ABSTRACT

By age 2, nearly all children have been infected with respiratory syncytial virus (RSV), with 1% to 3% hospitalized because of the infection. The economic costs of RSV are also significant, at least $9115 higher in the first year of life for infants hospitalized with RSV than for those who are not hospitalized. The regional seasonality of the disease enables specific geographic areas to identify key times for infection and time prophylaxis for high-risk children. Identifying the risk factors is also important. Recent studies find that levels of maternally transferred immunoglobulin antibodies predict the risk of severe RSV in preterm infants. Other risk factors include chronic lung disease, congenital heart disease, neuro-muscular disease, and immune suppression. Even in full-term infants with no medical conditions, the risk of RSV-related hospitalization increases with the number of people in the home, seasonality of birth, attendance in day care, and cigarette smoke exposure. Utilizing verified risk factors together with the knowledge of the seasonality of RSV could provide an opportunity for more precise identification of infants who could benefit from RSV immunoprophylaxis.

Respiratory syncytial virus (RSV) was first identified in the 1950s in chimpanzees with cold symptoms and coryza. It was originally called “chimpanzee coryza agent” until it was recovered from infants with lower respiratory illness and characterized by a syncytial cytopathogenic effect in tissue culture. The virus, a single-stranded, nonsegmented RNA virus, is a member of Paramyxoviridae, the same virus family as parainfluenza viruses.

The virus recruits macrophages, lymphocytes, and neutrophils to the lungs, triggering an inflammatory process that results in the production of a thick mucus that blocks alveoli in the bronchioles. Given the small size of the bronchioles in infants, this leads to hyper-inflation and, eventually, hypoxemia.

Clinical characteristics of RSV infection include upper respiratory infection marked by rhinorrhea and nasal congestion that lasts between 7 and 12 days. Between 6% and 83% of children overall are reinfected each year, demonstrating an inadequate immune response to the initial infection. By 2 years of age, nearly all children have been infected with RSV, and 1% to 3% are hospitalized because of the infection.

Approximately 33% of children develop RSV bronchiolitis, a lower respiratory tract infection (LRTI) marked by a low-grade fever, coughing, and wheezing followed by dyspnea and severe tachypnea. In addition, apnea occurs in premature infants and, in some cases, in full-term, normal infants aged younger than 6 weeks. The risk of RSV LRTI may be related to respiratory control center maturity. It is associated with significantly higher rates of intubation and oxygen administration.

BURDEN OF RSV

The global burden of RSV is significant. A recent meta-analysis suggests that up to 200 000 children...
aged younger than 5 years die worldwide each year because of RSV-related infections, with 33.8 million new RSV-associated acute LRTIs among children under age 5 (22% of all LRTI cases) each year. At least 3.4 million cases required hospital admission, and an estimated 66,000 to 199,000 of the children died, nearly all in developing countries.9

In the United States, RSV is the most common cause of hospitalization in infants aged younger than 1 year, associated with approximately 75,000 to 125,000 hospitalizations annually and accounting for 1 out of every 334 hospitalizations in children aged younger than 5 years.8,10,11 The virus is associated with approximately 17,000 all-cause deaths each year in the United States, including 3.3% of all deaths from pneumonia and influenza; 1% of all deaths from respiratory and circulatory deaths; and 0.8% of all-cause deaths. The majority of deaths occur in persons aged 65 years and older.12

Given the high rate of hospitalization, it is to be expected that medical costs related to RSV are significant. Indeed, a recent economic analysis found that infants with RSV LRTI had healthcare costs $9115 higher in the first year of life than those without. Late preterm infants with an RSV hospitalization incurred costs $21,977 higher (P < .001), and those with an outpatient RSV infection $3898 higher (P < .001), than children without the infection.11

**Seasonality of RSV**

The incidence of RSV varies significantly based on seasonality, with the majority of infections occurring in the fall and winter months and lasting an average of 6 months. However, there is wide geographic variation.

