Pediatric Respiratory Tract Infections: RSV and Influenza

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Common Respiratory Viruses

- Influenza
- Respiratory syncytial virus
- Adenovirus
- Parainfluenza virus
- Human metapneumovirus
Viral Etiology of Bronchiolitis

2,207 hospitalized patients < 2 yr of age, 2007-2010

- RSV 73%
- Human rhinoviruses 26%
- Adenoviruses 8%
- Coronaviruses 7%
- Human metapneumoviruses 7%
- Enteroviruses (EV D68?) 5%
- Parainfluenza viruses 1,2,3 3%
- Influenza A, B 1%
- Co-infection 32%

Arch Pediatr Adolesc Med 2012;166(8);700
Seasonality of Respiratory Viruses

- Human Metapneumovirus
- Respiratory Syncytial Virus
- Influenzavirus
- Parainfluenza Virus
- Adenovirus
RESPIRATORY Syncytial Virus (RSV)

- Paramyxovirus
- 2 subtypes: A and B
- Subtypes may circulate concurrently
- Some strains more virulent
RESPIRATORY Syncytial Virus

- Annual RSV epidemics occur during winter/early spring in temperate climates
- Epidemics typically last 4-5 months
- Viral shedding usually lasts 3-8 days
  - Can be prolonged in young infants or immunocompromised
- Incubation period: 2-8 days (usually 5 days)
RESPIRATORY Syncytial Virus

• Initial infection inevitable during the first 2-3 years of life

• Infections typically symptomatic
  – ~60% of primary infections confined to upper respiratory tract
  – ~40% of primary infections result in lower respiratory tract disease (bronchiolitis, pneumonia)
RESPIRATORY Syncytial Virus

- Re-infection is common in children & adults
- Most re-infections are limited to the upper respiratory tract ("colds")
- ~1% of children infected with RSV require hospitalization (RSV hospitalizations annually in USA = ~90,000-100,000 *JAMA Oct 1999)
  - ~500 deaths/year due to RSV *J Infect Dis Jan 2001
RSV Epidemiology

• Droplet, fomite transmission
• Primary infection inevitable in first 2 years
• Reinfection common
• Annual winter epidemics
• Small number hospitalized overall
• Viral shedding 3-8 days, sometimes weeks though in compromised host
RSV Clinical manifestations

- Bronchiolitis and pneumonia
- Premies and very young-sepsis like illness, apnea
- Older pts-URI, asthma exaserbation
- Common cause of pneumonia in the elderly
Pathology of RSV Bronchiolitis
Risk factors for severe RSV disease

• Cyanotic or complex cardiac disease especially with pulmonary hypertension
• BPD or other chronic lung disease
• Prematurity?
• Immunodeficiency
• Neuromuscular disease, unprotected airway
RSV: Burden of Disease

• All ages
  – RSV hospitalization rate 55/100,000
  – Influenza hospitalization rate 64/100,000

• Infants
  – RSV hospitalization rate 2.3/100
  – Influenza hospitalization rate 0.15/100

• Elderly
  – RSV deaths annually 14,000
  – Influenza deaths annually 3,000 to 49,000

• Globally
  – RSV causes 66,000 to 199,000 deaths annually
Trends in Bronchiolitis Hospitalizations in United States 2000-2009

Incidence Rates of Bronchiolitis Hospitalizations per 1000 person-years

- Bronchiolitis as primary diagnosis, age < 1 year and no high risk condition
  - Age 0–11 mo: 31.3 → 27.1 → 24.6
  - Age 12–23 mo: 4.7 → 5.3

- All bronchiolitis
  - 2000: 17.9
  - 2003: 16.9
  - 2006: 16.4
  - 2009: 14.9

- No high-risk condition
  - 2000: 13.8
  - 2003: 14.9
  - 2006: 13.8
  - 2009: 12.5

Trends in Bronchiolitis Hospitalization, United States, 2000-2009

• Among children <2 yrs, bronchiolitis hospitalizations decreased from 17.9 to 14.6/1000 person years <2 yrs (17% decrease)

