Prior receipt of palivizumab prophylaxis among patients admitted to the Pediatric Intensive Care Unit with Respiratory Syncytial Virus: A retrospective cohort study

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Citation

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Abstract

Objectives: To determine whether children in a pediatric intensive care unit (PICU) with respiratory syncytial virus (RSV) infection had been given palivizumab in the primary care setting when indicated and compare outcomes among those who had or had not.

Results: 118 patients (32%) met criteria for palivizumab. 71% of those were documented to have received it. Age, birthweight, gestational age, and rate of chronic lung disease did not differ between children who did or did not receive palivizumab. All who did not receive palivizumab had public insurance. Length of stay was longer for those who received palivizumab vs. not (p=0.047), and more patients who received it required mechanical ventilation (p=0.009).

Conclusions: A minority of PICU patients with RSV had missed palivizumab prophylaxis. Those who received palivizumab had worse outcomes, but in a retrospective study, this is most likely due to a selection bias rather than because they had received palivizumab.

First two authors share equal contributions as first authors

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BACKGROUND

In the United States, respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infections in children less than age two and also the most common reason for hospitalization among this age group.[1,2,3,4] In children who are at high-risk, it can cause significant morbidity, including hospitalization and ICU admission.[5]

The American Academy of Pediatrics (AAP) recommended RSV-IVIG (RespiGam) in 1997 for patients who fit the highest risk profile based on decreased hospitalization and disease severity in the the RSVIG Study Group and PREVENT trials.[6, 7] However, this immunoglobulin required monthly intravenous infusions and had the potential for significant side effects. In 1998, palivizumab, a humanized monoclonal antibody that could be administered as an intramuscular injection, was approved by the Food and Drug Administration. The AAP established guidelines for its use in high-risk children to help prevent RSV morbidity and mortality.[8, 9]

We conducted a retrospective chart review covering the five years following the approval of palivizumab to test the following hypotheses:

1. Many children admitted to the pediatric intensive care unit (PICU) with RSV disease who meet AAP criteria for palivizumab prophylaxis will not have received it.
2. Type of insurance (public, private, or self-insured) may affect whether children received prophylaxis.
3. Among patients who met criteria for palivizumab

prophylaxis, those who received it would have a shorter length of stay and less need for mechanical ventilation than those who did not.

METHODS

This study was conducted in a multidisciplinary PICU in an urban tertiary care University hospital. Approximately 30-40 children are admitted each season for management of RSV infections.

The Institutional Review Board granted exemption from informed consent for this retrospective study. Patients were identified from a hospital-wide virology laboratory database including all positive pediatric RSV antigen and culture results from November 1998-September 2003. This database included positive results from every intensive care unit, emergency room, and outpatient sample during that time. The database was filtered for PICU admissions of at least one full day and for age less than three years at admission in order to identify all children who might have been younger than 2 years at the start of the RSV season and therefore potential candidates for palivizumab. Children admitted with respiratory illness are routinely screened for RSV at the institution, and families are routinely asked about palivizumab prophylaxis on admission. We cross-referenced this database with a billing database and a PICU quality assurance database to identify any patients whose only laboratory testing was at outside hospitals.

Medical records of all patients identified were reviewed for birth date, RSV test date, birth weight, gestational age at birth, chronic lung disease (CLD), congenital heart disease (CHD), neuromuscular disease, tobacco smoke exposure, day care attendance, airway abnormality, history of asthma, history of other significant pulmonary disorder, history of immune disorder, receipt of palivizumab or RespiGam prophylaxis, days in the ICU, and days of mechanical ventilation (by endotracheal intubation or noninvasive positive pressure ventilation). Insurance coverage information was obtained from the University physicians' practice billing office. Patients were not recorded as having CLD unless they had required medical management during the preceding 6 months (oxygen therapy, steroids, or diuretics). We assumed that otherwise healthy, full-term (?36 week gestation) infants did not receive palivizumab if not noted. Children were considered to meet criteria for palivizumab prophylaxis if they qualified under the 1998 AAP guidelines (Table 1), using their age at the start of RSV season.

All statistical analyses were performed using Stata 8.0 (StataCorp; College Station, TX). We used two-tailed t-tests for continuous variables when the distribution was appropriate and Fisher's exact test for categorical variables. Length of stay (LOS) did not follow a normal distribution even after transformation so was analyzed using Wilcoxon rank sum.

RESULTS

A total of 139 patients less than three years of age were admitted to the PICU with RSV between 11/1998 and 9/2003. Of these, 118 (85%) were two years old or younger at the start of the season. We were able to collect primary risk-factor data for all but five patients. Characteristics of the cohort are outlined in Table 2. One child (term infant with no risk factors other than tobacco exposure in the home) was admitted twice, at age 4 months and the following season at 16 months of age.

The majority of children were male (55%), were less than 6 months of age at the beginning of the RSV season (60%), and were term or near-term and otherwise healthy. The frequency of daycare attendance increased with increasing age of the child. Fifteen infants (13%) had clinically significant CLD, but only 4 were on home oxygen.

