Blood Utilization and Transfusion Reactions in Pediatric Patients Transfused with Conventional or Pathogen Reduced Platelets

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Objectives To assess the safety and efficacy of a Food and Drug Administration-approved pathogen-reduced platelet (PLT) product in children, as ongoing questions regarding their use in this population remain.

Study design We report findings from a quality assurance review of PLT utilization, associated red blood cell transfusion trends, and short-term safety of conventional vs pathogen-reduced PLTs over a 21-month period while transitioning from conventional to pathogen-reduced PLTs at a large, tertiary care hospital. We assessed utilization in neonatal intensive care unit (NICU) patients, infants 0-1 year not in the NICU, and children age 1-18 years (PED).

Results In the 48 hours after an index conventional or pathogen-reduced platelet transfusion, respectively, NICU patients received 1.0 ± 1.4 (n = 91 transfusions) compared with 1.2 ± 1.3 (n = 145) additional platelet doses ($P = .29$); infants 0-1 year not in the NICU received 2.8 ± 3.0 (n = 125) vs 2.6 ± 2.6 (n = 254) additional platelet doses ($P = .57$); and PEDs received 0.9 ± 1.6 (n = 644) vs 1.4 ± 2.2 (n = 673) additional doses ($P < .001$). Time to subsequent transfusion and red cell utilization were similar in every group ($P > .05$). The number and type of transfusion reactions did not significantly vary based on PLT type and no rashes were reported in NICU patients receiving phototherapy and pathogen-reduced PLTs.

Conclusions Conventional and pathogen-reduced PLTs had similar utilization patterns in our pediatric populations. A small, but statistically significant, increase in transfusions was noted following pathogen-reduced PLT transfusion in PED patients, but not in other groups. Red cell utilization and transfusion reactions were similar for both products in all age groups. *(J Pediatr 2019;209:220-5)*.

Advances in clinical care, surgical approaches, and the implementation of more restrictive transfusion thresholds have led to a gradual, progressive decline in the number of blood transfusions in the US.[1] The precise frequency of pediatric transfusions is difficult to determine, with older reports finding that 1% of transfusions are administered to children under the age of 18 years.[2] Separate reviews of blood utilization in the Netherlands and the United Kingdom have reported that pediatric patients (<16 years of age) were responsible for ~4% of red blood cell, 8% of plasma, and 14% of platelet (PLT) transfusions.[3-5] It has been reported that approximately one-half of all pediatric transfusions occur in patients less than 1 year old.[4,6] Of patients admitted to neonatal intensive care units, 18%-35% have at least 1 recorded PLT count of $<150 \times 10^9$/L, and this percentage increases to 73% in extremely low birth weight neonates.[7-10]

Although the safety of allogeneic blood transfusion is well documented, as with any medical procedure there is always a risk of adverse events. Several studies have found that transfusion reactions typically occur at a higher rate in pediatric patients than in adults. One study reported the rate of transfusion reactions in a pediatric population in France to be 10.7 per 1000 transfusions, compared with 2.5 per 1000 transfusions in adults.[11,12] Despite advances in donor screening and infectious disease testing, the risk of transfusion transmitted infections continues to be of particular concern; viral pathogens continue to be transmitted and there have been reports of the emergence of new pathogens, including those with an expanded geographic range such as West Nile, Zika, and Chagas. Although

CCI	Corrected count increment
INF	Infants age 0-12 months not admitted to the NICU
NICU	Neonatal intensive care unit
PED	Children age 1-18 years
PLT	Platelet
UV	Ultraviolet

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testing is often implemented for these emerging pathogens, the delay in implementing routine blood supply testing can lead to increased risk of infection in recipients.

