RSV Bronchiolitis

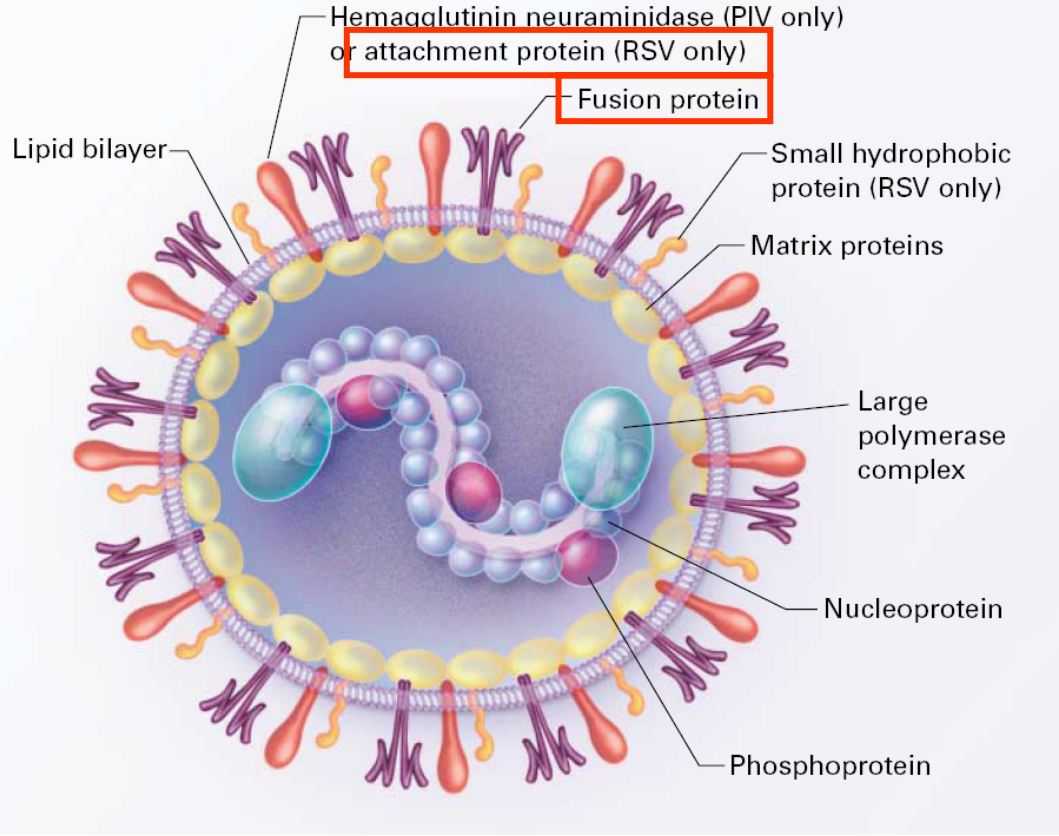
Korakot Thongkum, MD

Pediatric ulmonary Fellow

Department of Pediatrics

Ramathibodi Hospital

Respiratory Syncytial Virus



ssRNA enveloped virus

Family *Paramyxoviridae*

Genus *Pneumovirus*

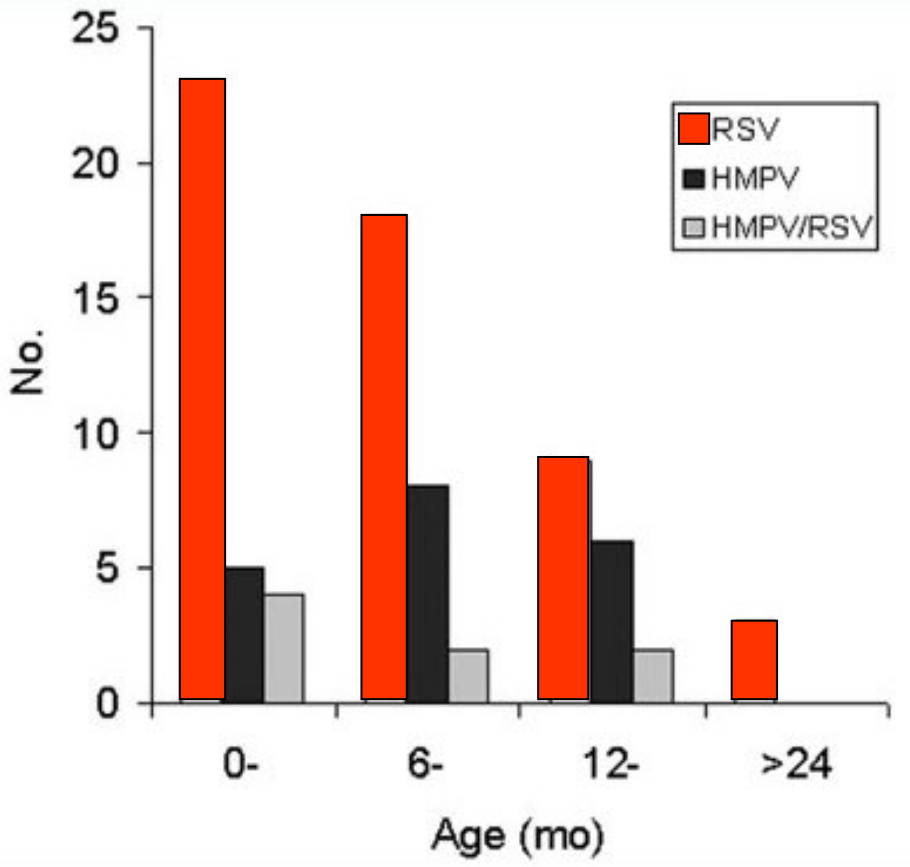
Subgroups *A and B*

N Engl J Med 2001;344:1917-28.

- 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 through out life is common



Emerg Infect Dis 2003; 9(12).

* Am J Epidemiol 1973; 98: 289-300.

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

J Med Assoc Thai 2002;85(4):S1111-9

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

