Correspondence

To the editor:

Deleterious consequences of allogeneic blood transfusion on postoperative infection: really a transfusion-related immunomodulation effect?

The purported deleterious effect of transfusion-related immunomodulation (TRIM) on postoperative infection and its prevention by leukoreduction of transfused blood are a matter of great controversy among transfusion medicine specialists. In a recent review on this issue, Vamvakas and Blajchman pointed out that current evidence supporting a beneficial effect of leukoreduction is inconclusive because randomized-controlled trials (RCTs) have produced contradictory findings. But a 10% increase in the risk of postoperative infection associated with transfusion of nonleukoreduced allogeneic blood could have passed undetected in some RCTs, and an unaffordable large number of patients should be enrolled in future trials in order to detect such a small effect. Because postoperative infection is a frequent, serious, and expensive complication of surgery, even a 10% decrease in its incidence would result in a public health benefit so large that regulatory agencies may decide to implement universal leukoreduction without waiting for the results of further trials. This may be a sound precautionary measure, provided that TRIM would really play a role in postoperative infection.

Allogeneic blood transfusion impairs T-cell–mediated immunoresponse, as measured by a decreased antigen-driven lymphoblastic transformation and natural killer activity. This is consistent with the protective effect that blood transfusion has on renal allografts, which is the only TRIM effect that has been unequivocally demonstrated at the clinical level. But at the present state of knowledge, it is hard to believe in a connection between impaired T-cell function and the postoperative events attributed to allogeneic blood transfusion. The latter includes surgical infections (wound, intra-abdominal abscesses, fistulization, mediastinitis), nosocomial infections (pneumonia, urinary tract), and other postoperative complications such as leakage from bowel anastomoses, aortocoronary suture dehiscence, and multiorgan failure. Each of these events has been found in some of the RCTs reviewed by Vamvakas and Blajchman to occur more frequently in the patients transfused with regular allogeneic red blood cells (RBCs) than in recipients of leukoreduced or autologous blood. Therefore, the question arises as to whether transfusion of leukoreduced or autologous blood might have been a surrogate for another mechanism by which blood transfusion could actually propitiate the above-mentioned postoperative complications.

In the RCT by Heiss et al., patients in the autologous transfusion arm had deposited 2 units of blood 10 and 7 days before surgery, whereas those in the allogeneic blood arm received standard blood bank RBCs (storage time not stated). In the study by Houbiers et al., patients in the leukoreduced blood arm were transfused with laboratory-filtered RBCs that were 2-3 days old, while patients in the control arm received stored RBCs (storage time not stated). In the RCTs by Jensen et al. and Tarter et al., patients in the leukoreduced arm received RBCs that were passed through a bedside filter, whereas control patients were transfused with conventional, unfiltered RBCs (storage times not mentioned). And van de Watering et al. who compared buffy-coat-depleted RBCs, fresh-filtered units, and stored-filtered units, stated that transfused blood was between 7 and 21 days old, without further specification by study arm. Because it is common practice to select RBC units stored for a short period for bedside filtration, whereas units closer to expiration date are selected for regular transfusion, it is plausible that leukoreduced or autologous blood may have been a surrogate for fresher blood in all the above RCTs.

Longer storage of transfused RBCs has been associated with higher incidence of postoperative infection after resection of rectal cancer or coronary artery bypass surgery, as well as with poorer outcomes in critically ill patients. The deleterious effect of stored blood may be due to accumulation upon storage of leukocyte-derived inflammation mediators, which could be prevented by prestorage leukoreduction, or to depleted levels of 2,3-diphosphoglycerate and decreased deformability of stored RBCs, both impairing oxygen delivery to the tissues. Both healing of surgical anastomoses and defense mechanisms against infection in wounds are critically dependent on an adequate oxygen supply. Rigid RBCs produce capillary slugging and occlusion, leading to local ischemia and poor delivery of prophylactic antibiotics. In the gut, this may further lead to bacterial translocation, a process that plays an important role in the development of multiorgan failure. Although transfused RBCs recover their normal function after 12-24 hours, the first few hours after tissue contamination by bacteria are critical for wound infection to be established. These observations suggest a biologically plausible alternative to TRIM for the postoperative complications attributed to allogeneic transfusion. Needless to say, such mechanism would not be influenced by prestorage leukoreduction.

