The Search for Effective Vaccines for Respiratory Syncytial Virus

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Objectives
- Discuss the developing data linking RSV and long-term consequences
- Understand the historical perspective on the morbidity and mortality associated with RSV vaccination
- Identify the current guideline recommendations, issued by the AAP, for the treatment of high-risk infants who present with RSV and for the management of children with bronchiolitis
- Discuss the current status of the development of anti-RSV therapies, including the results of the Phase 3 trial comparing motavizumab with palivizumab treatments in infants at high risk for serious RSV disease

RSV

What is Respiratory Syncytial Virus (RSV)?
- Negative ssRNA, enveloped virus
- 11 genes
  - 3 envelope proteins
    - F
    - G
    - SH
- Most important cause of LRTI during infancy worldwide
  - Infected small bronchioles & alveolar pneumocytes
  - Acute pulmonary dysfunction
- Pathogenesis: largely unknown
- No available vaccines

Clinical Features - RSV Bronchiolitis
- Symptoms (<3 yoa):
  - Runny nose
  - Cough
  - Fever
  - Sometimes wheezing
- Recovery 8-15d
- 25-40%
  - Bronchiolitis
  - Pneumonia
- 0.5-2%
  - Hospitalization
    - 25,000 in US
    - 500 die
  - <6 m of age

Disease Burden
- Leading cause of bronchiolitis in infants worldwide
- 64 million cases
- 160,000 deaths
- Healthcare costs: $365-$585M
- US hospitalizations: 85,000-144,000
- Mortality rates
  - Healthy: 0.005-0.02%
  - Hospitalized: 1-3%
The Cost of Pre-Term Infant RSV Infection

Table 1. Five-year trend costs.

<table>
<thead>
<tr>
<th>Year</th>
<th>Cost (2004$)</th>
<th>p-value</th>
<th>Adj. mean (95% CI)</th>
<th>p-value</th>
<th>Adj. difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>26,432</td>
<td>0.018</td>
<td>-0.891</td>
<td>-0.001</td>
<td>2.774</td>
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<tr>
<td>2005</td>
<td>31,595</td>
<td>0.001</td>
<td>-2.774</td>
<td>-0.001</td>
<td>7.168</td>
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<td>2006</td>
<td>21,341</td>
<td>0.011</td>
<td>-3.891</td>
<td>-0.001</td>
<td>4.416</td>
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<tr>
<td>2007</td>
<td>27,917</td>
<td>0.003</td>
<td>-1.981</td>
<td>-0.001</td>
<td>0.000</td>
</tr>
<tr>
<td>2008</td>
<td>23,246</td>
<td>0.002</td>
<td>-2.416</td>
<td>-0.001</td>
<td>5.474</td>
</tr>
</tbody>
</table>

*Estimated mean – presented costs based on reportable cases multiplied by following factors: 2004, 15.5% case rate of ILI; 2005, 21.2%; 2006, 13.7%; 2007, 11.2%; 2008, 15.1%. Data were adjusted for geographic and seasonality trends. *Mean and/or median difference between groups based on age group versus 2004. **RSV PCR tests performed on viral cultures.***

Diagnosis

- **Viral isolation**
  - I-5d (shell vial assay 1-26)
  - Sensitivity varies
- **Detection of viral antigens – immunoassays**
  - IF, ELISA
  - Sensitivity 53-96%
  - False positives most likely
  - Therefore CONFIRM
- **Detection of viral RNA**
  - Not as widely available
  - Very sensitive (adults)
  - Rise in serum antibodies
  - Sensitivity low
  - unreliable
  - Combination

Treatment

- **Mild**
  - Hydration
  - Acetaminophen (fever)
- **Severe**
  - Oxygen therapy &/or mechanical ventilation
  - Ribavirin aerosol
- **Immune compromised**
  - Neutralizing RSV antibody (Synagis® (palivizumab); IV) and ribavirin

* "AAP News" article

"Reducing RSV hospitalizations AAP modifies recommendations for use of palivizumab in high-risk infants, young children”