*Am J Epidemiol 1968; 88:257-66.

**J Med Assoc Thai 2002;85(4):S1167-75.

Epidemiology: in hospital

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

Infect Immun 1981; 33: 779-83.

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

Infect Immun 1981; 33: 779-83.

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)

J Infect Dis 1997; 175: 814-20.

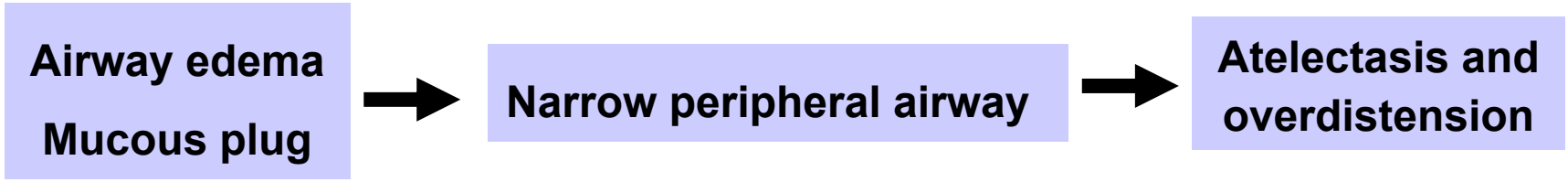
Pathogenesis

- 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

Adult and older child

Lower Respiratory Infection

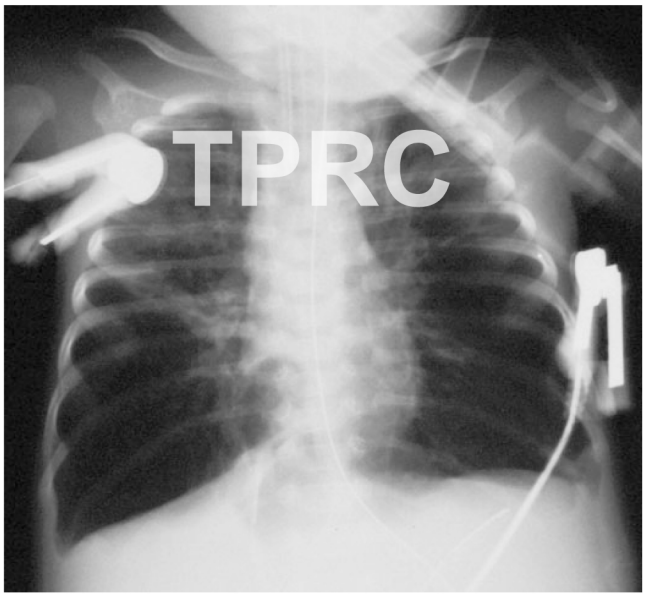
- Bronchiolitis, Pneumonia
- Cough
- Respiratory Distress (tachypnea, retractions)
- Apnea

