Viral Diseases
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Outline
- Herpesviruses
- Respiratory Viruses, including influenza
- Measles, Parvovirus B19, Rabies

Viral hepatitis, viral gastroenteritis, HIV covered elsewhere

Basic virology
- Basic Components
  - Genetic material – viral nucleic acid
    - DNA or RNA
  - Protein coat - capsid
    - Have symmetry: helical or icosahedral
  - +/- lipid envelope

Human Herpesviruses

<table>
<thead>
<tr>
<th>Common name</th>
<th>Latent site</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV-1 (herpes simplex)</td>
<td>Sensory neurons (trigeminal)</td>
</tr>
<tr>
<td>HSV-2</td>
<td>Sensory neurons (sacral)</td>
</tr>
<tr>
<td>VZV (varicella zoster)</td>
<td>Sensory nerve ganglia</td>
</tr>
<tr>
<td>CMV (cytomegalovirus)</td>
<td>Many cell types</td>
</tr>
<tr>
<td>EBV (Epstein-Barr virus)</td>
<td>B cells</td>
</tr>
<tr>
<td>HHV-6, roseola</td>
<td>T cells (CD4+)</td>
</tr>
<tr>
<td>HHV-7</td>
<td>T cells (CD4+)</td>
</tr>
<tr>
<td>HHV-8, Kaposi’s sarcoma assoc.</td>
<td>Monocytes, B lymphocytes, dendritic and endothelial cells</td>
</tr>
</tbody>
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Herpes Simplex Virus
- HSV-1: 90% positive by 5th decade (20-25% sx)
- HSV-2: 22% of general population (10-20% sx)
- Predominantly mucosal transmission, occasionally other sites with abraded skin (e.g. whitlow)

- Primary infection, reactivation
- Disease indistinguishable, but reactivation rates differ
- Gingivostomatitis, pharyngitis → orolabial disease
- Cervicitis, proctitis, urethritis, mucosal lesions
- Clinical vs subclinical (33% vs 67%)

Herpetic whitlow

Slide courtesy of Jay Steinberg, MD
Other sites

- Anywhere on the skin.....
  - Eczema herpeticum
  - HSV-associated erythema multiforme
- Esophagitis
- Retinitis
- Other viscera.... (liver)
- Neonatal disease

Antiviral therapy

- Acyclovir
- Valacyclovir
- Famciclovir

<table>
<thead>
<tr>
<th>Drug monophosphate</th>
<th>Herpesvirus Thymidine Kinase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug diphosphate</td>
<td>Cellular enzymes</td>
</tr>
<tr>
<td>Drug triphosphate</td>
<td>Cellular enzymes</td>
</tr>
<tr>
<td>Viral DNA polymerase</td>
<td>Foscarinet</td>
</tr>
</tbody>
</table>

Diagnosis

- HSV-1 and 2 type specific antibodies
- Tzanck prep (multinucleated giant cells)
- Direct fluorescent antibody (DFA)
- Culture
- PCR

70 yo male awoke from a nap, c/o HA, walked into the kitchen, poured cereal on the kitchen table, poured milk on the cereal, took the car keys and drove the car through the garage door. VS normal except for a T of 102. No papilledema, no skin lesions. Ox2. Dysarthric speech. Nl exam except min LUE weakness. Head CT w/contrast normal. CSF 20 WBC (no polys), prot 80, glu 54, gm stain neg. Your next step is:

1) start Vancomycin, ceftriaxone
2) start ampicillin
3) start high dose acyclovir and add an HSV PCR to the CSF labs
4) order an MRI
5) all of the above

HSV encephalitis

- Most common identified cause of viral encephalitis (10-20%) (and one of few that has a specific rx)
- Most commonly HSV-1
- Fever, focal symptoms, encephalitis

Diagnosis

- EEG, MRI with temporal lobe focus
- HSV PCR CSF
- Brain biopsy
- IV ACV (high dose) x 21 d
- Recovery in < 40%

