The Respiratory Viruses

Influenza, RSV, and Rhinoviruses

- Viruses that cause disease in the respiratory tract
- Some of the most common causes of symptomatic human infections
- Viral upper respiratory tract infections alone account for 26 million days of school absence and 23 million days of work absence in the US EACH YEAR!
Influenza virus

The Virus

- Orthomyxovirus Family
  - Influenza A, B, and C
- Enveloped viruses with single strand, negative sense RNA genomes
- RNA is segmented
  - 8 segments in influenza A and B
  - 7 segments in influenza C
Influenza Virus Proteins

**PB1, PB2, PA**: polymerase proteins

**NA**: neuraminidase protein - catalyzes removal of sialic acid residues and permits movement through mucous

**HA**: hemagglutinin - binds to sialic residues allowing viral attachment, mediates fusion of viral membrane with endosome

**NP**: nucleocapsid protein

**M**: M1 - matrix protein - provides rigidity
  M2 - ion channel present only in flu A

**NS**: nonstructural proteins

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Influenza A Virus Replication
Antigenic Drift and Shift

• Two properties of the HA and NA proteins
  – Ability to mutate while preserving function
  – Segmented genome allows for reassortment
• Drift- why the vaccine needs to change every year and you’re never fully immune to flu
• Shift- why we get pandemics

• Drift
  – Ongoing mutations within RNA encoding HA and NA proteins resulting in amino acid changes which decrease immune recognition
  – Seen in all types of flu, but influenza A has the greatest rate of change
  – Drift is responsible for the year to year variations in flu outbreaks
Antigenic Drift

Pneumonia and Influenza Mortality for 122 U.S. Cities
Week Ending 02/15/03
• **Shift**

  – Appearance of a new viral subtype with novel HA and/or NA due to reassortment of circulating human strains with strains of animal origin

  – Occurs in nature only with influenza A
Influenza nomenclature

- Strains named for:
  - Type of flu (A or B)
  - Place of initial isolation
  - Strain designation
  - Year of isolation
  - HA and NA subtype
- Example: A/Texas/1/77/H3N2

Deadly consequences of shift

- 1918- “Spanish” flu H1N1; mortality 20-40 million worldwide; 500,000 US
- 1957- “Asian” flu H2N2; mortality 70,000 US
- 1968- “Hong Kong” flu H3N2; mortality 30,000 US
  - Modern circulating strain
  - Lower mortality than previous pandemics
    - Only HA changed
    - Similar strain circulated in 1890’s- elderly had some protection
Clinical Manifestations

- Classical
  - fever- up to 106!
  - chills
  - headache
  - myalgia
  - arthralgia
  - dry cough
  - nasal discharge

- Acute phase usually 4-8 days followed by convalescence of 1-2 weeks
Complications

• Primary- viral (influenza) pneumonia
  • otherwise healthy adults
  • rapid progression of fever, cough, cyanosis following onset of flu sx’s
  • CXR with bilateral ISIF, ABG with hypoxia

Secondary- bacterial

• Classic flu followed by improvement then sx’s of pneumonia
• Pneumococcus most common; also see staph aureus and H.flu
Complications (cont.)

- Myositis
  - Most common in children after flu B infection
  - Can prevent walking: affects gastrocs and soleus
- Neurologic
  - GBS (controversial)
  - transverse myelitis and encephalitis
- Reye syndrome

Diagnosis

- Virus isolation and culture
- Antigen Tests
  - Performed directly on patient samples
  - Rapid
  - EIA for flu A
  - DFA for flu B
- Hexaplex
  - RT PCR for flu A and B, RSV, parainfluenza
  - Sens 100%; spec 98%
Influenza vaccine

• Major public health intervention for preventing spread of influenza
• Currently use inactivated viruses circulating during the previous influenza season
• This year includes
  – H1N1, A/New Caledonia/20/99/H1N1
  – H3N2, A/Panama/2007/99/H3N2
  – B/Hong Kong/330/2001-like virus strain*
• Generally 50-80% protective
  – Less efficacious in the elderly but decreases hospitalization by 70% and death by 80%