Infant and young child

Clinical Features of Bronchiolitis

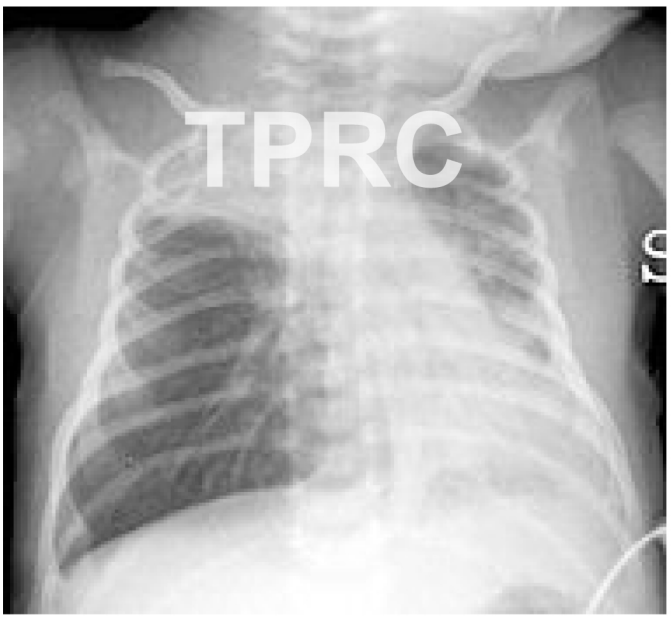
- Mild rhinorrhea, cough, low-grade fever
- Rapid respiration, chest retraction and wheezing
- 20% of patients →apnea as presenting symptom
- Associated with sudden infant death syndrome
- PE: tachypnea, tachycardia, conjunctivitis, otitis media
- Lungs: retraction, prolonged expiratory phase, wheezing

Radiologic features of RSV bronchiolitis



- Nonspecific
- Diffuse hyperinflation
- Fattening of diaphargm
- Bulging of intercostal space

Radiologic features of RSV bronchiolitis



- Atelectasis

Diagnosis: Method

- **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

NPA vs NTS

TABLE 3 **Sensitivity for the Detection of Different Viruses According to Specimen Type***

Virus	ARIs With Virus Identified[a]	NPA		NTS	
		Sensitivity	95% CI[b]	Sensitivity	95% CI[b]
RSV	72	97.2	90.3–99.7	93.1	84.5–97.7

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

Virus (no. of samples positive[a] by "gold standard") and test	NPA		NS	
	Sensitivity (95% CI)[a]	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
RSV (43)				
IF	0.93 (0.81–0.99)	1.00 (0.99–1.00)	0.70 (0.54–0.83)	1.00 (0.98–1.00)
Culture	0.88 (0.75–0.96)	1.00 (0.99–1.00)	0.65 (0.49–0.79)	1.00 (0.99–1.00)
PCR	0.88 (0.75–0.96)	1.00 (0.99–1.00)	0.67 (0.51–0.81)	1.00 (0.99–1.00)

*Pediatrics 2008;122(3):e615-20.

**J Clin Microbiol 2008;46(9):3073-6.

Transmission

- Incubation period range 2-8 days (common 3-6 days)
- **Transmission via direct or <u>closed contact</u>** 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 hygeine 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: β_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 → discontinue

*Pediatr Emerg Care 1992;8:184-8.
J Pediatr 1990;117:633-7.
**Pediatrics. 1994;93:907-12.
***Arch Pediatr Adolesc Med 2004;158(2):127-37.

