Herpesviruses and Smallpox

General Stuff

Common Features of Herpesviruses
- Morphology
- Basic mode of replication
- Primary infection followed by latency
- Ubiquitous
- Ability to cause recurrent infections (reactivation of latent virus), re-infections (with a new virus), persistent infections (chronic low grade virus multiplication), immortalizing infections (EBV only).
- The other form of infection is latent, and there is little viral gene expression, so the host cell survives.

8 Human Herpesviruses, 3 categories
- Alpha: short reproductive cycle, variable host range, latent in sensory neurons
  - Herpes simplex virus (HSV 1, 2)
  - Varicella-zoster virus (VZV)
- Beta: long reproductive cycle, narrow host range, latent in lymphoid cells & others
  - Cytomegalovirus (CMV)
  - HHV6, HHV7
- Gamma: narrow host range; latent in lymphoid cells, associated with tumors
  - Epstein Barr Virus (EBV)
  - Kaposi Sarcoma Virus (KSH, HHV8)

Replicative Cycle
1. Enveloped viral particle invades cell by utilizing receptors on the cell surface (HSV binds to members of Ig, TNF family and VSV to mannose-6 phosphate and heparan sulfate)
2. Glycoproteins (B, D, H, I) on virion – enable attachment of virus to cell (also used by the
3. Virus uncoats, DNA goes to nucleus and replicates
4. Nucleocapsids are formed there, which extrude into the perinuclear space with an early envelope
5. Fuses with the RER → naked nucleocapsid goes into cytosol
6. Nucleocapsid become enveloped by tegument proteins and glycoproteins in the trans Golgi Network (TGN)
7. Enveloped virion → incorporated into endosomes (HSV resists the acidic environment) → released extracellularly
8. Virus in cell to cell spread). They are components of a new HSV2 vaccine.
9. Lytic infection → cell death
10. Latency occurs when the cascade is interrupted
11. Latent infection occurs in sensory neurons
- Latency associated transcripts (LATs)
- Minimal transcription of DNA, no translation

Because of cell → cell spread, CMI is crucial in host response; Ab’s usually ineffective (except for VSV infection. Herpesviruses can also spread as a free enveloped particle.

- Encode targets for antiviral therapy
  – Thymidine kinase (TK), DNA polymerase

Clinical Presentation

<table>
<thead>
<tr>
<th>Genital Ulcers:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple, bilateral grouped umbilicated vesicles which become postular and coalesce into large PAINFUL ulcers (“shaggy”)</td>
</tr>
<tr>
<td>Severe painful vulvovaginitis or balanitis</td>
</tr>
<tr>
<td>With or without urthritis</td>
</tr>
<tr>
<td>Pain, itching, dysuria with or without urethral discharge</td>
</tr>
<tr>
<td>Tender inguinal lymphadenopathy</td>
</tr>
<tr>
<td>In 1/3 of patients, symptomatic complaints:</td>
</tr>
<tr>
<td>Headache, fever, malaise, and myalgia</td>
</tr>
</tbody>
</table>

Pathogenesis

| Transmitted via sexual contact |
| Invades local cell → causes local inflammatory response |
| Spreads to other cells locally |
| Moves along sensory nerves (Schwan cells) to ganglia |
| Becomes latent, reactivates |

Predisposing Factors/ Epidemiology

| Virus can be shed by symptomatic and asymptomatic individuals |
| Most common STD in higher socioeconomic groups |

Likely Pathogens

| Herpes Simplex Virus 2 mostly, HSV-1 rarely (from oral → genital transmission) |

Definitive Diagnosis

| Clinical: |
| Ulcerate leaving a shaggy ulcer |
| Lymph node involvement |

Microscopic:

| Wright-stained or Tzanck stained: see multinucleated giant cell in Herpes (cytopathic involvement) |

Serology:

| Rise in antibody titers |

Rule out syphilis, chancroid, LGV.

Complications

| Associated with primary disease: |
| Aseptic meningitis |
| Transverse myelitis |
| Sacral radiculopathy |
| Can be transmitted to newborn resulting in serious organ damage |

Treatment / Prevention

<p>| Acyclovir (ACV), famiclovir, valacyclovir |</p>
<table>
<thead>
<tr>
<th>Baby with:</th>
<th>Saliva transmission</th>
<th>HSV-1</th>
<th>May lead to poor nutrition and dehydration of a few days</th>
<th>No antiviral therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcers in oral mucosa (gingivostomatitis)</td>
<td>Usually transmitted by saliva</td>
<td>Examiners should wear saliva</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swollen friable gums</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary infection on the thumb from sucking on it (whitlow of the finger)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baby may have fever or be irritable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Although infection looks severe, it's self limited</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Corneal ulcers                                                          | Mouth → Hand → eye                  |                              |                                                          |                     |
| Lesions of the conjunctival epithelium (keratitis or keratoconjunctivitis) | transmission                       |                              |                                                          |                     |

| Severe infection of the skin                                            | Person with underlying eczema       |                              |                                                          |                     |

| Headache                                                                | Focal Encephalitis                  | Primary or recurrent HSV-1    |                                                          |                     |
| Fever                                                                   |                                     |                               |                                                          |                     |
| Personality change                                                      |                                     |                               |                                                          |                     |
| Focal seizures                                                          |                                     |                               |                                                          |                     |
| Skin lesions may be present (not helpful for diagnosis)                 |                                     |                               |                                                          |                     |

| Test findings:                                                          |                                     |                               |                                                          |                     |
| Abnormal EEG, CT, MR                                                    |                                     |                               |                                                          |                     |

| Newborn with:                                                           | Perinatal HSV                        | Usually HSV-2: HSV-1 in very cases |                                                          |                     |
| Skin, eye, mucous membrane (40%)                                        |                                     |                               |                                                          |                     |
| Skin vesicles                                                          | Perinatal HSV is usually due to     |                               |                                                          |                     |
| – Good prognosis with early treatment                                  | Type 2 virus                         |                               |                                                          |                     |
| Untreated 75% develop disseminated infection                            | • 95% neonatal, 5% congenital        |                               |                                                          |                     |
| CNS Infection (35%)                                                    | • Usually the mother is asymptomatic |                               |                                                          |                     |
| – Fever, lethargy, seizures, abnormal CSF                               | • Attack rate >10 times higher in  |                               |                                                          |                     |
| – 50% mortality; major sequelae if survive                              | maternal primary infection than    |                               |                                                          |                     |
| Disseminated disease (25%)                                              | recurrence; attack rate about 50%   |                               |                                                          |                     |
| Hepatosplenomegaly, jaundice, hepatitis, pneumonia                      | 1600 cases annually                  |                               |                                                          |                     |
| – 2/3 develop skin vesicles                                            | • Immunofluorescence                 |                               |                                                          |                     |
| – 70% mortality                                                         | • culture,                           |                               |                                                          |                     |
| In the body VZV spreads from cell-to-cell                               | • PCR                               |                               |                                                          |                     |
| Varicella (Chickepox)                                                  | • Antibody titers are not useful     |                               |                                                          |                     |
| • VZV → respiratory mucosa → blood (viremia) → T cells (long incubation period – 2 weeks from cell-cell spread) | Skin, mucous membrane infection →    |                               |                                                          |                     |
| – Slow spread prevents host from being overwhelmed before the immune response develops | untreated → disseminated infection |                               |                                                          |                     |
| Varicella Zoster Virus (VZV)                                            | • Culture, DFA, PCR, cytology on skin rash |                               |                                                          |                     |
| • Varicella is likely to be severe in the Immunocompromised (lack of TH1 response) | • Can distinguish the Oka virus from wild type virus |                               |                                                          |                     |
| Zoster (Shingles)                                                       | • Antibody titers, IgG               |                               |                                                          |                     |
| • Latent infection in dorsal root ganglia (DRG)                         | – Acute serum, early in illness      |                               |                                                          |                     |
| • 6 of 88 genes (also RNA and proteins) expressed during latency        | – Convalescent serum, 10- 14 days   |                               |                                                          |                     |
| • Proteins of regulatory genes are expressed in                         | after onset                          |                               |                                                          |                     |
| After primary infection                                                 | • Antibody titers, IgM               |                               |                                                          |                     |
| • Culture, DFA, PCR, cytology on skin rash                             | – False positives and false negatives can be a problem |                               |                                                          |                     |
|                        | Rule out smallpox                   |                               |                                                          |                     |

| Treatment                                                              | ACV (but not as useful as for HSV infections) | famiclovirrm, valacylovir for elderly patients with zoster | Prevention: | Live, attenuated, infectious virus (Oka strain) |
|                                                                     |                                                   |                                                   | Contraindications: pregnancy, immunocompromised, allergy to vaccine components | Major complaint afterwards: mild rash in 5% |
|                                                                     |                                                   |                                                   |                                         | This vaccine is extremely safe 80% completely protected; 20% partial immunity. Little evidence for waning immunity. |
| 12-14 days after exposure: | Resp mucosa → LN → viremia (asymptomatic) → secondary viremia (rash) | Bioterrorist Agent (currently eradicated around the world) | Smallpox virus | Rule out VCV (incubation similar, difference is prodome → where rash starts (smallpox = centrifugal), erythema multiforme) | Tx | No known treatment | Strict quarantine |
|---|---|---|---|---|---|---|---|---|
| **Exanthema** | Muculpapular rash (face mucosa → trunk → trunks and legs) → vesicles → pustules (can become confluent on face) Severe looking rash gets progressively worse | **Transmission** | **Immunity** | **Immunity** | | | | |

