Transfusion reactions in pediatric compared with adult patients: a look at rate, reaction type, and associated products

Fredrick D. Oakley,[1] Marcella Woods,[2] Shanna Arnold,[1,3] and Pampee P. Young[1,3]

BACKGROUND: The majority of reports on transfusion reactions address adult patients. Less is known about the types, incidence, and other clinical details of transfusion reactions in pediatric populations. Furthermore, to our knowledge, there have been no previous reports directly comparing these aspects between adults and pediatric patient populations to assess if there are differences.
STUDY DESIGN AND METHODS: Between the period of January 1, 2011, and February 1, 2013, all reported adult and pediatric transfusion reactions at Vanderbilt University Medical Center (VUMC) were evaluated by transfusion medicine clinical service. The information was subsequently shared with the hemovigilance database. Data provided to hemovigilance included age, sex, blood product associated with the reaction, severity of the reaction, and the type of transfusion reactions. These were collated with hospital and blood bank information system–acquired data on overall admission and product transfusion.
RESULTS: A total of 133,671 transfusions were performed at VUMC during the study period including 20,179 platelet (PLT) transfusions, 31,605 plasma transfusions, 79,933 red blood cell (RBC) transfusions, and 2154 cryoprecipitate transfusions. Over the same period, 108 pediatric and 277 adult transfusion reactions were recorded. This corresponds to an incidence of 6.2 reactions per 1000 transfusions within the pediatric (age < 21) population and an incidence of 2.4 reactions per 1000 transfusions within the adult population. In both adult and pediatric populations, transfusion reactions were most commonly associated with PLT, followed by RBC, and then plasma transfusions. Within the pediatric population, subset analysis identified multiple differences when compared to the adult population, including an increased incidence of allergic transfusion reactions (2.7/1000 vs. 1.1/1000, $p < 0.001$), febrile nonhemolytic transfusion reactions (1.9/1000 vs. 0.47/1000, $p < 0.001$), and hypotensive transfusion reactions (0.29/1000 vs. 0.078/1000, $p < 0.05$). Interestingly, while the reaction incidence was the same between sexes in adults, in pediatric patients, reactions were more common in male patients (7.9/1000 pediatric males vs. 4.3/1000 pediatric females, $p < 0.01$).
CONCLUSION: To our knowledge this is the first study to provide detailed comparisons of acute transfusion reactions to all blood products between pediatric and adult populations at a single institution and supported by a single transfusion service and culture. Collectively these data provide insight into pediatric transfusion reactions and demonstrate a general increase in the incidence of transfusion reactions within the pediatric compared to adult population.

Transfusions occur commonly in pediatrics, particularly preterm neonates, those with hematologic malignancies or disorders, and critically ill children in pediatric intensive care units.[1,2] In some high-risk intensive care populations, almost 5% of the pediatric patients receive at least one transfusion during the length of their stay.[3] Children are quite different from adults during growth and development and present a unique set of needs to be considered in therapeutic practice when determining product type, modification, dose, rate of delivery, and potential complications of transfusions. Yet data describing outcome and, in particular, transfusion complications within pediatrics are scarce.[1,3,4] Although the blood supply in the United States is safer than ever, the transfusion of blood and blood products is still associated with significant noninfectious risks.[5-7] In general, estimates of risk for pediatric patients for various types of acute transfusion reactions are assumed to be similar to adults, which may or may not be accurate.[5-7] Also lacking is information about noninfectious complications associated with specific blood components in pediatric populations. This information may be useful not only to clinicians as they balance the need for transfusion

ABBREVIATIONS: DSTR(s) = delayed serologic transfusion reaction(s); FNHTR(s) = febrile nonhemolytic transfusion reaction(s); HTR(s) = hypotensive transfusion reaction(s); PSI(s) = patient safety indicator(s); TACO = transfusion-associated circulatory overload; VUMC = Vanderbilt University Medical Center.

From the [1]Department of Pathology, Microbiology and Immunology and the [2]Department of Medicine, Vanderbilt University Medical Center; and the [3]Department of Veterans Affairs, Nashville, Tennessee.

Address reprint requests to: Pampee Young, MCN CC2217, 21st Avenue S, Nashville, TN 37232-2561; e-mail: pampee.young@vanderbilt.edu.