At the present time the largest infectious threat posed by PLTs is bacterial contamination. PLT components may become contaminated via inoculation of the PLT unit with organisms that colonize the donor's skin or following asymptomatic donor bacteremia. Bacterial contamination of PLTs is responsible for ~10% of all transfusion-related deaths.[11] It is widely accepted that passive surveillance PLT cultures drawn early in storage (ie, prior to release from the blood center) is an important, but ultimately inadequate, mitigation strategy for the threat posed by bacteria in PLT concentrates.[13-15] The incidence of bacterially contaminated PLTs was reported to be 1 in 2881 at a large hospital blood bank that inoculated cultures from PLTs at the time of receipt (day 3 or 4).[15] Various strategies have been proposed to enhance the sensitivity of PLT cultures, including additional culture time points and larger sampling volumes. However, given the limited shelf life of PLTs, all culture-based approaches run the risk of transfusing a septic PLT unit prior to bacterial detection, and a standardized definition of what constitutes a "true positive" culture is lacking in the medical literature.[15,16] Although a point of release test for bacteria is marketed in the US (Verax Biomedical, Marlborough, Massachusetts), the sensitivity of a first-time test is estimated to be only 60%.[17,18]

To address these concerns, several pathogen reduction technologies, which destroy the infectious potential of bacteria, viruses, or parasites that may contaminate PLTs, are being studied.[19,20] One pathogen-reduced system for single donor PLTs, INTERCEPT Blood System (Cerus Corporation, Concord, California), has received Food and Drug Administration approval in the US for the treatment of thrombocytopenic adult and pediatric patients.[21] Another PLT system, MIRASOL pathogen-reduced T (Terumo BCT, Lakewood, Colorado), has been licensed in Europe since 2007 and is currently enrolling in a phase III clinical trial in the US (clinicaltrials.gov Identifier: NCT02964325). These PLT pathogen-reduced systems are based on the photoactivation of compounds that, following exposure to light, prevent the replication of DNA and transcription of RNA. The INTERCEPT system uses amotosalen (a psoralen) as the photosensitizing agent which, following exposure to ultraviolet (UV)-A light, crosslinks DNA bases.[22] The MIRASOL pathogen-reduced T system uses riboflavin (vitamin B2) and damages nucleic acid bases following UV-A/B light exposure.[22] A third system, Theraflex-UV (Macropharma, Tourcoing, France), uses UV-C light exposure without a photosensitizing agent for pathogen-reduced PLT production and is undergoing a phase III clinical trial in Europe.[22]

The clinical efficacy and long-term safety of these products has been a major focus throughout their development. Clinical trials of the products, largely focused on adult populations, have shown that transfusion of pathogen-reduced PLTs is frequently associated with a smaller post-transfusion increase in PLT count.[23] Some investigators have reported the hemostatic efficacy of pathogen-reduced products to be slightly inferior to conventional PLTs, but these have been in limited cohorts, which in some cases, did not enroll sufficient numbers to achieve the statistical power to identify significance.[24,25] However, most large studies, supported by systematic meta-analyses, have found the hemostatic efficacy of pathogen-reduced PLTs to be similar to that of conventional, nonpathogen reduced PLT products.[23,26,27] The few trials that have included pediatric patients have shown comparable rates of clinically significant bleeding and mortality in pediatric patients transfused with conventional or pathogen-reduced products, but with a higher PLT transfusion requirement in some studies.[23,28] Given the limited number of pediatric patients assessed in these studies, ongoing postmarket surveillance of the clinical efficacy and safety of pathogen-reduced PLTs is needed in the pediatric population.[29] Here, we present our findings from an ongoing safety monitoring and quality assurance assessment on the use of conventional and pathogen-reduced PLT products in pediatric patients at an academic tertiary care medical center.

Methods

Transfusion data were collected during routine clinical care and captured in our electronic health record and blood bank management systems, Epic (Epic Corporation, Verona, Wisconsin) and SoftBank (SCC Soft Computer, Clearwater, Florida), respectively. Data from these systems were integrated within our clinical data warehouse and data analysis platform.[30] Conventional PLTs received by our institution were manufactured by the American Red Cross (ARC, Farmington, Connecticut) or the Rhode Island Blood Center (RIBC, Providence, Rhode Island). Conventional PLTs were either leukoreduced single donor apheresis PLTs or leukoreduced whole-blood derived PLT pools. In addition to the primary bacterial cultures of PLT products performed by the blood centers during component manufacture, all conventional PLT products within our institution underwent additional microbial testing on storage day 5 using the PLT PGD test (Verax Biomedical) as an additional safety measure. Pathogen-reduced PLTs were manufactured in platelet additive solution C (PAS-C) by the ARC or collected in plasma by the RIBC. Both pathogen-reduced and conventional PLTs were deemed by our institution to represent the standard of care during the timeframe of this quality assurance review. As this review was done for ongoing safety monitoring and quality assurance, data were not collected for human subjects research purposes. Therefore, there were no explicit inclusion or exclusion criteria, other than recipient age and date of transfusion. PLTs were ordered and provided during routine clinical care, and, therefore, providers were not blinded to the PLT product type and no effort was made to randomize the type of product issued for a patient.

