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ORIGINAL RESEARCH

Comparison of risk factors between preterm and term infants hospitalized for severe respiratory syncytial virus in the Russian Federation

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Background: Respiratory syncytial virus (RSV) is a leading cause of lower respiratory tract infection in infants. Preterm birth, in addition to several demographic and environmental factors, increases the risk for development of severe RSV infection. The purpose of this study was to describe differences in risk factors and protective factors between preterm birth (up to 35 weeks' gestational age) and term infants hospitalized for RSV lower respiratory tract infection in the Russian Federation during the 2008–2009 RSV season.

Methods: Infants up to two years of age hospitalized for a lower respiratory tract infection in Moscow, St Petersburg, and Tomsk were tested for RSV. Patient data, including risk factors and protective factors for RSV, were captured at admission. Differences in these factors were compared between preterm and term patients.

Results: A total of 519 infants hospitalized for lower respiratory tract infection were included in the study. Of these, 197 infants (182 term and 15 preterm) tested positive for RSV. Of all hospitalizations, 51.7% (15/29) of preterm infants versus 37.1% (182/490) of term infants had confirmed RSV ($P = 0.118$). Among the RSV-positive patients, preterm infants were more likely to have a lower weight at admission ($P = 0.050$), be of multiple gestation ($P < 0.001$), have more siblings ($P = 0.013$), and have more siblings under the age of eight years ($P < 0.007$) compared with term patients. The preterm infants were less likely to be breastfed ($P < 0.001$) and more likely to have older mothers ($P = 0.050$).

Conclusion: Compared with term infants, RSV was a more prevalent cause of hospitalization for lower respiratory tract infection in preterm infants. Of infants hospitalized for RSV, preterm infants were more likely to have additional risk factors for severe RSV. These findings suggest that preterm infants may be exposed to a combination of more strongly interrelated risk factors for severe RSV than term infants.

Keywords: respiratory syncytial virus, prematurity, protective risk factors, Russian Federation

Introduction

Respiratory syncytial virus (RSV) is considered to be the most common cause of severe childhood respiratory infection requiring hospitalization.[1,7] Almost all children will be exposed to RSV by two years of age,[7] with the highest rate of infection occurring in months 2–6 of life.[2] Up to 60% of children have been exposed to RSV before their first birthday. Most patients have mild symptoms of cough (98%), fever (75%), labored breathing (73%), and wheezing (65%).[3] In infants infected with RSV, the symptoms are mild, and usually last 6–7 days. RSV is the leading viral cause of lower respiratory tract infection in infants younger than one year of age, and accounts for up to 80% of pneumonia and bronchiolitis-related hospital admissions during the RSV season.[4]

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However, 1%–2.5% of infants infected with RSV develop severe lower respiratory tract infection requiring hospitalization and possible supplemental oxygen and mechanical ventilation. In Croatia, a study collected data for eleven consecutive RSV seasons in children aged from birth to ten years, and found RSV to be the most common causative agent of acute respiratory infection in 42.2% and of lower respiratory tract infection in 49% of infants 0–6 months of age. RSV was found in 56.5% of infants with bronchiolitis and in 36.5% of infants with pneumonia.[5] Mortality due to RSV is a concern. The mortality estimate due to severe cases requiring pediatric intensive care unit admission is 8.6%.[4] RSV does not elicit a substantial immune response, so reinfection is common.[6]

RSV represents a significant burden on the health care system. Among children under five years of age who present with RSV-related illness, 25% are treated in emergency rooms and 3% require hospitalization.[3] During the 1990s, hospitalization for RSV-associated illness cost an estimated $18 million annually in Canada alone.[7] In 2000, the costs in the US associated with the approximately 86,000 hospitalizations of children under five years of age that were attributable to RSV infection totaled $394 million.[8] Recent evidence suggests that the burden of disease is increasing in Western countries as admission rates increase due to RSV.[9,10]

To date, treatment has been limited to supportive measures, with no significant benefit from bronchodilators, adrenaline, steroids, or ribavirin.[11] Prevention strategies are important, because it is clear that RSV-related illnesses pose a significant public health risk. Proper hygiene is required to prevent the spread of RSV. To date, the only available strategy with demonstrated effectiveness for RSV prevention in preterm and other high-risk infants is prophylaxis using anti-RSV antibodies.[12]

RSV is a ubiquitous pathogen responsible for epidemics of disease globally, and the seasonality of RSV varies regionally. In general, RSV disease in temperate regions occurs in the cold season (ie, September through April), while outbreaks in tropical and subtropical areas north and south of the equator are seen in the cool, rainy seasons and in the cool, dry seasons, respectively.[13,14] Along the equator, RSV occurs all year round, with increases in the rainy season.[15]

The prevalence of severe RSV-related illness varies around the world, likely due to differences in health care practices (ie, diagnostic testing, disease management, and access to care). The prevalence of environmental risk factors (ie, smoking, daycare use) may also account for such differences. In the Russian Federation, infant mortality due to severe infection, including pneumonia, is 3–4 times greater than in other countries, such as Germany and the US.[16–18] Such estimates emphasize the importance of preventative innovations for infectious disease, particularly for children in countries more likely to experience severe and unfavorable outcomes.

