the children's hospital at Westmead

PUOs and Viral Diagnosis

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PUO

- "Fever higher than 38.3^{o}C on several occasions persisting without diagnosis for at least 3 weeks in spite of at least 1 weeks investigation in hospital."

  – Petersdorf and Beeson 1961

PUO

- Arbitrary definition but useful.
- The exacting definition is historic and not rigorously applied.
- Now there is “Fever Without Source” (FWS) for a fever of recent onset without explanation determined by history or examination.
- PUO is fever for 8 days with no obvious source after initial investigation.

FWS vs PUO

- Overlap exists
- Frequent cause of one may not be frequent cause in the other.
- Recent onset of fever usually warrants more immediate evaluation than PUO.
- PUO rarely presents as an emergency but does require timely, not urgent, diagnosis and treatment.
- Empiric antibiotics often indicated in FWS but not often in PUO.

Fever Without Source

- FWS is fever for 1 week with no obvious source.
- 5-10% with up to 20% of children
- Peak incidence is 2nd year of life
- Many are self limiting infectious diseases
- Some in prodromal phase of specific illness eg sinusitis, hepatitis, mononucleosis.
- May be indicator of Kawasaki disease

PUO

- Five main etiological categories
  - Infection
  - Neoplasm
  - Connective Tissue Disease
  - Miscellaneous
  - Undiagnosed

"Subtypes" of PUO

- Community acquired
- Nosocomial
- Immunodeficient
- HIV-related

Approach to Diagnosis of PUO

- History for Community Acquired PUO
  - Duration and pattern of fever
  - Age of patient
  - Sexual History
  - Contact with other ill people
  - Vaccination history
  - Travel History
  - Animal, insect exposure
  - Previous medical treatment inc blood products

Approach to Diagnosis of PUO

- Physical Exam - extras
  - Sinus tenderness
  - Mouth ulceration
  - Fundi – chorioretinitis
  - Chest – pneumonitis
  - Abdomen – hepatic tenderness, splenomegaly
  - Lymphadenopathy
  - Arthralgia / Arthritis
  - Rash

Approach to Diagnosis of PUO

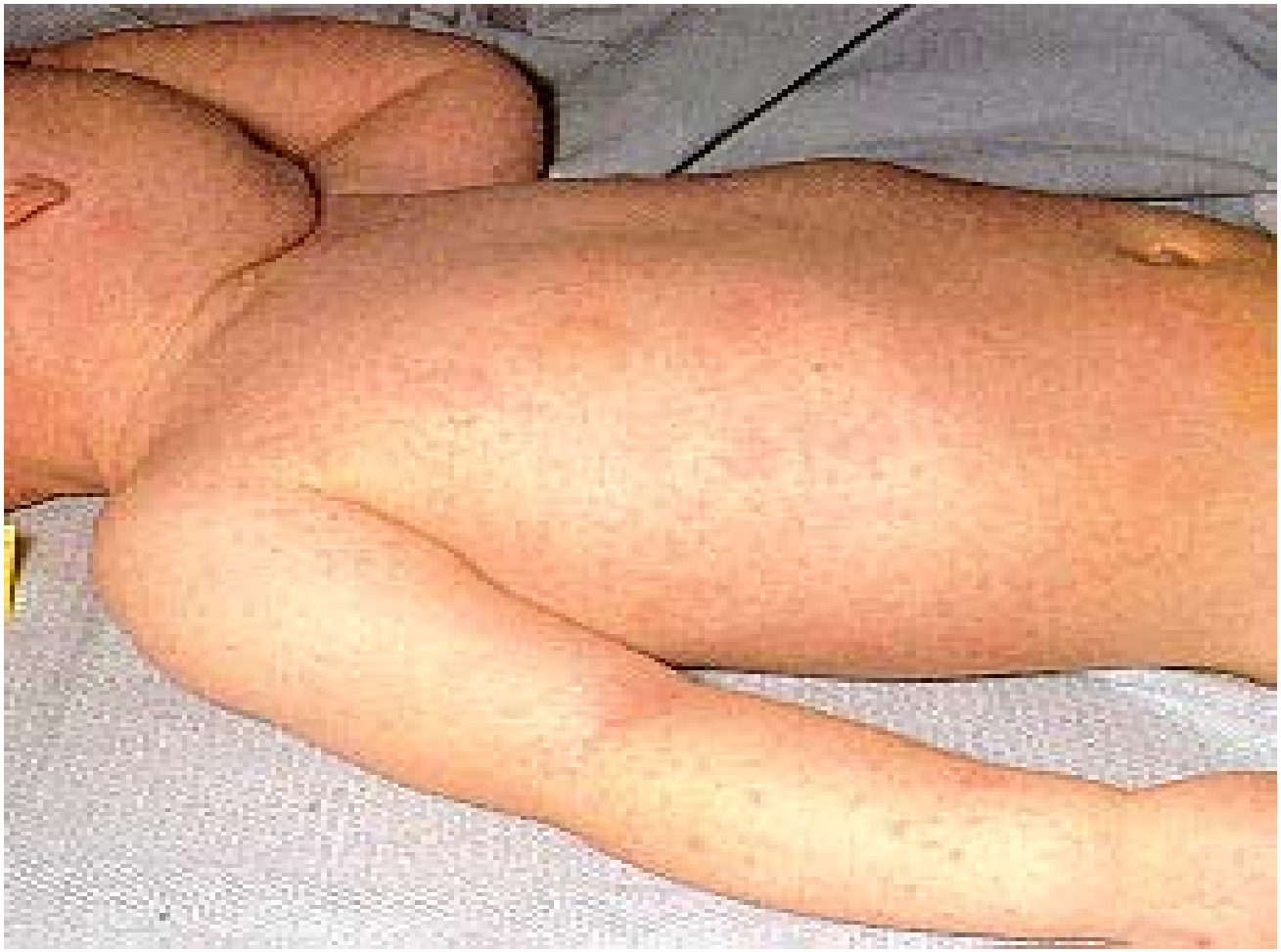
- Investigations
  - FBC and differential
  - EUC, LFTs, Amylase, CRP, ESR
  - Urinalysis + culture
  - Investigation for infectious causes guided by history and exam
  - Consider Rh F, ANA , ANCA

