ORIGINAL RESEARCH ARTICLE

Palivizumab Prophylaxis during Nosocomial Outbreaks of Respiratory Syncytial Virus in a Neonatal Intensive Care Unit: Predicting Effectiveness with an Artificial Neural Network Model

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Study Objective To identify subgroups of premature infants who may benefit from palivizumab prophylaxis during nosocomial outbreaks of respiratory syncytial virus (RSV) infection.

Design Retrospective analysis using an artificial intelligence model.

Setting Level IIIB, 35-bed, neonatal intensive care unit (NICU) at a tertiary care hospital in the United Arab Emirates.

Patients One hundred seventy six premature infants, born at a gestational age of 22–34 weeks, and hospitalized during four RSV outbreaks that occurred between April 2005 and July 2007.

Measurements and Main Results We collected demographic and clinical data for each patient by using a standardized form. Input data consisted of seven categoric and continuous variables each. We trained, tested, and validated artificial neural networks for three outcomes of interest: mortality, days of supplemental oxygen, and length of NICU stay after the index case was identified. We compared variable impacts and performed reassignments with live predictions to evaluate the effect of palivizumab. Of the 176 infants, 31 (17.6%) received palivizumab during the outbreaks. All neural network configurations converged within 4 seconds in less than 400 training cycles. Infants who received palivizumab required supplemental oxygen for a shorter duration compared with controls (105.2 $\pm$ 7.2 days vs 113.2 $\pm$ 10.4 days, p=0.003). This benefit was statistically significant in male infants whose birth weight was less than 0.7 kg and who had hemodynamically significant congenital heart disease. Length of NICU stay after identification of the index case and mortality were independent of palivizumab use.

Conclusion Palivizumab may be an effective intervention during nosocomial outbreaks of RSV in a subgroup of extremely low-birth-weight male infants with hemodynamically significant congenital heart disease.

Key Words artificial, neural networks, palivizumab, respiratory syncytial virus, nosocomial, outbreak, premature.

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Palivizumab shortens hospital stay, decreases the need for supplemental oxygen, and limits the number of days with moderate and/or severe lower respiratory tract illness due to respiratory syncytial virus (RSV) infection in various

outpatient pediatric populations.[1] The American Academy of Pediatrics (AAP) recommends monthly prophylactic palivizumab injections during RSV season in premature infants and children with chronic lung or congenital heart diseases who meet certain criteria.[2] Data published by the National Respiratory and Enteric Virus Surveillance System (NREVSS)[3, 4] demonstrates a biannual variation in virulence and different activity patterns of RSV between and within different regions of the United States. Our climate in the United Arab Emirates (UAE) resembles that of Florida in the NREVSS. Despite the lack of reported UAE-specific RSV activity databases, epidemiologic data from neighboring countries indicate that RSV is common from October through May.[5] Several reports have demonstrated differences in RSV activity (i.e., virulence, onset, and duration) during nosocomial RSV outbreaks.[6–11] In those studies, although palivizumab combined with infection control measures was successful in arresting outbreaks in the neonatal intensive care unit (NICU), there was little evidence to support its routine use in all patients in this setting.

Artificial neural networks (ANN) were employed to predict mortality risk on admission to a NICU in a previous report.[12] This software analyzes the relationships between clinical variables of interest from real cases by using simple user interfaces. Based on this analysis, one can develop models that will predict, with reasonable accuracy, outcomes such as mortality risk associated with specific clinical decisions. The ANN configurations can be broadly classified based on the outcome variable into two main types. Probabilistic networks (Figure 1), used for categoric outcomes, are partially connected and generate probabilities that reflect a level of confidence that the network has in each prediction it makes. For instance, the network may be 96% confident in predicting mortality. On the other hand, generalized regression networks (Figure 2), used for continuous outcomes, make predictions that can be plotted against actual outcomes. Ideal networks will, therefore, yield an identity curve for the entire dataset. The first hidden layer in both designs (one neuron/training case) ensures accurate performance. The second hidden layer reduces dimensionality to drive ANN toward fast convergence (i.e., an optimal solution that can be reliably used to predict outcomes).

