Impact of American Academy of Pediatrics Palivizumab Guidance for Children ≥29 and <35 Weeks of Gestational Age

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Objectives To evaluate the impact of the American Academy of Pediatrics revised recommendations (2014) for palivizumab prophylaxis on respiratory syncytial virus (RSV) admissions and severity of illness among children ≥29 weeks and <35 weeks of gestational age.

Study design We evaluated patients hospitalized with RSV infection from October 1, 2012, through April 30, 2017. RSV hospitalizations, community RSV activity, duration of hospitalization, disease severity, and mortality were reviewed. Data were compared before and after implementation of the guideline changes.

Results A total of 91 patients were born at ≥29 weeks and <35 weeks of gestational age and hospitalized within the first year of life during the evaluation period. Gestational age, birth weight, age at diagnosis, and sex remained constant over the seasons evaluated. RSV hospitalizations and activity in the community were unchanged over 5 years. Duration of hospitalization increased. There was no difference in need for intensive care, supplemental oxygen, or mechanical ventilation or mortality.

Conclusions Implementation of the 2014 American Academy of Pediatrics guidelines regarding eligibility for palivizumab prophylaxis in older infants born preterm did not increase RSV hospitalizations or disease severity among children hospitalized for RSV at our hospital. Our data support continued adherence to the guidelines. *(J Pediatr 2019;209:125-9)*.

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract illness in infants and young children worldwide.[1] Infants born premature and others with chronic cardiopulmonary diseases are more likely to be severely affected.[2,3] Palivizumab (Synagis; MedImmune, Inc, Gaithersburg, Maryland) is a monoclonal antibody used for prevention of severe lower respiratory tract illness in pediatric patients at risk for severe RSV infection.[4] RSV prophylaxis should be restricted to high-risk infants as directed by the American Academy of Pediatrics (AAP) due to limited clinical benefits and high costs.[2,3] The restriction is narrower than the Food and Drug Administration license, leading to controversy.

The AAP revised recommendations (2014) for palivizumab prophylaxis among infants and young children at increased risk for RSV infection.[2,3] Children ≥29 weeks of gestational age no longer qualify unless they meet other indications (eg, chronic lung disease, congenital heart disease). We provide data from a single children's hospital for 2 seasons before and 3 seasons after implementation of the revised guideline to evaluate the impact on RSV admissions and severity of illness among children ≥29 and <35 weeks of gestational age.

Methods

Patients hospitalized with confirmed RSV infection from October 1, 2012, through April 30, 2017, were identified from the electronic medical record using the *International Classification of Diseases, Ninth Revision*, codes (466.11, RSV bronchiolitis; 079.6, RSV infection; 480.1, RSV pneumonia) and *Tenth Revision* codes (J21.0, RSV bronchiolitis; B97.4, RSV infection; J12.1, RSV pneumonia). Records were crosschecked with virology laboratory results. RSV diagnosis was based on real-time polymerase chain reaction assays throughout the study period, a highly sensitive and specific test. Criteria for hospital admission and management of children with RSV were uniform during the study. Data were collected for quality improvement and medication use evaluation of palivizumab by the hospital. Patient identifiers were not recorded in the data set.

We retrospectively collected demographic data including weeks of gestational age at birth, birth weight, age at RSV diagnosis, and sex. Patients with missing data were excluded. We reviewed outcomes of care, including need for mechanical ventilation and/or supplemental oxygen, admission or transfer to intensive care, duration of hospitalization, and mortality. We compared data before and after

AAP	American Academy of Pediatrics
ICU	Intensive care unit
NICU	Neonatal intensive care unit
RSV	Respiratory syncytial virus

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implementation of the 2014 AAP palivizumab guidance. RSV seasons were defined as October 1, 2012, through April 30, 2013 (season 1); October 1, 2013, through April 30, 2014 (season 2); October 1, 2014, through April 30, 2015 (season 3); October 1, 2015, through April 30, 2016 (season 4); and October 1, 2016, through April 30, 2017 (season 5). Only the first RSV hospitalization (if applicable) during each season was included.

Receipt and timing of palivizumab administration during hospital stays were obtained from the electronic health record. The data set did not include information needed to evaluate whether patients who did not receive palivizumab were eligible to receive the medication. Likewise, we were unable to access outpatient databases for patients outside of the health system to ascertain the timing or number of palivizumab doses received for which they were eligible.

