Effect of Blood Transfusions on Intermittent Hypoxic Episodes in a Prospective Study of Very Low Birth Weight Infants

Kelley Z. Kovatis, MD[1], Juliann M. Di Fiore, BS[2,3], Richard J. Martin, MD[2,3], Soraya Abbasi, MD[4,5], Aasma S. Chaundhary, RRT[5], Stephen Hoover, MS[6], Zugui Zhang, PhD[6], and Haresh Kirpalani, MD[7]

Objectives To compare the number of intermittent hypoxia events before and after packed red blood cell (pRBC) and non-pRBC transfusions in very low birth weight infants, and to compare the time spent with saturations of ≤85% before and after transfusions in the same population.

Study design This prospective observational study was conducted from April 2014 to August 2017. It included 92 transfusions (81 pRBC, 11 non-pRBC) from 41 very low birth weight infants between $23^{0/7}$ and $28^{6/7}$ weeks of gestation. The primary outcome was number of intermittent hypoxia events. Secondary outcomes included the percent time of Peripheral capillary oxygen saturation (SpO2)of ≤85%, ≤80%, and ≤75%. A mixed ANOVA model was used to examine the relationship between event rate and covariates.

Results The mean number of intermittent hypoxia events per hour decreased from 5.27 ± 5.02 events per hour before pRBC transfusion to 3.61 ± 3.17 per hour after pRBC transfusions ($P < .01$) and intermittent hypoxia did not change after non-RBC transfusions (before, 4.45 ± 3.19 vs after, 4.47 ± 2.78; P = NS). The percent time with saturations of ≤80% and ≤75% significantly decreased after pRBC transfusions ($P = .01$). The time with saturations of ≤85% did not significantly change after non-pRBC transfusion.

Conclusions In very low birth weight infants with a hematocrit of 20%-42%, pRBC transfusions are associated with decreased frequency of intermittent hypoxia. No such diminution of intermittent hypoxia events was observed in infants who had received a non-pRBC transfusion. This finding suggests that the observed beneficial effects of RBC transfusions on apnea and its clinical manifestations of intermittent hypoxia are mediated through an enhanced oxygen carrying capacity. *(J Pediatr 2020;222:65-70)*.

Apnea of prematurity is common in infants <32 weeks gestation, indicating an immature respiratory neuronal center.[1] It is associated with multisystem morbidity and mortality, especially when events are >20 seconds in duration or associated with bradycardia and significant hypoxemia.[1-3] Apnea of prematurity may be exacerbated by anemia, when a decreased oxygen-carrying capacity results in decreased oxygen delivery to the central nervous system, and a decreased efferent output of the respiratory neuronal network.[4,5] Consequently, red blood cell (RBC) transfusions are often prescribed for anemic, premature infants with frequent apnea.

However, the association between apnea, anemia, and benefit from RBC transfusions is not consistently found in studies.[6-16] Some studies suggest that RBC transfusions are associated with a decreased frequency and severity of apnea, whereas others show no decrease in the frequency of apnea episodes after transfusions.[6-15] Some of these discrepancies may result from differing definitions of apnea, which is both difficult to identify and quantify. Nursing records are unreliable and impedance monitoring fails to identify mixed and obstructive events, making studies that attempt to establish a causal relationship between RBC transfusions and apnea exceedingly difficult.[3,4,17-20]

The potential benefit of RBC transfusion could be due to volume expansion or improved oxygen-carrying capacity.[16] Intermittent hypoxia likely represents a major clinically relevant consequence of apnea.[2,21] Identifying, recording, and quantifying intermittent hypoxia with pulse oximetry is a feasible, noninvasive, standard technique that could potentially establish the relationship between hypoxia, degree of anemia, and the impact of blood transfusions on the frequency of intermittent hypoxia. Only 1 prior study has assessed the impact of RBC transfusions on intermittent hypoxia. Abu Jawdeh et al showed that the severity and frequency of intermittent hypoxia decreased following the administration of RBC transfusion to extremely low birth weight infants after the first week of life.[6] However, the study did not include a non-RBC transfusion cohort to assess the impact of non-packed RBC

HUP	Hospital of the University of Pennsylvania
IVH	Intraventricular hemorrhage
pRBC	Packed RBC
RBC	Red blood cell
SpO2	Peripheral capillary oxygen saturation
VLBW	Very low birth weight