Prediction of mortality risk associated with nosocomial outbreaks of RSV by using ANN may guide clinicians to select the high-risk group of NICU patients who may benefit from receiving palivizumab prophylaxis in an inpatient setting. Moreover, neural network models may help health care teams predict the effects of palivizumab on important outcomes such as days of supplemental oxygen (DOSO) and length of NICU stay after the index case was identified (LOSA). In this study, we report the findings from three ANN trained to predict outcomes regarding the use of palivizumab during four RSV outbreaks in a NICU. Our primary objective was to identify subgroups, if any, who may benefit from palivizumab in this setting.

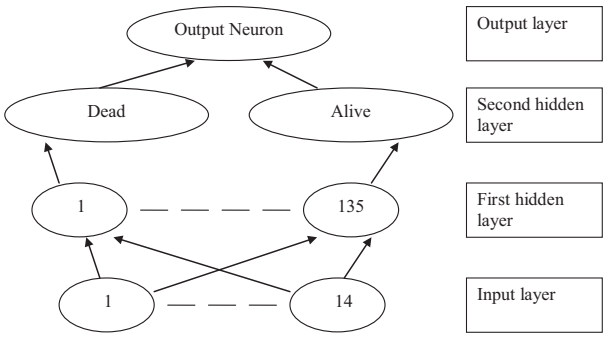

Figure 1. Probabilistic neural net used in our model to predict mortality. The input layer reflects the 14 variables used in our model. The first hidden layer consists of 135 neurons (one for each training case in our model). The second hidden layer consists of two neurons (one for each outcome category in our model). The arrows represent the weights between two interconnected neurons.

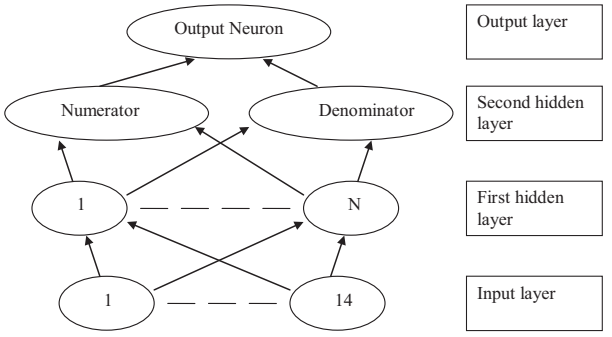

Figure 2. Generalized regression networks used in our model to predict length of stay in the unit before identification of index case (LOSA) and days of supplemental oxygen (DOSO). The input layer reflects the 14 variables used in our model. The first hidden layer consists of N neurons (one for each training case in our model; n=70 for LOSA and n=83 for DOSO). The second hidden layer consists of two neurons (i.e., numerator and denominator) that sum the negative and positive effects on the outcome studied. The arrows represent the weights between two interconnected neurons.

Methods

Study Design, Setting, and Patient Population

We retrospectively collected and analyzed data of patients born at a gestational age of 22–34 weeks during four outbreaks of RSV in a 35-bed, level IIIB NICU at a tertiary care hospital in the United Arab Emirates. These four outbreaks occurred over a period of about 2 years and 4 months (April 2005–July 2007). Total annual admissions to the NICU are approximately 500 neonates, with about 10% transferred from other hospitals.

We used a standardized data collection sheet and definitions (Table 1). In addition to the information summarized in Table 1, we gathered dates of birth, admission to the NICU, RSV tests, and death. Infection control personnel and microbiology staff flagged RSV-positive cases, whereas pharmacists and neonatologists collected the data. We conducted this research in accordance with the local institutional regulations and policies.

