Respiratory Syncytial Virus Bronchiolitis in Children, a Disease that has Come to Stay: Summary Review for Pediatricians and Health care Practitioners

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Abstract

Respiratory Syncytial Virus (RSV), the top cause of Lower respiratory tract disease in young children, continues unabated as a global health problem. Clinical presentations vary depending on age, prematurity, previous infections, and other co-morbid factors. Bronchial airway tissue pathogenicity is due to the interplay between viral replication and cytotoxicity and the host inflammatory immune response. The resulting inflammation of the small airways (Bronchiolitis) is characterized by acute inflammation, edema, and necrosis of epithelial cells lining small airways, with increased mucus production. Clinical presentations vary depending on age, prematurity, previous infections and other co-morbid factors. Supportive measures include hydration with use of supplemental oxygen and hypertonic saline nebulizer for hospitalized patients. Routine use of bronchodilators and steroids are not indicated.

We review RSV disease epidemiology, pathogenesis and clinical manifestations. Additionally, we summarize the updated American Academy of Pediatrics (AAP) management recommendations in an easy to read table format for practicing clinicians.

Introduction

Worldwide, Respiratory Syncytial Virus (RSV) is the most common cause of lower respiratory tract disease and hospitalization in young children causing about 33.1 million episodes, resulting in about 3.2 million hospitalizations and 59,600 in-hospital deaths in children <5 years of age. Children <6 months of age, accounts for 40-50% of disease burden [1]. Majority occurs in developing countries where effective diagnostic tests as well as supportive care management are not available. Additionally, underlying nutritional status with secondary bacterial or other disease on an already altered respiratory milieu may contribute to morbidity and mortality in developing nations. In developed countries, burden of disease is huge in terms of healthcare costs but mortality is low. By the age of 2 years, over 90% of the children have been infected by the virus [1-3].

In the US, Respiratory Syncytial Virus (RSV) is the most common cause of bronchiolitis; highest incidence occurs between December and March each year, representing winter and early spring. The Center for Diseases Control and Prevention (CDC) monitors RSV circulation through National Trends where participating laboratories report weekly total tests performed and positive tests. Data may be used in various regions of the US for monitoring trends, resource allocation planning and timing for prophylaxis in selected regions. Figure 1 shows seasonal variations in the US. Ninety percent of children are infected in the first 2 years of life [3] and up to 40% will have symptoms after initial infection [4,5]. In the US, it is also the most common cause of hospitalization in infants, contributing to about 100,000 admissions per year at an estimated cost of $ 1.73 billion [6]. The highest age-specific rate of RSV hospitalization occurs among infants between 30 days and 60 days of age (25.9 per 1000 children). For preterm infants (<37 weeks' gestation), the rate is higher at 4.6 per 1000 children [7].

Pathophysiology

RSV is an envelope, non-segmented, negative strand RNA virus of the family Paramyxoviridae. RSV F and G surface proteins promote virus attachment and virulence. There are multiple genotypes in each RSV subgroup based on the G protein gene. Some RSV strains may be more virulent than others, but severity of disease does not seem to be associated to a specific RSV strains. RSV spreads to the ciliated epithelial cells of the respiratory tract through mucous membranes at its site of inoculation in the nasopharynx or conjunctiva. The RSV G and F glycoprotein facilitates host receptor binding and fusion with cell membranes respectively. Tissue pathogenicity is due to the interplay between viral replication and cytotoxicity and the host inflammatory immune response from humoral and cytotoxic T-cell activation. Viral multiplication, epithelial tissue necrosis and immune system
activation leads to various sequela including small airway obstruction and plugging by mucus, cellular debris, and viral fragments, alveolar obstruction, impaired mucus clearance, airway edema, and decreased lung compliance.

The resulting inflammation of the small airways (Bronchiolitis) is characterized by acute inflammation, edema, and necrosis of epithelial cells lining small airways, and increased mucus production [8,9].

RSV is mostly spread by young children to other household and child care contacts. The period of viral shedding usually is 3 to 8 days but may last longer, especially in young infants and in immunosuppressed people. The incubation period ranges from 2 to 8 days. Due to its widespread in nature, most or all individuals would have been infected with RSV by two years of age. However, previous infection does not lead to complete protection against reinfection.

**Diagnosis**

**Clinical**

Signs and symptoms typically start with cough and coryza that may progress to tachypnea, wheezing, retractions, grunting and nasal flaring. Disease presentation varies and each child requires serial assessment over time. Suctioning and positioning promotes nasal flaring. Disease presentation varies depending on age, prematurity, other co-morbid factors especially respiratory and hemodynamically significant heart disease, and previous infections. Infants and young children with primary infections typically presents with lower respiratory tract infection; older children have mild or clinically in apparent upper respiratory tract symptoms. Infants can present with apnea, mechanism is mostly unknown but it is possible that RSV may increase sensitivity of laryngeal receptors and reinforce reflex apnea [9,10].

