

Acute transfusion reactions in the pediatric intensive care unit

France Gauvin, Jacques Lacroix, Pierre Robillard, Hélène Lapointe, and Heather Hume

BACKGROUND: Acute transfusion reactions (ATRs) are probably underdiagnosed in critically ill children because associated symptoms can frequently be attributed to the patient's underlying disease. This study was undertaken to determine the incidence, type, imputability, and severity of ATRs observed in a tertiary care pediatric intensive care unit (PICU).

STUDY DESIGN AND METHODS: All transfusions of labile blood product administered to consecutive patients admitted to our PICU, between February 2002 and February 2004, were prospectively recorded. For each transfusion, the bedside nurse recorded the patient's status before, during, and up to 4 hours after the transfusion, as well as the presence of any new sign or symptom suggesting an ATR. Three independent experts retrospectively reviewed all transfusion event reports and hospital charts. The presence, type, imputability, and severity of ATRs were adjudicated by consensus of two of three experts (Delphi method), with predefined criteria.

RESULTS: A total of 2509 transfusions were administered to 305 patients during the study. Forty transfusion events (1.6%) were confirmed to be ATRs by expert consensus: 24 febrile nonhemolytic, 6 minor allergic, 4 isolated hypotension, 3 bacterial contamination, 1 major allergic (anaphylactic shock), 1 TRALI, and 1 hemolytic reaction. Imputability of ATRs was probable or possible in 35 cases (88%). ATRs led to an immediate vital threat in 15 percent of cases.

CONCLUSION: Improved surveillance of transfusions given to PICU patients and better knowledge of these reactions by health care professionals should improve the safety of transfusions in the PICU.

Transfusion of blood products is often necessary and beneficial for critically ill patients. Nevertheless, transfusion can lead to serious adverse effects. Transfusion reactions can occur rapidly after transfusion (e.g., hemolytic reaction) or many days and/or weeks after transfusion (e.g., graft-vs.-host disease). By definition, acute transfusion reactions (ATRs) occur within 24 hours of transfusion administration,¹ although most occur during or within 4 hours after the end of a transfusion.²⁻⁴ The list of ATRs includes several different reactions, each having a different etiology, clinical presentation, and severity. Recognized ATRs include acute hemolytic reaction, febrile nonhemolytic reaction (FNHR), bacterial contamination, allergic reaction (minor and major), transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload, and isolated hypotension.^{2,5}

Recent reports, mostly addressing adult patients, estimate that ATRs occur in 0.2 percent to 10 percent of blood transfusions^{2,5-8} and are responsible for death in approximately 1 per 250,000 units.² There are few published stud-

ABBREVIATIONS: ATE(s) = adverse transfusion event(s); ATR(s) = acute transfusion reaction; CRF(s) = case report form(s); FFP = fresh-frozen plasma; FNHR(s) = febrile nonhemolytic reaction(s); HNF = Hemovigilance Network in France; HSCT = hematopoietic stem cell transplantation; PICU = pediatric intensive care unit; PLT = platelets; QHS = Quebec Hemovigilance System; RBC = red blood cells; SHOT = Serious Hazards of Transfusion; TRALI = transfusion-related acute lung injury.

From the Intensive Care Unit, Department of Pediatrics, and the Hematology Department, Sainte-Justine Hospital, University of Montréal, Montréal, Québec; and INSPQ, Hemovigilance Research Unit, Department of Epidemiology, Biostatistics and Health Care, McGill University, Montréal, Québec, Canada.

Address correspondence to: France Gauvin, MD, Service des Soins Intensifs, Room 3406, Hôpital Ste-Justine, 3175 Côte Ste-Catherine, Montréal, Québec, Canada H3T 1C5; e-mail: france_gauvin@ssss.gouv.qc.ca.

Research project supported by the Fond de Recherche en Santé du Québec.

Received for publication February 17, 2006; revision received March 22, 2006, and accepted March 27, 2006.

doi: 10.1111/j.1537-2995.2006.00995.x

TRANSFUSION 2006;46:1899-1908.

ies evaluating incidence and type of ATRs in pediatric patients. Most pediatric studies consist of case reports⁹⁻¹⁶ whereas larger studies evaluate only specific transfusion reactions associated with specific blood products.¹⁷⁻¹⁹ Other studies reporting ATRs in children do not evaluate specifically the pediatric population and involve mostly adult patients.^{6,20-26}

Hemovigilance programs such as the Quebec Hemovigilance System (QHS) in Canada, Serious Hazards of Transfusion (SHOT) in the United Kingdom, or the Hemovigilance Network in France (HNF) publish annual reports of adverse events associated with blood transfusion.^{7,27,28} These reports include very few pediatric cases and do not specify whether patients were transfused in intensive care units. Moreover, it is probable that not all incidents are reported to these systems²⁸ because reporting is done on a voluntary basis.