Table 1. Input and Output Variables in ANN Model for the 176 Premature Infants

Variables	Layer	Category (No. of Infants) or Median (Range) Value
BWT (g)	Input	1445 (480–3290)
Sex	Input	M: Male (111)
		F: Female (65)
Outbreak	Input	1: March–May 2005 (24)
		2: December–January 2006 (50)
		3: January–March 2006 (50)
		4: April–July 2007 (52)
Outbreak–LOSA[a]	Input	0: Other (76)
		1: April–July 2007 (52)
Group	Input	C: Control (145)
		P: Palivizumab (31)
Palivizumab prophylaxis	Input	No (116)
		Yes (60)
GA (wks)	Input	31 (21–34)
Apgar 1 score	Input	7 (1–9)
Apgar 5 score	Input	8 (2–10)
Apgar 10 score	Input	9 (1–10)
Age (days)	Input	0 (0–170)
CLD	Input	0: No (151)
		3: Yes (25)
CHD	Input	0: No (130)
		1: Insignificant (15)
		2: HSCHD (31)
RSV	Input	No (158)
		Yes (18)
LOSB (days)	Input	0 (0–147)
DOSO (days)	Output	6 (0–206)
LOSA (days)	Output	22 (0–224)
Mortality	Output	No: Alive (156)
		Yes: Dead (20)

ANN = Artificial Neural Networks; BWT = Birth Weight; CHD = Congenital Heart Disease; CLD = Chronic Lung Disease; DOSO = Days of Supplemental Oxygen; GA = Gestational Age; HSCHD = Hemodynamically significant congenital heart disease; RSV = Respiratory Syncytial Virus; LOSA = Length of Stay After identification of index case; LOSB = Length of Stay in the Unit Before identification of index case.

[a]Outbreak–LOSA replaced the Outbreak input variable in the LOSA network because there were 35 missing LOSA outcomes in the third outbreak.

Definitions

For the purposes of this study, we will use the term "pattern" to mean an individual patient case with its distinct clinical input variables. Outbreak was defined as more than one confirmed RSV infection by antigen testing for a duration of time from identification of first RSV antigen–positive case until the last test case was negative for two consecutive weeks. The four outbreaks that were investigated occurred from April–June 2005, December 2005–January 2006, January–March 2007, and April–July 2007. Chronic lung disease was defined as the need for supplemental oxygen at 36 weeks postconception or at discharge, whichever came first, in babies who were born less than 32 weeks' gestation or as who needed supplemental oxygen at discharge or age 28 days, whichever came first, in babies who were born at 32 weeks' gestation or after. Hemodynamically significant congenital heart disease (HSCHD) included both cyanotic and noncyanotic heart defects that compromise neonatal circulation. An example of HSCHD is moderate or severe patent ductus arteriosus. Patient's age was defined as the number of days from birth to the first day in the NICU during the RSV outbreak. Patients in the palivizumab treatment "Group" (Table 1) received the drug at the beginning of or during the outbreak while still RSV negative. Patients designated as "yes" for the variable "Palivizumab prophylaxis" (Table 1) received palivizumab within 1 month before or during the outbreak while RSV negative.

Artificial Neural Network Models

We constructed our ANN model by using Microsoft Excel add-in (Microsoft Corp., Redmond, WA), NeuralTools, version 1.0.1 (Palisade Corp., Ithaca, NY). Input nodes consisted of seven categoric and continuous features each (Table 1). We replaced missing input values (< 1%) with medians and the most common classes for continuous and categoric variables, respectively. The ANN model incorporated three outcomes: mortality, DOSO, and LOSA. We excluded patterns with

missing outcomes from training or testing. We used probabilistic networks for mortality (Figure 1) and generalized regression networks for DOSO and LOSA (Figure 2).