From the [1]Department of Neonatology, Christiana Care Health System, Newark, DE; [2]Division of Neonatology, Case Western Reserve University; [3]Division of Neonatology, Rainbow Babies & Children's Hospital, Cleveland, OH; [4]Division of Neonatology, Pennsylvania Hospital; [5]Division of Neonatology, University of Pennsylvania; [6]Value Institute, Case Western Reserve University, Cleveland, OH; and [7]Division of Neonatology, Children's Hospital of Philadelphia, Philadelphia, PA

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(pRBC) transfusions (rather than an improved oxygen carrying capacity) on intermittent hypoxia. Therefore, we sought to delineate the effect of both pRBC and non-pRBC transfusions on intermittent hypoxia.

Methods

This prospective observational study was conducted at the Hospital of the University of Pennsylvania (HUP) Special Care Nursery, Pennsylvania Hospital Intensive Care Nursery, and Temple University Hospital Infant Intensive Care Nursery. The institutional review boards at both institutions approved the study. Consent was obtained from parents of enrolled infants before initiation of the study. All infants were de-identified after demographic, clinical, and pulse oximetry data were extracted from the patient charts.

Inclusion criteria were very low birth weight (VLBW [<1500 g]) infants born between $23^{0/7}$ and $28^{6/7}$ weeks of gestation, admitted between April 2014 and September 2017. Infants with a birth weight of ≥1000 g were enrolled in the first day after admission. Infants <1000 g were enrolled after 1 week of age. Exclusion criteria were infants with a life-limiting diagnosis, cyanotic heart disease, in utero fetal transfusion, twin-to-twin transfusion syndrome, isoimmune hemolytic disease, severe acute hemorrhage, acute shock, sepsis with coagulopathy, and need for perioperative transfusion. Infants who had parents opposed to the transfusion of blood and parents with hemoglobinopathy or congenital anemia were also excluded. Data were collected from the time of enrollment until 6 weeks of age.

RBC transfusions included pRBCs. The amount and duration of transfusion were determined by individual unit protocols. Non-RBC transfusions included platelets and fresh frozen plasma. The amount and duration of transfusion were determined by individual unit protocols.

Intermittent hypoxia was defined as a decrease in Peripheral capillary oxygen saturation (SpO2)of ≤80% for ≥10 seconds and ≤3 minutes' duration.[20] The lower threshold of 10 seconds was based on previous data by Di Fiore et al.[22] The upper limit in duration (3 minutes) was chosen to distinguish intermittent hypoxia from sustained changes in baseline oxygenation.[20] Total time of SpO2 of ≤85%, ≤80%, and ≤75% included intermittent hypoxia events. The primary outcome was number of intermittent hypoxia events. Secondary outcomes included the total time of SpO2 at ≤85%, ≤80%, and ≤75%.

The study design compared all outcomes before and after a transfusion. Data were collected from the time that the medical team determined a blood transfusion (either RBC, platelets, or fresh frozen plasma) was clinically required. All such decisions did not involve the study team. To obtain study data, the pulse oximeter was placed on the patient until 8 hours after the completion of the blood transfusion. Oxygen saturation was recorded continuously using a high-resolution (2-second averaging time and 0.5-Hz sampling rate) pulse oximeter (Radical 87, Masimo, Irvine, California). The pretransfusion data were obtained in the hours before the start of the transfusion to the stop time of the transfusion. The post-transfusion data were recorded for ≤8 hours after the stop time of the transfusion. Transfusions that did not include pulse oximetry data before the start time of the transfusion were excluded from the analysis. Hours that contained >10% of missed pulse oximetry data or readings of 0% were excluded from analysis.

Demographic and clinical data were collected from the medical record. The hemoglobin and hematocrit obtained from the complete blood count or blood gas obtained immediately before the blood transfusion were recorded. The type of blood product, volume, and duration of the transfusion were recorded. Vital signs, oxygen requirement, and ventilator support data were collected before, at the start of, during, and after the transfusion.