Of the 118 patients, 37 (32%) would have met criteria for palivizumab prophylaxis under the 1998 AAP recommendations. The revised 2003 criteria were more specific in requiring 2 additional risk factors for children 32-35 weeks gestation. Thirty-two children would have qualified for prophylaxis using the revised guidelines which would not have been available during the time frame studied. Of the 37 meeting criteria, three patients had received RespiGam (all in the first season). We could find no documentation of whether palivizumab had or had not been given for 13 of the patients, so these patients are therefore excluded from analyses comparing patients who had and had not received prophylaxis. Of the remaining 21 patients who met criteria for prophylaxis, 15 (71%) had received palivizumab and 6 had not. An additional patient had received palivizumab but did not meet criteria under the AAP guidelines. Table 3 compares characteristics of patients who did and did not receive palivizumab among those who met criteria. The mean age at the start of the season was lower in those who received palivizumab, although the difference was non-significant and affected by outliers as the

median age was higher in this group. Non-parametric analysis (Wilcoxon rank sum) confirmed that there was no statistically significant difference in age between the two groups. There were no significant differences in gestational age, birthweight, smoke exposure (not shown) or daycare attendance (not shown) between the two groups. There were no statistically significant changes in how many children received prophylaxis based on the year of admission.

Twenty-one percent of patients had private insurance, and 79% had public insurance. No families were self-insured. All patients with private insurance who met criteria had received palivizumab, compared to only 60% of those with public insurance. This difference, however, was not statistically significant (p=0.26). Those with public insurance were more likely to be exposed to tobacco smoke in the home (62% vs. 30%, p=0.02).

There was only one death in a patient with a prolonged hospital course who died of causes unrelated to his RSV. In the entire group of patients admitted with RSV, those who received palivizumab had a longer hospital LOS (median 11 vs. 6 days, p=0.03) and ICU LOS (10 vs. 5.5 days, p=0.02) than those who did not. For the cohort who met criteria for palivizumab prophylaxis, those who received it had a longer ICU LOS and a nonsignificant trend towards a longer hospital LOS (Table 4).

Thirty-nine children (33%) required mechanical ventilation. Forty-nine percent of those requiring intubation were term infants without other underlying illness. Among those who met criteria for palivizumab, 18 (49%) required mechanical ventilation. Including only those with complete information, 10/15 (66%) of patients who met criteria and received palivizumab required mechanical ventilation, whereas zero of the six patients who met criteria but did not receive prophylaxis required ventilation (p=0.009).

Figure 1

Table 1: AAP recommendations for the use of palivizumab (8, 9)

Patient group	Age at start of RSV season
Premature, no CLD, no CHD:	
<= 28 weeks	≤ 12 months
29-32 weeks	≤ 6 months
32-35 weeks	≤ 6 months with other risk factors*

Adapted from CDC/AAP recommendations

* "Other risk factors" among the following triggered consideration of prophylaxis in the 1998 guidelines: child care center attendance, school-aged siblings, exposure to environmental air pollutants, congenital abnormalities of the airways, or severe neuromuscular disease. The 2003 revised guidelines specified the presence of 2 or more risk factors.

Figure 2

Table 2: Characteristics of patients ? age 2 years at the start of the season admitted or transferred to the PICU with RSV. Number with information available noted next to variable.

Characteristics of Sample	Number
Mean GA, wks (N=113)	35.95 (SD=4.9)
Male (N=118)	65 (55%)
CLD (N=115)	15 (13%)
CHD (N=115)	5 (4%)
Age at start of season (N=118)	
• < 6 months	71 (60%)
• 6 mos-1 year	17 (14%)
• 1-2 years	25 (21%)
• Age 2	5 (4%)
Birthweight, kg (N=98)	
• ELBW (<1000 gm)	5 (5%)
• VLBW (<1500 gm)	8 (8%)
• LBW (<2500 gm)	28 (29%)
• Normal weight (>=2500 gm)	57 (58%)
Insurance type (N=117)	
• Private	25 (21%)
• Public	92 (79%)
Attend daycare (N=73)	19 (26%)
Exposed to smoke (N=94)	52 (55%)
Met criteria for palivizumab (N=113)	37 (32%)
Prophylaxis if met criteria (N=24)*	
• Palivizumab	15 (63%)
• No prophylaxis	6 (25%)
• RespiGam	3 (12%)

*Excludes patients with incomplete information but includes those who received RespiGam.

