Recent Literature Review on Respiratory Syncytial Virus (RSV) Infection in Infants and Children
Yuh-Jyh Lin, Chyi-Her Lin
Department of Pediatrics, National Cheng-Kung University Hospital, Tainan, Taiwan

Abstract
RSV is the most common cause of viral bronchiolitis. This review presents recent literature on the epidemiology, risk factors, pathophysiology, diagnosis, later sequels, therapeutic options and prevention of RSV infection in infants and children. (J Pediatr Resp Dis 2013;9:6-10)

Key words: bronchiolitis, motavizumab, palivizumab, respiratory syncytial virus

Epidemiology
Each year in the United States, an estimated 75,000-125,000 hospitalizations related to RSV occur among children aged <1 year, and RSV infection results in approximately 1.5 million outpatient visits among children aged <5 years.1 In the United States, RSV season begins in the fall, peaks in winter, and ends in the late winter and early spring.3 However, the exact timing and duration vary from year to year and by geographic region.3 In USA, Groothuis et al. reported that a steady decrease in the yearly incidence of RSV-associated hospitalizations in children younger than two years with chronic lung disease of infancy (CLDI) over the period of 1998-2008. Possible explanation of this trend included improvement of neonatal intensive care and outpatient management of CLDI, increased public awareness with improved protection of these infants from RSV, and increased use of palivizumab for prophylaxis in preterm infants with CLDI.4 In a epidemiology study, Chen et al. found that the RSV season in Taiwan is different from United States, with RSV cases being diagnosed all year round, and its peak was in spring, especially in March and April.5 In another study, the seasonality of RSV infections in Taiwan showed a biennial pattern with peaks in spring and fall.6

Risk Factors
Several studies reported risk factors associated with RSV bronchiolitis and RSV hospitalization. Based on cohort of 298 healthy newborns in the Netherlands, Houben et al. reported a simple clinical prediction rule to identify healthy newborns at risk of RSV lower respiratory tract infection (LRTI). They found factors associated with increased risk of RSV bronchiolitis were: day care attendance and/or older siblings (odds ratio [OR] 5.8, 95% CI 0.76-44.4); high parental educational levels (OR 2.79, 95% CI 0.94-8.3); birth weight > 4 kg (OR 2.24, 95% CI 1.1-4.4); and birth between April and September (OR 2.17, 95% CI 1.1-4.4). The absolute risks of RSV LRTI range from 3% for children with the lowest prediction rule score to 32% for children with all predictive factors.7 Relative risks (RR) for RSV hospitalization have been studied in the previous case-control studies. Risk factors for RSV hospitalization were recurrent wheezing (relative risk [RR] 5.9, 95% CI 4.96-7.01), infrequent wheezing (RR 2.98, 95% CI 2.56-3.48), maternal asthma (RR 1.72, 95% CI 1.44-2.06), paternal asthma (RR 1.23, 95% CI
1.04-1.45), maternal atopic dermatitis (RR 1.11, 95% CI 0.95-1.29) in Danish cohort. Underlying medical conditions (primarily prematurity), and household crowding were risk factors for RSV hospitalization in Alaska study. Zachariah et al. carried out a population-based, retrospective cohort study and found that congenital malformations contribute to the risk and severity of RSV LRTI and prophylaxis should therefore be recommended in these populations. Kristensen et al. found several new chronic conditions, both congenital and acquired, as independent risk factors for RSV hospitalization. Belderbos et al. reported that vitamin D deficiency at birth is associated with subsequent RSV bronchiolitis. The authors suggested that improving maternal vitamin D status during pregnancy may be a strategy for reducing RSV bronchiolitis in their offspring. Prodhan et al. identified that the presence of lethargy, grunting, and an arterial partial pressure of carbon dioxide of 65mmHg or more at initial presentation were significantly associated with a subsequent respiratory failure among previously healthy children with RSV infection.

Pathophysiology

Infection of airway epithelial cells with RSV induces reactive oxygen species (ROS) formation, measured by oxidation of 2',7' dichlorodihydrofluorescein diacetate (DCFDA), which is trapped intracellularly after cleavage by cellular esterases and becomes fluorescent once oxidized. RSV infection of airway epithelial cells also results in activation of a subset of transcription factors, including NF-κB, AP-1, IRF, and STAT proteins, which control the expression of a variety of proinflammatory /immunological mediators. RSV-induced oxidative stress is likely to play a fundamental role in the pathogenesis of RSV-associated lung inflammatory disease, which correlate with the severity of clinical illness in children with RSV infection. Modulation of ROS production and oxidative stress therefore represents a potential approach to ameliorate RSV-induced lung inflammation and its long-term consequences. Oxidant species are associated with the pathophysiological features of airway diseases such as bronchoconstriction, airway hyper reactivity, mucous hypersecretion, epithelial damage, and microvascular leakage. Hosakote et al. measured changes of lung antioxidant enzyme expression and activation of NFE2-related factor 2 (Nrf2; a transcription factor that regulates detoxifying and antioxidant enzyme gene expression) in mice and infants with naturally acquired RSV infection. The authors found that RSV infection significantly reduces nuclear expression of Nrf2 and subsequent down-regulation of the airway antioxidant system.

