

Respiratory syncytial virus: diagnosis, prevention and management

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Abstract: Respiratory syncytial virus (RSV) is responsible for a large burden of disease globally and can present as a variety of clinical syndromes in children of all ages. Bronchiolitis in infants under 1 year of age is the most common clinical presentation hospitalizing 24.2 per 1000 infants each year in the United Kingdom. RSV has been shown to account for 22% of all episodes of acute lower respiratory tract infection in children globally. RSV hospitalization, that is, RSV severe disease, has also been associated with subsequent chronic respiratory morbidity. Routine viral testing in all children is not currently recommended by the United Kingdom National Institute for Health and Care Excellence (NICE) or the American Academy of Pediatrics (AAP) guidance and management is largely supportive. There is some evidence for the use of ribavirin in severely immunocompromised children. Emphasis is placed on prevention of RSV infection through infection control measures both in hospital and in the community, and the use of the RSV-specific monoclonal antibody, palivizumab, for certain high-risk groups of infants. New RSV antivirals and vaccines are currently in development. Ongoing work is needed to improve the prevention of RSV infection, not only because of the acute morbidity and mortality, but also to reduce the associated chronic respiratory morbidity after severe infection.

Keywords: cohorting, infection control, nosocomial infection, palivizumab, respiratory syncytial virus, RSV

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Introduction

Respiratory syncytial virus (RSV) is a ubiquitous pathogen infecting almost all children by 2 years of age.¹ RSV infection can present as a variety of clinical syndromes including upper respiratory tract infections (URTIs), bronchiolitis, pneumonia, exacerbations of asthma and viral-induced wheeze. The greatest burden of severe disease needing hospitalization is in infants under 1 year of age.¹ It was estimated that globally in 2015 there were 33.1 million episodes of RSV acute lower respiratory tract infection (ALRI), 3.2 million hospital admissions and 59,600 in-hospital deaths in children under 5 years of age.² Data combining both hospital and community deaths estimated 94,600–149,400 global deaths annually.² A Canadian study investigating factors associated with

RSV-related mortality in children found that the median age of death was 11 months and healthcare associated infections accounted for 36.7% of deaths. Although the majority of the deaths in this study were in children with chronic medical conditions or underlying immunocompromise, one in five deaths occurred in children with no known risk factors for severe clinical disease.³ Globally RSV is the most common cause of lower respiratory tract infections in childhood, accounting for 22% of all episodes of ALRI.^{1,4}

In the United Kingdom (UK), RSV accounts for an average of 29,160 hospital admissions and 83 deaths per RSV season (October to March).⁵ Furthermore, of the infants requiring hospital admission with RSV infection in the first year of

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life, 2–6% of them will require management in a paediatric intensive care unit.⁶ The impact extends beyond the hospital setting into the community, with an estimated 450,000 general practitioner (GP) episodes for children and adolescents annually.⁵ Although the greatest burden is in infants less than 6 months old, followed by those 6–23 months old, 36% of those GP consultations were in the 2–4 year-old age group.⁵

Healthcare costs associated with RSV infection in children younger than 5 years of age have been estimated at £50–57 million annually in the UK with approximately £37 million of this attributable to those children requiring hospitalization. The costs of hospitalization are roughly evenly split between infants less than 6 months old and those 6 months–5 years old.⁷ Annual costs related to GP consultations are estimated at £16–19 million.⁷

RSV bronchiolitis

Bronchiolitis is an inflammatory process in the small airways of the lungs and is the most common clinical syndrome associated with RSV infection. It typically presents in infants under 1 year of age but may be diagnosed in children up to 2 years old, and is characterized by a short history of low-grade fever, cough, coryza, difficulty in breathing and reduced feeding. The symptoms usually peak in clinical severity between day 3 and 5 of illness.⁸ It is important to remain vigilant to the fact that very young infants (under 6 weeks of age) may present with apnoea alone in the absence of other clinical signs or symptoms.⁸

There are a number of risk factors that predispose infants to developing RSV infection within a given season including the presence of an older sibling, birth proximity to the RSV season, low birth weight, male sex, young age (<6 months), exposure to smoking, young maternal age and suburban residence.¹ Risk factors for more severe disease include premature birth, congenital heart disease, chronic lung disease and immunodeficiency.⁸ Cystic fibrosis, Down syndrome, cerebral palsy and timing of birth in close proximity to the RSV season, that is, birth in September and October, are also associated with a higher risk of requiring hospital admission for RSV infection.⁹ However, 85% of infants admitted to hospital with RSV bronchiolitis are born at term without any known risk factors for severe disease.⁹