We evaluated data for all pediatric patients (≤18 years of age) receiving a PLT transfusion from November 2016 through July 2018. Patients were assigned to 1 of 3 groups:

neonatal intensive care patients (NICU), infants 0-12 months not admitted to the NICU (INF), and children age 1-18 years (PED). Each transfusion was assessed as an independent event and patient age was calculated at the time of each transfusion. The number of subsequent PLT or red cell doses transfused in the 48-hour period following each index conventional or pathogen-reduced PLT transfusion was calculated. Transfusions initiated within 2 hours of each index transfusion were excluded from these calculations, as these products likely would have been issued prior to assessing blood counts or response to transfusion.

Results shown represent the mean ± SD unless otherwise indicated. Boxplots in the figures represent the minimum, first quartile, median, third quartile, and maximum values. A 2-tailed Student *t* test was performed to assess for significance between pathogen-reduced and conventional products, with significance taken at $P < .05$. For those patients receiving multiple products, the time to subsequent PLT transfusion was calculated over the 48-hour time period following each index transfusion and density plots generated with a covariance factor of 0.2 using the Python SciPy library.

Transfusion reactions passively reported by primary clinical providers over the same time period were evaluated per the Centers for Disease Control and Prevention Hemovigilance Guidelines by a transfusion medicine physician.[31] Because of the Food and Drug Administration label for pathogen-reduced PLTs including a caution for the potential development of skin rashes in neonates receiving psoralen compounds and phototherapy, an attending neonatologist reviewed NICU charts to assess for possible skin reactions in patients undergoing concomitant PLT transfusion and phototherapy.

Results

Over the 21-month study (November 2016-July 2018), pathogen-reduced PLT inventory progressively increased, as did the number of pathogen-reduced products issued by the blood bank. By November 2017, pathogen-reduced PLTs were issued for a majority of transfusions for patients less than 18 years of age (Figure 1). A total of 240 patients under 18 years old received PLTs, and 1932 PLT transfusion events were recorded during this timeframe (Table I), which accounted for approximately 11% of all (pediatric and adult) PLT transfusions at our institution during this timeframe, consistent with previously published pediatric transfusion rates.[3-5] Approximately 61%, 67%, and 51% of transfusions provided to NICU, infant, and pediatric patients, respectively, were with pathogen-reduced products (Table I), with the remainder being conventional PLT products in either plasma or platelet additive solution.

An ongoing question related to the use of pathogen-reduced PLT products is whether additional transfusions are routinely administered to recipients of pathogen-reduced PLTs, because smaller increases in corrected count increment (CCI) have been noted with use of these products.[23] We assessed PLT utilization by calculating the number of additional PLT doses transfused in the 48-hour period after being given either a conventional or pathogen-reduced PLT product (Figure 2, A). As this was not a randomized clinical trial, this method was chosen because, over the period of the study, most patients who received multiple transfusions received a combination of both conventional and pathogen-reduced products, which prohibited analysis of patients receiving only a single type of product. Within the NICU population, a mean (±SD) of 1.0 ± 1.4 and 1.2 ± 1.3 subsequent PLT doses were issued after an initial conventional or pathogen-reduced product, respectively ($P = .29$). In the INF population (0-1 years old and not admitted to the NICU), 2.8 ± 3.0 and 2.6 ± 2.6 subsequent PLT doses were issued following an initial conventional and pathogen-reduced dose, respectively, which was not significantly different ($P = .57$). In the PED (1-18 years of