  - Other investigations and imaging as indicated

Viral Causes in CA-PUO

- Mononucleosis – EBV, CMV
- Zoster
- Enterovirus
- Adenovirus
- Respiratory viruses – parainfluenza, RSV
- Hepatitis – A,B,C,D,E
- Alphaviruses – Ross River, Barmah Forest virus. Sindbis
- Flaviviruses - Dengue

EBV rash



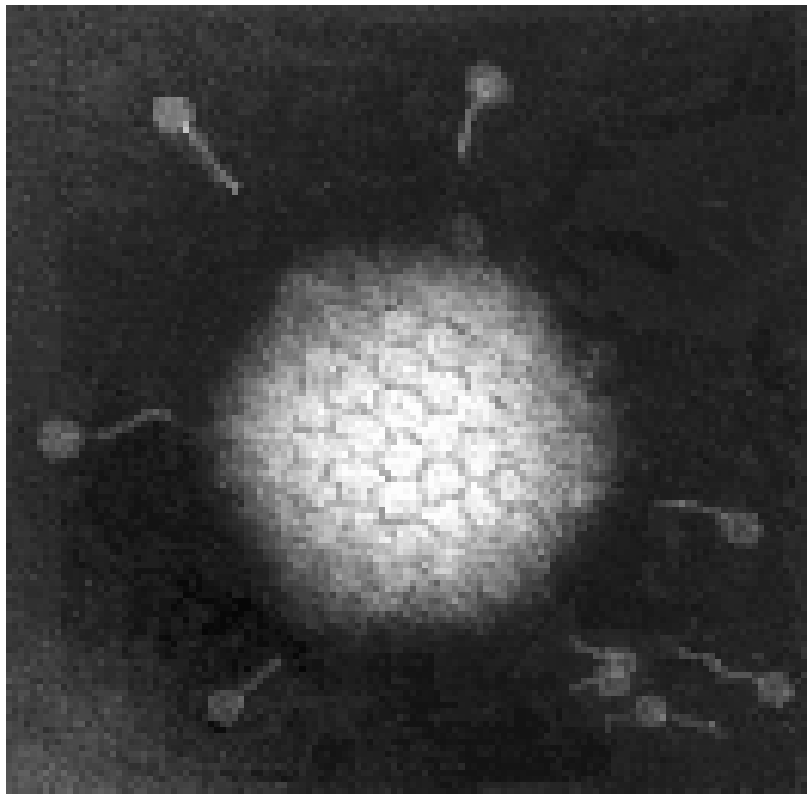
Mononucleosis

- Prodrome of 2 to 5 days
- Acute phase
  - Fever, sore throat, malaise, fatigue
  - Fever may last 4 to 5 weeks
  - Lymphadenopathy (80%), hepatomegaly (60%), splenomegaly (50%).
  - EBV causes 80-95% others usually CMV
  - Children <5 usually heterophile antibody negative.

Mononucleosis

- CMV induced mononucleosis
- Less common
  - Sore throat
  - Lymphadenopathy
  - Atypical lymphocytes
- Prominent splenomegaly

Adenoviruses



- ds DNA virus
- non-enveloped
- At least 52 serotypes are known
- classified into 6 subgenera: A to F