The Centers for Disease Control and Prevention finds that southern states typically demonstrate an earlier median season onset (week 47) and longer duration than other regions (16 weeks; Figure 1), with the Midwest demonstrating a much later median onset (week 1) with a shorter duration (13 weeks).13,14 In some states, such as Hawaii, infections continue throughout the year, with no clear peak,15 whereas in Colorado there appears to be a biennial pattern and small peaks occurring in alternate years.16 In addition, seasons appear to last longer in metropolitan areas than in rural areas, with approximately 50% of the United States experiencing 6-month seasons, 25% experiencing seasons of less than 4 months, and 25% experiencing seasons of more than 4 months.13

Geographic differences appear to be related to weather, particularly temperature increases and decreases, as well as rainfall. Demographic factors, such as overcrowding and population density, urban or rural location, also play a role in severity.17-19

Maternal antibody levels also are predictive of seasonality. A study using cord blood samples from the Danish National Birth cohort and data from a Danish RSV database on RSV hospitalizations in infants found lower levels of antibody titer predicted increased levels of RSV hospitalization for infants aged younger than 6 months for that season, with the RSV epidemic peaking shortly after the nadir of the

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**Figure 1. RSV Seasonality**

The titer of maternally derived RSV-neutralizing antibody in 457 cord blood samples from Danish infants born 1998–2003 and incidence of RSV hospitalization per 100,000 Danish infants younger than 6 months of age 1998–2003. 


RSV = respiratory syncytial virus.
Altitude can have numerous respiratory effects, including lower oxygen saturation values, nasal obstruction and impaired ciliary activity, and hypoxia-related pulmonary vasoconstriction.

Breast-feeding does not appear protective unless there are other risk factors. It also appears that the protective effects of breast-feeding may be stronger in Hispanic than white infants. Other studies, however, show no benefit.

Much of the data on risk factors associated with RSV-related hospitalization come from 4 large, prospective trials: The Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC), a prospective, multicenter, cohort study conducted in 16 regions across Canada during 2 successive RSV seasons in which 1860 infants, including those with underlying congestive and/or lung disease, were followed for a mean of 104 days; the Spanish Factors that Most Likely May Lead to Development of RSV-Related Respiratory Infection and Subsequent Hospital Administration Among Premature Infants Born 33 to 35 Weeks Gestational Age study (FLIP), which also compared premature infants hospitalized for RSV with matched controls (n = 186 cases and 371 controls); a follow-up to the FLIP trial that followed 5441 children over 2 RSV seasons; and a nested case-control Danish study that followed children from birth to 18 months (n = 2564 children with RSV and 12816 controls). The Table depicts the risk factors identified in each study.

**PREDICTING RSV IN PRETERM INFANTS**

Given the high cost of RSV prophylaxis, an algorithm that could identify high-risk infants with significant specificity and sensitivity could lead to significant reductions in morbidity, mortality, and cost. To that end, a robust European model for predicting which premature infants born 33 to 35 weeks gestational age are at highest risk for hospitalization has been developed using data from Spain and Germany and validated in studies from Denmark, Italy, and France.

The model assigns individual weights to the 7 most predictive factors from the FLIP study: birth ±10 weeks from the beginning of the RSV season; birth weight; breastfed 2 or fewer months; number of siblings aged 2 years or older; number of family members with atopy; number of family members with wheezing; and sex. It is currently being implemented in some countries to determine the most effective application of palivizumab in this population.

**RSV AND WHEEZING/ASTHMA RISK**

The long-term outcome of severe RSV is a very important issue. As demonstrated in the Danish study mentioned earlier, it is clear that an atopic background predisposes children to RSV. Infants between 6 and 12 months who wheeze infrequently have a nearly 2-fold increased risk of RSV hospitalization (odds ratio [OR], 2.7; 95% confidence interval [CI], 1.87–3.91), whereas those with recurrent wheezing have a nearly 12-fold increased risk (OR, 12.56; 95% CI, 8.23–19.15). Children between 12 and 18 months of age with infrequent wheezing have a 1.15 increased risk (OR, 2.15; 95% CI, 1.37–3.39), whereas those between 12 and 18 months with recurrent wheezing have a 6-fold increased risk (OR, 6.99; 95% CI, 4.34–11.23).

The opposite is also true, in that children with mild RSV LRTI within the first 3 years of life have an increased risk for frequent wheeze up to 11 years (P ≤.01), although not at 13 years. However, among a Swedish cohort hospitalized for RSV LRTI in the first year of life, the risk of wheeze was significantly higher at 13 years compared with controls (P <.001).

It appears that RSV LRTI may be the causative factor in the pulmonary sequelae (wheezing and/or asthma), given longitudinal studies demonstrating that children who have RSV LRTI at age younger than 3 years have recurrent wheezing rates 25% to 80% greater than controls 11 to 13 years later. However, among a Swedish cohort hospitalized for RSV LRTI in the first year of life, the risk of wheeze was significantly higher at 13 years compared with controls (P <.001).

