The ABCs of RSV

Abstract: Respiratory syncytial virus (RSV) is a common viral infection affecting many children in the United States. This seasonal virus is the leading cause of hospitalization of infants and neonates. This article reviews the current recommendations for diagnostic testing, treatment options, and prevention of RSV.

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Respiratory syncytial virus (RSV) bronchiolitis is a disconcerting respiratory illness that impacts 800,000 children during the first year of life in the United States.[1] According to the CDC, RSV is the leading cause of hospitalization in children in the United States, and accounts for 57,527 hospitalizations every year in children under age 5 years, with infants under 1 year affected at the highest rate.[2,3] Bronchiolitis in all of its forms, most of which are viral, accounts for an estimated $1.73 billion and causes 2 million children in the United States to visit outpatient clinics for related symptoms every year.[2,3]

Ninety percent of pediatric patients are infected with RSV during the first 2 years of life, with 40% developing a lower respiratory tract infection during the first exposure.[3] RSV is an unpredictable illness, as the majority of infants who are hospitalized were previously healthy without risk factors.[1,4] Fortunately, fewer than 100 deaths occur annually due to this virus.[1]

Throughout most of the United States, RSV's onset is seasonal, ranging from October to late January, and varies by region. RSV season in some states with warmer climates follows an atypical pattern, with an earlier onset and longer duration.[2,5] The highest incidence of infection is between December and March, but the timing of RSV circulation in a community can vary by the number of cases and weather.[5]

Environmental and meteorologic factors play a role in viral stability, host defenses, and patterns of human behavior.[1] For example, when it is cold and rainy, individuals may move indoors, which facilitates viral transmission. Other factors that play a role in the spread of RSV include latitude, temperature, humidity, wind, UV light, cloud cover, and local incidence of RSV.[1]

Pathophysiology

In children, the RSV pathogen selectively infects the lower respiratory tract in 33% of patients.[1] RSV causes a narrowing of the respiratory airway due to mucus secretion and obstruction of the bronchi and bronchioles due to inflammation.[6] Bronchiolitis is characterized by increased mucus, inflammation, edema, and necrosis of the lining of the small airways.[3]

RSV transmission from an infected individual spreads through large respiratory droplets (greater than 5 micrometers) that enter the body through the eyes, nose, or mouth.[1,7] (See *Slide image of RSV.*) The incubation

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period of RSV is between 2 and 8 days, with symptom onset beginning approximately 5 days after exposure. The clinical presentation includes rhinorrhea, anorexia, coughing, sneezing, fever, and sometimes wheezing.[7] Rhinorrhea and cough usually occur first, followed by an increased respiratory rate, wheezing, and crackles, which may progress to labored breathing.[3]

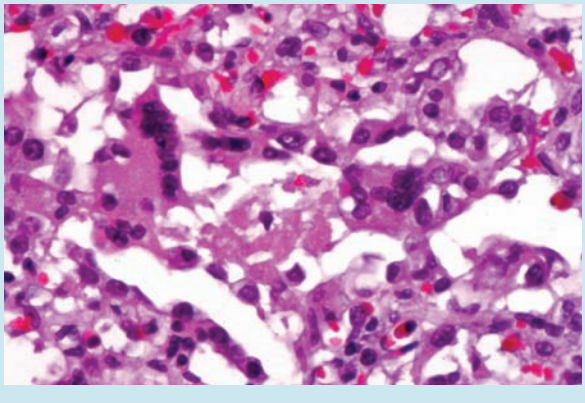
Risk factors

Premature infants have a higher chance of developing RSV, and infants younger than 12 weeks have the highest risk factors for RSV-related hospitalization.[1] Children who are not breast-fed also can be at increased risk, as they are not receiving the protective antibodies available through breast milk. Exposure to tobacco smoke and pollution also can compromise a child's narrower airway. Children with comorbid conditions such as immunodeficiency, neuromuscular disorders, and congenital cardiovascular disorders are at an increased risk of complications.[6]

Infants have anatomical differences in their airways as compared with older children and adults, which contribute to susceptibility to respiratory compromise. Children younger than 6 months are obligate nose breathers, and their nares have narrower air passages; they also have larger tongues, softer tracheas, shorter necks, and highly compliant chest walls. All of these features affect an infant's ability to expand his or her lung volume, thus making the child more prone to develop atelectasis.[6]

Slide image of RSV

This image of the respiratory syncytial virus shows amorphous inflammatory debris within the bronchiole and surrounding alveoli with syncytial giant cells throughout the area. The cytoplasmic viral inclusions stain positive for RSV.



Source: Husain AN, Stocker JT, Debner LP. *Stocker and Dehner's Pediatric Pathology.* 4th ed. Philadelphia, PA: Wolters Kluwer Health; 2016.

