Initial Palivizumab Dose Administration in Outpatient Clinic After Hospital Discharge

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Background: Palivizumab provides passive immunity for respiratory syncytial virus (RSV), but poor adherence compromises protection. A hospital initiative promoted administration of first palivizumab doses at an outpatient clinic immediately after discharge. The objectives of this study were to evaluate the impact of the initiative on location and timing of first palivizumab dose, patient adherence, reimbursement, acquisition cost and RSVpositive hospital readmissions.
Methods: This retrospective cohort study included pediatric patients who received palivizumab from 2012 to 2016. Three groups were compared: "before initiative," "transition" and "after initiative." Patients who did not qualify for palivizumab or who were eligible for palivizumab in previous RSV seasons were excluded. Multivariable logistic and linear regressions adjusted for patients' characteristics were used in outcome analysis.
Results: After adjusting for patients' characteristics, there was a 13.5-fold (95% confidence interval: 5.9–30.5, $P < 0.0001$) increase in odds that patients would receive outpatient administration of palivizumab and 2.7-fold (95% confidence interval: 1.3–5.7, $P = 0.0103$) increase in odds of receiving the second dose within 35 days after initiative implementation compared with before. Although there was no significant difference in reimbursement percentage after initiative implementation (32% ± 30% after initiative and 31% ± 22% before), calculated palivizumab acquisition costs were 20.8% lower. RSV readmissions were not significantly different.
Conclusions: Implementation of an initiative with defined workflow, multidisciplinary collaboration, and early case management efforts to obtain insurance authorization increased outpatient administration of first palivizumab doses. Patient adherence improved as demonstrated by more timely receipt of the second palivizumab dose. There was no difference in reimbursement; however, acquisition cost decreased which is valuable considering low reimbursement rates. RSV-positive readmissions did not change significantly.

It is estimated that approximately 2.1 million children less than 5 years of age require medical attention for acute respiratory tract infections caused by respiratory syncytial virus (RSV) each year.[1] Approximately 25% of these patients visit the emergency department, and 3% are hospitalized.[1] Palivizumab is an RSV F protein inhibitor monoclonal antibody approved by the Food and Drug Administration to provide passive immunity for the prevention of serious lower respiratory tract disease caused by RSV in children at high risk.[2,3] Palivizumab is available as a single-dose vial without preservatives.[2,3] The average wholesale price of a 50-mg vial of Synagis (MedImmune,

Gaithersburg, MD) was $1797.96 USD as of October 2017.4 Variations in acquisition costs and reimbursement may affect the financial impact of providing this expensive medication to patients.

Palivizumab is indicated for patients at "high risk" for RSV disease. The American Academy of Pediatrics (AAP) has published guidelines for determining which children are at increased risk.[2,5] The 2 most recent AAP guidelines, published in 2012 and 2014, recommend that hospitalized infants who qualify for palivizumab prophylaxis during the RSV season receive the first dose 48–72 hours before discharge or promptly after discharge.[5,6] Up to 5 monthly intramuscular injections are recommended during the RSV season.[2,5,6] Children who receive the first-dose inpatient have incomplete protection if they do not obtain insurance approval and receive subsequent doses postdischarge. Several studies have shown that patients who are fully compliant with the recommended prophylaxis have decreased risk of RSV-associated hospitalizations. [7–9]

This institution implemented a palivizumab utilization initiative designed to help patients navigate the healthcare system to obtain prophylaxis after hospital discharge; additionally, the initiative promoted administration of the first dose in an associated outpatient clinic on the day of discharge. The primary objectives of this study were to evaluate the impact of the initiative on location and timing of the first palivizumab dose administration, patient adherence, acquisition cost and reimbursement. The secondary objective was to evaluate RSV-positive hospital readmissions.

MATERIALS AND METHODS

Utilization Initiative

The outpatient clinic associated with this pediatric hospital has historically provided a venue for patients to receive monthly palivizumab injections. Before the initiative implementation, most patients admitted to the hospital who qualified for prophylaxis received the first dose in the hospital, before discharge.

Late in the 2014 to 2015 RSV season, the hospital implemented an initiative designed to assist patients who qualified for palivizumab prophylaxis navigate the healthcare system and obtain prophylaxis after discharge (Fig. 1). Case managers reviewed patient eligibility as soon as possible after admission and provided proactive assistance to obtain insurance authorization and establish follow-up at the clinic or another insurance-approved provider. Additionally, the initiative aimed to promote administration of the first prophylaxis dose in the clinic because of anticipated improved acquisition cost and more favorable financial reimbursement. Acquisition cost was expected to be lower in the outpatient setting because of availability of the 340B Drug Pricing Program. Inpatient reimbursement was expected to be less favorable because of per diem payment models.

