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ORIGINAL ARTICLE

Impact of Adopting 2014 Guidance for Palivizumab Prophylaxis for Children Previously Considered at High Risk for Severe Respiratory Syncytial Virus Disease

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Abstract

Objectives: This is a report of pediatric patients hospitalized with Respiratory Syncytial Virus Infection (RSV) during the season prior to, and 2 seasons following the 2014 palivizumab prophylaxis guidance release. The primary aim was to determine the effect of the 2014 guidance on children no longer considered eligible for prophylaxis. Secondary aims were to 1) Describe and compare morbidity among all children hospitalized with RSV following the 2014 guidance, 2) Assess adherence to the updated guidance, and 3) Assess associated drug cost savings.

Study design: We performed a retrospective chart review of pediatric patients admitted for RSV disease at our institution during the RSV season from October 2013 - March 2016. Patients who met prior palivizumab qualifications, but were excluded according to 2014 guidance were compared pre and post adoption of 2014 palivizumab guidance. Neonatal Intensive Care Unit (NICU) records were assessed for adherence to 2014 guidance and resulting palivizumab drug cost was compared.

Results: Among cases qualifying according to previous guidance, but excluded in the 2014 update, there were no significant differences seen in the rate of RSV hospitalization, admission to higher level of care, increased respiratory support requirement, or length of stay. Following the adoption of 2014 guidance, palivizumab dosing was reduced by 58%; the rate of appropriate prophylaxis among NICUs was 91%. This reduction resulted in an annual drug cost savings of $225,000.

Conclusion: Adoption of updated 2014 guidance at our institutions had little impact on hospitalization with RSV disease, while allowing for better resource management.

Keywords

Palivizumab (Synagis), Respiratory syncytial virus (RSV) bronchiolitis, Guideline, Prematurity

Introduction

Respiratory Syncytial Virus (RSV) is a common virus affecting nearly all children before the age of 2 years and is the leading cause of bronchiolitis and pneumonia during the first year of life [1]. Palivizumab has been used as prophylaxis for high risk infants since the late 1990s. Guidance for its use been updated 5 times during this period, as more data are available to aid in balancing risks, cost, and impact of its use on specific high risk infants [2]. The most recent updated guidance for the use of palivizumab prophylaxis for RSV disease in high risk infants and children was introduced by the American Academy of Pediatrics (AAP) in August of 2014 and was adopted by our hospital system for the subsequent RSV season [2,3]. This more restrictive guidance no longer recommends palivizumab prophylaxis for the gestational group category of $29^{0/7}$ to $34^{6/7}$ weeks, if they do not have other qualifying health conditions. Addition-

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ally, the updates include some restrictions on the use of palivizumab for children with Chronic Lung Disease (CLD) and Congenital Heart Disease (CHD), particularly during the second year of life [2,3].

The guidance remains controversial with literature in support of and against the new restrictions [4-8]. Farber, et al. studied infants born over a three-year period between 29-36 weeks gestation without chronic illness in Texas who were enrolled in managed Medicaid. Among those born between 29-32 weeks gestation, palivizumab prophylaxis receipt was associated with reduced hospitalization for RSV disease, but increased hospitalization for non-RSV bronchiolitis. They concluded that the more restrictive guidance of 2014 overall had little impact on this population [4]. Likewise, a study of hospital utilization of palivizumab found the restrictive guidance did not have an effect on nosocomial RSV and resulted in significant cost savings [6]. However, Rajah, et al. performed a study comparing cases born at 29-32 weeks gestation pre and post 2014 guidance and found that this group, now excluded from palivizumab guidance, had increased hospitalizations and morbidity [7]. Another study also highlighted the burden of RSV disease among mid-late preterm infants including high rates of mechanical ventilation and admission to Intensive Care Units (ICU) [8].

Information describing the effect of the guidance on the subset of children affected by the change is sparse and conflicting. Therefore, we sought to determine the effect of new guidance on children who previously qualified for prophylaxis, but no longer do in terms of rate of hospitalization and severity of disease course.

Methods

Our hospital system adopted the AAP palivizumab updated guidance, which was released in the summer of 2014, for the subsequent RSV seasons. We performed a retrospective chart review on pediatric patients admitted to a 240-bed freestanding children's hospital in Central Texas during the RSV season preceding the new guidance (2013/2014), and the two RSV seasons following the update (2014/2015 and 2015/2016).

The primary aim was to determine the effect of new guidance on children who previously qualified for prophylaxis, but no longer do in terms of rate of hospitalization and severity of disease. Outcomes for disease severity included respiratory support requirement, hospital length of stay, and admission to a higher level of care.