**Other Treatments**

- **β₂ agonists**
  - not recommended for routine care of first-time wheezing associated with RSV bronchiolitis
  - Elected - concern that reactive airway disease may be misdiagnosed as bronchiolitis
- **corticosteroid therapy**
  - No effect on disease severity or length of stay
  - Not recommended
Prevention

- Vaccines – not available
- Prevention
  - Neutralizing RSV antibodies (RSV-IGIV)
  - Good hygiene
    - unstable
- High risk groups
  - Premature infants (<35 wks gestation)
  - Infants with chronic lung disease (e.g. cystic fibrosis), <2 yo
  - Children with congenital heart disease
  - Immunosuppressed
  - Children with metabolic and neuromuscular disorders

RSV – Intriguing Facts

- Repeated infections throughout life
  - despite presence of serum antibodies
- Development of bronchiolitis leads to persistent wheeze/asthma?

The Neonatal Lung

- At birth - saccular
  - Humans
    - 15% alveoli
  - Rodents
    - 0% alveoli
- Neonatal development
  - Humans
    - 3yr of age
  - Rodents
    - 4-7d, alveoli
    - 10d, respiratory bronchioles

*Pictures are artistic renditions of lung development and are designed to emphasize terminal acinus development and not the entire conducting airway system


The Neonatal Immune System

Th1/Th2 Bias

Th1  Th2
Neonatal

Th1  Th2
Adult
**Th1/Th2 Bias**

- Early exposure (< 1 yr)
  - Th1
  - Th2
- Late exposure (> 1 yr)
  - Th1
  - Th2

**Age at Primary Infection Determines Secondary T-Cell Response**


**IS RSV INFECTION LINKED TO PERSISTENT WHEEZE?**

- RSV bronchiolitis & higher incidence of asthma

**RSV Bronchiolitis And Asthma?**

Normal lungs

- Viral infection
  - Weak lungs
  - Weak, asthmatic lungs

Other environmental factors

- Bad disease

**Association of RSV Bronchiolitis and Asthma**

- RSV bronchiolitis & higher incidence of asthma

**Pulmonary Dysfunction Persists Following Neonatal RSV**

- RSV Infection Schedule

11/17/2009


Other environmental factors

- Weak, asthmatic lungs

- Normal lungs

- Viral infection

- Weak lungs

- Bad disease
Evidence of a Causal Role of Winter Virus Infection during Infancy in Early Childhood Asthma

Increased Risk to Develop Asthma Associated with Infant Age at Winter Virus Peak

Timing of Infant Birth during Winter Virus Peak Predicted the Likelihood of Developing Clinically Significant Bronchiolitis

Possibilities to Explain the Relationship between Winter Virus Infection and Asthma

Possibilities to Explain the Relationship between Winter Virus Infection and Asthma

Timing of Infant Birth in Relationship to Winter Virus Peak Predicted the Likelihood of Developing Childhood Asthma
• 15-20% of all infants surviving their first RSV epidemic develop lower respiratory disease (wheeze).

**RESPIRATORY SYNCTIAL VIRUS DISEASE IN INFANTS DESPITE PRIOR ADMINISTRATION OF ANTIGENIC INACTIVATED VACCINE**

RYUN WEA RIM, JOHN G. CaNCHELA, CARL D. BLANDOY, GEOHRA PYEES, ROBERT M. CHANDOER, KEITH HINEEN, and NORMAN R. FARROR (Received for publication August 8, 1983)

- **FI-RSV + aluminum hydroxide adjuvant**
- **Administered to infants 2m-9m**
  - i.m.
  - 2 – 3 doses (1-3m apart)
- **Conducted in the absence of prior animal testing**

**PRIOR VACCINE APPROACHES**

- **FI-RSV + aluminum hydroxide adjuvant**
- Administered to infants 2m-9m
  - i.m.
  - 2 – 3 doses (1-3m apart)

- Conducted in the absence of prior animal testing

80% vaccinees required hospitalization vs 5%

Fl-RSV Vaccine

- Exacerbated disease
  - 80% vaccinees needed hospitalization (5% controls)
  - 2 deaths (31 vaccinees)
- Peribronchial inflammation
  - monocyte/macrophage
  - Eosinophils
  - $10^4$TCD$_{50}$/g lung
- Severity of illness dependent on age of vaccinee
AAP Recommendations