A workflow within the electronic medical record allowed case managers to propose an order to a physician for prompt referral to the hospital-associated clinic (Fig. 1). The physician reviewed and co-signed the orders for patients who qualified. Upon receipt of this electronic referral, the clinic coordinator initiated a request for insurance authorization. If insurance providers declined to cover palivizumab administration in the

clinic, the hospital case manager requested authorization for a site designated by the insurance, facilitated scheduling of an appointment and communicated appointment information to the family and provider. If authorization was obtained for dosing in the clinic, an appointment was scheduled for the day of discharge, the charge nurse followed up to confirm the appointment, and the patient was escorted by a nurse to the clinic upon discharge. In the clinic, palivizumab was administered, education was provided and the next appointment was scheduled. If insurance authorization was not obtained before discharge, qualifying patients could receive an inpatient dose. In the event of discharge when the clinic was closed (evenings, weekends or holidays), dosing could occur in the clinic on the next available clinic day or inpatient before discharge. During the 2015 to 2016 season, case managers proactively utilized this workflow to coordinate palivizumab prophylaxis and communicate with patients and caregivers.

The hospital promoted adherence to the most current AAP guidelines for palivizumab prophylaxis. Palivizumab 15 mg/kg was administered intramuscularly. Clinical pharmacists reviewed all inpatient orders for palivizumab to verify qualification per the AAP guidelines. Doses which did not meet guidelines criteria required approval from physicians who specialize in infectious disease or pulmonology.

Study Design and Population

This retrospective study evaluated a cohort of pediatric patients who received palivizumab at a 279-bed pediatric hospital or the associated outpatient clinic located on the hospital campus between September 1, 2012, and April 30, 2016. Because of the development and implementation of the initiative workflow over the course of the 2014 RSV season, without a defined implementation date, this season was considered a transition period. Therefore, 3 groups were compared: “before initiative” (2012 to 2013 and 2013 to 2014 RSV seasons), “transition” (2014 to 2015 RSV season) and “after initiative” (2015 to 2016 RSV season).

All palivizumab doses given at the hospital or clinic were identified through the electronic medical record. Patients who received their first dose of palivizumab during a hospital admission or who were discharged during the RSV season (November through April) before their first dose were included in the study. The focus of the initiative was to help patients navigate the healthcare system; therefore, only patients ≤7 months of age at the start of the RSV season were included. It was anticipated that patients older than 7 months of age were eligible for palivizumab in the previous RSV season and had established insurance coverage and primary care providers. Patients who did not need a dose at the time of discharge were excluded (eg, patient received a previous dose and was not due for the next dose, or patient was transferred to another inpatient institution). Patients who did not qualify for palivizumab per the AAP guidelines for that season were excluded. Records were not available to identify patients who received the first palivizumab dose at an alternate location because of insurance denial; therefore, these patients were excluded. Fig., Supplemental Digital Content 1 (http://links.lww.com/INF/D71) illustrates the patient selection criteria.

This study was approved by the Institutional Review Board and granted a waiver of informed consent requirements. Patients who received palivizumab were identified through the electronic medical record. Data collected from the electronic medical record

included the patient weight, age, gender, indication for palivizumab and insurance coverage at the time of the first dose. The dose, location and timing of palivizumab administration; charge and reimbursement; and timing of hospital discharge were recorded. Hospital admissions with a positive RSV laboratory result after palivizumab receipt and total RSV-positive admissions for each season were determined.

