risk from 25.5% to 8.3%
Vertical Transmission - Antiretroviral treatment:

HIVNET 012

- Oral nevirapine (NVP) single doses
  - to mother at onset of labour
  - to baby at 48 hours

vs modified 076 protocol

- Nearly all breast fed, RV at 14-16 w

Transmission:
  - NVP 13.1%, ZDV 25.1%

Cost-effective
Vertical Transmission - management of newborn:

Diagnostic PCR:
- 1st at 48 hrs pick up 38%
- 2nd at 2-4 weeks pick up 93%
  - IF NEGATIVE HERE:
    - CEASE ANTIRETROVIRALS
    - START SEPTRIN
- 3rd at 4 months pick up 99.7%
  - IF NEGATIVE HERE:
    - CEASE SEPTRIN
- 4th at 6m

serology at 12, 18 months
Vertical Transmission - drug management of newborn:

- Usually mother on HAART
- Intrapartum ZDV
- Neonatal ZDV
  - +/- 3TC
  - and NVP (intrapartum and neonatal)
  - and both
  - for 4-6 weeks
- Possible maternal viral resistance
HIV testing

**Serology:** screen with ELISA, confirm with Western blot. OK after 18 months, when maternal Ab waned.

**HIV DNA PCR:** Preferred test to diagnose HIV infection in infants and children younger than 18 months of age; highly sensitive and specific by 2 weeks of age and available; performed on peripheral blood mononuclear cells

**HIV p24 Ag:** Less sensitive, false-positive results during first month of life, variable results; not recommended

**ICD p24 Ag:** Commonly available; negative test result does not rule out infection; not recommended

**HIV culture:** Expensive, not easily available, requires up to 4 wk to do test

**HIV RNA PCR:** Not recommended for routine testing of infants and children younger than 18 months of age because a negative result cannot be used to exclude HIV infection
Are there risks of therapy?

- lactic acidosis/mitochondrial defects
  - relative potency inhibiting mitochondrial gamma DNA polymerase highest for:
    - ddC, followed by didanosine (ddl), stavudine (d4T), 3TC, ZDV and abacavir (ABC)
  - Keep watching this space
  - Adults/older children lipodystrophy synd
- preterm - not clear association
  - Raised for combination therapy
HIV: to treat or not?

**Infants**

- Always start if:
  - Stage C
  - CD4 < 20%
  - CD4 rapidly falling and persistent high VL > $10^6$/ml

- Consider in any infected infant
HIV: to treat or not?

Children >12m

- **Always start if:**
  - CD4%<15

- **Consider if:**
  - Stage B
  - CD4%<20 or VL>10^5

- **Defer if:**
  - Stage N or A
  - CD4%>20
  - VL<10^5
HIV therapies kids can take

- **NRTIs**
  - ZDV, ddl, ddC, d4T, 3TC, ABC

- **NNRTIs**
  - Nevirapine NVP, efavirenz EFV, delvaridine DLV

- **PIs**
  - Indinavir, ritonavir, saquinavir, nelfinavir, amprenavir, lopinivir/ritonavir
Topical viruses

- **Enterovirus 71**
  - HFM, neurological and systemic disease
  - SEA

- **Nipah virus Malaysia 1998**
  - flying foxes natural host

- **SARS**
  - coronavirus
Enteroviruses

- Small RNA viruses (Picornaviruses)
- ssRNA
- Rapid replication in host cell => cell lysis
- Groups:
  - A1-24
  - B1-6
  - Echoviruses (31)
  - Enteroviruses (types 68-71)
  - Polioviruses (types 1-3)
Enterovirus disease:

- distinct viruses, diverse array disease
- Summer peak time
- Humans only natural host
- Faeco-oral, resp, mother-infant transmission
  - Faecal shedding ~8w
  - Resp shedding ~1w
- Fomite spread possible
- Incub 3-6d
Enterovirus manifestations:

- Different tissue tropisms
  - Non-spec febrile illness
  - Resp: URTI….pneumonia
  - CNS disease: aseptic meningitis, encephalitis, paralysis
  - Skin exanthem/enanthem: HFM
    - A16, Echo19, EV71
  - Eye: acute haemorrhagic conjunctivitis
  - Cardiac: myocarditis, pericarditis
    - Coxsackie B1-5
  - GI: V, D, abdominal pain, hepatitis
EV meningitis

- can be neutrophilia in CSF early
- Many different serotypes possible
- Most in childhood
- Not associated with permanent sequelae
- Daily PCR cost-effective in US studies
- pleconaril
EV Dx:

Culture:
- Throat, faeces, rectal swab, blood, Bx
- Positive culture from anywhere except faeces diagnostic

PCR
- ?Gold standard

Serology
- Polio mainly