We expected, a priori, that three groups of patterns would need to be excluded from the training of the DOSO and LOSA ANN. First, patterns where infants died underestimate DOSO and LOSA. Second, patients who were extubated to room air on the first day of life give little information for the training and validation of the DOSO ANN. Third, patients whose length of stay before an outbreak starts (LOSB) that is more than 3 weeks may add "noise" to LOSA ANN. We used each pattern once for each outbreak in all trained ANN. We selected 5–7 patterns for external validation of ANN while NeuralTools version 1.0.1 automatically used 80% of the remaining cases for training and 20% for internal validation to prevent overtraining. We enabled all possible stop conditions: 2 hours of training, 1,000,000 trials, and error change of less than 0.01% within 60 minutes. NeuralTools version 1.0.1 generated variable impact (VI) for each input used in the training and validation of a given ANN. VI is a percentage that represents overall contribution of a given variable to the predicted outcome in the model. Furthermore, we reassigned inputs to study the effect of these modified values on outcomes by live predictions. Therefore, we were able to completely describe the ANN and role of palivizumab in our model.

Individualization of Palivizumab during an RSV Outbreak in the NICU

We present seven cases to briefly demonstrate how our established ANN model may assist clinicians in making decisions on palivizumab administration in individual patients in this setting. We randomly selected these cases as follows. First, we sorted our data for the variables "group" and "outbreak" with interest in the categories "P" and "4" (Table 1), respectively. Next, we generated random numbers for patients in each row, excluding missing DOSO and LOSA cases. Finally, we sorted the patterns for the random numbers and selected patterns at predetermined locations.

Statistical Analysis

We studied multivariates for a given outcome in one of two ways: reassignment of inputs and subgroup analyses. We used all univariate statistical tests. We used χ^2 or Fisher exact tests, as indicated, to evaluate statistical significance in case of unpaired categoric data. We opted to use McNemar's test for paired categoric data. We used unpaired and paired, 2-tailed, Student t tests as indicated to evaluate significance for continuous variables. Nonparametric tests were employed when normality assumptions failed. A p value of less than 0.05 was considered statistically significant. All statistical tests were performed by using SPSS, version 15.0.1, for Windows (IBM, Somers, NY).

Results

Model Description

We had a total of 176 cases: 135 were assigned to training, 34 to testing, and 7 were used for validation in the mortality network. Twenty patients (11.4%) died and therefore they were excluded from both DOSO and LOSA networks. Forty-six patients had DOSO of less than 1 day. As expected, adding these patterns to the DOSO ANN did not significantly change predictions, and therefore, they were excluded from the final DOSO network. The DOSO value was missing for one patient. Furthermore, 28 patients had LOSB more than 3 weeks. Adding these cases to the LOSA ANN did not change the results of the study, but it did worsen the performance of the LOSA network. As a result, these patterns were not used in the final LOSA network. We had 35 missing values in the LOSA for outbreak category 3. In this case, we replaced the variable "outbreak" with a dichotomous variable "outbreak–LOSA" with 1 for April–July 2007 and 0 for all other classes (Table 1). We summarize training, testing, and validation sets for each outcome (Figure 3). All networks converged within 400 trials and in less than 4 seconds.

Mortality

Among seven new cases that we assigned for external validation, 4 died and 3 survived. The ANN model predicted 50% of deaths and all survivals successfully. Overall, it performed well, with a sensitivity of approximately 82% and a specificity of 100%. All tested ANN had consistent performance and made similar predictions for new cases with associated probabilities of higher than 98%. Figure 4 presents VI associated with each input node in this model. We noted that patients who received palivizumab for

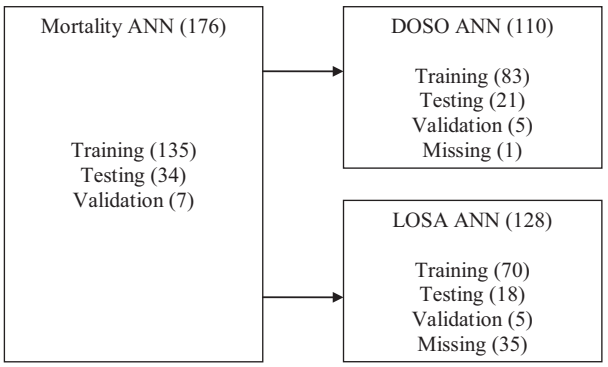

Figure 3. Summary of the artificial neural networks model (ANN) model. The numbers of cases (patterns) with missing outcome data, as well as those used in training, testing, and validation, are in parentheses. DOSO = Days of supplemental oxygen, LOSA = Length of Stay in the Unit After identification of index case.