Critically ill patients receiving transfusions are often unstable and can therefore present signs and/or symptoms compatible with ATRs during or after transfusion. Thus ATRs may be underdiagnosed in these critically ill children, with signs and symptoms being attributed to the patient's underlying disease.

The primary objective of this prospective epidemiologic study was to determine the incidence, type, imputability, and severity of ATRs in the PICU. Secondary objectives were: 1) to compare characteristics of transfused PICU patients with and without ATRs and 2) to determine mortality rates in transfused PICU patients.

MATERIAL AND METHODS

Study site

The PICU of Sainte-Justine Hospital is a multidisciplinary 22-critical-care-bed unit, serving both medical and surgical specialties and based in a tertiary-care university-affiliated pediatric hospital. Premature infants and neonates are not admitted to the PICU, unless they require cardiac surgery or were discharged home before admission to the PICU.

Study population

All consecutive patients admitted to the PICU, from February 25, 2002, to February 25, 2004, were followed prospectively for the full duration of their PICU stay. All patients who received at least one transfusion were included in the analysis.

Transfusions

All transfusion of labile blood products (red blood cells [RBC], platelets [PLTs], fresh-frozen plasma [FFP], cryoprecipitate, granulocytes, or reconstituted whole blood) administered to PICU patients during the study period were evaluated. Fractionated or recombinant products

(albumin, immunoglobulins, factor concentrates, etc.) were not evaluated.

A transfusion was defined as a single transfusional episode of any blood component, without regard to volume. For example, transfusion of a pediatric RBC pack, a PLT or cryoprecipitate pool, or a unit of reconstituted whole blood was considered one transfusion.

All RBCs and PLTs given during the study period were prestorage leukoreduced, as is standard care in Canada. The majority of RBC units were stored in an additive solution (AS-3) although some were CPDA-1 units. The large majority of PLTs were single units or pools (according to patient size) of whole blood-derived PLTs, as opposed to platelet pheresis units. Diversion of the first milliliters of blood at the time of donation and bacterial detection of PLT product had not yet been instituted by Quebec blood suppliers at the time of this study.

Clinical data

Transfusion data. Each transfusion given to any patient during the entire PICU stay was recorded on a case report form (CRF), completed by the bedside nurse administering the transfusion. The CRF was delivered with the blood product to the PICU. All nurses were informed to fill a CRF for each transfusion given. To be considered for analysis, the CRF had to be filled completely and signed by the nurse. Incomplete or unsigned CRF were rejected.

The following data were collected in each CRF: 1) type of blood product transfused, serial number of blood product transfused, time at the start and end of the transfusion; 2) patient's vital signs (oxygen saturation, respiratory rate, heart rate, blood pressure, and temperature) before, during, and up to 4 hours after each transfusion; and 3) any new sign(s) and/or symptom(s) occurring during and up to 4 hours after each transfusion: fever (defined as an increase in temperature $\geq 1^{\circ}\text{C}$ with a temperature at least $\geq 38.5^{\circ}\text{C}$), chills, dyspnea and/or hypoxemia (drop of saturation of 5%-10% for >2 min), rash and/or pruritus, pain (lumbar, thoracic, headache), anxiety and/or agitation, hypotension (drop of systolic or diastolic arterial pressure of at least 20 mmHg), hypertension (increase of systolic or diastolic arterial pressure of at least 20 mmHg), or red-colored urine (suspicion of hemoglobinuria). For each transfusion, the bedside nurse was required to indicate that either one or more of these signs and/or symptoms occurred or that no new sign and/or symptom was observed. Time of occurrence of sign(s) and/or symptom(s) was also specified. Each time one of these sign(s) and/or symptom(s) occurred, it was reported as a "transfusion event."

Patient data. The following clinical data were recorded for each transfused patient: age, sex, admission specialty, and mortality during PICU stay.

Management of transfusion event

A protocol was applied in the occurrence of a transfusion event. The transfusion was stopped and the medical staff was informed. An algorithm was provided on how to proceed with clinical and laboratory investigation (verification of the identification of the patient and blood product, blood culture from patient, culture from the blood product, direct antiglobulin test, as appropriate). Treatment was given to the patient, depending on the transfusion event, as deemed appropriate by the attending physician. The transfusion was restarted only in cases of isolated rash. For all other types of "transfusion event," the blood product was returned to the blood bank. If the sign(s) and/or symptom(s) occurred after the end of the transfusion, the blood bank was immediately informed and the investigation was initiated.

