Universal Leukoreduction of Cellular Blood Components in 2001?

Yes

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During the past 100 years, transfusion medicine has focused on introducing improvements in technology to increase the safety of blood transfusion. The initial obstacle to safe transfusion was the problem of acute hemolysis.\textsuperscript{1,2} During the first 8 decades of the 20th century, much attention was given to compatibility testing, such that, by the latter decades, incompatible transfusions became increasingly uncommon. At the present time, it is estimated that an incompatible transfusion resulting in an acute hemolytic reaction occurs with a frequency of approximately 1:100,000, and a fatal hemolytic transfusion reaction with a frequency of less than 1:1,500,000.\textsuperscript{3} In most instances, the cause is not a technical failure, but a clerical error.\textsuperscript{4,5}

In the period from 1960 to 1980, some attention was given to minor processing steps in the manufacture of different components from whole blood donation. These processes used to separate blood components were simple “centrifugational” steps, which were easily performed in hospital laboratories or regional blood centers. Thus, by the early 1980s, a substantial majority of all blood products were transfused as components, some stored in an additive solution, and others in anticoagulated plasma.\textsuperscript{6,7}

In the past 20 years, emphasis has shifted from compatibility testing and component manufacture to reducing the risk of infectious disease transmission by blood transfusion, with most effort addressing the risk of viral disease transmission by blood transfusion. The evolution of the AIDS epidemic in the early 1980s had a profound effect on blood transfusion practice, particularly with regard to manufacturing.\textsuperscript{8,9} Before 1980, only 2 tests were performed routinely on blood donations to detect infectious agents (syphilis serology and hepatitis B surface antigen). Since 1980, 9 new tests have been introduced, all with the intent of reducing the transmission of HIV-1 and HIV-2, hepatitis C virus, and human T-lymphotropic virus (HTLV)-I and HTLV-II. This recent emphasis on reducing viral disease transmission has been as successful as the reduction in hemolytic reactions that occurred during the first 8 decades of the 20th century. The residual risk of transmitting a viral disease by blood transfusion, which causes significant morbidity or mortality in a recipient, is certainly less than 1:100,000; current estimates for the risk of hepatitis C virus infection from a single blood component in the era of nucleic acid testing are on the order of 1:900,000 and are less than 1:1,000,000 for HIV-1.\textsuperscript{10,11}

Thus, if we look retrospectively at the evolution of blood transfusion safety during the 20th century, the early decades were concerned with improvements in compatibility testing and the latter decades were concerned with minimizing the risk of viral disease transmission by blood transfusion. Over the course of the entire century, great success was achieved in both areas. Reduction in the risk of viral disease transmission has brought the question of bacterial contamination to the forefront, since this risk is statistically higher than the current risk of viral disease transmission, perhaps by one order of magnitude.\textsuperscript{12,13} Technologic developments in pathogen-inactivation technology\textsuperscript{14,15} and modification of the RBC surface to reduce antigenicity\textsuperscript{16} are likely to occur during the next few decades. Furthermore, optimization of cellular storage conditions holds promise for improvement of the potency of currently transfused liquid stored products,\textsuperscript{17} and blood substitutes may complement, augment, or replace blood products in the middle of this century.\textsuperscript{18}

Importantly, most improvements in blood safety in the 20th century (compatibility testing and testing for viral diseases) were largely achieved by testing methods. In general, much less emphasis was placed on processing technologies.
As shown in Figure 1, the emphasis for the first few decades of the 21st century will shift from testing methodologies to processing steps. These processing steps will go further to improve the potency of the transfused product and to enhance product safety.

It is important to view the advent of universal leukocyte reduction (leukoreduction) within this historic context. Leukoreduction, a processing step performed to improve the safety of the blood product, represents the first in a series of more sophisticated processing steps to be used in the routine manufacture of blood products. It is possible that the current resistance to universal leukoreduction may well reflect a historic bias to improve blood safety using testing methods, with a lesser degree of interest in processing technologies. However, in contrast, processing technologies, as indicated in Figure 1, will be the dominant technology improving blood safety during the early 21st century.