**Preven:**

---

**Healthy Adult Host:**
- usually subclinical
- Mononucleosis- like syndrome occurs but is rare

**Immunocompromised:**
- Fever
- Pneumonia
- Retinitis
- Colitis
- Lymphadenopathy
- Rash
- Encephalitis
- Neutropenia, etc.

**Fetal (congenital) infections: can be severe**
- 40,000 annual cases (1% of all infants)
- 3,000 symptomatic at birth (jaundice, petechiae, microcephaly, prematurity)
- 8,000 with sequelae (deafness, -- immune evasion
- Down regulation of MHC class I expression to reduce effectiveness of cytotoxic T cells
- Host defense: cellular not humoral immunity
- Latency in bone marrow precursors of monocytic peripheral blood cells
- Differentiation of monocytes into macrophages due to antigenic stimulation reactivates CMV
- Adverse effects on transplantation

**Congenital**
Most common congenital viral infection in US
- Risk to the infant is highest in first trimester (13 weeks) maternal infection
- primary maternal infection poses greatest risk
- the fetus is not always protected when an “immune” mother is re-infected with a different strain of CMV

**Transmission**
- Close personal contact
  - Sexual, day care, saliva, tears, urine
  - Virus is not usually airborne
  - Cell-associated virus, no skin lesions
  - Spread from secretions, on hands

**Cytomegalovirus (CMV)**
- Largest of the herpesviruses
- Distinguish between congenital and perinatal
  - In congenital urine is culture → for CMV in first 3 weeks of life
  - Diagnosis of CMV
  - Histology: has limitations (not specific)
  - Basophilic inclusion bodies
  - H&E, Pap staining
  - Cell culture
  - Cytopathic effect, immunofluorescence
  - Serology: acute and convalescent antibody titers are of limited value

**Treatment of CMV**
- Ganciclovir
  - Phosphorylation by viral enzymes causes inhibition of viral DNA polymerase (related to acyclovir); toxicity: bone marrow suppression
  - Foscarnet
  - Inhibits viral DNA polymerase
  - Very toxic (renal, uric acid increase)
  - Pre-emptive approach
  - Identifies infection before the illness
  - Treatment used mostly for immunocompromised patients

**Control of CMV**
- Hand washing (eg, after diapering)
- Condoms, abstinence
- Beware of blood
<table>
<thead>
<tr>
<th>Young adults adult with:</th>
<th>Epstein-Barr Virus (EBV)</th>
<th>Herpesvirus 8 (KHSV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Positive heterophile antibody (monospot)</td>
<td>- Infections are rare in children</td>
</tr>
<tr>
<td>Adenopathy</td>
<td>EBV specific antibodies</td>
<td>- Encodes for human proteins (piracy)</td>
</tr>
<tr>
<td>Exudative pharyngitis</td>
<td>- Anti VCA (develops early, persists)</td>
<td>- IL-6, Bcl-2, chemokines and receptor</td>
</tr>
<tr>
<td>Rash (ampicillin)</td>
<td>- Anti EBNA (develops late persists)</td>
<td>- Causes primary-effusion lymphoma</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>- In situ hybridization</td>
<td>- Castleman’s disease</td>
</tr>
<tr>
<td>Fatigue</td>
<td>- PCR</td>
<td>- No effective antiviral treatment.</td>
</tr>
</tbody>
</table>

**Attachment**
- Major glycoprotein is gp 350 which binds to CD21 on B cells (C3d complement receptor)
- Virus practices immune evasion
  - Genes that mimic IL 10 and decrease IF response, inhibit apoptosis

**Transmission:**
- Patients with x-linked agammaglobulinemia can’t be infected
- Saliva (lytic)

**Latency**
- B cells are latently infected in mononucleosis; T cells (atypical lymphocytes) are the host response
- Latency persists in memory B cells
- EBV is not related to chronic fatigue syndrome, but rarely severe chronic illness follows mononucleosis

**Epstein-Barr Virus (EBV)**
- In mononucleosis, give steroids if airway obstruction, hemolytic anemia, severe cardiac, neurologic disease (no specific antiviral therapy)
- Experimental therapy for immunocompromised patients with severe infections/tumors
  - Decrease immunosuppressive therapy if possible
  - Monoclonal antibodies (rituximab)
  - Infusion of leukocytes

**Herpesvirus 8 (KHSV)**
- Closely related to EBV
- Infections are rare in children

**Normal Hosts:**
- Can cause non-specific fever and rash illness
- Elderly, HIV-infected
  - Causes Kaposi’s Sarcoma
  - Causes primary-effusion lymphoma
  - Castleman’s disease
## Enteroviruses and GI Viruses

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Pathogenesis</th>
<th>Predisposing Factors/ Epidemiology</th>
<th>Likely Pathogens</th>
<th>Definitive Diagnosis</th>
<th>Treatment</th>
<th>Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic infection most common (95%)</td>
<td>Infection •Enters via gut •Replicates in submucosal lymphoid tissue •Spreads to reticuloendothelial system •From there → blood → replicates in gray matter of motor neurons in brain, spinal cord → extensive necrosis</td>
<td>Immunity: •IgA, IgG response •Infection provides lifelong type specific immunity</td>
<td>Polioviruses •Picornavirus •Small •Non-enveloped •ssRNA (+) •icosahedral nucleocapsid</td>
<td>Isolation of the virus: •from throat secretions in first week of illness •from feces for several weeks •unlike other enteroviruses, rarely isolated from CSF •causes cytopathic effect</td>
<td>Symptomatic relief and support. No antiviral therapy.</td>
<td>2 vaccines: Oral Polio Vaccine (OPV): Live attenuated vaccine = mainstay of vaccination programs across world. Excreted in feces → allowed for further spread to unvaccinated individuals (if ya can’t beat em, join em). Rarely, vaccine led to paralytic disease. Therefore: Inactivated Polio Vaccine (IPV) – used, now just as immunogenic, and safer.</td>
</tr>
</tbody>
</table>
| Abortive poliomyelitis (4-8%) (Symptoms last a few days): •Fever •Headache •Sore throat •Listlessness •Anorexia •Vomiting •Abdominal pain •Normal neuro exam | Enteroviruses and GI Viruses

