Monoclonal Antibody Treatment of RSV Bronchiolitis in Young Infants: A Randomized Trial

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abstract

BACKGROUND: Monoclonal antibody to respiratory syncytial virus (RSV; palivizumab) is recommend for prophylaxis of high-risk infants during bronchiolitis seasons but not for RSV bronchiolitis treatment. Our aim was to determine if palivizumab would be helpful in young infants with acute RSV bronchiolitis.

METHODS: Eligible infants ≤3 months old presenting to the pediatric emergency service with RSV-positive bronchiolitis requiring inpatient admission underwent double-blind random assignment to single-dose intravenous palivizumab (15 mg/kg) or placebo. The primary efficacy outcome was the need for inpatient readmission in the 3 weeks after discharge. Secondary outcomes were time to readiness for hospital discharge, need for PICU on the initial admission, and need for revisit not requiring readmission for the same illness during 3-week follow-up.

RESULTS: A total of 420 infants (median age 49 days) diagnosed with RSV bronchiolitis were randomly assigned; 417 received treatment, and 413 completed follow-up. Readmission during follow-up was needed for 23 (11%) patients on palivizumab and 19 (9.3%) patients in the placebo group (difference 1.8%; 95% confidence interval −4.4% to 7.7%; P = .51). Geometric mean time to readiness for discharge was 29.5 hours for the palivizumab group and 30.2 hours for the placebo group (ratio 0.98; 95% confidence interval 0.81 to 1.20). No safety issues were reported.

CONCLUSIONS: Intravenous palivizumab did not appear to help or harm young infants with acute RSV-positive bronchiolitis.

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Drs Alansari, Toaimah, and Davidson did the literature search, study design, data analysis and interpretation, and primary drafting of the manuscript; Drs Almatar, El Tatawy, and Qusad conducted patient recruitment and collected data; and all authors contributed to manuscript revisions with important intellectual content, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

This trial has been registered at www.clinicaltrials.gov (identifier NCT02442427).

DOI: https://doi.org/10.1542/peds.2018-2308

Accepted for publication Dec 4, 2018

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WHAT'S KNOWN ON THIS SUBJECT: Monoclonal antibody to respiratory syncytial virus (RSV; palivizumab) neutralizes RSV, suppresses replication, and is recommended for prophylaxis of high-risk infants during bronchiolitis seasons but not for RSV bronchiolitis treatment.

WHAT THIS STUDY ADDS: In this first blinded randomized trial of 420 young infants, palivizumab treatment did not prevent repeat readmissions after discharge nor shorten time to discharge or need for ICU during the index hospitalization.

To cite: Alansari K, Toaimah FH, Almatar DH, et al. Monoclonal Antibody Treatment of RSV Bronchiolitis in Young Infants: A Randomized Trial. *Pediatrics.* 2019; 143(3):e20182308

Twenty percent of infants in the annual US birth cohort requires outpatient medical treatment during the first year of life because of respiratory syncytial virus (RSV), and 2% to 3% of children in their first year are hospitalized for bronchiolitis. Figures from 2009 put the hospital-associated charges for bronchiolitis at >$1.7 billion in children <2 years of age.[1] Persistent symptoms, frequent outpatient revisits, and hospital readmissions are features associated with bronchiolitis, especially in younger infants.[2–5] Age <12 weeks, history of prematurity, cardiopulmonary disease, and underlying immunodeficiency are risk factors for severe disease.[6] Among patients <12 weeks of age, RSV bronchiolitis required more intensive care and longer stays than in older infants.[7,8]

The pathogenesis of RSV bronchiolitis appears to arise from cellular damage associated with viral replication and perhaps a defective inflammatory response to the infection.[9] Whether intervening to reduce either component would ameliorate an episode of bronchiolitis remains unclear.

The role of palivizumab in RSV prophylaxis was recently singled out in a review in which authors described the promise of monoclonal antibody therapy for treatment of infectious diseases.[10] Palivizumab, a recombinant humanized immunoglobulin G1 monoclonal antibody, has high binding affinity to the RSV fusion protein and stops viral replication with potent antiviral neutralizing and inhibiting activity.[11] First approved by the Food and Drug Administration in 1998, palivizumab is currently recommended by the American Academy of Pediatrics as monthly prophylaxis during bronchiolitis seasons for infants at higher risk for severe disease after accumulated evidence revealed it halves the rate of RSV-associated hospitalization among preterm infants.[12] However, the few small randomized studies and case series reporting palivizumab treatment do not allow an estimation of treatment efficacy.[13] Reducing subsequent hospitalizations and the frequency of return visits for the same illness as well as shortening length of stay for the index RSV bronchiolitis presentation are each desirable goals. Therefore, we tested the efficacy of the anti-RSV monoclonal antibody palivizumab on infants ≤3 months of age with RSV bronchiolitis early in their hospital course in a randomized double-blind trial.