To control for possible differences in RSV burden in the community over successive years, we collected test results from the many practices affiliated with our hospital that use the same diagnostic laboratory. This "community activity" in children of all ages contributes heavily to and closely correlates with total RSV activity reported by the State of Wisconsin for the region. We also captured live discharges from our neonatal intensive care unit (NICU; the sole tertiary care unit within our region) within the targeted gestational age ranges by calendar year. In our region, RSV season comprises October 1 through April 30, with each calendar year contributing 3 months of the live discharges during RSV season.

Descriptive analyses were performed using frequency distributions or rates. Medians were used to summarize demographic data and outcomes. Associations between continuous variables and proportions were analyzed using the Student *t* test, Fisher exact test, or Wilcoxon rank-sum as appropriate. ANOVA was performed using a Kruskal–Wallis test to evaluate data across seasons. Linear regression (Microsoft Excel; Redmond, Washington) was used to describe changes in laboratory-confirmed RSV cases over time. We estimated possible enrichment of infections in the gestational age cohort affected by the change in the AAP guideline by the proportion of RSV hospitalizations of children ≥29 weeks to <35 weeks of gestation relative to total RSV hospitalizations as the denominator. We estimated the proportion of susceptible children infected in the gestational age cohort using hospitalized children of ≥29 weeks to <35 weeks of gestation relative to the average of live discharges for the 2 years spanning each RSV season (eg, fall 2012 and winter 2013 for RSV season 1). Seasonal differences were tested by the Fisher exact test with correction for multiple testing.

Results

A total of 664 patients were hospitalized with RSV during the 5 seasons. Of those hospitalized in the first year of life, 91 patients were born at ≥29 and <35 weeks of gestation, the age group affected by changes in the public health recommendation. One outlier (gestational age 33 weeks, birth weight 2.12 kg) was removed from the season 2 data set due to prolonged length of stay (931 days) unrelated to RSV diagnosis. We did not measure a significant increase in RSV hospitalizations among patients born at ≥29 and <35 weeks of gestation following the change in the AAP guideline over 3 subsequent seasons. A prominent increase in number of RSV-associated hospitalizations in the affected gestational age group occurred in the first season (season 3) after the change in guideline, but the number then diminished toward the overall mean in seasons 4 and 5 (**Table I**). There were no statistical differences in proportion of infants born at ≥29 and <35 weeks of gestation relative to total numbers of hospitalized children with RSV infection between successive years. There were upward and downward trends ($.05 < P < .2$) in proportion of infants hospitalized from this cohort between 3 of 4 successive seasons, without clear pattern. The first (8%) and fifth seasons (14%) had the lowest proportions of hospitalized children in this gestational age cohort, peaking in the third year (21%).

Demographic data for all patients hospitalized with RSV are shown in **Table II**. Most patients are born at term and hospitalized when <1 year of age. Demographic data for patients born at ≥29 and <35 weeks of gestation who were hospitalized with RSV in the first year of life are shown in **Table I**. Hospitalizations in this gestational age group accounted for 8%-21% of all RSV hospitalizations per season. Gestational age, birth weight, and sex remained constant over the study. Likewise, there were no shifts in age at RSV diagnosis after AAP-recommended changes in palivizumab administration to this gestational age group.

To control for annual differences in RSV severity in the region, we measured all RSV-associated hospitalizations and laboratory-confirmed RSV infections in affiliated community pediatric practices. RSV-associated hospitalizations (declining, $P = .07$) and RSV community activity ($P = .72$) among all gestational age groups were unchanged over the 5 seasons (**Figure**). To control for potential differences in the number of susceptible infants affected by the change in the AAP guideline, we recorded the number of live discharges born at ≥29 and <35 weeks of gestation from the sole regional NICU. The number of susceptible infants affected by the change increased over this study period (**Figure**). There were no statistical differences in proportion of susceptible infants infected by year using hospitalizations (**Table II**) and the mid-point of the number of live discharges from the regional tertiary care NICU (**Figure**).

Disease severity before and after implementation of the AAP palivizumab guidance among children born at ≥29 and <35 weeks of gestational age with RSV-associated hospitalization in the first year of life is described in **Table III**. Duration of hospitalization was longer after implementation (median 7.86 days, range 0.07-85.4 days) was longer compared with before implementation (median 5.86 days, range 0.05-36.2 days; $P = .02$). Rates of intensive care, supplemental oxygen, or mechanical ventilation trended greater, but not significantly. There was 1 death in

Table I. Demographics of patients born at ≥29 and <35 weeks of gestational age who were hospitalized with RSV in the first year of life (n = 91)

	Season 1, n = 14	Season 2, n = 16	Season 3, n = 30	Season 4, n = 21	Season 5, n = 10	*P* value
Gestational age, wk, median (range)	33 (30-34)	33 (30-34)	32 (29-34)	32 (29-34)	33 (29-34)	.79
Birth weight, kg, median (range)	1.73 (1.24-2.30)	1.90 (0.79-3.03)	1.60 (0.96-2.81)	1.81 (1.33-2.36)	1.73 (1.07-2.64)	.85
Age at diagnosis, d, median (range)	68 (21-356)	80 (35-309)	97 (20-320)	71 (25-242)	83 (27-279)	.84
Male, n (%)	6 (43)	12 (75)	21 (70)	10 (48)	7 (70)	.53

season 1 (before recommended changes), occurring 2 months following the RSV diagnosis.

