Feeling the burn: the significant burden of febrile nonhemolytic transfusion reactions

Robert Cohen,[1] Alioska Escorcia,[2] Farzana Tasmin,[2] Ana Lima,[1] Yulia Lin,[1,3,4] Lani Lieberman,[2,3,4] Jacob Pendergrast,[2,3,4] Jeannie Callum,[1,3,4] and Christine Cserti-Gazdewich[2,3,4]

BACKGROUND: Febrile nonhemolytic transfusion reactions (FNHTRs) are characterized by a post-transfusion temperature rise (of $\geq$ 1°C, to $\geq$ 38°C) or chills/rigors unrelated to the underlying condition. FNHTRs are provoked by inflammatory cytokines in the product or by host antileukocyte antibodies against residual donor leukocytes. FNHTRs are among the most commonly reported transfusion disturbances and are generally deemed nonserious events. However, their impact on patients and hospitals may be underestimated.

STUDY DESIGN AND METHODS: A search through two hemovigilance databases identified all known possible-to-definite FNHTRs over 3 years (2013-2015) at four academic hospitals using prestorage leukoreduced components. FNHTRs were assessed for frequency by product (red blood cells [RBCs], platelets [PLTs], intravenous immunoglobulin), diagnostics (bedside, chest imaging, serology, microbiology), and management (medications, disposition change). The definition of FNHTR was derived from Canada's Transfusion-Transmitted Injuries Surveillance System.

RESULTS: For 437 FNHTRs, the overall per-product rate across all sites was 0.24%, or 0.17% with RBCs alone and 0.25% with PLTs alone. One-third of patients had significant fevers ($\geq$ 39.0°C or a rise by $\geq$ 2.0°C). Approximately one-quarter underwent chest imaging within 48 hours, and 79% had blood cultures. A hospital admission directly attributable to the FNHTR, to exclude other causes of fever, occurred in 15% of FNHTR outpatients.

CONCLUSION: An analysis of FNHTRs reveals a substantial burden of postreaction clinical activity in addition to the disturbance itself. Efforts to avoid this adverse event may save resources, reduce patient distress, and encourage compliance with more restrictive transfusion strategies.

A febrile nonhemolytic transfusion reaction (FNHTR) is defined as an acute reaction to blood products, characterized by fever unrelated to the underlying condition. The rise in temperature (by 1-2°C) may be accompanied by chills, discomfort, and rigors.[1] FNHTR may result from recipient antibody-donor leukocyte interactions or from the accumulation of inflammatory mediators produced by leukocytes during storage.[2] FNHTRs are among the most frequent adverse reactions to a transfusion.[3,4] The incidence varies greatly, depending on the extent of reporting, the age and type of product, the use of leukoreduction (LR), presensitization of recipients, and the use of pretransfusion antipyretics.[5-7] FNHTR rates range anywhere from 0.08% for prestorage LR red blood cells (RBCs) to

ABBREVIATIONS: DBP = diastolic blood pressure; FNHTR(s) = febrile nonhemolytic transfusion reaction(s); LR = leukoreduction; SBP = systolic blood pressure; TSO = transfusion safety officer; TTISS = Transfusion-Transmitted Injuries Surveillance System.

From the [1]Department of Clinical Pathology, Sunnybrook Health Sciences Centre; the [2]Department of Clinical Pathology, University Health Network; the [3]Department of Laboratory Medicine and Pathobiology, University of Toronto; and the [4]Quality, Utilization, Efficacy & Safety of Transfusion (QUEST) Research Collaborative, Toronto, Ontario, Canada.

Address reprint requests to: Christine M. Cserti-Gazdewich, Toronto General Hospital, 200 Elizabeth Street, Room 3EC-306, Toronto, ON M5G 2C4, Canada; e-mail: christine.cserti@uhn.ca.

This work was presented in part as Poster 2532033 at the American Association of Blood Banks (AABB) Annual Meeting, Orlando, FL, October 22-25 (Recipient noninfectious adverse events. SP-350, Transfusion 2016; 56(S4): 164A-165A.

Received for publication November 4, 2016; revision received February 4, 2017; and accepted February 4, 2017.

doi:10.1111/trf.14099

TRANSFUSION 2017;57;1674–1683

27.2% for non-LR pooled platelet (PLT) concentrates[8,9]; whereas a meta-analysis estimated that the incidence was 0.33% for RBCs and 4.6% for PLT transfusions.[5] FNHTRs are more common from PLT and non-LR blood products than from RBC and LR products. Numerous studies have reported a reduction in the rate of FNHTRs through universal LR, the administration of pretransfusion antipyretics, supernatant reduction, or the use of shorter storage components, although the effectiveness and availability of each of these techniques varies significantly.[7]

Because of the potentially serious (and dose-dependent) causes of transfusion-associated fever, transfusion interruption for evaluation is indicated. Before the transfusion may be resumed, the associated features and severity of the disturbance are considered, while the evidence for more dangerous drivers (such as acute hemolysis or bacterial contamination) is assessed and ruled out. Although FNHTRs are considered to be benign events free from any lasting sequelae,[2] reaction reviews and management nevertheless consume hospital resources. The investigative process increases the duration of the transfusion care period and potentially exposes the patient to otherwise unplanned medication for fever, pain, or presumed bacterial infection. Furthermore, in the antimicrobial stewardship era, excessive precautionary use of antibiotics may also drive pathogen resistance and increase health care costs. Depending on the severity of the reaction or the case-specific implications of fever, patients may be admitted to hospital from an outpatient clinic or transferred to a higher intensity care area. Taken together, the consequences of FNHTRs can have negative impacts on the patient and the system at large.