METHODS

Patients were recruited during 3 bronchiolitis seasons between May 2015 and January 2018 in the infirmary-observation unit of the Hamad Pediatric Emergency Center, the only pediatric emergency facility in the state of Qatar. There are ~280 000 outpatient visits annually and 45 beds in the infirmary-observation unit where all inpatient services are provided except intensive care and surgery.

Infants aged ≤3 months presenting with a confirmed diagnosis of RSV bronchiolitis and requiring inpatient admission and treatment were eligible for the study. Inclusion required a prodromal history consistent with viral upper respiratory tract infection, including physical findings of bilateral chest crackles that could be associated with cough, rapid breathing, wheezing, and/or intercostal retractions in addition to a positive rapid RSV antigen test result on presentation. Patients were excluded for previous diagnosis of seizure disorder, suspected sepsis, previous history of renal or liver disease, known inborn error of metabolism, congenital heart disease or major congenital anomaly of the upper or lower respiratory tract, received steroid within 2 days before presentation, had received monoclonal antibody or intravenous immunoglobulin within the previous 3 months before random assignment, or known to have hypersensitivity to monoclonal antibodies or immunoglobulin products. Patients were assessed for study eligibility within 120 minutes of the initial physician assessment. Potentially eligible patients were examined on presentation in the emergency center, and those not medically ready for discharge from the emergency center after 120 minutes because of hypoxia (room air oxygen saturation <90%), inadequate feeding, prominent wheezing, or crackles or chest retractions were admitted as inpatients to the infirmary or observation unit. Written informed consent was obtained from 1 of the parents or legal guardians for consecutive eligible patients.

After enrollment, nasopharyngeal aspirate was obtained. Half the sample was processed within 30 minutes for an RSV antigen test (QuickVue RSV Test; Quidel Corporation, San Diego, CA), and half was sent to the main laboratory for a rapid respiratory virus panel capable of identifying 20 respiratory pathogens (multiplex real-time polymerase chain reaction [PCR] assay on ABI 7500 analyzer; Applied Biosystems, Foster City, CA). Patients with positive RSV antigen test results continued in the study, underwent chest radiography and intravenous line insertion, and were connected to a cardiorespiratory monitor. An unblinded study pharmacist used a computer-generated randomization list to prepare identical-appearing numbered syringes containing either 0.75 mL/kg (15 mg/kg) palivizumab or a similar volume of 0.9% sodium chloride for intravenous infusion by a syringe pump over 30 minutes. Then, patients were directed to the appropriate inpatient venue: the infirmary or observation unit, hospital, or PICU. Inhaled therapies, supplemental oxygen, respiratory

support, hydration, and other interventions were given at the discretion of the treating physician. Corticosteroids were not permitted as inpatient or postdischarge treatment. Patients were determined to be ready for discharge when they were not requiring supplemental oxygen (room air oxygen saturation >90%); were feeding adequately; had minimal or absent wheezing, crackles, and chest retractions; and Wang bronchiolitis severity score[14] <4. The Wang bronchiolitis severity score[14] ranges from 0 to 12 and has 4 variables, each receiving a score from 0 to 3, with higher scores denoting worse status. On discharge, patients were sent home with salbutamol metered-dose inhalers with an appropriately sized aerochamber mask attachment (Forest Laboratories, New York City, NY). Discharge on salbutamol, although not evidence-based, was a common practice elsewhere[15] and at our center. Daily telephone follow-up by a study nurse was mandatory for 3 weeks after discharge. Study participants returning for the same illness during the 3-week follow-up period were to undergo nasopharyngeal aspirates for RSV each time they revisited by using multiplex real-time PCR. Readmission during follow-up, if medically required, was to an inpatient service. For readmission during follow-up, a patient's disposition to an infirmary-observation or inpatient hospital bed was based on perceived less versus more serious illness and bed availability, whereas admission to the PICU was required if there was a need for hemodynamic monitoring, assisted ventilation, or related advanced monitoring and treatment. Heart rate and blood pressure were monitored in all study patients from the start of infusion for 4 hours. The study was approved by the hospital institutional review board and funded by Sidra Medicine and Hamad Medical Corporation.

