Hospitalization for Respiratory Syncytial Virus Bronchiolitis in the Palivizumab Prophylaxis Era: Need for Reconsideration of Preventive Timing and Eligibility

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ABSTRACT: **Background:** Respiratory syncytial virus (RSV)-related bronchiolitis is a common cause of morbidity in young infants. The recommendations for its passive prevention by palivizumab are currently under intensive debate.

Objectives: To elucidate the optimal prevention strategy by studying the morbidity of RSV disease under the current recommendations for palivizumab prophylaxis in Israel.

Methods: We collected demographic and clinical data of all children hospitalized with microbiologically confirmed RSV bronchiolitis during 2015–2016 at Schneider Children's Medical Center. The seasonality of RSV disease was also studied for the period 2010–2017 in sentinel clinics scattered throughout Israel.

Results: Of the 426 hospitalized children, 106 (25%) had underlying diseases but were not eligible for palivizumab prophylaxis according to the current criteria in Israel. Their course was severe, with a mean hospital stay of 6.7 days and a 12% admission rate to the pediatric intensive care unit (PICU). Palivizumab-eligible children who did not receive the prophylaxis before hospitalization had the most severe course, with 22% admitted to the PICU. More children were diagnosed with RSV disease in October than in March among both hospitalized and ambulatory children; 44% of the palivizumab-eligible hospitalized children were admitted in the last 2 weeks of October, before 1 November which is the recommended date for starting palivizumab administration in Israel.

Conclusions: According to the results of the present study we suggest advancing RSV prophylaxis in Israel from 1 November to mid-October. The precise palivizumab-eligible categories should be reconsidered.

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KEY WORDS: prevention, passive vaccination, risk factors, respiratory infections, respiratory syncytial virus (RSV)

Acute bronchiolitis is a leading cause of illness among infants, with 50–80% of the cases caused by respiratory syncytial virus (RSV) [1-3]. It has been estimated that 20% of all children require outpatient medical care for RSV bronchiolitis during their first year of life, while 2–3% require hospitalization [1]. In the United States, RSV infection results in > 57,000 hospitalizations and about 2 million outpatient visits each year among children aged < 5 years [1]. The disease has been associated with complications [1,4,5], admission to the pediatric intensive care unit (PICU) [4], long-term morbidity [5], and mortality [1,6,]. Studies in Israel confirmed the significant local burden of RSV bronchiolitis, causing 7% [7] to 18% [8] of all pediatric hospitalizations, with an estimate of 4100 nationwide hospitalizations each year [8]. Complications and mortality are seen mainly in high-risk groups with underlying diseases [1,4,6].

In the absence of effective specific treatment for RSV bronchiolitis, management is mainly supportive and usually includes oxygen supplementation and fluid administration [2,3,9,10]. Medications, such as inhaled bronchodilators, hypertonic saline and inhaled or systemic steroids, are usually not efficacious and their use continues to be controversial [3,9].

Prevention and reduction in the severity of RSV bronchiolitis is possible by passive immunization with palivizumab, a humanized immunoglobulin-1 monoclonal antibody directed against a conserved epitope of the fusion protein shared by all RSV serotypes [2,11,12]. Palivizumab is used in most developed countries for high-risk groups. Since RSV disease occurs in temperate climates in the fall and winter months [13], palivizumab is administered by monthly injections during that period [1,3]. In Israel, palivizumab is recommended as a five-dose regimen for the period 1 November to 1 March for high-risk groups, including premature infants who are oxygen-dependent (until the age of 2 years) and infants up to 1 year of age if they were born prematurely and are currently treated with diuretics; neonates born at < 33

gestational weeks or weighing < 1 kg; infants with cyanotic congenital heart disease, pulmonary hypertension or treated for heart failure; and infants with treatment-dependent chronic lung disease. It is recommended that premature infants born at 33–35 gestational weeks receive the vaccine up to the age of 6 months [14].