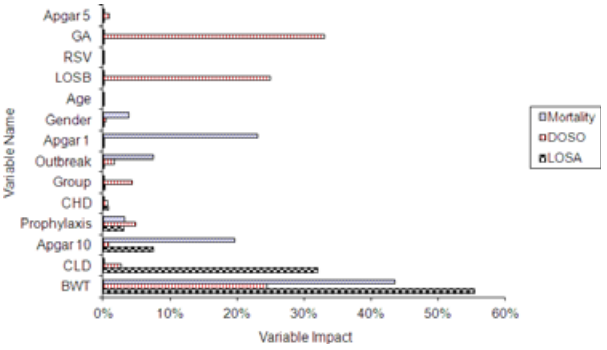

Figure 4. Impact variable analyses. BWT = Birth Weight, GA = Gestational Age, CLD = Chronic Lung Disease, CHD = Congenital Heart Disease, LOSB = Length of Stay in the Unit Before identification of index case.

prophylaxis, in accordance with AAP recommendations, before the outbreak were more likely to survive compared with those who received palivizumab only after the index case was identified (VI 3.2% and < 0.0001%, respectively). Palivizumab, given during the outbreak, was equivalent to control (ANN predicted the same 18 deaths in both groups after reassignments). Prophylactic palivizumab in the model resulted in three more survivals but was not statistically significant (15 vs 18 patients, p=0.25). These findings were true in all outbreaks analyzed in this study.

DOSO

Overall, performance of the model was fair (Figure 5). Palivizumab had greater impact on DOSO than the RSV outbreak (VI 4.3% vs 1.7%). However, the role of palivizumab was less important once an outbreak starts (VI 4.8% vs 4.3%).

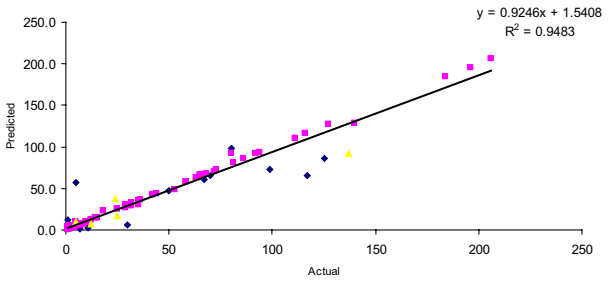

Figure 5. Performance of the artificial neural networks model for days of supplemental oxygen. Squares represent training, diamonds represent testing, and triangles represent validation.

Among 110 patients in this analysis, 19 (17.3%) would require less DOSO (range −17 to 0 days) if they received palivizumab after an outbreak started. In contrast, if palivizumab was used prophylactically before an outbreak starts, 55 patients (50%) would require less DOSO (range −64 to 0 days, p<0.001). After an outbreak starts, a greater percentage of patients who benefit from palivizumab had chronic lung disease (31.6% vs 13.2%, p=0.081) and HSCHD (36.8% vs 15.4%, p value = 0.049). On the other hand, patients who received palivizumab before the start of an outbreak will have similar distribution of chronic lung disease (5.5% vs 20%, p=0.44) and HSCHD (16.4% vs 21.8%, p=0.63) in the DOSO subgroups (i.e., those who benefit and those who do not). All other variables were distributed comparably in both scenarios. On further analysis, on average and after reassignment, newly admitted extremely low-birth-weight (< 0.7 kg) male infants with HSCHD who received palivizumab were extubated to room air a week earlier (105.2 ± 7.2 days vs 113.2 ± 10.4 days, p=0.003).