Secondary aims for the project included 1) A comparison of disease course among children hospitalized with RSV in the following groups: those who did not qualify for prophylaxis, those who qualified according to 2012 guidance, but were excluded in 2014, and those still qualifying for prophylaxis following the 2014 guidance update, 2) Assessing adherence to the guidance including our Neonatal Intensive Care Units (NICU) and patient reports of palivizumab receipt in the chart, and 3) Cost savings in our hospital system NICUs. We felt this secondary data was important to the discussion of the effect of the new guidance because it would clarify whether the new guidance was being followed appropriately, cost benefits related to drug administration, and add a point of reference regarding disease course among those hospitalized with RSV.

Patients were identified using the following inclusion criteria: age less than 2 years at admission, admitted during the RSV season, and having a documented diagnosis of RSV as one of the primary two diagnoses. The RSV seasons were defined in accordance with regional recommendations by the Texas Department of Health and Human Services: October 19, 2013 - March 22, 2014; September 23, 2014 to March 15, 2015; and October 1, 2015 to March 15, 2016 [9-11]. All cases either had a positive RSV test at our hospital or reported a positive test at an outside hospital or primary care office. Rapid antigen-based detection tests were most commonly used, though any type of established RSV testing was accepted. Patients diagnosed with RSV without evidence of a diagnostic test were excluded. Data were collected by manual chart review for the following variables: age at admission, sex, gestational age, Length of Stay (LOS), ICU and Intermediate Care Unit (IMC) admission, receipt of palivizumab, qualification for palivizumab prophylaxis based on available guidance for 2012 and 2014, antibiotic use for secondary bacterial pneumonia with evidence of a positive respiratory culture, and Comorbidities Including CLD, CHD, and any other chronic medical conditions excluding prematurity alone.

Patient cohorts were created for statistic comparisons among children who met qualifications for palivizumab prophylaxis previously, but were excluded according to the updated guidance: pre and post 2014 guidance.

We set to accomplish the primary aim of determining the effect of the updated 2014 guidance on children specifically affected by the restrictions in two ways. One was to compare the rate of hospital admission among children who qualified under previous 2012 guidance during the year prior to the change, when they were still eligible for prophylaxis, to the rate of hospitalization in this group following the updated 2014 guidance. The second was to compare severity of disease in this group before and after the guidance. We chose to include cases for 2 seasons following the guidance to cover a transition period and increase sample size. Outcome variables included hospital LOS, admission to a higher level of care (either ICU or IMC), and level of respiratory support needed. All respiratory support was documented and oxygen requirement beyond 2 liters by nasal cannula or simple face mask was considered to be an indication of a more severe disease course.

To address the secondary aim describing details, differences and disease course overall among children hospitalized with RSV, cases admitted following the 2014 guidance were categorized according to previous and updated palivizumab qualification and compared. To accomplish the secondary aim of describing the rate of appropriate utilization of palivizumab during the first eligible season in our hospital system, we assessed appropriateness of palivizumab utilization based on gestational age amongst patients discharged from the two largest NICUs (74 beds) in our hospital network. Additionally, charts for all cases admitted with RSV disease in the 2 seasons following the 2014 guidance were assessed for reported palivizumab use within the season of admission. Palivizumab use is not included in the routine history and physical and relies on patient reporting. Therefore, although every effort was made to find this information, some cases without documented palivizumab may in fact have received it. The number of palivizumab doses or completion of the series for the season was not assesses for the following reasons: details of palivizumab administration is largely absent from charts in the patients' history and the number of doses received would depend on the timing of the hospitalization within the RSV season.

Our hospital system includes five additional, smaller NICUs with centralized cost data. To assess the secondary aim of cost savings related to palivizumab drug dispensing overall, we collected palivizumab utilization data in our hospital network including all seven NICUs (102 beds) for the three RSV seasons 2013-2016.

Information was input into a Redcap database and statics were calculated using Rstudio software. Continuous variables were analyzed using Wilcoxon rank sum, medians, and Interquartile Range (IQR). Chi-squared and Fisher's exact tests were used depending on the sample size in each category, with 95% confidence intervals and a p-value < 0.05 being considered significant [12,13].

Results

A total of 938 pediatric patients were identified and met inclusion criteria for admission to the hospital for RSV disease across the three RSV seasons studied: 395 in the season prior to 2014 guidance and 543 in the 2 seasons following 2014 guidance. Among this total population of children hospitalized with RSV disease across the three RSV seasons, 54% were male, median age was 3.45 months (IQR 1-8 days), and median hospital length of stay of 2 days (IQR 1-4 days).

