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REVIEW

Overview of respiratory syncytial virus disease in young children

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J Michael Hoopes[1]
Veena R Kumar[2]

[1]Medical Information, [2]Medical and Scientific Affairs, MedImmune, LLC, Gaithersburg, MD, USA

Abstract: Respiratory tract illnesses associated with respiratory syncytial virus (RSV) were first reported more than 160 years ago and gained acceptance as a major respiratory pathogen in the late 1950s. Annual epidemics show a seasonal pattern typically beginning in the late fall and ending in early spring, averaging 5 months in length, and varying in time of onset, offset, and duration depending on geographic location. Manifestations of RSV illness primarily involve the upper respiratory tract but can spread to the lower airways and lead to bronchiolitis and/or pneumonia. Initial infection occurs in approximately two-thirds of children during the first year of life; nearly all children are infected at least once by 2 years of age. Reinfection is common throughout life, but initial illness during infancy generally presents with the most severe symptoms. Medical risk conditions that consistently predispose young children to serious lower respiratory tract infection (LRTI) include congenital heart disease, chronic lung disease, and premature birth. Serious LRTI due to RSV is the leading cause of hospitalization in infants and young children worldwide and annual mean hospital expenses have been estimated to exceed 1 billion dollars in the United States. Young children incur more inpatient and outpatient visits for RSV LRTI than for influenza. RSV has a greater impact than influenza on hospitalization in infants with respect to length of stay, severity/course of disease, and resultant needs for ancillary treatments. Unlike many other childhood illnesses, a vaccine is not currently available for preventing RSV disease.

Keywords: bronchopulmonary dysplasia, infants, hospitalization, prematurity, respiratory syncytial virus

History

Initial descriptions of an illness in young children that was later associated with respiratory syncytial virus (RSV) infections were first reported more than 160 years ago.[1] Approximately 90 years later, the clinical syndromes bronchiolitis and pneumonia, associated with cough, fever, and severe viral infection, were reported in infants over the period of two winter seasons.[2,3] This was soon followed by isolation of a virus in chimpanzees (initially termed "chimpanzee coryza agent" [CCA]),[4] as well as from a group of infants who developed bronchiolitis and pneumonia.[5,6] Given that the virus demonstrated the ability to induce formation of multinucleated cells surrounded by large syncytia, the term CCA was subsequently abandoned in favor of a more descriptive name, respiratory syncytial virus.

Investigators quickly became aware of the clinical consequences and importance of RSV infection; many hallmarks of serious RSV disease were identified from multiple epidemics reported during the late 1950s and early 1960s.[7–10] A pattern became

Correspondence: J Michael Hoopes
MedImmune, LLC, 1 MedImmune Way, Gaithersburg, MD 20878, USA
Tel +1 301 398 5520
Fax +1 301 398 8520
Email hoopesm@medimmune.com

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evident in which isolation of RSV from young children and infants occurred most frequently in the United States between the months of October and April, with peaks noted during January and February. Whereas most infected infants developed mild to moderate cold-like symptoms, severe RSV infection often resulted in bronchiolitis, pneumonia, and acute respiratory distress. Deaths occurred in rare cases.[7,11] Young children were shown to be susceptible to multiple RSV infections, but serious illness was most common during the first infection, particularly during early infancy.

Findings from these early reports facilitated further study into the epidemiology and prevention of RSV disease. It was subsequently observed that initial infection with RSV occurred in approximately two-thirds of children before their first birthdays, and nearly all were infected at least once by two years of age.[12] Re-infection was a common finding. An inverse relationship between age and lower respiratory tract involvement was established, and repeat infections were noted to result in less severe disease than that occurring during the initial occurrence.[13]

Initiatives aimed at preventing lower respiratory tract infection (LRTI) due to RSV began in the 1960s with field trials of a formalin-inactivated vaccine.[14–17] These early studies were met with unexpectedly disastrous results as the vaccine not only failed to prevent disease, but many children, particularly those younger than 12 months, developed serious respiratory illness, and deaths were reported upon reinfection with wild-type RSV.[16] Vaccine development was subsequently stalled for more than 20 years, but due to the prevalence of RSV disease in children, new vaccine research is currently ongoing. Because active immunization (ie, vaccination) was not initially successful, research efforts led to development of alternative passive immunization (ie, human antibodies) strategies ranging from monthly administration of standard or enhanced human immunoglobulins[18,19] to the development of monoclonal antibodies.[20,21]

Epidemiology of RSV infection

Clinical presentation of RSV disease in young children

Manifestations of RSV infection mainly involve the upper respiratory tract following large particle aerosol deposition or direct contact with the epithelium of the eyes and nasopharynx.[22] After an incubation period of approximately 4 to 6 days,[23] RSV-related illness in infants and young children typically starts as a mild to moderate upper respiratory tract illness that most often includes fever, cough, and runny nose. For some, however, spread to the lower respiratory tract a few days later can lead to more serious RSV-related bronchiolitis and/or pneumonia leading to hospitalization.[24]