Most studies involving FNHTRs have focused on incidence and mitigation measures. However, to our knowledge, no study has assessed the downstream actions that follow FNHTR. The primary objective of this retrospective analysis was to qualitatively and semiquantitatively assess the impact of FNHTRs on individual patients and on institutions in terms of FNHTR care-related activities. The secondary objective was to determine the reporting rate of FNHTRs at four academic hospitals. By appreciating the significance of FNHTR in these disruptive and resource-consumptive terms, an original evidence-based argument may be raised for more conservative patient blood management.

MATERIALS AND METHODS

Identification of FNHTR events

A transfusion safety officer (TSO) at each site prospectively investigated all reported transfusion reactions and completed the case report form of the Transfusion-Transmitted Injuries Surveillance System (TTISS) from the Public Health Agency of Canada. Data included the clinical history of the patient; the date, time, and place of the reaction; and clinicolaboratory results. Information about the implicated products, types of reactions, and relation of the adverse events to transfusions; the severity and sequelae; blood bank serologic investigations; cultures; and any interventions was collected.

All blood components, which were provided by Canadian Blood Services, have been subject to universal prestorage LR since 1999. LR RBCs have saline-adenine-glucose-mannitol (SAGM) added, whereas adult-dose PLT concentrates either comprise buffy coat-derived pools (of four) or apheresis products; pathogen-inactivation or additive solutions are not yet features of this supply.[10]

According to the TTISS, FNHTR is suspected when one or more of the following are observed: fever ($\geq$38°C and a change of $\geq$1°C from pretransfusion value), chills, sensation of cold, or rigors. Symptoms may be accompanied by headache or nausea, and disturbances occur during or within 4 hours of transfusion completion. FNHTR is a diagnosis of exclusion, which requires that alternatives be deemed less likely from the available charting or investigative evidence (e.g., hemolytic transfusion reaction, bacterial contamination, or underlying condition). In Table 1, the severity and relative certainty of FNHTR are defined within the TTISS framework.[11] Each case report was reviewed by a transfusion medicine specialist before it was reported in the electronic patient record.

A search through two separate hemovigilance databases identified all possible, probable, and definite FNHTRs at four academic hospitals in Toronto, Canada. All reactions to an RBC, PLT, or intravenous immunoglobulin (IVIG) order between January 1, 2013, and December 31, 2015, were included. IVIG events were counted as patient dispensations (multibottle sittings), that is, 2g/kg over 2 days in a 70-kg recipient counted as two dispensations (one for each of the 70-g infusion blocks, irrespective of the number or denominations of bottles administered in either of the scheduled infusions).

In establishing the dispensation denominator for products transfused, those with low imputability for FNHTR (albumin, plasma, or cryoprecipitate) were excluded, as were reactions in which the only product transfused was such a product, to prevent skewing of the incidence rate. We excluded any febrile reactions associated with other cellular therapeutics (e.g., granulocyte or stem cell infusions). Reactions listed as doubtful FNHTR were excluded. If a patient experienced more than one reaction during the study period, then all events for that patient were counted.

Research ethics board approval was obtained for each site before the analysis was conducted (276-2016 at Sunnybrook Health Sciences Centre [Site A]; and 16-5702-CE at University Health Network, representing Toronto General Hospital [Site B], Toronto Western Hospital [Site C], and Princess Margaret Cancer Centre [Site D]).

TABLE 1. TTISS definitions of the severity of the adverse event and the relationship of the adverse event to the transfusion*