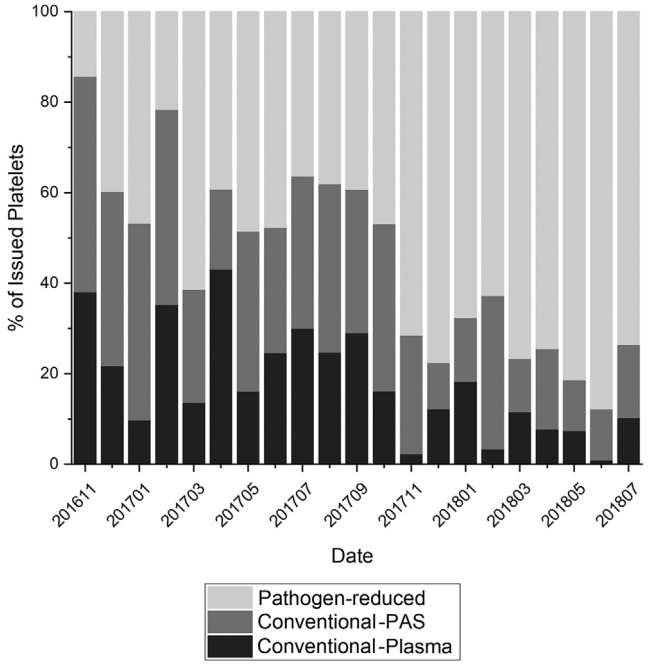

Figure 1. Frequency of conventional PLTs, in either plasma or platelet additive solution (PAS), and pathogen-reduced platelet units issued for all patients less than 18 years old over assessment period.

Table I. Total number of patients and transfusions between November 2016 and July 2018

Category	NICU	INF	PED	Total
Total patients	72	45	131	240
Total platelet transfusions	236	379	1317	1932
Conventional	91 (39%)	125 (33%)	644 (49%)	860 (45%)
Pathogen-reduced	145 (61%)	254 (67%)	673 (51%)	1072 (55%)

Groups include NICU, INF, and PED patients. Patient age was calculated at the time of transfusion, so total number of patients is less than the sum of each group, as patients may be listed in multiple age groups.

