

# Are red blood cell transfusions associated with nosocomial infections in pediatric intensive care units?\*

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**Objectives:** To determine whether red blood cell transfusion is similarly associated with nosocomial infections in pediatric intensive care unit patients and whether reduced lymphocyte numbers is a possible mechanism. In adult studies, red blood cell transfusions are associated with nosocomial infections.

**Design:** Historical cohort study.

**Setting:** Single-center, mixed medical-surgical, closed pediatric intensive care unit of a tertiary university-affiliated children's hospital.

**Patients:** All patients  $\leq 18$  yrs old admitted to the pediatric intensive care unit during a 6-month period from January 1 to July 3, 2005.

**Interventions:** None.

**Measurements and Main Results:** Nosocomial infections (respiratory, urinary tract, and bloodstream infections) were the primary outcome measure and were defined as post transfusion if occurring within 14 days after red blood cell transfusion. Of the 209 subjects enrolled, 32 (15%) acquired nosocomial infections and 45 (22%) received red blood cell transfusions. Patients with versus without nosocomial infections had received red blood cell transfusions significantly more often (odds ratio, 18.0; 95% con-

fidence interval, 7.6–45.9;  $p < .001$ ). In a dose-dependence analysis, we found that patients receiving  $\geq 3$  red blood cell transfusions had a similar prevalence of nosocomial infections compared with those receiving one to two red blood cell transfusions (61% vs. 44%,  $p = .365$ ), but greater mortality (22% vs. 0%,  $p = .04$ ). In a multiple logistic regression analysis controlling for gender, age, pediatric intensive care unit length of stay, presence of an invasive catheter, mechanical ventilation, and surgery, red blood cell transfusion remained independently associated with risk of nosocomial infection (odds ratio, 3.73; 95% confidence interval, 1.19–11.85,  $p = .023$ ). Transfused subjects had lower absolute lymphocyte counts compared with nontransfused subjects (1605 vs. 2054/ $\mu\text{L}$ ,  $p = .041$ ), but similar total white blood cell counts ( $10.4$  vs.  $11.4 \times 10^3/\mu\text{L}$ ,  $p = .52$ ).

**Conclusion:** Red blood cell transfusion in pediatric intensive care unit patients is associated with an increased risk of nosocomial infections. (Pediatr Crit Care Med 2010; 11:464–468)

**KEY WORDS:** red blood cell transfusions; bacterial infections; pediatric intensive care units; lymphocyte count; retrospective study; severity of illness index

**T**ransfusion of red blood cells (RBCs) is a common practice in the pediatric intensive care unit (PICU). Over one third of children receiving care in a PICU develop anemia (1), and 15% to 50% of all PICU patients receive a transfusion during their intensive care stay (2, 3). More than 11 million units of blood are transfused annually in the United States (4). Although PICU patients receive a signifi-

cant amount of blood products, the biological effects of blood transfusion in the developing immune system of children (5) has not been well studied.

Recent retrospective and prospective studies in adults revealed an association between blood transfusion and risk of nosocomial infections in trauma patients (6, 7), postoperative cardiac surgery patients (8, 9), and medical/surgical intensive care unit patients (10, 11). Two large observational trials, the Europe-based ABC study (12) and the U.S. CRIT study (13), demonstrated evidence of a link between transfusion of RBCs and lower survival rates in adults in medical and surgical intensive care units. Although multiple factors may explain the association between blood administration and decreased survival, transfusion-related nosocomial infection is likely to be an important contributor to morbidity and mortality. Basic mechanisms underlying transfusion-related immune modulation may include soluble white blood cell-derived biological modifiers in allogeneic RBC transfusions that alter effector or

suppressor T lymphocyte activity, suppression of natural killer cell function (14, 15), defective antigen presentation, and inhibition of lymphocyte proliferation in response to antigenic stimulus (16) (17, 18).