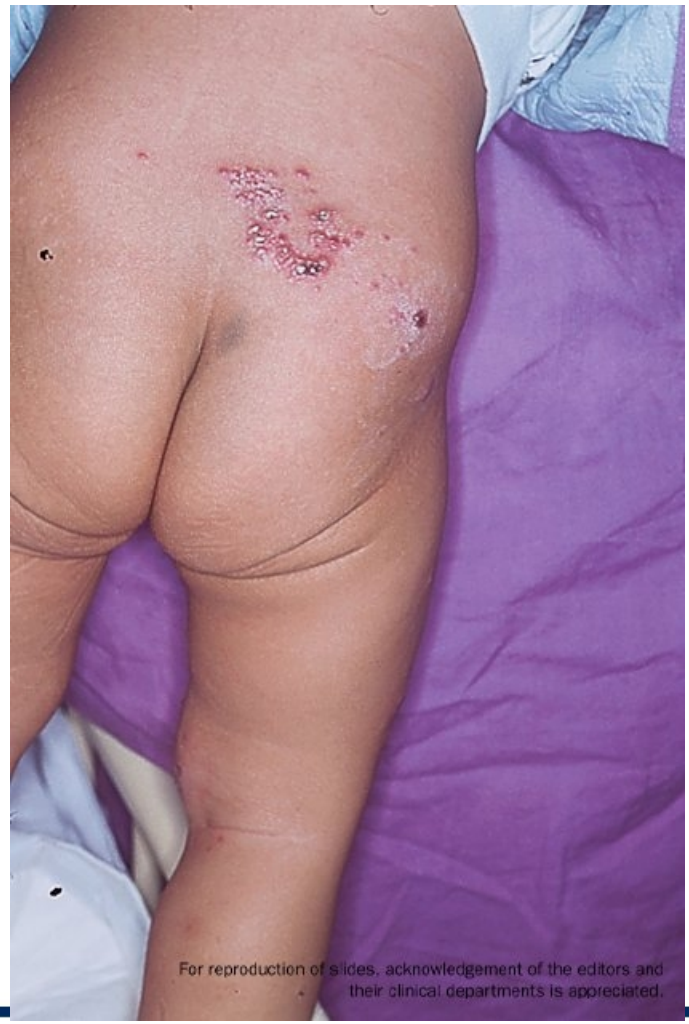
Adenovirus syndromes

- 1. Pharyngitis 1, 2, 3, 5, 7
  2. Pharyngoconjunctival fever 3, 7
  3. Acute respiratory disease 4, 7, 14, 21
  4. Pneumonia 1, 2, 3, 7
  5. Follicular conjunctivitis 3, 4, 11
  6. Epidemic keratoconjunctivitis 8, 19, 37
  7. Pertussis-like syndrome 5
  8. Acute haemorrhagic cystitis 11, 21
  9. Acute infantile gastroenteritis 40, 41
  10. Intussusception 1, 2, 5
  11. Severe disease in AIDS and other immunocompromised patients 5, 34, 35
  12. Meningitis 3, 7

Enterovirus Infections

- Enter and replicate in the GIT
- Prevalent summer and autumn
- Cause disease in variety of organs
  - Meningitis / encephalitis
  - Myocarditis
  - URTI, pneumonia
  - Hepatitis
  - Vomiting and diarrhoea – non-specific

Zoster in 2 year old



Zoster

- Zoster in children can be difficult to diagnose if there is no history of chickenpox.
- Maternal chickenpox in pregnancy is assoc with increased risk of zoster in young children.
- Zoster is usually less severe and much less associated pain.

Roseola

- Roseola infantum is a common acute illness of young children characterised by a fever of 3-5 days duration, rapid defervescence and then the appearance of an erythematous macular or maculopapular rash that persists for 1-2 days

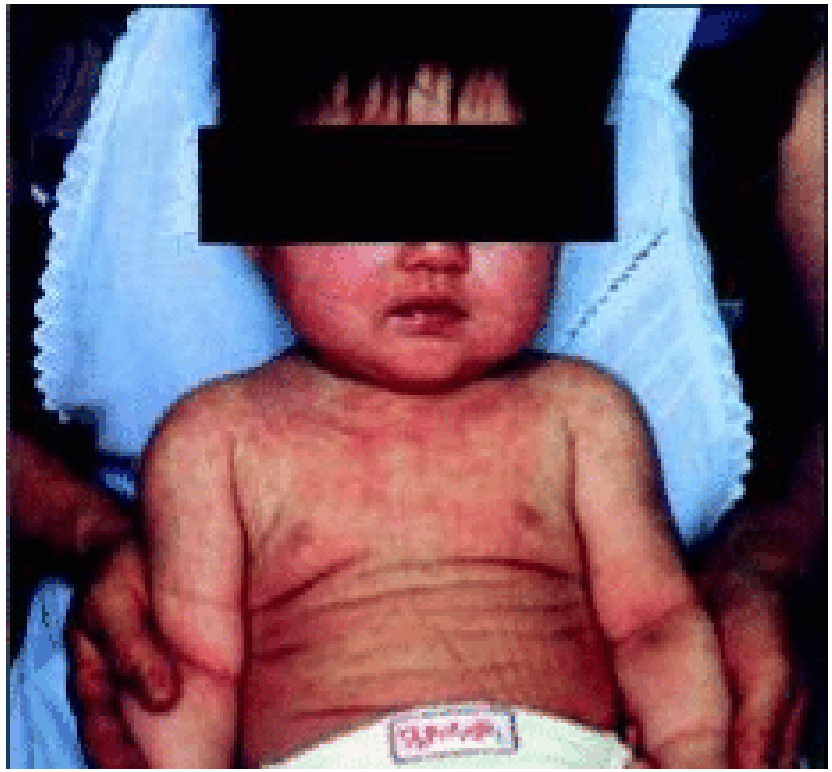
- The most important complication are convulsions and other neurological symptoms.