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Pathogenesis</th>
<th>Predisposing Factors/ Epidemiology</th>
<th>Likely Pathogens</th>
<th>Definitive Diagnosis</th>
<th>Treatment</th>
<th>Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonparalytic poliomyelitis</td>
<td>Systemic symptoms more severe than above •See meningeal signs •Full recovery is norm</td>
<td>Spinal paralytic poliomyelitis (0.1% of cases) – biphasic course w/ major, minor illnesses. Patient recovers after 1-3 days of mild illness, remains well for 2-5 days but then becomes abruptly ill with: •Headache •Fever •Vomiting •Neck stiffness This lasts for 1-2 days before: •Weakness •Flaccid paralysis ensue (on range of single muscle → quadriplegia)</td>
<td>Bulbar paralytic poliomyelitis (paralysis of muscles innervated by CN): •Dysphagia •Nasal speech •Dyspnea with (CN 9, 10 – most affected) •Vasomotor, respiratory centers may be involved</td>
<td>Poliomyelitis: •Confusion •Changes in mental status •Uncommon and occurs primarily in infants</td>
<td>Do not usually cause symptomatic infections of the gastrointestinal system</td>
<td>Distributed worldwide • More prevalent in summer and autumn in temperate climates (June-October) •Most infections occur in children &lt; 1 year</td>
</tr>
<tr>
<td>Do not usually cause symptomatic infections of the gastrointestinal system</td>
<td>Polioviruses</td>
<td>Polioviruses are small, non-enveloped, (+) ssRNA viruses with icosahedral nucleocapsid.</td>
<td>Coxsackieviruses, echoviruses, newer enteroviruses</td>
<td>PCR of spinal fluid usually reveals cause</td>
<td>Aseptic meningitis: Prodrome: fever, chills, malaise, URI Headache, fever, stiff neck, photophobia – CSF: 10-500 WBC, lymphocytes, nl to slightly elevated protein, nl glucose</td>
<td>Cerebrospinal fluid (CSF) accounts for 11-22% of viral encephalitis when you include polioviruses</td>
</tr>
<tr>
<td>Chronic meningoencephalitis</td>
<td>Prognosis, except in infants, is excellent</td>
<td>Seen in patients with acquired or congenital defects in B cell function</td>
<td>Echoviruses</td>
<td>Echoviruses can be recovered from CSF for months-years</td>
<td>Try to prevent with monthly IG</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------------------------------------</td>
<td>------------------------------------------</td>
<td>-------------</td>
<td>---------------------------------------------------</td>
<td>-------------------------------</td>
<td></td>
</tr>
<tr>
<td>Paralytic Infections</td>
<td>Occasionally associated with coxsackie and echovirus infections</td>
<td>Outbreaks of flaccid paralysis associated with coxsackievirus A7 and enterovirus 71</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exanthems</td>
<td>Common in summer months</td>
<td>Associated with echovirus 9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morbilliform rashes</td>
<td>Contagious especially amongst young children</td>
<td>Echovirus 16 most commonly associated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roseoliform rashes</td>
<td>Most common in children under age 10</td>
<td>Coxsackie A16 or enterovirus 71</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand-foot-and-mouth disease</td>
<td>Summer outbreaks</td>
<td>Group A coxsackievirus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exanthems</td>
<td>Cause majority of summer colds in children</td>
<td>Coxsackieviruses A21 and A24; echovirus 11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalized vesicular eruptions</td>
<td>Most frequently caused by coxsackievirus A9 and echovirus 11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herpangina</td>
<td>Group A coxsackievirus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory Disease</td>
<td>Enteroviruses, especially group B coxsackieviruses, group A types 4 and 16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidemic pleurodynia</td>
<td>Echoviruses 9 and 22 account for 50% of all cases of acute</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Chronic meningoencephalitis**
- Prognosis: except in infants, is excellent.
- Seen in patients with acquired or congenital defects in B cell function.
- Echoviruses: can be recovered from CSF for months-years.
- Try to prevent with monthly IG.

**Paralytic Infections**
- Usually less severe than poliomyelitis.
- Paralysis: not permanent.
- Occasionally associated with coxsackie and echovirus infections.
- Outbreaks of flaccid paralysis associated with coxsackievirus A7 and enterovirus 71.

**Exanthems**
- Morbilliform rashes: Fine, erythematous, maculopapular rashes.
- Rash appears simultaneously with fever and starts on face.
- Common in summer months.
- Associated with echovirus 9.

**Roseoliform rashes**
- Discrete, nonpruritic, salmon-pink macules and papules on the face and upper chest.
- Prodrome of fever and pharyngitis.
- Rash appears after defervescence and lasts 1-5 days.
- Contagious especially amongst young children.
- Echovirus 16 most commonly associated.

**Hand-foot-and-mouth disease**
- Distinctive vesicular eruption.
- Fever and vesicles in the mouth and on the hands and feet.
- Can look like chickenpox but illness is generally milder.
- Most common in children under age 10.
- Coxsackie A16 or enterovirus 71.

**Generalized vesicular eruptions**
- Lesions look like those of hand-foot-and-mouth but occur in crops on the head, trunk and extremities.
- Do not evolve into pustules or scabs (unlike chickenpox).
- Summer outbreaks.
- Group A coxsackievirus.

**Herpangina**
- Vesicular rash involving pharynx and soft palate.
- Fever, vomiting, myalgia and headache associated with prodrome.
- Summer outbreaks.
- Group A coxsackievirus.

**Respiratory Disease**
- Upper respiratory infections.
- Fever with sore throat, cough and coryza.
- Cause majority of summer colds in children.
- Coxsackieviruses A21 and A24; echovirus 11.

**Epidemic pleurodynia**
- Acute disease with fever and sharp, spasmodic pain in chest/upper abdomen muscles.
- Fever peaks one after onset of pain spasm.
- Lasts 4-6 days usually but can persist for months.
- Enteroviruses, especially group B coxsackieviruses, group A types 4 and 16.
- Echoviruses 9 and 22 account for 50% of all cases of acute.

**Myopericarditis**
- Inflammation of the myocardium and pericardium.
- Virus appears to replicate in the myofibers leading to myofiber necrosis and local inflammation.
- Special predilection for physically active adolescents and young adults.
- Males outnumber females 2:1.
- URI in 70% followed by Dyspnea, chest pain- precordial, dull.
<table>
<thead>
<tr>
<th>Fever, Malaise</th>
<th>EKGs usually abnormal, cardiac enzymes elevated</th>
<th>myopericarditis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complications: Can lead to chronic congestive heart failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterovirus infection of the newborn</td>
<td>Biphasic illness</td>
<td>Echovirus 11 Group B Coxsackieviruses</td>
</tr>
<tr>
<td>Mild non-specific symptoms between 3 and 7 days of life followed by 1-7 days of well-being</td>
<td>Neonates are especially susceptible to severe enterovirus infection</td>
<td>Diagnosis by PCR of urine, feces, blood, CSF</td>
</tr>
<tr>
<td>Generalized disease follows Myocarditis with encephalitis- Fulminant hepatitis- hypotension, bleeding, multiple organ failure</td>
<td>Most serious infections appear to occur perinatally and probably are acquired from the mother</td>
<td>Treatment is supportive; pleconaril disappointing</td>
</tr>
<tr>
<td></td>
<td>Lack of macrophage activity in the neonate is probably responsible for seriousness of infections</td>
<td></td>
</tr>
<tr>
<td>Acute hemorrhagic conjunctivitis</td>
<td>Epidemic outbreaks of eye pain, swelling and subconjunctival hemorrhage</td>
<td>Highly contagious</td>
</tr>
<tr>
<td>Usually bilateral</td>
<td>Enterovirus 70 associated</td>
<td></td>
</tr>
<tr>
<td>Most cases resolve spontaneously</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotavirus</td>
<td>Infection Spread by fecal-oral route</td>
<td>Rotavirus</td>
</tr>
<tr>
<td>– Virus enters and replicates in mature villus cells of the small intestine</td>
<td>– Reovirus family</td>
<td>– Clinical- febrile infant with diarrhea in the winter</td>
</tr>
<tr>
<td>– Infection kills cells and loss of absorptive area ensues</td>
<td>– Wheel-like appearance</td>
<td>– ELISA- detect rotavirus antigen in stool sample</td>
</tr>
<tr>
<td></td>
<td>– Most common cause of diarrhea requiring hospitalization in the world</td>
<td>– PCR</td>
</tr>
<tr>
<td></td>
<td>• Account for 10-20% of diarrhea-related deaths in children</td>
<td>– Electron microscopy</td>
</tr>
<tr>
<td></td>
<td>• Up to 120,000 hospitalizations in US/year</td>
<td>– Serology- epidemiological tool</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterovirus 70</td>
<td>Infection Spread by fecal-oral route</td>
<td>Enterovirus 70</td>
</tr>
<tr>
<td>– Virus enters and replicates in mature villus cells of the small intestine</td>
<td>– Large, non-enveloped RNA viruses</td>
<td>– Clinical- febrile infant with diarrhea in the winter</td>
</tr>
<tr>
<td>– Infection kills cells and loss of absorptive area ensues</td>
<td>– Eleven segments of double stranded RNA</td>
<td>– ELISA- detect rotavirus antigen in stool sample</td>
</tr>
<tr>
<td></td>
<td>– Reassortment occurs</td>
<td>– PCR</td>
</tr>
<tr>
<td></td>
<td>• Require RNA polymerase to make mRNA</td>
<td>– Electron microscopy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– Serology- epidemiological tool</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Viral Respiratory Infections, Anthrax, and TB