• Among infants <1 yr, bronchiolitis hospitalizations decreased from 27.1 to 19.2/1000 person yrs (29% decrease)

• 34% increase among children with high-risk conditions

• Estimated national charges increased from $1.34 to $1.73 billion (30% increase)

• Nationwide hospital mean charge increased from mean of $6400 to $8500 per case (33% increase)
RSV Diagnostic Testing

- Nasopharyngeal aspirates-optimal collection and transport necessary
- Viral isolation in 3-5 days
- Rapid testing-high sensitivity and specificity
- PCR is useful
Kansas City, MO RSV Epidemiology

- Diagnosis based on RSV ELISA detection
- >10 specimens with >10% positivity
- Quite reliably appears first weeks of November and gone by early May
Palivizumab-Key Points

• Humanized mouse monoclonal antibody
• Prevents entry of RSV into cells
• Monthly IM 15mg/kg gives trough serum level >40 mg/mL
• 99% ↓ in animal RSV
• Prevents 50% of admits but at a cost higher than that of admission
Goals of AAP Palivizumab Recommendations

• Target infants at highest risk for severe disease with risk factors that are most consistent and predictive

• Optimize balance of benefit and cost

• Simplify approach for providers
Cost Effectiveness of Palivizumab

- For the most cost-effective subgroup, a mean of $302,103 would be spent to prevent 1 RSV hospitalization (which cost on average $8,919)

- Palivizumab has not been shown to reduce:
  - ICU admission or deaths
“Almost all included studies that were sponsored by the industry supported the cost-effectiveness of palivizumab prophylaxis while practically all included studies that were not sponsored by the industry suggested that palivizumab was not cost-effective.”

Monoclonal antibody for reducing the risk of RSV infection in children. Cochrane Database of Systematic Reviews 2013;4, Art. No. CD006602
Influenza virus

• Orthomyxoviruses type A, B, and C
• A strains are subclassified by surface antigens: hemagglutinin (H) and neuraminidase (N)
• Antigenic shift and drift: drifts are minor variations, shifts occur only with A strains, usually every 10 years or so
Influenza Nomenclature

A / California / 7 / 2009 (H1N1)

Virus type | Geographic origin | # | Year of isolation
Hemagglutinin attaches to sialic acid on the cell

A. Binding to Sialic Acid

B. Virus Internalization

C. Uncoating and Replication
Pathogenesis

Damages Epithelial Cells
- Cellular Function Damaged

No Viremia Occurs

Symptoms Appear (1-5 days)

Viral Shedding 5 -10 Days

Acute Influenza Symptoms Resolve (~ 5 days)

Viral Pneumonia

Secondary Bacterial Pneumonia/Complications

1. CDC. Atkinson et al. Epidemiology and Prevention of Vaccine-Preventable Diseases, 1998, 221-222
Influenza epidemiology

- Winter outbreaks
- If 2 or 3 subtypes circulate, season can last 3 months
- Person to person spread, highly contagious
- Incubation period 1-3 days
- Viral shedding 7 days
Influenza epidemiology

- School age children
- 10-40% attack rate depending on “prior viral experience”
- 1% hospitalized; higher in neonates, other high risk children (hemoglobinopathies, CLD, CF, malignancies, diabetes, renal disease
Influenza Symptoms

- Headache
- Tiredness
- Fever & Chills
- Sneezing
- Runny Nose
Signs and Symptoms in Children <5 years

- Fever, rhinitis
- Pharyngitis
- Vomiting, diarrhea
- Bronchiolar-pulmonary signs

From Kilbourne ED. *Influenza*. 1987:161, with permission.
Influenza

• Pharyngitis
• Conjunctivitis
• Croup
• Pneumonia
• Sepsis like picture in young infants
• Acute myositis
• Reye syndrome
Influenza Clinical Manifestations

• Type A influenza illness typically more severe than Type B
  – Greatest number of hospitalizations and mortality occurs during type A epidemics
  – ~35,000 deaths per year