Diagnosis of ATR

The final diagnosis of ATR was adjudicated a posteriori by three experts (FG, HH, JL) who independently reviewed the CRFs of all transfusion events reported by the nurses, as well as the corresponding patient charts and laboratory

data. Based on predefined criteria and definitions (Tables 1 and 2), the experts reported independently, on an adjudicating form, their opinion as to whether or not the reported transfusion event represented an ATR. If an ATR was considered by the expert to be present, he or she had then to determine its type, imputability, and severity. Diagnosis was confirmed by the adjudicating process (Delphi method) with a consensus of two of three experts.²⁹

Data collection

Comprehensiveness of the CRF was verified before the study through a pilot study with 60 transfusions. The CRF was modified according to nurses' and/or physicians' comments obtained during this pilot study. Data collection entry was done at the end of the study by FG and was then validated by a second person (research assistant).

Statistical analysis

Results of descriptive statistics are expressed as a fraction of the total population (%), mean $\pm$ standard deviation

TABLE 1. Definitions and diagnostic criteria* of ATRs

Hemolytic reaction

Accelerated destruction of RBCs because of mismatch between the donor and the recipient⁵ or because of a nonimmune mechanism (mechanical hemolysis)

S/S: fever, chills, headache, nausea, pain, hypotension, anxiety

Tests: hemoglobinuria, hemoglobinemia, positive DAT

Febrile nonhemolytic reaction

Fever that cannot be explained by the patient's underlying condition or another type of ATR, attributed to the recipient's antibodies binding to donor's white blood cells and/or the accumulation of biologic response modifiers (complement, lipids, cytokines) in the blood product^{2,35,36}

S/S: fever, chills, headache, flushing, nausea, tachycardia

Minor allergic reaction (urticaria)

Cutaneous manifestation, without any systemic symptoms, due to a Type 1 hypersensitivity reaction³⁷

S/S: rash, pruritis

Major allergic reaction (anaphylaxis)

Systemic manifestations due to a Type 1 hypersensitivity reaction³⁷

S/S: dyspnea, stridor, wheezing, hypotension, nausea, vomiting, diarrhea, flushing, angioedema, shock

Bacterial contamination

Contamination of the blood product resulting in infection in the recipient, due to infection of the donor (underlying condition), skin flora introduced at the time of phlebotomy, or contamination during blood product processing⁵

S/S: fever, chills, dyspnea, tachycardia, hypotension, shock

Tests: positive culture (patient and/or blood product)

TRALI

Acute lung injury caused by the transfusion of a any blood product containing plasma³ attributed to reaction between the donor (presence of antibodies) and the recipient (priming of neutrophils)^{20,38}

S/S: dyspnea, hypoxemia, hypotension, tachycardia, fever

Tests: diffuse infiltrate on chest X-ray

Transfusion-associated circulatory overload

Respiratory distress due to circulatory overload causing congestive heart failure and acute pulmonary edema⁵

S/S: dyspnea, hypoxemia, headache, hypertension, high central venous pressure

Tests: pulmonary edema on chest X-ray

Isolated hypotension

Isolated hypotension probably due to generation of bradykinin in specific circumstances (negatively charged filters, use of angiotensin conversion enzyme inhibitor or abnormal bradykinin metabolism)²

S/S: sudden hypotension, flushing

* Diagnostic criteria: one or more of the following sign(s) and symptom(s) (S/S), occurring during or within 4 hours after transfusion and/or laboratory test when appropriate.

TABLE 2. Definitions of imputability and severity of ATR

Imputability

Definite: Clinical or biologic event occurring during or within 4 hr after the transfusion and for which the investigation (laboratory test, clinically evident signs and/or symptoms) supports the transfusion as the cause. For bacterial contamination: same bacteria identified in the recipient and the blood product.

Probable: Clinical or biologic event occurring during or within 4 hr after the transfusion and for which there is no other cause. For bacterial contamination: positive culture of blood product and negative blood culture of recipient or no blood culture done in recipient.

Possible: Clinical or biologic event occurring during or within 4 hr after the transfusion and for which another condition could be the cause (underlying disease, medication). For bacterial contamination: culture of blood product negative and blood culture of recipient positive, if nothing else than the transfusion can explain this result.