Seasonality of RSV disease

The Centers for Disease Control and Prevention (CDC) have been monitoring RSV outbreaks since the 1980s through the National Respiratory and Enteric Virus Surveillance System (NREVSS), a laboratory-based voluntary reporting program monitoring at least 39 states and the District of Columbia in the USA. Cumulative data of weekly and monthly RSV activity are routinely updated by the CDC from NREVSS reports, and yearly and multiyear analyses have been conducted to determine seasonality trends.[25,26] Reports show that in the northern hemisphere, RSV circulates at epidemic levels nationally most frequently between the months of November and March; however, regional or local activity is frequently observed in the shoulder months of October and April. The peak of activity is typically observed in January and February. Year-round outbreaks, however, have been noted in some states with warm climates such as Florida,[27] and the CDC acknowledges this observation in separate data analyses. Findings from multiseason analysis of the CDC surveillance program indicate a nationwide median season duration of 15 weeks with variable onset and offset dates depending on individual geographic location.[25,26] Variation in the timing of RSV activity has been reported in the same community from 1 year to another, making it difficult to predict the onset and duration of RSV outbreaks. Local RSV virology data are the most reliable guide to predicting the timing of onset and offset of the RSV season.

Risk factors for serious RSV disease

Many investigators have published findings regarding patient and environmental characteristics (risk factors) that increase the potential for serious lower respiratory tract disease secondary to RSV infection. Nearly two dozen risk factors have been identified, but findings have varied across studies.[28] This is likely due to differences in a variety of factors, including demographic (eg, gestational and postnatal ages of children studied), clinical (eg, RSV seasons of study, RSV strains, extent of exposure to potential risk factors), geographic, and social (eg, daycare attendance and/or crowded living conditions).

Well-established disease- and patient-specific risk factors have consistently been found to increase the likelihood of serious RSV disease, including congenital heart disease (CHD),[29] bronchopulmonary dysplasia (BPD),[30] and premature birth,[31,32] which, combined, accounted for 12.2% of all births in the

United States in 2009.[33] RSV-related hospitalization during the first two years of life has been reported for up to 30% of infants who have BPD or CHD.[29,30] Because RSV infection is spread by large droplet aerosols and direct contact, it is not surprising that the risk of serious RSV illness in premature infants is increased if they attend a child care facility or share a dwelling with multiple siblings or other children.[24] Conditions that compromise handling of respiratory tract secretions such as congenital abnormalities of the airway and severe neuromuscular disease are also largely believed to increase the risk of serious RSV disease, but fewer studies have been conducted to examine these factors.[24,34]

Burden of RSV disease

Young infants have narrow airways that are inherently susceptible to obstruction and often possess an immature immune system that is not capable of fending off infection. Thus, it is not surprising that RSV infection is associated with substantial morbidity in both the inpatient and outpatient settings.[31]

RSV-related hospitalization and associated costs

In the United States, RSV bronchiolitis has been reported to be the leading cause of hospital admissions among infants[35] and is the most frequently cited cause of hospitalization (ie, approximately 120,000 hospital admissions annually) due to serious lower respiratory tract disease in infants and young children.[22,31,35–38] Reported hospitalization rates reported for infants range from 13 to 27.4 per 1000 births, with most hospitalizations reported for patients <6 months of age, and particularly in infants aged 1 to 3 months.[37–42] Among young children worldwide, RSV is the most common cause of LRTI and is a major cause of hospitalization for severe RSV-related LRTI.[43] In contrast to influenza, recent data suggest that infants hospitalized due to RSV disease generally have longer hospital stays, a more severe course of disease, and a greater need for ancillary treatments such as supplemental oxygen.[44] Additionally, the likelihood of death among children <1 year of age has been reported to be greater for those with RSV-associated illness than for similarly aged children infected with influenza.[45]

Annual mean hospital expenses for RSV LRTI are estimated to be in excess of 1 billion dollars.[41] This cost estimate does not take into consideration the impact hospitalization has on the quality of life for the affected child, caregivers, and the child's family.[46] Reported mean costs associated with individual hospitalization of children for RSV illness vary widely and have been reported to range from US$3,355[47] to US$27,661.[48] Reasons for this variance include differences in child demographics such as age, underlying risk factors and present health conditions, severity of LRTI, local standards of care, and family insurance status. All of these variables can ultimately influence the length of hospitalization and requirement for treatment in a specialty intensive care unit and ancillary supportive therapy. For example, total costs for an RSV-related hospitalization of infants with risk factors predisposing one to more severe illness (ie, CHD, BPD, or prematurity) are, on average, 1.5 to 3 times higher than hospitalizations of other infants or young children with RSV LRTI.[48] Costs for children with CHD are historically the greatest, and it is not uncommon for the cost of an RSV-associated hospitalization in these children to exceed US$85,000.[49] These high costs result from the frequent need for mechanical ventilation and other ancillary support, which can lead to hospital stays of 1 week or longer.[50]