Roseola

- It is estimate that HHV-6 - 73.5%, HHV-7 - 10.2% and other - 16.2% of roseola cases.

- HHV6 appears to be the major cause of roseola.

Roseola infantum – HHV-6



Common Colds

- Common colds account for one-third to one-half of all acute respiratory infections in humans
- Rhinoviruses are responsible for 30-50% of common colds, coronaviruses 10-30%
- The rest are due to adenoviruses, enteroviruses, RSV, influenza, and parainfluenza viruses, which may cause symptoms indistinguishable to those of rhinoviruses and coronaviruses

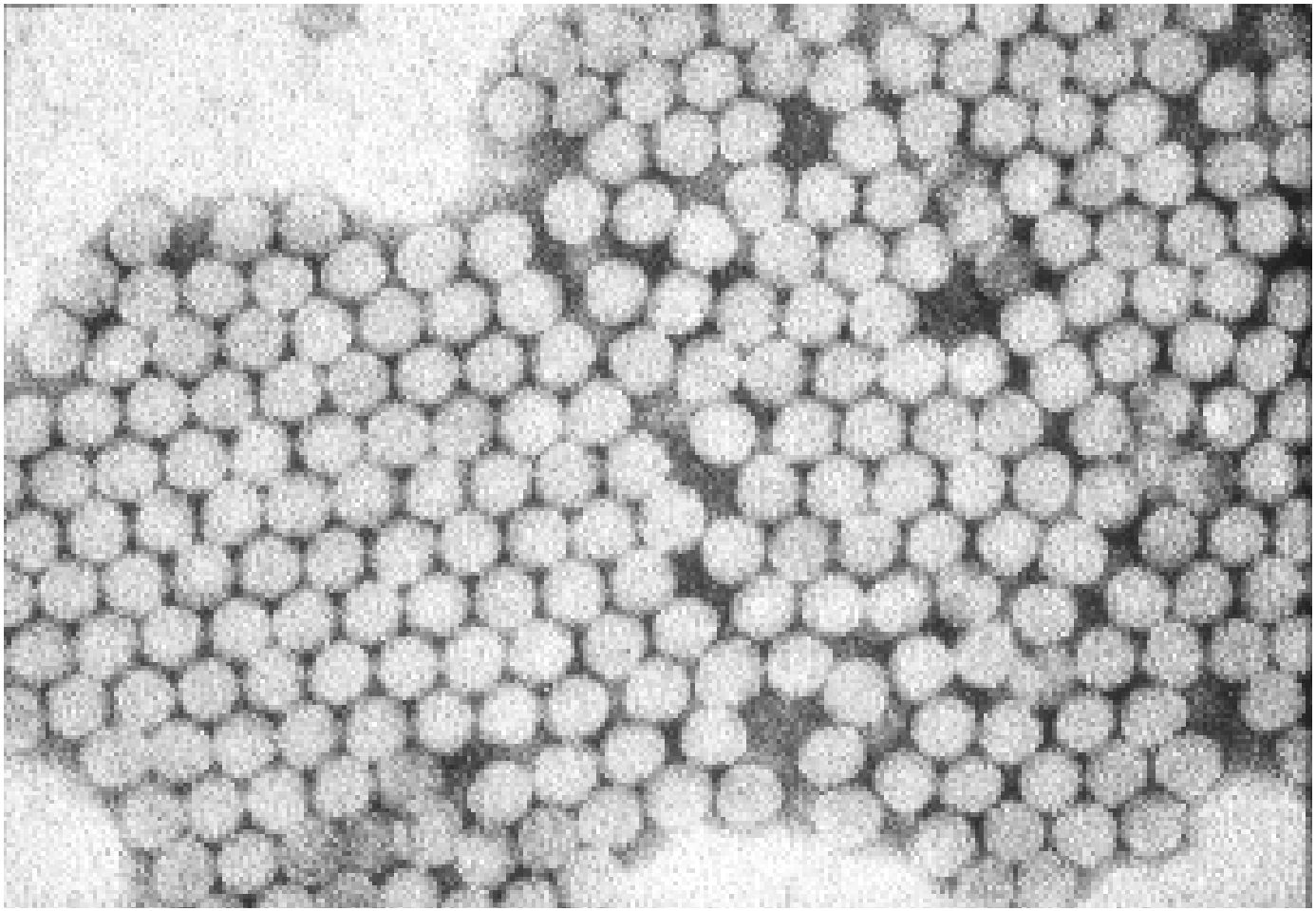
Hepatitis A

- Worldwide endemicity of HAV varies within and between countries.
- Clinical presentation varies with age of patient and reflects endemicity.
- Infection in childhood (pre-adolescence) often asymptomatic or mild