The precise delineation of the high-risk groups eligible for palivizumab prophylaxis is currently the subject of an intense debate [12,15,16]. The most recent update of the American Academy of Pediatrics (AAP) endorsed a much more restrictive use of palivizumab than previously recommended [17]. This change was criticized by some [18] but adopted in certain locations [16]. The AAP update stimulated discussions in Israel but did not lead to changing the recommendations [14]. The aims of the present study were to analyze hospitalization and complication rates, as well as outpatient medical care for RSV bronchiolitis, under the current Israeli recommendations for palivizumab prophylaxis, and to discuss future preventive strategies.

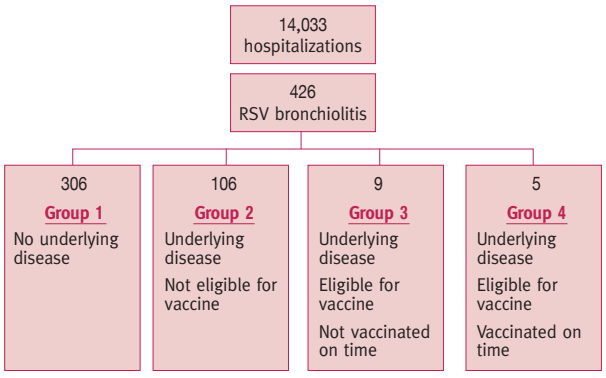
PATIENTS AND METHODS

The study included all patients with microbiologically confirmed RSV acute bronchiolitis at Schneider Children's Medical Center who were admitted during the 2-year study period January 2015 to December 2016. The children were categorized according to the presence of underlying medical conditions and eligibility for palivizumab prophylaxis [Figure 1].

CLINICAL DATA

The following data were collected from electronic medical records: demographic information, medical history (prematurity, background illness, previous episodes of wheezing), date of admission, clinical parameters (including fever and oxygen saturation at admission and throughout hospitalization), laboratory results, treatments during hospitalization (oxygen supplementation, IV fluids, antibiotics, systemic steroids, inhalations of hypertonic saline, beta-agonists, anticholinergic agents, budesonide and adrenaline), the need for PICU admission, and total length of hospitalization.

Figure 1. Flow chart of the study population by underlying diseases, palivizumab eligibility and compliance



MICROBIOLOGIC DIAGNOSIS

Examination for RSV is performed routinely in our medical center for children hospitalized with acute bronchiolitis. Samples were obtained by nasopharyngeal wash and examined for RSV by the polymerase chain reaction (PCR, Focus Diagnostics, Cypress, California, USA), which is FDA-approved and has a validated sensitivity and specificity of 95.1% and 99.6%, respectively [19].

RSV IN THE COMMUNITY

To further assess the patterns of RSV in the community, we analyzed data obtained by the Israel Center for Disease Control as part of the sentinel surveillance system in Israel for respiratory infections. Each year the sentinel system collects combined nasal-throat samples from patients presenting at 22–28 sentinel clinics throughout Israel with influenza-like illness, as previously described [20]. Samples are collected from week 40 of the year (usually from the end of September or the beginning of October) until April of the subsequent year. Each sample is analyzed by PCR for the presence of influenza and RSV viruses at the Israel Ministry of Health Central Virology laboratory, as previously described [21]. For the purpose of the current study, the numbers of RSV-positive samples from patients aged 0–2 years from October to March of each season were retrieved. RSV-positive patients during the last 2 weeks of October and March were calculated as a percentage of the total RSV-positive samples received from sentinel clinics in the respective season. A total of seven seasons were analyzed (2010/2011 to 2016/2017).

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS Statistics for Windows, version 21.0 (released 2012; IBM Corp. Armonk, NY). Continuous variables were compared among the groups using analysis of variance (ANOVA) for normally distributed variables and Mann-Whitney U test for non-parametric distribution. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. A P value ≤ 0.05 was defined as statistically significant.

