Universal leukoreduction decreases the incidence of febrile nonhemolytic transfusion reactions to RBCs

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BACKGROUND: Febrile nonhemolytic transfusion reactions (FNHTR) is a relatively common complication associated with allogeneic transfusion. Because WBCs have been implicated in the mechanism of FNHTRs, it has been proposed that the transfusion of leukoreduced RBCs should be associated with a decreased incidence of FNHTRs. These reactions are generally not life threatening, but they are expensive in their management, evaluation, and associated blood-product wastage. Over the past several years, the proportion of leukoreduced RBCs has increased at Johns Hopkins Hospital in an effort to move toward complete leuko-reduction. A retrospective analysis is reported here of FNHTRs in RBC recipients as the inventory increased in percentage of leukoreduced RBC units.

STUDY DESIGN AND METHODS: Between July 1994 and December 2001, all transfusion reactions (TRs) associated with the transfusion of allogeneic RBCs were retrospectively analyzed. Both computerized data and individual TR reports were reviewed. Patients who had both allergic and febrile features were included as part of both categories. TRs were reported as a percentage of total units transfused. Two time periods were selected for direct comparison. July to December 1994 represents the time period before the initiation of an increase in leukoreduction. July to December 2001 represents a time period when almost complete leukoreduction (99.5%) had been achieved. The TR data were compared between these two time periods, comparing a time before leukoreduction to a time period after leukoreduction had been achieved. The trends in TRs over the entire 7.5-year period of July 1994 to December 2001 were also assessed.

RESULTS: In the initial period before the initiative to move toward leukoreduction, 96 percent of our RBC inventory was non-leukoreduced. In the study period after leukoreduction, 99.5 percent of our RBC inventory was leukoreduced. When comparing these two time periods, the incidence of FNHTRs decreased from 0.37 percent to 0.19 percent (p = 0.0008). The trend over the entire 7.5-year study period confirms the decrease in FNHTRs as the percentage of leukoreduced RBCs increased. The incidence of allergic TRs has remained unchanged over this time period.

CONCLUSIONS: As our institution has increased its inventory of leukoreduced RBCs to approximately 100 percent, selective leukoreduced protocols have been discontinued. The incidence of FNHTRs has decreased significantly and the rate of allergic reactions has essentially remained unchanged. Leukoreduction is effective in decreasing FNHTRs associated with the transfusion of allogeneic RBCs.

Febrile nonhemolytic transfusion reactions (FNHTRs) are a common complication associated with the transfusion of allogeneic RBCs and platelets. Although they typically occur during the time of the transfusion, these reactions may arise within 4 to 6 hours after the transfusion has been completely administered. The frequency of febrile reactions in non-leukoreduced RBCs has been estimated to be 0.5 to 6.8 percent of all units transfused.¹² Patients with a history of FNHTRs are at a 15-percent risk of recurrence of this type of reaction.³ Most FNHTRs are self-limited; they are characterized by fever (>1°C), chills, and rigors. Nausea, vomiting, dyspnea, and hypotension may accompany these reac-

ABBREVIATIONS: FNHTR = febrile nonhemolytic transfusion reaction; TR = transfusion reaction.

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FNHTRs are believed to be WBC-mediated by two
different mechanisms. One mechanism is the interaction
between the recipient’s cytotoxic antibodies and HLA
and/or WBC-specific antigens located on donor WBCs.
Formation of antigen-antibody complexes leads to com-
plement binding and release of endogenous pyrogens.
Direct activity of various biological response modifiers
including cytokines also appears to play a role in these
reactions. A second mechanism, primarily related to the
storage of platelets, involves the continued production
and release of biologically active cytokines by residual
WBCs. Reaction rates are doubled or greater in 3- to
5-day-old platelets as compared to 1- to 2-day-old
platelets.
Therefore, leukoreduction of RBCs, as well as plate-
lets, should reduce the incidence of FNHTRs and associ-
ated clinical costs. Historically, leukoreduced RBCs have
commonly been used for patients with a prior history of
FNHTRs to nonleukoreduced RBCs. For selected patients,
use of leukoreduced blood components has been shown
in controlled studies to decrease certain complications of
transfusion, including FNHTRs. There is conflicting data
about its potential benefits in other patient populations.
Since the Blood Product Advisory Committee to the FDA
recommended universal leukoreduction, several studies
have been published on the value of prestorage universal
leukoreduction of RBCs to reduce FNHTRs with mixed
results. Most of the studies have been retrospective in
design. Because of the relatively low frequency of these
reactions, it has been difficult to study them using a ran-
domized control trial design.
Over the past several years, we have been gradually
increasing our inventory of leukreduced RBCs. We there-
fore have conducted a retrospective analysis of the
incidence of FNHTRs in all patients receiving RBC trans-
fusions at our institution between July 1994 and Decem-