Hepatitis A

- Can be non-specific with little or no jaundice.
- Diagnosis:
  - raised LFTs
  - HAV IgM pos
  - HAV PCR
- Protection by passive or active vaccination

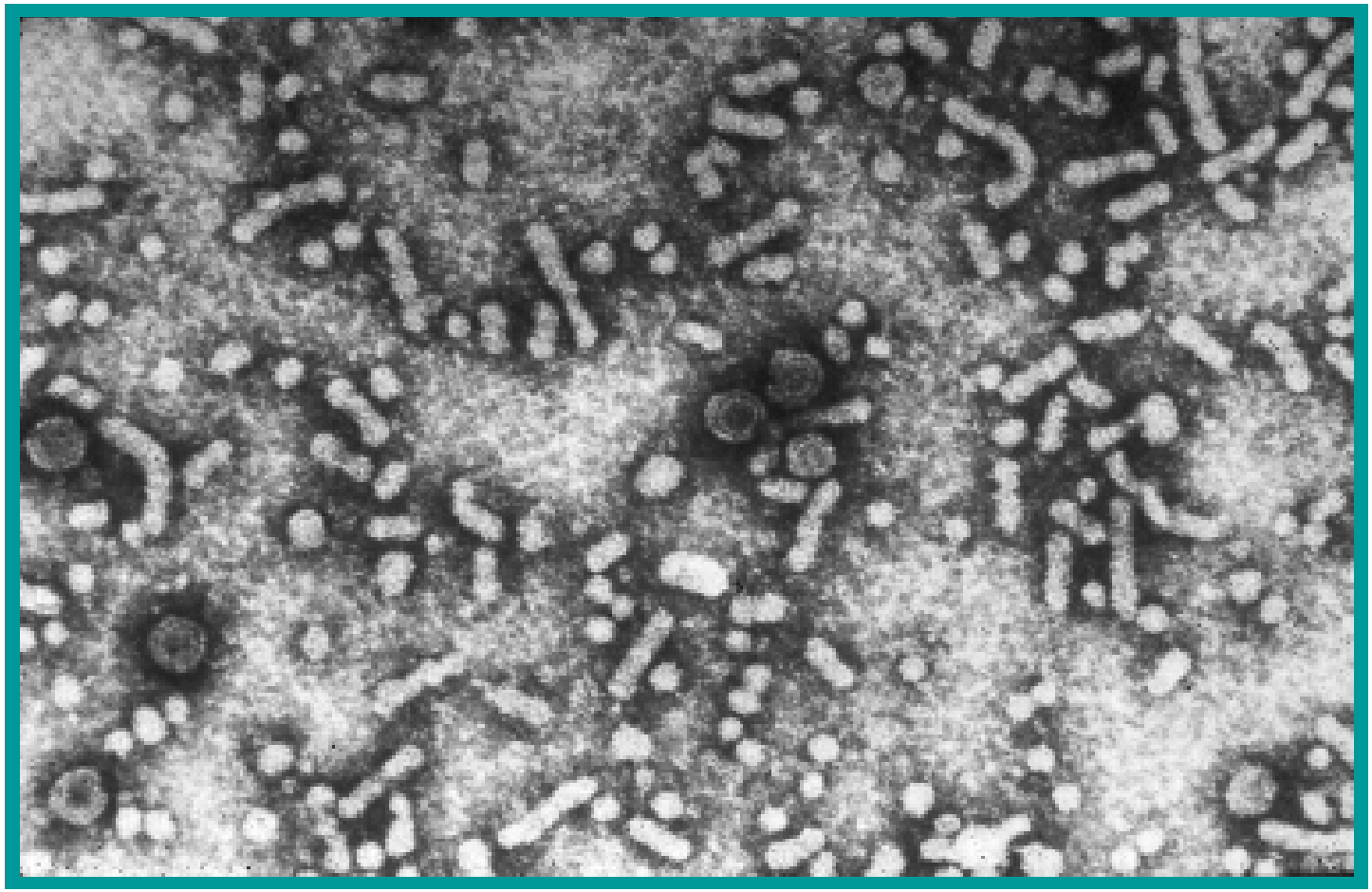
Hepatitis A virus



Hepatitis B

- Non-specific prodrome of fever, malaise and nausea.
- Clinical features non-specific and inc jaundice variable.
- Manifestations and outcome variable by age.
- Diagnosis
  - Serology
  - HBV DNA PCR
- Protection by passive or active vaccination