Vaccine: who should get it

• Any individual > 6mos who is at risk for complications of influenza
  – chronic cardiac, pulmonary (including asthma), renal disease, diabetes, hemoglobinopathies, immunosuppression
• Residents of nursing homes
• Individuals who care for high-risk patients
• Healthy people over age 50*
• Children between 6 mos and 2 years*

* New ACIP recommendation
Treatment

• Amantidine/rimantidine
  – Symmetric amines
  – Inhibit viral uncoating by interfering with M2 protein
  – Approved for both treatment and prevention
  – If given within 48 hours of onset of symptoms, will decrease duration of illness by one day

• Neuraminidase inhibitors
  – zanamivir and oseltamivir
  – Mimic sialic acid residues blocking neuraminidase
  – Efficacious against both influenza A and B
Respiratory Syncytial Virus

- Paramyxovirus family
  - Paramyxovirus- parainfluenza viruses 1 and 3
  - Rubulavirus- mumps and parainfluenza type 2 & 4
  - Morbillivirus- measles
  - Pneumovirus- RSV
- Grows well in human cell lines and forms characteristic syncytia
- Two groups of isolates have been identified and are designated A and B- circulate simultaneously during outbreaks

Microbiology
General Features of Paramyxoviruses

- Enveloped- lipid bilayer obtained from host cell
- Genome- single-stranded negative sense RNA
- 10 Viral proteins
  - HN/H/G- attachment proteins
  - F- fusion protein
  - M- matrix protein
  - N- nucleoprotein
  - P/L- polymerase proteins
  - NS1/NS2- nonstructural proteins

Paramyxovirus Replication
• **Pathogenesis**
  – Inoculation occurs through the nose or eyes and spreads through respiratory epithelium
  – Viral replication in the peribronchiolar tissues leads to edema, proliferation and necrosis of the bronchioles. Collections of sloughed epithelial cells leads to obstruction of small bronchioles and air trapping.
  – Pneumonia, either primary RSV or secondary bacterial may also develop. Pathology of RSV pneumonia shows multinucleated giant cells.

Multinucleated giant cell formation in RSV pneumonia
• **Epidemiology**
  - Ubiquitous
  - Virtually all children infected by age 2
  - Severe illness most common in young infants
    • Boys are more likely to have serious illness than girls
    • Lower socioeconomic background correlates with worse disease
  • Major cause of lower respiratory tract disease in young children

Striking seasonality in temperate climates
  • Peaks in Winter
  • Summer respite
- Clinical Features- hallmark is bronchiolitis
  - Primary infection is usually symptomatic and lasts 7-21 days
    - Starts as URI with congestion, sore throat, fever
    - Cough deepens and becomes more prominent
    - LRT involvement heralded by increased respiratory rate and intercostal muscle retraction
    - Hospitalization rates can approach 40% in young infants
  - Reinfection in adults and older children
    - Rarely asymptomatic
    - Generally resembles a severe cold
• **Immunity**
  – Incomplete, reinfections are common
  – Cell-mediated immunity, as opposed to humoral, is important in protecting against severe disease.
  – Humoral immunity, in the absence of cell-mediated immunity, may predispose to more serious disease.
    – Vaccine experience

• **High risk groups**
  – Very young infants (<6 weeks) especially preemies
  – Older adults
    • Mortality from RSV pneumonia can approach 20% in this group
  – Children with bronchopulmonary dysplasia and congenital heart disease
  – Immunocompromised individuals
    • SCID
    • Transplant recipients
    • Hematologic malignancies
• Diagnosis
  – Clinical, during outbreak
  – Virus isolation and growth
  – Rapid diagnostic techniques
    • Immunofluoresence
    • EIA/RIA
    • PCR
  – Serology