In a well-designed study of outcomes related to blood transfusion practices in pediatric patients, Lacroix et al (19) observed no differences in risk of mortality or infection in critically ill pediatric patients who were stratified to a high (hemoglobin [Hgb]  $< 9.5$  g/dL) or low transfusion threshold (Hgb  $< 7$  g/dL). An unrelated study (20) suggested that administration of RBCs increases the risk of sepsis in pediatric burn patients. To our knowledge, no published pediatric study has compared the prevalence of nosocomial infections in transfused vs. nontransfused, general, PICU patients. Furthermore, pediatric studies to date have not simultaneously demonstrated increased infection risk and altered immune status after blood product transfusion. We hypothesized that RBC transfusions are associated with in-

**\*See also p. 524.**

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creased risk of nosocomial infection in PICU patients and may be associated with decreased lymphocyte numbers. To gather preliminary data to test our hypothesis, we retrospectively evaluated the frequency of nosocomial infection associated with blood transfusions in general PICU patients. We report that PICU recipients of transfused RBCs had an increased risk of nosocomial infection and decreased circulating lymphocyte numbers.

## MATERIALS AND METHODS

**Study Design and Patient Population.** We performed a historical cohort study of all pediatric patients ( $\leq 18$  yrs of age) admitted to the 19-bed medical/surgical PICU at Mattel Children's Hospital at UCLA Medical Center from January 1 to July 3, 2005. The study protocol was approved by the Institutional Review Board of UCLA, which waived the need for informed consent. The inclusion criterion was age  $\leq 18$  yrs for any patient admitted to the PICU. Exclusion criteria included patients with transplanted organs, patients diagnosed with immune deficiencies, patients who had received chemotherapy within a year of enrollment into our study, and patients diagnosed with an infection  $< 48$  hrs before admission or within the first 48 hrs after admission to the PICU. Data were obtained by medical chart review by a single reviewer (M.W.).

**Blood Cell Measurements.** For nontransfused subjects, baseline Hgb was defined as the first Hgb value noted on admission to the PICU. For transfused subjects, baseline Hgb was the value noted immediately before transfusion. The posttransfusion Hgb was the first value noted after transfusion. If subjects were transfused multiple times, then the baseline Hgb was defined as the average of Hgb values assayed immediately before each transfusion, and posttransfusion Hgb was similarly defined as the average of Hgb values noted immediately after each transfusion. Consequently, in some recipients of serial RBC transfusions, posttransfusion Hgb value for one transfusion was also the pretransfusion value for the next RBC transfusion. However, using these definitions, each subject was represented in our analysis only once. Pre- and posttransfusion lymphocyte counts were defined in a similar manner to Hgb values. For analyses of dose response, we split patients by number of transfusions (1–2 vs.  $\geq 3$ ), rather than total volume transfused.

**Outcome Measures and Data Collection.** Primary outcome variables were pneumonia, urinary tract infection with positive bacterial culture, bacteremia, and clinical diagnosis of culture-negative sepsis. For the purposes of this analysis, we attempted to avoid confusion between transfusion-related acute lung injury (21) and infectious pneumonia by limiting our diagnosis of pneumonia to positive tracheal aspirates only. Therefore, the diagnosis of

pneumonia was based on positive bacterial cultures of tracheal aspirates and either new evidence of airspace disease by plain chest radiograph or, in the absence of a new chest radiograph infiltrate, a clinical diagnosis of pneumonia in the attending physician's note, usually based on a combination of rales, hypoxia, elevated leukocytes in the tracheal smear, leukocytosis, and/or ventilation abnormalities. We screened for the diagnosis of sepsis syndrome by searching attending physician medical notes. Infections occurring  $< 48$  hrs before, or within 48 hrs after admission to the PICU were not considered nosocomial PICU infections and were excluded. Infections were considered post transfusion if occurring  $\leq 14$  days after the last transfusion. In nontransfused subjects, any infection occurring  $> 48$  hrs after PICU admission and detected during the hospital stay was included for analysis. Transfused patients who had a documented infection before transfusion were considered infected and nontransfused.

Mortality during PICU stay was the main secondary outcome variable. Other data collected included age, gender, diagnosis, Pediatric Risk of Mortality (PRISM) score, PICU length of stay (LOS), number of RBC transfusions, presence of mechanical ventilation, presence of catheters (central venous catheter, ventriculoperitoneal shunt, ventriculostomy, peritoneal drain), baseline and posttransfusion Hgb concentration and absolute lymphocyte count (ALC). Exposure to a surgical procedure within 2 wks of admission was also documented.