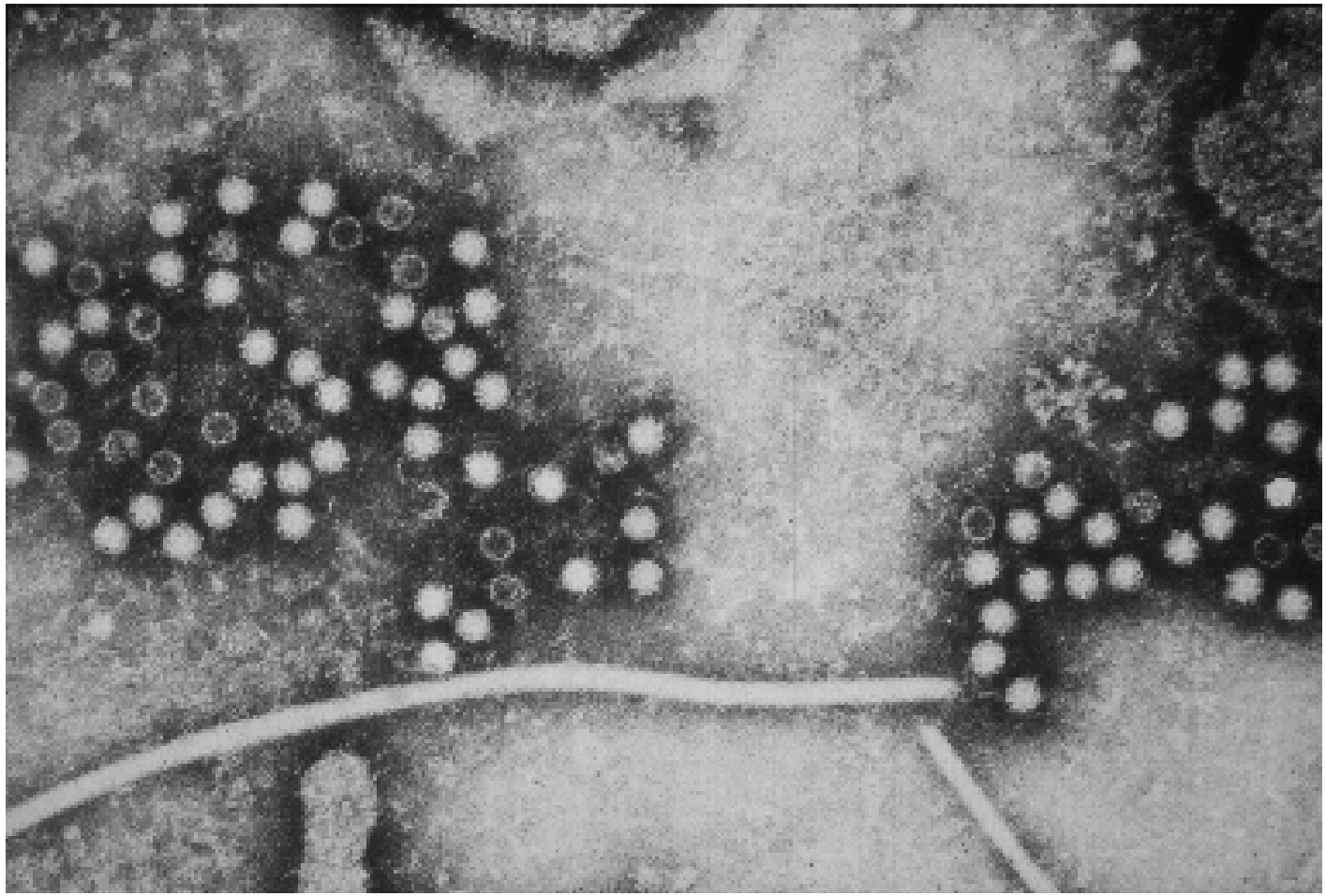
Hepatitis B virus



Hepatitis E Virus

- Similar incubation, prodroma and clinical presentation to hepatitis A
- History of travel to endemic area
- Diagnosis by serology
- Mortality of 10 to 20% in pregnant women