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with its risks, but also to provide to patients and their guardians so they are appropriately informed before signing consent.

In this study, we used hemovigilance reports to evaluate the incidence, type, and the associated blood product resulting in noninfectious transfusion reactions in both inpatient and outpatient areas. The study population is composed of patients from a large, academic pediatric hospital and compared to an adjacent and comparable adult patient population within the same institution. The list of reactions includes acute and delayed hemolytic transfusion reactions, febrile nonhemolytic transfusion reaction (FNHTR), allergic reaction, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), and isolated hypotension. Our objective is to provide data comparing the relative incidence of various transfusion reactions to all blood products in adults compared with pediatric patients to better inform providers and patient families of the relative likelihood of reaction with respect to both product and patient age.

MATERIALS AND METHODS

Cohort description

Between the period of January 1, 2011, and February 1, 2013, all reported adult and pediatric transfusion reactions at Vanderbilt University Medical Center (VUMC) were evaluated by transfusion medicine clinical service. VUMC (i.e., both adult and pediatric hospitals) follows a single blood administration policy, which includes aspects such as product verification, infusion guidelines (such as frequency of vitals and electronic charting requirements), nonemergent infusion rates, and signs and symptoms that require initiation of transfusion reaction workup. Institution-wide nurses are required to observe the transfusion closely for the first 5 minutes after product has entered the patient. Yearly training and competency around blood transfusion include video-based training that is uniform for both hospital and unit-specific training. Quarterly electronic audits of a defined number of transfusions (which includes the pediatric and adult hospital) are performed to evaluate proper charting of vital signs, volume transfused, and two-person verification by a centralized center for clinical improvement. In addition, the transfusion medicine service performs a quarterly observational audit of a small number of transfusions by following a product after issue from the blood bank until completion of the first 15 minutes of the infusion, including observing nurses obtaining and charting 15-minute vitals, both in the adult and in the pediatric hospital. These data are submitted to the medical center medical board annually. Categorization of the transfusion reactions was performed by the resident or trainee and attending on service in a team-based setting (which included input from the blood bank supervisor and quality manager) based on hemovigilance definitions. Per the hemovigilance protocol, the subset of reported transfusion reactions that fell outside the accepted definitions for transfusion reaction was reported as "other." The information was subsequently shared with the hemovigilance database. Data provided to hemovigilance included age, sex, blood product associated with the reaction, severity of the reaction, and the type of transfusion reaction. The pediatric population within the hemovigilance data was defined as all patients aged less than 21 years. The transfusion reaction data for this period were subsequently collated and obtained for analysis.

TABLE 1. Imputability designations of transfusion reactions

Imputability	Pediatrics (%)	Adult (%)
Definite	34.8	36.3
Probable	43.5	46.9
Possible	19.6	13.1
Not designated	2.2	3.7

Imputability for virtually all of the cases was reported to hemovigilance. Determinations were consistent with the suggested protocol. Imputability was categorized as "not applicable" for reactions designated as "other" or "unknown." In our analysis we incorporated all reactions including definite association, probable association, and possible association as well as those not otherwise given a designation. The distribution of imputability is outlined in Table 1, demonstrating that in more than 75% of cases in our data set were designated as either definitive or probable. Additionally, the breakdown of imputability is noted to be similar between the pediatric and adult populations.

Data set assembly

Unique blood product transfusions were identified within the pediatric and adult hospitals and VUMC during the study period. Blood product utilization for each type of blood product came from the Soft Blood Bank system. Patient demographics and patient volumes (inpatient and outpatient) were obtained from VUMC's Medipac system. Transfusions were attributed to our pediatric or adult hospitals according to the clinical care locations of treatment. Transfusions in both inpatient and outpatient settings were assessed. The number of inpatient discharges and number of completed outpatient appointments were used to calculate the inpatient and outpatient censuses.