**Statistical Analysis.** We performed a power calculation, using estimates based on previously published nosocomial infection incidences and RBC transfusion practices in the intensive care unit (6–11, 19, 20). To detect an absolute increase of 14% in infection rate in transfused patients, with a two-sided  $\alpha$  of .05 and a power of 80%, we estimated that a total of 399 subjects would be needed. A planned midpoint interim analysis was performed based on the primary infection outcome, using the  $p < .01$  criterion of O'Brien and Fleming (22). The difference in infection rates between transfused and nontransfused patients was statistically significant at  $p < .001$ , and data collection was terminated.

Continuous variables are reported as median and range, except where noted. The Wilcoxon's rank sum test was used to test for significance for continuous variables between groups. Categorical (binary) variables are reported as percentages of the respective group and were compared, using Fisher's exact test. Multivariate analysis to calculate corrected odds ratios for the independent effect of RBC exposure (yes or no) and other treatment effects on the risk of infection was performed, using logistic regression. In the logistic analysis, RBC exposure via transfusion was coded as yes (y) or no (n) (not the number of transfusions), and the analysis was carried out controlling for male vs. female gender, age in

years, PICU LOS in days, catheter (y/n), mechanical ventilation (y/n), and surgical procedure done (y/n). Variables included in the multivariate model either were statistically significant or were considered *a priori* clinically important risk factors (gender, age, surgical procedure done) and were forced in. Mechanical ventilation was analyzed as a binary variable, instead of continuous variable, because of the very skewed distribution of mechanical ventilation days in our population, with the large majority of our subjects receiving zero ventilation days. We report two-sided 95% confidence intervals, and considered  $p < .05$  to be statistically significant.

## RESULTS

**Patient Characteristics.** From January 1 to July 3, 2005, 358 PICU admissions were screened, and 149 were excluded (68 transplants, 57 infections, 11 immune deficiencies, 13 chemotherapy). A total of 209 patients were eligible for inclusion and enrolled. Of these, 21.5% ( $n = 45$ ) were transfused with RBCs. Baseline characteristics for the overall population, transfused patients, and nontransfused patients are shown in Table 1. Patients meeting the inclusion criteria and diagnosed with sepsis syndrome were all found to have positive blood cultures. All of the variables are significantly different between the treatment and control groups. The infection rate is 51.1% in the RBC group and 5.5% in the nontransfused group ( $p < .001$ ). Mortality (8.9% in RBC group vs. 1.8% in control group), presence of mechanical ventilation (64.4% vs. 15.2%) and catheters (80.0% vs. 39.0%), and PICU LOS (11 days vs. 1 day) are other clinically significant variables that are notably different between the two groups.

Of 209 subjects, 204 (98%) had PRISM scores of  $< 10$ , and 194 (93%) had a PRISM score of 0. These results precluded stratification and normalization of patients for further analysis according to illness severity. Because the overwhelming majority of the patients in this study occupy the low risk category of illness severity on admission to the PICU, PRISM categorization was not included in the multivariate analysis of nosocomial infections reported below.

**Dose Response of RBC Exposure.** The median number of RBC transfusions per patient in the transfused cohort was 2. In our dose-response analysis (Table 2), we noted a significant difference in mortality (0% vs. 22.2% for patients receiving 1–2

**Table 1.** Characteristics of overall study population and transfused or nontransfused cohorts

	All Patients	No RBC	RBC	<i>p</i>
Number of patients	209	164	45	—
Age, mos	55.9 (0.07–239)	68.0 (0.07–239)	58.6 (0.3–231)	.0052
Male, %	61.7	61.0	64.4	<.001
PRISM score, range	0 (0–40)	0 (0–40)	2.0 (0–12)	<.001
PICU LOS days, range	2 (0–108)	1 (0–38)	11 (1–108)	<.001
No. ventilated pts, %	25.8	15.2	64.4	<.001
Days ventilation, range	0 (0–65)	0 (0–12)	3 (0–65)	<.001
Mortality, %	3.4	1.8	8.9	.0401
Infections, %	15.3	5.5	51.1	<.001
Blood stream, n (%)	5 (2)	3 (2)	2 (4)	
Urinary tract, n (%)	11 (5)	4 (2)	7 (16)	
Pneumonia, n (%)	20 (10)	3 (2)	17 (38)	
Baseline Hgb, range	11.5 (4.8–20.0)	11.7 (4.8–20.0)	8.6 (4.8–14.3)	<.001
Catheter, %	47.8	39.0	80.0	<.001
Surgical procedure, %	50.7	54.9	35.6	.0283

