BACKGROUND: The American Academy of Pediatrics recommends palivizumab prophylaxis against respiratory syncytial virus (RSV) for infants at high risk for severe disease within 72 hours of hospital discharge to prevent community-associated RSV. The American Academy of Pediatrics does not recommend palivizumab to prevent health care–associated RSV (HA-RSV).

METHODS: A retrospective, multicenter cohort of hospitalized infants who received nondischarge palivizumab (NDP) between January 2009 and December 2013 was established from 14 hospitals. NDP was defined as a charge for palivizumab >7 days before hospital discharge and no previous documented RSV. Infants were considered high risk for severe disease if they had chronic lung disease, chronic heart disease, or prematurity. Nondischarge palivizumab use was examined for high- and low-risk infants. HA-RSV was defined as an RSV-positive test (polymerase chain reaction, enzyme immunoassays, or culture) >3 days after admission and the frequency was measured for infants who did and did not receive NDP.

RESULTS: We identified 1263 patients who received at least 1 dose of NDP, most of whom were classified as high risk (80%). Among high-risk patients, the predictors of receipt of NDP included longer length of stay, institution, and no comorbid conditions. Most of the low-risk patients (88%) who received NDP had no comorbid conditions. NDP use varied widely among institutions. Overall, 25 eligible patients developed HA-RSV; 17 of whom received NDP.

CONCLUSIONS: Despite current recommendations, palivizumab for prevention of HA-RSV was common, even among patients at low risk of severe RSV.
Respiratory syncytial virus (RSV) infects virtually all children by 2 years of age. The severity of RSV infection ranges from a mild, self-limited respiratory infection in healthy, older children to severe, but rarely fatal, infection in high-risk populations. Because there is no vaccine to prevent RSV or clinically effective treatment to administer to children with RSV infection, immunoprophylaxis is currently the only method for reducing morbidity associated with severe RSV in high-risk infants.

In 1998, the American Academy of Pediatrics (AAP) first recommended the seasonal administration of palivizumab, a monoclonal antibody, for passive prophylaxis against RSV to select groups of infants at high risk for severe disease. As additional data have become available, these recommendations have undergone several revisions. In 2009, the AAP recommended only 5 monthly doses of RSV immunoprophylaxis for high-risk infants due to prematurity, chronic lung disease (CLD), or congenital heart disease (CHD) during the RSV season. In 2014, the AAP cited the absence of compelling data supporting the use of palivizumab for the prevention health care–associated RSV (HA-RSV) and recommended that other strategies, such as transmission-based precautions, should be used to prevent HA-RSV. Thus, revised AAP guidelines included explicit recommendations that palivizumab should be used only to prevent community-associated RSV and administered within 72 hours of hospital discharge (or promptly after discharge).

Given these evolving recommendations, we examined the patterns of palivizumab administration in the NICU over the past 5 years that were inconsistent with updated AAP recommendations.

METHODS

Study Design and Data Source

We performed a retrospective, multicenter cohort study to (1) describe palivizumab use for prophylaxis against HA-RSV, and (2) identify predictors of receipt of palivizumab in infants discharged from a NICU from 2009 through 2013. Data were obtained from the Premier Perspective database maintained by Premier, Inc (Charlotte, NC). The Premier database is a comprehensive clinical and administrative database that contains information from >600 hospitals across the United States. Data elements present in Premier include hospital information, patient demographics, insurance information, International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) procedure and diagnosis codes, and resource utilization data including day of service-stamped billing data for pharmacy, imaging, and clinical services. We limited our analysis to hospitals that provided data on clinical viral diagnostic assays and administered palivizumab to at least 5% of high-risk infants (14 hospitals).

Study Definitions

Nondischarge palivizumab (NDP) was defined as a billing charge for palivizumab >7 days before hospital discharge along with a lack of a previous laboratory test positive for RSV. HA-RSV was defined as an RSV-positive test (polymerase chain reaction, enzyme immunoassays, or culture) >3 days after admission to a NICU. Infants with an ICD-9 code for prematurity (765.21–765.27), CHD (770.7), or CHD (745.0–745.69, 746.01–746.7, 747.0, and 747.1) were considered high risk for RSV infection, all others were considered low risk based on 2014 AAP guidelines.