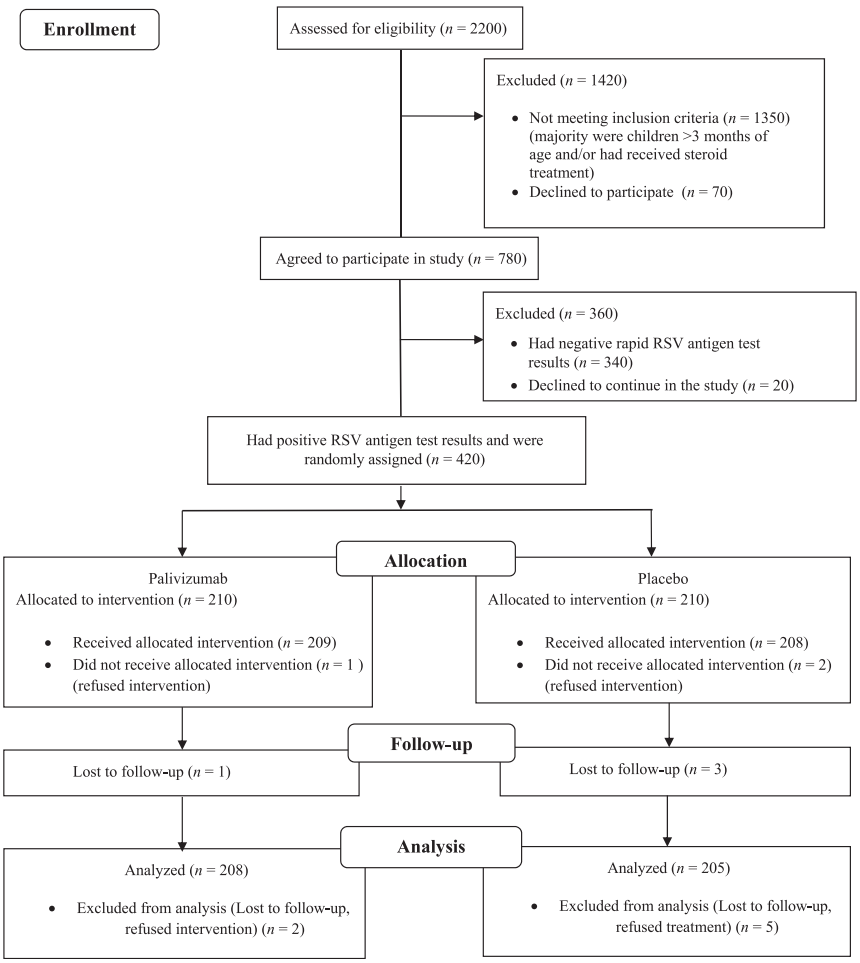

FIGURE 1
Patient flow in the study.

Study Outcomes

The primary efficacy outcome was readmission to either the infirmary-observation unit, hospital, or PICU during the 3 weeks after discharge. At study start, the primary outcome was the length of stay for the index episode, but this outcome and secondary outcomes were altered during a protocol review without data review in May 2016, a year after study start when additional funding became available for a larger study. Final secondary outcomes were time to medical readiness for discharge on the initial admission, revisit (but not requiring admission) to any medical facility for the same illness in the 3-week follow-up period, and need for transfer to the PICU during the initial admission. We further examined the subsets of patients presenting within 24 hours and within 48 hours of symptom onset and of patients with solely RSV-PCR positivity without other respiratory pathogen coinfection to optimize exploratory analysis of the specificity of the palivizumab intervention.

In response to editorial and reviewer requests, we also post hoc analyzed time to medical readiness for discharge in the subgroup of patients with the highest bronchiolitis severity scores.