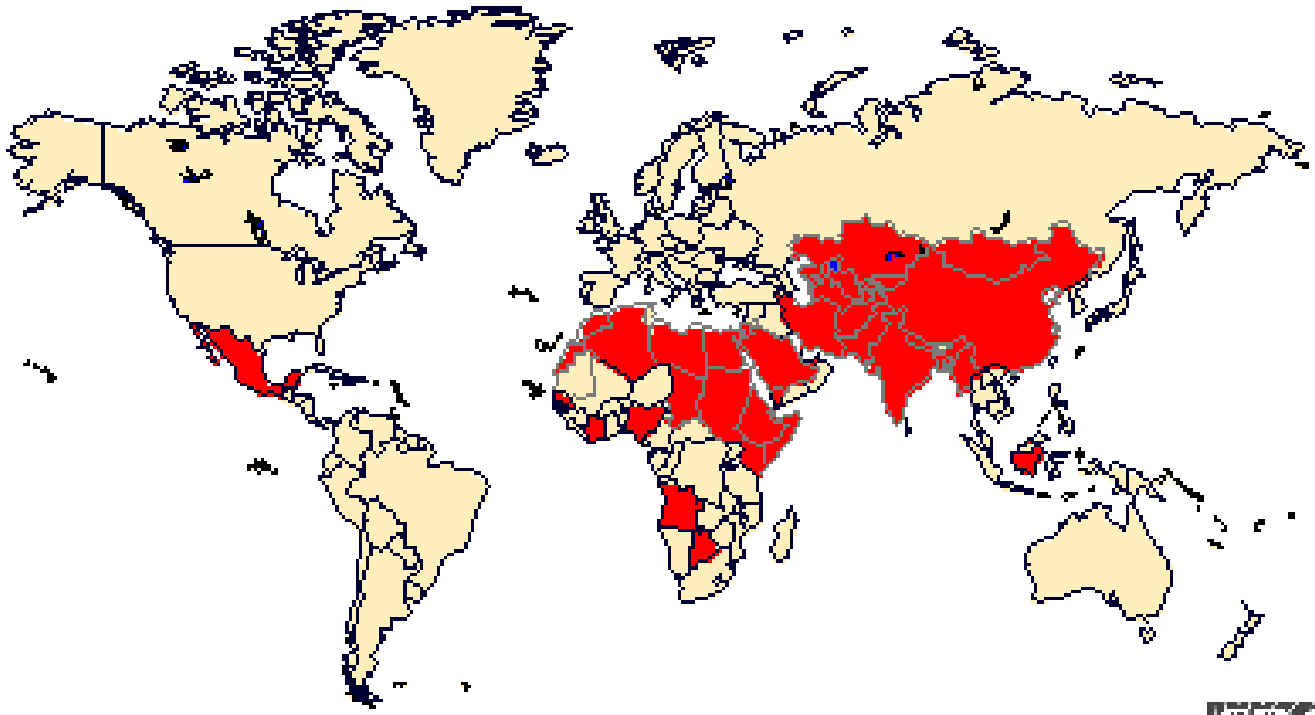
Hepatitis E Virus



Hepatitis E Virus

Geographic Distribution of Hepatitis E

Outbreaks or Confirmed Infection in > 25% of Sporadic Non-ABC Hepatitis



Nosocomial Acquired PUO

- Bacterial causes
  - Pneumonia, wound infection, UTI, IV lines etc
- Viral causes
  - Respiratory viruses
  - Hepatitis A, parvovirus, CMV from blood products