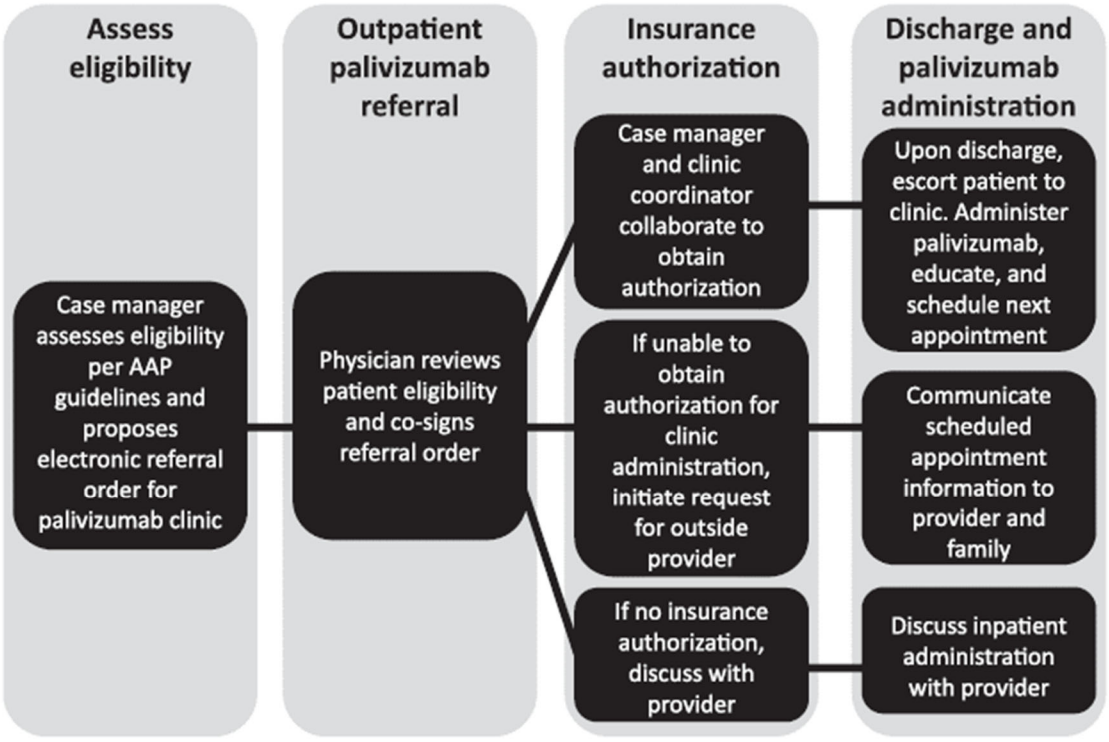

FIGURE 1. Palivizumab utilization initiative workflow.

Outcomes

Primary outcomes included location and timing of the first dose of palivizumab, patient adherence and reimbursement. To evaluate the location and timing, outcomes included the percentage of doses administered in the outpatient clinic and the percentage of outpatient doses given on the day of discharge.

Adherence was evaluated by 3 methods and only included patients who were considered eligible for a second dose during the same RSV season. Patients receiving their first dose in March or April were excluded. Data were not available for doses given at an outside provider. First, the percentage of patients who received the second dose ≤35 days after the first dose was compared for all patients. Second, the interval in days between first and second doses was compared. Only patients who received a second dose at the hospital or associated clinic were included in the analysis of dosing interval. Third, receipt of expected remaining doses for the season was evaluated. The expected number of doses was calculated based on month of hospital discharge in relation to the RSV season, assuming that doses were due beginning at discharge and continuing monthly through March. For example, a patient discharged in November would be expected to receive 5 doses, but a patient discharged in January would only be expected to receive 3

doses. For all patients, the expected number of doses was determined and compared with actual receipt.

The outcome measure for reimbursement analysis was the percentage of the charge for palivizumab that was reimbursed. Reimbursement data were only available as a percentage of total visit charges; therefore, reimbursement was assumed to be equally distributed. For example, if 45% of total visit charges were reimbursed, then it was assumed that 45% of the palivizumab charge was reimbursed. Overall reimbursement for inpatient doses compared with outpatient doses was also evaluated.

A calculation was performed to determine the difference in acquisition cost per initial dose dispensed before and after initiative implementation, based upon the following assumptions: (1) Wholesale acquisition cost and 340B Drug Pricing Program cost were applied to inpatient and outpatient doses, respectively. (2) Costs from the end of the study period were applied to all doses to eliminate inflation. (3) It was assumed that all inpatient doses given on the same day were prepared in a batch to minimize vial waste; therefore, the sum of inpatient doses each day was rounded up to the nearest 50 mg vial increment.

The secondary outcome was RSV-positive hospital admissions after receipt of palivizumab. An RSV-positive admission was defined as an admission at this hospital with a positive laboratory test result for the detection of RSV antigen during RSV season. The number of RSV-positive admissions to this hospital following palivizumab receipt and the total number of RSV-positive admissions was determined for each season.

Statistical Analysis

Descriptive statistics were calculated. $\chi 2$ tests or Fisher exact tests were used to assess the difference in categorical outcomes, while 1-way analysis of variance tests were used to test the homogeneity of continuous outcomes across the 3 initiative implementation groups. Wilcoxon-Mann-Whitney test was used to evaluate differences in reimbursement for inpatient or outpatient dosing.

Multivariable logistic regressions were used to evaluate the location of first-dose administration, adherence of second dose and adherence to remainder of prophylaxis course, adjusting for patients' characteristics of gender, age, weight, dose and type of insurance. Multivariable linear regression was used to evaluate the interval between first and second doses and to assess the relationship between reimbursement and initiative implementation, adjusting for patients' characteristics of gender, age, weight, dose and type of insurance.