LOSA

Overall, performance of the model was fair (Figure 6). Palivizumab use, as a variable, had

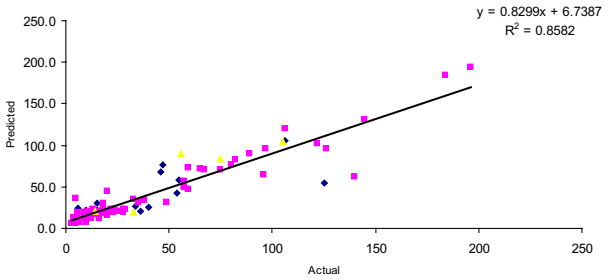

Figure 6. Performance of the artificial neural networks model for length of stay in the unit before identification of index case. Squares represent training, diamonds represent testing, and triangles represent validation.

greater impact on LOSA than the outbreak itself (VI 0.36% vs 0.08%). However, the role of palivizumab was less important once an outbreak starts (VI 3.1% vs 0.36%). Among 128 patients in this analysis, 62 (48.4%) had shorter LOSA (range −1.5 to 0 days) if they received palivizumab after an outbreak started. In contrast, if palivizumab was given prophylactically before an outbreak starts, 79 patients (61.7%) would have a shorter hospitalization (range −4.7 to 0 days, $p<0.001$). Patients who benefit from prophylactic palivizumab are more likely to have chronic lung disease (16.3% vs 2.5%, $p=0.004$) and, although nonsignificant, HSCHD (16.3% vs 6.3%, $p=0.06$). However, after reassignments for the variable group (Table 1), we failed to identify any subgroups with statistically significant reductions in LOSA after palivizumab.

Individualization of Palivizumab during an RSV Outbreak in the NICU

Table 2 summarizes information about seven patients who were randomly selected from our dataset. Patient 4 witnessed the third and fourth outbreaks, and thus both patterns are presented as patients 4 (3) and 4 (4). Based on mortality ANN predictions, we can exclude patient 7 from the list of candidates for palivizumab. Patients 4 (3) and 6 seem to benefit from palivizumab, with reductions in DOSO of 17 and 10 days, respectively. Patient 6 was discharged 1 day earlier based on the LOSA ANN as a result of receiving palivizumab.

Discussion

The cost of palivizumab use during RSV season is a major concern that shapes health care system performance around the peak of RSV season in winter. A number of previous studies have tried to identify the optimal and cost-effective criteria for selection of candidates for palivizumab.[13–17] However, during nosocomial RSV outbreak, economic considerations for clinical pharmacists and neonatologists who wish to help their patients may become more difficult to evaluate.[18] This study presents the first quasiexperimental research applying ANN to predict effect of palivizumab on mortality, DOSO, and LOSA during an RSV outbreak in the NICU. Therefore, we believe that our findings have

Table 2. Demographic and Clinical Characteristics of the Eight Patterns (in seven patients) from the Study Database

	Patient							
Variables	1	2	3	4 (3)[a]	4 (4)[a]	5	6	7
GA (wks)	24	30	32	24	24	34	23	24
BWT (g)	640	1430	1880	685	685	1425	585	510
Sex	F	F	F	M	M	M	M	M
Apgar 1 score	6	7	9	4	4	2	2	5
Apgar 5 score	7	9	9	5	5	5	5	7
Apgar 10 score	7	9	10	8	8	8	6	9
LOSB (days)	34	18	5	0	90	0	0	0
CHD	2	0	0	0	0	0	2	0
Palivizumab prophylaxis	No	No	No	No	No	No	Yes	No
Outbreak	4	4	4	3	4	4	4	4
Group	P	P	P	C	P	P	P	P
Age (days)	34	18	5	0	100	0	0	48
CLD	0	0	0	3	3	3	0	3
RSV	Yes	No	No	Yes	Yes	No	Yes	Yes
Mortality	No	No	No	No	No	No	No	Yes
DOSO (days)	99	1	5	127	127	11	94	181
LOSA (days)	80	18	18	137	47	12	105	133
ANN prediction								
Mortality[b]	No	No	No	No	No	No	No	Yes
Δ DOSO (days)[c]	–35	–8	–7	–17	–31	–1	+10	—
Δ LOSA (days)[d]	—	—	—	—	—	—	+1	—