Questionable: Clinical or biologic event occurring during or within 4 hr after the transfusion and for which another condition is more likely to be the cause, or there is presence of contradictory data. For bacterial contamination: culture of blood product is positive but strong suspicion that this result is due to contamination during sampling or in the microbiology laboratory.

Severity

Death: patient died during the transfusion or within 7 days of the transfusion (or later if imputability of transfusion is definite).

Immediate vital threat: patient required aggressive treatment following the transfusion (fluids, vasopressors, intubation and/or ventilation, increased therapeutic measures).

Long-term morbidity: patient suffered important sequelae.

No threat: any reaction considered minor, i.e., without significant immediate or long-term morbidity.

(SD), and median (range). The incidence rate of ATRs was calculated as follows: total number of ATRs (numerator) per total number of transfusions for which a case report was received (denominator). The total number of transfusions administered in the PICU during the study period is unavailable because the blood bank does not hold records of specific medical units where blood products are sent. Thus, the denominator reflects the number of transfusions recorded on CRF and not necessarily all transfusions administered in the PICU. Continuous variables were compared with a *t* test; categorical variables were compared using the chi-square statistic. Results were considered significant with a *p* value of less than 0.05. All statistical analyses were done with computer (SPSS 13.0 for Windows, SPSS Inc., Chicago, IL).

Ethical approval

Scientific and ethical approval for this study was obtained from the institutional review board (Ethics Committee) of the Sainte-Justine Hospital Research Center. Owing to the observational nature of this study, the institutional review board did not require that informed consent be obtained.

RESULTS

Transfusion data

The number of transfusions recorded on CRF during the study was 2570 (Fig. 1). Sixty-one CRFs were rejected from analysis for the following reasons: 4 reported on the administration of intravenous immunoglobulins, 14 were incomplete, and 43 were not signed. No CRF with a "transfusion event" was present in these 61 exclusions. Thus, a total of 2509 transfusions were analyzed in the study. Characteristics of these transfusions are shown in Table 3. There were three autologous donations and no directed donation in this cohort.

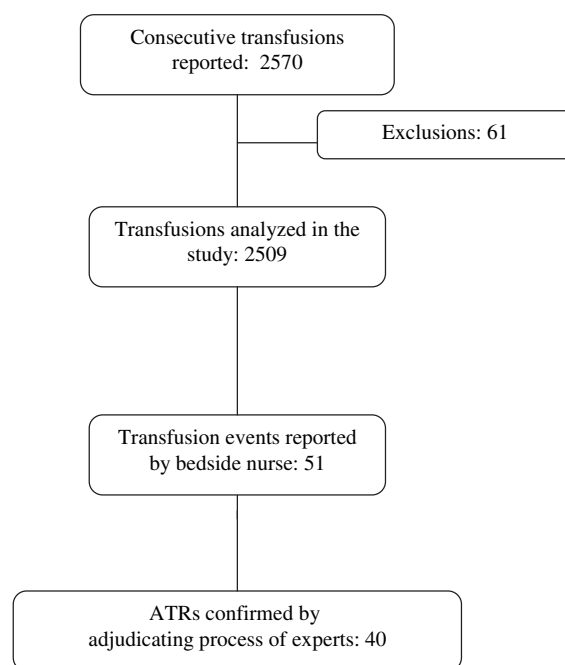


Fig. 1. Diagram of transfusions included and analyzed in the study.

Blood products transfused were mostly RBCs (35%), PLTs (31%), and FFP (32%). Transfusions were mostly used in general pediatrics (32%), cardiac surgery (29%), and hematooncology (20%).

Transfusion events

Among the 2509 transfusions evaluated, occurrence of new sign(s) and symptom(s) was reported by the bedside nurses in 51 transfusions, corresponding to 51 transfusion events. There was more than one sign(s) and/or symptom(s) in 28 of 51 transfusion events (55%). Frequency of

sign(s) and/or symptom(s) were (number; %): fever (30; 59%); chills (11; 22%); hypotension (7; 14%); rash and/or pruritus (6; 12%); dyspnea and/or hypoxemia (5; 10%); hypertension (4; 8%); hemoglobinuria (2; 4%); and anxiety and/or agitation (1; 2%). Signs(s) and symptom(s) occurred on average $1:28 \pm 1:17$ hours after the beginning of transfusion (median, 1:00 hr; range, 0:05-5:05 hr).