**Timing and Methods of Leukoreduction**

Leukoreduction performed at the time of blood product manufacture is termed *prestorage leukoreduction*; immediately before or concurrent with administration, it is termed *poststorage leukoreduction*. There are several known advantages associated with prestorage leukoreduction Table 1. Allogeneic leukocytes contribute to the storage lesion of RBCs, and prestorage leukoreduction improves potency, but this contribution is a modest one, perhaps on the order of a 2% difference in 24-hour recovery. Furthermore, prestorage leukoreduction seems to be an effective strategy for reducing transfusion reactions associated with platelet products, although this advantage, while present, is less with RBC concentrates. Prestorage leukoreduction also allows the opportunity to achieve quality control of the leukoreduction process, therefore, providing a greater degree of assurance to the prescribing physician. Prestorage leukoreduction, furthermore, has not been associated with the rare acute hypotensive episodes, especially in patients taking angiotensin-converting enzyme inhibitors. Furthermore, “red eye syndrome” was reported with prestorage leukoreduced RBC products in 1998, but this was associated primarily with one manufacturer and has not recurred since that year.

### Advantages of Universal Prestorage Leukoreduction

There are some accepted and some controversial advantages associated with universal leukoreduction Table 2. First, it is widely accepted that leukoreduction is an effective technology for reducing recurring transfusion reactions. Until 1998, approximately 20% of all RBCs and up to 60%

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**Table 1**

<table>
<thead>
<tr>
<th>Prestorage vs Poststorage Leukocyte Reduction</th>
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<tr>
<td>Prestorage leukocyte reduction (leukoreduction) removes leukocytes before they can contribute to the storage lesion (RBCs) or transfusion reactions (platelets/RBCs).</td>
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<td>Prestorage leukoreduction allows the opportunity for better quality control of the leukoreduction process.</td>
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<tr>
<td>Prestorage leukoreduction has not been associated with acute hypotensive episodes.</td>
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<td>Prestorage leukoreduction eliminates the need for transfusion services to manage filter inventories and for nursing staff to maintain multiple blood administration protocols.</td>
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<td><strong>However,</strong></td>
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<td>Prestorage leukoreduction, at the present time, is more costly than poststorage leukoreduction.</td>
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<td>Poststorage filtration may be beneficial because the filter may remove undesired substances that accumulate during storage.</td>
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of platelets were transfused as leukoreduced products, almost all poststorage. It is likely that the use of selective leukoreduced blood for these recipients eliminated many of the recurring nonhemolytic transfusion reactions. It has been argued that the application of universal leukoreduction would result in a substantial fall in reported transfusion reactions for RBCs. However, populations of patients who historically have received nonleukoreduced blood (eg, surgical patients, patients with acute gastrointestinal bleeding) account for a very small percentage of the total number of reported transfusion reactions. Because of this selection bias, when an institution changes from selective leukoreduction to universal leukoreduction, only a small decrease (perhaps not statistically significant) will be observed in the reported transfusion reaction rates, although formal studies designed to detect milder reactions may show a significant decrease. A recent analysis of the effect of a policy of universal leukoreduction on transfusion reaction rates is shown for a large tertiary care hospital in Rhode Island.

**Table 3.**

<table>
<thead>
<tr>
<th>Selective Leukoreduction</th>
<th>Universal Leukoreduction</th>
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<tbody>
<tr>
<td>Total components transfused</td>
<td>60,735</td>
</tr>
<tr>
<td>Reported reactions</td>
<td>202</td>
</tr>
<tr>
<td>Reported reaction rate</td>
<td>0.33%</td>
</tr>
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CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV, human herpesvirus; HTLV, human T-lymphotropic virus; ICU, intensive care unit.