This raises the question of whether long-term pulmonary effects could be avoided with prophylactic measures to prevent RSV in high-risk infants. One small (n = 13 patients, 26 controls) follow-up trial to evaluate the long-term effects of RSV IgG prophylaxis on respiratory and allergic outcomes in children with CLD and/or chronic airway disease found that the treated children demonstrated a significantly better ratio of forced expiratory volume in 1 second to forced vital capacity (P = .02), had less atopy (P <.04), and were less likely to have missed school (P = .006), or have had an asthma attack (P = .03). However, large-scale, prospective studies are needed.

Such a trial has been conducted to examine the effect of palivizumab prophylaxis on wheezing. This multinational, double-cohort design trial occurred at
Table. Infant Characteristics Associated with RSV-Related Hospitalization

<table>
<thead>
<tr>
<th>PICNIC*†</th>
<th>FLIP-1‡</th>
<th>FLIP-2‡</th>
<th>DNBC (n = 2564)††</th>
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<tbody>
<tr>
<td>Age at start of RSV season</td>
<td>3.95 mo (OR, 4.89; 95% CI, 2.57–9.29)</td>
<td>Absolute chronological age ≤10 wk at the onset of RSV season (OR, 3.95; 95% CI, 2.65–5.9)</td>
<td>Absolute chronological age ≤10 wk at the onset of RSV season (OR, 2.99; 95% CI, 2.23–4.01)</td>
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<td>Breast-feeding</td>
<td>Not significant</td>
<td>Breast-feeding for ≤2 mo total (OR, 3.26; 95% CI, 1.96–5.42)</td>
<td>Not significant</td>
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<td>Siblings</td>
<td>Preschool-aged sibling(s) (OR, 2.76; 95% CI, 1.51–5.03)</td>
<td>Presence of ≥1 school-aged sibling (OR, 2.85; 95% CI, 1.88–4.33)</td>
<td>Presence of school-aged siblings or daycare attendance (OR, 2.04; 95% CI, 1.53–2.74)</td>
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<td>Crowding in home</td>
<td>&gt;5 people, counting the subject (OR, 1.79; 95% CI, 1.02–3.16)</td>
<td>≥4 residents and visitors at home (discounting school-aged siblings and the case/control him/herself) (OR, 1.91; 95% CI, 1.19–3.07)</td>
<td>Not significant</td>
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<tr>
<td>Sex</td>
<td>Male; (OR, 1.91; 95% CI, 1.1–3.31)</td>
<td>N/A</td>
<td>Not significant</td>
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<td>Birth weight</td>
<td>&lt;10th percentile (OR, 2.19; 95% CI, 1.14–4.22)</td>
<td>Not significant</td>
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<td>Smoking</td>
<td>≥2 smokers in the home (OR, 1.87; 95% CI, 1.07–3.26)</td>
<td>Smoking during pregnancy (OR, 1.62; 95% CI, 1.08–2.42)</td>
<td>Maternal smoking during pregnancy (OR, 1.61; 95% CI, 1.16–2.25)</td>
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<tr>
<td>Day care attendance</td>
<td>OR, 12.32; 95% CI, 2.56–59.34</td>
<td>N/A</td>
<td>Not significant</td>
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<tr>
<td>Family history</td>
<td>Family history of eczema (OR, 0.42; 95% CI, 0.18–0.996)</td>
<td>Family history of wheezing (OR, 1.9; 95% CI, 1.19–3.01)</td>
<td>Not significant</td>
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<td>Other</td>
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*Included infants with congenital and/or lung disease; †Did not include infants with congenital and/or lung disease. 
CI = confidence interval; DNBC = Danish National Birth Cohort; FLIP = Factors that most Likely may lead to development of RSV-related respiratory Infection and subsequent hospital administration among Premature infants born 33–35 weeks gestational age; NA = not applicable; OR = odds ratio; PICNIC = The Pediatric Investigators Collaborative Network on Infections in Canada study; RSV = respiratory syncytial virus.

Data from Law et al; Figueras-Aloy et al; Stensballe et al; and Figueras-Aloy et al.
for 2 years. The outcome demonstrated a nearly 50% reduction in the number of children with physician-documented recurrent wheezing and in the incidence of wheezing. Similar effects were seen in the time-to-event analyses for both outcomes.