CNS Infection with HSV

- Aseptic meningitis
  - Classically after episode of primary genital herpes, usually benign and self-limited
  - Usually HSV-2
  - Lacks encephalitis
70 yo male awoke from a nap, c/o HA, walked into the kitchen, poured cereal on the kitchen table and not a bowl, poured milk on the cereal, took the car keys and drove the car through the garage door.
VS normal except for a T of 102.
No papilledema, no skin lesions. Ox2. Dysarthric speech. NL exam except min LUE weakness.
HCT w/contrast normal.
CSF 20 WBC (no polys), prot 80, glu 54, gm stain neg.
Your next step is:
1) start Vancomycin, ceftriaxone
2) start ampicillin
3) start high dose acyclovir and add an HSV PCR to the CSF labs
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Varicella Zoster Virus (VZV)
- 1° infection – chicken pox
  - Varicella
  - > 15x † mortality for adults
  - Lesions (dew drop on rose petal)
    - Multiple stages: papules, vesicles, scabs
    - Trunk and spreads centripetally
  - Complications: 2° bacterial infection, pneumonitis, cerebellar ataxia

Herpes Zoster (VZV)
- Reactivation disease: shingles
  - Approximately 30% will develop over lifetime
    - Age, immune status
  - Dermatomal distribution
    - HZ opthalmicus: CN V (trigeminal nerve)
    - Ramsey Hunt: CN VII, VIII (geniculate ganglion)
    - External auditory meatus, ant 2/3 tongue, Bell’s palsy
  - Complications
    - Post herpetic neuralgia
    - HZO ->granulomatous angiitis (stroke syndrome)
  - Dx: classical syndrome, culture, DFA, PCR

Therapy / Prevention: VZV
- Antiviral therapy
  - Same active agents as for HSV
  - 7 days therapy within 72 hours rash onset can hasten rash healing, reduce severity of acute pain and decrease viral shedding
- Vaccination (Oka strain, live attenuated)
  - Contraindicated in pregnancy, significant immunosuppression, immunodeficiencies
Immunization for VZV

- Varivax (for Varicella)
  - 1350 plaque forming units
  - Adults who lack immunity or clinical history of varicella
  - 2 doses
  - 6-47% get vaccine-induced rash
    - Increased risk if immunocompromised

- Zostavax (for Herpes zoster)
  - 19,400 plaque forming units
  - Adults > age 60 y regardless of prior episode
  - Approved for age > 50 y but not endorsed
  - No need to check immune status prior to administration
  - 1 dose
    - Zoster by 51%, post-herpetic neuralgia by 67%, efficacy increases with “younger” (<70) elderly.
    - Rash less common than with Varivax

The exposed HCW

35 yo nurse is exposed to a patient with chicken pox. As she had no history of disease, VZV serologies were sent and were negative. At day 7 she is asymptomatic. What do you do?

- Valacyclovir x 3 weeks
- Move her to care for non-immunocompromised patients and send her on furlough if she develops clinical illness
- Work furlough for days 10-21 post exposure
- Vaccinate her with Varivax to prevent infection from this exposure
- Administer VZIG

19 yo M presents with rash and fever. Ill for 3 weeks with flu-like symptoms, including fever, fatigue, pharyngitis and myalgias.

UCC prescribed amoxicillin for a possible strep throat.

PE: T 103. Pharyngeal exudate. Enlarged tender AC and PCNs. Fullness in his LUQ and mild tenderness at his hepatic edge. Diffuse maculopapular rash.

