Epstein-Barr Virus – Primary Infection

- In U.S., about 50% of children are seropositive before age 5
- Second wave of infections occurs in adolescents and young adults
- Symptomology
  - In young children
    - Many primary infection are asymptomatic.
    - Symptomatic cases commonly involve sore throat and fever. Diarrhea, abdominal complaints, otitis media, and infectious mononucleosis may occur but are less common in this age group
  - In adolescents and adults
    - Infectious mononucleosis is common
    - Fever, sore throat, nausea, anorexia, lymphadenopathy, splenomegaly, hepatomegaly, lymphocytosis, heterophile antibodies

EBV – Pathogenesis

- Primary means of transmission is thought to be oropharyngeal secretions, principally saliva.
- Primary infection is thought to occur in the epithelial cells of the upper respiratory tract.
- Spread to B lymphocytes
  - EBV can cause either lytic or latent infections in B cells
  - In some cases, as many as 10% of peripheral B cells are EBV-infected
  - Once infected, resting B cells may become activated, undergoing cell division and secreting antibodies. This is the source of “heterophile antibodies”.
  - Lymphocytosis is due to the presence of large numbers of “atypical lymphocytes” in the blood. These are actually activated T cells and NK cells responding to the infection.
- After primary infection is “cleared”, about 1 in 1,000,000 B cells remain latently infected. Reactivation of these cells gives rise to subclinical virus shedding.

EBV and Cancer

- Burkitt’s Lymphoma (BL)
  - Sporadic form of BL – Occurs worldwide, not EBV-associated
  - Endemic form
    - Most common childhood cancer in equatorial Africa
    - Tumor cells are EBV+ B cells and express one viral protein, ENBA-1
    - Tumor cells also have myc gene translocations
    - Malaria infection may be a cofactor, possibly by causing excess replication of B cells.
    - A genetic predisposition in the affected population has not been ruled out.
Nasopharyngeal Carcinoma
- Relatively rare except in southern China
- EBV found in tumor cells
- Tumor cells express several EBV proteins
- Genetic or environmental cofactors are suspected to have role in the development of this tumor

Post-transplant lymphoproliferative disorders and lymphomas
- 1 – 10% of transplant patients
- B cell proliferation, sore throat, fever are common manifestations
- B cell tumors tend to be aggressive and difficult to treat

AIDS-associated lymphomas
- Incidence is increased 50 – 100 fold over general population
- Late manifestation of HIV-1 infection
- Tend to occur in the CNS

Cytomegalovirus
- Very common infection
- Usually asymptomatic
- May cause a mononucleosis-like disease (heterophile antibody negative) with enlarged spleen and/or liver
- Virus may be shed in urine, saliva, and other body fluids
- Virus shedding may persist for months
- Immunocompromised patients are at risk of CMV pneumonia, CMV retinitis
- Neonatal and fetal CMV are a major problem: 1 -2% of US neonates infected. Major risk of death, mental retardation, deafness
Adenoviruses
- Structure
  - Nonenveloped
  - Icosahedral
  - Fibers at vertices
- Genome
  - Linear, double-stranded DNA
  - 35 kb, ≥ 30 genes
  - Replication in the nucleus
- Over 49 serotypes known – each serotype is designated by a number

Adenovirus infection
- Host cell preference – mucosal epithelial cells
  - Respiratory tract
  - Small intestine
  - Epithelial tissue of the eye

Adenovirus Entry and Spread
- Portals of entry
  - Upper respiratory tract
  - Alimentary canal
  - Conjunctiva/cornea
- Modes of transmission
  - Respiratory spread
  - Fecal/oral spread
  - Iatrogenic spread

Clinical Manifestations of Adenovirus Infection
- Acute respiratory infection
- Pharyngconjunctival fever
- Acute Respiratory Disease (ARD)
- Pneumonitis
- Epidemic keratoconjunctivitis
- Gastrointestinal Disease
- Urethritis, cystitis

Acute Respiratory Infection
- Acute febrile pharyngitis
  - fever, sore throat, cough, nasal congestion
  - tonsilitis possible
- Highly infectious
- Typically acquired during childhood
Several serotypes are common: 1, 2, 5, 6, and others
- Little or no cross-immunity between types
- Not easily distinguished from other viral respiratory infections

**Pharyngoconjunctival Fever**
- Conjunctivitis (“pink eye”)
  - Redness, watering, discomfort, photophobia
- Upper respiratory tract infection
  - Fever, sore throat, cough, nasal congestion
- May occur in localized outbreaks
- Types 3, 4, 7, 21 are common

**Acute Respiratory Disease (ARD)**
- Identified in and common among military recruits
- Thought to spread easily among this population due to crowded living conditions combined with stress
- Ranges from mild URT infection to pneumonia
- Vaccines
  - Live, attenuated vaccines for types 4, 7
  - Military use only

