RSV Bronchiolitis

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Respiratory Syncytial Virus

ssRNA enveloped virus
Family *Paramyxoviridae*
Genus *Pneumovirus*
Subgroups *A* and *B*

- Fusion (F) proteins → viral penetration
- Attachment (G) proteins → viral adherence to the host cells
Epidemiology: age

- Important cause of lower respiratory disease in young infants (bronchiolitis and pneumonia)
- Peak incidence is at age 2 months*
- Most infected at least once by age 2 yrs of age and re-infection throughout life is common

Epidemiology: incidence

Central Thailand

The first year:
• 12.6/1,000 child-year, 35.8 % of all LRI

The second year:
• 5.8/1,000 child-year, 17.5 % of all LRI

Epidemiology: seasonality

- Seasonal outbreaks throughout the world*
  - **Northern hemisphere**: November to April (a peak in January or February)
  - **Southern hemisphere**: May to September (a peak in May, June or July)
  - **Tropical climates**: the rainy season (no peak)

- Thailand**
  - Rainy season, Peak August or September

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During RSV epidemic

- 45% of 1 week hospitalized infant was infect
- 40% of hospital staff was source of spreading
- Mode of transmission: large airborne particles

Risk Factors

- Low level of Ab in cord blood
- Gender (male > female)
- Birth month
- Absence of or minimal breast feeding
- Crowded living conditions
- Being a twin or triplet
- Low socioeconomic status

Severe disease in...

Study in 134 hospitalized infants of group A
131 hospitalized infants of group B

Found that severe disease relate with...

• Prematurity (odd ratio 1.84)
• Underlying medical condition (odd ratio 2.84)
• Group A RSV infection (odd ratio 3.26)
• Age younger than 3 month (odd ratio 4.39)

Pathogenesis

- Entry through mucosa of nose and eye
- Viral replication in nasopharynx
- Cell to cell spread within respiratory tract
- Attachment via G protein to respiratory epithelium
- Fusion with cell membrane - F protein
- Syncytium formation (tissue culture) with multinucleated giant cells
Pathology

- Respiratory epithelial cells and ciliated epithelial cells necrosis
- Peribrochiolar infiltration with lymphocytes and neutrophils
- Submucosal edema
- Cellular debris and fibrin form plugs within the bronchioles
- Alveoli usually normal
- Regeneration of bronchiolar epithelium after 3-4 days, cilia after 15 days
- Mucous plug - removed by macrophage
Pathophysiology

Mechanics of respiration are abnormal:

- High lung volume
- Elevate functional residual capacity
- Arterial hypoxemia from V/Q mismatch
- PaCO2 is variable
Clinical Features

Upper Respiratory Infection
- Fever
- Rhinitis
- Pharyngitis

Lower Respiratory Infection
- Bronchiolitis, Pneumonia
- Cough
- Respiratory Distress (tachypnea, retractions)
- Apnea

Adult and older child

Infant and young child
Clinical Features of Bronchiolitis

- Mild rhinorrhea, cough, low-grade fever
- Rapid respiration, chest retraction and wheezing
- 20% of patients → apnea as presenting symptom
- Associated with sudden infant death syndrome
- PE: tachypnea, tachycardia, conjunctivitis, otitis media
- Lungs: retraction, prolonged expiratory phase, wheezing
Radiologic features of RSV bronchiolitis

- Nonspecific
- Diffuse hyperinflation
- Fattening of diaphragm
- Bulging of intercostal space
Radiologic features of RSV bronchiolitis

- Atelectasis
• **Viral isolation:**
  - definite diagnosis with identification of typical plaque morphology with syncytium formation
  - 4 days to week → not practically

• **Antigen detection:**
  EIA, IF → specificity and sensitivity 80-90%

• **Antibody detection:** not useful clinically
  - maternal Ab in infants
  - sustained level of RSV-specific Ab due to recurrent infection

Redbook 2006
Diagnosis: Specimens

- **Non-intubated**: nasal wash, nasopharyngeal swab, throat swab
- **Intubated**: tracheal aspirate, bronchoalveolar lavage
- Transport in viral culture medium and on ice
- Process immediately
### TABLE 3
Sensitivity for the Detection of Different Viruses According to Specimen Type*

<table>
<thead>
<tr>
<th>Virus</th>
<th>ARIs With Virus Identified&lt;sup&gt;a&lt;/sup&gt;</th>
<th>NPA</th>
<th>NTS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>95% CI&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Sensitivity</td>
</tr>
<tr>
<td>RSV</td>
<td>72</td>
<td>97.2</td>
<td>90.3–99.7</td>
</tr>
</tbody>
</table>

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### TABLE 2
Comparison of the sensitivity and specificity of NPA and NS specimens for the detection of respiratory viruses by IF, culture, and PCR**

