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Incidence of transfusion reactions: a multi-center study utilizing systematic active surveillance and expert adjudication

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Abstract

Background—Prevalence estimates of serious hazards of transfusion vary widely. We hypothesized that the current reporting infrastructure in the United States fails to capture many

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transfusion reactions, and undertook a multi-center study utilizing active surveillance, data review, and adjudication to test this hypothesis.

Study Design and Methods—A retrospective record review was completed for a random sample of 17% of all inpatient transfusion episodes over 6 months at 4 academic tertiary care hospitals, with an episode defined as all blood products released to a patient in 6 hours. Data were recorded by trained clinical research nurses, and serious reactions were adjudicated by a panel of transfusion medicine experts.

Results—Of 4857 transfusion episodes investigated, 1.1% were associated with a serious reaction. Transfusion associated circulatory overload (TACO) was the most frequent serious reaction noted, being identified in 1% of transfusion episodes. Despite clinical notes describing a potential transfusion association in 59% of these cases, only 5.1% were reported to the transfusion service. Suspected transfusion related acute lung injury (TRALI/possible TRALI), anaphylactic, and hypotensive reactions were noted in 0.08%, 0.02%, and 0.02% of transfusion episodes. Minor reactions, including febrile non-hemolytic and allergic, were noted in 0.62% and 0.29% of transfusion episodes, with 30–50% reported to the transfusion service.

Conclusion—Underreporting of cardiopulmonary transfusion reactions is striking among academic, tertiary care hospitals. Complete and accurate reporting is essential to identify, define, establish pathogenesis, and mitigate/treat transfusion reactions. A better understanding of the failure to report may improve the accuracy of passive reporting systems.

Keywords

transfusion; reactions; pulmonary; TACO

INTRODUCTION

Although blood transfusion can be a lifesaving therapy, each transfusion carries a small risk of a serious reaction¹. In particular, cardiopulmonary complications of transfusion are recognized to be a leading cause of transfusion associated deaths in the United States. Among these complications, transfusion related acute lung injury (TRALI) and transfusion associated circulatory overload (TACO) are the top two causes of transfusion mediated death reported to the FDA over the past 5 years². In addition to being potentially deadly, both TRALI and TACO also significantly contribute to morbidity³.

Prevalence estimates of cardiopulmonary and other serious transfusion hazards vary widely based on study design. A national recipient hemovigilance system that relies on passive reporting was initiated in the United States in 2010⁴ with similar reporting systems in place in other countries^{5–7} for many years. Active reporting systems uniformly report higher rates of transfusion reactions than passive systems^{3,8,9}, both in the US and abroad¹⁰. This trend exists not only for cardiopulmonary complications, but also for other non-infectious transfusion reactions.

Recognition followed by complete and accurate reporting of all transfusion reactions is necessary to describe the clinical spectrum of the reaction, to define the responsible pathophysiology, and to establish optimal means to prevent and/or to treat transfusion

reactions. However, identifying symptoms of potential transfusion reactions is not always simple. Further, assigning transfusion associated causality to observed symptoms is, at times, even more difficult, even for experienced transfusion medicine experts. Although standard diagnostic criteria for reactions have been established in many countries and by multiple organizations^{4,11}, an index of suspicion that a transfusion is responsible for the observed symptoms is necessary to apply these diagnostic criteria.

In accord with other previously published studies, we hypothesized that the current surveillance and reporting infrastructure in the US fails to capture many transfusion reactions. We undertook an active surveillance study utilizing systematic retrospective review of electronic medical records at 4 academic tertiary care hospitals in the US to investigate this hypothesis.

METHODS

Study design

This retrospective chart review was funded by the National Heart, Lung and Blood Institute as part of the Recipient Epidemiology and Donor Evaluation Study–III (REDS-III). At each of 4 academic tertiary care hospitals in the US, active surveillance on adult inpatient transfusion episodes was completed. For the purposes of this study, a transfusion episode was defined as all blood products released to a single patient separated by an interval of six hours from other blood products released. De-identified information on all blood components transfused to inpatients over 18 years of age at each hospital during July–December 2014 was submitted to the REDS-III data coordinating center (RTI International; Rockville, MD). Research nurses at each site then performed chart reviews and data extraction on 200 randomly selected transfusion episodes per month that involved confirmed transfusions. The number of transfusion episodes evaluated per month was chosen based upon workload estimates for one research nurse at each hospital, with a goal of targeting 15–20% of all transfusions at a given hospital.