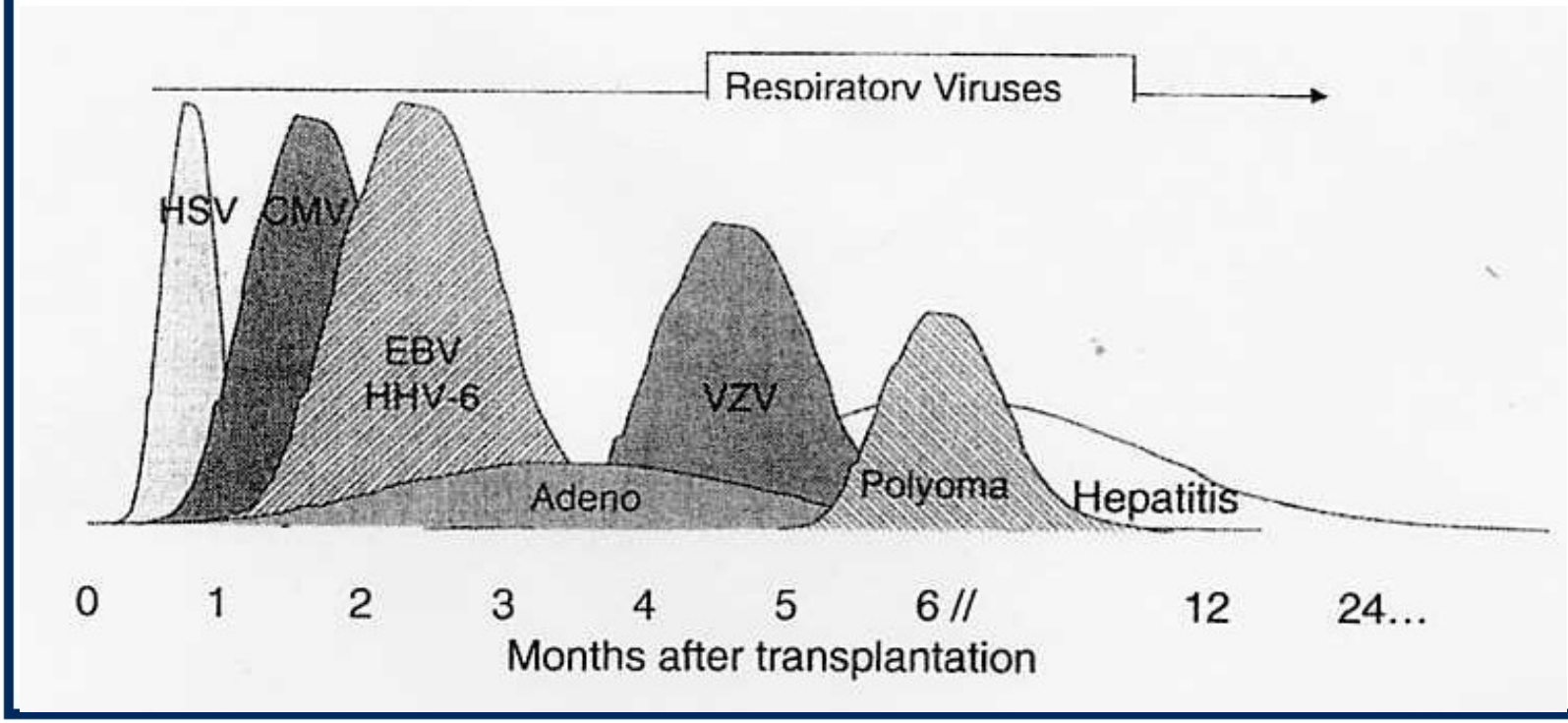
PUO in Immunodeficient patients

- Neutropenic patients not responding to antibiotics
  - CMV, HHV-6
  - EBV and PTLD
  - HSV
  - VZV
  - Resp viruses – Parainfluenza, Influenza, RSV
  - Blood products – CMV, Parvovirus, Hep A.

PUO in Immunodeficient patients

- The probability of viral infection and type of viral infection is related to the degree of immunosuppression.
- Disease is a function of both infection and the immune response.
- PUO due to viral infection common in this group as they have difficulty clearing infection and partial immunity may confound the clinical picture.

Timing of most frequent virus infections post-transplantation



Solid Organ Transplants - CMV

- Solid organ transplants in children, unlike in adults, are often CMV mismatched
  - CMV-P/ CMV+D
- CMV prophylaxis given but seroconversion occurs often with non-specific febrile illness and difficult to diagnose.
- Severity of CMV disease related to transplant with renal<liver<lung<BMT.

Solid Organ Transplants - CMV

- CMV infection often associated with rejection and a careful balance between immunosuppression and CMV therapy must be achieved.
- May progress to pneumonitis with significant morbidity / mortality if unrecognised.
- Diagnosis by serology, culture, p65 antigenaemia and/or CMV PCR.

Solid Organ Transplants - EBV

- Post-transplant lymphoproliferative disorder (PTLD) is due to EBV.
- Due to uncontrolled proliferation of EBV infected B cells where cellular immunity is suppressed.

Solid Organ Transplants - EBV

- EBV – PTLP presents as
  - infectious mononucleosis like syndrome or
  - fever and lymphomatous infiltrate into lymph nodes, spleen, liver, lung, brain, intestine, kidney, bone marrow.

Solid Organ Transplants - EBV

- EBV-PTLD more common in transplant patients with severe T cell immuno-suppression
  - BMT
  - Anti-thymocyte globulin
  - Primary EBV after solid organ transplant.
- Can occur in any patient with high dose immuno-suppressive therapy or inherited T cell deficiency.

Solid Organ Transplants - EBV

- Diagnosis
  - EBV seroconversion – insensitive
  - EBV PCR – qualitative or quantitative

Solid Organ Transplants - HSV

- If unrecognised and untreated mouth ulceration may extend to oesophagus and lung.
- Asymptomatic shedding with systemic disease e.g. hepatitis
- Extensive visceral involvement of GIT, liver, bone marrow, adrenals.
- Genital infection.
- Aciclovir prophylaxis decreases incidence but resistance can develop.

Solid Organ Transplants – HHV-6

- Most individuals infected with HHV-6 by 2 years.
- HHV-6 detected in immunocompromised individuals often associated with CMV .
- Difficult to assign disease to HHV-6
- Evidence of disease in patients with high HHV-6 viral loads by PCR testing.

Solid Organ Transplants – HHV-7

- Biologically and epidemiologically related to HHV-6 implies they should share disease manifestations.
- Sporadic descriptions of encephalitis, hepatitis and pityriasis rosea.
- May be broad undefined spectrum of disease.
- No strong evidence of disease

Solid Organ Transplants

- Blood transfusion risks
  - HCV, HBV, HIV, HTLV-1/2 and CMV low risk with screened blood and products.
  - Hep A and West Nile virus (USA).
  - Parvovirus with significant haemopoietic suppression

PUO in BMT Patients

- In children who have MUD BMT or T cell depleted allografts there is a high risk of disseminated disease from adenovirus infections.
- Present as:
  - Haemorrhagic cystitis
  - Persistent diarrhoea
  - Pneumonitis
  - Hepatitis
  - Encephalitis - rarely

Fever in HIV patients

- Primary HIV infection – mononucleosis like syndrome
- Opportunistic Infections
- Immune reconstitution disease.

Fever in HIV patients

- CMV
- B cell lymphomas very similar to PTLD.
- All CNS lymphomas are EBV pos. Others are 60-70% EBV pos

Summary

- History and Physical Exam
- Consider immunological status
- Consider non-infectious causes.
- Be strategic in approach to optimise predictive value of tests.

Thank You