Transfusion and facility details

VUMC includes a 600+ bed adult hospital that includes the region's only Level I trauma center as well as

TABLE 2. Transfusion and reaction rate

	Pediatric	Adult
Inpatient visits	28,702	77,624
Transfusions per 1000 inpatient visits	610/1,000	1,500/1,000
Reactions per 1000 inpatient visits	3.8/1,000	3.6/1,000
All visits	750,356	2,953,699
Transfusions per 1000 visits	24/1,000	39/1,000
Reactions per 1000 visits	0.15/1,000	0.094/1,000
Reactions per 1000 transfusion	6.16/1,000	2.38/1,000

large stem cell and solid organ transplant programs. In addition, we serve the adjacent 300+ bed children's hospital with the region's only Level IV neonatal intensive care unit, transplant program, and specialized cardiac surgeries. Pediatric patients are transfused in a weight-based manner, typically 10 to 15 mL/kg. Vanderbilt purchased 90% of all blood products during this time from the American Red Cross. All products were leukoreduced before storage. Platelet (PLT) products were all apheresis single-donor PLTs.

Statistical analysis

Statistical analysis of the data comparing all transfusion reactions, transfusion reaction subtypes, and transfusion reactions associated with specific blood products was performed with the chi-square test using a software package (Statistica, StatSoft, Tulsa, OK). Data are presented as rate of transfusion reactions per 1000 transfusions. Multivariable logistic regression analyses were performed to assess the association of age with each type of transfusion reaction. Variables included in the logistic regression model were age, sex, blood group, and transfusion product type. Age was assessed as both a continuous variable and a dichotomous variable (pediatric < 21 years old). All statistical analyses were performed at a two-tailed significance of 0.05. Logistic regression analysis was performed with statistical software (SPSS 22, IBM Corp., Armonk, NY).

RESULTS

Frequency and type of acute transfusion reactions in pediatric versus adult populations

A total of 335 transfusion reactions, 227 adult and 108 pediatric, were reported over the 25-month study period. Table 2 provides data on the number of inpatient visits and total visits for both the adult and the pediatric hospitals from which we calculated the overall reaction rate normalized to visits. There were a total of 28,702 unique discharges from the pediatric inpatient service and a total of 77,624 discharges from the adult inpatient service. On an outpatient basis there were 721,654 unique pediatric visits and 2,876,075 unique adult patient visits. Adult patients were more likely to receive a transfusion than pediatric patients both overall (approx. 1.6-fold) and in the inpatient setting (approx. 2.6-fold higher). The reaction rate, when normalized to inpatient visits, was virtually identical between adults and pediatrics but when reaction rate was normalized to total visits, the pediatric population exhibited an approximately 1.5-fold higher rate than the adult population. The types of reactions and their observed frequency are depicted in a pie graph (Fig. 1). Ten different types of transfusion reactions were observed in the adult population versus six types observed in the pediatric population (Fig. 1). Acute hemolytic, delayed serologic, transfusion-associated dyspnea, and TRALI reaction events were identified only in the adult population during the study period. Breakdown of the reported reactions revealed that allergic reactions were the most frequently reported and febrile nonhemolytic reactions were the second most frequent type in both populations (Fig. 1).

Implicated blood products in pediatrics versus adults

We further evaluated the incidence of reactions by blood product (Fig. 2). A total of 116,130 unique blood product transfusions were performed in the adult population and 17,541 blood product transfusions were performed in the pediatric population. Approximately 60% of these were red blood cell (RBC) transfusions, whereas plasma and PLTs each comprised approximately 30% of the transfusions for both adults and pediatrics. Cryoprecipitate contributed to less than 3% of transfusions. Within both the adult and the pediatric populations, transfusion reactions occurred with the highest rate with PLT transfusions followed by RBCs and then plasma. No transfusion reactions in either population were observed to be associated with cryoprecipitate. Comparison between the two age groups demonstrated that the pediatric patients had a significantly higher incidence of transfusion reactions associated with PLT ($p < 0.001$) and RBC ($p = 0.001$) transfusions, but had a similar incidence of plasma associated transfusion reactions (Fig. 2).