Patients receiving their first dose in March or April were excluded from the analysis of adherence for subsequent doses. These patients were not expected to receive additional doses. Patients who did not receive a second dose at this institution or the associated outpatient clinic were excluded from multivariable linear regression analysis of interval in days between first and second dose.

SAS version 9.4 procedures FREQ, ANOVA, GLM and LOGISTIC (SAS Institute, Cary, NC) were used for analysis. Two-sided tests with $P < 0.05$ were considered statistically significant.

RESULTS

Over 4 RSV seasons, 386 initial doses of palivizumab were evaluated. Patient and first-dose characteristics for "before initiative," "transition" and "after initiative" groups are presented in Table 1. Of the 386 patients included in the study, 242 patients were in the "before initiative" group (62.7%), 82 patients were in the "transition" group (21.2%) and 62 patients were in the "after initiative" group (16.1%). Qualifying AAP guidelines criteria could not be evaluated for differences across implementation groups because of a change in guidelines in 2014.

TABLE 1. Patient and First-Dose Characteristics by Initiative Implementation Groups

Characteristic	Overall (n = 386)	Before Initiative (n = 242)	Transition (n = 82)	After Initiative (n = 62)	*P* Value*
Location of first palivizumab dose, n (%)					
Inpatient	244 (63.2)	195 (80.6)	36 (43.9)	13 (21.0)	<0.0001
Outpatient	142 (36.8)	47 (19.4)	46 (56.1)	49 (79.0)	0.0035
Age (d), Mean (SD)	73.30 (58.79)	65.13 (53.48)	76.21 (56.37)	101.36 (72.26)	<0.0001
Weight (kg), Mean (SD)	3.44 (1.32)	3.18 (1.24)	3.72 (1.32)	4.11 (1.31)	<0.0001
Gender, n (%)					
Female	163 (42.23)	99 (40.91)	37 (45.12)	27 (43.55)	0.7794
Male	223 (57.77)	143 (59.09)	45 (54.88)	35 (56.45)	
Insurance, n (%)					
Private	142 (36.79)	95 (39.26)	25 (30.49)	22 (35.48)	0.5373
Public	242 (62.69)	146 (60.33)	56 (68.29)	40 (64.52)	
No insurance	2 (0.52)	1 (0.41)	1 (1.22)	0 (0)	
Eligibility for second dose, n (%)†					
Not eligible	79 (20.47)	60 (24.79)	11 (13.41)	8 (12.90)	0.0239
Eligible	307 (79.53)	182 (75.21)	71 (86.59)	54 (87.10)	

*P values for continuous variables are from 1-way analysis of variance tests; P values for categorical variables are from $\chi 2$ tests; and P value for insurance is from Fisher exact test.
†Patients were not considered eligible for a second dose if they received the first dose in March or April.
SD indicates standard deviation.

After adjusting for patients' characteristics, there was a 13.5-fold [95% confidence interval (CI): 5.9–30.5, P < 0.0001] increase in odds that patients would receive the initial palivizumab dose in the clinic after initiative implementation compared with before (Fig. 2). Patients who were privately insured were 57% [odds ratio (OR) = 0.4, 95% CI: 0.2–0.8, P = 0.003] less likely to receive the first dose in the clinic than patients with public insurance. Patients who received their first palivizumab dose in the clinic had a 3.1-fold (95% CI: 1.2–8.0, P = 0.0227) increase in odds of receiving that dose on the day of discharge after initiative implementation compared with before. None of the other patient characteristics evaluated in multivariate logistic regression had a significant impact.

Adherence was evaluated by 3 methods. After adjusting for patients' characteristics, patients had a 2.7-fold (95% CI: 1.3–5.7, P = 0.0103) increase in odds of receiving their second palivizumab dose at the clinic within 35 days after initiative

implementation compared with before (Fig. 3). Privately insured patients were less likely to receive their second dose within 35 days compared with patients with public insurance (OR = 0.6, 95% CI: 0.3–0.9, P = 0.0259). Additionally, among patients who returned for a second dose at this hospital or clinic, the interval between first 2 doses was 4.5 days (95% CI: −8.7 to −0.2, P =0.0393) shorter after initiative implementation compared with before initiative implementation after adjusting for patients' characteristics. The average number of days between the first 2 doses was 36.5 ± 13.9 days before the initiative and 30.4 ± 3.6 days after the initiative. Finally, patients had a 2.5-fold (95% CI: 1.3–4.6, P = 0.0038) increase in odds of receiving the remainder of the expected prophylaxis course without missing any doses in the transition period compared with before initiative (Fig. 3); however, the increase after initiative implementation was not statistically significant (OR = 1.6, 95% CI: 0.8–3.1, P = 0.1808). None of the other patient characteristics evaluated significantly influenced adherence.

