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!

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 |

Influenza virus

(From RDavis Am Fam Phys 44: 74, 1991.)
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

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

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

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

Nations With Confirmed Cases H5N1 Avian Influenza (July 7, 2006)
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

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

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%

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

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

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
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.

**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

**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

**Striking seasonality in temperate climates**
- Peaks in January
- Summer respite

![Multinucleated giant cell formation in RSV pneumonia](image)
• **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

  • **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

• **Diagnosis**
  – Clinical, during outbreak
  – Virus isolation and growth
  – Rapid diagnostic techniques
    • Immunofluorescence
    • EIA/RIA
    • PCR
  – Serology

• **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
<table>
<thead>
<tr>
<th>Virus Group</th>
<th>Antigenic Types</th>
<th>Percentage of cases</th>
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<tr>
<td>Rhinoviruses</td>
<td>100 types and 2 subtypes</td>
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<tr>
<td>Coronaviruses</td>
<td>3 or more</td>
<td>&gt;10</td>
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<td>Parainfluenza virus</td>
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<tr>
<td>Respiratory syncytial virus</td>
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<tr>
<td>Adenovirus</td>
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<td>10-15</td>
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<tr>
<td>Other viruses</td>
<td></td>
<td>30-35</td>
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</tbody>
</table>

Adapted from Mandell, 5th edition

**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

**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

**Transmission**

- 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

**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

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)

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

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