Reaction types in pediatrics versus adults by sex

The increased rate of transfusion reactions in pediatric patients is further affirmed when we calculated the rate per 1000 transfusions (6.2/1000 in pediatrics vs. 2.4/1000 in adults, $p < 0.001$; Fig. 3). Subgroup analysis revealed that the incidences of allergic transfusion reactions (2.7/1000 vs. 1.1/1000, $p < 0.001$), FNHTRs (1.9/1000 vs. 0.47/1000, $p < 0.001$), and hypotensive transfusion reactions (HTRs; 0.29/1000 vs. 0.078/1000, $p < 0.05$) were all significantly increased in the pediatric population compared to

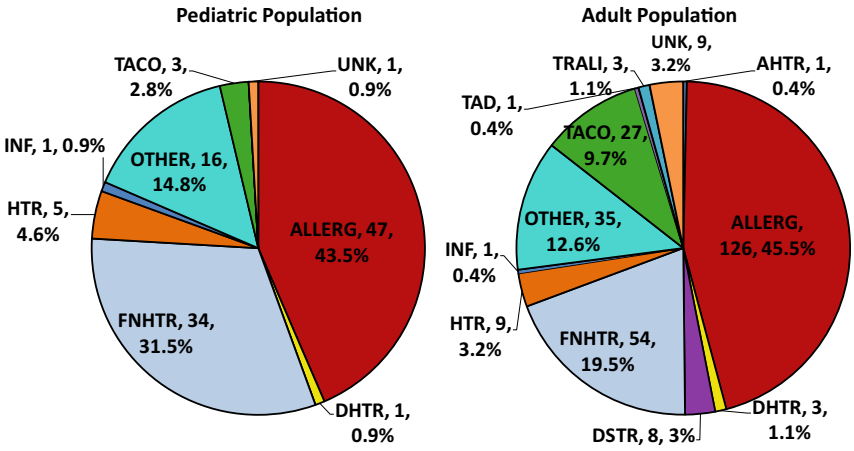

Fig. 1. Distribution of the observed transfusion reactions in the pediatric and adult populations. The proportion and types of transfusion reactions recorded in pediatric (ages 0-20 years) versus adult (age > 20 years) patient populations. Both the number of reactions and the percentage of the total it constitutes are provided under each reaction type. AHTR = acute hemolytic transfusion reaction; DHTR = delayed hemolytic transfusion reaction; INF = infectious culture positive product; TAD = transfusion-associated dyspnea; UNK = unknown.

the adult population (Fig. 3). Examination of severe and life-threatening transfusion reactions displayed no significant difference between the adult and pediatric populations (0.51/1000 vs. 0.32/1000, p = 0.28).

Interestingly, whereas transfusion reactions within the adult population occurred at similar rates between males and females (2.36/1000 vs. 2.42/1000), pediatric males had significantly more transfusion reactions compared to females (07.88/1000 pediatric male vs. 4.28/1000 pediatric female, p < 0.01) with males demonstrating a significantly higher incidence of FNHTRs (2.6/100 vs. 1.2/100, p = 0.047) and trending toward a higher incidence of allergic (3.3/1000 vs. 2.0/1000, p = 0.143) transfusion reactions (Fig. 4).

Next, we graphed the percentage of the major types of reactions with respect to age. The graphs reveal that HTRs are particularly common in infants and fall off markedly thereafter. As expected, delayed serologic transfusion reaction (DSTRs) are highly uncommon in pediatric populations. As one would anticipate, incidence of TACO is comparable in infants and adults but is infrequent in small children and adolescents (Fig. 5). Although we do not have data for total numbers of neonates (age, 0-120 days) transfused from our hospital records, our hemovigilance data identified seven unique transfusion reactions in neonates. In males we observed one allergic reaction (RBCs), two FNHTRs (RBCs), and two HTRs (1 RBC unit, 1 plasma unit). In females we observed one allergic reaction (RBC) and one HTR (plasma). It would have been of great interest to determine the percentage of these reactions with respect to the neonatal cohort as there is nothing reported specifically with respect to incidences to our knowledge for this age group.[8,9]

In addition, multivariable logistic regression analyses were performed to assess the correlation of age with each transfusion reaction type after adjusting for sex, blood group, and product type. Age was not significantly associated with any particular transfusion reaction type, whether it was treated as a continuous variable (p = 0.704) or a dichotomous pediatric variable (<21 years; p = 0.423; Table 3). Not surprisingly, our analysis showed that plasma and PLTs were significantly associated with an increased risk of allergic reaction compared to RBCs (plasma—p < 0.0001, odds ratio [OR] 11.3, 95% confidence interval [CI] 5.4-23.7; PLTs—p < 0.0001, OR 13.9, 95% CI 8.0-24.3; Table 3).