Blood administered to neonates at HUP was stored using adsol and administered <7 days after collection. The average hematocrit per blood unit at HUP was 55%-65%. Blood administered to neonates at Temple University was stored using adenine-saline or citrate-phosphate-dextrose, citrate phosphate dextrose adenine. Blood stored using adenine-saline was administered <42 days and blood stored using citrate-phosphate-dextrose and citrate phosphate dextrose adenine was administered <21 days after collection. The average hematocrit per unit at Temple University Hospital was 55%.

Di Fiore et al previously reported that in VLBW infants, intermittent hypoxia events increased over the first 3 weeks of life and averaged 140 events per day, or approximately 47 events per 8 hours.[22] Using these data, a sample size of 42 infants was needed to detect a 10% difference in intermittent hypoxia events before and after blood transfusions, with a 0.05 alpha and 80% power.

Statistical Analysis

Infants' characteristics and outcomes were reported as mean ± SD or count and percentages. Continuous data were compared using the Student *t* test or Wilcoxon rank-sum test if necessary. Categorical data were analyzed using Pearson χ^2 test. A mixed ANOVA for repeated measures model was used to examine the relationship between event rate and covariates, including infant's sex, race, birthweight, gestational age, gestational age at the time of transfusion, hematocrit, caffeine dose, history of patent ductus arteriosus, history of intraventricular hemorrhage (IVH), group, time, and the interaction of type of transfusion and time. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, North Carolina). A P of <.05 was considered significant.

Results

A total of 75 infants were consented and enrolled in the study (**Figure 1**). Of the 75 infants enrolled, 24 did not receive transfusions; an additional 10 infants did not have complete data or pulse oximeter available before or at the

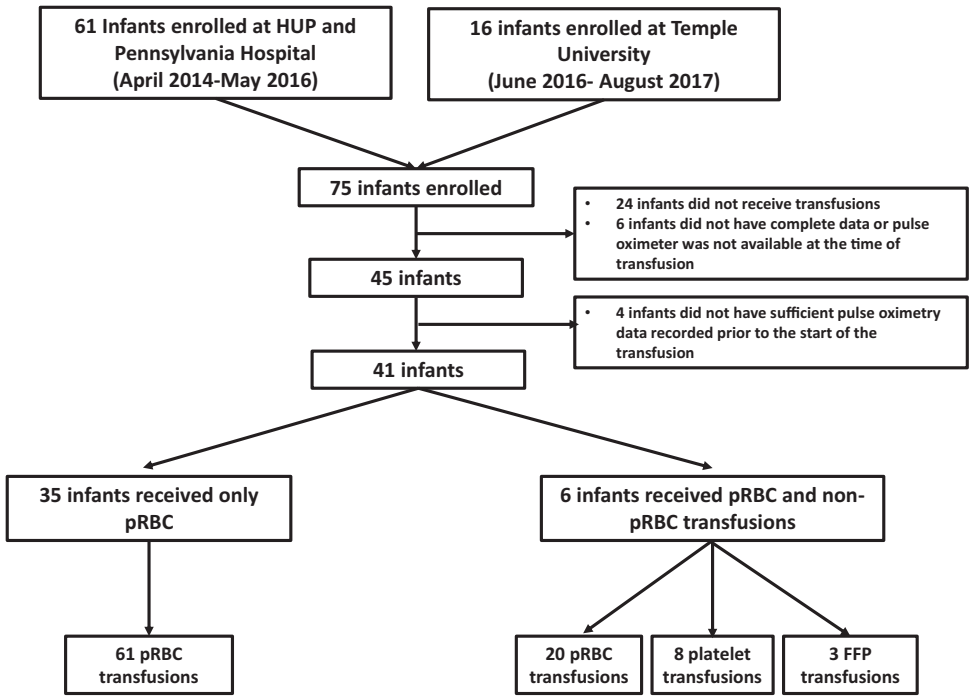

Figure 1. Flow diagram for identification of study cohort.

time of transfusion. Complete data were collected during 92 transfusions for 41 infants. Of these 92 transfusions, 81 were pRBC and 11 were non-pRBC transfusions (8 platelets, 3 FFP). The average transfusion rate and volume for the pRBC group was 2.96 ± 0.65 hours and 14.6 ± 3.0 mL/kg. The average transfusion rate and volume for the non-pRBC group was 1.81 ± 0.78 hours and 14.4 ± 3.9 mL/kg. Each infant included in the cohort received an average of 1.98 ± 1.13 transfusions during the study period and 60% of the transfusions (55/92) were administered between the hours of 7 a.m. and 7 p.m. The average recorded pretransfusion time was 6.40 ± 2.43 hours and the average post-transfusion time was 7.37 ± 1.35 hours. A majority of the transfusions were given for anemia (80.2%). Other indications for transfusion included apnea (6.9%), thrombocytopenia (7.9%), coagulopathy (3%), and other (2%).