<table>
<thead>
<tr>
<th>Virus (no. of samples positive&lt;sup&gt;c&lt;/sup&gt; by &quot;gold standard&quot;) and test</th>
<th>NPA</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity (95% CI)</td>
<td>Specificity (95% CI)</td>
</tr>
<tr>
<td>RSV (43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IF</td>
<td>0.93 (0.81–0.99)</td>
<td>1.00 (0.99–1.00)</td>
</tr>
<tr>
<td>Culture</td>
<td>0.88 (0.75–0.96)</td>
<td>1.00 (0.99–1.00)</td>
</tr>
<tr>
<td>PCR</td>
<td>0.88 (0.75–0.96)</td>
<td>1.00 (0.99–1.00)</td>
</tr>
</tbody>
</table>


Transmission

- Incubation period range 2-8 days (common 3-6 days)
- **Transmission via direct or closed contact** with contaminated secretion (droplet, fomite)
- Virus survives on surfaces for up to 6 hours
- Viral shedding 3-8 days
- Prolonged viral shedding
  - immunocompromised hosts
  - young infants (may be last 3-4 weeks)

Redbook 2006
Prevention spread of RSV

• “Contact precaution”
  - Hand hygiene practices
  - Disinfection of surfaces
  - Gloves, masks, goggles, gowns
• Isolated patients with RSV infection in single room or cohort nursing
• Early identification of RSV-infected patient
Management of RSV bronchiolitis

Supportive
• Fluids, oxygen, respiratory supports

Controversy
• Bronchodilators
• Corticosteroids
• Antiviral agents
• Antibiotics
Inhaled bronchodilator: $\beta_2$ agonist

- Clinical score and oxygen saturation improve shortly after nebulized albuterol *
- Not improve in clinical score and oxygen saturation after 30 min in hospitalized patient **

Systematic review*** and AAP guideline not recommend routinely use in acute bronchiolitis

If no rapid improvement $\rightarrow$ discontinue

Racemic Epinephrine

- Racemic epinephrine produced greater improvement in oxygen saturation and clinical score than saline and albuterol*
- Randomized trial → no change in length hospital stay, compare to placebo**

Cochrane Review 2008

254 patients

- Nebulized 3% NaCl vs 0.9% NSS
- Nebulized 3% NaCl had …
  - Shorter mean length of hospital stay
  - Lower post-inhalation clinical score
  - No adverse events related to 3% NaCl inhalation were reported.
Corticosteroids

- Reduce airway obstruction by decrease bronchiolar swelling
- A Cochrane database review of 13 studies, 1198 patients → no significant change in length of stay

“Corticosteroids not be used routinely in previous healthy patients hospitalized with first episode of bronchiolitis”

- May be benefit in asthma patient, previous episode of wheezing (may be at risk for asthma), chronic lung disease

**Antiviral agent:** Ribavirin

- A synthetic nucleoside analogue
- Inhibit viral protein synthesis
- Aerosol route administration
- Significant ↑ SpO2 during acute infection
- An expensive drug
  
  (cost approximately = 1,400 US$/day)
Evidence from Systematic reviews*
12 trails, 158 patients
- Reduce mortality 5.8% vs 9.7% (OR 0.58, 95%CI 0.18-1.85)
- Fewer respiratory deterioration (OR 0.37, 95%CI 0.12-1.18)
- ↓ days of hospitalization = 1.9 days (95%CI -4.6-0.9)
- ↓ days of mechanical ventilation = 1.8 days (95%CI -3.4--0.2)
- Not significant difference in long-term pulmonary function and recurrent wheezing

- Not recommended routinely for treatment in all case
- Reserved for high-risk infants with confirmed RSV

*Cochrane Database of Systematic Reviews 2007
### Children at highest risk for severe RSV

<table>
<thead>
<tr>
<th>Condition</th>
<th>Risk Factors</th>
</tr>
</thead>
</table>
| Premature birth                  | • Altered airway anatomy  
                                     • Absence of maternal antibody                                         |
| Chronic lung disease             | • Bronchial hyperresponsiveness  
                                     • Reduced lung capacity                                                   |
| Congenital heart disease         | • Pulmonary vascular hyperresponsiveness  
                                     • Pulmonary hypertension  
                                     • Increased pulmonary blood flow                                           |
| Neuromuscular disease            | • Decreased respiratory muscle strength and endurance                        |
| Immune deficiency                | • Decreased host defenses  
                                     • Impaired capacity to eliminate virus                                      |
5 post lung transplant recipients with RSV lower respiratory tract infection

Oral ribavirin 15 to 20 mg/kg in 3 divided doses for total of 10 d or until NPS negative + solumedrol 10 to 15 mg/kg/day IV x 3 d