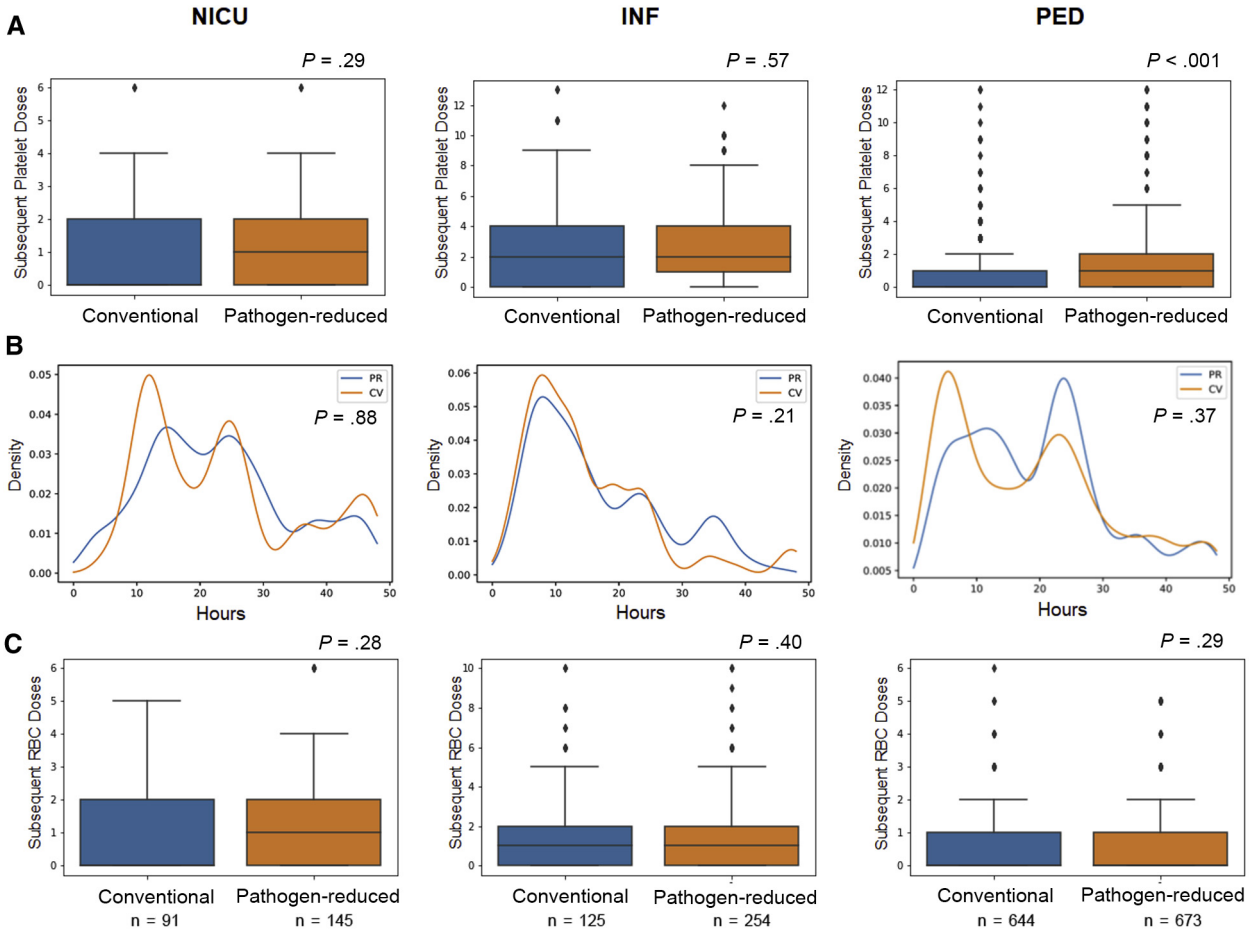

Figure 2. **A,** Subsequent platelet utilization in the 48-hour period following each conventional or pathogen-reduced platelet transfusion in NICU, INF, and PED populations. Boxplots represent the minimum, first quartile, median, third quartile, and maximum values for each category. **B,** Density plots demonstrating the hours to subsequent platelet transfusion in the 48-hour period following each index transfusion in NICU, INF, and PED populations receiving more than 1 transfusion in a 48-hour period. **C,** Subsequent red blood cell utilization in the 48-hour period following each conventional or pathogen-reduced platelet transfusion in NICU, INF, and PED populations.

age) population, a clinically small, but statistically significant difference was noted with a mean of 0.9 ± 1.6 and 1.4 ± 2.2 subsequent doses for conventional and pathogen-reduced products, respectively ($P < .001$). However, for patients receiving multiple PLT products within 48 hours, the time until the next PLT transfusion was similar ($P > .05$) in all age groups (Figure 2, B).

To determine whether the hemostatic efficacy of pathogen-reduced and conventional PLT products was similar, we used the number of red cell doses transfused in the 48-hour period following PLT transfusion as a proxy measurement for clinically significant bleeding, similar to previous analyses.[32] We found that NICU patients had a mean of 1.0 ± 1.3 and 1.1 ± 1.3 red cell doses issued ($P = .28$) following conventional or pathogen-reduced PLT transfusion, respectively (Figure 2, C). Similarly, the INF group had 1.8 ± 2.2 and 1.6 ± 1.9 red cell doses issued ($P = .40$) and the PED group had a mean of 0.5 ± 0.9 and 0.6 ± 1.0 ($P = .29$) red cell doses issued following conventional or pathogen-reduced PLT transfusion, respectively.

We also assessed the frequency and type of transfusion reactions for both conventional and pathogen-reduced PLT products during the study time period (Table II). We identified 10 passively reported transfusion reactions associated with PLT transfusion in all patients less than 18 years old during the period of our study. Only allergic and febrile nonhemolytic transfusion reactions were reported during the study period, with the number and type of transfusion reactions similar in each group. A total of 6 reactions over 860 transfusions (0.70%) were identified in patients receiving conventional PLT products, and 4 reactions over 1072 transfusions (0.40%) were reported in patients receiving pathogen-reduced PLT products. To assess whether the use of pathogen-reduced PLTs was associated with any reactions during the use of phototherapy, manual chart review was performed by an attending neonatologist on a subset of NICU patients receiving only pathogen-reduced PLTs (n = 29). Of these, 11 patients received concomitant phototherapy. No episodes of new rash were associated with concomitant use of phototherapy and transfusion of pathogen-reduced PLT products.

Table II. Transfusion reactions.