Severity of adverse event
Grade 1 (nonsevere)
If the recipient may require medical intervention (e.g., symptomatic treatment) but lack of such would not result in permanent damage or impairment of a body function
Grade 2 (severe)
• If the recipient requires in-patient hospitalization or prolongation of hospitalization directly attributable to the event; or
• If the adverse event results in persistent or significant disability or incapacity; or
• If the adverse event necessitates medical or surgical intervention to preclude permanent damage or impairment of a body function
Grade 3 (life-threatening)
If the recipient required major intervention after the transfusion (vasopressors, intubation, transfer to intensive care)
Not determined
If the consequences of the transfusion reaction are not certain
Relationship of adverse event to the transfusion
Definite
If a clinical and/or laboratory event occurred within a time period consistent with the administration of the blood, blood component, or blood product (plasma derivative) and was proven by investigation to have been caused by transfusion
Bacterial contamination is considered "definite" if it meets ALL of the following criteria:
• The same bacteria are found in the recipient and the blood, blood component, or blood product (plasma derivative)
• Contamination of the blood sample or laboratory contamination is not suspected
Probable
If a clinical and/or laboratory event occurred within a time period consistent with the administration of the blood, blood component, or blood product (plasma derivative) and did not seem to be explainable by any other cause
Bacterial contamination is considered "probable" if it meets the following criteria:
• Positive blood, blood component, or blood product (plasma derivative) culture
• Contamination of the blood sample or laboratory contamination is not suspected
• The recipient presents signs and symptoms of sepsis (nothing else explains it)
• The recipient's blood culture was either not obtained/performed, or was negative
Possible
If the clinical and/or laboratory event occurred within a time period consistent with the administration of the blood component, but could also be explained by a concurrent disease or by the administration of a drug or other agent
Bacterial contamination is considered "possible" if it meets the following criteria:
• The recipient's blood culture is positive
• Contamination of the blood sample or laboratory contamination is not suspected
• The recipient presents signs and symptoms of sepsis (nothing else explains it)
• A blood product culture was either not obtained/performed or was negative
Doubtful
If the clinical or laboratory event occurred within a reasonable time period but the preponderance of data supports an alternative explanation
Bacterial contamination is considered "doubtful" if:
• The blood product culture is positive for one pathogen and the recipient's blood culture is positive for a different pathogen; or the blood product culture is positive or the recipient's blood culture is positive but contamination of the sample or laboratory specimen is suspected
Ruled out
If the clinical and/or laboratory event occurred within a time period inconsistent with the administration of the blood product or if it occurred within a consistent time period and it was proven to have no relationship to the transfusion
Not determined
If it remains to be determined whether the event was related to the administration of the blood product and further information is forthcoming

* See[11]

Impact of FNHTR and escalation in patient care

The relationship of the adverse event to the transfusion and the likelihood of FNHTR were both determined after review by the TSO and transfusion medicine physician. Both of these variables were qualitatively ranked on a certainty scale ranging from definite to doubtful by assessing for alternative explanations. These included microbial cultures, patient investigations for other causes of fever (e.g., chest radiograph to rule out pneumonia), pre-existing neutropenia and the duration thereof (as a risk for febrile neutropenia), and other transfusion reactions in which a fever may be a clinical manifestation. The severity of the FNHTR was determined by the clinical status of the patient, the medical interventions required, and disposition changes (unplanned admission to hospital or stay prolongation).

The "risk category" of the fever was deemed as either high or low according to policies designed to allocate appropriate testing resources. "High risk" reflected a post-transfusion temperature greater than or equal to approximately 39°C (≥38.8°C), with a change in temperature by 1°C or greater to achieve the zenith. Alternatively, high risk was designated if the patient experienced chills or rigors; nausea or vomiting; dyspnea/shortness of breath; diffuse hemorrhage or bleeding; oliguria, hematuria, or hemoglobinuria. If these criteria were not met, then the fever was classified as "low risk," and investigations were deferred according to hospital policy, acknowledging the low

pretest probability (and testing yield) for acute hemolytic reactions or transfusion-transmitted sepsis.

Testing for immune hemolytic incompatibility consists at a minimum of a new blood bank sample (for evaluation of postcentrifugation visible plasma hemoglobinemia, new discrepancies, and intercurrent seroconversion changes on antibody screen or direct antiglobulin test). Additional investigations are obliged with any serologic changes, for the nature and specificity of sensitization, and for parameters demonstrating associated hemolysis (e.g., absolute and/or relative increases in unconjugated/total bilirubin, lactate dehydrogenase, reticulocyte count, creatinine, and coagulation times; absolute and/or relative decreases in hemoglobin, haptoglobin, fibrinogen, and complement; and morphologic evidence of hemolysis on peripheral blood film). Testing for bacterial contamination consists of the return of the implicated product(s) for microbiologic culture and parallel testing of the patient's blood (at the point of infusion if through an indwelling catheter, and/otherwise by peripheral venous stab).

Fever risk grade (high vs. low), clinical symptoms, vital signs, measures taken, and escalations in care were also evaluated. Disturbance-directed medications included acetaminophen, antihistamines, diuretics, corticosteroids, meperidine (specifically for rigors), and other narcotics (typically for acetaminophen-unresponsive pain). If a patient had already received any of these medications before the reaction, then it was not counted as reaction-provoked. Antibiotics were considered a new post-transfusion medication if the patient was not on antibiotics before the transfusion or if the post-transfusion antibiotic differed from the pretransfusion regimen. A stopped transfusion was defined as a transfusion in which the product was not fully transfused due to the disturbance, while a restarted transfusion was defined as a transfusion which had been stopped but later resumed.

Statistical analysis

Categorical variables were summarized as frequencies and percentages, and continuous variables were expressed as means with standard deviations or as medians with interquartile ranges if data were skewed. Wilcoxon matched pairs were used to assess difference in pretransfusion and post-transfusion vital signs, and an unpaired t test was used to compare differences in incidence rates. All p values less than 0.05 were considered significant. Calculations were performed using spreadsheet software (Excel 2016; Microsoft Corporation).

Estimated cost of diagnostics in FNHTRs

Current (2016) Canadian dollar (CAD) values from Ontario/regional chest radiography ($24), blood cultures ($32), reaction-oriented serologic investigations ($98), and case review/reporting workloads ($53) were used to estimate the costs of case investigation according to ordering patterns.