RBC, red blood cells; PRISM, Pediatric Risk of Mortality score; PICU, pediatric intensive care unit; LOS, length of stay; Hgb, hemoglobin concentration.

Continuous variables are expressed as median (range). Binary variables are expressed as a percentage. The *p* values are presented for the comparison of transfused (RBC) vs. nontransfused (No RBC) patients.

**Table 2.** Comparison of transfused patients who received  $\leq 2$  (median) transfusions versus those who received  $> 2$  transfusions

	1–2 RBC Transfusions	$> 2$ RBC Transfusions	<i>p</i>
Number of patients	27	18	
Age, mos (range)	18 (0.4–231)	10.4 (0.3–219)	.487
Male, %	55.6	77.8	.204
PRISM score, range	2 (0–10)	2 (0–12)	.624
Surgical procedure, %	40.7	27.8	.527
PICU LOS, range	9 (1–108)	14.5 (1–66)	.044
Mortality, %	0	22.2	.021
Infections, %	44.4	61.1	.365
Blood stream, n (%)	1 (4)	1 (6)	1.000
Urinary tract, n (%)	5 (19)	2 (11)	.684
Pneumonia, n (%)	8 (30)	9 (50)	.216

RBC, red blood cells; PRISM, Pediatric Risk of Mortality score; PICU, pediatric intensive care unit; LOS, length of stay.

Continuous variables are expressed as median (range). Binary variables expressed as percentage of the group. A *p* < .05 is considered significant.

**Table 3.** Comparison of patients with infection versus patients without infection

	Infection	No Infection	<i>p</i>	Odds Ratio	95% Confidence Interval
Number of patients	32	177	—	—	—
Age, mos (median)	49.4	68.0	.0087	0.992/mo	(0.985, 0.997)
Male, %	62.5	61.6	.999	1.040	(0.48, 2.32)
PRISM score, mean	1.9	1.4	.479	1.03/pt	(0.93, 1.12)
PICU LOS, median	12.5	1.0	<.001	1.15/day	(1.10, 1.22)
Transfusions, %	71.9	12.4	<.001	18.0	(7.6–45.9)
Catheter, %	90.6	40.1	<.001	14.4	(4.9, 61.9)
Mechanical ventilation, %	75.0	17.0	<.001	14.7	(6.3, 37.9)
Surgical procedure, %	46.9	51.4	.703	0.833	(0.39, 1.77)

PRISM, Pediatric Risk of Mortality score; PICU, pediatric intensive care unit; LOS, length of stay.

Continuous variables are expressed as median values except the PRISM score, which is expressed as a mean value. Binary variables are expressed as percentage of the group.

RBC transfusions vs.  $> 2$  RBC transfusions, respectively; *p* = .021), but no effect of RBC dose on frequency of nosocomial infection.

*Factors Associated With Nosocomial Infection.* We performed univariate analyses to screen for risk factors for nosocomial infection in the overall group of

PICU patients. Variables that were significantly associated with nosocomial infection are presented in Table 3. Of the four statistically significant variables—PICU LOS, RBC transfusions, presence of catheter, and presence of mechanical ventilation—RBC transfusions was associated with the highest odds ratio for infection (odds ratio, 18.0; 95% confidence interval, 7.6–45.9). PICU LOS (odds ratio, 1.15/day; 95% confidence interval, 1.10–1.22) has a weaker yet significant association with infection.

Using variables identified in our univariate tests or variables considered clinically important, we performed a multiple logistic regression analysis (Table 4). After controlling for gender, age, PICU LOS, presence of catheter, mechanical ventilation, and surgical procedure, RBC transfusion remained independently associated with an increased risk of nosocomial infection. The receiver operating characteristic area value for this multivariate model is 0.927.