Statistical Analysis

Study data were analyzed by the authors. For the primary and secondary outcomes, we planned a proof-of-concept per-protocol analysis, excluding patients lost to

TABLE 1 Baseline Characteristics of Enrolled Infants

Characteristics	Palivizumab (n = 210)	Placebo (n = 210)
Age, mean (SD), d	46 (20)	49 (20)
Boy/girl, *n*	123/87	127/83
Birth wt, mean (SD), kg	3.2 (0.6)	3.2 (0.5)
Gestational age at birth, mean (SD), wk	38.3 (1.3)	38.4 (1.4)
Gestational age ≤34 wk, *n* (%)	3.0 (1.4)	2.0 (0.9)
Past admission to the NICU, *n* (%)	11 (5.2)	13 (6.2)
Patients presenting with upper respiratory symptoms, *n* (%)	210 (100)	209 (99.5)
Duration of upper respiratory symptoms before enrollment, mean (SD), d	3.2 (1.8)	3.3 (1.7)
Patients presenting with fever, *n* (%)	129 (61.4)	119 (56.7)
Duration of fever before enrollment, mean (SD), d	1.1 (1.2)	1.0 (1.1)
Patients presenting with cough, *n* (%)	209 (99.5)	209 (99.5)
Duration of cough before enrollment, mean (SD), d	2.9 (2.0)	3.0 (1.6)
Patients presenting with difficulty breathing, *n* (%)	167 (79.5)	179 (85.2)
Duration of difficulty breathing before enrollment, mean (SD), d	1.4 (1.2)	1.4 (1.0)
Baseline respiratory rate, mean (SD)	55.3 (8.6)	53.6 (9.6)
Baseline heart rate, mean (SD)	164 (14.7)	164 (16.8)
Baseline temperature, mean (SD), °C	37.8 (0.6)	37.8 (0.6)
Baseline room air oxygen saturation, mean (SD)	97 (2)	97 (3)
Palivizumab received previously, %	0	0
Bronchiolitis severity score before enrollment, mean (SD)	5.5 (1.6)	5.3 (1.5)
Positive pathogens other than RSV by PCR testing, *n* (%)		
1 positive other than RSV	55 (26.2)	57 (27.1)
≥2 positive other than RSV	12 (5.7)	13 (6.2)
Adenovirus	2 (1.0)	2 (1.0)
Bocavirus	2 (1.0)	2 (1.0)
Coronavirus	2 (1.0)	4 (1.9)
Human metapneumovirus	0	1 (0.5)
Influenza and/or parainfluenza virus	7 (3.3)	8 (3.8)
Rhinovirus	28 (13.3)	35 (16.7)
Parechovirus	14 (6.7)	6 (2.9)
Enterovirus	2 (1)	0
Mycoplasma pneumoniae	1 (0.5)	1 (0.5)
Chest plain radiograph, *n* (%)		
Normal	153 (72.9)	149 (71.0)
Collapse or lobar consolidation	11 (5.2)	14 (6.7)
Lesser infiltrates	44 (21.0)	47 (22.4)
Received antibiotic(s) during hospitalization, *n* (%)	56 (26.7)	54 (25.7)
Patients who received PRN epinephrine nebulization, *n* (%)	12 (5.7)	12 (5.7)
Patients who received PRN salbutamol nebulization, *n* (%)	11 (5.2)	12 (5.7)
Patients who received corticosteroid during or after hospitalization	0	0

PRN, pro re nata (when necessary).

follow-up. χ^2 test or Fisher's exact test as appropriate were used for qualitative variable and outcome comparisons. Time to medical readiness for hospital discharge was plotted by univariate Kaplan-Meier survival analysis, and the geometric mean time to readiness for discharge for each treatment group was determined by accelerated failure time analysis. We estimated a 20% readmission rate[4] and hypothesized a reduction to 10%, consequent to investigational palivizumab treatment. For 80% power to find such a difference at a 2-sided P value of .05, 199 patients per group were required. We increased each group by 10 patients to account for dropouts. This expanded sample size was determined during protocol review without data review in May 2016, a year after study start. The initial sample size planned (65 patients per treatment group) had been based on convenience and limited funding that was subsequently increased.

Categorical and continuous data values were expressed as frequency (percentage) and mean (SD). Descriptive statistics were used to summarize baseline demographic, laboratory, and clinical characteristics of the patients. Quantitative variable means between the 2 independent groups were analyzed by using unpaired t and Wilcoxon rank sum tests. Associations between 2 or more qualitative variables were assessed by using the χ^2 test. Significant values and differences were reported with their corresponding 95% confidence intervals (CIs). Statistical analyses were performed by using a statistical software package (SPSS version 22.0; SPSS Inc, Chicago, IL). Data were transferred from SPSS package to

Stata SE 14.0 (Stata Corp, College Station, TX) for geometric mean times to readiness for discharge for each treatment group.