There were no significant differences among the 3 initiative implementation groups for percentage of palivizumab charge reimbursed. The average reimbursement for all doses was 31% ± 23% (32% ± 30% after initiative implementation and 31% ± 22% before). Two patients who did not have private or public insurance were excluded from multivariable linear regression analysis of reimbursement. These patients were classified as self-pay for insurance status. There was no significant difference in reimbursement between doses administered in the hospital or outpatient clinic. The average reimbursement was 31% ± 22% for inpatient doses and 29% ± 24% for outpatient doses. Although no differences in reimbursement were found, an overall decrease in acquisition cost was observed. In addition to decreased total acquisition cost, the acquisition cost per initial palivizumab dose dispensed was calculated to be 20.8% lower after initiative implementation than before, assuming batching of doses and pricing associated with administration location.

According to Fisher exact test, RSV-positive readmissions to this hospital after palivizumab receipt were not significantly different among the 3 groups (Fig. 4). Five patients were readmitted with RSV-positive laboratory tests at this institution after receipt of palivizumab: 2 patients before initiative implementation, 2 patients in the transition year and 1 patient after initiative implementation. The total number of admissions with a positive RSV laboratory test at this institution for each season were as follows (irrespective of palivizumab receipt): 458 admissions in 2012 to 2013 RSV season, 276 admissions in 2013 to 2014 RSV season, 426 RSV admissions in 2014 to 2015 RSV season and 305 in 2015 to 2016 RSV season.

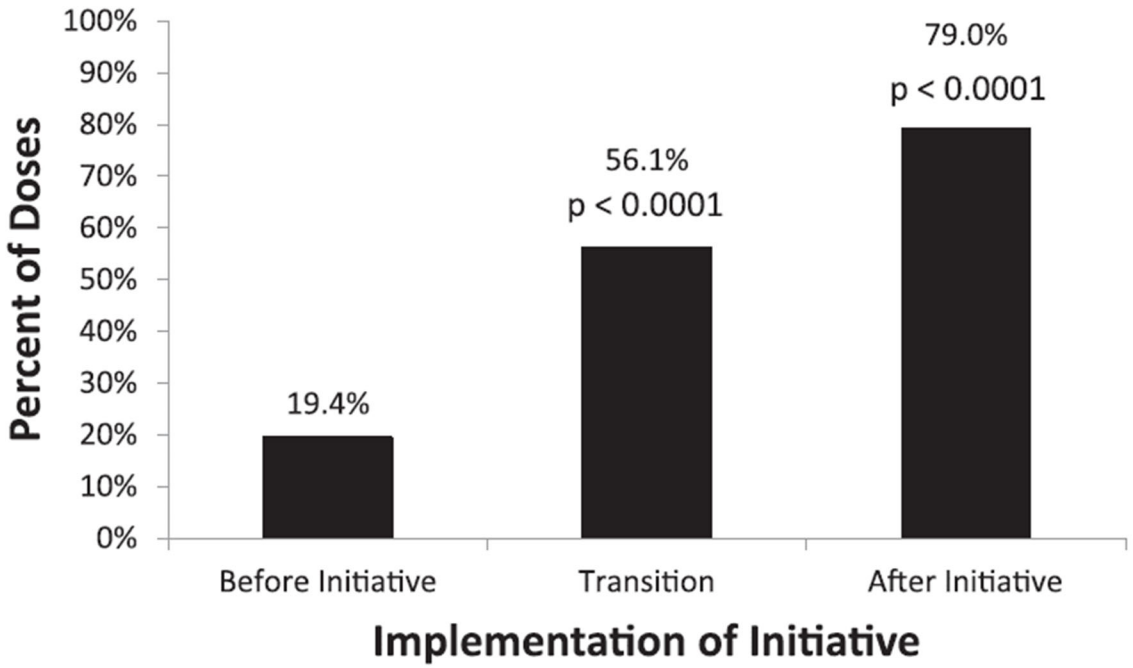

FIGURE 2. Percentage of first palivizumab doses administered in outpatient clinic.