Cost estimates have assumed the lowest possible number of studies and the simplest, most affordable option. For example, chest imaging may have consisted of computed tomography scans instead of, or in addition to, a chest x-ray. Patient cultures may have exceeded a single peripheral venous stab (e.g., sampling each port in a multilumen indwelling catheter). Product cultures may have reflected the retrieval and analysis of more than one product if a reaction followed polytransfusion. To establish the minimum local cost of FNHTR investigation and to prevent inflation from excessive case-specific activities, the estimates use one chest x-ray (per imaged patient), one patient culture (per reaction with patient culture activity), and one product culture (per reaction with product culture activity).

RESULTS

Institutions assessed and patient demographics

Four medium-to-large hospitals with intensive care units were included in the analysis. Site A (627 beds) is a large general hospital with a cancer center, a regional trauma service, obstetrics, and a wide variety of surgical services. Site B (457 beds) is also a large general hospital with a significant proportion of the transfusions supporting a regional inherited RBC disorders program, apheresis, and surgical services (complex cardiac and multiorgan transplantation). Site C (280 beds) is a medium-sized general hospital specializing in orthopedic and neurosurgery. Site D (129 beds) is a large cancer center that performs allogeneic and autologous hematopoietic stem cell transplantations.

In total, 437 FNHTRs in 407 unique patients were reported during the 3-year study period. All sites had a comparable mean age and proportion of males and females (Table 2). Most patients (83%) had a history of prior transfusions, whereas less than one-quarter had experienced a previous transfusion reaction. Reactions occurred predominantly on a medical/surgical ward (49%) or in an outpatient clinic (36%).

Incidence rate

In total, 178,730 blood products that were considered high risk for FNHTRs (RBCs, PLTs, and IVIG) were transfused across all four sites between January 1, 2013, and December 31, 2015 (Table 2). The total number of products transfused across all sites remained relatively stable in each of the 3 years. Site B was the largest overall user of blood products, whereas 60% of the total PLT use was from a single institution (Site D).

FNHTRs to RBCs alone accounted for over one-half of the FNHTRs, whereas IVIG represented only 3% of

TABLE 2. Three-year study metrics for denominator exposures and numerator parameters in FNHTRs

Parameter	Site A	Site B	Site C	Site D	All sites
No. of products, 2013-2015					
RBCs	31,873	61,247	9,343	35,364	137,827
PLTs	4,258	7,790	899	19,178	32,125
IVIG	907	7,871*	8,778		
Demographics and patient history					
No. of FNHTRs	79	123	41	194	437
2013	34	34	12	60	130
2014	23	38	17	67	140
2015	22	51	12	67	139
No. of affected patients	77	115	38	177	407
Mean ± SD patient age, y	60 ± 15	53 ± 18	64 ± 18	58 ± 16	58 ± 17
Female, %	43	41	39	42	42
History of pregnancy (females = denominator), %†	—	52	63	73	65
History of transfusion, %	59	85	71	93	83
History of transfusion reaction, %†	—	20	12	27	23
Severe neutropenia†	—	14	5	39	27
Patient location, %					
Outpatient	28	18	2	57	36
Emergency department‡	10	8	10	0	5
Medical/surgical ward	49	58	54	43	49
Intensive care unit	10	16	32	0	9
Operating room (+ recovery room)	3	0	2	0	1

* Data are reported as the sum for IVIG at Sites B, C, and D.
† These data elements were not collected at Site A. Severe neutropenia is defined as an absolute neutrophil count of $\leq 0.50 \times 10^9$/L.
‡ There is no emergency department at Site D (patients are admitted through emergency at Site B).

these reactions. The overall FNHTR incidence was 1 in every 409 products, with variation by site and product. FNHTRs were more frequent with PLTs alone than with RBCs alone ($p = 0.0034$) (Fig. 1A) and were more common at Site D than at Site A ($p < 0.001$) (Fig. 1B). During the review period, nine febrile reactions met criteria for possible or probable bacterial contamination (Sites B-D).

The widest variation was observed between reported reaction rates to IVIG at Site A (0.77%) and Sites B, C, and D (0.10%; $p < 0.0001$).

Severity and symptoms of the reactions

Two-thirds of FNHTRs were classified as minor, with one-half noting concomitant chills/rigors (Table 3). A statistically significant change was observed in all vital signs measured (temperature, heart rate, systolic blood pressure [SBP], diastolic blood pressure [DBP], respiration rate, and peripheral oximetry saturation), including an increase (by 1.4°C) in the post-transfusion temperature (Fig. 2). In 19% of patients, post-transfusion decreases in both SBP and DBP were reported; whereas, in 43% of patients, an increase in both SBP and DBP was noted. New post-transfusion hypotension (≤90/60 mmHg) and hypertension (≥140/90 mmHg) were reported in 2% and 4% of patients, respectively. A minority of patients (17%) saw an increase in SBP of 30 mmHg or greater, whereas 23% of patients had a post-transfusion temperature greater than or equal to 39°C. Over one-third of patients (37%) had no reported symptoms despite a temperature rise by 1°C or greater, whereas the majority had fevers that were considered high risk (Fig. 3A). Most FNHTRs were "possible" events (as opposed to a probable or definite diagnosis); the presence of concurrent infections paralleled the uncertainty (Fig. 3B),

Management of FNHTRs

FNHTR management by site was compared and contrasted (Table 4). Nearly one-half of FNHTRs occurred at or after completion; however, among those noted during the transfusion itself, greater than 90% of infusions were interrupted for evaluation, irrespective of site, with only a minority attempting resumption thereafter (with Site A appearing more likely to do so than Sites B-D). This left more than 40% of the implicated products incompletely transfused.