Leukoreduction is a known effective strategy for reducing the transmission of cell-associated viruses. The most prominent among these viruses are the herpesviruses, particularly cytomegalovirus (CMV or human herpesvirus [HHV]-5). There also should be reduction in the transmission of other herpesviruses, such as Epstein-Barr virus (HHV-4) and HHV-6 and HHV-8, although the clinical implications of this are largely unknown. Again, a policy of selective leukoreduction probably achieves most of the same benefit of preventing primary CMV disease in recipients at risk for this complication. However, the clinical implications of transmitting CMV infection by blood transfusion to people who are not at risk for CMV disease are unclear. Conventional thinking is that this is innocuous. At least on theoretical grounds, avoiding CMV infection by blood transfusion would be desirable, as a current blood transfusion recipient may develop a medical condition at some time in the future.
the future for which CMV reactivation could cause substantial morbidity, eg, a renal allograft recipient in which the occurrence of CMV disease could be a serious, life-threatening postoperative complication. Of considerable importance (which has received little attention) is that leukoreduction likely would be an effective strategy for preventing the transfusion-associated transmission of some retroviruses, such as HTLV-I and HTLV-II, which are known to be transmitted only by the transfusion of cellular blood products.49 This is an important principle in that a processing step (leukoreduction) could obviate the need for a testing step (enzyme-linked immunosorbent assay for anti–HTLV-I and anti–HTLV-II).49

There also is the question of improved RBC potency with prestorage leukoreduction.21,22 This effect on improving quality (approximately 2%) tends to offset to some extent (although not totally) the reduction in quantitative potency owing to the filtration process itself (approximately 5%-10% RBC loss).50 With the recent introduction, however, of 500-mL collections, the residual potency of many blood products collected is higher than in the era before universal prestorage leukoreduction, even after filtration. It is unlikely, therefore, that filtration-associated potency loss will result in a noticeable increase in total RBC units transfused.

There are additional possible benefits associated with universal leukoreduction. Leukoreduction filters bind Trypanosoma cruzi promastigotes and may reduce the risk of transfusion-associated Chagas disease.51 In the case of RBCs, bacterial sepsis from Yersinia enterocolitica may be reduced by prestorage leukoreduction of the RBC product.52 Some cases of transfusion-related acute lung injury have been attributed to the presence of allogeneic leukocytes in the stored RBC product,53 although most cases are due to the passive transfusion of anti–HLA antibodies, which react with recipient neutrophils.54

There are other possible areas that are controversial but have considerable implications for the benefits of universal leukoreduction. First, there is literature on the value of prestorage leukoreduction (mostly poststorage) for preventing postoperative complications in patients undergoing surgery.55-62 This is one of the more contentious and difficult areas. Eight “controlled” studies have been reported. In 6 of the 8 studies,55,58-62 leukoreduction seemed to benefit the recipients, and in 2,56,57 no benefit seems to have been achieved. There is controversy about the design, data analysis, and credibility of some of the reported data, and, as a result, these studies have been the subject of considerable scrutiny and meta-analyses and will not be discussed in further detail.63,64 The reader is referred to an excellent editorial to gain a balanced view of the subject.65 At the present time, it cannot be concluded scientifically that leukoreduced blood reduces postoperative infections in patients undergoing abdominal surgery, although some of the data highly suggest this conclusion.

There also is reported evidence of improvement in morbidity and mortality in cardiac surgery. Two reports have been published,61,62 one involving a large series of patients in whom the mortality rate was 50% less in patients receiving leukoreduced blood (regardless of whether it was prestorage or poststorage leukoreduced). The findings of this large study62 suggest that leukoreduction should be applied for patients undergoing cardiac surgery in order to improve patient outcome. Although not the primary end point, this study also showed a reduction in postoperative infection in the leukoreduced arms, when both arms were pooled and compared with the single nonleukoreduced arm. Last, during RBC storage, changes occur that are, as indicated previously, partly related to the presence of allogeneic leukocytes. Older blood has been shown to be detrimental to patients, particularly in the intensive care unit setting.66-70 Although the mechanism is unknown, fresh blood, if needed, would seem desirable for such patients. It is possible that leukoreduction may attenuate this effect.70 Thus, taken together, aged RBCs that have been stored for longer periods would not seem to be the most desired product, although it is unclear whether leukocytes are the principal contributors to this storage-related adverse effect.