Discussion

We did not encounter a deleterious public health effect of the revised 2014 AAP guideline on older infants born premature in our regional referral center. The AAP publishes guidance on the use of RSV immunoprophylaxis among infants and young children at increased risk of hospitalization for RSV infection. The 2014 iteration of the guideline narrowed the population for which prophylaxis is recommended, to focus on individuals with an increased risk and severity of RSV disease.[2,3] The guideline no longer recommends palivizumab in the first year of life for infants born preterm who are otherwise healthy if born at ≥29 weeks of gestational age. After implementing the updated recommendations at our institution, we did not detect any difference in rates of hospitalization over the next 3 years. Furthermore, we reduced the number of palivizumab doses dispensed by more than 50%, which translated to a cost savings of greater than $300 000 annually.[4] Public health cost savings are aggregated over multiple doses rather than just the starter dose before discharge, so they should be proportionately larger. However, there is controversy surrounding the guideline changes and reports of increased hospitalization and disease severity.

Rajah et al described the impact of the updated guidance for palivizumab prophylaxis against RSV infection at Nationwide Children's Hospital in Columbus, Ohio, over 2 seasons.[5] This study included infants born at 29-34 weeks of gestational age who were <12 months of age at the time of RSV hospitalization (n = 91) and compared differences in clinical outcomes according to chronological age at hospitalization with disease severity, intensive care unit (ICU) admission, mechanical ventilation, and length of stay. There was an insignificant increase in RSV hospitalizations (7.1%-9.8%, $P = .1$) after adoption of the AAP guideline. Data mining suggested that disease severity of younger patients hospitalized after the AAP-recommended change worsened. Our results also confirmed an increase in hospitalizations in the first year but was not replicated in subsequent years, demonstrating the importance of programmatic evaluations spanning several years.

Anderson et al described RSV hospitalizations among US infants born at 29-35 weeks of gestational age who did not receive palivizumab during the 2014-2015 season when the revised guideline was in effect.[6] This multicenter, observational registry included 709 infants with laboratory-confirmed RSV who were <12 months of age at the time of admission. Parents consented retrospectively to provide data on severity of illness and subsequent costs. A baseline cohort, the existence of other indications for prophylaxis (eg, chronic lung disease), and enumeration of failures of prophylaxis were not included in the registry. Earlier gestational age and younger chronologic age were associated with an increased frequency of RSV hospitalization, ICU admission, and requirement for mechanical ventilation. Our study was quasi-experimental and included a control group. The design avoided referral bias. Our study is restricted to a single site, albeit with stable RSV incidence over the study period, and under-powered relative to the disease registry.

McLaurin et al describe a mathematical model to describe the potential impact of the 2014 palivizumab guidance on infants born preterm at ≥29 and <35 weeks of gestational age on RSV outcomes.[7] The authors concluded that implementation of the 2014 AAP guidance was expected to result in additional adverse outcomes, such as RSV hospitalization, ICU admission, and mechanical ventilation. Our findings did not support projections of increased hospitalizations, and the effects on ICU admission and mechanical ventilation were insignificant.

Newby et al examined the theoretical effect of a more restrictive guideline in British Columbia that antedated those adopted by the AAP and the Canadian Pediatric Society in their recent 2014 and 2015 guidelines.[8] In that province,

Table II. Demographics of all patients hospitalized with RSV (n = 664)

	Season 1, n = 182	Season 2, n = 128	Season 3, n = 143	Season 4, n = 137	Season 5, n = 74	*P* value
Gestational age in weeks at birth, median (range)	38 (23-42)	38 (25-41)	38 (24-48)	38 (25-41)	38 (24-41)	.63
Birth weight, kg, median (range)	3.03 (0.48-4.45)	3.01 (0.51-4.80)	2.89 (0.51-4.37)	2.86 (0.38-4.53)	2.92 (0.51-4.33)	.93
Age at diagnosis, d, median (range)	122 (10-898)	134 (1-754)	114 (11-904)	99 (0-859)	116 (14-862)	.81
Male, n (%)	101 (56)	81 (63)	78 (55)	76 (56)	37 (50)	.08