A reanalysis of the raw data of published RCTs, as the one proposed by Vamvakas and Blajchman, including the length of storage of transfused RBCs, if available, could provide insight on the existence of explanations other than TRIM for the observed beneficial effects of leukoreduced or autologous blood transfusion. Otherwise, further studies aimed at clarifying this point are needed before universal leukoreduction is accepted as a worthy health intervention. The alternative would be the implementation of a very expensive intervention that may eventually prove to be useless.

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Deleterious clinical effects of transfusion-related immunomodulation: unresolved questions and recommendations for further research

Pereira proposes that the apparent association between allogeneic blood transfusion (ABT) and postoperative infection, reported by some of the randomized controlled trials (RCTs) reviewed in our recent article,1 might have been due to the transfusion of fresher units to patients who received either white-cell (WBC)–reduced or autologous (as compared with non-WBC–reduced) red blood cells (RBCs) in those studies. We agree that (1) alternative mechanisms exist that might explain the apparent association between ABT and postoperative infection and (2) definitive evidence justifying the implementation of universal WBC reduction for the prevention of the purported deleterious clinical effects of transfusion-related immunomodulation (TRIM) has not been presented. But universal, prestorage WBC reduction likely will be implemented soon,2 despite the absence of such definitive evidence. Thus, the implementation of universal WBC reduction will preclude the undertaking of further RCTs investigating TRIM effects mediated by allogeneic WBCs. We also agree with Pereira that further research into these questions is necessary, and we present 2 clinical research designs that could, in an era of universal WBC reduction, (1) establish the existence of a deleterious TRIM effect of allogeneic WBCs and (2) bolster (or refute) the possibility of an alternative mechanism for the association between ABT and postoperative infection proposed by Pereira.

In our review,1 we demonstrated that the available RCTs reporting on an association between ABT and postoperative infection produced discordant findings, which are impossible to reconcile by a meta-analysis of the published results. But a meta-analysis of the raw patient data—often referred to as meta-analysis of individual-patient data (IPD)—might be able to explain the disagreements between the studies based on (1) the distribution of confounding factors between the treatment and control arms, (2) the appropriateness of the recorded diagnoses of postoperative infection, (3) differential effects of the blood products transfused to the treatment and control arm of each study, and/or (4) elements of the design and analysis of each RCT (eg, lack of stratification by participating hospital in multicenter designs, exclusion of randomized subjects, violation of the intention-to-treat principle, etc).

Provided that the disagreements among the studies are explained, the accumulated patient data from the 7 published RCTs may prove sufficient to resolve definitively the question whether ABT predisposes to postoperative infection.3,4

Alternatively, the risk of postoperative infection could be compared between patients transfused before or after the implementation of universal WBC reduction.5 Such observational comparisons should present data on the length of storage of the transfused blood components to investigate the 3 hypotheses presented in Table 1. As suggested by Pereira and, previously, by us,6,7 the transfusion of stored, rigid RBCs depleted of nitric oxide (NO) could impede blood flow to the viscera (through vascular obstruction and/or vasoconstriction), predisposing to ischemia and thus, perhaps, infection. Relevantly, both we6 and others8 have reported that increased length of storage of (non-WBC–reduced) transfused RBCs is associated with an increased risk of postoperative infection. This relationship could be due to ischemia, secondary to the presence in the circulation of old, rigid RBCs (as Pereira indicates) or to biologic response modifiers, released from deteriorating WBCs and accumulating in the supernatant fluid of cellular blood components in a time-dependent manner during storage.9 If either of these 2 hypotheses were to be confirmed, a longer storage time of (non-WBC–reduced) transfused RBCs would be associated

Table 1. Possible mechanisms underlying an increased risk of postoperative infection in association with white-cell–containing allogeneic blood transfusion

<table>
<thead>
<tr>
<th>Hypothesis</th>
<th>Reduction in the risk of postoperative infection following the implementation of prestorage WBC reduction?</th>
<th>Increased risk of postoperative infection as the length of storage of the transfused cellular blood components increases?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Transfusion of older RBCs results in tissue hypoxia, which predisposes to postoperative infection.</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>2. Biologic response modifiers, released from deteriorating WBCs and accumulating in the supernatant fluid of cellular blood components, mediate adverse TRIM effects.</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3. Immunologically active, intact allogeneic WBCs mediate adverse TRIM effects.</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Expected results from observational comparisons of patients transfused before or after the implementation of universal WBC reduction.
with an increased risk of postoperative infection. Therefore, as suggested by Pereira, the length of storage of the transfused RBCs should be investigated as a possible explanation for the disagreements among the available RCTs in any future IPD meta-analysis of these studies.