Severity

Several algorithms and scoring tools have been developed to address the severity of RSV in infants and to manage the condition, but few have been validated for interrater reliability, and therefore use of these tools is not recommended.[6] These tools have low predictability as to whether or not symptomatology will progress to complications that would require intensive care.[1] By 3 years old, most children have been infected with the virus, but this still does not provide full protection from reinfection, although subsequent infections are not as disconcerting.[7]

Diagnostic testing

The most recent American Academy of Pediatrics (AAP) guideline focuses on minimizing unnecessary diagnostic testing and interventions and emphasizes that routine lab or radiologic studies are not needed to evaluate children with symptoms of bronchiolitis.[3,8] "At the individual patient level, the value of identifying a specific viral etiology causing bronchiolitis has not been demonstrated."[3] However, testing for RSV is recommended in hospitalized children who receive monthly prophylaxis with palivizumab. Otherwise, routine virology testing is not recommended.[3]

To decrease exposure to ionizing radiation, avoid unnecessary invasive approaches, decrease antibiotic use, and save both time and money, X-ray imaging and lab studies should not be routinely performed on pediatric patients with RSV.[3] The AAP recommends that providers focus on evaluating the child for disease severity and identifying any other causes through a differential diagnosis that would require further intervention. The focus should be placed on evaluating the child for adequate hydration and feeding patterns while remaining cognizant of underlying conditions that can influence the child's ability to recover.[3]

Coinfection

The available literature on viral testing for bronchiolitis has expanded over the last several years with the implementation of polymerase chain reaction assays.[3] The sensitivity of antigen testing (also called the *true positive rate*, defined as the proportion of individuals with the disease who will have the positive result) is 80% to 90% in children. Among infants hospitalized for bronchiolitis, 60% to 70% have tested positive for RSV, and as many as 33% of infants have coinfections with other organisms.[3]

Currently, there is conflicting research surrounding coinfection with other respiratory viruses, with

ongoing debate as to how viral coinfection impacts the severity of illness.[1,9] Mansbach and colleagues refute the current recommendations and hypothesize that other viruses play a role in infection, arguing that identification of the causative organism is important.[9]

Other viruses that cause bronchiolitis include rhinovirus, metapneumovirus, influenza, adenovirus, coronavirus, and parainfluenza virus.[3] Children with bronchiolitis often have coinfection with more than one virus, such as human rhinovirus, which can impact severity of illness and also lead to hospitalization. Rhinovirus is the second most common cause for hospitalization of pediatric patients with bronchiolitis.[9]

Children who develop severe RSV bronchiolitis at an early age are at risk for asthma that may persist into adulthood [1,10] However, it is unclear whether bronchiolitis in early life alters lung development due to injury, which causes them to wheeze, or if an alteration in immune or airway function puts infants at risk for bronchiolitis and recurrent wheezing.[1] A genetic variation of chromosome 17q21 locus is associated with acquiring rhinovirus at a young age and increased risk for an asthma diagnosed in childhood.[1]

Management

The AAP's guideline does not address individuals with comorbid conditions, such as bronchopulmonary dysplasia, neuromuscular disease, cystic fibrosis, and congenital heart disease. Furthermore, the guideline does not address treatment options for children with recurrent wheezing or children with increased risk of developing asthma.[3] The current medication treatment options available for use are comprehensive.

However, it is important to note that there are no currently available pharmacologic options that have been shown to improve outcomes or to provide meaningful benefit for children with RSV.[11] Decreasing exposure to RSV and limiting transmission of the virus are the best ways to prevent this illness.[1]

The most common medications used to care for children with RSV are beta-agonists, even though there is strong supporting evidence that beta-agonists do not reduce hospital admission rate or duration of stay.[11] There have been some improvements in decreasing the use of unnecessary medications given to these children, but excessive care, overuse of ineffective medications, and variations in practice persist.[11] The AAP currently has a B recommendation to not administer albuterol to children who have been diagnosed with bronchiolitis. This is a change from the 2006 guideline, which stated that a trial of beta-agonists was included as an option.

Current research has provided stronger evidence demonstrating no benefit. The AAP guideline further states that there is a group of children with bronchiolitis who do have reversible airway obstruction. However, defining the subgroup of children that meets these criteria has been unsuccessful, which further justifies the change in the previous recommendation.[3] The authors acknowledge that conflicting evidence exists, but that ultimately due to lack of convincing evidence, albuterol is not recommended at this time.[3]

The adverse reactions associated with bronchodilators include tremors, tachycardia, and dysrhythmias; therefore, the overall risks of beta-agonist treatment outweigh the potential benefits.[6] Research has shown that although bronchodilators may improve clinical symptom scores, they have failed to impact measurable outcomes, such as the length of illness, requirement for hospitalization, or duration of hospital stay.[6]

Antibacterial medications should not be administered to children with bronchiolitis unless a secondary bacterial infection is present (see *Treatment options for RSV bronchiolitis*). Bronchiolitis is a viral illness, so antibiotics are not routinely recommended; however, it is possible that coinfection with a bacterial infection may take place, especially during the later phases of bronchiolitis.