**Epidemic Keratoconjunctivitis**
- Involvement of both cornea and conjunctiva
- Permanent corneal damage may occur and cause degradation of vision
- Highly contagious
- Minor corneal abrasions increase the risk of infection
- Has been associated with iatrogenic spread
- Often associated with AdV types 8, 19, 37

**Gastrointestinal Disease**
- Most AdV types replicate in the GI tract but normally do not cause GI disease
- However, AdV types 40 and 41 are associated with infant gastroenteritis
  - Estimated to account for 5 – 15% of cases
  - Types 40 and 41 are very difficult to culture

**Urethritis and Cystitis**
- Uncommon forms of Adenovirus infection
- AdV 27
  - Associated with some cases of cervical lesions and male urethritis
  - Probably spread by sexual transmission
- Types 11, 21
  - Reports of hemorrhagic cystitis in boys, mostly from Japan
Parvoviruses

- Family: Parvoviridae
  - Subfamily: Parvovirinae
    - Autonomously replicating
    - Parvovirus B19 – only Parvovirus known to cause human disease
  - Subfamily Dependovirinae
    - Require helper viruses (Adenoviruses, Herpesviruses)
    - Adeno-associated viruses types 1 – 5
    - Not known to be associated with any human disease
    - AAV-based gene therapy vectors are under development

Parvovirus Properties

- Small, nonenveloped icosahedral virions
- Linear, single-stranded DNA genome
  - 5 genes
- Nuclear replication

Parvovirus B19

- Cause of Erythema Infectiosum (Fifth Disease)
  - Primary B19 infection
    (Note: Many B19 infections are asymptomatic)
  - Typically occurs in school age children, sometimes in adults
- Prevalence of B19 antibodies increases with age
  - 10 year olds: 20 – 40%
  - 50 years and older: 75 – 90%

Erythema Infectiosum Pathogenesis

- Transmission – respiratory?
- First phase
  - Nonspecific, flu-like symptoms: Fever, chills, malaise, myalgia, itching
  - Dispersion of virus by viremia
  - Shedding of virus from upper respiratory tract
  - Formation of IgM-parvovirus immune complexes
- Second phase – deposition of immune complexes
  - Erythematous rash
  - Symptoms of arthritis

Transient Aplastic Crisis

- B19 infection of persons with hemolytic anemia
  - e.g., sickle cell anemia patients
- B19 infection of bone marrow
  - B19 replicates extensively in erythroid precursor cells in the bone marrow
Causes a profound but transient reduction in erythrocyte production
- Not a major problem in normal individuals
- Causes a large drop in erythrocyte numbers in hemolytic anemia patients – may be life-threatening

Transfusion therapy

B19 and Immunocompromised Patients
- Chronic infection of the bone marrow
- Persistent anemia
- Immune globulin therapy

B19 congenital Infections
- Primary B19 infection of pregnant women
- Transmission to the fetus may cause hydrops fetalis
  - Fatal anemia of the fetus
  - Overall risk of death ~ 10%
  - No evidence of congenital abnormalities in survivors
Study Questions

1) A 25-year old woman presents at your clinic with fever and a severe sore throat. She also reports a loss of appetite. A physical examination reveals that both the liver and spleen are enlarged. The most likely cause of this condition is:
   A) Infectious mononucleosis
   B) Hepatitis B Virus infection
   C) Hepatitis E Virus infection
   D) Adenovirus infection
   E) B19 Virus infection

2) A seven-year old child is brought to the clinic with a rash on his torso. His mother reports he was running a fever for several days prior to the development of the rash, although his temperature is normal now. During the physical exam, the child complains that his knees and elbows hurt. Which of the following is the most likely diagnosis:
   A) Exanthem subitum
   B) Roseola
   C) Erythema infectiosum
   D) Adenovirus 40 or 41
   E) Varicella

3) A 16-year old has conjunctivitis and symptoms of an upper respiratory tract infection. An ophthalmic examination shows that the corneas are clear and undamaged. Cultures made from eye swabs come back negative for pathogenic bacteria. Which diagnosis do you think is most likely?
   A) Pharyngoconjunctival fever caused by Adenovirus infection
   B) Keratoconjunctivitis caused by Adenovirus infection
   C) Cytomegalovirus
   D) Zoster
   E) Parvovirus B19
Study Question Answers

1) A. This combination of symptoms is typical of Infectious Mononucleosis. Test should be done for atypical lymphocytes, heterophile antibodies and virus-specific antibodies and/or PCR.

2) C. Development of rash as fever declines is characteristic of Erythema Infectiosum (B19 infection), as is the development of joint pain. Both rash and arthritis are due to deposition of immune complexes. Keep in mind that development of rash as fever declines may be seen in HHV-7 infection (Exanthem Subitum or Roseola) as well.

3) A. The symptoms match those of classic adenoviral phyngoconjunctival fever. The cornea is not involved, so a diagnosis of keratoconjunctivitis is incorrect. HSV-1 (not one of the listed answers) can cause eye infections, although these usually involve both the cornea and conjunctiva.