- Palivizumab (1998)
  - Biosynthetic humanized form of a murine monoclonal antibody to the F surface glycoprotein
  - RSV prophylaxis in high-risk infants
  - Not for treating RSV
- Eligible high-risk infants
  - Chronic lung/heart disease of prematurity (<24m)
  - Born before 32 weeks’ gestation (31wks, 56d)
  - Born 32-35 weeks’ gestation (32wks, 0d – 34wks, 6d)
  - Lives in areas of greatest risk:
    - Age ≤3m at start of RSV season
    - Born during RSV season and increased risk of exposure (decompenating <1y)
    - Considered if <3m at start of RSV season
- Initiation and termination of prophylaxis
  - 1st dose administered during the first week of November
  - 5th and last dose to be administered in March
  - RSV season - FL

*Administration of palivizumab is not advised under the updated recommendations for these infants after they reach 90 days of age

Table 3.59. Palivizumab Prophylaxis for Infants and Young Children With Chronic Lung Disease of Prematurity or Congenital Heart Disease

<table>
<thead>
<tr>
<th>Geographic Location</th>
<th>Date of First Dose for Infants</th>
<th>Date of First Dose for Young Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>bronchial Florida</td>
<td>September 15</td>
<td>November 1</td>
</tr>
<tr>
<td>North central and southeast Florida</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most other areas of the United States</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Factors to be Considered for Vaccine Development

- Immaturity of the immune system
- Must target A & B subtypes
- Incomplete immunity
- Historical context requires well established safety profile

Interventional

- Intranasal ALN-RSV01 (Alnylam Pharmaceuticals): Phase II
  - siRNA directed against the mRNA encoding the N-protein of RSV
  - Single dose reduced viral loads >10,000 fold in mice
  - Delivered using the BD Accuspray™, a device designed to deliver live attenuated intranasal vaccines to the nasopharynx without exposing the lower respiratory tract
  - Safe

- Motavizumab (MedImmune; MEDI-524): Phase III
  - Anti-RSV humanized IgG1 MAb that is 10-20 times more potent than palivizumab at neutralizing RSV in tissue culture (i.m.)
  - Suspended - 2010

- RSV Vaccine (MedImmune; MEDI-539): Phase I
  - Intranasal, recombinant, live attenuated, temperature sensitive respiratory syncytial virus (RSV) vaccine being developed, in conjunction with the National Institute of Allergy and Infectious Disease (NIAID)

- RSV/PIV Vaccine (MedImmune; MEDI-534): Phase I
  - Live attenuated, intranasal vaccine being developed for the prevention of lower respiratory tract disease in young infants that is caused by RSV and PIV3.

Clinical Trials

- Interventional
  - Intranasal ALN-RSV01 (Alnylam Pharmaceuticals): Phase II
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Motavizumab (Numax)

- Recombinant, humanized monoclonal IgG1 antibody to RSV F protein
- Production
  - In vitro affinity maturation of palivizumab (CDR)
**Directed Evolution Approach**


- Recombinant, humanized monoclonal IgG1 antibody to RSV F protein
- Production
  - In vitro affinity maturation of palivizumab (CDR)
  - Selected for binding affinity, lung biodistribution (i.m.)

**Selected for Absence of Tissue Cross-Reactivity**

**Ability to Reduce Viral Load In Vivo**


**Motavizumab vs. Palivizumab**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Motavizumab</th>
<th>Palivizumab</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSV hospitalisation, n(%)</td>
<td>46 (1.4)</td>
<td>62 (1.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Patients requiring ≥1 supplemental oxygen</td>
<td>26 (0.8)</td>
<td>43 (1.3)</td>
<td>0.038</td>
</tr>
<tr>
<td>Patients admitted to ICU</td>
<td>10 (0.3)</td>
<td>19 (0.6)</td>
<td>0.092</td>
</tr>
<tr>
<td>Patients requiring ventilation</td>
<td>2 (0.1)</td>
<td>12 (0.4)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

**Summary:**
- Rate of hospitalisation similar
- Motavizumab reduced overall illness

THANK YOU!