Overall, more than one-half of patients received acetaminophen. There was a poor correlation between imposing a hold on the infusion and the administration of antipyretics. Interim-fever management sequences consisted either of a stop/medicate/discontinue approach or a stop/medicate/continue approach. The ratio of these approaches ranged from 1:1 (Site A) to 6:1 (Sites B-D). Sites B, C, and D were also more likely to culture both the patient and the product and to initiate new antibiotics (or change a current regimen), while also being more likely to admit if the transfusion occurred in an outpatient.

All sites had similar practices in the rates of chest imaging, diuretic, and antihistamine use. Patients at Site D were given meperidine considerably more often than at any other site despite a comparable proportion of patients

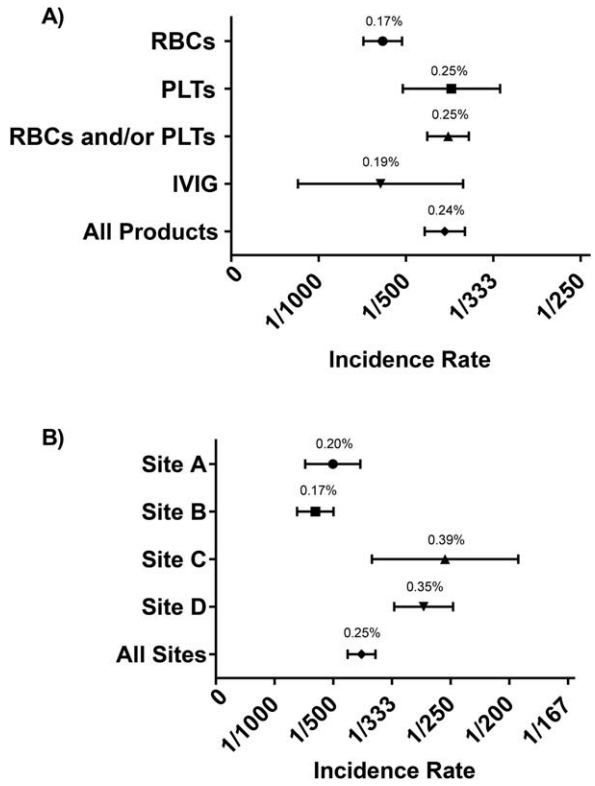

Fig. 1. (A) Product-specific incidence rate of FNHTRs and (B) site-specific incidence rate. Product-specific incidence is illustrated for RBC-only exposures, PLT-only exposures, any cellular component exposure (RBCs alone, PLTs alone, or a mix thereof), and IVIG sittings. Data are reported as means with 95% confidence intervals.

at Sites A and C with rigors as a symptom. Site D also had the greatest percentage of hospital admissions from patients who had received transfusions in an outpatient clinic and the largest number of patients with pre-existing, severe neutropenia. For those admitted as outpatients, the incurred length of stay was a median of 2 days (interquartile range, 1-4.5 days; Sites B-D). Although FNHTRs were managed differently at each site, the severity of the reactions was similar.

Estimated cost of diagnostics in FNHTRS

This cohort of 437 patients who had FNHTRs was exposed to 105 thoracic imaging studies, whereas 344 patients underwent cultures, with the product(s) of 258 orders also cultured. In 254 patients (at Sites B-D [with data unknown for Site A]), serologic tests were conducted to rule out hemolytic incompatibility. This accounted for a minimum of $70,000 in diagnostics (or an average of $160 per patient), excluding the costs of additional medications or transfers of care.

DISCUSSION

By passive hemovigilance, the frequency of FNHTRs across four Canadian study sites was 2.4 per 1000 transfusions, which was in keeping with rates reported in similar systems. FNHTRs were most frequently observed with PLTs, followed by RBCs and IVIG. These fevers provoked a range of responses, proportions of which were specific to sites in some regards (i.e., case-culturing with or without empiric antimicrobials) or more consistently applied in others (i.e., acetaminophen treatment). Roughly one-fourth of patients underwent chest imaging, and approximately 15% had disposition escalations (such as transfers to higher intensity units or admissions from ambulatory care).