ATRs

Among the 51 transfusions events reported, 40 ATRs were confirmed by expert consensus, resulting in an ATR incidence rate of 1.6 percent (40 ATR/2509 transfusions). Results of expert consensus on the type of ATR, as well as imputability and severity, are shown in Table 4. The types of ATRs were 24 FNHRs, 6 minor allergic reactions (urticaria), 4 isolated hypotension reactions, 3 bacterial

contaminations, 1 major allergic reaction (anaphylactic shock), 1 TRALI, and 1 hemolytic reaction. Imputability of ATRs was mostly probable (55%) or possible (33%). ATRs presented an immediate vital threat in 15 percent of cases; all other cases were considered minor. Details on ATRs that represented an acute vital threat to the patients are shown in Table 5. The bacterial contamination was due to *Stomatococcus mucilaginosus*, which was found in the plasma aliquot (in a syringe) administered to the patient and in the original bag of plasma. The patient was not neutropenic. Fluid bolus was required to control hypotension. The patient who presented a major allergic reaction was known to have a congenital factor XII deficiency. Immunoglobulin A deficiency was ruled out. The patient was treated with fluid bolus, increased inotropes, and increased oxygen. The patient who had a TRALI required noninvasive mechanical ventilation with increased oxygen for approximately 48 hours. Of the three hypotensive reactions, two occurred in the same patient. No patient was on ACE inhibitors before the reaction and no bedside leukoreduction filters were used. All patients required a fluid bolus to control the hypotension.

All 40 ATRs occurred with RBCs (48%), PLTs (40%), or FFP (12%); none occurred with granulocytes, cryoprecipitate, or reconstituted blood (Table 3). No autologous donation was implicated in ATRs. Most ATRs occurred in two specialties: hemato-oncology (52.5%) and cardiac surgery (20%). Duration of transfusion was similar between transfusions with and without reaction ($p = 0.17$). Overall, 2.2 percent of RBCs, 2.1 percent of PLTs, and 0.6 percent of FFP were involved in ATR.

Patient data

A total of 1753 consecutive patients were admitted to the PICU during the 2-year period. Of these patients, 305 (17.5%) received at least one transfusion of labile blood products. Characteristics of transfused patients are shown in Table 6. The mean age of transfused patients was 65.5 ± 77.8 months. Transfused patients received on aver-

TABLE 3. Characteristics of transfusions

Data*	All transfusions (n = 2509)	Transfusions with reaction (n = 40)
Type of blood product†		
RBC	872 (35)	19 (48)
PLTs	778 (31)	16 (40)
FFP	791 (32)	5 (12)
Cryoprecipitate	63 (2.8)	0 (0)
Granulocyte	2 (0.1)	0 (0)
Reconstituted blood	3 (0.1)	0 (0)
Admission specialty†		
General pediatrics	795 (32)	2 (5)
Cardiac surgery	720 (29)	8 (20)
Hematooncology	511 (20)	21 (52.5)
Gastrohepatology	349 (14)	6 (15)
General surgery	59 (2)	0 (0)
Cardiology	32 (1)	1 (2.5)
Orthopedics	23 (1)	1 (2.5)
Others	20 (1)	1 (2.5)
Duration of transfusion (hr)	$1:57 \pm 1:10$	$1:41 \pm 1:14$

* Data are presented as number (%) or mean $\pm$ SD.
† The percentage represents the frequency of variable/total number of transfusions per column (number).

TABLE 4. Description of type, imputability, and severity of ATRs, as confirmed by expert consensus (adjudicating process)

Types of ATRs (number)	Imputability of ATR				Severity of ATR			
	De	Pr	Po	Qu	Death	AVT	LTM	NT
Febrile nonhemolytic (24)		12	11	1				24
Minor allergic (6)	2	4						6
Isolated hypotension (4)		4				3		1
Bacterial contamination (3)	1	2				1		2
Major allergic (1)	1					1		
TRALI (1)			1			1		
Hemolytic reaction (1)			1					1
Total (40)	4	22	13	1	0	6	0	34

Abbreviations: De = definite; Pr = probable; Po = possible; Qu = questionable; AVT = acute vital threat; LTM = long-term morbidity; NT = no threat.