RESULTS

From May 2015 to January 2018, until the enrollment goal was reached, 420 previously healthy infants diagnosed with RSV viral bronchiolitis (median age 49.0 days [range 4–97 days]) were enrolled in the study (patient flow is summarized in Fig 1). Data for 7 of the enrolled infants were not included in the analysis; 3 parents refused the intervention after preparation of study medication, and 4 infants were lost to follow-up. Of the 413 (98.3%) infant episodes remaining, 208 had been randomly assigned to receive intravenous palivizumab, and 205 received the placebo. Subjects' baseline characteristics were similar in the 2 treatment arms at enrollment (Table 1). Among palivizumab recipients, 193 remained in infirmary-observation, 5 were cared for on the ward, and 10 were cared for in the PICU. Among placebo recipients, there were 189 in the infirmary-observation unit, 3 on the ward, and 13 in the PICU. Treatment with nebulized albuterol, nebulized epinephrine, and systemic antimicrobial agents occurred with similar frequencies in both patient groups (Table 1).

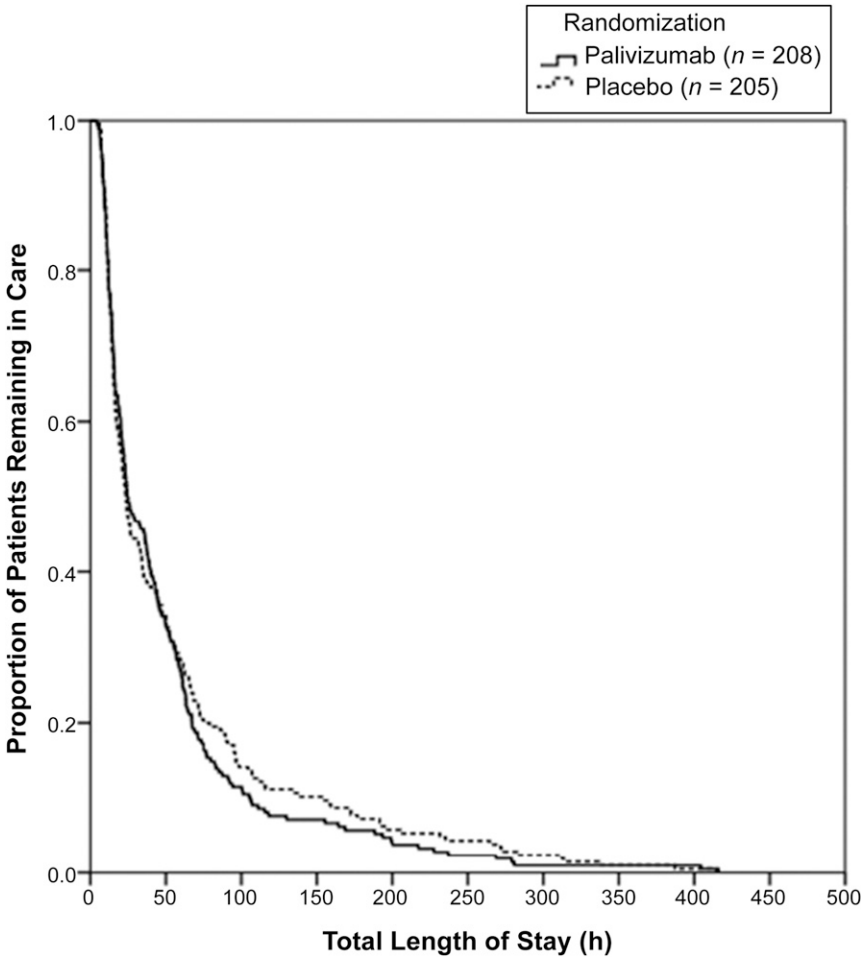

FIGURE 2
Time to clinical readiness for discharge during the index admission for RSV bronchiolitis for all completing patients.

Efficacy

For the primary outcome, 23 of 208 (11.1%) infants treated with palivizumab required readmission to the infirmary or observation unit, hospital, or PICU during the follow-up period compared with 19 of 205 (9.3%) placebo recipients (difference 1.8%; 95% CI −4.4% to 7.7%; P = .51).