ETHICAL CONSIDERATIONS

The study was approved by the institutional review board for data retrieved from the Schneider Children's Medical Center (approval number 0565-16-RMC). Sentinel surveillance of influenza and RSV was carried out pursuant to the Israel Public Health Ordinance.

RESULTS

During the period 1 January 2015 to 31 December 2016, 426 (3%) of the 14,033 hospitalizations in the pediatric department of our medical center were due to RSV bronchiolitis. The median age was 6 months [Figure 1]. The mean duration of hospitalization was 5.5 days, and that of oxygen supplementation 1.9 days. Altogether, 23 children (5.4%) were admitted to the PICU.

Most hospitalized children received supportive treatments with oxygen and fluid supplementation, as needed. In specific settings, additional treatments were used, including inhalation of 3% hypertonic saline, adrenaline, anticholinergic agent (ipratropium bromide), budesonide or a beta-agonist (terbutaline sulphate), and systemic steroids or antibiotics.

CATEGORIZATION BY UNDERLYING DISEASES AND VACCINE ELIGIBILITY [FIGURE 1]

Of the 14,033 children hospitalized with RSV bronchiolitis, 306 (71.8%) had no underlying disease (group 1). The second largest group comprised the 106 children (24.9%) who had underlying diseases but were not eligible for palivizumab prophylaxis according to the current criteria in Israel (group 2).

The underlying conditions of patients in group 2 were diverse and can be categorized into four subgroups [Table 1]; some children had underlying conditions of several subgroups:

- Immune deficiency – 21 (19.9% of group 2), either primary or secondary deficiency due to immunosuppressive therapy or a malignancy
- Chronic lung disease – 20 (18.9%), secondary to prematurity or other conditions, such as cystic fibrosis, recurrent aspiration or bronchiolitis obliterans
- Congenital heart diseases – 42 (39.6%), comprising a broad range of cardiac abnormalities that did not render eligibility for palivizumab prophylaxis [Table 1].
- Prematurity – 49 (46.2%), who were mostly born at 35–36 weeks gestation.

Groups 3 and 4 comprised 14 children who had underlying medical conditions and were eligible for RSV prophylaxis yet were hospitalized with RSV bronchiolitis. Their characteristics are detailed in Table 2. Most of these patients (9/14, 64%) were not vaccinated before their hospitalization for RSV bronchiolitis (group 3) [Table 2A]. Of these, 7 (78%) were hospitalized in October or November. Five children were vaccinated before hospitalization but still needed hospitalization for RSV bronchiolitis (group 4). As detailed in Table 2B, the admission occurred 13 days or more after vaccination.

DISEASE SEVERITY

The hospitalizations for RSV bronchiolitis were associated with significant morbidity, as evidenced by the duration of hospitalization, the need for IV fluids or oxygen supplementation, and admissions to the PICU. Complications included respiratory distress with a need for nasal and mechanical

Table 1. Children hospitalized with RSV bronchiolitis who had underlying diseases but were not eligible for palivizumab prophylaxis (group 2)

Category of underlying disease	No. of patients	% of RSV hospitalization
Immune deficiency Functional hyposplenia Hyper-IgM syndrome Immunosuppressive therapy & malignancy	21 2 1 18	4.9
Chronic lung disease RDS, BPD Recurrent aspiration CF Respiratory malformation BOOP Bronchial asthma Recurrent pneumonia	20 10 4 1 2 1 11 1	4.6
Congenital heart disease Cyanotic heart defect Acyanotic heart defect	42 9 33	9.8
Prematurity ‹ 35 gestational weeks 36–36 gestational weeks	49 16 33	11.5

RSV = respiratory syncytial virus, RDS = respiratory distress syndrome, BPD = bronchopulmonary dysplasia, CF = cystic fibrosis, BOOP = bronchiolitis obliterans with organizing pneumonia

Table 2. Children eligible for RSV prophylaxis who were hospitalized with RSV bronchiolitis

[A] Not vaccinated before hospitalization (Group 3)