Mono-like syndromes

- Epstein Barr virus (acute mononucleosis)
- Cytomegalovirus (CMV mono)
- Acute Toxoplasmosis
- Acute viral hepatitis
- Acute HIV infection
- Strep throat

<table>
<thead>
<tr>
<th>CMV</th>
<th>EBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical Lymphocytosis</td>
<td>+</td>
</tr>
<tr>
<td>Heterophile (monospot)</td>
<td>neg</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>+/-</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>+/-</td>
</tr>
<tr>
<td>Prolonged fever</td>
<td>+++</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>rare</td>
</tr>
<tr>
<td>Rash</td>
<td>rare</td>
</tr>
<tr>
<td>Elevated transaminases</td>
<td>+</td>
</tr>
</tbody>
</table>

Complications
*indications for corticosteroids

- Splenic rupture, AIHA*, thrombocytopenia*, airway obstruction*, encephalitis

*indications for corticosteroids

- Splenic rupture, AIHA*, thrombocytopenia*, airway obstruction*, encephalitis
19 yo M presents with rash and fever. He has been ill for 3 weeks with flu-like symptoms, including fever, fatigue, pharyngitis and myalgias. He saw an urgent care physician who prescribed amoxicillin for a possible strep throat. On exam, he is febrile to 103. He has enlarged and tender anterior and posterior cervical LN. He has a pharyngeal exudate. There is fullness in his LUQ and mild tenderness at his hepatic edge. He has a maculopapular rash diffusely.

**Work-up:**
- Monospot or EBV serology – VCA IgM + EBNA neg
- CMV IgG + IgM, Toxo IgM
- HIV RNA PCR and HIV Ag/Ab test, Strep culture

**Most suspicious:** EBV mono
- spleen, exudates, amox-related rash?
- abstain from contact sports

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**CMV: Immunocompromised host**
- Transplant recipients
- Transmission from donor vs. reactivation
- Onset delayed until d/c of prophylaxis – 3-6 month window
- HIV-infected patients
- CD4 < 50 at greatest risk
- Manifestations
  - Retinitis
  - Esophagitis, Gastritis, Colitis
  - Bone marrow suppression
  - Pneumonitis
  - Polyradiculopathy
  - Ventriculitis, Meningoencephalitis
- Dx: CMV PCR, tissue biopsy (pneumonitis, GI disease)

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**EBV: neoplastic potential**
- Integrates into host genome, can transform cells
  - African Burkitt’s lymphoma
  - Nasopharyngeal carcinoma
  - Primary CNS lymphoma (AIDS)
  - B cell lymphomas
  - Post transplant lymphoproliferative disorder (PTLD)

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**HHV-8 (KSHV)**
- Kaposi’s sarcoma
- Multicentric Castleman’s disease
- Primary effusion lymphoma

**Transforms cells, immunocompromised pts, most commonly HIV-infected**

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**Respiratory Viruses**

<table>
<thead>
<tr>
<th>Virus</th>
<th>Clinical Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinovirus</td>
<td>Upper respiratory infection (common cold, pharyngitis)</td>
</tr>
<tr>
<td>Parainfluenza</td>
<td>pharyngitis, croup / tracheobronchitis, bronchiolitis</td>
</tr>
<tr>
<td>virus</td>
<td>Immunocompromised: pneumonia</td>
</tr>
<tr>
<td>Respiratory</td>
<td>croup / tracheobronchitis, bronchiolitis, pneumonia (extremes of age, immunocompromised)</td>
</tr>
<tr>
<td>Syncytial Virus</td>
<td>(RSV)</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>URI (longer fever), pharyngoconjunctival fever, hemorrhagic cystitis. Pneumonia in immunocompromised.</td>
</tr>
<tr>
<td>Metapneumovirus</td>
<td>Respiratory tract infection, more severe and LRTI in very young and old</td>
</tr>
</tbody>
</table>
Influenza

- A and B
- Influenza A described by types of 2 of 8 genes
  - Hemagglutinin (HA)
  - Neuraminidase (NA)
- Denoted as HxNx

Influenza-like Illness (ILI)

- Abrupt onset fevers, chills, HA, myalgias, malaise, anorexia, eye pain
- Fever: 100-104°F, mean 3 days
- Dry cough, pharyngeal pain, clear rhinorrhea overshadowed by systemic sx
- Abdominal pain, diarrhea
- Complications: viral pneumonia, bacterial pneumonia (S. pneumoniae, H. flu, S. aureus), rhabdomyolysis, CNS: (encephalitis, Guillian Barre Syndrome)
- Dx: Rapid test, DFA, culture, PCR