Need for positive pressure ventilation and ICU admission are low. Tachypnea, defined as a respiratory rate ≥70 per minute, may be associated with increased risk of severe disease. The use of scoring systems has not been well validated. Emergency room triage and serial evaluations helps identify children needing ICU care. Infection with RSV during the first few weeks of life may produce minimal respiratory tract signs, but lethargy or irritability, poor oral intake and apnea can also occur especially in younger infants. The American Academy of Pediatrics (AAP)/Clinical practice guideline recommends that clinicians should diagnose bronchiolitis and assess disease severity on the basis of history and physical examination and if clinical diagnosis is made, routine radiographic or laboratory studies should not be obtained [10].

**Laboratory tests**

Nowadays rapid diagnostic assays, including Direct Fluorescent Antibody (DFA) assay and enzyme or chromatographic immunoassay techniques are available. These rapid tests detect the viral antigen in nasopharyngeal specimens and in children; the sensitivity in comparison with culture varies between 53% and 96%.

Molecular tests using Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) that are cleared by the US Food and Drug Administration (FDA) have become widely available. Molecular diagnosis has led to increased yield with identification of viral etiology in >95% of bronchiolitis cases; two or more viruses are detected in approximately one-third of young children hospitalized with bronchiolitis. The third option is RSV isolation from respiratory tract secretions in cell culture, but this type of test requires 1 to 5 days for diagnosis and results and sensitivity vary among laboratories, which makes RT-PCR the preferred method for RSV infection diagnosis.

**Differential diagnosis**

Many viruses that infect the respiratory system can cause similar signs and symptoms. Different types of viruses cause bronchiolitis and among them are the human rhinovirus, human metapneumovirus, influenza, adenovirus, corona virus and parainfluenzaviruses [9,10]. A study published in 2013 that included admitted patients and outpatients with bronchiolitis, showed that 76% of patients had RSV, 39% had human rhinovirus, 10% had influenza, 2% had corona virus, 3% had human metapneumovirus, and 1% had parainfluenza viruses (some patients had coinfections, so the total is greater than 100%) [11].

**Management**

Different therapies have been used by physicians when managing patients with bronchiolitis. The most recently updated AAP guideline is a revision of the clinical practice guideline, “Diagnosis and Management of Bronchiolitis” published in 2006. This recent publication from 2014 (Clinical Practice Guideline: The Diagnosis, Management, and Prevention of Bronchiolitis) applies to children from 1 through 23 months of age. Table 1 summarizes the recommendations. Special considerations are necessary to manage patients in the acute critical care settings. These patients

![Figure 1: RSV season by US regions.](image-url)
Alcohol-based rubs can be used for hand decontamination when patients and after contact with inanimate objects close to the patient. Diseases [12,13]. Hand washing decreasing risk of disease spread: behaviors and vaccinating the population against known infectious to hazards, altering unhealthy or unsafe behaviors, altering risky

Prevention recommend for routine use due to the lack of a clinically significant the past as a treatment option for children with bronchiolitis is not used for respiratory support in hospitalized infants with bronchiolitis. However, only limited data are available to evaluate the effectiveness of these therapies. Management of severely or critically ill infants with bronchiolitis, should be used only in consultation with a critical care or pulmonary specialist. Aerosolized ribavirin that was used in the past as a treatment option for children with bronchiolitis is not recommended for routine use due to the lack of a clinically significant effect on outcome.

Table 1: summarizes the recommendations.

| 1. | Clinicians should diagnose bronchiolitis and assess disease severity on the basis of history and physical examination. Serial examinations should be done and management based on risk stratification. |
| 2. | Clinicians should assess risk factors for severe disease, such as age <12 weeks, a history of prematurity, underlying cardiopulmonary disease, or immunodeficiency, when making decisions about evaluation and management of children with bronchiolitis. |
| 3. | Clinicians should not administer albuterol (or salbutamol) |
| 4. | Clinicians should not administer nebulized epinephrine |
| 5. | Nebulized hypertonic saline may be administered in an inpatient setting. Physiologic evidence suggests that hypertonic saline increases mucociliary clearance in both normal and diseased lung and evidence suggests that 3% saline is safe and effective at improving symptoms of mild to moderate bronchiolitis after 24 hours of use and reducing hospital length of stay |
| 6. | Clinicians should not administer systemic corticosteroids |
| 7. | Clinicians may choose not to administer supplemental oxygen if the oxyhemoglobin saturation exceeds 90% |
| 8. | Clinicians may choose not to use continuous pulse oximetry. Transient hypoxemia is common in healthy infants. Continuous pulse oximetry measurement is not well studied and potentially problematic for children who do not require oxygen. Families of infants hospitalized with continuous pulse oximeters are exposed to frequent alarms that may negatively affect sleep. |
| 9. | Clinicians should not use chestphysiotherapy |
| 10. | Clinicians should not administer antibacterial medications unless there is a concomitant bacterial infection, or a strong suspicion of one |
| 11. | Clinicians should administer nasogastric or intravenous fluids when oral hydration cannot be maintained |
| 12. | Supplemental oxygen provided for infants not requiring additional respiratory support is best initiated with nasal prongs. |
| 13. | For selected patients, use of humidified, heated, high-flow nasal cannula to deliver air-oxygen improves physiologic measures of respiratory effort and can generate continuous positive airway pressure in bronchiolitis reducing reduces work of and may decrease need for intubation |
| 14. | Clinicians and nurses should educate personnel and family members on evidence-based diagnosis, treatment, and prevention in bronchiolitis |