Underlying disease	Age (mos)	Gender	Hospitalization date
Prematurity	3	Male	16/10/2015
Prematurity	3.5	Female	19/10/2015
CHD	8	Female	25/10/2015
CHD	6	Male	26/10/2015
Prematurity	5	Female	21/11/2015
CHD	9	Female	24/11/2015
Prematurity	5	Male	26/12/2015
Prematurity and CLD	5	Male	26/12/2015
Prematurity	5	Female	07/11/2016

[B] Received palivizumab before hospitalization (group 4)

Underlying disease	Age (mos)	Gender	Vaccination date	Hospitalization date
Prematurity	0.8	Male	23/12/2014	12/01/2015
CHD	6	Female	16/11/2015	29/11/2015
CHD	1.1	Female	11/12/2015	07/12/2015
Prematurity	2	Male	16/11/2015	13/12/2015
Prematurity and CLD	1.1	Male	Not documented	19/12/2015

CHD = congenital heart disease, CKD = chronic lung disease

ventilation, vasopressor therapy, and the need for treatments such as corticosteroids, adrenaline, inhaled bronchodilators, and antibiotics. No deaths occurred due to RSV bronchiolitis during the study period.

Disease severity was related to the presence of underlying conditions and the receipt of palivizumab prophylaxis as categorized above. The duration of hospital stay, the duration of oxygen supplementation, and the rate of PICU admissions were significantly associated with the above-mentioned groups *(P* < 0.01). Children with no underlying disease (group 1) had a relatively mild disease, with oxygen administration for 1.5 ± 1.9 days, PICU admission of 2%, and 5 ± 2.2 days hospitalization. Children with underlying conditions who were not eligible for palivizumab (group 2) had a more severe course, with hospital stay of 6.7 ± 5.4 days, oxygen therapy for 2.4 ± 3.7 days, and a 12% PICU admission rate. The most severe course was noted in children who were eligible for palivizumab but did not receive it prior to hospitalization (group 3). They had the longest hospitalization (8.7 ± 7.3 days) and duration of oxygen supplementation (4.1 ± 4 days), and the highest rate of PICU admission (22%, $P < 0.001$ for all parameters). Children who received palivizumab prior to hospitalization had a relatively mild course, with the shortest hospitalization (4 ± 1.4 days) and a relatively short oxygen therapy (1.6 ± 1.2 days); two of them were hospitalized in the PICU for a single day.

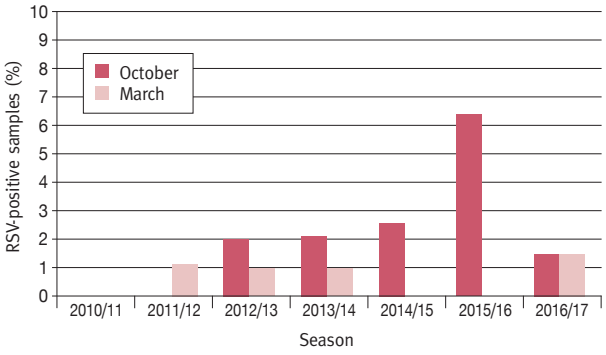
SEASONALITY OF RSV HOSPITALIZATION

Of the total 426 RSV hospitalizations for RSV bronchiolitis during the 2-year study period, the numbers (%) hospitalized each month were as follows: 25 (5.7%) in October, 119 (27.9%) in November, 129 (30.2%) in December, 117 (27.4%) in January, 23 (5.3%) in February, 6 (1.4%) in March, and 2 (0.46%) in April. Thus, the vast majority of hospitalizations were between November and January. However, the number of admissions due to RSV bronchiolitis in October was 4.2-fold higher than in March ($P < 0.001$) and even mildly higher than that in February. Of the nine children who were eligible for palivizumab but did not receive it prior to their hospitalization, four were hospitalized in the last 2 weeks of October, before 1 November, the date of the first dose of palivizumab in Israel. In the last 2 weeks of March, only three children with RSV were hospitalized, none of whom had underlying disease.