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Test Findings</th>
<th>Pathogenesis</th>
<th>Predisposing Factors/ Epidemiology</th>
<th>Likely Pathogens</th>
<th>Definitive Diagnosis</th>
<th>Complications</th>
<th>Treatment</th>
<th>Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Classic presentation</strong> (nasty, self-limited):</td>
<td>Chest X-ray:</td>
<td>Infection is limited primarily to epithelium of the respiratory tract.</td>
<td><strong>Season:</strong> Winter months</td>
<td><strong>Influenza Virus</strong></td>
<td><strong>Clinical presentation:</strong> Adequate for diagnosing most individuals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Required:</td>
<td>• In severe cases (i.e. bacterial) see bilateral, rapidly progressing pneumonia</td>
<td><strong>Key virulence factors:</strong></td>
<td><strong>Transmission:</strong></td>
<td>• 3 types: A, B → disease; C → subclinical</td>
<td><strong>Complications:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Fever above 101 F</td>
<td>(primary viral)</td>
<td><strong>Neuraminidase protein (NA):</strong></td>
<td>• Respiratory droplets</td>
<td>• enveloped</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• At least one</td>
<td>• Surface protein (antigenic)</td>
<td><strong>Hosts:</strong></td>
<td><strong>Hosts:</strong></td>
<td>ssRNA (-)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>systemic symptom</td>
<td>• Allows virus to escape the host cell and move through mucous membranes</td>
<td><strong>Healthy young adults:</strong></td>
<td></td>
<td>C type – lacks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(myalgia, chills, malaise)</td>
<td>• Can also see lobar infiltrate (secondary bacterial: S. pneumonia)</td>
<td>deaths during pandemics most often caused by primary viral pneumonia</td>
<td></td>
<td>Neuraminidase protein (key virulence factor)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• And, at least one respiratory symptom</td>
<td>• Necrotizing pneumonia (secondary bacterial: S. aureus)</td>
<td><strong>Older adults, chronically ill:</strong></td>
<td></td>
<td>Nomenclature:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(cough, nasal discharge)</td>
<td></td>
<td>bacterial pneumonia = major cause of mortality</td>
<td></td>
<td>A/Texas/1/77/H3N2 =</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Incubation period = 1-2 days</td>
<td></td>
<td><strong>Children:</strong> more susceptible to myositis, Reye’s syndrome</td>
<td></td>
<td>Type A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Sx can persist for 2 weeks</td>
<td></td>
<td></td>
<td></td>
<td>Isolated in Texas</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Rarely: GI Sx</td>
<td></td>
<td></td>
<td></td>
<td>In 1977</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Complications are quite common: (pneumonia, myositis, neurological, Reye syndrome)</td>
<td></td>
<td></td>
<td></td>
<td>•1 = strain designation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 – 7 days after exposure to someone who has been in Asia or Toronto recently with:</td>
<td><strong>Influenza Virus</strong></td>
<td></td>
<td></td>
<td>• H3N2 = subtype</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• prodrome of fever – Chills, headache, malaise, myalgia, diarrhea may also be present</td>
<td></td>
<td></td>
<td></td>
<td>Review session:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• In 10-20% disease may be rapidly progressive and require mechanical ventilation</td>
<td></td>
<td></td>
<td></td>
<td>Binds to sialic acid residues, enters cell through receptor mediated endocytosis, mechanism of viral uncoating is well worked out.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Other viral proteins:</strong></td>
<td></td>
<td></td>
<td>Neurologic:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• RNA polymerase (PB1, PB2, PA) for replication</td>
<td></td>
<td></td>
<td>• Post-infectious encephalitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• NP = nucleocapsid. Covers the genome</td>
<td></td>
<td></td>
<td>• Guillain-Barre syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• M1 protein: provides stability for type A, B viruses</td>
<td></td>
<td></td>
<td>Respires syndrome:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• M2: acts as ion channel within endosome for type A (allows the DNA to get out; also a drug target)</td>
<td></td>
<td></td>
<td>• Changes in mental status, liver function when given aspirin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• NS: nonstructural, function unknown</td>
<td></td>
<td></td>
<td>• Mortality from increased ICP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

#### Emerging Infection

**Evolving pathogen and new disease.**

The outbreak of SARS has been traced from a single individual from Southern China. The patient traveled to Hotel Metrop in Hong Kong infecting other travelers there, who subsequently went back to their own countries and infected persons there.

**Mortality**

To date there have been 8,427 cases in 29

**SARS - Coronavirus**

- **Member of the Coronaviridae family**
- **Pleomorphic 100-150 nm particle with characteristic surface projections**
- Single stranded, (+) sense RNA genome (27-32 kb)
- Cytoplasmic replication
- Viral assembly in Golgi apparatus and endoplasmic reticulum
- Clinical suspicion – Particularly in a traveler from an endemic region or someone exposed to a possible/probable case
- Still investigational
  - Sputum, blood and body fluids for viral cultures and PCR
  - May not be positive for up to 28 days

**Treatment** is supportive

**Vaccine**

Inactivated virus (reduces hospitalization, death). Lower efficacy in immunosuppressed.

**For:**
- Individuals > 50, cardiac, pulmonary, renal diseases, diabetes, immunosuppressed, Hb disorders, nursing home residents, health care providers.
  - Admin: 1/yr.
  - 5% low grade fever (not the flu)

**Antivirals:** Can be used for people who’ve been exposed.
| Young health person 14-17 days after exposure to rodents with: myalgia, malaise, and fever (mild flu-like symptoms). General GI disturbances (anorexia, nausea, vomiting, and abdominal pain) and non-specific respiratory complaints (cough, tachypnea, and tachycardia) may be observed. Symptoms may rapidly progress to respiratory failure. | **Chest X-ray:** Bilateral interstitial infiltrates (moderate to rapid progression), bilateral alveolar infiltrates, and pleural effusion. **Labs:** a. elevated hemocrit (Hct) b. leukocytosis with left shift; atypical lymphocytes seen c. thrombocytopenia d. elevated liver enzymes, proteinuria, elevated creatinine may be seen. **Hantavirus Pulmonary Syndrome** Deposition in terminal respiratory bronchiole or alveolus. - Cell invasion may be mediated by B3 integrins - Infiltration by CD4 and CD8 cells - Loss of vascular integrity in lungs - Capillary leak syndrome - Myocardial depression also seen. **Epidemiology:** Basically localized to the western hemisphere all over the U.S. but less than 50 cases a year. However, when it does infect a patient, it is usually a young healthy person, and it is usually fatal. **Reservoirs:** rodents (deer mice) **Transmission** To humans via inhalation of contaminated aerosolized excreta, especially urine. | **Emerging infection** New agent and disease First described in 1993 in Four Corners area, New Mexico. **Hantaviruses (Sin Nombre viruses)** Bunyaviridae family, segmented RNA, enveloped viruses. **PCR of viral RNA in lung** Serologically **Hemorrhagic fever with renal syndrome (HFRS)** a. elevated hemoconcentration b. leukocytosis with left shift; atypical lymphocytes seen c. thrombocytopenia d. elevated liver enzymes, proteinuria, elevated creatinine may be seen. **Passive immunity:** No vaccine. | **Ventilation** countries, and 813 deaths. • infect multiple species | | **Infant presents with:** pneumonia **Bronchiolitis** **History:** Sx start with • Nasal congestion • Sore throat • Fever • Cough develops in first few days and becomes deeper and more prominent as infection proceeds **Physical:** • Increased RR, retraction of lower intercostals (indicates lower resp. tract involvement) **Adults:** • Common cold-like symptoms • May be worse depending on immune status **Chest X-ray:** •“Peribronchial cuffing”: infiltrate with edema of bronchial walls **Infection involves primarily lower respiratory tract in infants with without systemic spread (although may just be upper tract infection). Immune response probably contributes to pathogenesis. **Infection:** •Inoculation: through eyes and nose •Lyphocytic peribronchial infiltrate with edema of bronchial walls •Later proliferation and necrosis of bronchioles develops •Collections of sloughed epithelium → obstruction of small bronchioles → air trapping •Viral infection → may lead to pneumonia **Immune Response** •Most sever infections: when Ab titer high, CMI low (e.g. early infancy when maternal Ab present; vaccinated infants had worse outcomes) •CMI key for protecting against serious lower tract infections **Viral proteins:** •Attachment: F, G, SH •Nucleocapsid: N, L, P •RNA polymerase: NS1, NS2 **Host:** • Virtually all children infected by age 2. Premature infants (esp. w/ bronchopulmonary dysplasia, congenital heart disease, pulmonary disease) and those from low SES are at greater risk for serious disease • Immunocompromised: (CMI esp.) **Season:** • Winter bug: outbreaks begin in Nov., peak in Jan., continue until April **Transmission:** • Respiratory droplets **Geography:** • everywhere **Respiratory Syncytial Virus (RSV)** • Paramyxoviridae family • Enveloped • ssRNA (+) **Respiratory Syncytial Virus (RSV)** **Cell culture:** • multinucleated giant cells (syncytia cells) • immuno-fluorescence • serology not useful **Pneumonia** **Supportive care:** • mainstay for sick infants • Epinephrine, supple- mental 02 for hypoxic infants **Antiviral (Ribivirus):** • Aerosol for very sick infants • Interferes with RNA polymerase, and depletes intracellular nucleotide pools **Passive immunity:** • Monoclonal Ab (palivisum ab) • Immune globulin • Given 1X/month for at-risk infants • Doesn’t benefit patients with congenital heart disease • No vaccine. **Hand washing**
<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
<th>Serology</th>
<th>Clinical Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common cold in adults</strong></td>
<td>Virus can be detected in nasal secretions as early as 10 hours after inoculation (but not usually done). Paranasal sinuses may be seen in CT scan.</td>
<td>Serology: Ab titer rise</td>
<td>Rhinoviruses: Small, nonenveloped virions; picornavirus; 100's of serotypes</td>
</tr>
</tbody>
</table>