The geometric mean time to readiness for discharge was 29.5 hours (95% CI 25.7 to 33.9) for the palivizumab group and 30.2 hours (95% CI 26.3 to 34.7) for the placebo group, resulting in a ratio of 0.98 (95% CI 0.81 to 1.20; P = .83; Fig 2). Revisits for the same illness not requiring readmission during the 3 weeks after discharge occurred in 41 palivizumab recipients (19.7%) and 45 placebo recipients (22.0%). Altogether, 64 palivizumab and 64 placebo recipients made 85 and 94 visits, respectively (difference −0.4%; 95% CI −8.9% to 9.8%; Table 2). Transfer to the PICU due to worsening illness severity during the initial admission was required for 10 patients (4.8%) in the palivizumab group and 13 (6.3%) in the placebo group (difference −1.5%; 95% CI −5.8% to 3.2%).

Subgroup Analyses

We considered that evidence favoring palivizumab in patients with short symptom duration before presentation and in patients without a pathogen other than RSV would support a positive efficacy hypothesis. Among palivizumab recipients with symptoms ≤1 day before presentation, 3 of 18 (16.7%) required readmission during the 3 weeks after discharge compared with 1 of 17 (5.9%) placebo recipients (difference 10.8%; 95% CI −13.0% to 21.6%). Among patients with symptoms ≤2 days before presentation, 8 of 78 (10.3%) palivizumab recipients and 7 of 71 (9.9%) placebo recipients were

TABLE 2 Primary, Secondary, and Subgroup Outcomes

Outcome	Palivizumab (n = 208)	Placebo (n = 205)	P
Primary outcome, n (%)			
Children admitted to the infirmary, hospital, or PICU within 3 wk after discharge	23 (11.0)	19 (9.3)	.51
Children admitted to the infirmary within 3 wk after discharge	14 (6.7)	16 (7.8)	.43
Children admitted to the hospital within 3 wk after discharge	7 (3.4)	1 (0.5)	.06
Children admitted to the PICU within 3 wk after discharge	2 (1)	2 (1)	.99
Secondary outcomes			
Children requiring revisits but not admission within 3 wk after discharge, n (%)	41 (19.7)	45 (22.0)	.63
Total no. of revisits within 3 wk after discharge, n	85	94	—
Children transferred to the PICU during initial admission, n (%)	10 (4.8)	13 (6.3)	.53
Subgroup primary outcome			
Index presentation after ≤1 d of symptoms, n	18	17	—
Children admitted to the infirmary, hospital, or PICU within 3 wk after discharge, n (%)	3 (16.7)	1 (5.9)	.31
Index presentation after ≤2 d of symptoms, n	78	71	—
Children admitted to the infirmary, hospital, or PICU within 3 wk after discharge, n (%)	8 (10.3)	7 (9.9)	.93
Index presentation PCR positive solely for RSV, n	142	138	—
Children admitted to the infirmary, hospital, or PICU within 3 wk after discharge, n (%)	15 (10.6)	12 (8.7)	.69

—, not applicable.

readmitted within 3 weeks (difference 0.4%; 95% CI −9.7% to 10.0%). For the subgroup of patients without PCR evidence of coinfection with a respiratory pathogen other than RSV, readmission within 3 weeks occurred in 15 of 142 (10.6%) palivizumab recipients and 12 of 138 (8.7%) placebo recipients (difference 1.9%; 95% CI −5.5% to 8.8%). The time to medical readiness for discharge and frequency of other secondary outcomes for each subgroup comparison were also similar for the palivizumab and placebo treatment groups (data not shown) as were subjects' baseline characteristics for each comparison (data not shown).

A post hoc secondary analysis of efficacy in patients with Wang bronchiolitis severity scores[14] well above the mean and median (≥7; Figs 3 and 4) suggested a (not statistically significant) reduced time to medical readiness for discharge for patients treated with palivizumab: 33.1 hours (95% CI 24.0 to 45.7) for the palivizumab (n = 37) patients versus 52.5 hours (95% CI 35.5 to 75.9) for placebo (n = 33) recipients (ratio 0.66; 95% CI 0.41 to 1.06; P = .08). Baseline characteristics and other outcomes were similar for the 2 treatment subgroups.

