RISK FACTORS FOR BRONCHIOLITIS HOSPITALIZATIONS IN CHILDREN WITH CHRONIC DISEASES

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ABSTRACT

Background: Respiratory syncytial virus (RSV) bronchiolitis is the most common lower respiratory tract disorder causing hospitalization in infants. Palivizumab has shifted the profile of the hospitalized population away from premature infants and towards those with chronic morbidities who are not eligible for prophylaxis.

Aim: To characterize RSV bronchiolitis hospitalizations in infants with chronic diseases, compared to otherwise healthy infants.

Methods: A four consecutive RSV season retrospective analysis of patients younger than two years admitted with bronchiolitis. Background demographic and clinical data, including vital sign measurements, laboratory tests, and pediatric intensive care unit (PICU) admissions during hospitalization, were analyzed.

Results: Of 1124 hospitalizations due to RSV bronchiolitis, 244 (22%) were in infants with chronic diseases. Although 20/1124 qualified for RSV prophylaxis, only 8 had been vaccinated. Compared to otherwise healthy infants, children with chronic diseases had longer hospitalizations, median 4 days (IQR 4-7) vs 3 days (2-5), $p<0.001$; and higher PICU and readmission rates (9% vs 4.5%, $p=0.007$ and 3% vs 1%, $p=0.055$, respectively). Children with Down's syndrome comprised 2% of all hospitalizations, but 8% of PICU admissions; their median length of hospitalization was 11 days. Respiratory tract malformations were present in 2% of hospitalizations, and comprised 4% of PICU admissions.

Conclusion: Infants with chronic diseases admitted with RSV bronchiolitis are prone to longer hospitalization and PICU admission. Children with Down's syndrome and respiratory tract malformations may benefit from RSV prophylaxis.

INTRODUCTION

Bronchiolitis is the most common lower respiratory tract infection and cause of hospitalization in infants. It is usually caused by viral infections, mainly Respiratory Syncytial Virus (RSV) [1].

The updated guidelines for Palivizumab prophylaxis published by the American Academy of Pediatrics (AAP) in 2014 did not recommend routine immunizations for otherwise healthy infants born at or after 29 weeks of gestation [2]. It was recommended to consider immune prophylaxis for infants with pulmonary abnormalities, neuromuscular diseases, and those severely immunocompromised. For children with cystic fibrosis and Down's syndrome, the evidence was considered insufficient to recommend routine prophylaxis.

RSV immune prophylaxis with Palivizumab has been implemented in Israel since 2001. The criteria have been revised over the years and since 2011include: Infants born before 35 gestational weeks, infants with bronchopulmonary dysplasia (BPD) or other severe chronic lung disease, and infants with congenital heart disease or pulmonary hypertension requiring medical treatment [3].

Studies conducted following the 2014 AAP guidelines [4–6] have shown high RSV related hospitalization rates among infants born at 29-34 weeks gestation, particularly those of a younger chronological age. Substantial morbidity and economic burden were incurred from preterm non vaccinated infants based on the 2014 AAP guidance; thus, preventing severe RSV disease in this population was assessed as providing significant health benefits [5,6]. Given the controversy among clinicians and policy makers regarding the adequacy of the AAP recommendations issued in 2014, the current Israeli criteria for Palivizumab immunization have not changed since 2011.

The administration of immune prophylaxis to premature infants has shifted the profile of the hospitalized population away from premature babies and towards those with chronic conditions [7]. In addition, some reports on RSV bronchiolitis in infants with chronic diseases support the use of immune prophylaxis for some of these infants, mainly children with Down's syndrome, immunodeficiency, neuromuscular disorders, and respiratory tract malformations [8–12].

Given the changing face of admissions with RSV bronchiolitis, the aim of the present study was to compare the clinical course of RSV hospitalizations of infants with chronic diseases, with that of otherwise healthy infants. This research may contribute to the knowledge base of policy makers and enable them to consider a re-evaluation and update of the current criteria for RSV immune prophylaxis concerning additional high-risk populations.

METHODS

This retrospective longitudinal single tertiary center study included all patients under two years of age who were clinically diagnosed with acute bronchiolitis and admitted to Schneider Children's Medical Center in Israel during four consecutive RSV seasons (October 2014 to April 2018).