Finally, we performed a subgroup analysis and found that pediatric patients were five times less likely to develop allergic reaction from plasma compared to adults and relative to RBCs (OR, 2.5 vs. 13.3; Table 4). In fact, in pediatric patients, plasma is no more likely, statistically, to lead to allergic reaction than RBCs (Table 3; pediatric patients p = 0.338 vs. adult patients p < 0.0001). Furthermore, the subgroup analysis revealed that pediatric patients were almost two times more likely to develop allergic reaction from PLTs compared to adults and relative to RBCs (OR, 12.1 vs. 22.4; Table 4).

DISCUSSION

To our knowledge, this is the first study providing a direct comparison of all types of transfusion reactions between the pediatric and adult populations. A strength of this study is that it was performed at a single institution with one set of policies and physicians running the blood transfusion service. Therefore, this intrainstitution comparative study benefits by avoiding the inherent population limitations in regional exposures, values, population diversity, and variations in practice. Additionally, the retrospective use of hemovigilance data to evaluate types and frequency of transfusion reactions is likely much more accurate than relying on ICD-9 codes and is particularly powerful paired with hospital and blood bank information system containing data for admission and blood product usage, respectively.

This study appears to correlate well with the limited data published by other studies on transfusion reactions in the pediatric population.[2,10,11] A study to assess the

A

Transfusion product	Total Peds	Rxn	Peds rxn / 1000	Total Adult	Rxn	Adult rxn / 1000	P value
RBCs	10346	59	5.70	69387	129	1.86	<0.0001
PLTs	3363	38	11.3	16816	89	5.29	0.0001
Plasma	3341	5	1.50	28264	43	1.52	0.97
Cryo-precipitate	491	0	0	1663	0	0	—
Not recorded	—	6	—	—	16	—	—
Total	17541	108	6.16	116130	277	2.38	

B

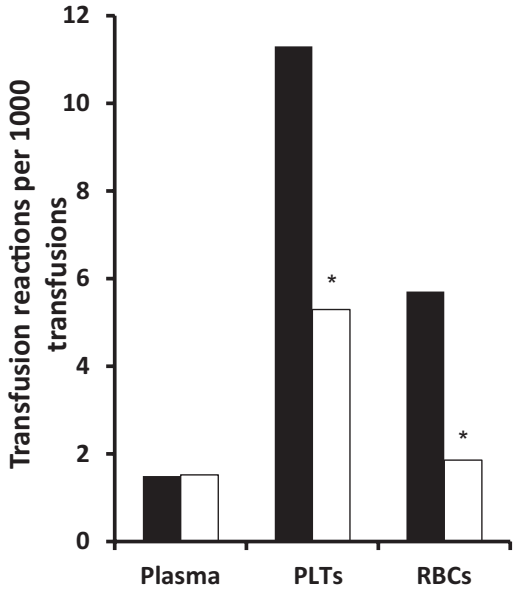

Fig. 2. PLTs and RBCs cause higher frequencies of transfusion reactions in pediatric patients. (A) Number of transfusions by product type and associated acute transfusion reactions. (B) Graph of rate of transfusion reactions associated with plasma, RBCs, and PLTs. Within both populations, transfusion reactions are most commonly associated with PLT transfusions. Compared to adults (□), pediatric patients (■) have a higher incidence of transfusion reactions after both PLT and RBC transfusions. *p < 0.001, chi-square test. Rxn = reaction.