*Decreased Lymphocyte Counts in Transfused Subjects.* Previous basic science literature suggested multiple potential mechanisms for the association between RBC transfusions and invasive bacterial infections (17, 18). Among these potential mechanisms, suppression of lymphocyte proliferation (16) was a candidate that could be screened in retrospective data. Therefore, we evaluated ALC before and after RBC transfusion. We found that ALC measured post transfusion, but not pre transfusion, are significantly lower than ALC in nontransfused patients, whereas white blood cell is unchanged (Table 5).

## DISCUSSION

In this retrospective study, we observed an independent association between RBC transfusion and infection risk in a general medical/surgical population of PICU patients and found a reduction in ALC that may contribute to this infection risk. We also observed a dose-response relationship between RBC transfusions and risk of mortality.

One strength of our study is that we detected a difference in infections, using a conservative time-limited criterion to define infection after packed RBC transfusion, but we did not impose a time limitation on the nontransfused control group. Whereas posttransfusion infections were restricted to only the 14-day period after transfusion, infections in the

Table 4. Results of multivariate logistic regression analysis to evaluate risk of infection

Variable	Odds Ratio	95% Confidence Interval	<i>p</i>
RBC Transfusion (y/n)	3.72	(1.19, 11.85)	.023
Gender	0.91	(0.30, 2.76)	.870
Age (per mo)	0.99/mo	(0.98, 1.00)	.244
PICU LOS (per day)	1.08/day	(1.02, 1.15)	.015
Catheter (y/n)	4.71	(1.23, 24.08)	.035
Mechanical ventilation (y/n)	5.29	(1.70, 17.61)	.005
Surgical procedure (y/n)	1.43	(0.47, 4.62)	.534

RBC, red blood cells; y, yes; n, no; PICU, pediatric intensive care unit; LOS, length of stay.

Table 5. Comparison of post transfusion absolute lymphocyte counts in transfused patients versus baseline absolute lymphocyte counts in nontransfused patients

	No RBC	RBC	<i>p</i>
Number of patients	164	45	—
ALC (cells/μL)			
Pre transfusion (range)	2054 (556–9522)	2405 (470–7548)	.5336
Post transfusion (range)		1605 (384–3375)	.041
WBC (×10 <sup>3</sup> cells/μL)			
Pre transfusion (range)	11.4 (4.1–37.0)	11.0 (3.7–21.9)	.5262
Post transfusion (range)		10.4 (3.4–49.8)	.5222

RBC, red blood cell transfusion; ALC, absolute lymphocyte count; WBC, white blood cell count.

Values expressed as median (range). The *p* values are reported for comparisons between No RBC vs. RBC columns.

control group were included for the duration of their hospital course, regardless of LOS. If we had limited our analysis of the nontransfused group to 14 days only, the total number of infections in the nontransfused group would have been less and would consequently have increased the strength of association between packed RBC transfusion and nosocomial infection that we observed.

These findings are similar to many adult retrospective and prospective studies (6–11) that have investigated this phenomenon. Jeschke et al (20) noted an association between RBC transfusions and increased risk of sepsis in pediatric burn patients. We believe the current report is one of the first studies to evaluate the risk of infection in transfused patients in a medical/surgical PICU patient population.

A recent prospective trial by Lacroix et al (19) evaluated different transfusion thresholds in pediatric patients and revealed no difference in infection or mortality between a transfusion trigger of Hgb <7 g/dL vs. Hgb <9.5 g/dL. Several distinctions should be drawn between the study by Lacroix et al and our current study. First, cystitis was not included in the infections documented, whereas in our study a significant proportion of infected patients had a positive catheterized urine culture. More importantly, our re-

port compares the prevalence of infection in transfused vs. nontransfused PICU patients, whereas nearly half of the patients in the lower transfusion threshold group received red cell transfusions in the report by Lacroix et al. Finally, the red cell units in the study by Lacroix et al (19) underwent universal prestorage leukocyte reduction, which may reduce in-hospital mortality and infections after cardiac surgery through as yet undetermined mechanisms (18, 23). Prestorage leukocyte reduction has not yet been mandated in the United States. Data regarding prestorage leukocyte reduction was not available for analysis in our report.