We observed the rank-order FNHTR risk expected with PLTs over RBCs. If indeed FNHTRs are independently caused by mediators that are differentially present in components, the odds of fever should follow those most laden

TABLE 3. Severity and symptoms of the reactions

Parameter	Site A	Site B	Site C	Site D	All sites
Severity, %					
Grade 1 (nonsevere/minor)	96	67	68	55	67
Symptoms, %					
Chills/rigors	59	46	34	53	50
Hemolytic coagulopathy (diffuse hemorrhage/bleeding)	0	1	0	0	0
Hemolytic renal injury (oliguria/ hematuria/hemoglobinuria)	0	0	2	0	0
Urticaria/rash	3	7	7	10	8
Dyspnea	16	9	10	12	12
Wheeze	3	3	5	6	4
Lip/tongue swelling	0	2	0	2	1
Nausea or vomiting	5	6	0	5	5
Pain	11	12	10	5	9
Other*	35	11	5	6	12

* Other symptoms include transient hypertension or hypotension, cough, confusion, crackles, profuse sweating/diaphoresis, tachycardia, and tachypnea.

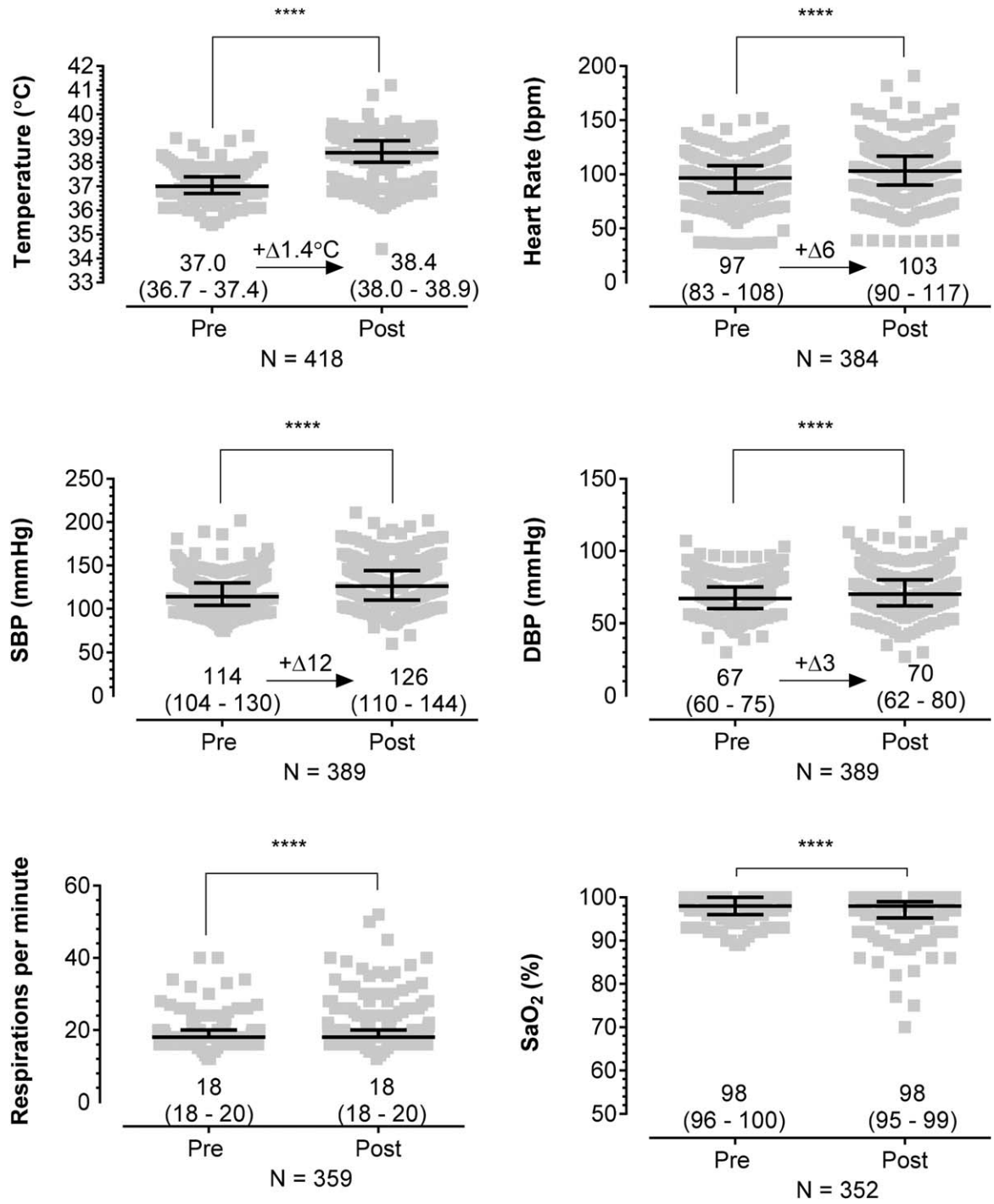

Fig. 2. Values of vital signs before and after the FNHTR. Temperature, heart rate, SBP, DBP, respiration rate, and peripheral oximetry saturation are expressed as medians with interquartile ranges. Statistical significance was determined with the Wilcoxon matched pairs test. ** Indicates $p < 0.001$.**

with these pyrogens. Boudreau and colleagues demonstrated that storage-induced PLT microparticles released inflammatory cytokines,[12] thereby explaining the persistent disproportion of FNHTRs with PLTs versus RBCs despite LR of all cellular products at all sites.