**Common-cold symptoms (for about a week):**
- Rhinorrhea
- Congestion
- Sneeze

Also:
- **Sore throat** (pharyngitis can be severe, can be exudative)
- **Hoarseness, cough** (less common, but more persistent – lasting up to several weeks)
- **Yellow-green sputum may be seen**
- **High fevers, myalgias, and chills** NOT usually seen (should prompt other diagnoses)

**Upper and lower respiratory tract disease, especially pharyngitis and pneumonia**

**Measles (serious disease)**

**Maculopapular rash**

**Congenital malformations, cardiovascular, and CNS**

**Inhalational Anthrax**
After 1-6 day incubation period (closer to 1 day, but could be much longer): Flu-like symptoms -> Chest X-ray Non-specific clinical CXR – widened mediastinum, pleural effusions

**Anthrax**
**Inhalational (more lethal)** Hemorrhagic mediastinitis -> malignant edema with regional lymphadenitis -> toxic induced

**Bioterrorist Agent**
Cutaneous to goal to get into the blood stream Inhalational -> more dangerous

**Bacillus anthracis**
Non-motive, gram positive, rod, spore former, not contagious
Does occur naturally

**Inhalational Dx**
Non-specific clinical CXR – widened mediastinum, pleural effusions (key)

**Antibiotics** are effective against vegetative form, non spore form
Empiric – cipro or doxy

**Vaccine**
Attenuated form
Good at preventing skin anthrax
6 doses –
<table>
<thead>
<tr>
<th><strong>Septic</strong></th>
<th>untreated</th>
<th>nontoxic</th>
<th>mediastinitis</th>
<th>death</th>
</tr>
</thead>
</table>

**Cutaneous**

- Days up to 14 after being exposed to white powdery substance:
  - Pustular macule
  - Vesicle
  - Round ulcer
  - Black eschar
- Surrounding edema/erythema (pretty profound), but painless
- +/- painful regional lymphadenopathy
- Untreated 5%-20% mortality rate
- If treated, do well

| **septicemia** | **Cutaneous** | **Path** | **Spores are viable for years** | **Gm stain, culture, PCR** of blood and CSF
Large gram pos rods, rough, grayish colony, non-
emolytic, non-motile
- Usually penicillin susceptible
- Send culture to CDC/NYDOH

| **Cutaneous Dx** | Vesicular fluid or border of skin lesion (gram stain, culture, sensitivity, PCR)
| Skin biopsy (culture, PCR, special CDC immuno test)
| Serologies – take while to develop

| **History** | commonly: Fever
Fatigue
Night sweats
Weight loss
Anorexia
Chills
| **Pulmonary Sx** (non-specific): Productive Cough
Hemoptysis
Pleuritic chest pain
| Physical:
- Fever
- Cachexia
- Perhaps pulmonary consolidation

| **Extrapulmonary** | Lymph
Bone/joint
Miliary
GU
CNS (meningeal) | **Lab findings:**
- Mild anemia
- Normal WBC, normal differential
- Elevated ESR
| **Chest X-ray:**
- Suggestive – apical infiltrates or cavities, hilar adenopathy. Different X-rays for HIV patients.
| If meningeal involvement → Subarachnoid space infection
- Glucose: normal, or low
- Protein: up
- Lymphocytic predominance
| **Biopsies:**
- LN: cervical node
- Miliary: granulomas
- Pleural: AFB staining often negative for some reason

| **Primary Infection:**
- Impeded replication and dissemination → secondary to lack of host immune response
| Development of immune response:
- CD4 → cytokines → recruit Mac’s → kill MTB, cause tissue damage (form Langhans giant cells, granulomas)
| Clinical events – primary infection → mild viral like syndrome, PPD comes out positive. If not progressive, resolves into Ghon complex.
| Progressive primary disease: (in immunocompromised, young children): military, CNS involvement, pleural disease (in absence of parenchymal involvement) = more common
| Persistence of viable organisms: at secondary sites (lung apices, LNs, meninges, bones, kidneys). 85-90% of immunocompetent individuals do not progress further...
| Reactivation (remaining 10-15%): weeks to decades later often depends of weak host immune status → can’t contain infection. 85% located in apical-posterior lungs, rest extrapulmonary. Get caseating necrosis of lungs
| Exogenous reinfection: occurs in developing countries, homeless shelters. Positive PPD converts some protection.

| **Transmission:**
- Inhalation of respiratory droplets
- GI (contaminated milk), skin exposure unusual
| Risk of infection:
- Directly proportional to length of exposure to organisms
| Risk of disease:
- Greatest in infants <6 mo
- Time: highest after 1 year following primary infection
| Decreased nutritional, immune status increase risk

| **Mycobacterium Tuberculosis** | **Clinical**
- PPD test
- Interferon production by WBC’s exposed to MTB Ag’s
- AFB culture
- PCR, DNA probes

| Exposure, no risk of infection: need to get repeated testing
PPD (+), asymptomatic: monitor Sx, chest X-ray. Indications for Tx in this population:
- Recent development of PPD (2 yrs)
- Close contacts of known cases of infectious TB
- Persons in hospitals, prisons, shelters, nursing homes
- Children < 5 y.o.

- Those with increased risk for progression:
  - Fibrotic changes, apical scarring
  - Immunosuppressed
  - Underlying disease
  - Immigration within 5 years from area with high TB rate
  - Underweight persons
  - IDUs
  - People less than 35 y.o.

| Isoniazid
Rifampin
| Prevention:
Primary-vaccination at risk (military)
Secondary
## HIV Infection