• Influenza infection typically results in:
  – 3-4 days lost work/school
  – 3-4 days bedrest
  – 5-6 days restricted activity
  – 1-2+ weeks convalescent recovery
Influenza-Associated Hospitalizations By Age Group*

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Hospitalizations Per 100,000 Person Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 4 Yrs</td>
<td>115</td>
</tr>
<tr>
<td>5 - 49 Yrs</td>
<td>22</td>
</tr>
<tr>
<td>50 - 64 Yrs</td>
<td>90</td>
</tr>
<tr>
<td>&gt; 65 Yrs</td>
<td>472</td>
</tr>
</tbody>
</table>

*Thompson, CDC, 2004, unpublished data
High Risk Groups

- Children < 5yo and > 65yo
- Chronic medical conditions
  - Respiratory including asthma
  - Cardiovascular
  - Renal
  - Hepatic
  - Hematologic
  - Neurologic or Neuromuscular

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High Risk Groups

- Immunosuppressed
- Pregnant and postpartum (2 weeks) women
- ≤18yo on chronic aspirin therapy
- American Indian/Alaskan Native
- Morbidly Obese (BMI ≥ 40)
- Residents of nursing homes and other chronic care facilities
Influenza-associated Hospitalizations per 10,000 Healthy and High Risk Persons by Age Group*

Complications

- Primary viral pneumonia
- Secondary bacterial pneumonia
- Sepsis
- Croup
- Myositis
- Toxic shock syndrome
- Myocarditis
- Neurologic- Seizures, encephalitis
Complications

• 2003-2005 study from California of severe influenza infections
• 160 patients identified
  – 85% Lower or middle respiratory tract disease
  – 5% Febrile seizures
  – 5% Multi-organ failure/sepsis
• 41% required mechanical ventilation

Louie, JK, et. al. Pediatrics 2006;117; 610-618
Severe Influenza Infections

- 2003-2004
  - 0-5: 26%
  - 6-11: 16%
  - 12-17: 13%
  - 18-23: 8%
  - 24-29: 6%
  - 30-35: 6%
  - 36-41: 4%
  - 42-47: 3%
  - 48-53: 6%
  - 54-59: 1%
  - 60-132: 20%
  - 133-216: 14%

- 2004-2005
  - 0-5: 24%
  - 6-11: 8%
  - 12-17: 6%
  - 18-23: 6%
  - 24-29: 6%
  - 30-35: 5%
  - 36-41: 3%
  - 42-47: 5%
  - 48-53: 6%
  - 54-59: 3%
  - 60-132: 6%
  - 133-216: 6%

N = 125
N = 35

Categories:
- 6-23 mo (33%)
- 2-4 y (25%)
- 5-11 y (9%)
- 12-17 y (8%)
Influenza Diagnostic Testing

• Nasopharyngeal aspirates
• Viral isolation in 2-6 days
• Rapid diagnostic testing-sensitivity 70%, specificity 96%
  – A rapid test does not exclude disease
  – PCR has better sensitivity and good specificity
2014-2015 Influenza Season

- This year on par with last big H3N2 season (2012-2013)
- Multiple concurrent circulating strains
  - H3N2 influenza A-2 different circulating viruses
    - Vaccine matched strain <<Drifted strain predominant
    - Strain not matched to vaccine-cross protection
- Heavy burden of disease
- Higher hospitalizations for those <5 years and >65 years
- Major pathogens bacterial superinfection complicating influenza include *Staphylococcus aureus*, GAS, pneumococcus
Influenza Virus Detection
CMH 2014-2015 Season

Influenza B
Influenza A
Weekly Influenza Activity Estimates Reported by State & Territorial Epidemiologists*

Week ending January 17, 2015 - Week 2

* This map indicates geographic spread & does not measure the severity of influenza activity.
Percentage of Visits for Influenza-like Illness (ILI) Reported by the U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet), Weekly National Summary, 2014-15 and Selected Previous Seasons

*There was no week 53 in the previous influenza seasons displayed above; therefore the week 53 data point for those seasons is an average of weeks 52 and 1.
Laboratory-Confirmed Influenza Hospitalizations