We stratified our population by risk status to understand other patient characteristics associated with receipt of NDP.

Study Population

Discharges from a NICU in a Premier hospital between January 1, 2009, and December 31, 2013, were eligible for inclusion if they were continually hospitalized in a NICU from birth. Infants discharged from a NICU were identified through the presence of a NICU billing charge. To be included, children had to have the opportunity to receive NDP to protect against HA-RSV. Therefore, children with a length of stay (LOS) <7 days were excluded. In addition, we excluded children who had their entire hospital admission between April and June because they were not eligible to receive RSV prophylaxis.

Data Collection

All data used for this study were obtained from the Premier database. Demographic and clinical information collected for each patient included gender, race, presence and type of comorbid condition, and receipt of mechanical ventilation, defined as billing charge for mechanical ventilation. The presence and type of comorbid condition was classified by using a previously validated classification system that groups ICD-9-CM diagnostic codes into pediatric chronic conditions.

Statistical Analysis

Summary statistics were constructed by using frequencies for categorical variables and medians for continuous variables. We used Pearson χ² test or Fisher’s exact test for categorical variables and Wilcoxon rank-sum test for continuous variables to compare receipt of NDP in high-risk patients. All variables with a P < .05 were included in the final multivariable logistic regression model comparing receipt of NDP to identify predictors of NDP use. All analyses were performed by using SAS 9.3 (SAS Institute, Cary, NC) or Stata 12.1 (Stata Corp, College Station, TX).

RESULTS

Cohort Characteristics

We identified 11,418 discharges from a NICU from 14 hospitals between January 1, 2009, and December 31, 2013 (Fig 1). Median LOS for the entire cohort was 20 days (interquartile range [IQR]: 12–37). Among all infants, 1263 (11%) received NDP and 1362 received palivizumab within 3 days of discharge per current guidelines (Table 1). There were 5266 (46.1%) infants classified as high risk for severe RSV. Most were premature (86.3%), had only 1 high-risk condition (71.1%), and had at least 1 underlying comorbid condition (52.9%). Among high-risk infants, the prevalence of CLD was 10.3%. The median LOS of high-risk infants was 37 days (IQR 23–60). In contrast, 6152 (55.9%) infants were categorized as low risk for severe RSV. Most were premature (86.3%), had only 1 high-risk condition (71.1%), and had at least 1 underlying comorbid condition (52.9%). Among high-risk infants, the prevalence of CLD was 10.3%. The median LOS of high-risk infants was 13 days (IQR 10–19). Among high-risk infants, 1008 (19.1%) received NDP, whereas 783 (14.5%) received palivizumab within 3 days of discharge. In addition, among low-risk infants, 255 (4.1%) received NDP and 579 (9.4%)
received palivizumab within 3 days of discharge. The median interval between last NDP administration was 18 days.

**Predictors of NDP Use**

In univariate analysis, high-risk patients who received NDP were more likely to have CLD, prematurity, respiratory disease, or be of white race compared with high-risk patients who did not receive NDP (Table 2). In addition, high-risk patients who received NDP were less likely to have CHD and had fewer or no comorbidities. In the final multivariable model, factors associated with receipt of NDP included longer LOS, institution where care was provided, prematurity, and lack of a comorbid condition (Table 2). There were no significant differences in underlying comorbidities and basic demographics between low-risk infants who did and did not receive NDP (data not shown). However, low-risk infants who received NDP had a longer LOS compared with those who did not receive NDP ($P < .001$).

**HA-RSV**

Overall, 31 (0.3%) infants in our cohort developed HA-RSV. Of the 5266 high-risk infants, 8 (0.8%) who did and 17 (0.4%) who did not receive NDP developed HA-RSV. Among the 5897 low-risk infants who did not receive NDP, 6 (0.1%) developed HA-RSV. None of the 255 low-risk infants who received NDP developed HA-RSV.

**NDP Use by Hospitals**

NDP use varied significantly by institution. The median proportion of high-risk infants who received NDP by institution was 13.7% (IQR 8.5–34.3). Among the 14 hospitals giving NDP to >5% of their eligible population, 11 (79%) also gave NDP to patients at low risk of RSV (Fig 2). The hospital that most frequently administered NDP to high-risk patients (51%) also had the highest NDP administration to their low-risk population (15%). There was no association between the overall incidence of HA-RSV and NDP use within a given hospital (data not shown).