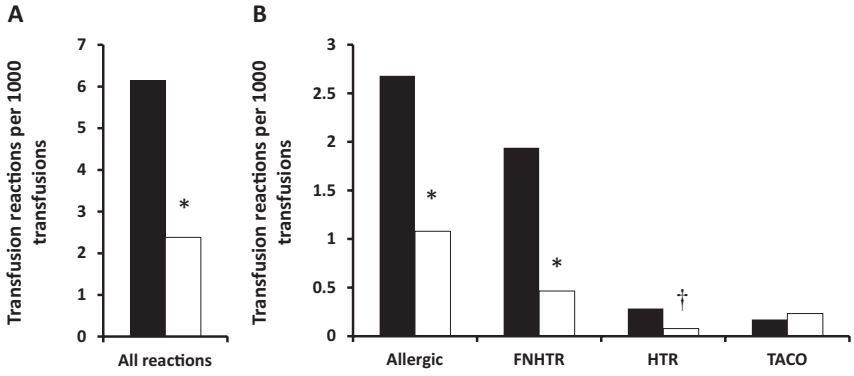

Fig. 3. Pediatric patients (■) have a significantly higher incidence of transfusions reactions compared to adult patients (□). (A) There was a 2.6-fold increase in the incidence of all transfusion reactions within the pediatric population (6.2/1000 vs. 2.4/1000). *p < 0.001 chi-square test. (B) Breakdown of specific categories of transfusion reactions demonstrated a significant difference in the incidence of allergic reactions (2.68/1000 vs. 1.08/1000), FNHTRs (1.94/1000 vs. 0.47/1000), and HTRs (0.29/1000 vs. 0.0078/1000) between the adult and pediatric populations. No significant difference was identified for TACO (0.17/1000 vs. 0.23/1000) transfusion reactions. *p < 0.001, †p < 0.05, chi-square test.

scope and clinical severity of medical errors included as key patient safety indicators (PSIs) by the Agency for Healthcare Research and Quality found that transfusion reaction was a common PSI event in children and those transfusion reactions associated with a PSI event resulted in a significantly longer length of stay and in hospital mortality.[4] By comparison, the report documented a rate of 0.17 per 1000 transfusion reactions per visit (pediatric inpatient plus pediatric outpatient visits), which is similar to the rate we observed of 0.15 per 1000 (Table 2). A second study involving 35 participating US hospitals found a higher reaction rate of 0.95% or a rate of 10.7 per 1000 units transfused.[3] More recently the types and severity of acute transfusion reactions occurring in a pediatric intensive care unit were reported to be much higher than general pediatric hospitalized population. Specifically, in the pediatric intensive care unit population, transfusion reactions occurred at a rate of 1.6% (16/1000) and consisted primarily (60%) of FNHTRs and minor allergic reactions or isolated hypotensive (24%).[12] By comparison, our rate for pediatrics was approximately six per 1000 transfused for pediatrics and comparable to the published rate for the hospitalized pediatric population. This pediatric rate was approximately threefold higher than the adult rate of approximately two per 1000 transfusions. Much of the published

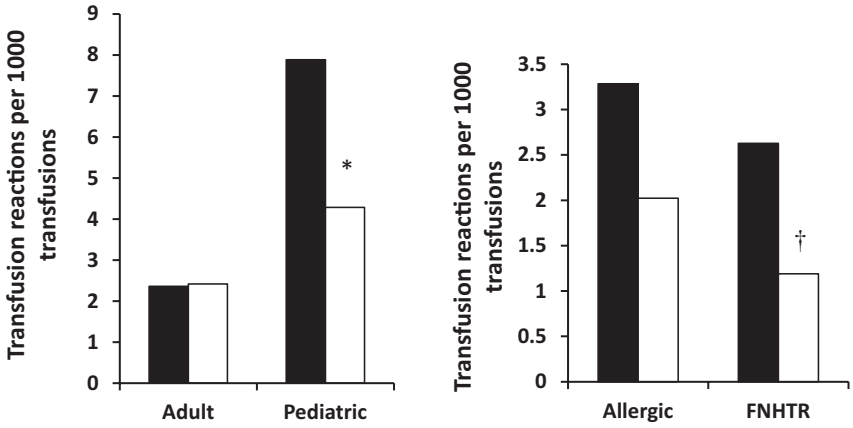

Fig. 4. Pediatric male patients (■) have higher incidence of transfusions reactions than female patients (□). (A) Within the adult population males and females exhibited a similar incidences of transfusion reactions. In the pediatric population males demonstrated an approximately 1.8-fold increase compared to the pediatric females. *p < 0.01 by chi-square test. (B) Allergic reactions were not significantly different between the sexes. However, FNHTRs were significantly higher in the pediatric male population (†p = 0.047, chi-squared test) compared to the pediatric female population, while no significant difference was observed within the adult population.

data describing rate and frequency of transfusion reactions in adults were obtained from countrywide hemovigilance data and, therefore, do not specifically segregate pediatric from adult data, although these numbers are often referenced as "adult" data since the majority of hospitalized patients are adults.[13-16] These data reference a range of approximately 2.5 to 3.3 in 1000.[15,16] Thus, by excluding the pediatric population, we think an additional benefit of our study is to provide a more accurate picture of the rate and frequency of acute transfusion reactions in the adult population.