SEASONALITY OF RSV DISEASE IN THE COMMUNITY

Analysis of the RSV-confirmed disease in a nationally based ambulatory survey showed seasonality that was very similar to that in the hospitalized children, with more cases in October than in March in most years. This is illustrated in Figure 2, which presents the percentage of ambulatory RSV-positive patients in the last 2 weeks of October as compared to the last 2 weeks of March over the seven RSV seasons examined. In five of the seven seasons RSV disease was more common in October than in March, while in two seasons the rates were the same in these 2 months. Thus, the distribution of RSV-confirmed illness in sentinel clinics in Israel validated the findings of the hospitalized patients.

Figure 2. RSV-positive specimens of infants 0–2 years old from sentinel clinics in Israel, during the last 2 weeks of October vs. the last 2 weeks of March (expressed as the percentage of the total RSV-positive samples received from sentinel clinics in the respective season)



DISCUSSION

The current study reports two new findings regarding the epidemiology of RSV bronchiolitis in Israel in the current palivizumab prophylaxis era. The findings were observed in hospitalized children with RSV-confirmed acute bronchiolitis and were validated in a national ambulatory-based prospective study of RSV-confirmed respiratory illness in sentinel clinics scattered throughout Israel.

The first finding was the decisive delineation of the seasonality of RSV bronchiolitis in Israel. This observation highlights a discrepancy between the seasonality of the disease and the current recommended timing of initiating palivizumab administration each fall. According to our findings in hospitalized patients, the number of admissions due to RSV bronchiolitis in October was 4.2-fold higher than in March ($P < 0.001$), and even mildly higher than in February. The seasonal distribution of RSV-confirmed disease in sentinel clinics in Israel was in concert with that of hospitalized children, since in five of seven RSV seasons more cases were recorded in the last 2 weeks of October as compared with the last 2 weeks of March.

Despite the above, palivizumab prophylaxis is initiated in Israel on 1 November. Our findings suggest that initiating the five-dose vaccination regimen in mid-October could have prevented 44% of the RSV-related hospitalizations and 22% of PICU hospitalizations of the palivizumab-eligible infants in our medical center. It should be emphasized that this change and its benefits can be achieved with no additional dose of palivizumab or increased cost. On the contrary, costs

will actually be reduced since palivizumab dose is based on infants' body weight, which is obviously lower in October than in March. This highlights the need for updated and precise epidemiological data on infection with RSV to optimize prevention of the latter by immunoprophylaxis.

RSV disease presents with well-documented seasonality, which is geographically dependent: disease onset peaks in temperate climates during the fall and winter months [13]. However, the precise timing of RSV disease varies among countries located in temperate climates and might actually change with time [1,2,13,20]. Indeed, a recent nationwide survey in the United States, conducted by the Centers for Disease Control and Prevention and based on molecularly confirmed diagnosis, demonstrated a change in the seasonality of RSV disease [22]. Nationally, RSV onset in the 2014–2017 seasons occurred 2 weeks earlier than in the 2012–2014 seasons; the median RSV onset changed from late October-early November to early to mid-October [22]. These findings are in line with ours. According to the recommendations of the AAP, palivizumab immunoprophylaxis should be initiated in October, depending on the precise seasonality of RSV infection in each location [17]. The above-mentioned study also showed that the exact timing of RSV onset depends on the location within the United States: mid-September in Florida and Georgia but mid-November in Colorado and California [22]. The reasons for these differences are not completely clear, as many factors might influence national, regional and state-level RSV activity, including climate, social and demographic factors, population density, and pollution [1,13].

The second main finding of the current study was the significant morbidity of RSV disease among children with underlying conditions who are not palivizumab-eligible under the present recommendations in Israel. This group of children comprised 25% of those hospitalized with RSV bronchiolitis, constituting the second largest group of hospitalized children. These children presented a more severe course than those without underlying conditions: a longer hospital stay, longer oxygen therapy, and a higher PICU admission rate.