**DISCUSSION**

We identified that palivizumab was frequently administered to hospitalized...
infants at high risk of severe RSV >7 days from discharge. This practice is inconsistent with AAP recommendations, which advise against the administration of palivizumab to prevent or treat HA-RSV. In addition, many hospitals also administered NDP to infants who were at low risk for severe RSV. Identifying nonadherence to current AAP recommendations can identify targets for improved utilization of resources. In this large observational study, we documented that off-guideline use of palivizumab was common, even among patients who were not at high risk for severe complications.

Although recent studies have demonstrated that nonadherence to AAP guidelines for palivizumab use is common, our study provides the first detailed description of palivizumab use for hospitalized infants. It is important to note, however, that many hospitals that submitted data to the Premier database did not frequently administer NDP. We also observed significant variation in palivizumab use by institution. Although some hospitals only administered NDP to their high-risk patients, many institutions also administered NDP to their low-risk patients. Two hospitals administered NDP to at least 50% of their high-risk patients. In addition, the overall incidence of HA-RSV at the institutional level was not associated with administration of NDP. These results suggest that overall administration of NDP may be determined by institutional or provider-level practices and beliefs. Therefore, improved adherence to the AAP's Bronchiolitis Clinical Practice guidelines and recommendations for palivizumab use are likely to achieve marked cost-savings without worsening patient outcomes.

Our study has several limitations. The use of ICD-9-CM codes may have led to misclassification of patients as high or low risk for severe RSV. However, receipt of palivizumab to prevent HA-RSV is not recommended by the AAP for any patients and therefore all palivizumab use would be considered nonadherent to current AAP guidelines. Because palivizumab is indicated at discharge for high-risk infants, some children might have been given palivizumab previously in anticipation of a planned discharge that was subsequently postponed. Additionally, the Premier database does not include the actual calendar dates of palivizumab administration. Therefore, we were not able to describe the timing with respect to RSV season of the palivizumab doses or the

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**TABLE 2** Predictors of Receipt of PPP in High-Risk Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Univariate Odds Ratio (95% Confidence Interval)</th>
<th>Multivariable Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOS</td>
<td>1.01 (1.01–1.02)</td>
<td>—</td>
</tr>
<tr>
<td>Institution</td>
<td>0.99 (0.99–0.99)</td>
<td>0.99 (0.99–0.99)</td>
</tr>
<tr>
<td>Race</td>
<td>0.87 (0.80–0.95)</td>
<td>—</td>
</tr>
<tr>
<td>Any comorbidity*</td>
<td>0.84 (0.73–0.97)</td>
<td>1.32 (1.13–1.56)</td>
</tr>
<tr>
<td>Respiratory condition</td>
<td>1.51 (1.25–1.81)</td>
<td>—</td>
</tr>
<tr>
<td>Premature</td>
<td>3.03 (2.30–4.00)</td>
<td>3.69 (2.72–4.98)</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>1.75 (1.43–2.15)</td>
<td>—</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>0.79 (0.68–0.91)</td>
<td>—</td>
</tr>
</tbody>
</table>

—, these factors were not included in the final multivariable model. Characteristics that were not significant in univariate analysis were not included in multivariate analysis.

* Malignancy, cardiovascular disease, respiratory disease, renal disease, gastrointestinal disease, hematologic/immunologic disorder, genetic disorder, metabolic disorder, or neuromuscular disease.

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**FIGURE 2** Frequency and proportion of high-risk and low-risk patients receiving NDP (>7 days before discharge) by hospital.
CONCLUSIONS

This study found that palivizumab was commonly administered >7 days before discharge, presumably to prevent HA-RSV despite the paucity of rigorous data supporting the use of palivizumab to prevent HA-RSV. These findings highlight potential opportunities to reduce unnecessary resource utilization among hospitalized infants.

REFERENCES

Administration of Palivizumab in the NICU
Neika Vendetti, Jeffrey S. Gerber, Julia Shaklee Sammons, Brian T. Fisher, Theoklis E. Zaoutis and Susan E. Coffin
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