There were no statistical differences in demographics between the 2 transfusion groups (**Table I**). The mean gestational age for all infants was 25.11 ± 1.65 weeks and the mean birthweight was 714 ± 165 g. There were no differences in the frequency of patent ductus arteriosus, IVH, or necrotizing enterocolitis history between the 2 transfusion groups at the time of the transfusion. The mean hematocrit before pRBC transfusions was 29.77% ± 4.02 compared with 34.35% ± 4.52 in the non-pRBC group (P = .001; **Table I**).

The number of intermittent hypoxia events before the transfusion for all transfusion groups was 5.18 ± 4.83 per hour of oximetry recording. Hematocrit ranged from 20% to 42% for all infants. Hematocrit inversely correlated with the change in number of intermittent hypoxia events after a transfusion (P = .017). There was no correlation between hematocrit and percent time with saturations of <75%, <80%, and <85%.

The mean number of intermittent hypoxia events per hour of oximetry recording significantly decreased from 5.27 ± 5.02 (median, 4.08; IQR, 0.95-8.47) events per hour

Table I. Demographic and clinical data for all transfusions

Characteristics	pRBC transfusions (n = 81)	Non-pRBC transfusions (n = 11)	*P* value
Male	52 (64.2)	7 (63.63)	.971
Black	60 (73.33)	7 (63.63)	.776
Gestational age at birth (weeks)	25.11 ± 1.65	25.14 ± 1.27	.943
Birth weight (g)	714 ± 165	731 ± 130	.748
Gestational age at time of transfusion (weeks)	28.11 ± 2.34	27.17 ± 1.16	.195
PDA diagnosis	63 (78)	9 (82)	.908
NEC diagnosis	5 (6)	1 (1)	.876
IVH diagnosis	28 (35)	2 (18)	.494
Dosage of caffeine at time of transfusion (mg/kg)	6.80 ± 2.46	6.00 ± 2.11	.328
Hematocrit before transfusion (%)	29.77 ± 4.02	34.35 ± 4.52	.001

NEC, necrotizing enterocolitis; *PDA*, patent ductus arteriosus.
Values are number (%) or mean ± SD.

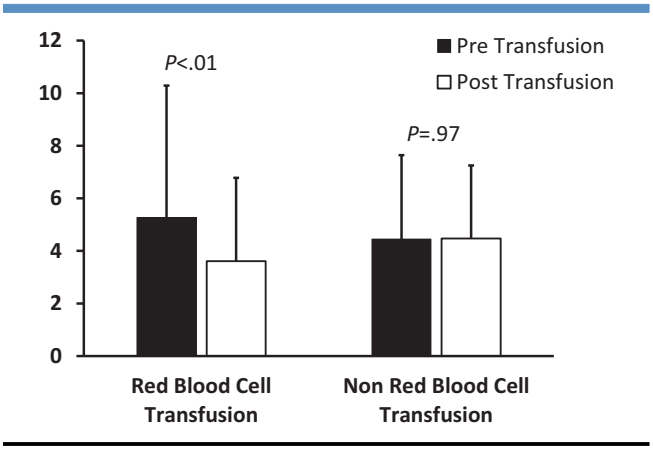

Figure 2. Number of intermittent hypoxic events per hour before and after transfusion of pRBCs compared with non-pRBCs (mean ± SD).

before pRBC transfusion to 3.61 ± 3.17 (median, 2.65; IQR, 1.25-5.25) events per hour after pRBC transfusions ($P < .01$) (Figure 2). The percent time with saturations of ≤80% and ≤75% significantly decreased after pRBC transfusions ($P = .01$) (Table II). There was no difference in the percent time with saturations of ≤85%. This significance persisted after controlling for sex, race, birthweight, gestational age, postmenstrual age at the time of transfusion, hematocrit, caffeine dose, history of patent ductus arteriosus, and history of IVH in a mixed effect model, suggesting that the pRBC transfusion is the contributing factor for the observed decreased.