Results of RSV cost analysis studies should be interpreted with several limitations in mind and an understanding that reported costs are likely an underestimation of actual total costs incurred. Studies that retrospectively assess comparative costs of hospitalization among infants typically rely on *International Classification of Diseases, Ninth Revision*[51] diagnoses identified from a claims database. Using this method may result in underreporting of the cohort size for the conditions of interest.[48] Indirect costs, such as caregiver out-of-pocket expenses and lost work time, as well as expenses related to outpatient medical care visits immediately before and after hospitalization, are routinely excluded from cost analysis studies.

RSV infection in the outpatient setting

The number of visits to an emergency department (ED) or outpatient primary care facility for medical attention to treat RSV LRTI in young children far exceeds those of RSV-related hospitalizations.[52] From 1992 to 2000, nearly 2 million children <2 years of age presented to the ED for a bronchiolitis illness.[53] Paramore et al conducted a retrospective cohort study of data from a national claims database to determine rates for outpatient, nonhospitalized visits for RSV LRTI among high-risk (ie, premature birth, BPD) infants ≤6 months of age.[54] The rate of overall outpatient RSV LRTI-related visits (ED and ambulatory) for high-risk infants ranged from 180–270/1000 infants during the infants' first RSV season. Notably, the BPD cohort had the highest overall rate of outpatient encounters (ie, 212.2–272.6/1000

infants). Although prematurity is an independent risk factor for developing serious RSV illness, no significant trends between medical encounters and degree of prematurity as defined by gestational age were observed.

Hall et al conducted a prospective, population-based surveillance of acute respiratory infection among children born primarily at term to determine the burden of documented RSV infections among those presenting as outpatients in the ED and primary care settings from 2002 through 2004.[31] Overall, RSV was associated with 18% and 15% of ED and office visits for acute respiratory infections, respectively. The estimated rates of outpatient visits were higher for office than for ED visits and were significantly greater for children younger than 6 months with RSV infection than for those of a similar age with influenza.

Mansbach et al conducted a prospective, multicenter, ED-based study to determine the viral etiology of bronchiolitis and clinical characteristics of children younger than 2 years who presented to the ED with bronchiolitis during the period from December 14, 2005 to March 19, 2006.[55] RSV was the most frequently isolated virus and was detected in 64% (176/277) of children versus 16% for rhinovirus, 9% for human metapneumovirus, and 6% for influenza A. Major presenting symptoms included cough, wheeze, and fever.

Bourgeois et al evaluated the relative impact of RSV and influenza infections in young children in terms of ED visits, clinical care requirements, and overall resource use as determined from state (ie, Massachusetts) and national data.[56] There were approximately twice as many visits for an RSV-related illness than for an influenza-related illness at both the state and the national level. Similarly, children infected with RSV were significantly more likely than children with an influenza-related illness to have medications administered (74% versus 49%, $P < 0.001$), have a radiologic study performed (69% versus 44%, $P < 0.001$), or be admitted to the hospital (40% versus 14%, $P = 0.02$). Children younger than 2 years and infected with RSV had 64.4 visits/1000 children versus 15.0 visits/1000 children for those with influenza. RSV-related illness has a substantial impact on caregivers. Caregivers miss nearly 3 times as many work days per year due to RSV-related illness at the national level compared with influenza-related infections (ie, 716,404 days versus 246,965, respectively).[55] An earlier population-based study design by the same group was used to estimate the rate of ED visits for acute respiratory infections during a 12-year period (ie, 1993–2004) in Massachusetts.[57] Overall, at the state level, there were approximately four times as many outpatient visits for RSV than for influenza and nearly three times more visits among children 6 to 23 months of age.

Potential long-term consequences of serious RSV infection

RSV bronchiolitis early in life is thought to be an important independent risk factor for developing bronchial hyperresponsiveness and recurrent wheezing later in life, but the reasons for this hypothesis have not been clearly elucidated or clinically proven.[58–63] Additionally, this association has been observed with other viruses (eg, rhinovirus) and the interaction of such infections with RSV and the contribution of individual predisposition due to a family history of asthma or allergies remains unknown.[64–66]

Conclusion

RSV is a prominent pathogen acquired during early childhood and is the leading cause of hospitalization due to serious lower respiratory tract disease in infants and young children worldwide. The economic burden of this disease is enormous as RSV is responsible for more medically-attended inpatient and outpatient visits than influenza in children younger than 1 year. RSV infection is a common childhood viral disease for which a vaccine is currently not available.

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