Within the United States almost 200,000 blood product transfusions are provided to the pediatric population children each year.[17] This study has demonstrated that once the choice has been made to transfuse the rate of expected transfusion reaction in the pediatric population is almost three times as high as the adult population. More specifically, this increased rate is attributed to a higher rate of reaction associated with RBCs and PLTs. Conversely, the rates of transfusion reactions to plasma (and cryoprecipitate) were similar. While it is well accepted that both donor recipient- and product-specific factors modulate transfusion reactions,[18] the physiologic factors that resulted in increased susceptibility to transfusion reactions in pediatrics is not yet understood. The findings of this study will help both caretakers and families of children make an informed decision regarding risks when considering the option of a transfusion.

Breakdown of transfusion reactions by type demonstrated that the majority of increased transfusion reactions associated with pediatric transfusions were classified as allergic or FNHTR. FNHTR rates in adults at our institution (0.465/1000) are comparable to those published for adults after leukoreduction (0.6/1000).[19] With either our own institutional or the published data for the adult rate, the rate of FNHTR in pediatrics was more than threefold higher. The rate of allergic reactions in pediatrics was more than 2.5-fold higher than adults. Of note, our institution does not require that mild allergic reactions consisting of solely urticaria be submitted as a formal transfusion reaction; this is consistent with hemovigilance guidelines that do not require recording mild allergic reactions. Thus, our analysis underestimates allergic reactions in both adult and pediatric populations by under reporting mild urticarial reactions. Our data also demonstrated a significant increase in HTRs within the pediatric population that on further analysis was primarily seen in children between 0 and 1 year of age. No significant difference was observed within the other categories of transfusion reaction; however, given the paucity of these reactions within the data set analyzed no definitive conclusions may be reached.

In the comparison of severe and life-threatening reactions nine events were recorded within the pediatric population and 37 were observed within the adult population. Chi-square analysis was nonsignificant. Therefore, while the rate of transfusion reactions observed overall is 2.6 times as high in the pediatric population, our data suggest that severe reactions occur with similar rates between the two populations or at most there is a trend toward a slight increase in the pediatric population (0.51/1000 vs. 0.32/1000, p = 0.28).

In published reports, the rate of transfusion reactions within the adult population in male and female patients was similar to previously published studies.[13] We expected to see a similar comparison in the pediatric population; however, unexpectedly we observed a significantly higher rate of transfusion reactions in the male pediatric patients. This pattern was significant overall ($p < 0.01$) in the pediatric males as well as for those who experienced a FNHTR ($p = 0.047$). The reasons for these findings are unknown. For both sexes the standard of care is the same both at the clinic level as well as in regard to blood product transfusion practices. It would be beneficial to repeat this study at another institution to gain greater confidence in these findings.

In conclusion, acute transfusion reactions occur at a rate of 2.6 times those seen in adults per unique