In 2010, Tatochenko et al reported on the epidemiology of RSV in children up to two years of age hospitalized with lower respiratory tract infection in the Russian Federation.[19] The prevalence of RSV in this population and region had not been surveyed for over ten years,[20] and Tatochenko et al were the first to characterize the associated risk factors for RSV in the Russian Federation.[19] By secondary analysis of the data collected in the original study, this paper seeks to describe differences in both risk factors and protective factors for severe RSV infection between preterm and term infants hospitalized for RSV lower respiratory tract infection in the Russian Federation during the 2008–2009 RSV season.

Methods

A prospective, multicenter, observational cohort study involving nine large university and pediatric hospitals was done in Moscow, St Petersburg, and Tomsk. Subjects were recruited between September 2008 and April 2009 during the cold season. All children aged up to two years who were hospitalized in participating centers for a lower respiratory tract infection were potentially eligible for inclusion. Lower respiratory tract infection was defined as a diagnosis of acute bronchiolitis, bronchitis, and/or pneumonia. Diagnosis was made based on: presence of clinical symptoms (cough, coryza, rhinorrhea, fever) and signs (wheezing, crackles or rales, retractions); imaging (chest radiograph indicative of lower respiratory tract infection) in the presence of at least one symptom; or by the presence of an apneic event with symptoms (fever or coryza), signs (wheezing, crackles or rales), or chest radiographic evidence of a lower respiratory tract infection. Exclusion criteria included any specific RSV prophylaxis within 100 days of admission.

Eligible children were enrolled in the study within 24 hours of hospital admission and following informed parental consent, and RSV testing was performed via rapid immunochromatographic analysis of nasopharyngeal lavage (QuickStripe™ RSV, Savyon Diagnostics, Ashdod, Israel). The parent(s) of all enrolled children was interviewed, and their medical records were reviewed to obtain relevant patient and family medical and social history. Children who tested positive for RSV were followed for the duration of their

hospital stay, with additional data collected retrospectively based on a review of their hospital medical records. Children with RSV-negative lower respiratory tract infection were excluded from further data collection.

The study received approval from the institutional ethics boards of the participating centers. Written informed consent was signed by at least one of the patient's parents and obtained for each study participant prior to any study-related screening procedures.

Statistical analysis

Descriptive statistics were used to describe the study cohort and to report the percentage of patients admitted with lower respiratory tract infection due to RSV. These results were then compared across the study groups (preterm versus term infants). For patients admitted to hospital with RSV, demographic data, risk factors, and protective factors were summarized descriptively with the means and standard deviations for continuous variables and numbers and percentages calculated for categorical variables. Independent *t*-tests and Chi-square tests were applied to determine the statistical significance of continuous and categorical variables, respectively. Statistical significance was set at $P < 0.05$. Statistical analysis was performed using SAS (SAS Institute Inc, Cary, NC).

Results

A total of 593 infants were assessed for eligibility and 520 were enrolled in the study; one infant was removed after withdrawal of parental consent, resulting in 519 infants admitted to hospital with a lower respiratory tract infection, of which 197 (38%) had confirmed RSV infection. Of these 519 patients, the mean age was 8.8 months, and 63.5% were male. A total of 490 infants were born at term and 29 were born preterm.

The mean age of the 197 RSV-positive patients was 7.5 (± 5.9) months, and 60.9% were male. Table 1 compares the distribution of RSV status by gestational age of the patients hospitalized for a lower respiratory tract infection. Of preterm patients admitted to hospital for a lower respiratory tract infection, 15/29 (51.7%) had a confirmed RSV diagnosis, compared with 182/490 (37.1%) of term infants ($P = 0.118$). In addition to the difference in distribution between preterm and term infants, infants with a confirmed diagnosis of RSV were younger at the time of hospital admission ($P < 0.001$) and had a lower body weight ($P < 0.001$, Table 2).