The incidence of FNHTRs with RBC-only exposure was 0.17% (range, 0.15%-0.19%), which was within the ranges of 0.2 to 0.33% reported in the literature.[5,13] However, the FNHTR incidence with PLT-only exposure was 0.25% (range, 0.20%-0.31%); this was significantly lower

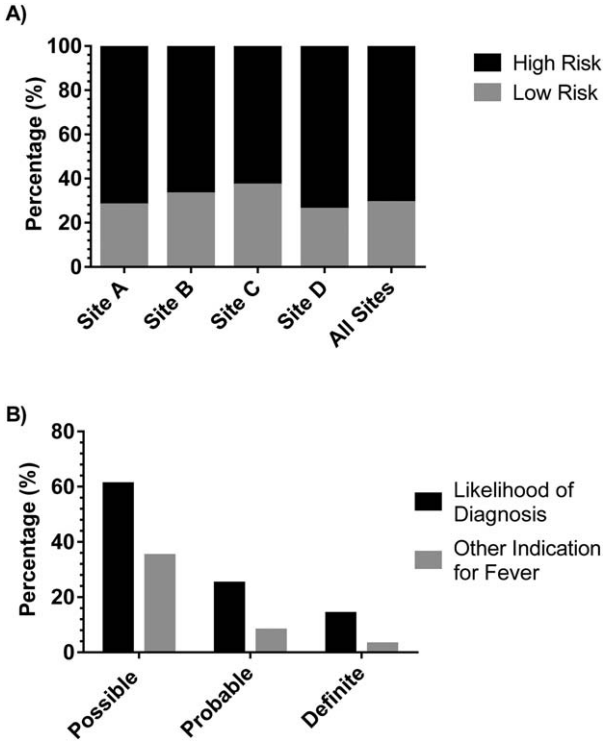

Fig. 3. Site-specific risk of fever accompanying FNHTR. (A) A high-risk fever is defined as a post-transfusion temperature of 39°C or greater (± 0.2°C), by a change in temperature of 2.0°C or greater, or at least one of the following symptoms: chills/rigors, dyspnea/shortage of breath, bleeding/oozing, diffuse hemorrhage, hematuria, hemoglobinuria, oliguria, nausea or vomiting, and pain. (B) The likelihood that an adverse transfusion event was an FNHTR and the percentage of reactions with other possible indications for a fever are illustrated. Alternative explanations for FNHTR include pre-existing severe neutropenia, discovery of a focus of concurrent infection, or pertinent microbiologic findings on case review.

than the 4.6 to 6.7% rate described elsewhere.[5,13,14] It is unclear whether this reflects a true era-specific risk reduction or an under-representation of confounders. Perceived incidence will vary with reporting vigor, the criteria applied for FNHTRs, the use of LR, and the extent of pre-transfusion antipyretic use. However, these factors were not expected to be any different with PLTs, although it is possible that those most likely to receive PLTs are also most likely to be neutropenic and disarmed from crossing the threshold to fever. Notwithstanding this speculation, we interpret our rates to suggest ongoing under-recognition and/or under-reporting, despite aggressively promoted hemovigilance.

Site-specific FNHTR rate variations may reflect populations and procedures. Site B had the highest blood utilization of any of the four sites as well as an extensive surgical and transplantation program. Many transfusions are thus administered intraoperatively, where anesthesia has the power to either prevent FNHTRs from manifesting (as with paralytics quelling rigors) or from being voiced by the patient altogether (by unconsciousness and intubation). Therefore, reporting relies exclusively on thermometer data and the extent to which it is captured and transmitted alongside the hemodynamic tracings. Site A, like Site B, has a similar proportion of intraoperative transfusion activity, which explains the lower all-product incidence rates compared with Sites C and D (Fig. 1B).

Our study revealed that most patients who experience FNHTRs exhibit disturbances in other vital signs. These reactions were typically accompanied by elevations not only in body temperature but also in heart rate, SBP, DBP, and respiratory rate. Nevertheless, it was the temperature change that drove (fever-oriented) postreaction actions. In roughly two-thirds of patients, the fever was of a high-risk nature, thereby obliging more intensive review to rule out serious sequelae, such as incompatibility or bacterial contamination. This is in contrast to assumptions that most FNHTRs are generally mild in the sense of being limited to "low-risk" (subclinical, $T_{max} < 39°C$) excursions. The disproportion of high-risk fevers (and the lower proportion of minor-severity events at Sites B-D), however, may reflect under-reporting of the true burden of low-risk temperature elevations.

In addition to the toll taken by FNHTRs on individual patients, there is an inevitable system cost with the management of these events. They lead to an increased use of hospital resources through the conduct of tests and administration of medications otherwise not required. When patients experience a reaction, numerous tests check for hemolytic incompatibility, while cultures of the patient and product assess for a source of sepsis. Chest imaging is oriented at determining whether or not an occult respiratory tract infection is driving fever, with or without other radiographically evident reactions (such as transfusion-associated circulatory overload). Dyspnea itself may be a feature of FNHTR in 9 to 16% of patients after the exclusion of other pathologies. In this cohort, we calculated a minimum cost of $160 CAD for the diagnostics applied to the average patient with an FNHTR, noting major (underestimation bias) limitations in the derivation.