Diagnosis

Bacteremia is rare in children with RSV infection and uncommon in infants within 2 month of age with RSV infection. WBC does not predict bacteremia in febrile children with RSV LRTI. Chest x-ray is almost consistent with the diagnosis in typical bronchiolitis presentation, but often misinterpreted. Using pulse oximetry to assess oxygen saturation is considered routinely at RSV hospitalizations, but no studies have established appropriate cutoff values for decision-making. There are several methods for rapid viral testing. Viral illnesses may be mistaken for bacterial infection, and antibiotic therapy may be prescribed. Overprescribing of antimicrobials for viral illness is a factor contributing to increasing antimicrobial resistance among bacterial pathogens encountered in pediatrics. Rapid viral testing with direct fluorescent assay (DFA) for RSV is associated with decrease in inappropriate antibiotic use. Some rapid RSV antigen tests (Pathfinder RSV rapid antigen test, Binax NOW RSV rapid antigen test) appears to have insufficient sensitivity to rule out RSV infection.

Later Sequels

Previous literatures demonstrated that RSV bronchiolitis was associated with increased risk for wheezing through early childhood but not later. Infants hospitalized for bronchiolitis may be at higher risk of asthma or recurrent wheezing.

Therapeutic Options

Several studies have shown a wide variation in how bronchiolitis is diagnosed and treated. These
conditions reflect that there is a lack of consensus among clinicians. In 2006, AAP published a guideline on the diagnosis and management of bronchiolitis.\textsuperscript{29} Their recommendations are summarized as following:

1. Clinicians should diagnose bronchiolitis and assess disease severity on the basis of history and physical examination. Several studies have showed prematurity, age < 12 weeks, hemodynamically significant congenital heart disease, chronic lung disease, immunocompromised state are risk factors of severe disease.

2. A carefully monitored trial of \( \alpha \)-adrenergic or \( \beta \)-adrenergic medication is an option. Inhaled bronchodilators should be continued only if there is a documented positive clinical response to the trial using an objective means of evaluation.

3. Corticosteroid medications, ribavirin, chest physiotherapy should not be used routinely in the management of bronchiolitis.

4. Antibacterial medications should be used only in children with bronchiolitis who have specific indications of the coexistence of a bacterial infection.

5. Clinicians should assess hydration and ability to take fluids orally.

6. Supplemental oxygen is indicated if oxyhemoglobin saturation (\( \text{SpO}_2 \)) falls persistently below 90% in previously healthy infants. If the \( \text{SpO}_2 \) does persistently fall below 90%, adequate supplemental oxygen should be used to maintain \( \text{SpO}_2 \) at or above 90%. Oxygen may be discontinued if \( \text{SpO}_2 \) is at or above 90% and the infant is feeding well and has minimal respiratory distress.

7. Infants with a known history of hemodynamically significant heart or lung disease and premature infants require close monitoring as the oxygen is being weaned.

Several studies also showed some beneficial therapies:

1. Nebulized epinephrine might reduce hospital admissions in children with acute viral bronchiolitis.\textsuperscript{30}

2. Nebulized hypertonic saline appears more effective than nebulized normal saline in improving symptoms and reducing hospital stay.\textsuperscript{31} In addition, a retrospective cohort study of the use of nebulized hypertonic saline without adjunctive bronchodilators for children with bronchiolitis showed a 1.0% adverse event rate (95% confidence interval: 0.3%–2.8%).\textsuperscript{32} Adverse events were generally mild. One episode of bronchospasm was documented, for a rate of 0.3% (95% CI: 0.01%–1.6%).\textsuperscript{32}

3. Montelukast may reduce postbronchiolitis symptoms at 2-4 weeks,\textsuperscript{33} but inconsistent evidence for reducing clinical severity, length of hospital stay or long-term symptoms.\textsuperscript{34, 35}

Some other therapies, however, showed conflicting or insufficient evidence of benefit:

1. Heliox has insufficient evidence to assess clinical benefit.\textsuperscript{36}

2. Noninvasive modes of respiratory support also has insufficient evidence to support benefit.

### Prevention

1. Glove and gown precautions can substantially reduce the nosocomial transmission of RSV.\textsuperscript{37}

2. Passive immunoprophylaxis is associated with decreased risk of hospitalization for RSV in premature infants with bronchopulmonary dysplasia or acyanotic congenital heart disease. However, it has no effect in harder endpoints of RSV disease severity.\textsuperscript{38}

3. Clinicians may administer palivizumab prophylaxis to selected infants and children with CLD or a history of prematurity. When given, prophylaxis with palivizumab should be given in 5 monthly doses, usually beginning in November or December, at a dose of 15 mg/kg per dose administered intramuscularly.\textsuperscript{29} Since the seasonality of RSV infections in Taiwan is different from United States, a different prophylactic regimen is used in Taiwan. Palivizumab is given in 6 monthly doses for premature babies 1) with gestational age less than 28\textsuperscript{16} weeks, and 2) those suffered from CLD and their gestational age below 36\textsuperscript{16} weeks.

4. Infants should not be exposed to passive smoking.\textsuperscript{29}

5. Motavizumab is monoclonal antibody with greater affinity for RSV fusion protein than palivizumab. In a phase 3 trial, children receiving prophylaxis
with motavizumab or palivizumab had low rates of RSV hospitalization; motavizumab recipients experienced 50% fewer RSV LRTIs than palivizumab recipients. AEs were similar in both groups, although cutaneous AEs were higher for motavizumab recipients. Motavizumab may offer an improved alternative in prophylaxis for serious RSV disease in infants and children at high risk. However, clinical use of motavizumab is not approved by FDA now.

In summary, RSV infection is the most common cause of bronchiolitis in infants and young children. The prompt management of bronchiolitis in infants and young children is still controversial. Clinician taking care of these patients should update their knowledge frequently about the management of RSV infection.

REFERENCES
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