ANN = Artificial Neural Networks; BWT = Birth Weight; CHD = Congenital Heart Disease (0 = no CHD; 2 = hemodynamically significant CHD); CLD = Chronic Lung Disease (0 = no CLD; 3 = CLD present); P = palivizumab; C = control; DOSO = Days of Supplemental Oxygen; GA = Gestational Age; RSV = Respiratory Syncytial Virus; LOSA = Length of Stay After identification of index case; LOSB = Length of Stay in the Unit Before identification of index case.

[a]Patient 4 witnessed the third and fourth outbreaks, and thus both patterns are presented as patients 4 (3) and 4 (4).

[b]Mortality network prediction. In all of these cases associated probability is almost 100%.

[c]Change in DOSO network prediction if the variable "group" is reassigned.

[d]Change in LOSA network prediction if the variable "group" is reassigned.

significant clinical and economic implications in this setting.

We observed that our ANN models consistently converged to optimal solutions that favor prophylactic use of palivizumab before the start of an RSV outbreak. Our current understanding of palivizumab's mechanism of action supports this finding.[19] Palivizumab binds to an epitope in the A antigenic site of the F protein on the surface of RSV. As a result, it neutralizes RSV, halts its replication, and prevents it from infecting human cells. However, an infected patient is expected to have already produced a large number of viral copies that make neutralization of all particles difficult to achieve. Consistent with this, other investigations have confirmed that palivizumab offers limited, if any, benefit in halting progression from upper to lower respiratory tract infection with RSV.[20]

We also noted that use of palivizumab during an outbreak has consistently greater impact on DOSO and LOSA than the variable "outbreak." Previous reports about palivizumab use in nosocomial outbreaks fail to study this proposition.[6–11] Our observation is important for two main reasons. First, we may expect that regardless of the severity of an RSV outbreak, a group of patients who are at high risk for RSV infections may benefit from palivizumab use. Second, our database combines cases from four different outbreaks at different times over a period of 2 years and 4 months. Consequently, palivizumab use in this setting may be independent of the biannual variation in RSV severity in the community or even the geographic location of the NICU. However, we need more evaluations before we can reach definitive conclusions.

We agree that closing the NICU during RSV outbreaks, heightened attention to infection control measures, and prophylactic palivizumab all may have a role in the control of RSV outbreaks in the NICU.[8, 21] In our NICU, we implement all infection control measures according to international standards. Strict hand washing for 2 minutes with antiseptic soap is mandatory for all health care providers and visitors. In addition, we apply hand washing or hand sanitizer before and after each patient contact. However, closing the NICU and compliance with effective infection control measures may prove to be a difficult undertaking in many busy nurseries.[22] Moreover, it is quite impossible to measure and compare infection control variables during different RSV outbreaks in the NICU and for individual patients. In our model, we had four outbreaks that may have been associated with RSV strains of different virulence as well as different overall compliance with infection control measures. Nevertheless, despite inclusion of outbreak categories as a variable, the ANN converged to optimal solutions that consistently generated greater variable impacts for palivizumab use before and during outbreaks than those generated for this variable. Therefore, the value of using palivizumab in this setting may prove to be more important than we think.