The major limitation of our study relates to the longstanding issue of whether the observed association between RBC transfusion and nosocomial infection represents a mechanistic link or a coincidental observation confounded by the greater severity of illness of patients who require blood product transfusions (24). To control for the effect of severity of illness on risk for nosocomial infection, we considered stratifying our analysis by PRISM score as an overall estimate of illness severity. We found that after applying our exclusion criteria (transplant recipients, immunocompromised conditions, and presentation to the PICU with infection), PRISM scores were low and

similar between comparison groups, whether broken down by transfusion or infection status. These data suggest that severity of illness was not the defining risk factor for either RBC transfusion or nosocomial infection developing in the PICU. Therefore, rather than controlling for illness severity, we constructed a multivariate model of nosocomial infection to control for known major risk factors for nosocomial infection. In our multivariate analysis, we found that RBC transfusion remained significantly and independently associated with nosocomial infections.

A second limitation of our study was insufficient data to draw meaningful conclusions regarding differences within the transfused group. Specifically, we would have liked to analyze the change in ALC (delta ALC) before, compared to after transfusion, to see whether there was a difference in delta ALC between transfused patients with or without infection; and we would have also liked to compare this with the corresponding change in ALC in those not transfused over the same time period. Of the 23 transfused patients with infections, 17 had enough data to calculate the delta ALC, whereas only ten of 22 transfused patients without infection had sufficient data.

Although we did not specifically note the length of time after RBC transfusion that the posttransfusion ALC was measured, it is our standard clinical practice to measure a complete blood count within 6 hrs to 24 hrs after transfusion to determine the new Hgb level and to decide if another transfusion is needed. Due to our study's retrospective design, the nontransfused group had no time-delimited or event-related second ALC to serve as a suitable control group for the posttransfusion ALC. Instead, we note a systematic and prospective evaluation of lymphocyte counts in consecutive medical/surgical PICU patients by Felmet et al (25), which demonstrated no significant variation in lymphocyte counts in PICU patients (except in the presence of multiple organ failure), even over the course of weeks. From these data, we might presume that lymphocyte counts will not drop precipitously over a short (or long) period of time in PICU patients who were not transfused. As it is likely that our posttransfusion ALC were determined generally within 24 hrs of the RBC transfusion, the decrease in lymphocyte count could possibly be associated with the RBC transfusion. It is not likely, based on the reference by Felmet et al (25), that the

decrease in lymphocyte count would have happened simply by virtue of being a critically ill patient in the PICU.

Furthermore, the median ALC value in those not transfused is similar to the pretransfusion ALC value in the transfused patients. So, although a follow-up fully prospective study monitoring ALC over time in all patients with and without transfusion and infection is desirable, these findings should be regarded as suggestive within the limitations of a historical cohort design.

A third and potentially important limitation of our study was our requirement for a positive tracheal aspirate culture to diagnose pneumonia. We chose this definition to avoid the confounder of transfusion-associated lung injury (21). However, this conservative definition of pneumonia requires endotracheal intubation. Because mechanical ventilation was required in a much greater proportion of transfused than nontransfused patients in our population, this may present some bias, although we did attempt to minimize this effect by including mechanical ventilation in our multivariate model.

## CONCLUSIONS

In conclusion, our study confirms and extends previous observations in adults (6–11) that RBC transfusion in critically ill pediatric patients is associated with nosocomial bacterial infections. Notably, our study is distinct from previous studies in that we also identify an association between RBC transfusion and decreased ALC. To our knowledge, the current study is the first to report concurrent observations of increased risk for nosocomial infection and altered lymphocyte numbers in a cohort of transfused patients. By identifying both a predisposition to infection and a potential biological basis for that susceptibility, we hope that our report adds to the controversy over whether transfusion-related immunomodulation truly contributes to infectious risk (24, 26). We propose that future prospective research should seek to determine the cellular mechanisms by

which RBC transfusions are related to bacterial infections in the critically ill.

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