Chest physiotherapy is not recommended in children with RSV. Vibration or percussion has not demonstrated clinical benefit.[3] Epinephrine should not be administered to children with RSV. Nebulized adrenaline affects both alpha-adrenergic and beta-adrenergic receptors as well as the smooth muscle of the airway, but it negatively impacts cardiovascular function.[6] There is currently no evidence that demonstrates effectiveness for children with RSV.[6] Based on the current evidence, a routine role for epinephrine in an outpatient setting is not supported. Further research is still needed.

Nebulized saline (hypertonic saline) is another treatment option for children with bronchiolitis. Physiologic evidence supports empiric observations that inhaled aerosolized saline solution rehydrates the airway surface, aids in the ability to clear mucus from the lungs, and improves the ability of cilia to remove mucus plugs.[3,6,12] Research has shown that inhaled aerosolized saline has the largest impact in children who are hospitalized and reduces duration of hospital stay.[6]

The AAP supports nebulized saline as an option to provide to children, further stating that a 3% saline

concentration is safe and effective, improves symptoms after using for 24 hours, and reduces time to hospital discharge, specifically for stays exceeding 3 days.[3] The research currently has not been critically appraised extensively enough to support the use of inhaled aerosolized saline in the ED, pediatric ICU, or for those children with mild or moderate disease.[3]

Supplemental oxygen is not recommended for children who have oxygen saturations greater than 90%; however, children with oxygenation levels lower than this may benefit from using supplemental oxygen. This may be provided either through nasal cannula or high-flow humidified oxygen. Using a high-flow nasal cannula allows for the delivery of an oxygen-air mixture that is heated and humidified and provides a form of positive airway pressure.[12]

Nasogastric and I.V. routes are recommended for fluid administration for children who are not able to tolerate oral intake.[3] Children with complications of RSV may develop elevated respiratory rates that impact coordination of breathing and swallowing. Coupled with increased nasal secretions, there is the possibility of malnutrition, dehydration, and aspiration. Current research indicates that approximately 30% of infants hospitalized with bronchiolitis require fluid replacement.[6]

Continuous pulse oximetry is not recommended for infants and children with RSV due to measurement errors that may occur. Pulse oximetry monitors contribute to alarm fatigue. Overall, pulse oximetry has not been studied comprehensively; current data are problematic for children who are not using oxygen because hospital-based studies might have overestimated the association of pulse oximetry with benefit and reduce external validity. Research has demonstrated that the correlation between respiratory distress and oxygen saturation is poor.[3]

The use of oral and I.V. corticosteroids is not recommended in any setting for children who have bronchiolitis. Rationale for the use of corticosteroids in RSV bronchiolitis infections has been for suppression of the inflammatory response, but the role of corticosteroids in RSV has not been demonstrated in outcomes data that measure reduced admissions or length of stay.[6]

The impact of corticosteroids in young children has not been studied sufficiently in well-designed clinical trials, and therefore, the risks have not yet been determined.[6] It is known in observational studies that the use of corticosteroids can prolong the time of viral shedding, thus subsequently increasing the risk of RSV exposure to other children.[6]

Treatment options for RSV bronchiolitis[3]

Treatment	Recommendation	Summary of findings	Level of evidence
Albuterol	Not recommended	Albuterol has not impacted the length of illness, requirement for hospitalization, or duration of hospital stay	Level B
Antibiotics	Not recommended	Only recommended with a secondary infection	Level B
Chest physiotherapy	Not recommended	Vibration or percussion has not demonstrated clinical benefit	Level B
Epinephrine	Not recommended	Negative cardiovascular effects	Level B
Hypertonic saline	Select populations	Reduces hospital duration	Level B
Oxygen	Select populations	Not routinely recommended for oxygen saturations greater than 90% but may be beneficial for those with an oxygen saturation <90%	Level D
Artificial nutrition and hydration	Select populations	If unable to tolerate oral intake, may need nasogastric or I.V. fluids	Level X
Pulse oximetry	Select populations	Research has demonstrated that the correlation between respiratory distress and oxygen saturation is poor	Level D
Systemic corticosteroids	Not recommended	Have not been shown to reduce admission or length of stay	Level A

The evidence-based approach reflects the quality of evidence and balances the benefit to harm ratio:

Level A: Thorough research conducted such as meta-analysis and gold standard studies; Level B: Consistent findings and diagnostic studies with minor limitations; Level C: Few observational studies or multiple studies with findings that are inconsistent or contain gross limitations; Level D: Supported by expert opinion, case reports; Level X: There is a clear preponderance of benefit or harm but validating studies cannot be executed.