There are some useful practical aspects to be considered once a policy of universal prestorage leukoreduction is adopted vs a policy of selective (poststorage) leukoreduction. From the transfusion service perspective, the time-consuming need to search for CMV-seronegative blood products can be eliminated. Inventory of multiple filters for RBCs and platelets can be eliminated. Inadequate inventory control may cause these filters to be unavailable at particular times, creating urgent situations and logistic difficulties. Furthermore, some patients (eg, in the operating room) require transfusion of RBCs at a more rapid rate than is customary with elective RBC transfusions. Under these circumstances, different filters capable of achieving leukoreduction at rapid RBC infusion rates need to be in stock. Although it is difficult to estimate the amount of time and resources consumed in all of these processes, in the aggregate, they are likely to be quite substantial. The application of a policy of universal leukoreduction has some practical advantages for blood administration, whereby this process essentially can be standardized, and further modifications of this process incorporating the use of bedside leukoreduction filters for subpopulations of patients are no longer necessary. This eliminates the need for nurses to be trained specifically in the technology of using bedside filters for defined (selected) transfusion recipients. Also, procedure manuals do not need to reference specific filters, avoiding documentation difficulties associated with vendor changes. Furthermore, clogging of
filters is a perennial problem (particularly with platelets), causing considerable frustration for patients and nurse transfusionists alike. Application of universal prestorage leukoreduction is sometimes seen as improving the efficiency of transfusion, particularly for outpatients, not only in terms of a reduction in transfusion reactions but also in improved patient throughput. Little attention has been given these practical benefits of a policy of universal leukocyte reduction.

**Disadvantages of Leukoreduction**

The major disadvantages associated with leukocyte reduction are those of cost and logistics. Logistics and cost are clearly interrelated, since incurring extra expenditures and resource consumption is, when properly applied, an effective means of overcoming logistic difficulties. As stated previously, there is some loss in product potency associated with leukoreduction technology, although, at the present time, for RBCs this is unlikely to cause an increased demand for blood transfusion because of the concurrent increase in the volume of whole blood collections that offsets this loss in product potency. With regard to the loss in platelet potency, a substantial number of platelets already are being leukoreduced in the institutions that use a policy of selective leukoreduction. In the remaining platelet transfusion situations, eg, cardiac surgery and trauma, there is already considerable uncertainty about the therapeutic dose of platelets, such that a 10% to 15% quantitative reduction is unlikely to be noticeable clinically. As in the case of RBCs, the increase in whole blood collection will increase the platelet potency of whole blood–derived platelets by 11%, negating the filtration effect.

**The Cost of Leukoreduction**

The cost incurred with the application of a policy of universal leukoreduction has been the source of conjecture in the United States. A cost in the range of $600 million per year has been suggested without the basis for this number being adequately explained. It is unclear whether this is a community cost, a charge, a gross cost, a net cost, etc. To make an unbiased, fully informed decision, it is essential to quantify the actual community cost of applying a policy of universal leukoreduction. Recently, universal prestorage leukoreduction has been implemented in the state of Rhode Island Table 4. Rhode Island has a population of 1 million, a convenient denominator! All leukoreduction in Rhode Island currently is performed prestorage at the point of manufacture in a single blood center. All RBC products are produced by in-line filtration of whole blood or RBC concentrates: platelets derived from whole blood are produced by in-line filtration of platelet-rich plasma. Prestorage leukoreduced apheresis platelets are manufactured using the COBE-LRS device (Gambro, Lakewood, CO). The increased costs associated with the manufacture of prestorage leukoreduced blood have been estimated. The total manufacturing cost of leukoreduction is estimated at $1,466,250, but the net community cost, at most, is $1,136,250. With an estimated US population in the year 2001 of 281 million, the apparent increased community manufacturing cost (not yet the total net cost) is about $319 million, which is half the previous estimates of total US costs. There are also cost savings associated with improvements in the efficiency of the transfusion service and nursing personnel, which will further reduce the net community cost; however, it is unlikely that these cost savings in resources and time and effort would offset the increased manufacturing costs incurred by the community.