Antiviral therapies: influenza

- Amantadine, rimantadine
  - NOT active against Influenza B
  - Resistance developing, H3N2 now resistant
- Neuraminidase Inhibitors
  - Oseltamivir (Tamiflu), Zanamivir (Relenza), Peramivir (Rapivab) – IV only
  - Activity against Influenza A and B
  - Pre-2009 H1N1 with significant resistance to oseltamivir
  - Current H1N1 susceptible to oseltamivir (some resistance) and zanamivir

Influenza: Immunization

- Vaccination is indicated in ALL PERSONS > 6 mos
- High risk
  - Children < 5, especially < 2 yo
  - Pregnant women
  - Adults age 65 or older
  - Those with chronic health conditions
  - BMI > 40
  - < 19 yo on long term ASA therapy
- Focus on contacts of the above groups also
- Options:
  - Inactivated tetravalent influenza virus vaccine
  - Inactivated high dose tetravalent vaccine for age > 65y
  - Live attenuated vaccine (nasal spray, Flumist) (ages 2-49 yrs, nonpregnant)

Childhood Illnesses

<table>
<thead>
<tr>
<th>First disease</th>
<th>Measles (Rubeola)</th>
</tr>
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<tbody>
<tr>
<td>Second disease</td>
<td>Scarlet fever</td>
</tr>
<tr>
<td>Third disease</td>
<td>Rubella (German measles)</td>
</tr>
<tr>
<td>Fourth disease</td>
<td>??</td>
</tr>
<tr>
<td>Fifth disease</td>
<td>Parvovirus B19 (erythema infectiosum)</td>
</tr>
<tr>
<td>Sixth disease</td>
<td>Roseola (exanthem subitum): HHV-6</td>
</tr>
</tbody>
</table>

Measles/Rubeola virus: A reemerging infection

- 2014 saw 668 cases, highest since 1994
- Back down to 189 in 2015
- 23 outbreaks, largest with 383 cases in Amish
- 90% associated with importation
- 86% unvaccinated or unknown status (2011)

One hospital outbreak in Arizona – 2011
14 cases, 7195 contact investigations among HCW and cost $800,000
Measles / Rubeola virus

- Prodromal phase: fever > 101, malaise, cough, coryza, conjunctivitis
- Koplik’s spots on mucous membranes with later sloughing
- Rash lasting >3 days beginning on face/head to trunk, extremities last including palms and soles
- 7-10 day course
- Complications: pneumonia, CNS (encephalitis)
- Dx: Measles-specific IgM or Measles RNA PCR by NP or throat swab

Parvovirus B19

- Classic Erythema Infectiosum
  - Fever, coryza, HA, nausea, diarrhea
  - Rash 48 hrs to 5 days later, “slapped cheek”
  - Second stage rash: maculopapular exanthem on trunk, extremities
- Complications (more common in adults)
  - Symmetric arthritis, small joints, often prolonged, can mimic RA
  - Transient Aplastic Crisis
  - Pure Red Cell Aplasia (immunocompromised)
  - Giant pronormoblasts in marrow
  - Hydrops fetalis
  - Dx: PCR, serologies

Rabies – post exposure prophylaxis

- A medical urgency, not an emergency
- Assess exposure – bite vs nonbite
  - Most exposures are wild carnivores or bats
  - The bat and the sleeping child…
- Immediate wound care
- Observe the animal for 10 days or test
- Passive Ab administration (Human Rabies Immunoglobulin) for previously unvaccinated, as much as possible into and around wound
- 4 IM doses of rabies vaccine (days 0, 3, 7, 14); 2 doses for previously vaccinated.

Cases of rabies among wildlife in the United States, by year and species, 1983 to 2014

There are a lot of other viruses, but……

Remember immunization as an important preventive measure

Good luck!