Patients were identified by searching the electronic medical records database. To maximize the yield, we searched using the following diagnostic key words in the discharge report: Bronchiolitis, respiratory, dyspnea, and RSV. Excluded for the purpose of data analysis were hospitalizations due to respiratory complaints not attributed to bronchiolitis and RSV negative bronchiolitis admissions.

The following data were collected for each patient: Demographic status, past medical history, RSV immunization status, date of admission, vital signs, clinical parameters, laboratory and microbiology tests, admission to the pediatric intensive care unit (PICU), total length of stay (LOS) and re-admissions.

Microbiological diagnosis for specific viral etiology is routinely performed at our hospital. Samples were obtained from nasopharyngeal aspirates and examined for RSV, influenza and adenovirus by polymerase chain reaction (PCR, Focus Diagnostics, Cypress, California, USA).

Patients were categorized according to past medical history as previously healthy or with a chronic disease, defined as any non-curable medical condition or illness lasting at least 3 months [13]. This subgroup was further subclassified into the following categories: Recurrent respiratory morbidity; congenital heart defects (cyanotic and non-cyanotic); neurological morbidities; respiratory tract malformations; Down’s syndrome; other genetic syndromes; immunosuppression (congenital of acquired); BPD; pulmonary hypertension and other diseases, including

gastrointestinal morbidities, urinary tract defects and failure to thrive. Patients with more than one chronic disease were sub-classified into more than one group.

The statistical analysis was performed using SPSS Statistics software for Windows, version 25.0. (IBM Corp, New York, USA). All variables are expressed as means and standard deviations (SD), medians and interquartile ranges, or frequencies and percentages. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Ordinal variables were compared using the Mann–Whitney test, and continuous variables analyzed by the Student's t-test. Univariate and multivariate logistic regression analyses of available variables were performed to identify factors independently associated with a longer hospital stay and PICU admission. In the multivariate analysis, a compound outcome of severe hospitalization course was defined as ≥6 days of hospitalization or PICU admission. A two-tailed p-value < 0.05 was regarded as statistically significant. A p-value < 0.1 was required for inclusion in the multivariate analysis. Odds ratio (OR) and 95% CI were computed.

The study was approved by the Rabin Medical Center review board, RMC-9649-17. Parental consent was not required as the patients were retrospectively identified by searching the computerized medical records database. Following data retrieval, subjects were anonymized.

RESULTS

Patient characteristics

During the study period, 1673 hospitalizations due to bronchiolitis were documented; of those, 1124 (67%) were positive for RSV. All further data analysis was restricted to the RSV positive population.

Overall, 244 (21.7%) hospitalizations were of infants with chronic diseases (Table 1). Compared to otherwise healthy children, those with chronic diseases showed a greater predominance of males (63.1% vs 54.4%, p=0.016) and the mean age at admission was older (9.5 months (range 14 days-2 years) vs 3.2 months (10 days-2 years), p<0.001). Among those with chronic diseases, the rate of prematurity was higher (5.7% vs 0.8%, p<0.001); consequently, the proportion of children who fulfilled the indication for immune prophylaxis was also higher (5.7% vs 0.7%, p<0.001).

Description of chronic diseases

Of the 244 hospitalizations of infants with chronic diseases, 90 (36.9%) had recurrent respiratory morbidity; this included repeated events of pneumonia, atelectasis, and wheezing. Forty-four (18.0%) had non-cyanotic heart defects; 17 (6.9%) cyanotic heart defects, of which 6 (2.4%) were not fully repaired; 42 (17.2%) neurological morbidities; 23 (9.4%) respiratory tract malformations, including tracheoesophageal fistula and tracheomalacia; 21 (8.6%) infants had Down's syndrome; 8 (3.3%) other genetic syndromes, including DiGeorge, Noonan and Cri-du-chat; 11 (4.5%) immunosuppression; 10 (4.1%) BPD; 6 (2.5%) pulmonary hypertension and 89 (36.5%) other diseases. The latter included 19 (7.8%) urinary tract defects, 24 (9.8%) gastrointestinal morbidities, and 29 (11.9%) infants with

failure to thrive. 68 (28%) patients had multiple chronic diseases; thus, the sum of morbidities is greater than the total number of patients.