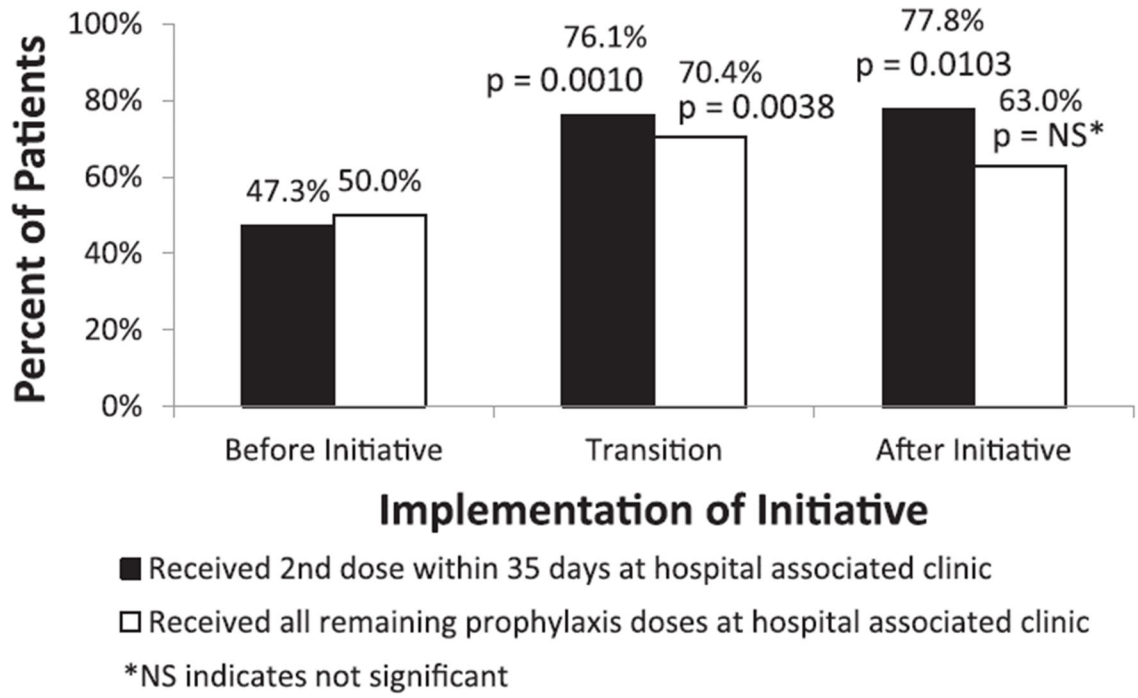

FIGURE 3. Patient adherence for subsequent doses in palivizumab prophylaxis regimen.