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Test Findings</th>
<th>Pathogenesis</th>
<th>Predisposing Factors/ Epidemiology</th>
<th>HIV Structure / Replicative Cycle</th>
</tr>
</thead>
</table>
| Early, Acute Stage a.k.a. Acute retroviral syndrome (mononucleosis like picture): | Blood test:  
• leukopenia  
• CD4 cells normal  
Serologies:  
• Abs appear 3-4 weeks after infection (so prior testing results in false-negatives)  
• HIV can still be transmitted during this period | In acute infection:  
• Virus encounters DC’s on mucosal surface (DC-sign is a co-receptor on DC)  
• Virus is delivered to LN where active replication takes place  
• primary infection – R5 tropic (Mac’s)  
• high levels of viremia and viral dissemination occur  
• Down regulation of the virus by CMI occurs  
• Viral set point reached after about 6 months  
• Immune response, chemokine receptor status and HLA type are important co determinants of outcome | Emerging Infection  
New agent, new disease  
Determinants of Outcomes  
Viral Factors:  
• Escape from immune response: under immune selective pressure (CMI, humoral), mutations in gag, pol, env  
• Attenuation: nef deleted viruses associated with slow or long-term non progression in patients  
• Tropism: R5 → X4 virus conversions associated with increase in pathogenicity (there may be mix of these)  
• Subtypes: a bunch of them. Subtype B in US. Potential for varied subtypes to exhibit differential transmissibility and virulence. Potential for greater heterosexual.  
Host Factors:  
• CMI:  
• CTL’s: eliminate virus infected cells, play prominent roles in control of viremia  
• T help: vital for CTLs  
• Humoral immunity: role unclear in prevention of transmission, progression  
• Chemokine receptors:  
• CCR5-delta32: homozygosity associated with decreased susceptibility to R5 virus infection; heterozygosity → delayed disease progression  
• Other genetic factors:  
• Class I alleles: B35, …  
• faster progression; …  
• slow progression  
Transmission  
• Sexual: hetero; male to male  
• Blood: transfusion; IV drug use; needle stick  
• Perinatal: intrapartum; breast feeding  
• Epidemi: Stable in US (NYC, DC, Puerto Rico most affected)  
• Not stable in subsaharran Africa, developing regions  
Risk Factors: Male  
• Male → male (53%)  
• IDU (28%)  
Female  
• Heterosexual contact (64%) | Structure:  
• Retrovirus family  
• ssRNA virus with an icosohedral nucleocapsid and lipid envelope  
• two identical copies of RNA and carries a reverse transcriptase  
Replication:  
• binding and infection  
• reverse transcription and integration of viral DNA  
• transcription and translation  
• Modification and assembly  
• Budding and final assembly |
| Middle Stage (long latent period, measured in years, usually ensues):  
• Patient is usually asymptomatic at this time and without complications  
• Rarely, patients may have have AIDS-related complex (ARC) with persistent fevers, fatigue, weight loss, and lymphadenopathy | Blood tests:  
• Progressive CD4+ depletion (pt. loses 50-75 CD4+ cells per year if RNA is above 30,000)  
PCR:  
• Average pt. has viral load set point of 30,000 copies of HIV RNA / ml | Once HIV infection is established:  
• acute viral response present throughout course of the disease  
• major reservoirs of infection exist outside of blood compartment: lymphoreticular tissues (most important), CNS, Genital tract  
• Virus exists as multiple quasispecies  
• Mixtures of viruses with differential phenotypic and genotypic characteristics may exist (drug resistance mutations vary across clones, compartments)  
• At least 10 * 10^9 virions produced and destroyed each day (even in asymptomatic individual), and combine this with:  
• High turnover rate: 1/2 of HIV in plasma is < 6 hr and may be as short as 30 minutes (very dynamic infection even in asymptomatic individual) | |
| Late stage HIV infection (AIDS)  
• most often manifested by Pneumocystis Pneumonia (PCP) or Kaposi’s sarcomas  
Diseases or symptoms of other opportunistic infections include:  
Lung:  
• Pneumonia  
• Tuberculosis  
Mouth  
• Thrush  
• Hairy leukoplakia  
Ulcerations  
Esophagus  
• Thrush  
• Esophagitis  
GI  
• Diarrhea  
CNS  
• Meningitis  
• Brain abscess  
Progressive multifocal leukoencephalopathy  
Eye  
• Retinitis  
Skin  
• Kaposi’s sarcoma  
• Zoster  
Subcutaneous nodules  
Reticularendothelial system  
• Lymphadenopathy or splenomegaly | | | |
### HIV Infection (cont.)

<table>
<thead>
<tr>
<th>Definitive Diagnosis / Prognosis</th>
<th>Complications</th>
<th>Treatment</th>
<th>Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELISA:</td>
<td></td>
<td></td>
<td>Prophylaxis</td>
</tr>
<tr>
<td>HIV Ab detection (30 min – 1 hr)</td>
<td></td>
<td></td>
<td>PCP – TMX (&lt;200)</td>
</tr>
<tr>
<td>Western blot:</td>
<td></td>
<td></td>
<td>Toxo – TMX or Dapsone + Pyrimethamine (&lt;100)</td>
</tr>
<tr>
<td>Detects serum Ab’s to specific HIV proteins that are separated on a gel</td>
<td></td>
<td></td>
<td>MAC – Clarithro/Azithromycin (&lt;50)</td>
</tr>
<tr>
<td>PCR:</td>
<td></td>
<td></td>
<td>TB – INH (9 months) (PPD+) -- problems: high risk individuals have lost skin reactivity (therefore PPD reaction set at lower level); also other problem – in developing countries INH and PPD skin test not used in many areas</td>
</tr>
<tr>
<td>RNA plasma levels (this would be positive in acute infection, when ELISA and Western blot would be false negatives – but would still do these together in acute infection to rule out established infection).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prognosis:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Can develop prognosis based on CD4 and viral load</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIDS like impending train wreck: viral load = speed of train, CD4 count = distance from site of crash</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Independent predictors of outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More viral load, less CD4 -&gt; AIDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute CD4 count: best established surrogate marker to predict time to AIDS, risk of specific OIs (near term), or death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combine with viral load -&gt; can give very accurate prediction of time to AIDS in 5 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RNA above 30,000 copies -&gt; 75 cell loss per year: higher RNA, faster CD4 count will decline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender specificity: after seroconversion – women have lower viral loads</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment decisions should be individualized</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Non-progressors:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>May last for 10+ years, but will eventually get AIDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Determined by host-factors primarily (chemokine receptor co-receptors key (CCR5) heterozygous individuals just as infectable -&gt; but not as progressive = lower viral load set point i.e. cells have less dense receptors for HIV)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral factors less so: nef deletion, non-clade B subtypes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Need to look at person with 351-500 CD4 count -&gt; if viral load over 100k -&gt; get ready to start treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Opportunistic disease (often in a cascade pattern with dropping CD4+ levels)**
- <300 – TB (any level of CD4 count)
- Opportunistic infections occur at CD4 <200
- <200 – PCP
- <100 – TE
- <75 – CMV, dMAC – many people don’t survive until this point

**Treatment**

**Epiiope war: When do you start treatment?**
- Patient’s disease stage: any symptomatic individual; CD4 count; plasma HIV-1 RNA level
- Patients commitment to therapy in light of side effects
- Philosophy of treatment

**Initiation of Retroviral Therapy**
- Clinical outcome compromised if Tx begun when CD4 <200
- Markedly decreases rate of death from disease from protease inhibitors -> most effective way to prevent OIs -> restore host immune function
- OI related events:
  - MAC adenitis (may suddenly appear as inflammatory illness after retroviral therapy due to immune system recovery)
- Inflammatory flare of CMV retinitis
- Previously stable hepatitis
- Development of cavitary TB

**Antiretroviral therapy**

- Markedly decreases rate of death from disease from protease inhibitors -> most effective way to prevent OIs -> restore host immune function
- OI related events:
  - MAC adenitis (may suddenly appear as inflammatory illness after retroviral therapy due to immune system recovery)
- Inflammatory flare of CMV retinitis
- Previously stable hepatitis
- Development of cavitary TB

**Pathogenesis after administration of retroviral therapy** (measured in log of viral load over time):

1st phase: t1/2 = 1 day (productively infected CD4)
2nd phase: t1/2 = 2-4 weeks (mac’s, lately infected CD4s, release of trapped virions from LN’s)
3rd phase: t1/2 = 6-44 months (resting, memory CD4s): may not be a decline -> irreducible reservoir. Can reemerge.

**Therapeutic Implications for 1st and 2nd phase declines**
- Can assess antiviral potency in first 7-14 days (should see 1-2 log decline in first two weeks of therapy)
- Trajectory over first 1-8 weeks can be predictive of subsequent response

**3rd phase (Latent reservoir): Therapeutic implications**
- Resting naive CD4 cell activated by Ag gets exposed to HIV -> virus integrated into host cell -> rapid production kills most of cells -> some resting memory CD4 cells remain (only 1 million to 10 million cells total)
- Viral eradication not possible with current drugs
- Archive of replication competent history established
- Despite presence of reservoir, minimal degree of drug resistance over 2-3 years

**Drug Resistance**
- Genetic variants are continuously produced as a result of high viral turnover and inherent error rate of RT
- Viral replication 10^6-10^10 per day
- RT error rate 10^-4 base/cycle
- Emerge with drug selective pressure
- Resistance emerges before exposure to drugs -> quickly afterwards
- Single mutation drugs most dangerous
### HIV Opportunistic Infections
(Note: These are based on the information on the slides, see Lynn’s Chart for more info)