TABLE 5. Details of ATRs representing an acute vital threat to recipients

ATR	Age (years)	Primary diagnosis/admission diagnosis	Blood product	Signs and/or symptoms	Transfusion duration (min) before symptoms occurred
Bacterial contamination	2	Cirrhosis/liver transplantation	FFP	Fever ($\uparrow$ 2.4°C), $\downarrow$ BP 20 mmHg	120
Major allergic	17	Cardiopathy/mitral valve replacement	RBC	$\downarrow$ BP 20 mmHg, erythrodermia, dyspnea	30
TRALI	17	Alagille syndrome after liver transplantation/upper GI bleeding	RBC	Dyspnea, desaturation ($\downarrow$ 82%), $\downarrow$ BP 10 mmHg	60
Hypotensive*	14	LAL after HSCT/respiratory insufficiency	PLTs	$\downarrow$ BP 25 mmHg	30
Hypotensive*	14	LAL after HSCT/respiratory insufficiency	PLTs	$\downarrow$ BP 25 mmHg	10
Hypotensive	2	LAL/respiratory insufficiency	PLTs	$\downarrow$ BP 20 mmHg	10

* Same patient for these two reactions.

Abbreviations: BP = blood pressure; FFP = fresh frozen plasma; GI = gastrointestinal; HSCT = hematopoietic stem cell transplantation; LAL = lymphoblastic acute leukemia.

TABLE 6. Comparison between transfused patients with and without ATRs

Data*	All transfused patients (n = 305)	Patients without ATRs (n = 272)	Patients with ATRs (n = 33)	p Value
Age (months)	65.5 $\pm$ 77.8; 19 (0-285.8)	63.7 $\pm$ 73.4; 17.5 (0-221.5)	82.1 $\pm$ 88.8; 36.9 (0-285.8)	0.26
Number of transfusions/patient	8 $\pm$ 20; 3 (1-222)	6 $\pm$ 16; 2 (1-222)	25 $\pm$ 38; 11 (1-163)	0.01
Admission specialty†				
General pediatrics	137 (45)	130 (48)	7 (21)	0.01
Cardiac surgery	91 (30)	84 (31)	7 (21)	0.25
Hemato-oncology	27 (9)	14 (5)	13 (40)	<0.001
General surgery	13 (4)	13 (5)	0 (0)	0.20
Orthopedics	11 (4)	11 (4)	0 (0)	0.24
Cardiology	10 (3)	8 (3)	2 (6)	0.34
Gastrohepatology	9 (3)	6 (2)	3 (9)	0.03
Others	7 (2)	6 (2)	1 (3)	0.29
Mortality	56 (18.4)	49 (18)	7 (21)	0.66

* Data are presented as number (%) or mean $\pm$ SD; median (range).

† The percentage represents the frequency of variable/total number of transfusions per column (number).

age 8 $\pm$ 20 transfusions (median, 3; range, 1-222) during the study. Most transfused patients were admitted in general pediatrics (45%) or cardiac surgery (30%). Hemato-oncology patients accounted for 9 percent of transfused patients.

Among transfused patients, 33 presented an ATR (10.8%). Patients with and without ATRs were similar for age. Patients with ATRs received significantly more transfusions than patients without ATRs (6 $\pm$ 16 vs. 25 $\pm$ 38; p = 0.01). In hemato-oncology and gastrohepatology there were significantly more patients with ATRs (p < 0.001 and p = 0.03, respectively), whereas in general pediatrics there were significantly fewer patients with ATRs (p = 0.01).

Characteristics of patients with ATR

Among the 33 patients with ATRs, 27 presented only one ATR during the study, whereas 5 patients presented two ATRs and 1 patient presented three ATRs. A history of previous transfusion was present in 31 of 33 patients (94%). A history of previous ATR (before the study) was present in 8 of 33 patients (24%). A history of previous transplantation was present in 14 of 33 patients (42%): hematopoi-

etic stem cell transplantation (HSCT) in 10, hepatic transplantation in 3, and renal transplantation in 1. There were more patients with previous HSCT in the ATR group than in the non-ATR group (10/33 or 30% vs. 11/272 or 4%; p < 0.001).

Mortality

The overall mortality rate of patients admitted into the PICU during this study was 5.5 percent (98/1753). For PICU patients receiving at least one transfusion, the mortality was 18.4 percent (56/305). Mortality rate was significantly different (p < 0.001) according to the number of transfusions received: 1 to 9 transfusions, 14 percent (36/250); 10 to 24 transfusions, 14 percent (4/28); 25 to 50 transfusions, 61 percent (11/18); 50 to 222 transfusions, 55 percent (5/9). There was no significant difference in mortality rate between patients presenting ATRs and those without ATRs (21% vs. 18%; p = 0.40) or between patients presenting one ATR (19%) and patients presenting multiple ATRs (19% vs. 33%; p = 0.37). No death was attributable to ATRs in this study.