Prior to study initiation, nurse study coordinators at each of the 4 sites underwent centralized training by subject matter experts, focused on recognizing transfusion reactions. After an interval of approximately three months post-transfusion, the nursing coordinators retrospectively reviewed the electronic medical records, focusing initially on blood components transfused, vital sign trends, chest x-ray (CXR) results, arterial blood gas (ABG) results, other laboratory results, and clinical notes (including nursing, resident/fellow/attending, respiratory therapy, and significant event notes) in close proximity to the transfusion(s). Data collection forms were developed to ensure accurate and systematic capture of information, and data were validated for accuracy. The screening data form (Supplemental Appendix 1), capturing recipient age, gender, ethnicity, diagnosis, blood type, and components transfused, was completed for all 4857 transfusion episodes. When the nurse coordinators or local study physicians felt that a serious transfusion reaction (pulmonary, hemolytic, septic, hypotensive, or anaphylactic) may have occurred based on the data captured by the screening form, extended data forms (Supplemental Appendix 2) were completed. Diagnostic criteria for severe cardiopulmonary reactions included, at a minimum, new onset hypoxemia (as evidenced by $\text{PaO}_2/\text{FiO}_2 < 300$, $\text{SpO}_2/\text{FiO}_2 < 300$ or

oxygen saturation <90%) and evidence of new or worsening pulmonary edema on CXR. The extended data form included detailed questions regarding clinical signs and symptoms, laboratory values, CXR, EKG, and echocardiogram results. In addition to completing an extended data form for patients who experienced a potentially serious transfusion reaction, the nurse coordinators also prepared a clinical synopsis/time line that included a detailed clinical and laboratory narrative.

Expert panel adjudication

All extended data forms and clinical synopses were reviewed independently by a panel of 3 transfusion medicine experts (Y.W., P.N., R.S.) in a blinded fashion. Individual cases were assigned to 2 experts and if, after independent review, they both agreed with the transfusion reaction diagnosis, then the case was considered adjudicated and closed. If a diagnosis was not agreed upon, then the 3rd panel member independently reviewed the case. If the 3rd reviewer agreed with one of the initial reviewers, the case was considered adjudicated and closed. If agreement on a diagnosis was not reached, then a subsequent teleconference was held among all expert panel members to reach agreement. An intensive care physician was available for consultation on particularly complicated cases.

Besides establishing a diagnosis, the expert panel members that reviewed each case provided input, based on pre-defined criteria, on the imputability and severity of the transfusion reaction being considered (Supplemental Appendix 3). To ensure the most accurate analysis, an imputability judged to be “definite” or “probable” by at least one expert panel member was required for classification of serious transfusion reactions. To categorize the cases (Supplemental Appendix 4), the expert panel relied on their clinical expertise plus predefined criteria reported by a number of organizations including the Centers for Disease Control¹² as part of the US Biovigilance System⁴ and the International Society of Blood Transfusion/International Society for Blood and Transplant¹¹.

Statistical Analyses

Analysis were conducted using SAS/STAT software, Version 9.4, Cary, NC, USA. Descriptive statistics for all the screened patients were presented as the mean with a standard deviation or median and range for continuous variables and absolute number and percentages for categorical variables (Table 1). Incidence rates were calculated by taking the number of reactions and dividing that number by the total sampled number of transfusion episodes. Statistical analysis, including Chi-Square and Fisher’s Exact Test, were completed where appropriate. Logistic regression models were conducted to estimate Odds Ratios (ORs) and 95% Confidence Intervals (CI) and to compare the odds of having a risk factor between patients with and without TACO. We considered a p-value < 0.05 or a 95% CI that did not include 1.00 to be statistically significant.

Study approval

This study was approved by the Institutional Review Boards of all the participating hospitals and RTI, and was monitored by an NHLBI observational study monitoring board.