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Test Findings</th>
<th>Pathogenesis</th>
<th>Predisposing Factors/ Epidemiology</th>
<th>HIV Structure / Replicative Cycle</th>
<th>Definitive Diagnosis / Prognosis</th>
<th>Treatment</th>
<th>Prevention</th>
</tr>
</thead>
</table>
| **Pneumocystic pneumonia**<br>
- Presents as subacute illness (fever, cough, dyspnea)<br>- Predicted by CD4 count: by time reach CD4 <200 → begin seeing PCP after 6 months | • Diffuse interstitial infiltrate on xray | • Most common life threatening infection of AIDS patients in US | | | | | | |
| **CNS toxoplasmosis**<br>
- Reactivation in AIDS associated with CD4 <100 | | | | | | | | |
| **Cryptococcal Disease**<br>
- Initial asymptomatic pneumonia<br>- Meningitis most common presentation, but wide dissemination frequent<br>- May see ulcers in skin (most commonly recognized sites)| • Spinal tap: good test for Ag | • Ubiquitous soil fungus | | | | | | |
| **CMV disease**<br>
- Retinitis most common clinical form in AIDS population (pneumonia more common for transplant pop)<br>- Other sites: colon, CNS| • Reactivation at CD4 <50<br>- Colonoscopy: colitis | | | | | | | |
| **MAC**<br>
- Local lung disease known prior to AIDS<br>- Non-specific features, liver, and spleen | • Wide spread visceral dissemination in AIDS | | | | | | | |

**Addition of corticosteroids to antimicrobials cuts mortality of in severe disease of 50% (not intuitive: element of reaction to pathogen is not deficient, therefore reduce host response related disease)**

**Fully preventable with trimethoprim-sulfa (bactrin)**
### Rabies/Prions

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Pathogenesis</th>
<th>Predisposing Factors/Epidemiology</th>
<th>Likely Pathogens</th>
<th>Definitive Diagnosis</th>
<th>Treatment</th>
<th>Prevention</th>
</tr>
</thead>
</table>
| A week to a year after an animal bite: | **Classical Rabies** | • Foot prorome and spasms of large muscle
• Leads to hydrophobia because it hurts to swallow;
• Also accounts for salivary retention and drooling.
• And eventually leads to coma and paralysis.

**Non-specific Symptoms & Signs:**
These include itching, large pupils, stiffness, hypersensitivity to sounds, light, change in temperature.

Rarely presents as Guillain Barre Syndrome (ascending paralysis).

- Prodromal Phase, 2-4 days: It’s non-specific so people have any kind of viral complaint. It depends on whether the virus is replicating in CNS or peripherally.
- Excitation Phase: Here they develop weakness, weird ocular palsies, uninnediation and constipation. Basically you’re just documenting their demise because you can’t save them.
- Paralysis Phase: You die of peripheral vascular collapse with flaccid paralysis if you don’t drown in your own secretions first.

**High Mutation Rate**
No proofreading activity of the RNA polymerase.
This leads to a greater mutation rate of about 1 in 1000 that allows for flexibility & enhanced fitness. It results in a quasi-species (heterogeneous population of different RNA molecules that has certain predominant consensus genotypes).

**High Mortality Rate**
100% fatality rate if left untreated.
60% estimated human fatality 30K in India.

**After long incubation period:**

- **In New Guinea (Kuru):**
  - Prodromal: headaches, arthritis
  - Neuromuscular: cerebellar ataxia, action tremor, involuntary movement → progressively worse dementia → death

- **Creutzfeld-Jakob Disease:**
  - Lack of coordination, dementia, motor weakness (Rule out Alzheimers in elderly)

- **Fatal familial insomnia**
  - Autonomic dysfunction and sleep disturbances in middle → late life

- **Germans-Strausser-Schneider**
  - Midlife progressive spino cerebellar degeneration with associated dementia,

**Hardy proteins:**
- Resistant to heat, formaldehyde, UV light
- Role of PrPc may include synaptic plasticity since knockout mice developed subtle sleep defects. What is certain is that it’s essential to TSE pathogenesis.

<table>
<thead>
<tr>
<th>KO mice are resistant to TSE.</th>
</tr>
</thead>
<tbody>
<tr>
<td>The key determinant of disease is the cellular gene itself and its susceptibility of going through conformational change as result of coming into contact with prion protein in diet (i.e. PrPc exposure to PrPsc changes it to PrPsC).</td>
</tr>
</tbody>
</table>
| Creutzfeld-Jakob Disease:
  - Most common in elderly
  - Hereditary: rare autosomal dominant
  - Agonistic: exposure to growth hormone in pituitary, corneas, contaminated surgical instruments
  - Variant: Ingestion of BSE infected meat or bone marrow (seen in younger populations)

**Three phases:**
1) First six months, little risk to humans; 2) prion concentrated in CNS and animal is asymptomatic and infectious; 3) animal symptomatic and infectious
BSE endemic in UK ("mad cow")

<table>
<thead>
<tr>
<th>FFI and GSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary/genetic</td>
</tr>
</tbody>
</table>

**Prions:**
Proteinaceous infectious particles associated with transmissible spongiform encephalopathies (TSEs).

| PrPc (cellular) – protein product thought to be target of prion disease. 
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal host protein encoded by single exon of a single copy gene in chromosome 20. It is attached to the neuronal surface by G proteins, are protease sensitive, and have a &quot;α-helical secondary structure.</td>
</tr>
</tbody>
</table>

- **PrPsc (prion scrapie) is protease insensitive so they accumulate in cytoplasmic vacuoles, eventually blocking normal physiological. They have a "β-sheet secondary structure.**

**Definitive diagnosis is made by:**
- Fluorescent rabies antibody (FRA) test on brain tissue (more specific for rabies but present in only 50% of cases. (Cytoplasmic inclusions in pyramidal neurons in hipocampaus and Purkinje cells in cerebelnum)

**Spinal tap:**
To determine which of the differential diagnoses of GBS, HIV, polio, and rabies your patient has. This comes up on boards.

**Find and observe animal for ten days**

**Diagnosis:**
RT-PCR saliva, CSF, urine, nerve tissue

**Active Vaccination (Pre and Post Exposure):**
- The best is the human diploid cell vaccine
- Pre: for high risk groups (vets, Peace Corps vol.)
- Amidrin: It’s painful, administered intradermally, and give on days 0, 7, 14, 28 post-exposure.
- It is successful if given in time, but once they’re in the excitation stage, you give it to them but without expectation of any effect.

**Passive Vaccination:**
Infiltrates the wound site and vicinity with antibodies to prevent it from propagating and spreading centrifugally within CNS. You can use human rabies Ig and some people use horse rabies Ig though that can lead to serum sickness. Admin: it’s done just once.

**Definitive diagnosis is made by:**
- Taking a brain or lymphatic biopsy, using antibodies to identify the proteins, then digesting them with protease. After digestion, only the PrPsc signal has been preserved because of its protease insensitivity whereas PrPc has been chewed up.

**Usually, on basis of clinical syndrome and history.**

**Definitive diagnosis is made by:**
- Taking a brain or lymphatic biopsy, using antibodies to identify the proteins, then digesting them with protease. After digestion, only the PrPsc signal has been preserved because of its protease insensitivity whereas PrPc has been chewed up.