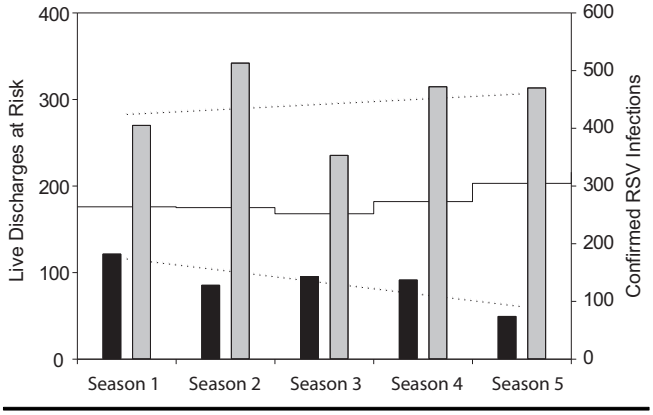

Figure. RSV activity over 5 seasons (reflecting RSV infection pressure in the community) and number of live discharges from the sole regional tertiary care NICU with gestational ages of ≥29 to <35 weeks (susceptible population) over 6 overlapping calendar years (see text). The number of laboratory-confirmed patients (all gestational ages) hospitalized with RSV is represented in *black*. The number of laboratory-confirmed patients with RSV in the community is represented in *light gray*. The *dotted lines* represent trends by linear regression over 5 seasons. The *solid black line* represents live discharges at risk. Slopes for total RSV hospital admissions and confirmed community infections are not significantly different from zero. The number of susceptible infants discharged into the community increased over the study period (P = .031). Changes in RSV prophylaxis occurred between seasons 2 and 3.

Table III. Disease severity before and after implementation of AAP guidance for palivizumab prophylaxis among children born at ≥29 and <35 weeks of gestational age with RSV-associated hospitalization in the first year of life

	Before (seasons 1-2), n = 30	After (seasons 3-5), n = 61	*P* value
Duration of hospitalization, d, median (range)	5.86 (0.05-36.2)	7.86 (0.07-85.4)	.02
Patients requiring intensive care, n (%)	15 (50)	43 (70)	.06
Patients requiring supplemental oxygen, n (%)	22 (73)	53 (87)	.11
Patients requiring mechanical ventilation, n (%)	5 (17)	18 (30)	.19
Death within the RSV season, n (%)	1 (3)	0 (0)	.15

palivizumab use required additional risk-based criteria for infants born at 29-32 weeks of gestational age. The frequency of RSV-positive hospital visits did not differ between infants who received and those who did not receive approval for palivizumab. Our data support their model.

Farber et al reported changes in medical claims in 9 healthcare systems in Texas for 2 seasons preceding and 1 following the AAP guideline.[9] It should be noted that palivizumab uptake among those receiving medical assistance in their population during the observation period was poor, so the effect of more restrictive palivizumab use was likely minimal. There was an effort to exclude patients with cardiopulmonary indications for palivizumab use. Among infants not receiving palivizumab, 4.97% had RSV-associated admissions, and among those receiving >80% of indicated doses, 1.41% were admitted. The protective effect of high palivizumab compliance was balanced by a greater rate of hospitalizations for non-RSV bronchiolitis among those compliant with palivizumab, suggesting confounding by indication. Like our study, the findings of Farber et al support the recommendations of the 2014 AAP guideline, which advises against the use of palivizumab for otherwise-healthy infants ≥29 weeks of gestation. We could not capture compliance with palivizumab in our study and did not study non-RSV bronchiolitis.

The IMpact-RSV study was a multicenter, randomized, double-blind, placebo-controlled trial that included 1502 patients who were either (1) ≤35 weeks of gestational age AND ≤6 months of age; or (2) ≤24 months old plus a clinical diagnosis of bronchopulmonary dysplasia requiring ongoing medical treatment.[10] Monthly palivizumab was associated with a 55% (95% CI 38%-72%) reduction in hospitalization as a result of RSV. A substantial proportion (45%) of infants born at gestational ages ≥29 and <35 weeks should therefore be hospitalized despite palivizumab. Given the studies of Rajah et al and Anderson et al, we speculated that the insignificant trend we observed toward increased disease severity among hospitalized patients in this age cohort might be related to a palliative effect of palivizumab even when protection against hospitalization was not met.