Univariate analysis revealed statistically significant differences between RSV-positive term versus preterm subgroups in the proportion of patients with certain risk factors (Table 3). When compared with term infants, preterm patients had lower body weight at hospital admission ($P = 0.050$), were more likely to be of multiple gestation ($P = 0.001$), less likely to have ever been breastfed ($P = 0.001$), and had more siblings in the home ($P = 0.013$), including siblings under eight years of age ($P = 0.007$). The preterm infants were also more likely to have an older mother ($P = 0.050$).

The prevalence rates for passive and maternal smoking were high, but were not significantly different between the study groups. In addition, the educational level of parents and daycare attendance were not significantly different. In fact, the number of children attending daycare was low. Host factors, such as age at admission and gender, were not associated with an increased risk among the preterm patients. Likewise, medical factors, such as family history of atopy, wheezing/asthma, congenital heart disease, or chronic lung disease, were not disproportionately reported in the preterm group.

Discussion

While data regarding risk factors for severe RSV infection in infants, such as gestational age and breastfeeding, are well documented, there are no data for the impact of risk factors or protective factors in term versus preterm infants.

Premature infants are known to be at increased risk for severe RSV illness. Lung maturity occurs in the 37th week of gestation, so lung weights and volumes are significantly lower in preterm infants compared with term babies.[21] Premature lungs also have fewer and narrower alveoli compared with those in term babies.[21] Given that much of the RSV-related morbidity can be understood as stemming from airway occlusion secondary to inflammation, epithelial sloughing, and edema, it is clear that those with the smallest and narrowest airways would be the most vulnerable.

Preterm infants also suffer from immature immune systems. Neutrophilic and complement functions are less

Table 1 Distribution of RSV among infants hospitalized for a lower respiratory tract infection

Patients, RSV status	All patients (n = 519)	Term patients (n = 182)	Premature patients (GA < 36 weeks, n = 15)	*P* value
RSV + n (%)	197 (38.0)	182 (37.1)	15 (51.7)	0.118

Abbreviations: RSV, respiratory syncytial virus; GA, gestational age.

Table 2 Patient demographics of RSV-positive and RSV-negative patients

Demographics	All patients (n = 519)	RSV-positive infants (n = 197)	RSV-negative infants (n = 322)	*P* value*
Age, months (mean, SD)	8.8 (6.4)	7.5 (5.9)	9.7 (6.6)	<0.001
Weight at admission (kg) (mean, SD)	8.5 (2.7)	7.9 (2.6)	8.8 (2.0)	<0.001
Gender, male (n, %)	330 (63.5)	120 (60.9)	210 (65.2)	0.323
Premature (<36 weeks) (n, %)	29 (5.6)	15 (7.6)	14 (4.4)	0.118
Congenital heart disease (n, %)	8 (1.5)	2 (1.0)	6 (1.9)	0.447
Chronic lung disease (n, %)	1 (0.2)	1 (0.5)	0 (0)	0.201

Note: *$P < 0.05$ RSV-positive versus RSV-negative infants.
Abbreviations: RSV, respiratory syncytial virus; SD, standard deviation.

developed than in term babies. It has been hypothesized that complement activation serves to neutralize RSV, thus preterm infants are left with fewer defenses against the virus.[21] Preterm infants also lack the neutralizing antibodies from the mother that help them fight RSV infection.[6]

Among the subjects hospitalized with severe RSV disease in this study, preterm infants were more likely to have been exposed to several risk factors known to be associated with severe RSV illness. The cumulative effect of multiple risk factors potentially puts these infants at risk for more severe outcomes, but this needs to be explored further in sufficiently powered studies. Risk of hospitalization, a proxy for severe RSV disease, has been shown to increase incrementally with the number of risk factors present.[22]

Several risk factor models have been devised to identify the most important independent risk factors associated with severe RSV.[23–25] The Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) study, published in 2004, examined risk factors associated with severe RSV disease (defined as hospitalization due to a lower respiratory tract infection with proven RSV infection) in preterm infants (gestational age under 35 weeks) over two consecutive seasons.[23] Independent risk factors identified were birth just before or during the RSV season, male gender, birth weight ≤ 10th percentile in relation to gestational age, attending daycare, and preschool-aged siblings under six years of age, crowding (more than five people in the home), and exposure to cigarette smoke (more than two smokers in the home).[23]

Table 3 Distribution of risk factors for infants hospitalized for a RSV-positive lower respiratory tract by subgroup