Use of palivizumab before or during an outbreak in the NICU does not improve survival in our model, which is consistent with results from the Impact RSV study.[1] On the other hand, palivizumab was associated with a reduction in mortality from RSV in another hospitalized population.[23] In our model, the mortality ANN had no false-positives in identifying deaths. Future research may use artificial intelligence models to predict patients at high mortality risk to exclude them from the list of candidates for palivizumab during RSV outbreaks. Moreover, these models may be tested and validated on larger sets of data to develop simple algorithms that can easily assist clinicians in deferring palivizumab in more patients. Therefore, we suggest that future research in the NICU outbreak setting should probably retain mortality as an outcome of interest.

Male premature infants are at high risk for increased supplemental oxygen, ventilation, and chronic lung disease.[24] Previous studies have also shown that in patients with HSCHD, there was an association between palivizumab use during RSV season and reduced DOSO.[25, 26] For example, a 73% reduction in total RSV hospital days with increased supplemental oxygen/100 children ($p=0.014$) due to palivizumab prophylaxis in these patients.[26] In our study, the risk of more DOSO in extremely low-birth-weight male infants was proportional to the benefit we may expect from use of palivizumab. Patient 6, who was already at extremely high risk—male with a birth weight of 585 g—would have less improvement in DOSO with palivizumab if he had HSCHD (−10 days vs –37 days). On the other hand, patient 4 (3)—male with a birth weight of 685 g—would have double improvement in DOSO with palivizumab if he had HSCHD (–34 days vs –17 days). Although individual patients may also have reduced LOSA, we were not able to find a statistically significant improvement in LOSA after palivizumab in this setting.

According to the AAP recommendations, graduates from NICU who qualify for RSV prophylaxis during the season may receive the first dose within 48–72 hours before discharge.[2] There are no evidence-based recommendations with regard to the use of palivizumab in the NICU during RSV outbreaks. If we use the same AAP criteria used during the season, all eight patterns (patients) reviewed in our testing scenarios for ANN would be great candidates for prophylaxis with palivizumab in this setting. However, based on our findings, we support using more stringent criteria for palivizumab during nosocomial RSV outbreak in the NICU. First, we should exclude cases with high mortality risk from the list of candidates. Then, we believe that our study identifies extremely low-birth-weight male infants with or without HSCHD as the group most likely to benefit from palivizumab. Finally, other babies may be offered prophylactic palivizumab based on estimated benefit from prediction models balanced against the risk of losing cost-effectiveness.

Our ANN model combined with competent clinical judgment should assist clinicians in making individualized decisions. It is interesting to note that patients 6, 4, 7, and 1 all tested RSV antigen positive. The remaining three (patients 2, 3, and 5) were all RSV antigen negative. Therefore, in this model, the decision to use palivizumab during a nosocomial RSV outbreak will be based on more than the mere probability of a baby converting to RSV positive. Patient 4 is especially interesting because this patient witnessed the third and forth outbreaks. In our model, he would have benefited from palivizumab only in the third outbreak. Other than palivizumab use, LOSB, outbreak, and age were the input variables that changed for this patient in the two outbreaks in this model. We recommend that future ANN models elaborate more on LOSB as a predictor of DOSO. Inclusion of other factors such as current weight may be warranted. Eventually, our findings may be further refined to defer more patients from palivizumab candidacy.

Lastly, our study has two important limitations. First, one may argue that the timing and number of doses for palivizumab could have improved performance. However, it was quite impractical to attempt an evaluation of this chronology in reality. One reason is that it is almost impossible to know with certainty when infection with RSV occurs and when viral shedding stops. Second, generalizability of this model requires more external validation. However, the consistency of ANN in converging to solutions that favor the use of palivizumab in newly admitted extremely low-birth-weight males with or without HSCHD makes us doubt that future validations will contradict these results.

Conclusion

Based on our study findings, we advocate a revision of current AAP recommendation for the use of palivizumab prophylaxis during RSV outbreaks in the NICU. Premature, extremely low-birth-weight male infants (< 0.7 kg) newly admitted to NICU, with or without HSCHD, are candidates for palivizumab. Palivizumab may prove to be a cost-effective intervention in this subgroup.

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