MATERIALS AND METHODS
Evaluation of TRs
TRs are routinely reported to our transfusion medicine
service in a timely fashion. The clinical service reporting
the reaction completes a standard form that includes a
brief clinical history, date and time of reaction, unit(s)
transfused, time of transfusion, amount transfused, clini-
cal symptoms (i.e., fever, chills, itching, hives), and vital
signs before transfusion and after the reaction. The
remaining product is returned to the laboratory, along
with a posttransfusion blood sample for appropriate work
up. Urine samples are sent to the clinical laboratory for
analysis. The blood bank work-up includes a clerical
check, a hemolysis check of the posttransfusion serum
sample by visual inspection, urine Hb level and micro-
scopic examination if indicated, DAT, antibody screening
tests, and repeat cross-matches on both the pre- and
posttransfusion samples associated with RBC transfu-
sions. If the reaction has been assessed by the transfusion
medicine physician as solely allergic in nature, the extent
of the serologic evaluation may be limited. For febrile
reactions, a ram stain and culture of the blood product is
obtained. The clinical service is requested to check a pre
and post-complete blood count (CBC) and a chemistry
for LDH. All TRs are handled as an emergency. The above
information is entered into the computer template by the
transfusion medicine team.
As soon as a TR is reported to the transfusion ser-
vice, a transfusion medicine physician is notified of the
reaction. The physician does an immediate evaluation of
the reaction with the clinical service and the patient,
if necessary. The physician makes recommendations
to the clinical and transfusion services concerning the
most appropriate treatment for the patient and preven-
tive plans for future transfusions. Each reaction is
reviewed at the following morning’s daily rounds, which
includes a transfusion medicine attending and fellow.
Standard criteria are used for classifying the type of TR. FNHTRs are characterized by fever (>1°C increase) and
shaking chills. Allergic reactions typically present with
itching and hives. The final evaluation and recommenda-
tions are entered into the computer, typically within
24 hours, and signed by an attending transfusion medi-
cine physician.

TR analysis
TRs were evaluated retrospectively by assessment of both
computerized data and original reports. Our transfusion
medicine computer system has data templates that allow
for thorough analysis of all TRs. Reaction data is catego-
rized on a monthly basis, as is the data for all components
transfused. Additionally, the original reports of each reac-
tion were reviewed. TRs involving multiple blood compo-
ents transfused at the same time are considered as a
single reaction (i.e., if the patient received two units of
leukoreduced RBCs, even though each is reported in the
computer as a reaction; for this analysis, it is considered a
single TR event). Reactions classified as unrelated to trans-
fusion are excluded. TRs are reported as a percentage of
total units transfused. Patients who had both allergic and
febrile components to their reaction were counted as part of both categories.

Patients
The primary analysis includes the following two patient groups: (1) all patients who received allogeneic RBCs between July and December 1994 and (2) allogeneic RBC recipients between July 2001 and December 2001. For the assessment of TR trends, all patients who received allogeneic RBCs from July 1994 through December 2001 were included.

RBC units
All RBC units, both nonleukoreduced and leukoreduced, were AS-1 units obtained from our component provider (the Greater Chesapeake and Potomac Red Cross) from volunteer whole-blood donations. For the leukoreduced RBC units, leukoreduction was performed prestorage.

Statistics
Data was analyzed using a two-sample test of proportions deeming significance at a p value of less than 0.05. All statistical analyses were done using software (Intercooled StataTM version 7, Stata Corporation, College Station, TX).

RESULTS
We compared FNHTRs before and after the initiative to increase our inventory toward virtual complete leukoreduction. Between July 1994 and December 1994, our transfusion service administered 16,246 RBC units, of which 96 percent of units were nonleukoreduced RBCs. Between July and December 2001, we administered 19,916 units. In contrast to the earlier time period, 99.5 percent of the RBC inventory consisted of leukoreduced RBCs in 2001.

Between July 1994 and December 1994, 91 total TRs were reported, including 24 TRs with allergic features and 60 FNHTRs. These FNHTRs occurred in 51 patients, 47 patients having a single TR event and 4 patients with repeated FNHTRs. Between July 2001 and December 2001, 79 total TRs were reported, including 34 allergic reactions and 37 FNHTRs. These FNHTRs occurred in 34 patients with 31 patients having a single reaction episode and 3 patients with repeated reactions. When evaluating the number of patients with repeat reactions (four in 1994 and three in 2001), this difference was not significant.

As summarized in Table 1, there was a significant difference between the incidence of TRs between the two time periods (0.56% in 1994 vs. 0.40% in 2001, p = 0.024). The incidence of allergic TRs was not significantly different between the two time periods (0.15% in 1994 vs. 0.17% in 2001, p = 0.59). However, there was a significant difference in the incidence of FNHTRs seen between the two time periods (0.37% in 1994 vs. 0.19% in 2001, p = 0.0008).