DISCUSSION

To our knowledge, this is the first prospective study evaluating the incidence of ATRs in a PICU. Furthermore, this is the first prospective study evaluating all types of ATRs associated to any labile blood products in the specific pediatric population. Our results show that 10.8 percent of transfused patients in a PICU present an ATR, for an incidence of 1.6 ATRs per 100 transfusions of labile products. These results compare with a prospective study on ATRs in a neonatal intensive care unit¹⁹ that has shown an incidence of transfusion reactions of 1.3 per 100 transfusions. In that study, however, the only blood product transfused was RBCs and the only ATR reported was FNHR. Another prospective pediatric study by Couban and colleagues¹⁷ has evaluated ATRs after leukoreduced PLT transfusions. The authors found seven ATRs associated with 66 transfusions (11%). ATRs consisted of two FNHRs, four allergic reactions, and one mixed reaction. Again, in that study, PLT transfusion was the only one blood product evaluated; FNHRs and allergic reactions were the only ATRs reported.

Incidence rates from hemovigilance reports are also available in the literature.^{5,6,28} A report from the Transfusion Service of Puerto Rico Medical Services Administration (ASEM) found an ATR in 0.2 percent of labile blood product transfusions.⁶ The study evaluated hospitalized patients from five centers, including one pediatric center. No specific incidence of ATR was available for pediatric patients. The Hemovigilance Network in France (HNF) reports, between 1994 and 1998, a rate of 0.25 incidents per 100 blood components.²⁸ Again, no specific incidence of ATR is available for pediatric patients. The SHOT 2003 annual report found 59 cases (13%) involving patients less than 18 years of age, 53 of which were cases of incorrect blood component transfused.³⁰ Nine pediatric patients suffered morbidity or potential morbidity. Owing to different ATR definitions in SHOT (e.g., minor reactions not reported, TRALI defined separately), it is difficult to compare our results to these data. Furthermore, the incidence rate of ATRs in children is not available in the report.

The Canadian province of Quebec established a hemovigilance system for adverse transfusion events (ATEs) reporting in 2000.⁷ The QHS is based on voluntary reporting. Because all large hospitals have officers who are required to investigate and report ATEs, 82 percent of transfusion activity in the province was covered in 2001.⁷ ATEs included in reports from the QHS are defined as acute ATE (occurring within 7 days after transfusion) or delayed ATE (occurring between 8 and 28 days after transfusion). According to the 2001 QHS report, the incidence of ATE was 0.35 percent for labile blood components. The proportion of all ATEs reported in children less than 1 year old was 20 of 1841 (1.1%) and in children 1 to 17 years old was 154 of 1841 (8.4%).³¹

The incidence of ATRs reported in our study (1.6%) is different from what is found in these hemovigilance reports. This could be due to several reasons. 1) Most hemovigilance systems are based on voluntary reporting; therefore underreporting could be an issue. 2) In these hemovigilance system reports, the proportion of pediatric patients is usually very low and the incidence rates reported are therefore applicable mainly to an adult population. 3) The scope of the reactions covered in our study and in hemovigilance systems differed in terms of time period after the transfusion and type of reactions; the definitions of the reactions may also have differed in terms of criteria used. 4) All blood products are leukoreduced in Canada, which is not always the case in other countries.

According to the QHS 2001 report, the most frequent immediate transfusion reactions was FNHR (12:10,000 transfused units), followed by minor allergic reactions (10:10,000).⁷ The ASEM report also showed that FNHRs and minor allergic reactions were the most frequent ATRs.⁶ Our findings were similar with FNHRs being the most frequent ATEs (96:10,000 transfusions), followed by minor allergic reactions (24:10,000).

With respect to imputability and severity of cases, we can compare our observations to those reported by the QHS and the HNF because we used the same definitions for imputability and severity.⁷ The QHS and the HNF reports, respectively, 85 and 75 percent of minor events.^{7,28} The proportion of immediate vital threat was, respectively, 5.5 and 3.2 percent, long-term morbidity was 8.4 and 22 percent, and death was 0.8 and 0.7 percent. In our study, we also found that most ATRs constituted minor events (85%). Nevertheless, we found more patients with immediate vital threat (15%) and fewer patients with long-term morbidity (0%). It is possible that vital threat was more frequent in our study because critically ill patients are already very unstable; the ATR could have more severe consequence on critically ill children than for the general population of hospitalized patients. We must also underline that, in our study, patients were not followed after discharge from PICU so it is possible that long-term morbidity was not reliably evaluated in our cohort.