The question of prestorage universal leukoreduction as a clinical cost minimization strategy now becomes an important consideration. We calculate that if only 3% of surgical patients actually benefit in terms of an improved outcome, ie, a reduction in postoperative infections or other complications associated with blood transfusion, then, on average, patients who benefit would have to achieve a cost savings of only approximately $4,000 each to neutralize the $1 million of net increased manufacturing expense. Published data suggest that in subpopulations of patients who benefit from leukoreduction, this is the approximate cost saving actually achieved.

An alternative strategy to universal leukoreduction would be to approach leukoreduction in a staged manner in which subpopulations of transfusion recipients are studied sequentially or concurrently in randomized control trials in order to define benefit, as measured by clinical outcome(s). The problem with this approach is that minor differences in

### Table 4

<table>
<thead>
<tr>
<th>Item</th>
<th>Total (US dollars)</th>
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<tr>
<td>Acquisition cost of</td>
<td></td>
</tr>
<tr>
<td>In-line RBC and platelet filters</td>
<td>796,250</td>
</tr>
<tr>
<td>In-line whole blood filters</td>
<td>525,000</td>
</tr>
<tr>
<td>Quality control testing</td>
<td>20,000</td>
</tr>
<tr>
<td>Subtotal</td>
<td>1,341,250</td>
</tr>
<tr>
<td>Additional labor cost</td>
<td></td>
</tr>
<tr>
<td>3 full-time equivalents</td>
<td>125,000</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1,466,250</strong></td>
</tr>
<tr>
<td>Cost savings</td>
<td></td>
</tr>
<tr>
<td>Poststorage (bedside) filters</td>
<td>285,000</td>
</tr>
<tr>
<td>Cytomegalovirus testing</td>
<td>45,000</td>
</tr>
<tr>
<td>Subtotal</td>
<td>330,000</td>
</tr>
<tr>
<td><strong>Net apparent community cost</strong></td>
<td><strong>1,136,250</strong></td>
</tr>
</tbody>
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outcomes may be missed (type II error). Large multicenter studies will, therefore, be necessary to enroll a sufficient number of patients within a reasonable time frame. However, site differences could create controversies in the interpretation of the outcome, thus, potentially confounding interpretation of the study results.

The Future

What is lost in the general arguments of the pros and cons of selective vs universal leukoreduction is an overall perspective of events in transfusion medicine during the last 4 decades of the 20th century and the likely events during the first few decades of the 21st century. Some of these historic features are shown in Figure 2, in addition to some projections and time frames for technologic events during the next few decades. When universal leukoreduction is seen in the context of changes in blood component manufacturing and/or administration during this 60-year period, universal leukoreduction is only one of a number of improvements in blood safety. These early manufacturing interventions or changes in practice were not introduced after randomized controlled studies! Universal leukoreduction, therefore, can largely be seen as an important processing step that will improve the safety and purity of blood components and is likely to be nothing more than a preliminary processing step to further processes, such as surface modification of RBCs or pathogen-inactivation technology. Leukoreduction could be conceptualized as a quantitative reduction in allogeneic leukocytes, and, in conjunction with pathogen inactivation technology, it provides a qualitative attenuation of adverse events due to allogeneic leukocytes. Although opponents of universal leukocyte reduction are correct in their assertion that the clinical value of universal leukoreduction has not been unequivocally demonstrated, I believe that the application of this rigid standard to all changes in manufacturing practices or clinical practices is not appropriate and will retard advances in transfusion medicine. Prestorage leukocyte reduction will become a standard in the manufacture of blood products and, when viewed retrospectively several decades from now, will be seen as nothing more than an initial processing step in a whole series of processing steps, ultimately resulting in a much safer product for transfusion recipients.

References

Sweeney / Universal Leukoreduction in 2001?


50. van der Meer PF, Pietersz RNI, Nelis JT, et al. Six filters for the removal of white cells from red cell concentrates, evaluated at 4°C and/or at room temperature. Transfusion. 1995;35:723-726.