RESULTS

General information and demographics

There were 58,487 components administered in 27,846 transfusion episodes to inpatients 18 years old across the 4 hospital systems from July – December of 2014. In total, 4857 transfusion episodes (17.4% of all transfusion episodes at the 4 sites) were evaluated by the nurse coordinators over the course of this 6-month retrospective study (Figure 1).

Characteristics of the patients are shown in Table 1. Fourteen percent of the studied patients were deceased at the time of the chart review, which was completed approximately 3 months after the transfusion episode; none of the deaths were directly attributed to transfusion.

Serious transfusion reactions

For purposes of this study, “serious” transfusion reactions included cardiopulmonary, hemolytic, septic, hypotensive, or anaphylactic reactions. Extensive clinical and laboratory details of these cases were gathered by the nursing coordinators, for adjudication by a panel of transfusion medicine experts. A total of 102 transfusion episodes met these “serious” reaction criteria (Figure 1), with 99 of these being potential cardiopulmonary transfusion reactions. Of the 102 serious transfusion reactions, 48 were determined by the transfusion medicine expert panel to be TACO, with 39/48 cases scored as having an imputability of definite or probable by at least 1 reviewer (Figure 2). None of these reactions were directly attributed to the death of a patient. Additional demographic data of the studied patients, including those determined to have serious cardiopulmonary reactions, are shown in Table 1.

Differences were observed in the number of cases adjudicated to be TACO by hospital, ranging from a low of 4 cases over the 6-month period at one hospital to a high of 18 cases over the 6-month period at another hospital. Of all adjudicated TACO cases, the incidence rate with definite or probable imputability was 0.8% per transfusion episode. The incidence rate of TACO with any imputability was 0.99%. Two of two expert panel members agreed on the diagnosis in 27/48 (56%) cases. The imputability of the diagnosis (definite, probable, or possible) was agreed upon by the reviewers in 20/48 cases (42%).

Five (4.9%) of the 102 serious reactions were classified as TRALI/possible TRALI, with four having an imputability of definite or probable according to least one reviewer. The incidence rate of TRALI/possible TRALI with definite or probable imputability was 0.08. Of note, two of these cases had underlying ALI risk factors (aspiration and sepsis/pneumonia) such that they fit the Canadian Consensus Conference definition¹³ of possible TRALI.

Six of the 102 (5.9%) potential serious reaction cases were determined to be transfusion reactions that were not TACO or TRALI. Of these, one was adjudicated to be a septic reaction (possible imputability), one was adjudicated to be a hypotensive reaction (probable imputability), and one was adjudicated to be an anaphylactic reaction (definite imputability). Three were adjudicated to be pulmonary reactions that did not fit TACO or TRALI criteria, and thus could be classified as transfusion associated dyspnea according to CDC criteria¹². No acute hemolytic transfusion reactions were identified.

Details of serious transfusion reactions: TACO

Of the 39 reactions determined by the expert panel to be TACO with definite or probable imputability, 29 (74.3%) had symptoms within 6 hours of the cessation of the transfusion. Pre-transfusion co-morbidities of the patients with TACO are shown in Figure 3A, with 2 or more co-morbidities noted in 25 (64.1%). Signs and symptoms of the 39 TACO cases, extracted from clinical notes by the nursing coordinators, included dyspnea (n=12, 30.7%), rales (n=10, 25.6%), tachypnea (n=10, 25.6%), and fever (n=7, 17.9%). Diuretics were administered at or after the time of the transfusion in 27 (69.2%) of these patients. Nine (23.1%) patients were transferred to the ICU post-transfusion. Six (15.4%) patients that were not previously intubated were intubated during or immediately post-transfusion. Twenty-four (61.5%) required supplemental oxygen, 8 (20.5%) received a fluid bolus around the time of the transfusion, 9 (23.1%) had new onset hypertension, and 4 (3.3%) had new onset hypotension. Five patients had documented elevation of central venous pressure.