Table 2: Eligibility Criteria for Prophylaxis of High-Risk Infants and Young Children due to cost and affectivity [8,13].

| 1. | Palivizumab prophylaxis may be considered for preterm infants born <29 weeks, 0 days gestation who are younger than 12 months at the start of the RSV season. Maximum of 5 monthly doses (15 mg/kg/dose) should be administered during the RSV season in the first year of life. |
| 2. | Prophylaxis may be considered during the RSV season during the first year of life for preterm infants who develop Chronic Lung Disease (CLD) of prematurity, previously called bronchopulmonary dysplasia. CLD is defined as gestational age <32 weeks, 0 days, and a requirement for >21% oxygen for at least the first 28 days after birth. |
| 3. | Addendum: During the second year of life, consideration of palivizumab prophylaxis is recommended only for infants who satisfy this definition of CLD of prematurity and continue to require medical support (chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) during the 6-month period before the start of the second RSV season. |
| 4. | Children with hemodynamically significant Congenital Heart Disease (CHD) who are most likely to benefit from Palivizumab include infants with acyanotic heart disease who are receiving medication to control congestive heart failure and will require cardiac surgical procedures and infants with moderate to severe pulmonary hypertension. |

should undergo careful assessment of respiratory status, suction of the upper airway, and if necessary, intubation and mechanical ventilation. High-Flow Nasal Cannula (HFNC) therapy, nasal Continuous Positive Airway Pressure (CPAP), and Heliox have been used for respiratory support in hospitalized infants with bronchiolitis. However, only limited data are available to evaluate the effectiveness of these therapies. Management of severely or critically ill infants with bronchiolitis, should be used only in consultation with a critical care or pulmonary specialist. Aerosolized ribavirin that was used in the past as a treatment option for children with bronchiolitis is not recommended for routine use due to the lack of a clinically significant effect on outcome.

Prevention

Primary preventive measures include preventing exposures to hazards, altering unhealthy or unsafe behaviors, altering risky behaviors and vaccinating the population against known infectious diseases [12,13]. Hand washing decreasing risk of disease spread: people should disinfect hands before and after direct contact with patients and after contact with inanimate objects close to the patient. Alcohol-based rubs can be used for hand decontamination when caring for children with bronchiolitis. When alcohol-based rubs are not available, individuals should wash their hands with soap and water. Encouraging breastfeeding for first 6-months of life decreases risks of respiratory infections including RSV. Infants should never be exposed to tobacco smoke as studies have shown increased severity of RSV infection in hospitalized children exposed to secondhand smoke. Pre-exposure or passive vaccination available for prophylaxis of RSV infection: Palivizumab (Synagis®) is a humanized monoclonal immunoglobulin G1K antibody produced by recombinant DNA technology. The antibody is directed against a epitope of an antigenic site of the fusion protein (F) and it works through neutralization and inhibition of the fusion activity. When RSV encounters Palivizumab in the lower respiratory tract, the antibody attaches and prevents the conformational change that is necessary for fusion of the viral envelope with the plasma membrane of the host respiratory epithelial cell. If there is no fusion, the virus is unable to enter the cell and is unable to replicate Table 2.

Conclusion

Despite advances made in combating lower respiratory tract disease worldwide, RSV remains a top cause of morbidity and
mortality worldwide and a seasonal cause of high morbidity with associated huge health care burden for children and their families in developed countries. In the US, season typically runs from winter to early spring. Recently published AAP guidelines discourage routine use of bronchodilators which is still prevalent in many settings. For majority of hospitalized infants, supportive care and use of supplemental oxygen as clinically indicated is all that is indicated. Hand washing prevents disease transmission. Palivizumab prophylaxis may be considered for selected preterm infants and children with hemodynamically significant Congenital Heart Disease. There are no available vaccines against RSV. Due to its unabated and continued prevalence, it seems that RSV has come to stay.

References