It is possible that future research will not corroborate the reported association between increased length of storage of the transfused blood components and an increased risk of postoperative infection. If the TRIM effects were mediated by immunologically active, intact allogeneic WBCs, fresher (as opposed to older) blood components would be associated with an increased risk of infection. Table 1 presents 3 mechanisms that may underlie an association of ABT with postoperative infection as mutually exclusive hypotheses and shows the expected results from future observational comparisons of patients transfused before or after the implementation of universal WBC reduction, in the event that these 3 hypotheses were indeed mutually exclusive and only 1 of them was correct.

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To the editor:

Relationship between HLA alleles and cytomegalovirus infection after allogeneic hematopoietic stem cell transplant

Cytomegalovirus (CMV) infection remains associated with increased mortality in immunocompromised populations, particularly in allogeneic hematopoietic stem cell transplant (HSCT) recipients. Risk factors for reactivation include serostatus and occurrence of graft-versus-host disease (GVHD). Identifying new factors that modify the immune response against CMV might be of importance in HSCT recipients. There has been one study on the association between HLA alleles and CMV pneumonitis after hematopoietic stem cell transplantation (HSCT), but no study has tested the influence of a large number of alleles on CMV reactivation. We initiated a retrospective study on the effect of HLA alleles on CMV reactivation in the 144 consecutive recipients with a positive CMV serostatus at the time of transplantation who received an allogeneic transplant in our unit between October 1, 1996, and August 31, 1999. The donor was related in 98 patients. Weekly monitoring started from engraftment until day 100 after transplantation or longer. CMV reactivation was defined as a CMV pp65 antigenemia of at least 2 in 2 × 10⁵ leukocytes. CMV infection was treated with ganciclovir or foscarnet, for 2 to 3 weeks or until 2 consecutive negative tests. Because immunity recovers essentially from the graft, we studied the effect of the HLA alleles of the donor. HLA alleles were considered if their phenotype frequency exceeded 10%. Univariable and multivariable prognostic analyses, performed on SAS 6.12 software (SAS Institute, Cary, NC), were based on Cox models, and assessing the effect of acute grade II-IV GVHD as time-dependent. Multivariable prognostic analysis used a stepwise selection, introducing covariates either previously selected as associated with outcome at the 10% level or reported as prognostic factors from the literature. As of December 1, 1999, the median follow-up was 20 months after transplantation (range, 2 to 38 months). Ninety patients had developed CMV reactivation; only 12 had developed a CMV disease. The estimated rate of CMV reactivation was 64% at 3 months after transplantation. The estimated median time to CMV reactivation for patients with CMV infection, using time-to-event methods, was 45 days (95% CI, 39–48 days). Seventy-two patients had experienced acute grade II-IV GVHD. The estimated median time to GVHD was 18 days (95% CI, 16–21 days). In univariable analyses, GVHD was associated with CMV reactivation (HR [hazard ratio] = 1.73, P = .01), and 5 HLA alleles were associated with outcome at a 10% level. HLA-A11 (HR = 0.40, P = .03) and HLA-B51 (HR = 0.59, P = .07) were potentially protective against CMV reactivation, while HLA-D97 (HR = 1.48, P = .08), HLA-DR15 (HR = 1.56, P = .06), and HLA-A24 (HR = 1.56, P = .08) increased the risk of CMV reactivation. These 5 alleles were introduced into a multivariable Cox model, jointly with age, type of donor (related vs unrelated), T-cell depletion, donor CMV serostatus, and acute grade II-IV GVHD. The 2 factors that were selected with prognostic influence were GVHD (HR = 1.71, P = .01) and HLA-A11 (HR = 0.41, P = .04). The median peak of antigenemia was not significantly different between HLA-A11 recipients and non-HLA-A11 recipients (22 and 13 positive leukocytes, respectively, P = .50, Wilcoxon rank sum test). But none of the 17 HLA-A11 patients suffered from CMV disease.
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Arturo Pereira