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**

*Arch Dis Child 1993; 69: 650-4.
J Pediatr 1993; 122: 145-51.
Adoles Med 1995; 149: 686-92.
J Pediatr 1995; 126: 1004-7.
**N Eng J Med 2003; 349: 27-35.

Hypertonic saline

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.

Cochrane Database Syst Rev 2008.

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

Cochrane Database Syst Rev 2004.

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)

Efficacy of Ribavirin

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-tem 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

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

Oral Ribavirin

- 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

J Heart Lung Transplant 2009;28:67–71.

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

Isolate	Bacterial pneumonia*		Bacterial sepsis†	
	Community acquired	Nosocomial	Community acquired	Nosocomial
Haemophilus influenzae	8	9		
Moraxella catarrhalis	6	6		
Streptococcus pneumoniae	5	4	2	
Streptococcus pyogenes				1
Staphylococcus aureus	3	5		
Pseudomonas aeruginosa				1

*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*).

Arch Dis Child 2004; 89: 1155-7.

Recurent RSV infetion
or Sequelae ?

Clinical course and sequelae

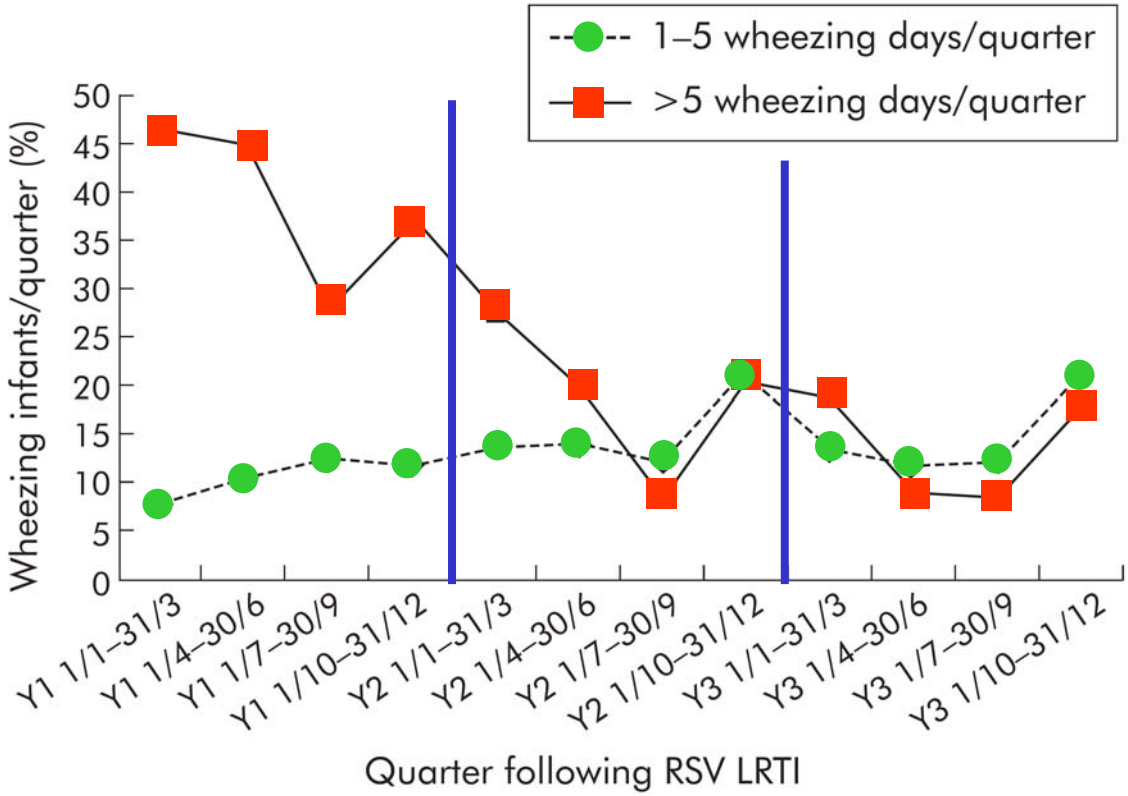
- Respiratory status typically improved over 3-4 days, normal within 2 wk
- Wheezing may be persist in some infants for a week or longer
- Prolonged wheezing in younger and patient with co-morbid conditions
- Associated with airway reactivity/asthma