Indications for RSV prophylaxis vs actual administration

Out of the 244 hospitalizations of children with chronic diseases, 14 (5.7%) fulfilled local RSV immune prophylaxis indications: 11 with congenital heart diseases, one with pulmonary hypertension, one with oxygen dependent severe BPD and one with late prematurity. Of them, only 6/14 had been vaccinated.

Among the patients without chronic diseases, 6/880 (0.7%) fulfilled indications for RSV immune prophylaxis, all due to prematurity, but only 2/6 were vaccinated (table 1).

Clinical outcomes and hospital course

The clinical course was more severe among children with chronic morbidities than those without (Table 2), and the LOS was longer: median 4 days (IQR 4-7) vs 3 days (2-5), $p<0.001$. Furthermore, the rate of admission to PICU was double among those with than those without chronic morbidities (9% vs 4.5%, $p=0.007$), and the rate of readmission due to non-RSV respiratory tract infections was three times higher, although with only marginal statistical significance (3% vs 1%, $p=0.055$).

No statistically significant differences were found between children with and without chronic morbidities with regards to C-reactive protein (CRP), rate of oxygen saturation <90%, and rate of co-infections (Table 2).

Sub-population analysis

Down's syndrome: Out of the 21 admissions of children with Down's syndrome (1.9% of all the admissions), 11 (52.3%) had cardiac defects, 5 atrioventricular septal defects post-repair and 6 other non-cyanotic heart diseases. Only one had an indication for immune prophylaxis due to pharmacologically treated

heart failure, although it had not been administered. The median age at admission was 13.9 months, and the median LOS was 11 days (range 4-39 days). Five of the children with Down's syndrome were transferred to the PICU, 8% (5/62) of all the PICU admissions. Four of these five had cardiac defects: Two atrioventricular defects post-repair and two non-cyanotic defects. The length of admission in the PICU ranged from 1 to 15 days, median 9 days. Furthermore, 5/21 were readmitted to the hospital during the study period.

Respiratory tract malformations: These were present in 23 children (2.0% of all admissions); the median length of hospitalization was 5 days (range 2-39). Only one child had indication for immune prophylaxis, due to pulmonary hypertension; however, this had not been administered. Three patients were transferred to the PICU; the length of stay was 1-7 days. All three patients admitted to the PICU had multiple morbidities; two had obstructive sleep apnea; of whom one also had Down's syndrome, and one had sub-glottic stenosis.

Multiple morbidities: The number of co-morbidities was positively associated with a severe hospitalization course (compound outcome consisting of ≥6 days of hospitalization or PICU admission) (Figure 1).

Risk factors for severe disease

In a multivariate analysis, risk factors for a severe hospitalization course were: Higher number of co-morbidities [OR=3 (CI 1.5-5.9) for 2 co-morbidities, and OR=17.9 (CI 6.8-47.3) for ≥3 co-morbidities], co-infection (OR=1.7 (CI 1.3-2.7)) and age younger than 1 year (OR=1.5 (CI 0.9-2.4)) (table 3).

Compared to patients with other comorbidities, for those with Down’s syndrome, the OR for a severe outcome was 10.3 (CI 5.8-53.6), and for those with

respiratory tract malformations, the OR was 2.6 (CI 1.1-6.2), adjusted for age, prematurity, and co-infection (table 4).

DISCUSSION

In the present study, we compared the course of hospitalizations due to RSV bronchiolitis between infants with chronic diseases and otherwise healthy children. A substantial proportion of the hospitalizations were of children with chronic morbidities, 244/1124 (21.7%). This concurs with recently published reports [7,8]. Only 5.7% of these children with comorbidities were eligible for RSV immune prophylaxis according to the current local guidelines.