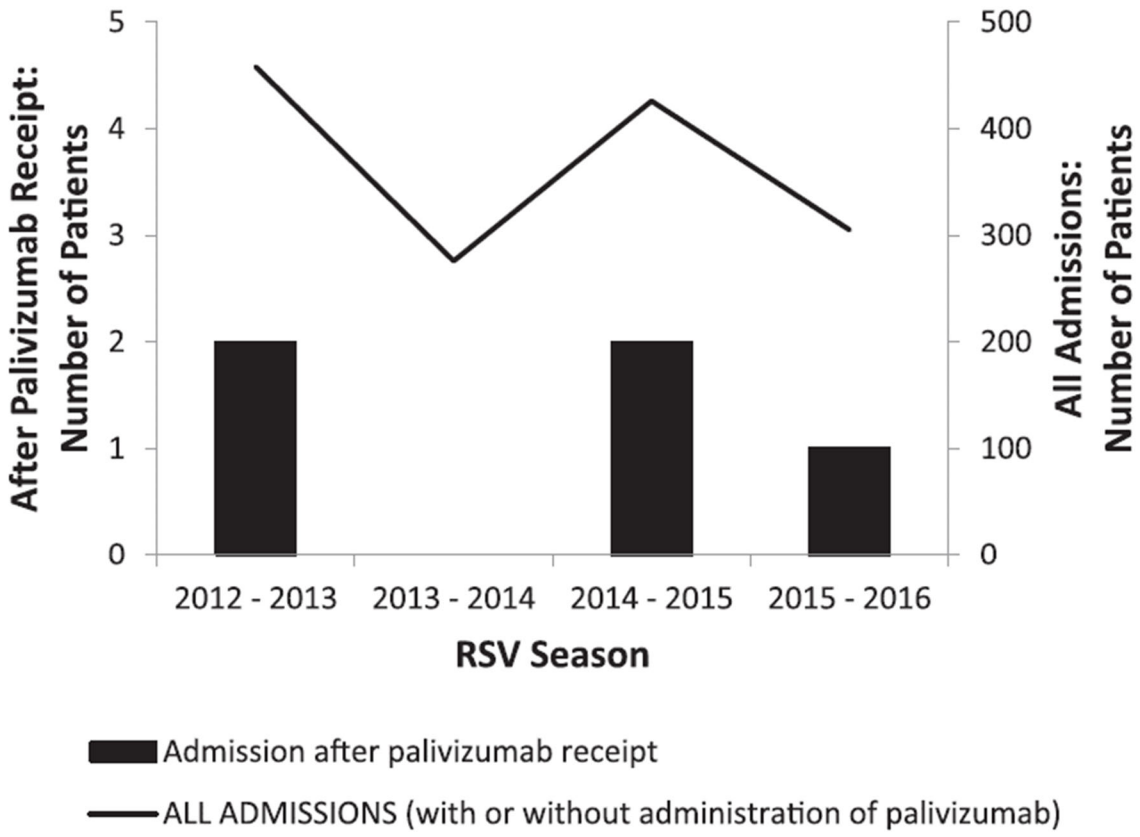

FIGURE 4. RSV-positive hospital admissions.

DISCUSSION

According to a recent survey, the most frequently reported obstacles to RSV prophylaxis included parental refusal, unclear eligibility criteria and lack of or insufficient insurance.[10] The initiative implemented at this institution promoted early case management efforts to clarify eligibility and establish insurance authorization, with a goal of assisting patients to obtain prophylaxis after discharge. Additional goals of the initiative included improved acquisition cost and financial reimbursement.

Many hospitals administer the first dose of palivizumab prophylaxis before discharge, and subsequent doses are given in the outpatient setting.[10] Although most patients at this institution received their first dose before discharge before the initiative was implemented, the primary administration location shifted to the outpatient clinic after implementation. An analysis of the palivizumab authorization process in the North Carolina Medicaid program indicated that the average number of days to coverage determination for authorization requests was 8.5 days (standard deviation = 15.4) for all claims and 18.4 days (standard deviation = 12.7) for claims that were escalated for additional medical review.11 Considering the time required to confirm coverage, early case management efforts and collaboration with the outpatient clinic are critical components in establishing authorization before discharge.

In a global survey, the most commonly identified reasons for noncompliance included inconvenience, cost and lack of caregiver understanding.[12] In this study patient adherence improved after the initiative implementation, as seen by an increased percentage of patients receiving their second dose within 35 days of initial dose and decreased interval in days between the first 2 doses administered at the hospital-associated clinic. Increased administration of first doses in the clinic may have improved timely receipt of subsequent doses because of the convenience of established eligibility and insurance authorization before discharge, familiarity with the clinic location and procedures and a scheduled follow-up appointment.

Privately insured patients were less likely to receive their first dose in the clinic or a second dose at the clinic within 35 days of initial dose compared with patients with public insurance. These differences may be reflective of restrictions from some insurance companies, which prevented authorization at the clinic. Multivariate logistic regression was used to adjust for patient characteristics, including type of insurance, to account for these differences during analysis of adherence.

Several studies have examined the number of patients who received all palivizumab doses within 35 days of the previous dose. Lundeen et al[11] found that 62.8% of patients with Medicaid received all of their palivizumab doses within 35 days. Based upon data from a large United States registry, Frogel et al[8] found that 65.2%–69.5% of patients received each dose within 35 days. Chan et al[7] determined that 72% of patients in a large Canadian registry received all doses within 35 days. The percentage of patients who received the first 2 doses of palivizumab within 35 days at this institution was initially much lower than these reported adherence rates; however, after initiative implementation, the adherence rate for timely administration of first 2 doses at this institution improved significantly from 47.3% to 77.8%.

More patients in this study received all expected doses at the hospital-associated clinic during the transition period (70.4%) compared with before initiative (50.0%). After initiative implementation, the full prophylaxis course adherence rate (63%) showed a trend of improvement, but was not statistically significant. There is a range of adherence rates for receipt of full prophylaxis course reported in the literature. Lundeen et al,[11] Frogel et al[8] and Chan et al[7] reported that 61.1%, 79.9% to 82.7%, and 81% of patients received all expected doses, respectively. After implementing a program to improve education on AAP guidelines and establish approval at a single clinic, Afghani et al[13] found that 71% of patients received all expected doses. Stewart et al[9] reviewed private insurance claims and found that 75% of the patients received all doses. The highest adherence rates were reported by studies with multi-center data, which may increase ability to evaluate subsequent doses.

Overall, the percentage of patients at this institution who received a full course of prophylaxis without missed doses was lower than the percentage of patients who received their second dose within 35 days of the first dose. Other studies have also found decreasing adherence rates over the course of the RSV season.[7] Additional methods to sustain adherence would be beneficial.