**No reasonable treatments.**
### Arboviral Infections / Encephalitides

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Pathogenesis</th>
<th>Predisposing Factors/ Epidemiology</th>
<th>Likely Pathogens</th>
<th>Definitive Diagnosis</th>
<th>Complications</th>
<th>Treatment</th>
<th>Prevention</th>
</tr>
</thead>
</table>
| 4-10 day after insect bite (spectrum of severity): | Aboviral Encephalitis | Host | Major US causes:  
(post 1999) West Nile Encephalitis (WNE),  
Eastern Equine Encephalitis (EEE),  
LaCrosse (LAC).  
Others (don't need to know):  
St. Louis Encephalitis (SLE), Western Equine Encephalitis (WEE),  
and Powassan encephalitis (POW).  
(Don't need to know): Japanese B Encephalitis (JBE) predominates in South East Asia and Australia.  
Venezuelan Equine Encephalitis (VEE) in South America, WNE in Northern Africa and the Middle East,  
and Tick-Borne Encephalitis (TBE) in Eastern Europe and Russia.  
| Serologically (positive IgM or 4x increase in IgG titer),  
CSF PCR test. | | | | |
| to sever cases: | | | | | | | |
| fever,  
headache,  
mental status changes,  
and possibly focal neurologic signs. | | | | | | | |
| Asymptomatic Infections: | | | | | | | |
| Arboviruses stay around by finding reservoirs of cells that are resistant to its cytopathic effects, such as mosquito cells, and muscle and neuronal cells in humans.  
CNS Invasion → Encephalitis:  
Arboviruses invade the CNS either through the vasculature from viremia or retrogradely through the olfactory nerves. Neuroinvasiveness and neurovirulence is primarily determined the age of the host.  
Perivascular inflammation:  
A histologic hallmark of arboviral encephalitis. The immune response can be damaging through excessive cytokine release.  
Arboviruses can also directly induce neuronal apoptotic death. | | | | | | | |
| After mosquito bite: | | | | | | | |
| Most commonly an infection is asymptomatic.  
an abrupt onset flu-like illness with:  
moderate to high fever,  
headache,  
sore throat,  
backache,  
myalgia,  
arthralgia,  
fatigue,  
rash,  
lymphadenopathy.  
More serious cases:  
temperature above 38.0°C  
and either focal neurologic signs,  
 altered level of consciousness,  
 or diffuse profound motor weakness  
Negative for structural brain lesions. | | | | | | | |
| May see motor weakness in encephalomyelitis (West Nile documented to affect anterior spinal cord neurons). | | | | | | | |
| Emerging Infection | West Nile Virus | West Nile Virus | Flavivirus; reservoir = bird; vector = mosquito | 1. CSF: Pleocytosis and positive IgM  
or  
2. Serum: 4x rise in IgG titer or  
PCR for West Nile in serum or CSF  
are required for definitive diagnosis.  
Rule out: Bacteria, fungi, and structural lesions on brain imaging suggesting another diagnosis are also required. | | | |
| Previously described agent, in a new location → now an established infection | | | | | | | |
| Incidence | | | | | | | |
| Largest recorded arboviral encephalitis epidemic in US history, with over 8,470 human cases in 45 states to date | | | | | | | |
| Progression | | | | | | | |
| 1 in 5 infections → West Nile Fever  
1 in 150 → West Nile encephalomyelitis | | | | | | | |
| Host | | | | | | | |
| The more serious form of disease, West Nile encephalomyelitis, strikes mainly those over 50  
and/or the immunocompromised. | | | | | | | |
| Geography:  
Eastern US | | | | | | | |
| Season | | | | | | | |
| Summer/fall | | | | | | | |
| Outbreaks | | | | | | | |
| Occasional in humans, frequent in | | | | | | | |
| Eastern Equine Encephalitis (EEE) | | | | | | | |
| Alphavirus; vector = mosquito; reservoir = birds, horses | | | | | | | |

### Epidemiology

**Major US causes:**

- **Aboviral Encephalitis**
  - 4-10 day after insect bite (spectrum of severity):
    - mostly asymptomatic cases
    - mild “flu-like” illness
  - to sever cases:
    - fever,
    - headache,
    - mental status changes,
    - and possibly focal neurologic signs.

**Host**

- Japanese B Encephalitis (JBE) predominates in South East Asia and Australia.
- Venezuelan Equine Encephalitis (VEE) in South America, WNE in Northern Africa and the Middle East, and Tick-Borne Encephalitis (TBE) in Eastern Europe and Russia.

**CNS Invasion**

- Arboviruses invade the CNS either through the vasculature from viremia or retrogradely through the olfactory nerves.
- Neuroinvasiveness and neurovirulence is primarily determined the age of the host.

**Perivascular inflammation**

- A histologic hallmark of arboviral encephalitis. The immune response can be damaging through excessive cytokine release. Arboviruses can also directly induce neuronal apoptotic death.

**Patterns of Infection**

- Infections occur seasonally with peaks in late summer/early fall correlating with mosquito activity.

**Seasons**

- Summer/fall

**Emerging Infection**

- Previously described agent, in a new location → now an established infection

**Incidence**

- Largest recorded arboviral encephalitis epidemic in US history, with over 8,470 human cases in 45 states to date

**Progression**

- 1 in 5 infections → West Nile Fever  
1 in 150 → West Nile encephalomyelitis

**Host**

- The more serious form of disease, West Nile encephalomyelitis, strikes mainly those over 50  
and/or the immunocompromised.

**Definitive Diagnosis**

- Serologically (positive IgM or 4x increase in IgG titer),  
CSF PCR test.

**Complications**

- Treatment is supportive with IFN-α, ribavirin, and other investigational trials not proving conclusive yet.

**Treatment**

- Aerial spraying, personal protective measures from bites.
- Inactivated human vaccines are available for JBE (also available for the amplifying hosts – pigs – to reduce reservoir) and TBE.  
live attenuated equine vaccines are available for VEE, EEE, and WEE (not for humans).
<table>
<thead>
<tr>
<th>After mosquito bite:</th>
<th>Mortality</th>
<th>Human Host</th>
<th>Yellow Fever</th>
<th>Serology, Viral isolation, PCR</th>
<th>Henomagric diathesis, circulatory failure, and shock</th>
<th>Treatment is supportive.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 in 5-20 infections have clinical disease with jaundice.</td>
<td>1(^{st})/3 of cases are fatal – regardless of age</td>
<td>Anybody</td>
<td>Flavivirus; vector = mosquito; reservoir = primates</td>
<td>but NOT liver biopsy because of bleeding diathesis.</td>
<td></td>
<td>Preventable with mosquito controls, and improved sanitation/water systems, yet lapses in Africa has led to increasing epidemics. The live attenuated Yellow Fever 17D vaccine is effective and contraindicated in infants less than 6 months of age, in pregnant women, in the immunosuppressed, and in those with hypersensitivity reactions to eggs.</td>
</tr>
<tr>
<td>3 stages:</td>
<td>Geography</td>
<td>Epidemiology patterns:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) infection (viremia) with fever, chills, headache, back pain, nausea, malaise, minor gingival hemorrhages, epistaxis, and relative bradycardia (Faget sign)</td>
<td>South-Saharan Africa and South America (never Asia)</td>
<td>Endemic&lt;br&gt;&quot;Jungle yellow fever&quot;: non-human primate hosts and tree-hole breeding mosquito vector.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2) remission</td>
<td>Epidemic&lt;br&gt;&quot;Urban yellow fever&quot;: human hosts and urban mosquito vector (Aedes aegypti).</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3) intoxication with jaundice and black vomit, delirium, stupor, acidosis, and shock.</td>
<td>Mortality</td>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Also present are leuko/thrombocytopenias, liver and kidney abnormalities, and coagulopathies.</td>
<td>High case-fatality rate of 20-50% in patients with jaundice.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2-7 days after mosquito bite:</th>
<th>Incidence</th>
<th>Vector</th>
<th>Transmission</th>
<th>Dengue Fever</th>
<th>Dengue Fever</th>
<th>Dengue Shock Syndrome (DSS), defined as DHF with hypotension, circulatory failure and shock.</th>
<th>Dengue Fever can progress (30%) to Dengue Shock Syndrome (DSS), defined as DHF with hypotension, circulatory failure and shock.</th>
<th>Treatment with supportive measures can lower the case fatality rate of DHF from &gt;10% to &lt;1%.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biphasic disease…</td>
<td>100 million cases annually in all tropic and warm temperate zones.</td>
<td>Aedes aegypti and humans are the primary hosts.</td>
<td>Air travel from viremic humans.</td>
<td>Flavivirus; vector = mosquito; reservoir = primates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early phase:</td>
<td>Vector</td>
<td>Transmission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• major lumbosacral, joint, bone pain</td>
<td>Dengue Hemorrhagic Fever (DHF), a more serious disease which occurs almost exclusively (&gt;90%) in those with prior immunity to a heterotypic serotype, is on the rise because there is increasing endemicty and co-circulation of the 4 Dengue serotypes.</td>
<td>Incidence of DHF is only 1 in 14,000 with primary Dengue infections but 1 in 90 with secondary Dengue infections.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• fever, chills, headache, transient maculopapular rash, and Faget sign over the first two days and</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Then anorexia, vomiting, and respiratory symptoms for days two to six.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late phase following:</td>
<td>Dengue Fever</td>
<td>Dengue Fever</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• defervescence results in fever, limb/face rash, lymphadenopathy, and minor hemorrhages.</td>
<td>Flavivirus; vector = mosquito; reservoir = primates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Labs show leuko/neutro/thrombocytopenia.</td>
<td>Due to increased vascular permeability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>There are no fatalities.</td>
<td>Incidence of DHF is only 1 in 14,000 with primary Dengue infections but 1 in 90 with secondary Dengue infections.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DHF</td>
<td>DHF can progress (30%) to Dengue Shock Syndrome (DSS), defined as DHF with hypotension, circulatory failure and shock.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Dengue fever</td>
<td>Treatment with supportive measures can lower the case fatality rate of DHF from &gt;10% to &lt;1%.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• with thrombocytopenia and hemoconcentration (from diffuse capillary leakage and major hemorrhages).</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>