Overall, the clinical course was more severe among children with chronic morbidities than those without, as illustrated by a longer hospitalization, a two-fold PICU admission rate, and a three-fold higher percentage of readmissions. The cumulative number of comorbidities was found to be a predictor for a more severe course of hospitalization. Likewise, in a multivariate analysis, a higher number of co-morbidities was a strong predictor for a more severe course of hospitalization. Although the more severe course poses a greater demand for medical resources, those patients with comorbidities were mainly not eligible for RSV prophylaxis according to the local and updated guidelines. This requires further discussion and consideration.

Of 21 hospitalizations of patients with Down's syndrome, only one met the criteria for immune prophylaxis due to heart failure, but eventually was not vaccinated. Children with Down's syndrome had a severe hospitalization course, including a longer hospital length of stay, and a large proportion of transfers to the PICU, with a prolonged stay. In a multivariate analysis, they were found to have more than a tenfold higher risk for a more severe course of hospitalization, compared to patients with other diseases, presumably due to multiple co-morbidities. In a report by the Israeli Ministry of Health published in 2017 [14], the annual incidence

of Down's syndrome in Israel is 0.057%. Based on the prevalence of Down's syndrome in the current study, the theoretical calculated annual incidence of Down's syndrome is 0.47%, ten times higher than anticipated. Our findings are in line with previously published studies: a meta-analysis of children hospitalized with RSV [15], estimated a 6.8 times increased risk for hospitalization among those with Down's syndrome. In another retrospective study [16], Down's syndrome was found to be an independent risk factor for hospitalization due to RSV bronchiolitis (adjusted risk ratio of 3.46), with longer hospitalization and higher need for respiratory support. Taken all together, the remarkably high rate of hospitalizations and severe hospital course of children with Down's syndrome during RSV bronchiolitis, in our and other populations, support the consideration of RSV prophylaxis for these children.

Similarly, only one out of the 23 patients with respiratory tract malformations in our cohort had an indication for immune prophylaxis, due to pulmonary hypertension. Likewise, this group of children had longer hospitalization and a higher rate of transfer to the PICU. Our findings concur with other studies that described respiratory tract malformations as a risk factor for hospitalization due to RSV bronchiolitis [7,10]. Furthermore, in an observational study [11], respiratory tract malformations were found to significantly increase the risk for RSV bronchiolitis and hospitalization among children who received immune prophylaxis, compared to children with the standard indications for the vaccine.

Overall, in our cohort, we found male predominance, especially among patients with chronic morbidities. Of the PICU hospitalizations, 63% were males, like the 63% proportion reported in another retrospective study [17]. However, male gender was not found to correlate with a more severe course of hospitalization in our multivariate analysis. Interestingly, the Tucson Children's Respiratory cohort, which

assessed infant lung function from birth [18], reported a more severe course of lower respiratory tract illnesses among males, which they concluded could be due to smaller airways. We may speculate a similar explanation to our finding.

At admission, our patients with chronic diseases were significantly older than previously healthy children. This could be explained by a higher risk of hospitalization among younger than older otherwise healthy infants [1,8,9]. In contrast, among children with chronic diseases, notably in those with respiratory and cardiac morbidity, the risk for a severe course persists over time [2,9].

Since premature infants tend to have secondary morbidities, it was not surprising that the rate of prematurity was higher among our patients with, compared to patients without chronic diseases. In addition, otherwise healthy premature infants were likely to have received RSV prophylaxis, lowering their risk for hospitalization. Nevertheless, the large proportion of premature children among the group with comorbidities did not explain the differences in clinical course between the patients with and without chronic diseases, according to the multivariate analysis.

The present study's limitations include its retrospective design, as well as the heterogeneity of clinical diagnoses required grouping diagnoses together. In addition, the conduct of the study in a tertiary medical center may have biased the cohort toward children with chronic diseases. A large multi-center study that will include data on cost-effectiveness is warranted.

In conclusion, among children hospitalized with RSV, those with chronic diseases had a statistically significant longer length of hospitalization and twice the risk for PICU admission than otherwise healthy children. Notably, children with Down’s syndrome had a particularly high risk for hospitalization and more severe outcomes, including PICU admission. Children with respiratory tract malformations

were also found to be at higher risk for a longer hospital length of stay. The findings suggest that children with Down's syndrome or respiratory tract malformations might benefit from RSV immune prophylaxis.

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