FEV$_1$ fell 21% during infection and return to baseline at 565 d

There were no death

A 10-day course of oral ribavirin cost $700
A 10-day course of nebulized ribavirin cost $14,000

Antibiotics use in acute bronchiolitis

- Approximate 34-99% of uncomplicated case received antibiotics
- **Antibiotics are not recommended** for bronchiolitis unless concern about complications such as secondary bacterial pneumonia
- Systematic reviews → no evidence support the use of antibiotics for bronchiolitis

Cochrane Database of Systematic Reviews 2007
# Co-infection in RSV

## Table 2  Bacteria isolated in tracheal aspirates and blood specimens from infants with RSV bronchiolitis and bacterial co-infections

<table>
<thead>
<tr>
<th>Isolate</th>
<th>Bacterial pneumonia*</th>
<th>Bacterial sepsis†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Community</td>
<td>Nosocomial</td>
</tr>
<tr>
<td></td>
<td>acquired</td>
<td></td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*n = 25 infants, 15 tracheal aspirates with >1 microorganism (maximum 3 microorganisms).
†n = 3 infants, 1 blood culture with 2 microorganisms (*Streptococcus pyogenes* and *Pseudomonas*).
Recurrent RSV infection or Sequelae?
Clinical course and sequelae

• Respiratory status typically improved over 3-4 days, normal within 2 wk
• Wheezing may be persist in some infants for a week or longer
• Prolonged wheezing in younger and patient with co-morbid conditions
• Associated with airway reactivity/asthma
Airway reactivity after RSV

- RSV LRTI ass. with an increased risk of frequent wheeze (odd ratio 4.3, 95%CI 2.0-5.0) by age 6, but decreased markedly with increasing age and not significant by age 13
- Children who wheezed at age 6 had lower FVC than normal at age 13 (odd ratio 2.11, 95%CI 2.05-2.15) and reversed with salbutamol
- There is no ass. with markers of atopy
- A sharp decrease of 50% in wheezing during the first year (p 0.001)
- An increase in wheeze occurred during the winter periods (p 0.001)
Airway reactivity after RSV

“Asthma may be direct consequence of RSV infection, independent of atopy”

RSV-infection

specific IgE response

Airway reactivity

Progressive decrease

Asthma

Airway reactivity after RSV

“virus may trigger changes in pulmonary physiology in patients predisposed to develop asthma”

Allergen sensitization

Specific IgE response

Airway reactivity

Asthma

Treatment of respiratory symptoms of post-RSV

• Significantly elevated levels of leukotriene C4 in nasopharyngeal secretion of infant with LRTI VS URTI

• Higher level of cysteiny1 leukotriene levels in the bronchoalveolar lavage of children with acute RSV-induced bronchiolitis
Montelukast

The cysteiny1 leukotrienes receptor antagonist

Evidence from RCT, Bisgaard H, et al. 2003*

n = 116
• % symptom free days, Montleukast vs placebo
  (6 days vs 1 days, p 0.015)

Bisgaard H, et al. 2008**

n = 979
Dose: once daily 4 mg granules and 8 mg granules
• No significant effect (%symptom free day) in RSV-induced bronchiolitic respiratory symptoms over 24 wk period

RSV prevention

• Limiting exposure to contagious setting
• Hand hygiene of caregivers in all setting (esp during respiratory infection)
• Immunoprophylaxis: “Palivizumab”
Palivizumab

- Humanized mouse monoclonal antibody to F-protein
Palivizumab

- n = 1502 infants with GA < 35 wk and/or CLD
- Palivizumab 15 mg/kg IM q 1 mo. x 5 mo.
- 55 % overall reduction in hospitalization for RSV infection in palivizumab group.
- Treatment group significant lower in hospital rate, total days of admission, need of oxygen supplement, illness severity score, the need of intensive care
- Adverse effects were similar in both groups

AAP recommendation 2003

Palivizumab prophylaxis in...

- Preterm <32 wk with age < 6-12 mo
- Preterm 32-35 wk with risk factors
  - Birth within 6 mo. of RSV season
  - Child care attendance
  - School-age siblings
  - Severe neuromuscular disease
  - Airway abnormality
- Children age < 24 mo. with
  - Chronic lung disease, need medical treatment within 6 mo. prior to the start of RSV season
  - Cyanotic heart disease
  - Moderate to severe pulmonary hypertension
  - Congenital heart disease required medication
The average wholesale price is
$824 for the 50 mg Synagis® vial
$1557 for the 100 mg vial. (Sep 2009)

BW 10 kg, dosage: 15 mg/kg/dose

150 mg of palivizumab = $2,381
= 83,335 Baht/mo
= 416,675 Baht/course