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 ratio2.11, 95%CI 2.05-2.15) and reversed with salbutamol
- There is no ass. with markers of atopy

Lancet 1999;354:541-5

Characteristic of wheezing following RSV

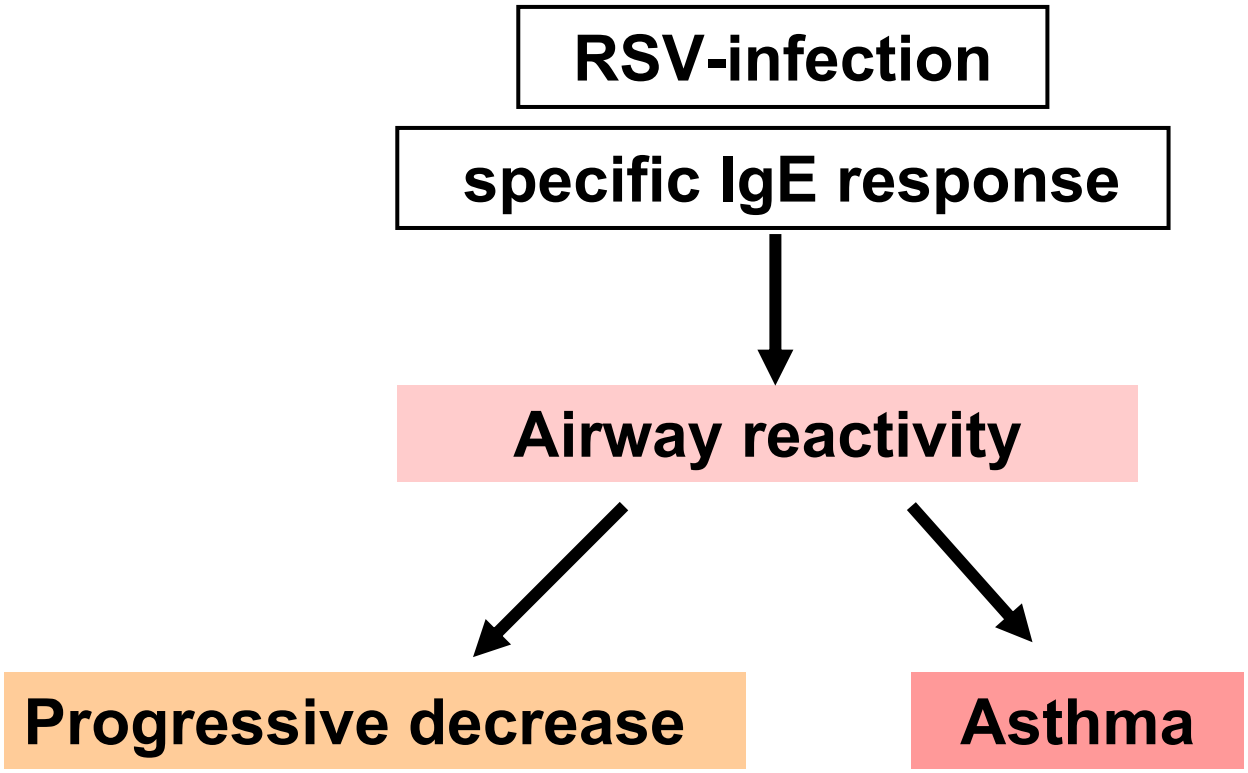


- A sharp decrease of 50% in wheezing during the first year (p 0.001)
- An increase in wheeze occurred during the winter periods (p 0.001)

Thorax 2004; 59: 512–6.