RSV bronchiolitis presents a significant clinical burden with hospital admissions in the UK of 24.2 per 1000 infants.⁹ Rates are similar in the United States (US) where between 1997 and 2006 the rate of RSV associated hospitalization in children under one year of age was 26.0 per 1000 infants.¹⁰ In the UK, infection with RSV is responsible for up to 80% of all cases of bronchiolitis, similar to that of 65–70% in the US.^{6,11}

RSV infection in older children

In older children, RSV typically presents as an URTI, viral pneumonia, episodic viral-induced wheeze or an acute exacerbation of asthma. Viral pneumonia is a common illness with 5 million cases reported in children in developed countries annually.¹² A meta-analysis of nine studies involving over 4000 children investigating viruses identified by polymerase chain reaction, found that RSV was the causative organism in 11% of community-acquired pneumonia cases.¹²

Viral-induced or episodic wheeze is the clinical syndrome of wheezing associated with periods of clinically evident viral infection with no interval symptoms. It most commonly presents in preschool-aged children and RSV is among the most common causative agent with one study finding it in 33% of symptomatic children.^{13,14} Episodic viral wheeze is a very common clinical syndrome with one study across the US and six European countries showing that 42% of preschool children reported recurrent days of wheeze in the preceding 6 months over winter.¹⁵ Some children included in this study may have been exhibiting the initial symptoms of asthma rather than episodic wheeze. Atopic asthma is a clinically distinct syndrome in which symptoms tend to be persistent and may have multiple triggers. RSV is associated with acute exacerbations of asthma in school-aged children; however, unlike in younger children, RSV plays a relatively minor role in this cohort, with rhinovirus being the most significant contributory pathogen (rhinovirus 50–60% *versus* RSV 1.5%).^{16,17}

Clinical usefulness of respiratory virus testing

Respiratory viral testing may be used in a clinical setting to increase confidence in the diagnosis of a viral, rather than bacterial, cause for respiratory illness.^{18,19} Given the typically short duration of the clinical illness, a rapid diagnostic test is required in

order to have an impact on clinical decision-making. A meta-analysis of RSV rapid diagnostic tests found that summary sensitivities and specificities for these tests were 75.3% and 98.7% respectively.²⁰ This suggests that although false negatives are not uncommon, a positive result may increase confidence in the diagnosis and could support decision-making, such as reducing the likelihood of prescribing an antibiotic inappropriately. A number of studies have demonstrated that the use of point-of-care respiratory virus testing reduces the number of prescriptions for, and duration of, antibiotic treatment as well as reducing investigations such as blood tests, urinalysis and chest X-rays.^{18,21–24} Studies investigating the use of respiratory viral testing in the emergency department (ED) have also demonstrated a reduction in the length of time spent in the ED by an average of 40 min.^{22,23} Clinicians, however, need to maintain an awareness of the possibility of concomitant viral and bacterial infection. One study highlighted that two patients (1.2%) who had tested positive for a respiratory virus also had a culture-proven bacterial infection.²¹

The National Institute for Health and Care Excellence (NICE) guidelines and American Academy of Pediatrics (AAP) guidelines for bronchiolitis do not recommend respiratory viral testing routinely in children in whom bronchiolitis is clinically suspected.^{8,11} The AAP guideline comments that the benefit to the individual patient of respiratory viral testing has not been established and only recommends testing in the specific event that a child receiving monthly palivizumab injections has been admitted with bronchiolitis. In this circumstance, a positive result could mean that further doses of palivizumab would not be needed.¹¹ Respiratory virus testing may be considered in other circumstances and has previously been reviewed in detail.¹⁹ A national survey looking at management practices of bronchiolitis across the UK found that routine testing of hospitalized infants for respiratory viruses dropped from 72% prior to the NICE guideline publication to 44% after.²⁵

Investigations and treatment for RSV infection

As discussed above, respiratory viral testing may be of some benefit in the investigation of children with symptoms suggestive of RSV infection. However, further investigation including blood

tests or chest X-rays are not currently routinely recommended in children with bronchiolitis or episodic viral wheeze.^{8,26} A chest X-ray may be considered in children in whom intensive care is being proposed or those with atypical disease, and blood gas measurement if there is severe worsening respiratory distress or suspected impending respiratory failure.^{8,26}