	Conventional		Pathogen-reduced	
Adverse reaction	NICU/INF	PED	NICU/INF	PED
Allergic	2 (0.93%)	1 (0.16%)	0 (0%)	2 (0.30%)
FNHTR	0 (0%)	3 (0.47%)	0 (0%)	2 (0.30%)
Total	2 (0.93%)	4 (0.62%)	0 (0%)	4 (0.59%)

FNHTR, febrile nonhemolytic transfusion reaction.
Similar rates and types of transfusion reactions were seen in patients transfused with either conventional or pathogen-reduced products. Number of reactions and rate based on total number of transfusion episodes for each population are shown.

Discussion

The use of blood products for the prophylaxis and management of bleeding patients remains a critical component of routine clinical care. Despite significant improvements in the screening of blood products for infectious agents, the risk of transfusion transmitted infections remains as one of the primary risks of blood transfusion.[11,33] Several approaches for pathogen-reduced have been developed to decrease this risk. In this study, we have added to the current literature by focusing specifically on the safety and hemostatic efficacy of pathogen-reduced PLT products in our pediatric and neonatal populations.

Prior work has shown that the use of pathogen-reduced can lead to decreased corrected count increments, possibly because of damage from either the inactivation process or because of the manipulation of the PLT product during inactivation.[22] Because of this, some studies have found that patients who receive pathogen-reduced products may be given more transfusions than patients who receive conventional products.[24,25,32] Consistent with this previous work, we found that PED patients had a small, but statistically significant, increase in the number of subsequent PLT doses issued when receiving pathogen-reduced products. As no significant difference was identified in either INF or NICU patients, and the time to subsequent transfusion was similar in all groups, our data suggest that the additional transfusion burden seen in younger patients receiving pathogen-reduced PLTs is small and, in our assessment, the benefit of pathogen-reduced likely outweighs this possible drawback.

Limitations of this study include that patients were not randomized to receive only conventional or pathogen-reduced products, that patients were able to receive multiple product types, and that although larger than previously published studies in pediatric pathogen-reduced use, the absolute study size remains relatively small.

A second concern given the potential decrease in CCI because of pathogen-reduced is the functional impact of these agents on PLT activity. Prior studies in adults have generally found that although post-transfusion PLT counts may be lower, the use of pathogen-reduced PLTs does not appear to cause an increase in clinically significant bleeding.[23,26,27,34] Furthermore, the Platelet Dose Study did not find that dose-related changes in CCI correlated with bleeding risk (the sole patient in that trial who died of hemorrhage was randomized to the highest dose platelet transfusion group).[35] However, children are known to be at higher risk of bleeding-related complications during medical treatment compared with adults, regardless of PLT count, and, thus, it is important to verify that no tendency toward bleeding was observed in our patients.[36] We assessed red cell transfusion patterns in the 48-hour period following PLT transfusion as a proxy for the assessment of hemostatic efficacy. Given the similar rates of red cell transfusion in patients receiving either conventional or pathogen-reduced PLTs, our data suggest that the use of pathogen-reduced PLT products in our pediatric patient cohort did not lead to increased episodes of significant bleeding that required supportive transfusion.

The safety of pathogen-reduced products has been demonstrated in many studies, but ongoing assessment is necessary to review for potential long-term effects, particularly in young patients. We found similar rates and types of reported transfusion reactions following transfusion with either conventional or pathogen-reduced products. Our manual review in the NICU population verified that there were no instances of new rash associated with pathogen-reduced PLT transfusion and the use of phototherapy. The lack of pathogen-reduced PLT-associated rashes was expected given that phototherapy devices approved for use in the US have a peak energy wavelength higher than the pathogen-reduced PLT label's recommended wavelength cut-off of 425 nm, and nearly all have a lower-end emission higher than the 375 nm wavelength cut-off where an interaction with psoralen would be of concern.[29,37,38] Although this quality assurance review was retrospective and observational, it provides a broad assessment of the use of pathogen-reduced PLT products in the clinical setting. Long-term follow-up in chronically transfused patients and assessment of this and other pathogen-reduced techniques in other blood products will require additional research. However, taken with the growing body of literature from clinical trials, these data support the safe use of pathogen-reduced PLTs in pediatric patients, including those who are critically ill. ■

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