In the QHS and HNF reports, imputability was, respectively, definite in 23 and 17 percent of adverse events and/or incidents, probable in 37 and 29 percent, possible in 22 and 34 percent, and questionable in 13 and 14 percent.^{7,28} We found a similar distribution in our study, the "probable" category being the most frequent one (55%).

In our study, patients with ATRs received more transfusions. Although there is no literature to compare our results, it seems logical that patients receiving more transfusions, thus exposed to more products and donors, should have an increased risk of ATR. Patients admitted in hemato-oncology and gastro hepatology presented more ATRs. This is probably due to the fact that patients from

these two specialties received more transfusions; in fact, they represented only 12 percent of the total cohort, but used 34 percent of all transfusions. We also found that there were more patients with previous HSCT in the ATR group. Due to the design of this study, it is impossible to evaluate whether HSCT is a risk factor for ATR. A larger prospective study looking at risk factors for ATR could help confirm these findings.

In our study, mortality was higher in transfused patients and increased with increasing number of transfusions administered. This has been reported in other studies and is most likely due to an increased severity of the underlying diseases in patients receiving many transfusions.³²⁻³⁴ A causal association cannot be established given the design of our study. There was no difference in mortality rate between patients with ATRs and patients without ATRs; furthermore, no death was attributed to ATRs according to expert consensus. No specific mortality data for children are available in the hemovigilance system reports. Nine deaths were reported by the QHS in 2001; among those deaths, three were considered attributable to the transfusion, which gives a mortality rate of 1.1:100,000 transfused units. Our cohort was too small to evaluate the rate of mortality attributable to transfusion in the PICU.

This study has several strengths. First, the prospective design probably makes it more reliable than voluntary reporting to hemovigilance systems to evaluate incidence rates in a population. Moreover, this study examined all consecutive transfused patients over a period of 2 years, in a representative North American PICU. All transfusions were monitored closely by the bedside nurse. Finally, the diagnosis, type, imputability, and severity of ATRs were evaluated with an adjudicating process, with predefined criteria. This study has some limitations, however. First, the cohort is too small to allow for subgroup analysis and generalization of results. A prospective multicenter study would be necessary to evaluate attributable mortality rates and types of ATRs according to different blood products administered. Second, this study was not designed to identify determinants or risk factors in patients who presented an ATR. To be able to find risk factors, the whole cohort would have to be followed prospectively and daily, which was not done in our study. A future study looking at these risk factors could help find preventive measures to reduce ATRs in PICU patients. Third, even if ATRs can occur up to 24 hours after transfusion administration, only transfusion events occurring during or within 4 hours after the end of the transfusion were reported in this study. Although this could underestimate the number of ATRs found, we decided to use a shorter period of observation for technical reasons (same nurse would administer the transfusion and observe for transfusion events) and because we considered that most clinically significant ATRs occur rapidly after transfusion. Fourth, the incidence

of ATRs in our study could be overestimated because it was not possible to verify the accuracy of our denominator data (total number of transfusions given in the unit). Fifty-six CRFs were rejected from analysis because they were incomplete, which represents 2.2 percent of all transfusions reported. These exclusions, however, would not change the reported incidence of ATRs significantly. We cannot assure that there was absolutely no CRFs not submitted by the bedside nurse, in special circumstances. Nevertheless, because all nurses were given information on the importance of the research project regularly and because the CRF was attached to the blood product to be administered, we do not believe that this was a significant issue. Finally, the fact that the diagnosis, imputability, and severity of ATRs were evaluated retrospectively could be a limitation. It would probably be more accurate to evaluate these when the ATR occurs, with all data available at the bedside and then to confirm it with knowledge of laboratory results and evolution of the patient.

In conclusion, ATRs occurred in 1.6 percent of transfusions administered in our PICU and affected 10.8 percent of transfused PICU patients. In 15 percent of cases, these ATRs represented a vital threat to already critically ill patients. Improved surveillance of transfusions given to PICU patients and better knowledge of these reactions by health care professionals should enhance the safety of transfusions by early recognition of reactions and by increasing product retrieval and/or donor investigation where appropriate. Better surveillance should also improve our capacity to estimate appropriately the risk-benefit ratio of the transfusion of blood products. Future studies should evaluate incidence rate of transfusion reactions reported by hemovigilance systems compared to prospective studies.

Hemovigilance systems should aim at identifying specifically the number and types of adverse transfusion reactions that occur in the pediatric population because the incidence of the events may differ from the adult population.

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