Treatment of RSV infection remains supportive (oxygen supplementation and feeding support) in most clinical scenarios. In infants with bronchiolitis there is no evidence of benefit for bronchodilators, corticosteroids, antibiotics, nebulized epinephrine, leukotriene inhibitors, nebulized hypertonic saline or chest physiotherapy.^{27–33} Ribavirin is licensed for use as a treatment for infants with bronchiolitis. However, the most recent Cochrane review of its use in 2007 suggested that the available evidence at that time was insufficient to confidently state whether or not ribavirin is clinically effective at treating RSV bronchiolitis.³⁴ Therefore, due to its side-effect profile and lack of reproducible data on efficacy it is not currently recommended for routine use in RSV bronchiolitis in infants in the UK or US. The inhaled form of the drug is also extremely costly with wholesale prices for a single day of treatment quoted at US\$29,000 in the US.³⁵

There is limited evidence for use of ribavirin in certain high-risk groups of children, such as those who have undergone a haemopoietic stem cell transplant (HSCT) or those who are severely immunocompromised. One small study looking at 28 patients who had undergone HSCT, 24 of whom received ribavirin showed a reduction in mortality in those receiving ribavirin with a risk ratio of 0.33 [95% confidence interval (CI) 0.17–0.64, $p=0.001$].³⁶ A review of studies reporting a total of 273 cases of RSV infection in HSCT patients found 44 patients with an URTI were treated with ribavirin, of which 25% progressed to a lower respiratory tract infection (LRTI) in comparison with 47% of those who did not receive ribavirin ($p=0.01$).³⁷ Of 128 patients with a LRTI, 50% treated with ribavirin died compared with 89% not treated ($p=0.04$).³⁷ Although these results suggest a role for ribavirin in this population the included studies had small numbers of patients and different study designs and cannot be easily used to produce a single summary statistic.

Another treatment that has been considered in the treatment of RSV is intravenous immunoglobulin (IVIG), either standard or RSV-specific. A Cochrane review looking at four studies using immunoglobulin therapy found that although it may be effective at lowering viral titres, it did not appear to correlate with improved clinical outcomes.³⁸ However, of the four studies included, one looked at intravenous human normal immunoglobulin (IVIG), two at RSV-specific immunoglobulin and one at aerosolized immunoglobulin. Overall, two studies were performed on otherwise healthy children with RSV infection and two on children with risk factors for severe disease. RSV-specific immunoglobulin was removed from the market in 2004 and is no longer available. Palivizumab, a humanized mouse monoclonal antibody, is an effective prophylactic agent against RSV but has also been trialled as an RSV treatment. However, even among immunocompromised patients it has not been shown to reduce mortality or progression to LRTIs when used as a treatment.^{39,40}

Ribavirin and immunoglobulin given together has also been investigated as a therapeutic option. A review of 13 studies in adults who had undergone HSCT showed a reduced risk of progression from URTI to LRTI (12% versus 25%, $p=0.13$) and reduced RSV-specific mortality (24% versus 50%, $p<0.001$) in patients who received dual therapy when compared with those using ribavirin alone.⁴¹ The British Society for Haematology currently recommends that adult patients who have undergone an allogeneic stem cell transplant and who have risk factors for progression of RSV URTI to LRTI should receive aerosolized or oral ribavirin in combination with IVIG.⁴² We are not aware of any similar paediatric data or guidance.

In older children with episodic viral wheeze or an exacerbation of asthma, inhaled bronchodilators are recommended, along with a short course of oral corticosteroids in children with asthma or those with episodic wheeze and a clear history of atopy.^{26,43} There is no role for antiviral treatment in this clinical scenario.