	Term (n = 182)	Premature (n = 15)	*P* value
Host risk factors			
Age (months) at admission (mean, SD)	7.4 (5.8)	8.0 (6.9)	0.768
GA (mean, SD)	39.4 (1.4)	32.4 (2.8)	<0.001
Weight (kg) at admission (mean, SD)	8.0 (2.5)	7.1 (2.9)	0.050
Gender (male, %)	112 (61.5)	8 (53.3)	0.531
Multiple gestation (n, %)	7 (3.9)	5 (33.3)	<0.001
Ever breast-fed (n, %)	171 (94.0)	8 (53.3)	<0.001
Medical risk factors			
Congenital heart disease (n, %)	2 (1.10)	1 (0.0)	0.683
Chronic lung disease (n, %)	1 (0.55)	0 (0.00)	0.773
Neurological disease (n, %)	4 (2.2)	2 (13.3)	0.016
Family history of atopy (n, %)	35 (19.2)	3 (20.0)	0.942
Family history of wheezing/asthma (n, %)	22 (12.1)	1 (6.7)	0.530
Social risk factors			
Siblings (mean, SD)	0.7 (0.8)	1.3 (0.7)	0.013
Siblings ≤ 8 years (mean, SD)	0.6 (0.7)	1.1 (0.6)	0.007
Daycare attendance (n, %)	4 (2.2)	0 (0)	0.337
Individuals in home (mean, SD)	3.3 (1.2)	3.7 (0.9)	0.215
Smokers in home (n, %)	84 (46.2)	6 (40.0)	0.646
Maternal smoking (n, %)	26 (14.4)	2 (13.3)	0.913
Mother's age (mean years, SD)	29.0 (4.7)	32.9 (7.3)	0.050
Father's age (mean years, SD)	32.4 (6.0)	35.1 (7.0)	0.167

Abbreviations: RSV, respiratory syncytial virus; SD, standard deviation.

A second study of similar methodology and study population was conducted in Spain.[24] The results revealed similar risk factors to those found in PICNIC, and also identified breastfeeding for less than two months and family history of wheezing to be major risk factors for severe RSV. The results of this study were validated in a larger cohort study, FLIP-2, also conducted in Spain and published four years later.[25] In contrast with the earlier FLIP study, breastfeeding for more than two months did not show a protective effect against RSV infection. The FLIP-2 study demonstrated a 3.3–9.89 times greater risk of hospitalization among infants who had at least two risk factors, thus demonstrating the additive effects of risk factors.[25]

Overall, boys are at higher risk of hospitalization for RSV-related illness than girls. Male gender has been shown to be an independent predictor for hospitalization due to RSV illness among preterm (gestational age 33–35 weeks) infants.[23,25] Preterm male infants were 91% more likely to be hospitalized for severe illness than their female counterparts.[23]

In this study, an increased total number of siblings and siblings under eight years of age in the home were found to be significantly more prevalent among the preterm infants compared with term infants. Preterm infants may be more vulnerable to the negative impact of household crowding, such as increased exposure to RSV through contact with more people. Preterm infants were also more likely to be the product of multiple gestation, a known risk factor for severe disease, and were less likely to have benefited from being breastfed.

There were limitations associated with this study. Firstly, and most importantly, the study was only able to assess the difference in frequency of risk factors between preterm and term infants already hospitalized for a severe RSV infection. It would be of interest to understand the risk factor prevalence in preterm and term infants in the general population, as well as those contracting RSV and not requiring hospitalization. A further limitation of this study was the small number of infants (15 preterm) examined, which limits the ability to draw definitive conclusions. It was impossible to perform subgroup analysis on categories of prematurity, ie, gestational age 32–35 weeks versus gestational age less than 32 weeks. A larger population of preterm infants would be required to confirm these findings.

Risk factors associated with serious complications of RSV have been identified. Understanding an infant's risk can result in appropriate preventive interventions, whereby targeted prevention can both minimize disease cost and maximize the effectiveness of prophylaxis.

This study was conducted in only three regions in the Russian Federation, so these study findings may not be generalizable to other regions within Russia or other countries. At the time of the study, no specific RSV prophylaxis (eg, palivizumab) was approved in the Russian Federation, therefore these data represent a prophylaxis-naive population.

Conclusion

In this study, risk factors associated with serious complications of RSV were identified, the key ones being a lower body weight, multiple gestation, more young siblings in the home, and limited breastfeeding. Results from this study indicate that, compared with infants born at term, RSV is a more prevalent cause for lower respiratory tract infection hospitalization in preterm infants. In addition, of infants hospitalized for RSV lower respiratory tract infection, preterm infants may be more susceptible to severe illness than term infants. The reasons for these differences require further evaluation.

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Disclosure

Abbott Laboratories contributed materials essential for this study. KG, GN, GS, KG, KB, and AC are employed by Abbott Laboratories. KG, AC, GS, KB, and GN hold stocks in Abbott Laboratories. HK has served as a consultant for Abbott Laboratories.

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