Post-transfusion CXRs were available for evaluation in all 39 cases (Figure 3B). Post-transfusion EKGs were completed in 19/39 (48.7%) of cases. Post-transfusion echocardiograms were completed in 17 (43.6%) cases, with some abnormality reported in 15/17 (88.2%): a decreased ejection fraction was noted in 8 cases, diastolic dysfunction was noted in 4 cases, and an elevated right atrial pressure was noted in 4 cases. Of note, pre-transfusion echocardiograms were completed in 16 (41%) cases, with some abnormality reported in 14/16 (87.5%): a decreased ejection fraction was noted in 3 cases, diastolic dysfunction was noted in 6 cases, and an elevated right atrial pressure was noted in 1 case. ABGs were completed in 22/39 (56.4%) of cases post-transfusion, with a mean PaO₂/FiO₂ ratio of 223.3 (median 188.4, sd 119.6). In contrast, pre-transfusion ABGs were completed in 16/39 (41%) of cases, with a mean PaO₂/FiO₂ ratio of 373.2 (median 368.9, sd 135.9). Post-transfusion BNP or NT pro-BNP labs were not obtained in any of the cases.

Details of serious transfusion reactions: other

The small number of other serious transfusion reactions identified in this study limits the value of extensive sub-group descriptions. All 4 of the cases identified to have TRALI/possible TRALI with definite or probable imputability had 1 or more co-morbidity noted, with 2 (50%) having 2 or more co-morbidities. Three of 4 (75%) required ICU transfer during or immediately after the cessation of the implicated transfusion. Post-transfusion CXRs were available for evaluation in all 4 cases, with bilateral infiltrates noted by the radiologists in 2 cases, radiographic evidence of COPD noted in 2 cases, and pulmonary edema noted in 3 cases; pulmonary edema was not noted on any of the pre-transfusion CXRs. ABGs were completed in 4/4 cases post-transfusion, with a mean PaO₂/FiO₂ ratio of 224.1 (median 184.4, sd 188.9). In contrast, ABGs were completed in 2/4 of cases pre-transfusion, with a mean PaO₂/FiO₂ ratio of 299.8 (median 299.8, sd 145.2). Post-transfusion BNP or NT pro-BNP labs were not obtained in any of the cases.

Blood components transfused

RBCs only (i.e. no other blood components) were transfused to 56.4% of the 39 TACO cases and 58.9% of the 4818 non-TACO cases. Plasma only was transfused to 18% of TACO cases and 8.7% of non-TACO cases. Platelets only were transfused to 2.6% of TACO cases and

17.9% of non-TACO cases. Cryoprecipitate only was transfused to 0% of TACO cases and 1.2% of non-TACO cases. More than one blood component was transfused to 23.1% of TACO cases and 11.9% of non-TACO cases (Figure 4A). Patients who were transfused with more than one component were more likely to have TACO compared to patients who received only RBCs, but this was not a statistically significant finding [OR = 2.03, 95% CI = 0.93 – 4.43]. Patients who were transfused with plasma only were more likely to have TACO compared to patients who were transfused with RBCs only, but this was also not a statistically significant finding [OR = 2.15, 95% CI = 0.91–5.07].

Among TRALI/possible TRALI cases, RBCs only were transfused in 1 case, plasma only was transfused in 1 case, and a mixture of different blood components were transfused in 2 cases. The single patient who had an anaphylactic reaction received 2 pools of cryoprecipitate, and the patient who had a hypotensive reaction received several different blood components.

The total number of components (1 unit, 2 units, and 3 or more units) transfused per episode (Figure 4B) was significantly different for TACO patients compared to all the non-TACO screened patients [p-value < 0.0001 by logistic regression analysis]. Patients who received 3 or more units were more likely to have TACO compared to patients who received 1 or 2 units per transfusion episode. The odds ratio for having TACO if receiving 3 or more units vs. 1 unit was 4.5 [95% CI= 2.2, 9.3], and odds ratio for 3 or more units vs. 2 units was 3.1 [95% CI= 1.4, 7.2]. Patients who received 2 units were not significantly more likely to have TACO compared to patients who received 1 unit.

Minor transfusion reactions

For purposes of this study, “minor” transfusion reactions included febrile non-hemolytic, minor allergic, and delayed serologic reactions which did not have clinical data to suspect severe cardiopulmonary, hemolytic, septic, hypotensive, or anaphylactic reactions. Non-hemolytic febrile reactions were identified in 30 transfusion episodes (0.62% of total episode), with minor allergic transfusion reactions identified in 14 episodes (0.29% of total episodes). Delayed serologic transfusion reactions were identified in 2 episodes (0.04% of total episodes). These minor transfusion reactions were not reviewed by the panel of transfusion medicine experts.