• Treatment
  – Supportive care
  – Bronchodilators
    • Studies suggest inhaled epinephrine more efficacious than inhaled β-agonists
  – Ribavirin
    • Aerosol
    • High-risk individuals only
• Prevention
  – Gown and glove isolation in hospital
  – RSV immune globulin (RespiGam®) and palivizumab (Synagis®)- AAP recommendations
    • Children < 2 years with bronchopulmonary dysplasia and oxygen therapy in the 6 months prior to RSV season
    • Infants with gestational age < 32 weeks
    • Not approved for children with congenital heart disease
    • Being used anecdotally in immunocompromised individuals
  – No vaccine yet

Rhinoviruses

• Most common cause of the common cold
• Cause 30% of all upper respiratory infections
• Over 110 different serotypes- prospects for a vaccine are pretty dismal
### Viruses associated with the common cold

<table>
<thead>
<tr>
<th>Virus Group</th>
<th>Antigenic Types</th>
<th>Percentage of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinoviruses</td>
<td>100 types and 2 subtypes</td>
<td>30-40%</td>
</tr>
<tr>
<td>Coronavirus</td>
<td>3 or more</td>
<td>≥ 10</td>
</tr>
<tr>
<td>Parainfluenza viruses</td>
<td>4 types</td>
<td></td>
</tr>
<tr>
<td>Respiratory syncytial virus</td>
<td>2 types</td>
<td></td>
</tr>
<tr>
<td>Influenza virus</td>
<td>3 types</td>
<td></td>
</tr>
<tr>
<td>Adenovirus</td>
<td>47 types</td>
<td>10-15</td>
</tr>
<tr>
<td>Other viruses</td>
<td></td>
<td>30-35</td>
</tr>
</tbody>
</table>

Adapted from Mandell, 5th edition

### Molecular Biology

- Members of the picornavirus family
- Also includes enteroviruses and hepatitis A
- Small, non-enveloped, single stranded RNA viruses
- Grow best at 33°C - temperature of the nose
- Most use ICAM-1 as receptor
• Enter through the nasal or ophthalmic mucosa
• Infect a small number of epithelial cells
• NO viremia; not cytolytic
• Symptoms most likely due to host immune response- especially IL-8

Epidemiology

• Kids are the reservoir for rhinoviruses and have the most symptomatic infections
• Worldwide distribution
• Seasonal pattern in temperate climates
  – Seen in early fall and spring
  – Less common in winter and summer
Clinical Manifestations

- You all know the symptoms
- Rhinovirus colds rarely have fever associated with them
- Most colds last about a week
- A non-productive cough following a cold can last up to 3 weeks- this is NOT bronchitis
Complications

• Sinusitis
  – 87% of individuals with colds will have CT evidence of sinusitis - this is mostly viral!
• Exacerbation of chronic bronchitis and asthma
• Distinguishing normal post-cold symptoms from true bacterial superinfection is tough

Treatment

• Tincture of time
• Symptomatic relief
  – Decongestants
  – Antihistamines
  – NSAIDs
• Randomized, controlled clinical trials have failed to show a benefit from vitamin C, zinc or echinacea
• Virus specific therapies not practically useful
DO NOT GIVE ANTIBIOTICS FOR THE COMMON COLD

Myths of the Common Cold

- susceptibility to colds requires a weakened immune system.
- Central heating dries the mucus membranes of the nose and makes a person more susceptible to catching a cold.
- Becoming cold or chilled leads to catching a cold.
- Having cold symptoms is good for you because they help you get over a cold, therefore you should not treat a cold.
- Drinking milk causes increased nasal mucus during a cold.
- You should feed a cold (and starve a fever).

* From J. Gwaltney and F. Hayden’s common cold website
Lifelong Lessons

• You can’t get flu from the flu vaccine
• You can’t get worse flu because you were vaccinated
• You don’t get a cold because you’re cold/not wearing a hat/wet
• There is no moral or immunologic superiority associated with not getting colds
• Stand firm- Don’t give out antibiotics for colds (or any other viral infections)