Transmission of RSV and preventing nosocomial infections in hospital

RSV is a human restricted pathogen and typically spreads *via* hands, fomites and the aerosol route.⁴⁴

The basic reproduction number (R_0 , the number of cases one case generates on average over the course of its infectious period, in an otherwise uninfected population) of RSV is estimated to be between 1.2 and 3.0 (similar to that of influenza).^{45,46} This knowledge is important for preventing RSV transmission, both in the community and in the hospital setting. Within families, RSV has been shown to spread rapidly with one study investigating 52 families with a child hospitalized for RSV infection finding that in 77% of families at least one other member was RSV-positive.⁴⁷ Furthermore, in 58% of cases, a parent or older sibling was considered to be the likely primary case within the family highlighting the importance of preventing transmission where possible.⁴⁷

Within the hospital setting, the NICE guideline on bronchiolitis does not give advice on cohorting infants or infection prevention and control procedures to prevent nosocomial spread.⁸ A national survey in the UK found that individual trusts use a variety of cohorting practices including cohorting infants with the same causative virus, cohorting those with RSV, cohorting all infants with a clinical diagnosis of bronchiolitis in cubicles and cohorting all infants with a clinical diagnosis of bronchiolitis together, regardless of the causative virus.²⁵ These practices did not change significantly with the publication of the NICE guidance in 2015.²⁵ The AAP guideline recommends decontamination of hands with alcohol-based gel before and after every patient contact when managing patients with RSV.¹¹ A systematic review of infection control measures to prevent nosocomial RSV transmission found that multicomponent interventions appeared to be most effective, with reductions in transmission of up to 50%.⁴⁸ The interventions studied included case-finding, screening on admission, patient and staff cohorting, restriction of visitors, staff training and use of personal protective equipment.⁴⁸ Prevention of nosocomial transmission of RSV is particularly important as it has been demonstrated that infants with nosocomial infection have a more severe clinical course compared with those with community-acquired disease.⁴⁹ Some studies have suggested that infants with nosocomial infection may have a higher mortality rate (0–12.2% higher) than those with community-acquired infection.⁵⁰ A study in Canada looking at mortality from RSV infections found that 36.7% of deaths from RSV were attributable to nosocomially acquired infection.³ Given

that these infants tend to have a more severe clinical course, the associated cost of nosocomial infections is higher. A study in the US compared costs between children with nosocomial and community-acquired RSV infection. They found that the mean cost per patient was between US\$20,347 and US\$45,335 higher in nosocomial infections than in community-acquired infections.⁵¹

Preventing severe RSV infection

A number of independent risk factors have been shown to be associated with RSV hospitalization as highlighted above. Some of these risk factors are modifiable, for example, parents should be encouraged not to smoke. For certain groups of infants at high risk of severe RSV infection palivizumab, a monoclonal antibody directed against an antigenic site in the RSV fusion (F) protein, is recommended as a preventive measure.⁵² Palivizumab is currently recommended for use in the UK in the following groups of children:⁵²

- Preterm infants who have moderate or severe bronchopulmonary dysplasia (BPD) at specific chronological ages at the start of the RSV season.
- Infants with respiratory diseases (e.g. pulmonary hypoplasia due to congenital diaphragmatic hernia and interstitial lung disease) requiring oxygen or long-term ventilation at the start of the RSV season.
- Preterm infants with haemodynamically significant acyanotic congenital heart disease.
- Children with cyanotic or acyanotic congenital heart disease with significant comorbidity.
- Children under 24 months with severe combined immunodeficiency (SCID).⁵²

Palivizumab is given as an intramuscular injection monthly (up to five doses) during the RSV season.⁵² Although it is currently licensed for use in the above groups of children, its high cost of £3000–£5000 per patient per season has meant that there have been ongoing cost-effectiveness controversies. It may only be cost effective in the subgroups of infants at the highest risk of severe disease.^{53–55} A systematic review and subgroup analysis has suggested that at a willingness-to-pay threshold of £30,000 per quality-adjusted life

year, the subgroups in which palivizumab is cost-effective may be much more restrictive.⁵⁴ For example, one subgroup in which palivizumab was found to be cost-effective was those with congenital cyanotic heart disease who are less than 6 weeks old at the start of the RSV season and were born at less than 25 weeks of gestational age.⁵⁴ Palivizumab currently remains the only preventive medication licensed for use in the UK or US.