Primary aim

Assessing the effect of 2014 guidance on children admitted with RSV disease that previously qualified for palivizumab, but are excluded according to 2014 guidance: Pre and post guidance adoption:

The rate of cases that qualified for previous palivizumab guidance, but were excluded in the 2014 guidance among the total number of children hospitalized with RSV disease was similar at 2.5% (10/395) prior to, and 2.9% (16/543) following the adoption of 2014 guidance (p = 0.857).

Table 1 shows a comparison of specific outcome measures among children in this category pre-versus post-guidance adoption. There were no significant differences among this group before versus after the introduction of 2014 palivizumab guidance.

Secondary aim 1

Describe and compare cases post - 2014 guidance grouped according to palivizumab qualification.

In the total population of 543 patients admitted after the 2014 guidance, 55% of patients were male, 83% were previously healthy, and 80% were born at full term the 2014 (≥ 37 weeks gestation). Demographic information and severity of RSV disease among those hospitalized after guidance, categorized according to qualification for palivizumab prophylaxis, is shown in Table 2.

Table 1: Cases hospitalized with RSV who previously qualified for palivizumab and were excluded according to 2014 guidance: Pre versus Post 2014 guidance adoption.

	Pre 2014 Guidance 2013/14 RSV Season (n = 10) N(%) or Median (IQR)	Post 2014 Guidance 2014/15 and 2015/16 RSV Seasons (n = 16) N(%) or Median (IQR)	P-value
Sex (% males)	70% (7)	25% (4)	0.064
Previously healthy	70% (7)	62.5% (10)	1.0000
Premature (< 37 weeks)	80% (8)	87.5% (14)	0.625
Age (median months)	3.78 (IQR 1.8-8.16)	3.48 (IQR 1.62-6.27)	0.732
Length of stay (median days)	3 (IQR 1.25-5.75)	4 (IQR 2.65-9)	0.205
CLD	10% (1)	6% (1)	1.00
CHD	10% (1)	6% (1)	1.000
Concurrent bacterial pneumonia	0	19% (3)	0.262
Palivizumab for current season	40% (4)	6% (1)	0.107
Admission to higher level of care (ICU/IMC)	50% (5)	62.5% (10)	0.689
Oxygen requirement > 2 L	50% (5)	62.5% (10)	0.689
Mechanical ventilation	20% (2)	25% (4)	1.000

Table 2: RSV illness in children less than 2 years of age with comparisons among high risk groups admitted post-2014 guidance.

	Not Eligible for Palivizumab in 2012 or 2014 (n = 509) N(%) or Median (IQR)	Eligible per 2012; Excluded per 2014 (n = 16) N(%) or Median (IQR)	Eligible per 2014 (n = 18) N(%) or Median (IQR)	P-value
Sex (% male)	56% (283)	25% (4)	50% (9)	0.253
Previously healthy	86% (439)	62.5% (10)	5% (1)	0.001
Receipt of palivizumab	< 1% (2)	6% (1)	56% (10)	0.007
Premature (< 37 weeks)	16% (82)	87.5% (14)	67% (12)	0.306
Age in months	3.24 (IQR 1.44-7.92)	3.48 (IQR 1.62-6.27)	11.04 (IQR 6.72-15.15)	0.006
CLD	< 1% (3)	6% (1)	50% (9)	0.016
CHD	0% (0)	6% (1)	33% (6)	0.127
Length of stay	2 (IQR 1-4)	4 (IQR 2-9.25)	4 (IQR 1.25-6)	0.510
ICU or IMC admission	30% (154)	62.5% (10)	56% (10)	0.951
Oxygen requirement > 2 L	44% (223)	62.5% (10)	61% (11)	1.000
Mechanical ventilation	47% (2)	25% (4)	6% (1)	0.260
Bacterial pneumonia	10% (49)	19% (3)	6% (1)	0.510

There were 16 patients hospitalized with RSV who qualified for palivizumab prophylaxis according to 2012 guidance, but were excluded in 2014 guidance in the two-year period following its adoption. In this group, 62.5% reported being previously healthy, not including a history of prematurity as a chronic comorbidity. Age at admission for this group was similar to that of the group without risk factors for prophylaxis under either guidance with a median of 3.48 months and 3.24 months, respectively (Table 2). Patients excluded from the 2014 prophylaxis guidance were primarily excluded due to gestational age alone (88%, 14/16 patients). One case with CLD, not requiring treatment, was excluded due to gestational age > 32 weeks. One case with Congenital Heart Disease (CHD) was excluded due to age at the start of the RSV season of greater than 12 months. Of the 14 remaining cases, six patients had gestational age of 29-32 weeks and eight had gestational age of 32-34 weeks with a sibling less than five years of age or daycare attendance.