Our study's main strength is that it included 2 seasons before the AAP guideline changes and 3 seasons after, to better account for single-season differences in RSV activity. We also provided a background estimate of community RSV activity, constituting "infection pressure" on the at-risk population, and an estimate of the number of "susceptible infants" constituting the at-risk population, minimizing potential confounding in the study. The study was conducted at a single center, so decisions regarding the need for intensive care, supplemental oxygen, and mechanical ventilation were likely to be consistent over time, compared with multicenter studies, in which such decisions are likely to be more variable. There was little difference in gestational age, birth weight, and age at RSV diagnosis before and after guideline implementation, indicating the comparison involved similar risk factors, and the infants were reasonably well matched. RSV diagnosis was laboratory confirmed by a sensitive and specific polymerase chain reaction test. The at-risk population discharged from our regional NICU increased over time, enhancing sensitivity to detect a deleterious change in outcomes following withdrawal of palivizumab prophylaxis.

Our study is from 1 academic hospital center singly serving a wide region. Like other published studies, the statistical power is low. Based on an RSV infection rate of 8% relative to

≥29 to <35 weeks of gestation live discharges or total RSV hospitalizations in year 1 of our study, 882 infants would be needed to detect the loss of 55% efficacy of palivizumab reported in the IMpact-RSV study. This subject number exceeds the 704 subjects reported in the manufacturer-sponsored national registry active at 43 academic centers in 1 year.[6] As this study illustrates, collection of data over at least 3 years is necessary to avoid faulty inferences predicated on a single RSV season.

Our study has other major limitations. Adherence to the guideline and medication adherence outside of the hospital could not be assessed. Gestational age among individuals with RSV in the community was not available. This study did not identify or exclude patients with nosocomial RSV; however, we have previously reported a nosocomial transmission rate of <0.05% at our hospital.[4] Referral patterns, medical practice, population structures, climate, and geography may limit generalization. The study is retrospective, so it is possible that *International Classification of Diseases* classification errors, unmeasured confounders, or missing data may have influenced the results. Insignificant trends in rates of hospitalization, intensive care, supplemental oxygen use, or mechanical ventilation might have resolved or become evident with a larger sample size. A societal cost-benefit analysis was beyond the scope of this hospital-based study.

Implementation of the revised 2014 AAP guideline regarding eligibility for palivizumab prophylaxis in older infants born preterm did not increase RSV hospitalizations or disease severity among children hospitalized for RSV at our hospital. Our data support continued adherence to the guideline. Meta-analyses of many reports like our small study are needed to achieve the statistical power to resolve this controversy. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

References

1. Simoes EA. Respiratory syncytial virus infection. Lancet 1999;354:847-52.
2. American Academy of Pediatrics Committee on Infectious Diseases; American Academy of Pediatrics Bronchiolitis Guidelines Committee. Policy Statement: Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Pediatrics 2014;134:415-20.
3. American Academy of Pediatrics Committee on Infectious Diseases; American Academy of Pediatrics Bronchiolitis Guidelines Committee. Technical Report: updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Pediatrics 2014;134:e620-38.
4. Zembles TN, Gaertner KM, Gutzeit MF, Willoughby RE. Implementation of American Academy of Pediatrics guidelines for palivizumab prophylaxis in a pediatric hospital. Am J Health Syst Pharm 2016;73:405-8.
5. Rajah B, Sanchez PJ, Garcia-Maurino C, Leber A, Ramilo O, Mejias A. Impact of the updated guidance for palivizumab prophylaxis against respiratory syncytial virus infection: a single center experience. J Pediatr 2017;181:183-8.
6. Anderson EJ, Krilov LR, DeVincenzo JP, Checchia PA, Halasa N, Simoes EA, et al. SENTINEL 1: an observational study of respiratory syncytial virus hospitalizations among US infants born at 29 to 35 weeks' gestational age not receiving immunoprophylaxis. Am J Perinatol 2017;34:51-61.
7. McLaurin KK, Chatterjee A, Makari D. Modeling the potential impact of the 2014 American Academy of Pediatrics respiratory syncytial virus prophylaxis guidance on preterm infant RSV outcomes. Infect Dis Ther 2015;4:503-11.
8. Newby B, Sorokan T. Respiratory syncytial virus infection rates with limited use of palivizumab for infants born at 20 to 31+6/7 weeks gestational age. Can J Hosp Pharm 2017;70:13-8.
9. Farber JH, Buckwold FJ, Lachman B, Simpson JS, Buck E, Arun M, et al. Observed effectiveness of palivizumab for 29-36-week gestation infants. Pediatrics 2016;138(2).
10. The Impact RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. Pediatrics 1998;102:531-7.