In a literature search, no other studies were found that compared reimbursement for inpatient and outpatient administration of palivizumab. Reimbursement did not change significantly with the initiative implementation and shift toward outpatient administration; however, there was a cost savings benefit to the healthcare system in the

form of decreased acquisition costs. This decreased cost is reflective of lower 340B Program pricing available in the outpatient setting. The average reimbursement was low across all implementation groups; therefore, the potential for decreased acquisition cost is valuable.

Several studies have evaluated RSV hospitalizations after palivizumab receipt. Frogel et al[8] found that RSV hospitalization after prophylaxis ranged from 0.7% to 2.9% over 4 RSV seasons. Stewart et al[9] determined that 3.3% of patients who received palivizumab had an RSV hospitalization, and noncompliant patients had a higher rate of hospitalization than compliant patients (6.1 per 100 infant RSV seasons vs. 2.8 per 100 infant RSV seasons; $P < 0.001$). Chan et al[7] also reported a higher RSV hospitalization rate for nonadherent patients compared with adherent patients (1.6% and 1.2%, respectively).

This study evaluated RSV hospitalizations among implementation groups to see if administering the first palivizumab dose in the clinic resulted in benefit because of improved follow-up or harm because of delayed administration. The differences in readmissions were not significant based upon Fisher exact test. Further multivariate regression analysis to account for the RSV season severity could not be performed because of the low incidence for this outcome. RSV incidence rates for this study were similar to those reported in the literature and did not significantly increase with initiative implementation.

The AAP currently recommends giving the initial palivizumab dose 48–72 hours before discharge or promptly after discharge. 5 The initiative workflow implemented at this hospital aimed to provide the initial dose to patients immediately after discharge. While the percentage of doses given on day of discharge increased significantly with initiative implementation, some patients received doses after the day of discharge. Hospital discharges during evening, weekend or holiday hours may account for this delay.

This study had limitations because of the retrospective, single-center design. There were no data available to identify patients who received the first palivizumab dose at an outside provider because of insurance denial for the hospital-associated clinic; therefore, these patients were not included in the study. For patients included in the study, if subsequent doses were not received at the clinic, it was assumed that the patient was nonadherent; however, the patient may have elected to receive subsequent doses at another provider. It is likely that most of the patients who qualified for palivizumab would follow-up in the clinic because the pulmonologists and cardiologists that treat patients in the hospital often continue to treat the patients in the clinic after discharge. Additionally, there were no readmission data available if the patient was admitted to an outside hospital.

The AAP guidelines for palivizumab prophylaxis changed in 2014, resulting in a decrease in absolute number of doses and simplifying the qualification criteria.[5,6] This study evaluated outcomes as a percentage of qualifying patients to account for the change in AAP guidelines and variation in number of qualifying patients. However, it is possible that the increased familiarity of staff with guidelines and workflow over time, the absolute decrease in qualifying patients or the simplified AAP guidelines criteria may have improved the ability to manage patients who did qualify.

Also among the changes in the AAP guidelines published in 2014, premature infants with gestational age ≥29 weeks no longer qualified for palivizumab based on gestational age alone.[5,6] This difference in the guidelines may have contributed to the differences in baseline weight and age. Less premature patients, who may have earlier hospital discharge and initial palivizumab dose at a younger postnatal age, no longer qualified for prophylaxis after initiative implementation. Multivariate regression was used to adjust for these differences.

Ability to evaluate RSV readmissions was limited by the low incidence of RSV-associated readmission after palivizumab receipt, lack of data from outside providers and provider discretion for RSV testing. Future studies would be needed to confirm these findings.

Overall, implementation of a utilization initiative with defined workflow, multidisciplinary collaboration and early case management efforts to initiate palivizumab insurance authorization requests can benefit patients. Collaboration with the outpatient clinic and proactive efforts of inpatient case managers resulted in improved adherence for subsequent doses and did not increase RSV-associated admissions. Although there was no difference found in reimbursement rates, outpatient acquisition costs may be lower for some institutions. If a decreased acquisition cost can be achieved with initial doses administered in the clinic, this is a valuable benefit considering the low reimbursement rates. Future studies with the ability to incorporate data from outside providers would be valuable to further evaluate adherence and RSV readmission rates.

ACKNOWLEDGMENTS

We sincerely thank Aaron Tse, Information Systems Pharmacist, and Vong Viratham, Financial Planning & Decision Support, for their assistance in data collection for this study.

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The project described was partially supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant UL1 TR001414.
The authors have no conflicts of interest to disclose.
The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.
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