The increased morbidity of RSV infection among children with chronic underlying medical conditions is supported by previous studies [12,23,24]. A systemic review that included 58 studies published between 1995 and 2015 [24] concluded that children with Down syndrome, immunosuppression, cystic fibrosis, and neurologic conditions had an increased risk of RSV hospitalization [24]. Pre-existing disease was also associated with severe RSV disease and was shown to be a predisposing factor for RSV-related mortality, although with a low strength of evidence [24]. It should be emphasized, however, that the most severe course in our study was observed in children with underlying conditions who were vaccine-eligible, indicating that the current recommendations in Israel indeed focus on children with the highest risk.

The present study has several limitations. It comprised a retrospective analysis of all children hospitalized with RSV bronchiolitis in a single medical center, although this facility is large with three departments of pediatrics and a large capture area. In addition, the results achieved from the hospitalized children were validated in a prospective national ambulatory-based study of RSV-confirmed respiratory illness in sentinel clinics scattered throughout Israel.

In conclusion, on the basis of the present results in hospitalized and ambulatory children with microbiologically confirmed RSV disease, we strongly recommend advancing the first dose of palivizumab prophylaxis by 2 weeks to mid-October. This is expected to reduce RSV morbidity in the community, RSV hospitalizations and complications, at no additional cost. In addition, target populations for palivizumab prophylaxis should be re-evaluated periodically according to updated data. Optimal utilization of passive immunization is crucial until long-term prevention by an active RSV vaccine, which is currently under intensive studies, becomes available [1,25].

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Capsule

A single pathway protects against skin infection and wrinkling

Wrinkles are a natural part of aging and are largely caused by the breakdown of the nutrient-rich fat layer under our skin. Subcutaneous fat cells (adipocytes) not only provide volume and plumping but also produce antimicrobial peptides that help protect against skin infection. **Zhang** et al. studied how specialized cells called dermal fibroblasts transform into adipocytes from birth to adulthood. Activation of the protein transforming growth factor-β (TGF-β) reduced the production and quality of adipocytes and impaired antimicrobial defense. The study raises the possibility that drugs targeting the TGF-β pathway might have a double benefit of tackling wrinkles and skin infection.

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Eitan Israeli

Capsule

Impact of tumor necrosis factor inhibitor in early ankylosing spondylitis

Won Park et al. investigated the impact of tumor necrosis factor inhibitor (TNFi) treatment and inflammation control on radiographic progression in early ankylosing spondylitis (AS) over 4 years. They included a total of 215 patients with early AS (symptom duration ‹ 10 years) treated with TNFi (the TNFi group; n=135) or with non-steroidal anti-inflammatory drugs (NSAIDs) (the control group; n=80). Two blinded readers assessed radiographic progression using the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS). Inflammation control was inferred from C-reactive protein (CRP) levels time-averaged between two radiologic assessments. Linear mixed modeling was used to estimate mSASSS changes over radiographic intervals as well as the impact of clinical factors on outcomes. The TNFi group had longer disease duration, a higher baseline CRP level, and a higher Bath Ankylosing Spondylitis Disease Activity Index than did controls. The time-averaged CRP level over radiographic intervals was lower with TNFi treatment than with NSAID treatment (mean ± SD 0.27 ± 0.30 mg/dl vs. 0.61 ± 0.68 mg/dl; P ‹ 0.001). Overall, mean ± SD mSASSS change over the 2-year interval was 1.30 ± 2.97 units. In the multivariable model adjusted for age, smoking status, baseline CRP level, and the presence of syndesmophytes at baseline, the TNFi group showed less mSASSS change over the 2-year interval (β = –0.90, 95% confidence interval [95%CI] -1.51, -0.29). However, when a time-averaged CRP level was additionally included, it significantly influenced the mSASSS change (β = 1.02, 95%CI 0.32–1.71), decreasing the estimated group difference (β = –0.52, 95%CI –1.17–0.14). NSAID indices of both groups were not associated with either time-averaged CRP levels or mSASSS changes.

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