Transfusion reaction reporting

Although 23/39 (59%) of the charts of cases adjudicated to be TACO contained clinical notes mentioning the possibility that the pulmonary symptoms could be transfusion associated, only two (5.1%) of these cases were reported to the transfusion service as a potential transfusion reaction (Figure 5A). Similarly, although all 4 of the charts of the cases adjudicated to be TRALI/possible TRALI contained clinical notes mentioning the possibility of the symptoms being transfusion associated, only 1 case was reported to the transfusion service as a potential transfusion reaction. The anaphylactic and the hypotensive reaction were both reported to the transfusion service as potential transfusion reactions.

Of the minor transfusion reactions, 9 of 30 transfusion episodes (30%) identified by the nursing coordinators to be potential febrile non-hemolytic transfusion reactions were

reported by the clinical teams to the blood bank, as were 7 of the 14 transfusion episodes (50%) identified as potential allergic transfusion reactions (Figure 5B).

DISCUSSION

This study, which retrospectively surveyed 4857 transfusion episodes of adult inpatients > 18 years old over a 6-month period at 4 academic tertiary care hospitals in the US, found serious cardiopulmonary transfusion reactions to occur in approximately 1% of all transfusion episodes. TACO was the most common reaction noted in this study, consistent with the relatively high incidence rates reported by active surveillance studies^{8,14,15}. The incidence of other serious transfusion reactions was difficult to accurately estimate due to their low levels of apparent occurrence, which was not unexpected given our moderate sample size. Minor reactions (febrile and allergic), which were not targeted for intensive investigation in this study, occurred in 0.62 and 0.29% of all analyzed transfusion episodes; these rates are lower than the 1% (febrile) and 1–3% (allergic) historically described¹⁶.

One of the most striking findings of this study was the sharp contrast in the number of cardiopulmonary reaction cases identified by nursing study coordinators compared to the number of potential reactions actually reported to the transfusion medicine service/hospital blood bank. Despite 27/43 (63%) of adjudicated TACO or TRALI/possible TRALI cases having documentation in clinical notes suggesting the possibility of transfusion being associated with the cardiopulmonary symptoms, only 3 reactions (2 TACO, 1 TRALI/possible TRALI) were reported to the transfusion medicine service/hospital blood bank. Under-reporting of transfusion reactions has been described in prior studies^{8,9,17,18}, with one study finding that only 14% of TRALI/possible TRALI and 11% of TACO cases were reported to the transfusion service¹⁷. A better understanding of why cardiopulmonary transfusion reactions are less likely to be reported to the transfusion service than febrile or allergic reactions is an important step in improving such reporting. A survey of physicians and mid-level providers providing direct patient care may provide insight into their thought process in this regard: Do they think the transfusion reaction work-up of a patient with pulmonary edema is unlikely to change clinical care of the patient? Are they less likely to report potential pulmonary transfusion reactions in patients with underlying lung disease¹⁹? Are they aware that TRALI mitigation strategies include identifying at risk donors and removing them from the donor pool?

The TACO incidence identified in this study is at the lower end of the 1–8% range reported in other active surveillance studies^{14,15,20–23}, and is significantly higher than rates reported by hemovigilance which are at least 10–100 fold lower^{20,6,7,24}. Interpretation of published incidence rates must take into consideration issues of recognition and reporting, as well as the denominator utilized. It is likely that the reported TACO rates in this study would have been higher had all patients with new onset hypoxia noted around the time of a transfusion (but with no CXR available for auditing) been evaluated. Further, the reported TACO rates might have been higher had a select group of patients (e.g. those undergoing joint replacement) been studied, instead of all transfused patients. In contrast, the number of TRALI/possible TRALI cases identified in this study is higher than previously reported. However, 2 of the 4 TRALI/possible TRALI cases had acute lung injury risk factors.

Characteristics of factors previously identified to be associated with TACO were identified in this study. For example, co-morbidities previously associated with TACO such as renal insufficiency and COPD^{3,25–27} were also noted in this study. TACO patients were more likely to be transfused with 3 or more products during the studied episodes as compared to patients without TACO, with transfusion volume being a known TACO risk factor. Unlike what has been noted in some studies^{3,20,28}, however, advanced age was not more common in TACO cases in this study.