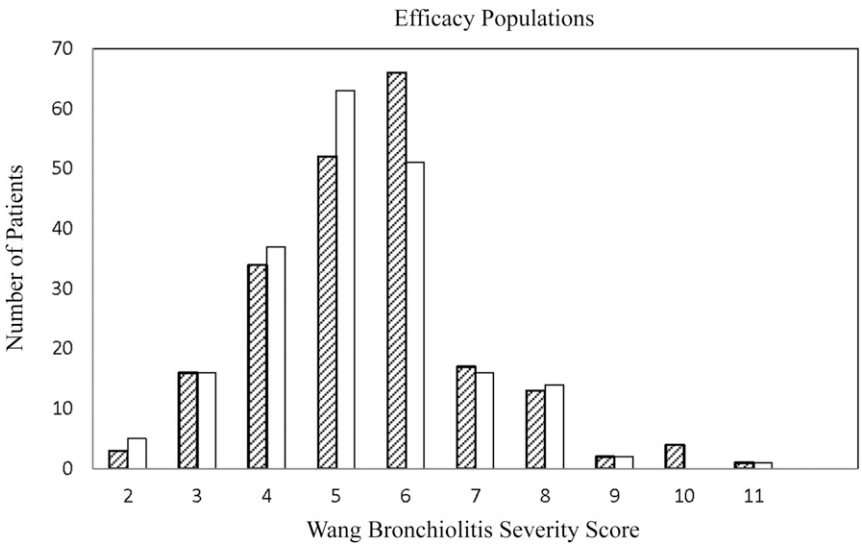

FIGURE 3
Frequency histogram of Wang bronchiolitis severity score[14] for completing patients. Lined bars represent palivizumab recipients (n = 37), open bars are placebo recipients (n = 33).

Nasopharyngeal Swab Results

During the 3 weeks of follow-up, 64 infants in the palivizumab group and 64 in the placebo group made at least 1 revisit for the same illness (Table 2). However, protocol nasopharyngeal aspirates for RSV were repeated for only 19 infants in the palivizumab group and 16 infants in the placebo group. PCR was RSV-positive for 17 palivizumab and 14 placebo patients. When compared with the initial PCR results, 7 children in the palivizumab group and 6 in the placebo group now tested positive for a respiratory pathogen not previously present.