The mean number of intermittent hypoxia events per hour of oximetry recording did not significantly change after non-pRBC transfusion (before, 4.45 ± 3.19; median, 6; IQR, 0.75-6.77 vs after, 4.47 ± 2.78; median, 4.25; IQR, 2.63-7.02; $P = .97$) (Figure 2). There was no significant difference in the percent time with saturations of <85%, <80%, and <75% before and after non-pRBC transfusions (Table II).

Although the mixed ANOVA accounts for repeated measures, we also performed an additional analysis where only the first transfusion was used. There was no statistical difference in the clinical data between the 2 transfusion groups when only the first transfusion for each patient was assessed. The mean number of intermittent hypoxia events per hour of oximetry recording significantly decreased from 5.13 ± 5.15 (median, 3.71; IQR, 0.41-8.68) to 3.09 ± 2.45 (median, 2.50; IQR, 1.38-4.50) for pRBC transfusions. The mean number of intermittent hypoxia events per hour of oximetry recording did not significantly change after non-pRBC transfusion (before, 3.76 ± 3.67; median, 3.02; IQR, 0.52-6.63 vs after, 3.43 ± 2.48; median, 3.38; IQR; 1.50-4.75; $P = .83$). The percent time with an SpO2 of ≤85%, 80%, and 75% did not statistically differ before or after the transfusion for both the pRBC and the non-pRBC groups when only the first recorded transfusion was analyzed.

Discussion

This prospective study of VLBW infants confirms observations by Abu Jawdeh et al that pRBC transfusions are associated with decreased frequency of intermittent hypoxia and percent time with saturations of ≤75% and ≤80%.[6] In our study, VLBW infants with a hematocrit of 20%-42% had a mean of 5.18 events of intermittent hypoxia per hour. We also observed no diminution of intermittent hypoxia events in infants with higher hematocrits who received non-pRBC transfusions. This finding suggests that the observed beneficial effects of red cell transfusions on apnea and its clinical manifestations of intermittent hypoxia are mediated through an enhanced oxygen-carrying capacity.

Intermittent hypoxia is frequent in VLBW infants. In a cohort of infants at 24-28 weeks of gestation, Di Fiore et al found that the frequency of intermittent hypoxia episodes increases during weeks 2-4 of life, plateaus at 4-6 weeks, and decreases by 6-8 weeks. In our study, the average age at the time of transfusion was 3 weeks, consistent with the finding from Di Fiore et al. Di Fiore et al also suggests the incidence of intermittent hypoxia episodes in this population is 50-100 events per day.[2] These findings were further supported by a more recent study that observed a high frequency of intermittent hypoxia in a subcohort of the 115 preterm infants

Table II. Intermittent hypoxia events and percent time with saturations ≤85%, ≤80%, or ≤75% for all pRBC and non-pRBC transfusions

	pRBC transfusions (n = 81)			Non-pRBC transfusions (n = 11)		
Events	**Before transfusion**	**After transfusion**	***P* value***	**Before transfusion**	**After transfusion**	***P* value†**
Intermittent hypoxia	5.27 ± 5.02 4.08 (0.95-8.47)	3.61 ± 3.17 2.65 (1.25-5.25)	<.01	4.45 ± 3.19 6 (0.75-6.77)	4.47 ± 2.78 4.25 (2.63-7.02)	.97
Percent time with saturations <85%	22 ± 15 20 (7.3-33.3)	19 ± 13 16 (10.2-26.9)	.06	27 ± 16 27 (15.0-41.2)	26 ± 13 26.5 (17.0-28.6)	.91
Percent time with saturations <80%	12 ± 10 8.8 (2.4-18.5)	9 ± 8 7.2 (3.3-13.8)	.01	14 ± 11 14.8 (3.1-25.1)	12 ± 8 12.4 (4.8-16.6)	.51
Percent time with saturations <75%	6 ± 7 3.9 (0.7-10.6)	5 ± 5 3.1 (1.1-7.2)	.01	8 ± 6 8.3 (1.9-14.0)	6 ± 5 4.6 (0.7-7.5)	.22

Values are mean ± SD and median (IQR).
*P value adjusted for repeated measures, n = 41 infants.
†P value adjusted for repeated measures, n = 6 infants.

enrolled in the SUPPORT study with an increased number of intermittent hypoxia events in infants randomized to an oxygen saturation of 85%-89% compared with 91%-95%.[22] Our study support these findings with an average number of intermittent hypoxia events of approximately 120 events per day.