**CONCLUSIONS**

Approximately 33% of children with RSV develop LRTIs, with at least 3.5 million children under age 5 requiring hospitalization each year. Medical costs for RSV are significant, as is the mortality rate in developing countries. However, recent studies provide important information on the seasonality and risk factors associated with hospitalization of children with RSV. Among the most important risk factors are birth ±10 weeks from the beginning of the RSV season; birth weight; number of siblings aged 2 years or older; number of family members with atopy; number of family members with wheezing; and sex.43-46

Information about the risk of hospitalization in children with RSV could be used to develop algorithms to determine which children are at highest risk of RSV complications and thus should be given immunoprophylaxis.

The ability of immunoprophylaxis to prevent wheezing and/or asthma in children who develop severe RSV is under study. Although it is clear that a family history of atopy increases the risk of RSV-related hospitalization, the data are still sparse as to any causative link between RSV and wheezing/asthma in the child. Nonetheless, some research suggests that immunoprophylaxis may reduce the risk of such long-term complications, although larger trials are required.

**DISCUSSION**

**Dr Rich:** Eric, we were talking briefly about the transition from neonatology care to pediatric care within the community. Are you noticing any issues with that as far as coordinating doses? When does the baby, a premature infant, move from neonatology care to community-based pediatric care? Is it just upon discharge, or does the neonatologist see the infant for some time?

**Dr Simões:** I think it varies by hospital and by site. Around the country, probably 80% or 90% of children go from the neonatal intensive care unit (NICU) to private practice, or to a pediatrician’s care, whereas another 10% to 20% are still taken care of by follow-up neonatologists. Thus, there is definitely a place

where children fall through the cracks and, in fact, it happens quite often (ie, between discharge from the NICU, being seen in the private practice, and receiving prophylaxis). Thus, it is important to get the doses in, at least the first dose, before they leave the NICU.

**Dr Rich:** Do you have any recommendations about coordinating with the infant’s health plan to get the pediatrician involved earlier so the hospital is not responsible for the cost of the drug? In some states, palivizumab is considered an outpatient drug by payors so hospitals do not get extra reimbursement just because we have treated with this very expensive drug.

**Dr Simões:** Consider putting RSV prophylaxis in the contract with the insurers. You know what proportion of your children is premature and who will need prophylaxis before discharge in the RSV season. Because giving prophylaxis means doing it correctly, in my opinion doing it correctly means you protect the child before they leave the NICU, especially during respiratory season.

**Dr Lee:** Such negotiations, for some reason, have not worked well in our hospital. I do not know if it is just our state being separated out as several TennCare organizations instead of Medicaid.

**Dr Simões:** In my opinion, immunoprophylaxis is part of the inpatient care. You treat your bone marrow patients. They get far more expensive drugs than palivizumab.

**Dr Burgoyne:** Those drugs are not coded as outpatient.

**Dr Lee:** That is the difference. Those drugs are considered inpatient drugs.

**Dr Rich:** When you have a patient in the NICU, even if you do give that first dose we find problems with the managed care organization getting involved so that the next dose is given on time. Any suggestions based on your experience working with that?

**Dr Simões:** I work with this all the time. If a newborn baby comes into the hospital for 3 months and the parents lose their insurance by the time the child leaves the hospital, that is the time when it is a problem. But if they have insurance, it is not a problem. The neonatologists coordinate with the pediatricians and then it goes more smoothly.

**Dr Rich:** Well, we have a problem getting that information in a timely enough manner to make that decision to approve continuation of doses. We may not hear about that until we get an emergency request because the
We have tried to encourage discharge planners to make sure that if the infant got a dose of palivizumab that they are communicating and making sure that the child has a pediatrician and a follow-up appointment with the pediatrician prior to discharge. It is still not hugely successful, but we have tried. We also have tried to get the outpatient pediatrician who will be following the child throughout the season to initiate the prior authorization while the child is an inpatient but that did not work either.

Dr Rich: Let me ask another question. Let us assume we have started somebody on RSV prophylaxis in the community and he or she is hospitalized for something not related to RSV and the next dose comes due in the hospital. How are you handling that? Eric, are you giving the next dose in the hospital then and then trying to bill for it at that point?

Dr Simões: Yes, the hospital will not get reimbursed. So that is just the cost of doing business.

Dr Lee: We discourage using the hospital supply and we ask the caregiver of the patient to bring it in from their pediatrician’s office supply and we give it in the hospital.

Dr Simões: The other aspect is that probably 50% or 60% of children in Denver are getting their doses at home. In that case, we ask them to bring the dose in. But in other cases, we just bite the bullet and give it. We certainly do not send them home without protection.

REFERENCES

ness in patients with underlying heart or lung disease.