Figure 1 graphically displays the trend we have found in FNHTRs over the 7.5-year study period. Since 1994, our transfusion service’s inventory of leukoreduced RBCs progressively increased.
from 4 to 99.5 percent. Figure 1 shows that FNHTRs decreased as the percentage of nonleukoreduced RBCs decreased. The percentage of allergic TRs has remained relatively unchanged over the same time period, providing a useful internal control.

**DISCUSSION**

Over the past several years, our institution has increased its inventory of leukoreduced RBCs with a final goal of administering only leukoreduced RBCs. In 1994, our inventory was approximately 4 percent leukoreduced; by 1998, about 35 percent leukoreduced; and by 2000, approximately 75 percent of our RBC inventory was leukoreduced. Currently, our RBC inventory is over 99 percent leukoreduced.

In previous years, our institution had a policy of selective leukoreduction for patients; these protocols were primarily for oncology patients and multitransfused patients who had previously experienced a FNHTR. When we analyzed our TR data at an earlier point, we observed and attributed this observation to a possible selection bias in our patients receiving the selective leukoreduction protocols at a time when our transfusion service had an inventory that consisted of approximately 60 percent leukoreduced RBCs.

Because our inventory is now almost completely leukoreduced, our service no longer has a selective transfusion protocol. Additionally, there is controversy in the literature as to the actual efficacy of leukoreduced RBCs in reducing FNHTRs. Therefore, we performed this retrospective analysis to assess the incidence of TRs in patients who receive leukoreduced RBCs.

Our institution has a strong capability to assess TRs. First, our transfusion service has a very aggressive and comprehensive method for the surveillance of TRs. We have a staff of five transfusion coordinators who follow the transfusion needs of all oncology patients, assisting in the reporting and evaluating of TRs. Second, our transfusion service has an excellent rapport with the other clinical services, facilitating a high rate of reporting of suspected reactions from the hospital to our transfusion service. Third, our transfusion service has a resident, fellow, and attending on call 24 hours a day, 7 days a week, allowing for immediate follow-up and evaluation as soon as a TR is reported. Finally, our computer system has built-in templates that allow for a thorough and complete analysis of the TR data. Because of such data-collecting capabilities, we were able to uncover and compare data at a time when our service had an inventory of nearly 100 percent nonleukoreduced RBCs to a time when our service consisted nearly entirely of leukoreduced RBCs. This infrastructure also allowed us to compare the composite data in the intervening years as we gradually increased the percentage of leukoreduced RBCs in our inventory.

Table 1 represents our TR data before and after our RBC inventory underwent the transition to leukoreduction. Initially, our inventory consisted of only 4 percent leukoreduced RBCs (July-December 1994); after this increase toward leukoreduction, our inventory was 99.5 percent leukoreduced (July-December 2001). We found a significant difference in the incidence of FNHTRs (0.37% vs. 0.19%, p = 0.0008), with no significant difference in allergic TRs (0.15% vs. 0.17%, p = 0.59). The difference in the overall TR rate was 0.56 percent versus 0.40 percent, which is significant (p = 0.024).

As shown in Fig. 1, the incidence of FNHTRs decreases in an almost parallel fashion to the decrease in transfusion of nonleukoreduced RBCs. During this same time, the allergic TR rate remained unchanged. This represents an important internal control because the mechanism of allergic TRs is attributed to plasma proteins and not WBCs and should not be affected by leukoreduction.

Our reaction rates are comparable with those reported in the literature for nonleukoreduced RBCs and overall incidence of TRs in RBCs. Our study demonstrates the efficacy of leukoreduced RBCs in reducing the incidence of FNHTRs. This is most evident in the direct comparison of our reaction rates in 1994 versus 2001, as discussed above. We have also seen a striking parallel decrease in the incidence of FNHTRs since 1994 as our inventory of nonleukoreduced RBCs has decreased, as shown in Fig. 1. Our study supports the findings of several recent studies. There are several reasons our data may differ from publications reporting no benefit from leukoreduction. First, our institution’s protocol for transfusion of blood components does not include initial premedication of all patients, which may mask potential FNHTRs. Second, we believe our institution has better overall cooperation from the clinical services in reporting TRs. Third, our institution has a TR surveillance algorithm that includes transfusion coordinators and transfusion medicine physician availability at all times, immediate and complete follow-up and evaluation, and attending recommendation within 24 hours. Finally, our department has a robust computer system that allows us to retrieve and analyze many different transfusion components, variables, and permutations.

It should be noted, however, that there are limitations in this retrospective study. For example, unrelated changes in medical practice over the 7.5-year study period could have influenced the frequency of suspected TRs. Further, the participation of several transfusion medicine physicians may be problematic. Although the physicians all used the same criteria for classifying TRs, their final medical assessment of reported reactions may have differed.
Our findings indicate that prestorage leukoreduction of RBCs is beneficial in reducing the incidence of FNHTRs. This reduction of FNHTRs is one of several arguments supporting the use of universal leukoreduction of blood components.

REFERENCES