Limitations to any study must always be taken into consideration. As with any chart review, the data evaluated are only as thorough as the information contained in the chart. Further, all 4 hospitals were tertiary care centers and inpatients 18 years old were studied, so our findings may not apply to other types of hospitals, to outpatients, or to children. Differences in the incidence of TACO between the 4 hospitals suggest possible underlying differences in patient populations and/or transfusion practices. In fact, the TACO cases at the hospital that reported the largest number of TACO cases were more likely to have received 3 or more units and a mixture of blood components than those at the other 3 hospitals. Although all patients studied were confirmed to have received blood products, transfusion duration and detailed fluid input/output data were not collected. Given that this study involved “transfusion episodes,” some of the same patients were evaluated more than once during the 6 month study period. As such, the data are presented as reactions per transfusion episode, and not reactions per patient. One notable study finding includes the differences in diagnosis/imputability of serious transfusion reactions observed between expert panel members; these highlight the way that individual interpretation of data and definitions may impact biovigilance reporting. Finally, although this study was designed to investigate serious transfusion reactions, incidence rates of rare reactions (including hemolytic reactions) could not accurately be estimated due to sample size, and delayed reactions may not be accurately estimated due to study design.

In summary, this large retrospective analysis of transfusion reactions via active surveillance of electronic medical records by trained study nurse coordinators and transfusion medicine experts found TACO to be the most prevalent transfusion reaction, with significant discrepancies in the number of cardiopulmonary reactions identified in the study versus the number of reactions reported to the transfusion medicine service/blood bank. Open communication between transfusion medicine physicians and physicians providing direct patient care, with continued education regarding the importance of reporting suspected transfusion reactions, is needed for appropriate transfusion reaction evaluation. Such communication and education will improve the accuracy of passive surveillance reporting systems, will lay the groundwork for studies investigating the pathogenesis of post-transfusion pulmonary edema, and will serve as stepping stones for future studies aimed at minimizing the morbidity and mortality of transfusion complications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Schematic of study design with identification of serious and minor transfusion reactions

Figure 2. Adjudication and imputability of serious transfusion reactions

(A) 102 cases were identified by nurse study coordinators as having potential serious transfusion reactions. (B) Consensus in diagnosis and imputability among the transfusion medicine expert panel members.

Figure 3. Information on cases adjudicated to be TACO

(A) Co-morbidities associated with the 39 cases adjudicated to be definite or probable TACO. (B) CXR findings for these 39 TACO cases.

Figure 4. Blood components released for transfusion for TACO cases and all screened cases
(A) Distribution of blood components released for transfusion in the 6-hour episode for the 39 TACO cases (black bars) and for the >4800 other screened cases that did not have TACO (grey bars). **(B)** Number of total products released for transfusion in the 6-hour episode for TACO cases (black bars) and other screened cases (grey bars).

Figure 5. Serious and minor transfusion reaction reporting

(A) Serious transfusion reactions determined to be definitely or probably associated with transfusion, in comparison to those with notes in the chart potentially implicating the transfusion and in comparison to those reported to the transfusion service. (B) Minor transfusion reactions identified by the study nurse coordinators, in comparison to those reported to the transfusion service.

Table 1

Patient characteristics for TACO, TRALI, and all screened patients

Characteristic *	TACO (n=39)	Possible TRALI (n=4)	All screened cases (n=4857)
Age (years)	61 (sd 17)	58 (sd 9)	59 (sd 16)
Sex (female %)	41	50	47
Race (%)			
White	72	50	70
Black	8	0	11
Hispanic	8	25	5
Asian	8	0	4
Other or unknown	4	25	10
Location of transfusion (%)			
General ward	33	25	50
ICU	41	75	34
OR	21	0	10
Other	5	0	6
Blood type (%)			
A	31	25	36
B	26	0	13
AB	3	0	5
O	40	75	45
Missing	0	0	1
Deceased (%)	15	25	14

* no statistically significant differences were found between any of these variables for TACO cases or all screened cases.