This group had the highest mechanical ventilation rate (25%, 4/16 patients) amongst the three groups. In all four of these patients requiring mechanical ventilation, gestational age 29-32 weeks or gestational age 32-34 weeks with a sibling less than 5 years was the only factor that would have qualified these patients for prophylaxis. Three of the four patients that required mechanical ventilation in this group were also treated with antibiotics for concurrent bacterial pneumonia; one was treated for necrotizing enterocolitis and bacteremia. Three of the four patients had no significant medical history. The fourth case had Downs Syndrome. This patient qualified for prophylaxis based on gestational age between 32-34 weeks with a sibling under 5 and less than 3 months of age at the start of the RSV season, but not on the basis of cardiac or pulmonary history. This fourth case actually did receive palivizumab during the current season despite 2014 guidance.

There were 18 patients who qualified for palivizumab prophylaxis according to 2014 guidance admitted in the subsequent two RSV seasons. An underlying medical condition was present in 95% of patients; 83% of patients had a history of CHD or CLD. History for CLD was present in 50% of patients, which is significantly higher than the group previously qualifying for palivizumab, but excluded according to 2014 guidance ($p < 0.016$). Gestational age alone qualified 17% of patients for palivizumab prophylaxis. This group was older on admission than any other group with a median age of 11 months. This was the second eligible RSV season for 55% of the patients. One of the 18 patients in this group required mechanical ventilation and one other patient was concurrently treated for a bacterial pneumonia.

Secondary aim 2

Palivizumab utilization: Using data collected from the two largest NICUs (74 beds) in our hospital system for all neonates who met gestational age criteria for the 2014 guidance, the rate of prophylaxis given in in accordance with this guidance was 91%. This rate reflects only doses given in our NICUs and does not account for the overall rate of prophylaxis in an outpatient setting. As a result of utilizing updated guidance, the number of patients who received palivizumab within our system as a whole decreased by 58% from 130 patients in the 2013/14 season to an average of 54 patients in the two subsequent RSV seasons.

Following the 2014 guidance, among the children who still met prophylaxis qualifications, 56% (10) had documentation of receiving palivizumab for the season of admission. These doses would have largely been given in an outpatient setting.

Secondary aim 3

Cost savings due to decreased palivizumab use: Comparing the 2013/14 season to the 2015/16 season, the decrease in palivizumab use resulted in approximately $225,000 savings based on the hospital cost for the initial dose of palivizumab administered prior to discharge.

Discussion

Primary aim

When comparing pediatric patients hospitalized before and after the adoption of 2014 guidance, we see a similar rate of hospitalization for RSV among the cohort of patients who meet qualifications for 2012 palivizumab guidance, but are excluded according to 2014 guidance. None of the outcome variables comparing these cohorts were significantly affected by this change in practice including length of stay, admission to higher level of care, and increased need for respiratory support beyond 2 L of oxygen.

Real data assessing the impact of updated palivizumab guidance is sparse. An attempt at predicting the impact that 2014 palivizumab restrictions would have on children hospitalized with RSV found a potential relative decrease in eligible cases for prophylaxis of 40.9%. Given this decrease, there was fear that adopting this guidance would result in an increase in RSV hospitalizations that may have been preventable [14]. Our data do not show this to be the case.

Secondary aim 1

Secondary aims were added to our analysis with the goal of providing a more well-rounded presentation of children with RSV disease who are affected by the change in palivizumab guidance. By describing cases within the groups of hospitalized children qualifying for palivizumab guidance (previous and current), we can provide a more robust representation of which children were affected by the change. Other reports have noted severity of disease in children born 29-32 weeks gestation who are younger in age at the time of illness (less than 3 months), including increased admission to higher levels of care and respiratory support [7,15]. Overall, we did not find significantly higher rates of IMC and ICU admission or increased respiratory support among this group, but we did not separate according to age upon admission. A larger sample size may allow for this in future research.