While awaiting test results to guide management, antibiotics may be prescribed for ultimately culture-negative cases. Patients with rigors may be frightened and distressed by the force and duration of the shivering response, and may justify the use of meperidine. Pain may be addressed with other controlled substances. These medications are not inconsequential. Antibiotic over-use promotes the public hazard of antimicrobial resistance.

Depending on the severity of the reaction, patients may be sent to the emergency room or admitted from the outpatient setting. Inpatients may be transferred to the

TABLE 4. Measures taken and medications administered for FNHTR

Parameter	Site A	Site B	Site C	Site D	All sites
Reactions at or after completion, %	37	43	39	60	49
Completed transfusions, %	58	47	46	68	58
Measures taken, %					
Interruption for evaluation*	96	93	92	91	93
Resumptions among stops†	31	6	9	14	15
Serologic testing‡	N/A	71	66	73	72
Patient culture	49	78	83	90	79
Product culture	41	60	54	67	59
Chest imaging (within 48 hr post-transfusion)	20	33	22	21	24
Supplemental oxygen	14	3	2	6	6
Admission to hospital from outpatient clinic directly due to FNHTR	5	14	0	18	15
Post-transfusion medications (new), %					
Acetaminophen	67	47	45	52	54
Antibiotics (new/changed)	13	28	38	56	37
Antihistamines	14	8	10	14	12
Diuretics	8	8	3	6	7
Corticosteroids	0	1	3	13	6
Meperidine	1	0	0	12	5
Narcotics (nonmeperidine)	N/A	2	0	1	1

* The denominator is the number of patients whose fevers occurred during (not at or after completion), with an opportunity to impose a hold.
† The denominator is the number of patients whose transfusions were suspended for evaluation.
‡ Serologic testing entailed a postreaction sample submission to the blood transfusion laboratory for clerical check, inspection after centrifugation for visible plasma hemoglobinemia, retyping, rescreening, and performance of the direct antiglobulin test.
N/A = data not available.

intensive care unit. These events reflect an increased workload, excess resource consumption, and failed fulfillment of the transfusion sittings themselves. Transfusions are frequently discontinued when fever is observed because of the concern for bacterial contamination, although such events only occur in roughly 1 of every 10,000 PLT transfusions and in 1 of every 250,000 RBC transfusions.[4]

To our knowledge, this is the first study to assess the impact of FNHTRs on patients in terms of the resource-consuming activities that follow. However, this study is not without limitations. Because of challenges in gathering complete information, without the benefit of a categorically diagnostic test, an FNHTR is often neither ruled in nor out. Due to the retrospective nature of the study, it was challenging to definitively assign whether or not new interventions were applied only because of the FNHTR, or occurred as a result of the patient's evolving and underlying morbidities. We were conservative in making judgments, such that when the reasons for an intervention or medication were unclear, they were not deemed to have been provoked by the FNHTR. As such, we have likely underestimated the impact of FNHTRs. Another issue is that reactions are evaluated by one or more of five transfusion physicians and by one of three TSOs. Despite referencing shared definitions, individual interpretations may have varied, although our capacity to statistically examine reviewer-specific assignments was not possible. Finally, the absence of a database comprising transfusion recipients who do not experience a reaction thus leaves us without a control. However, it is unlikely that transfusion recipients who are reaction-free would require such a level of additional medication, monitoring, or intervention.

A large proportion of the reactions occurred in patients who were severely neutropenic and who may have been independently mounting a fever from opportunistic infections. Despite the use of universal prestorage LR, residual leukocytes and pyrogenic mediators may have the power to directly cause, or additively hasten, the manifestation of fever. Patients without underlying risks may not suffer the reaction, but others at a tipping point will. FNHTRs therefore may be a summative signal of an underlying pyrogenic pathology, despite the temporal pattern suggesting a fever caused by the product alone.

Overall, we have demonstrated that FNHTRs impose a meaningful burden on both the patient and the hospital. They consume hospital resources by summoning additional medications, diagnostic testing, and clinician review. The majority of cases (range, 60%-80%) entail microbiologic studies, whereas roughly one in three patients receive empiric antimicrobials, and one in seven has a disposition escalation (emergency room transfer or admission from an outpatient setting). A recent audit from the sites assessed in this study revealed that approximately one in five RBC transfusions is unnecessary.[15] Inappropriate transfusions expose patients to preventable risks, such as FNHTRs and other transfusion reactions. In our experience, FNHTRs accounted for 20 to 40% of reported reactions.[16] A more restrictive transfusion approach, especially in patients at high risk of developing

a fever, may help mitigate the occurrence of FNHTRs and reduce directly attributable costs. More research on prevention (e.g., premedication) is also warranted to address the inconclusive interpretations of literature to date.[7] Further investigations should also assess whether additional manufacturing steps (such as pathogen inactivation) can decrease FNHTR occurrence. A stronger awareness of the material impact of FNHTRs may promote better utilization of blood products to avoid FNHTRs and the costs that follow.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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