Airway reactivity after RSV

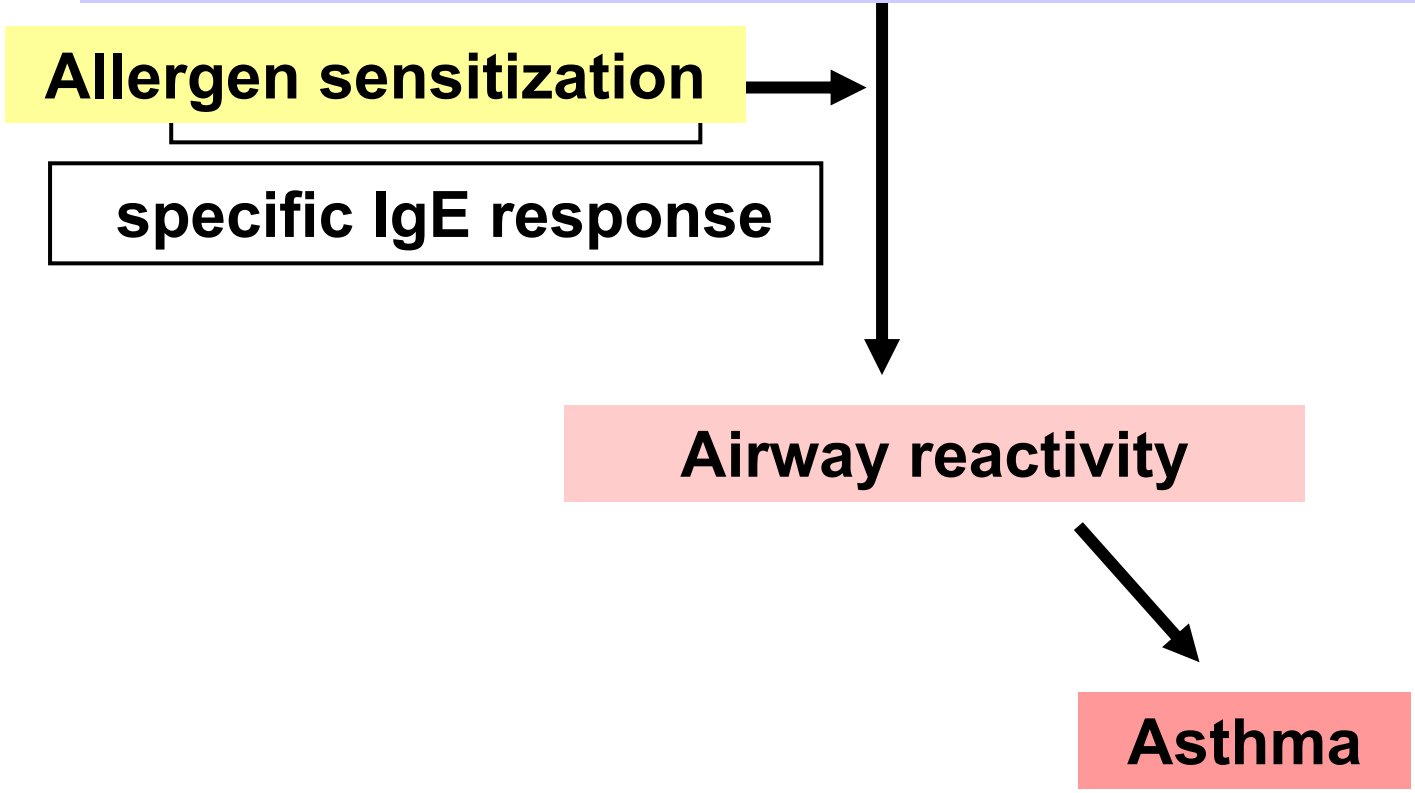
"Asthma may be direct consequence of RSV infection, independent of atopy"



Pediatr Infect Dis J 2007; 26: 733-9.

Airway reactivity after RSV

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



Pediatr Infect Dis J 2007; 26: 733-9.

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 **cysteinyl leukotriene** levels in the bronchoalveolar lavage of children with acute RSV-induced bronchiolitis

Montelukast

The cysteinyl leukotrienes receptor antagonist

Evidence from RCT,Bisgaard H, et al. 2003*
n = 116

- % symtom 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

*Am J Respir Crit Care Med 2003; 167: 379-83.

**Am J Respir Crit Care Med. 2008;178(8): 854-60.

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

The Impact-RSV Study Group. Pediatrics 1998;102:531-7.

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

Palivizumab Price

- 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