Our study demonstrated that pRBC transfusions were associated with a decreased frequency of intermittent hypoxia in VLBW infants. These findings support previous studies. Abu Jawdeh et al demonstrated that pRBC transfusions are associated with a decreased frequency of intermittent hypoxia in extremely low birth weight infants who received transfusions during days 8-28 and >28 days.[6] Zagol et al a demonstrated decreased frequency of computer-detected apneic events for 10-, 20-, and 30-second apneas after a blood transfusion in VLBW infants.[4] Zagol et al also demonstrated an association between apneic events and hematocrit, similar to our findings.[4] No difference in the frequency of intermittent hypoxia was observed after non-pRBC transfusions. Although the number of infants in this group was small, thereby limiting our interpretation of this result, these data may suggest that increased oxygen-carrying capacity results in a decreased frequency of events.

Five large, randomized, blinded, controlled studies within the last 10 years have studied the association between hypoxia and neonatal morbidity and mortality.[23-26] Despite these studies, conclusions on the ideal oxygen target remains elusive. However, avoiding severe, prolonged, or repeated hypoxia is desirable and is recommended by the American Academy of Pediatrics.[27] Intermittent hypoxia is associated with severe retinopathy of prematurity, bronchopulmonary dysplasia, IVH, and a prolonged course in the neonatal intensive care unit.[28-30] Studies in neonatal animal models suggest an association between hypoxia and sleep disordered breathing, weight gain, and cardiovascular regulation.[31-35] Finally, in a secondary analysis of the Canadian Oxygen Trial, Poets et al found an association between hypoxia and increased risk of death or disability among extremely premature infants at 18 months corrected age.[36]

Strengths of our study include a prospective design, identification of events from a high-resolution pulse oximeter rather than from nursing documentation or impedance monitoring, and comparison of blood vs plasma or platelet effects on the frequency of event. Our study was powered to detect a difference in the number of intermittent hypoxia events before and after a pRBC transfusion; therefore, the lack of difference a observed in the non-pRBC transfusion group may be due to the small sample size. More studies are needed to assess the impact of non-pRBC transfusions on intermittent hypoxia. The percent time with an SpO2 of ≤85%, 80%, and 75% was no longer significant when only the initial blood transfusion was used. Because a mixed ANOVA was used to account for the repeat measures, this finding may reflect decreased power. Other limitations include possible selection bias of the study population because not all infants receiving transfusions were studied, infants may have received pRBC or non-pRBC transfusions that were not recorded, the specific age and hematocrit concentration of blood products administered at each transfusion is not known, and the statistical model included multiple variables. Platelet transfusions were often administered at the discretion of the medical team. Presumably, infants who received platelet transfusions were clinically sicker than infants that received only pRBC transfusions. However, because each infant served as their own control, the bias that this factor may have introduced is minimized.

In conclusion, pRBC transfusions were associated with a decreased frequency of intermittent hypoxia and percent time with saturations ≤80% and non-pRBC transfusion had no apparent effect on hypoxia-based variables. This study adds to the growing literature supporting the clinical practice of transfusing pRBCs to anemic premature infants with frequent intermittent hypoxia. Two ongoing but soon to be completed double-blinded randomized controlled trials attempt to establish the optimal transfusion threshold for RBC transfusions. Both the Transfusion of Prematures (TOP) trial (NCT01702805) and the Effects of Transfusion Threshold on Neurocognitive Outcomes (ETTNO) trial (NCT01393496) are designed to compare the effect of restrictive vs liberal RBC transfusion thresholds on the primary outcome of death or neurodevelopmental impairment at 2 years of age. These studies will further elucidate the impact of pRBC transfusions on the frequency of apnea and other neonatal outcomes. ■

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Reprint requests: Kelley Z. Kovatis, MD, Department of Neonatology, 4745 Ogletown-Stanton Road, MAP1, Suite 217, Newark, DE. E-mail: Kelley.Kovatis@christianacare.org

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