Safety

No patient was withdrawn from the study because of apnea, cyanosis, or

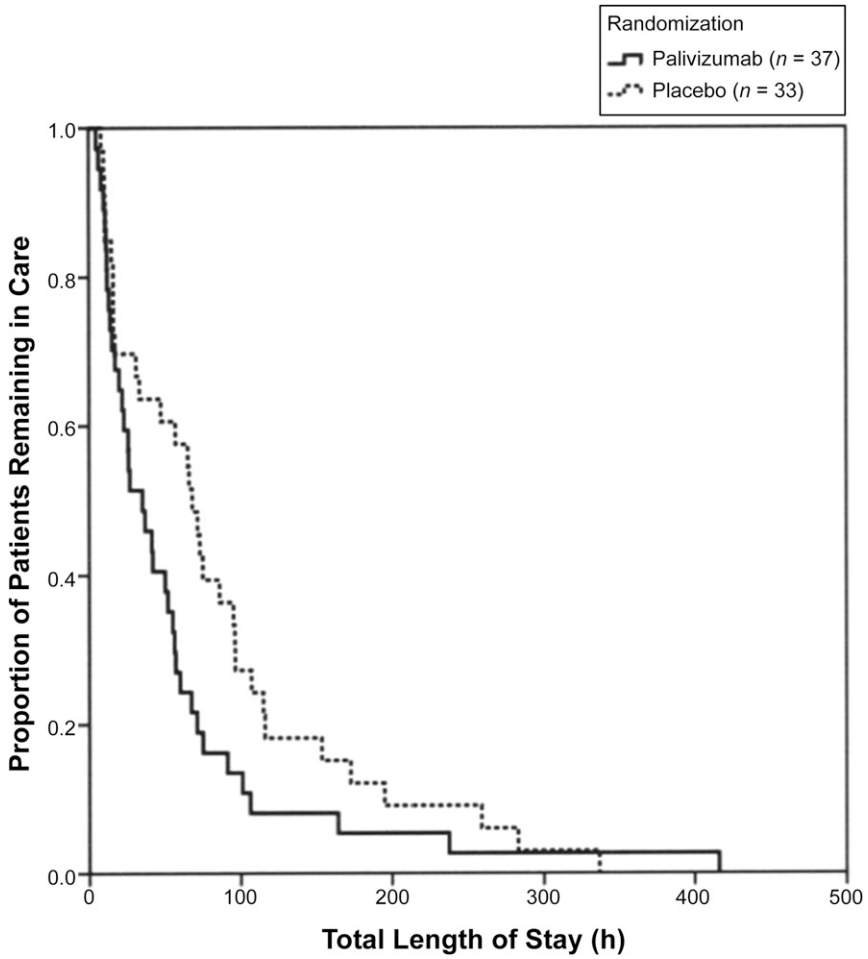

FIGURE 4

Time to clinical readiness for discharge during the index admission for RSV bronchiolitis, severely ill patient subgroup (Wang bronchiolitis severity score[14] ≥7). The geometric mean time to medical readiness for discharge was 33.1 hours (95% CI 24.0 to 45.7) for the palivizumab group versus 52.5 hours (95% CI 35.5 to 75.9) for the placebo group (ratio 0.66; 95% CI 0.41 to 1.06; P = .08).

hemodynamic instability. Blood pressure and heart rate profiles were similar between the palivizumab and placebo groups throughout the period of monitoring.

DISCUSSION

For young infants with RSV-associated bronchiolitis, treatment with intravenous recombinant monoclonal anti-RSV antibody was not superior to normal saline for preventing the need for readmission, reducing time to medical readiness for discharge, and the remainder of the secondary and exploratory outcomes.

A systematic review[13] of the available evidence for monoclonal RSV antibody treatment of acute RSV bronchiolitis presented studies conducted on patients with advanced disease who mostly required ICU and ventilatory support. Two small placebo-controlled randomized trials of human polyclonal anti-RSV antibody in children <2 years of age were conducted 2 decades ago, with 1 regarding previously healthy infants[16] and the second regarding infants at high risk[17] for severe RSV infections. Both revealed safety but were unconvincing regarding efficacy. Palivizumab was well tolerated, found to be safe when given intravenously,[13,18–25] and produced adequate serum antibody levels for at least 3 weeks when given at 15 mg/kg.[26] Yet, there was no survival benefit despite a decrease in RSV quantified from tracheal secretions.[13] A randomized trial using motivizumab[27] in hospitalized infants with RSV infection did not show reduced viral load or severity of illness. Motavizumab, which is derived from palivizumab, had considerably more potent RSV neutralizing activity in tissue culture.

Our findings do not support the routine use of RSV monoclonal antibody to treat acute RSV bronchiolitis in young infants, particularly considering the high cost of treatment. We think these results are robust because we strictly applied enrollment criteria in a population at high risk for severe disease in a randomized double-blind trial. Our study outcomes allowed ample time for the treatment to reveal a difference on clinical grounds should one exist, because our considerably enlarged patient sample was managed for 3 weeks after discharge, with <2% dropouts. We chose need for readmission during 3-week follow-up as our primary outcome because previously published work revealed that 25% of such children remained symptomatic at 21 days and 37% had further unscheduled medical visits after discharge.[2] A 33% shortened time to medical readiness for discharge after palivizumab treatment in the 17% of patients with the most severe bronchiolitis presentation is a tantalizing finding but requires confirmation in robust and prospective investigation.

A complex host inflammatory response to RSV infection has been described, with massive peribronchial inflammatory cell infiltration with activation of cytokines and chemokines, leading to bronchial structural damage, cell necrosis, and intraluminal obstruction.[28–30]

From our study, we speculate that host inflammatory response appears to be the more important factor affecting disease severity and resolution in the overall patient group we studied.

Our study has limitations. We did not attempt to quantify viral load in upper and lower specimens to validate palivizumab's mechanism of action. Our study follow-up was not long enough to examine possible time-remote effects, such as the incidence of future wheezing or the possibility of the type of disease enhancement that followed the use of an inactivated RSV vaccine. Our protocol for nasopharyngeal aspirate reexamination upon revisit after discharge had poor adherence. Finally, despite randomizing >400 patients, we may have failed to identify a small group of children who might have benefitted from palivizumab therapy, such as those presenting with the highest bronchiolitis severity scores or a group with a lesser clinical benefit than our sample size allowed us to detect.

CONCLUSIONS

We conclude that intravenous palivizumab, which is known to suppress replication of RSV, did not help or harm young infants with acute RSV-positive bronchiolitis and did not improve any of multiple relevant clinical outcomes.

ACKNOWLEDGMENT

We thank Dr Rajvir Singh for his thoughtful guidance in biostatistical analysis.

ABBREVIATIONS

CI: confidence interval
PCR: polymerase chain reaction
RSV: respiratory syncytial virus

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported by Sidra Medicine and Hamad Medical Corporation.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

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