Preliminary rates as of Jan 17, 2015

Age Group
- 0-4 yr
- 5-17 yr
- 18-49 yr
- 50-64 yr
- 65+ yr
**Number of Influenza-Associated Pediatric Deaths**

**by Week of Death: 2011-12 season to present**

- **2011-12**
  - Number of Deaths Reported = 37

- **2012-13**
  - Number of Deaths Reported = 171

- **2013-14**
  - Number of Deaths Reported = 109

- **2014-15**
  - Number of Deaths Reported = 56
2014-2015 Influenza Vaccine

• IIVs available-IM in both trivalent (IIV3) and quadrivalent (IIV4) formulations

• IIV4 and LAIV4 contain the identical influenza strains

• Intranasal LAIV in a quadrivalent formulation (LAIV4)
  – Preference for using LAIV for healthy children 2-8 years

• Implications this year: rare H1N1; covers 3 of 4 major circulating strains, possible cross protection against drifted strain

• Estimate of VE-33%
Influenza Vaccine Doses Distributed in the United States, By Season

Graphic by CDC, data reported by influenza vaccine manufacturers and selected influenza vaccine distributors.
Influenza-treatment and prevention

• Treatment should be offered to all with severe or complicated disease (regardless of immunization status)
  – All Hospitalized children
  – Consider bacterial superinfection

• Neuraminidase inhibitors
  – Drug of choice-oseltamivir (oral)
    • Dosing available from CDC for younger children
  – Zanamivir inhaler for older children
  – Zanamivir IV compassionate use available for critically ill children
Neuraminidase allows the virus to exit the cell
## Treatment Benefit

**TABLE 1** Risk Factors Associated With Fatal Outcomes in 784 Critically Ill Cases Aged 0 to 17 Years With Laboratory-Confirmed Influenza in California, April 2009 through September 2012

<table>
<thead>
<tr>
<th>Characteristic present, n (% fatal)</th>
<th>Characteristic absent, n (% fatal)</th>
<th>Univariate</th>
<th>Multivariate</th>
<th>OR (O)</th>
<th>( \chi^2 ) P</th>
<th>OR (CI)</th>
<th>( \chi^2 ) P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuraminidase inhibitor treatment&lt;sup&gt;a&lt;/sup&gt;</td>
<td>653 (6)</td>
<td>131 (8)</td>
<td>0.7 (0.3–1.4)</td>
<td>.3</td>
<td>0.4 (0.2–0.8)</td>
<td>.02</td>
<td></td>
</tr>
<tr>
<td>Characteristics of severe disease&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>ACIP comorbid conditions for severe influenza&lt;sup&gt;a&lt;/sup&gt;</td>
<td>521 (8)</td>
<td>249 (3)</td>
<td>3.0 (1.3–6.9)</td>
<td>.005</td>
<td>2.4 (1.0–5.6)</td>
<td>.05</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>539 (8)</td>
<td>202 (2)</td>
<td>6.0 (1.9–19.7)</td>
<td>.0007</td>
<td>3.2 (0.9–11.0)</td>
<td>.06</td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>292 (16)</td>
<td>428 (0.2)</td>
<td>81.9 (11.2–597.4)</td>
<td>&lt;.0001</td>
<td>70.1 (9.5–517.3)</td>
<td>&lt;.0001</td>
<td></td>
</tr>
<tr>
<td>Secondary bacterial infection&lt;sup&gt;f&lt;/sup&gt;</td>
<td>74 (8)</td>
<td>710 (6)</td>
<td>1.4 (0.5–3.3)</td>
<td>.5</td>
<td>n/a</td>
<td>n/a</td>
<td></td>
</tr>
</tbody>
</table>

Louie JK. Pediatrics 2013;132;e1539
Treatment Benefit

Louie JK. Pediatrics 2013;132;e1539
Summary

- RSV and Influenza are important viruses circulating each winter
- RSV and Influenza cause significant morbidity
- Influenza vaccination is important and protective
- Influenza infection can be treated with oseltamivir and has been shown to reduce mortality