GA=Gestational Age CLD= Chronic Lung Disease with treatment in last 6 months
CHD= Congenital Heart Disease, hemodynamically significant
LBW=Low birth weight, VLBW=Very LBW, ELBW=Extremely LBW

Figure 3

Table 3: Characteristics of patients who did receive palivizumab vs. those who did not among those who met AAP criteria for prophylaxis (n=21)

	Received PZ (SD)	Did not receive PZ (SD)	p value*
GA (weeks)	30.5 (± 2.7)	29.0 (± 3)	.28
BW (kg)	1.6 (± 0.5)	1.55 (± 0.4)	.84
Age†(months)	0.5 (± 3.5)	4 (± 10)	.27
CLD	7	2	.66
CHD	1	1	.5
Public insurance	9/14 (64%)	6/6 (100%)	.26

† mean age at start of RSV season *Student's t test or Fisher's exact test

GA=Gestational Age BW=Birth weight (kg) CLD= Chronic Lung Disease with treatment in last 6months CHD=

Congenital Heart Disease, hemodynamically significant
PZ=palivizumab SD=standard deviation

Figure 4

Table 4: Hospital and ICU length of stay (LOS) for those with complete information who met criteria for palivizumab prophylaxis (n=21).

	LOS, mean +/- SD (days)	LOS, median (days)	p value*
Hospital LOS			
Received palivizumab	24 +/- 39	11	0.07
Did not receive	7.5 +/- 5.8	6	
ICU LOS			
Received palivizumab	13.1 +/- 9.6	10.5	0.047
Did not receive palivizumab	5.5 +/- 4.8	4.5	

* Wilcoxon rank sum, SD = standard deviation

DISCUSSION

The landmark IMpact-RSV study[10], a randomized, placebo-controlled trial of palivizumab in 1502 patients with prematurity (<= 35 weeks) or CLD, showed a reduction in RSV related hospitalizations in treated patients from 10.6% to 4.8%. Several later studies using predominantly historic controls have also shown decreased hospitalization[11,12,13,14,15,16,17,18] and acceptable safety[19,20,21] with the use of palivizumab.

There are fewer studies which focus on how palivizumab affects patients admitted to ICUs with RSV. Studies prior to the use of palivizumab have documented the burden of RSV disease in PICUs.[22,23,24] The original IMpact study showed a decrease from 3% to 1.3% in PICU admissions for high-risk infants, but no difference in the rates of mechanical ventilation,[10] while another study showed no impact of palivizumab on PICU admission or mechanical ventilation.[14] A recent study of all patients admitted to the 13 PICUs in Israel with RSV during one year before the institution of palivizumab prophylaxis compared to the following year after similar guidelines were instituted for palivizumab use as in the United States could not assess the impact of palivizumab use as only 12 patients met criteria for prophylaxis, 3 of whom had received it.[22]

The distributions of gestational age, birthweight, gender, and chronic lung disease in our PICU patients were similar to another study.[24] As seen in some other studies,[22,23,24,25,26,27] we found that the majority of patients admitted to the PICU with RSV disease were term or near-term and would not have been candidates for prophylaxis with palivizumab by AAP criteria.

Our study showed a 71% compliance with recommendations for palivizumab prophylaxis, much better than another study showing a 35% rate of administration [28]. Because of the number of patients with incomplete data, however, the appropriate prophylaxis rate may have been as low as 44% (if all those without a notation one way or the other had not received it). We were surprised to find that among patients who met criteria, receiving palivizumab was associated with requiring mechanical ventilation as well as a longer ICU length of stay. We attempted to determine if these findings could be due to a potential bias of clinicians' choosing to administer palivizumab to patients who were somehow sicker at baseline, yet we were unable to show that they were younger, more premature, or had more chronic health issues. Our inability to do so could have been due to the fairly small number of patients with complete information available and the retrospective nature of the study. It is possible, however, that primary care clinicians are using clinical judgment to immunoprophylax those at higher risk of eventually having more severe disease. As this study was not a randomized trial of palivizumab prophylaxis and not a population-based study, the results do not imply that palivizumab worsened outcomes in patients admitted to the PICU. Although the association of type of insurance with whether appropriate palivizumab prophylaxis was given was not statistically significant, the fact that all patients who did not receive it had public insurance is intriguing and bears further investigation with a larger study. We are unable to tell in this study if these patients had not been given palivizumab due to parental factors such as missed visits or poor access to care versus healthcare provider factors.

A major limitation of this study is that the small number of patients with complete data available on retrospective review probably limited our ability to detect important differences between patient groups. In addition, as we were dependent on what the admitting residents noted in the chart, we were unable to tell if children who received palivizumab had received a full course. Also, this is a single-center study, and not all PICUs will have similar admission criteria; the wide variability in how many PICU patients with RSV require mechanical ventilation (from 29% to 80% in published studies[12, 22, 24, 26, 27]) highlights the varying acuity level in different PICUs. In our center, children with apnea were admitted to the PICU even if not in severe distress, but otherwise stable patients with tachypnea and an oxygen requirement or poor feeding would be on the general pediatric floor.

CONCLUSIONS

Although a majority of patients admitted to the PICU who met criteria for palivizumab had received it, rates of prophylaxis in compliance with the AAP guidelines could still be improved. Infants who had received appropriate prophylaxis had a longer LOS and were more likely to require mechanical ventilation; however, this difference may reflect a bias in providers self-selecting which patients would receive palivizumab rather than a detrimental effect of the drug. Limitations of the study prevent drawing definitive conclusions about outcome but suggest further areas of inquiry.

The authors have no competing interests to declare.

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