Universal Leukoreduction of Cellular Blood Components in 2001?

No

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Leukocytes are known to have a number of biologic effects associated with allogeneic blood transfusion [Table 1]. The potential clinical importance of these effects, which are the focus of current debate over the merits of “universal” leukocyte reduction (leukoreduction; cellular components with <5 x 10^6 leukocytes) include the following: febrile-associated transfusion reactions (FATRs), transfusion-related alloimmunization to platelets, and transfusion-related immunomodulation. Several recent reviews1,2 of this topic, along with commentaries3-6 about the use of leukocyte-depleted blood components, have been published. The Blood Products Advisory Committee (BPAC) to the US Food and Drug Administration (FDA) voted 13-0 on September 18, 1998, in favor of universal leukoreduction of blood components,7 but the minutes stated that many committee members agreed there were insufficient good studies, and everyone wanted more data.8 To date, both leukoreduced and nonleukoreduced blood components remain FDA-approved. This commentary will summarize my view of this controversy and the need for additional controlled clinical trials to provide data to resolve this issue.

[Table 2] summarizes the percentage of blood components transfused that were leukoreduced in the United States in 1994 and 1997. The percentages for RBCs (17.6% and 18.3%) and platelets (16.5% and 15.5%) remained static, despite commercial advertisements to clinicians about leukocyte-depletion filters during this period.9 For the first 9 months of 1999, 3,592 (13%) of 27,663 RBC units transfused at our hospital were leukoreduced; our indications for leukoreduction reflect those published previously,4 and are summarized in [Table 3].

FATRs occur in only 0.5% of RBC transfusions; of these, 18% and 8% of patients experience a second or third FATR.10 Approximately 18% of platelet transfusions are

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**Table 1**

Potential Adverse Effects of Leukocytes in Blood Components

<table>
<thead>
<tr>
<th>Effect</th>
<th>1994</th>
<th>1997</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunologic effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alloimmunization (HLA and leukocyte antigens)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile reactions</td>
<td></td>
<td></td>
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<tr>
<td>Refractoriness to platelet transfusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transplant rejection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfusion-induced acute lung injury</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graft-vs-host disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunomodulation (possibly)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infectious disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTLV-I infection</td>
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</tbody>
</table>

HTLV, human T-cell lymphotropic virus.

Adapted from Lane et al.2

Caused exclusively by leukocytes in blood components.

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**Table 2**

Leukocyte-Reduced Blood Components Transfused in the United States, 1994 and 1997

<table>
<thead>
<tr>
<th>Component</th>
<th>1994</th>
<th>1997</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte-reduced RBCs</td>
<td>1,950</td>
<td>2,102</td>
</tr>
<tr>
<td>Storage</td>
<td>613</td>
<td>734</td>
</tr>
<tr>
<td>Bedside</td>
<td>1,337</td>
<td>1,328</td>
</tr>
<tr>
<td>All RBCs (%)†</td>
<td>11,107</td>
<td>11,476</td>
</tr>
<tr>
<td>Leukocyte-reduced platelets</td>
<td>1,301</td>
<td>1,402</td>
</tr>
<tr>
<td>Storage</td>
<td>409</td>
<td>516</td>
</tr>
<tr>
<td>Bedside</td>
<td>892</td>
<td>888</td>
</tr>
<tr>
<td>All platelets (%)†</td>
<td>7,866</td>
<td>9,037</td>
</tr>
</tbody>
</table>


Percentages in parentheses were calculated by dividing the number of leukocyte-reduced RBCs or platelets by the total numbers or RBCs or platelets, respectively.
It is now general agreement that bedside leukoreduction filters are now characterized as severe occur in only 2% of platelet transfusions. These reactions are caused mostly by plasma supernatants, and platelets leukoreduced by bedside filtration have not been found to reduce the overall prevalence of FATR. Bedside leukoreduction filters are now recognized to cause clinically significant hypotensive events by activation of the bradykinin-kininogen systems, particularly in patients taking angiotensin-converting enzyme inhibitors. There is now general agreement that bedside leukoreduction filters are not an appropriate technology to address FATRs; the Canadian Blood Service has implemented prestorage universal leukoreduction to address the problem of FATRs. However, a recent study indicates that prestorage leukoreduction does not affect the prevalence of FATR compared with bedside leukoreduction, and FATRs to platelets may be due in large part to the release of platelet-specific chemokines.