Despite the lack of significant findings among children excluded from 2014 guidance, we recognize the burden of RSV disease in these children. After the 2014 guidance was adopted, we found patients who no longer qualified palivizumab prophylaxis had an increased rate of mechanical ventilation support at 25%, compared with those still qualifying for palivizumab and those without risk factors according to either guidance. This difference was not statistically significant and it is unclear whether they would have required such a high level of care or support for RSV disease alone because these patients were treated for concurrent bacterial infection. However, data from daily chest radiography for these patients is largely suggestive of bronchiolitis, with only one patient having a pleural effusion. These patients required ventilation between 5-12 days (median 6.5 days) and had a longer total length of stay with a median of 12 days (range 9-19 days). Three of these cases had apneic episodes that lead to the decision to intubate.

It is unsurprising that the group of cases still qualifying according to 2014 palivizumab guidance has a significantly higher rate of CLD because the updated guidance only contains minor changes within the CLD criteria and focuses on very premature infants (less than 29 weeks). The fact that the group still qualifying for prophylaxis under the updated guidance is significantly older was an unexpected finding, and may help identify a problem in palivizumab administration in the second eligible year.

Palivizumab utilization Secondary aim 2

As another secondary goal, we felt it important to identify the rate at which palivizumab was actually being used appropriately in our NICUs in order to give evidence that measurable and concrete changes in palivizumab administration took place as a result of adopting the 2014 guidance.

Data from our NICUs is encouraging and shows a successful implementation of the guidance. Adherence to the new guidance by gestational age was 91% and resulted in a marked decreased in doses given annually.

However, receipt of palivizumab reported by patients' points to a potential problem in the outpatient setting. In the group qualifying for palivizumab prophylaxis according to 2014 guidance, roughly half (56%) had any documentation of palivizumab administration for the season of hospitalization. We recognize the possibility that some children in this group may have received palivizumab and not reported this in the chart.

Several studies point to suboptimal utilization of palivizumab [16-18]. This problem affects multiple aspects of an RSV prophylaxis program including administration of prophylaxis outside the recommended guidance, failure to administer prophylaxis for those who do qualify, and administration of incomplete dose series.

Our data show that most of the patients qualifying for, but not reporting receiving prophylaxis, are in their second RSV season (6/8 patients) and therefore, prophylaxis for that season would have been initiated in an outpatient setting. This emphasizes the need for coordinated prophylaxis programs for proper identification of these high risk children in the outpatient setting.

Secondary aim 3

Cost savings due to decreased palivizumab use: Finally, cost is a consideration in analysis of any change within a hospital system. Adherence to the 2014 palivizumab guidance at our institution resulted in significant drug cost savings. These savings only include the initial dose and therefore, the expense of the remaining doses to complete the series in an outpatient clinic presum-

ably represents far greater drug cost savings overall. Although we cannot account for specific children whose hospitalization may have been avoided if the child was eligible for palivizumab, we found that the rate of hospitalization among children who previously qualified and were excluded according to 2014 guidance remained similar before and after the new guidance was adopted.

Our data show reduction in cost associated with the 58% decrease in initial doses of palivizumab given at discharge from our NICUs of about $225,000 annually. This is similar to another study of palivizumab utilization following 2014 guidance which found and annual decrease in palivizumab administration of 56%, resulting in $303,227 in cost savings [6]. We did not assess the impact on hospitalization charges. However, in a study to determine the cost effectiveness of palivizumab among preterm infants 29-32 weeks gestation, the number of infants needing to be treated with palivizumab to avoid a single hospital admission with RSV disease was 20, resulting in a drug cost of $90,000 to prevent a hospitalization cost of $29,000 [19].

Conclusions

Our findings show the disease course and proportion of young children affected by the 2014 guidance restrictions and admitted to the hospital with RSV disease pre and post 2014 guidance is similar. Based on this information, we feel adoption of this guidance has had little effect on this population overall, while providing for significant drug cost savings.

There were additionally no significant differences in variables or outcomes among the post-guidance comparison between the group that qualified according to 2014 guidance and the group that was excluded according to 2014 guidance. Despite this, we recognize the higher rate of mechanical ventilation among the group excluded from prophylaxis, suggesting this remains a vulnerable population.

Limitations

This is a retrospective study including hospitalized patients with RSV within a single system. The data reflect the patients who were admitted to our institution and are not intended to follow a cohort of neonates receiving or qualifying for palivizumab. We recognize the small sample size of patients qualifying under either palivizumab guidance. This study serves to contribute to the data regarding the outcome of RSV-related hospitalization based on the changes made to palivizumab prophylaxis guidance.

Ethical Statement

There are no conflicts of interest or sources of external funding to disclose. This is an IRB approved study. All authors have contributed substantially to the work leading to the manuscript and have approved the final version.

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