Chronic respiratory morbidity after RSV infection in infancy

Severe RSV bronchiolitis in the first year of life is associated with an increased risk of wheeze and asthma in later life.^{56–58} A study investigating infants with mild RSV infection in the first year of life not requiring hospitalization showed that RSV was associated with an increased risk of wheezing at 1 year of age (OR = 1.6).⁵⁹ It has been debated whether early-life RSV infection causes damage to the lungs resulting in a predisposition to wheeze later in life, or whether these infants already have a subclinical underlying problem with their lung function that predisposes them to both severe RSV infection and later-life wheezing.⁶⁰ A causal relationship between early RSV infection and later wheezing is supported by data suggesting prophylactic palivizumab reduces recurrent wheezing episodes in infants born prematurely.^{61,62} One study found that in infants born at less than 35 weeks of gestation, the incidence of recurrent wheezing in those who received palivizumab was 13% *versus* 26% in those who did not ($p = 0.001$), giving a risk ratio of 0.51 (95% CI 0.33–0.78).⁶¹ A second placebo-controlled, double blind study of infants born at 33–35 weeks of gestation found a relative reduction in total number of wheezing days in the first year of life of 61% in infants who received palivizumab *versus* those who received placebo (95% CI 56–65%).⁶² It has been debated whether these effects, if true, are long lasting and follow up of the infants in the study by Blanken and colleagues at 6 years of age showed a reduction in parental-reported asthma but no difference in the proportion of children with physician-diagnosed current asthma or lung function between those who received palivizumab or placebo.⁶³ Another 6-year follow-up study of children administered with palivizumab during their first RSV season, showed a reduction in physician-diagnosed recurrent wheeze over the study period (15.3% in those who received

palivizumab *versus* 31.6% in those who did not, $p=0.003$).⁶⁴ However, it did not show a significant difference in the prevalence of atopic asthma at 6 years of age between the two groups (15.3% *versus* 18.2%, $p=0.57$).⁶⁴

In contrast with this and not supportive of a causative link between severe RSV infection and subsequent chronic respiratory morbidity, term-born infants receiving another similar F-specific monoclonal antibody against RSV, motavizumab, did not show a difference compared with placebo in the presence of wheeze when followed up to 3 years of age.⁶⁵ These differences may be due to inherent differences in the lungs or immunity of prematurely and term-born infants. It is thus still not clear what role severe RSV infection in infancy plays in the development of chronic respiratory morbidity.

Future horizons in RSV vaccines and other anti-RSV therapeutics

Given the huge burden of disease and the associated costs caused by RSV globally there is much ongoing research into the development of a well-tolerated and effective vaccine. The main target populations for vaccination include infants, school age children, pregnant women and older adults. Multiple different vaccine approaches are being considered including live-attenuated/chimeric, whole-inactivated, particle-base, subunit, nucleic acid and gene-based vectors. There are also ongoing efforts to develop long acting (to cover a whole RSV season) monoclonal antibodies (mAbs) for infants. These vaccines and mAbs have recently been reviewed by Mazur and colleagues.⁶⁶ A phase III clinical trial (ClinicalTrials.gov identifier: NCT02624947) of an RSV maternal vaccine has recently completed. Unfortunately, it did not reach its primary endpoint of prevention of medically significant RSV LRTI but did show vaccine efficacy of 44% against RSV LRTI hospitalizations and 48% against RSV LRTI with severe hypoxaemia.⁶⁷ It is likely that a licensed RSV vaccine is several years away at least. In addition, three agents have been extensively used and investigated as antiviral treatments for RSV (namely ribavirin, IVIG and palivizumab). None have proven to be an unequivocally beneficial and effective treatment and so research continues into future therapies. There are at least 14 anti-RSV treatment products undergoing clinical trials (phase I and II only), of which 5 have so far included paediatric patients.⁶⁸

Types of novel therapeutic molecules that have been developed include fusion inhibitors, nonfusion inhibitors, polymerase inhibitors, antibodies, nucleoside analogues, small-interfering RNAs and a benzodiazepine. They have various targets on RSV such as the F protein, RNA polymerase, nucleoprotein and nucleocapsid mRNA.⁶⁸ Over the coming years it is hoped one of these products will become a licensed treatment for RSV infection in children (and adults).

Summary

RSV is a ubiquitous infection with a significant global clinical and financial burden. Currently the management of RSV in infants and children is primarily supportive with antiviral medications reserved for only the most vulnerable populations. Palivizumab continues to be the only effective prophylactic medication licensed for use; however, its high cost prevents it from being used in all infants. Given these factors, the development of a well-tolerated, clinically effective and cost-effective RSV vaccine and therapeutic agent remains a major unmet global health priority.

Author's Note

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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