The issue of transfusion-related alloimmunization to platelets was studied in a National Heart, Lung, and Blood Institute–sponsored multicenter trial of newly diagnosed patients with leukemia. Clinical platelet refractoriness associated with HLA antibody serosity occurred in 18% of patients who received transfusions of unprocessed platelet concentrates compared with 8% of patients receiving leukoreduced apheresis platelets, leukoreduced platelet concentrates, or psoralen/UV-B treated platelets. While this difference achieved statistical significance, no important clinical differences were found among the patient cohorts, including prevalence of transfusion reactions, hemorrhagic events, mortality, length of stay, number of platelet transfusions, or number of RBC transfusions. A possible clinical benefit has been proposed for these patients during later hospitalizations for therapy, such as bone marrow or stem cell transplantation. A subsequent study, however, indicated that clinical platelet refractoriness in this setting is multifactorial and dependent on patient and treatment variables, rather than the presence of HLA antibodies. Furthermore, an audit of transplant programs found that two thirds of hemorrhagic events occurred in patients whose morning platelet count exceeded $20 \times 10^9/µL$ ($20 \times 10^9/L$); clinical bleeding episodes frequently were related to disease or anatomic pathophysiology (ulcers, infections, graft-vs-host disease) rather than to the degree of thrombocytopenia. The current debate about “low-dose” vs “high-dose” platelet transfusions is related in part to some of these issues.

Transfusion-related immunomodulation has been cited previously to be clinically important in 2 clinical settings: in patients undergoing renal transplantation and in women who have had multiple miscarriages. One recent commentary supporting universal leukoreduction concluded that allogeneic leukocytes were shown to be beneficial and widely accepted to be clinically effective for the treatment of recurrent spontaneous abortions; however, a multicenter, controlled study published shortly thereafter found no evidence of such an effect, and the authors recommended against allogeneic mononuclear infusions as a treatment for unexplained, recurrent miscarriage. Similarly, patients who have received transfusions before renal transplantation have been identified to have superior 1-year renal allograft survival compared with patients who did not receive transfusions. This effect is present even in patients undergoing immunosuppressive therapy with cyclosporine. Nevertheless, when patients who had not received transfusions before surgery were subsequently analyzed for blood transfused at the time of transplantation surgery, no effect was found for 1-year renal allograft survival.

Whether allogeneic blood exposure causes clinically significant immune suppression in any other settings remains a subject of debate. A number of observational, retrospective reports have described an association between exposure to allogeneic blood and earlier recurrences of malignant neoplasm or increased rates of postoperative infection. Only a few prospective studies of this issue have been performed to clarify the potential immunomodulatory effects of allogeneic transfusion. A study of 120 patients undergoing curative resection of colorectal carcinoma failed to demonstrate a difference in relapse-free survival time or a difference in the prevalence of serious postoperative infection between patients randomized to allogeneic or autologous transfusion. In another study of 423 patients, there was no
difference in relapse-free survival time or in infectious complications when comparing allogeneic with autologous RBC transfusions. Houbiers et al compared transfusion of leukocyte-depleted (a 3 log₁₀ reduction) components with buffy coat–depleted components (a 1 log₁₀ reduction) and found no difference in cancer recurrence risk after colorectal surgery. van de Watering et al found no effect of leukoreduction on postoperative infection rates in cardiac surgery patients, which was the primary study outcome; they also concluded that the use of leukoreduced units was associated with half (3.4%) of the 60-day mortality rate (7.8%) observed in the control group. However, mortality in this study was a secondary outcome, with no stratification at randomization for patients who presented with preoperative risk factors known to be predictive for postoperative morbidity and mortality.

While the data available at present raise questions about the immunosuppressive effect of allogeneic blood transfusion, they do not allow formulation of a definitive statement about its clinical importance and, consequently, whether universal leukocyte depletion is appropriate. Similarly, while some guidelines suggest that leukoreduced products are “cytomegalovirus safe,” data to support this conclusion are scant, and there is no consensus on this issue.

The University HealthCare Consortium (UHC) sponsored a conference on universal leukoreduction on October 24 and 25, 2000. A consensus statement was developed by an expert panel convened to consider data presented at that conference. The first sentence of the conclusion of this document states: “The UHC expert panel concluded that the benefit-to-risk ratio associated with leukoreduction, absent economic considerations, is insufficient to justify the universal leukoreduction of the United States blood supply.”

Table 3 lists the indications and nonindications published in a review in 1992; these continue to be applicable in 2001, pending future controlled prospective clinical trials that may provide additional data that lead to reevaluation.

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References