Comprehensive systematic reviews of recently published research using the best-available clinical evidence and large multicenter randomized trials (as outlined in the current AAP guidelines) clearly describe that corticosteroids alone do not provide benefit to children with RSV. Further research is needed to determine if corticosteroid therapy combined with alpha-agonist and beta-agonist activity provides benefits to these children.[3]

Suctioning is often implemented to reduce the amount of secretions that are present in the nasopharynx (although there is no recommendation due to a lack of evidence). Retrospective studies found that deep suctioning contributed to longer durations of stay for those ages 2 to 12 months. There are not enough data available to make a recommendation about suctioning at this time, but research shows that deep suctioning is not beneficial.[3]

Prevention

There are simple measures that can be enacted to aid in the prevention or spread of RSV within the household. Frequent hand washing for a total of 20 seconds, avoiding close contact or sharing of utensils, avoiding kissing the infected individual, and cleaning contaminated surfaces are recommended.[2] AAP guidelines support the use of alcohol-based rubs when providing care to children with bronchiolitis. Soap and water can be used if alcohol-based rubs are not available.[3] Once infected with RSV, most individuals are contagious for 3 to 8 days. However, individuals with weakened immune systems and some infants can spread the virus for up to 4 weeks.[2]

Palivizumab, a RSV F protein inhibitor monoclonal antibody, is a recent drug that shows promise in preventing serious lower respiratory tract disease from RSV.[13] The drug focuses on a specific antigenic site of the RSV fusion glycoprotein.[10] AAP guidelines support the administration of palivizumab to 32-week premature infants who required oxygen during their first month of life and children with heart disease or chronic lung disease who are younger than age 1 year. Monthly doses are given during the RSV season to those who qualify.[3]

Implications for advanced practice in education, practice, and research

As leaders in the community, NPs can influence change through education, practice, and research. Because prevention is fundamental in controlling RSV, it is essential that NPs play a role in educating families, providers, and the general community on preventive measures. RSV management is supported through comprehensive evidence-based medicine that guides the provider on how to care effectively for these children, but it needs to be better disseminated. When families and providers are aware of the current evidence-based guidelines, shared decision-making with the parents may help improve outcomes for these children.

Education. Parents should be educated about ways to decrease exposure and transmission of RSV through proper hand washing, disinfecting surfaces, and avoiding close contact with infected individuals.[2] Infants at high-risk for RSV need to receive palivizumab. This biologic therapeutic agent is an FDA-approved prescription injection to help protect high-risk infants from severe RSV disease throughout the RSV season.[13]

The provider should assess for the caregiver's ability to care for an ill child and to have the child follow up for further evaluation if needed. Providers should be familiar with the variability of the disease and may require serial observation of the child. The respiratory rate in infants and children is variable depending on age, and the provider should be aware of these normal changes. Respiratory rates should be assessed for 60 seconds.

Practice. NPs should emphasize the importance of using the best-available data from high-level, evidence-based research as well as the importance of following the AAP consensus practice guideline. More emphasis should be placed through seminars and publications on the guideline's removal of the recommended use of albuterol. There is no current treatment available that shortens the course of RSV bronchiolitis or offers curative therapy, and this information needs to be shared in an effective manner.

The primary available treatment for RSV is supportive therapy, and the majority of children who are diagnosed with bronchiolitis seem to do well regardless of how it is managed.[1] Due to increasing costs with the healthcare system, it is essential that the focus remain on avoidance of therapies and tests that have demonstrated no benefit in children with bronchiolitis.[14] For NPs treating patients with worsening respiratory symptomatology and negative serology, referral to pediatric allergy/pulmonary specialist services for management of symptoms should be initiated. Consult disease specialty experts when concerned about coinfection.

Research. There is currently no safe, effective vaccine for RSV, but several approaches to vaccine development are currently underway. A live attenuated vaccine is

currently under development and shows promise, with trials continuing in spite of production challenges.[15] Immunizing pregnant women with a nonreplicating vaccine seems to be promising in early-phase trials. The ideal vaccine would target both strains of RSV and be safe, well tolerated, and immunogenic. Development of a vaccine would benefit the public through protection for those who are immunized but also improve herd immunity by decreasing spread to those who are at risk.[15]

NPs must keep current with scientific literature to be knowledgeable about ongoing clinical trials. The development of cost-effective strategies to treat RSV infections will be necessary to make further progress toward controlling RSV bronchiolitis hospital admissions in the United States. As NPs, an understanding of the basic concepts underlying an RSV diagnosis, what options are available, how to begin evidence-based treatment regimens, and when to hospitalize should guide the plan of care for patients.

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