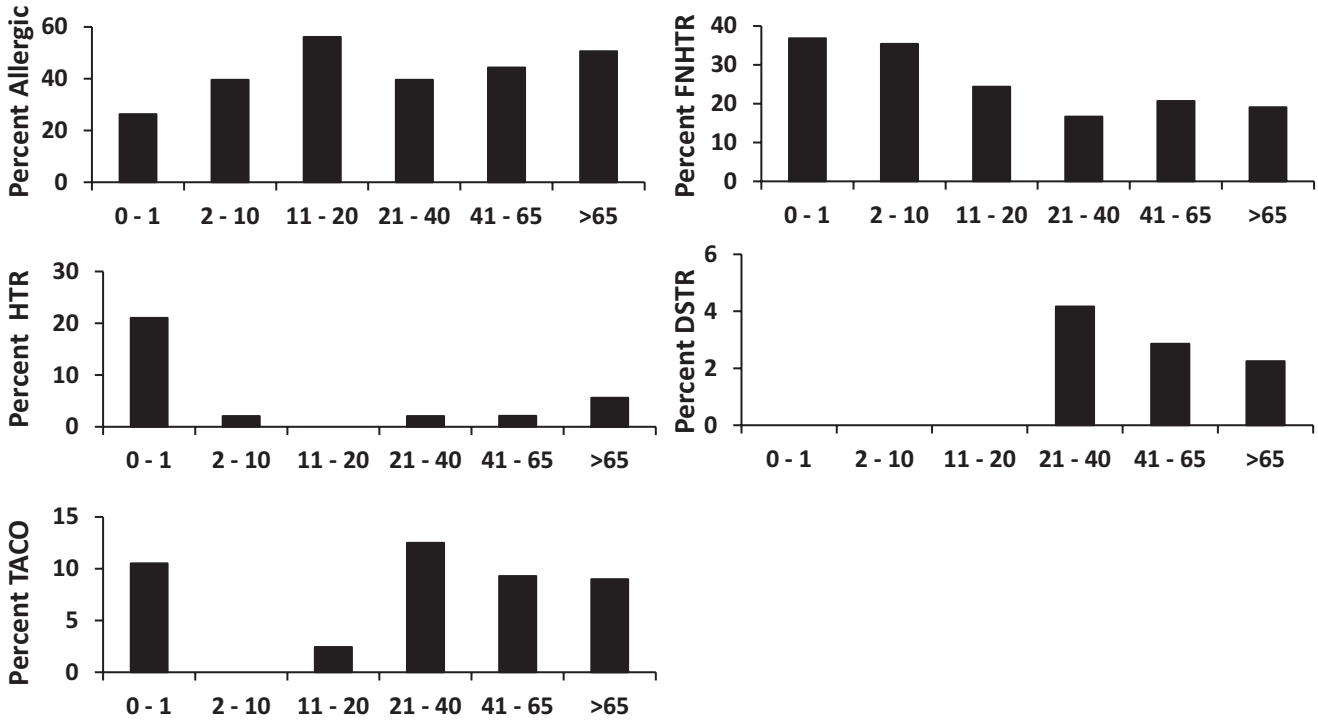

Fig. 5. Transfusion reaction trends between different age groups. Of the reported transfusion reactions, there were 19 within the 0- to 1-year age group, 48 within the 2- to 10-year age group, 41 within the 11- to 20-year age group, 48 within the 21- to 40-year age group, 140 within the 41- to 65-year age group, and 89 within the over 65-year age group. No trends based on age reached the level of significance as assessed by logistic regression analysis.

TABLE 3. Logistic regression: contribution of age to allergic transfusion reaction

	Significance	OR	95% CI
Age (years)	0.704	1.002	0.992-1.012
Sex (ref. female)	0.329	1.291	0.773-2.157
Blood group	0.875	1.007	0.920-1.103
Product type (ref. RBCs)			
RBCs			
Plasma	<0.0001	10.333	4.906-21.763
PLTs	<0.0001	13.711	7.887-23.835
Pediatric (dichotomous)	0.423	1.264	0.713-2.240
Sex (ref. female)	0.366	1.268	0.758-2.123
Blood group	0.872	1.008	0.920-1.104
Product type (ref. RBCs)			
RBCs			
Plasma	<0.0001	11.267	5.353-23.717
PLTs	<0.0001	13.929	7.995-24.267

TABLE 4. Logistic regression: pediatric subgrouping and allergic transfusion reaction

	Significance	OR	95% CI
Adults			
Sex (ref. female)	0.146	1.561	0.856-2.847
Blood group	0.842	1.011	0.907-1.127
Product type (ref. RBCs)			
RBCs			
Plasma	<0.0001	13.332	5.797-30.664
PLTs	<0.0001	12.122	6.236-23.562
Pediatric			
Sex (ref. female)	0.396	0.637	0.226-1.801
Blood group	0.787	1.026	0.854-1.231
Product type (ref. RBCs)			
RBCs			
Plasma	0.338	2.548	0.376-17.257
PLTs	<0.0001	22.437	7.404-67.998

transfusion event. Adults do, however, receive more transfusions and in our study, both adults and pediatric patients had a similar rate of severe or life-threatening transfusion reactions.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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