The Respiratory Viruses

Influenza, RSV, and Rhinoviruses

- Viruses that gain access to the body through 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**

(From RDolin Am Fam Phys 14:74, 1976.)

**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
Antigenic Drift and Shift

• 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
• **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
From Shift to Pandemic

- Need a virus with HA and/or NA to which human population has little immunity
- Virus must replicate well in humans
- Virus must be transmissible from human to human
Pandemics

• 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

The Next Pandemic: H5N1?

• Why is this one different?
  – Kills birds and humans
    • Highly cleavable hemagglutinin
    • Enhanced replication
    • Increased resistance to IFN and TNF-α
    • Causes macrophages to produce more cytokines
  – Little innate human immunity
• Other possibilities
  – H9N1
  – H2N2
Will this be another 1918?

• Pandemic preparedness
• Better health care
• Vaccines
  – Standard H5N1 vaccine disappointing
  – Much better when given with adjuvants
  – New “pan-influenza” vaccines
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
- Many people are asymptomatic

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
  A/New Caledonia/20/1999 (H1N1)-like
  A/Wisconsin/67/2005 (H3N2)-like, and
  B/Malaysia/2506/2004-like viruses.
- Generally 50-80% protective
  - Less efficacious in the elderly but decreases hospitalization by 70% and death by 80%
Flumist

- Live attenuated flu vaccine licensed for use in healthy individuals aged 5-49
- Efficacious, some concern about viral shedding, useful for contacts of at-risk individuals (as long as they’re not very immunocompromised)
- Trials underway in children 6-23 months

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
  - Children aged 6 mos to 59 months
- Residents of nursing homes
- Household contacts of infants < 6 mos
- Individuals who care for high-risk patients
- Healthy people over age 50*

* New ACIP recommendation
Most important groups to vaccinate

- all children aged 6–23 months;
- adults aged 65 years and older;
- persons aged 2–64 years with underlying chronic medical conditions;
- all women who will be pregnant during the influenza season;
- residents of nursing homes and long-term care facilities;
- children aged 6 months–18 years on chronic aspirin therapy;
- health-care workers involved in direct patient care; and
- out-of-home caregivers and household contacts of children aged <6 months

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**
  - Genome encodes 10 viral proteins
    - F, G, SH- glycosylated surface proteins that mediate attachment of the virus to the host cell and fusion of the viral and cell membranes
    - N, L, and P- associate with RNA genome and form nucleocapsid and polymerase complex
    - M and M2- matrix proteins
    - NS1 and NS2 are non-structural proteins
  - 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

General Features of Paramyxoviruses

- Enveloped- lipid bilayer obtained from host cell
- Genome- single-stranded negative sense RNA
- Viral proteins
  - HN/H/G- attachment proteins
  - F- fusion protein
  - M- matrix protein
  - N- nucleoprotein
  - P/L- polymerase proteins
• 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
Striking seasonality in temperate climates
- Peaks in January
- Summer respite

![Image of graph showing percentage of positive specimens for respiratory syncytial virus, with peaks in January and summer respite.]

*Laboratory group mean, smoothed using 5-week moving average.

• Clinical Features
  - 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.

• 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
    • Immunofluorescence
    • 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</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
Transmission

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 bacterial 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 or Echinacea
- Virus specific therapies not practically useful
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)
DO NOT GIVE ANTIBIOTICS FOR THE COMMON COLD