Why implement universal leukoreduction?

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The improvement of transfusion medicine technology is an ongoing process primarily directed at increasing the safety of allogeneic blood component transfusions for recipients. Over the years, relatively little attention had been paid to the leukocytes present in the various blood components. The availability of leukocyte removal (leukoreduction) techniques for blood components is associated with a considerable improvement in various clinical outcomes. These include a reduction in the frequency and severity of febrile transfusion reactions, reduced cytomegalovirus transfusion-transmission risk, the reduced incidence of alloimmune platelet refractoriness, a possible reduction in the risk of transfusion-associated variant Creutzfeldt-Jakob disease transmission, as well as reducing the overall risk of both recipient mortality and organ dysfunction, particularly in cardiac surgery patients and possibly in other categories of patients. Internationally, 19 countries have implemented universal leukocyte reduction (ULR) as part of their blood safety policy. The main reason for not implementing ULR in those countries that have not appears to be primarily concerns over costs. Nonetheless, the available international experience supports the concept that ULR is a process that results in improved safety of allogeneic blood components.

The term paradigm was introduced into science and philosophy by Thomas Kuhn in 1962 to refer to the set of concepts that define particular scientific thinking during a given period of time. The term refers to the predominant worldview in a particular realm of human thought. Kuhn hypothesized that paradigm shifts occur when new and more accurate theories (which represent approximations of the understanding about a topic) replace earlier, less comprehensive theories.

The medical intervention known as blood transfusion is associated with both beneficial effects and adverse events in recipients. Over the past 100 years, transfusion medicine has experienced many challenging periods resulting in the introduction of improvements in technology to increase the safety of allogeneic blood transfusion. There have thus been six major paradigmatic shifts associated with transfusion medicine science and technology (Table 1). Conceptual and technological developments in transfusion medicine are thus ongoing processes and more paradigm shifts are to be expected in the future. These may include modification of the red blood cell (RBC) surface to reduce antigenicity and the development of novel ways to produce blood products in vitro (for example, RBCs).

Considerable progress has been made over the past two decades to reduce the risk of the adverse events associated with the transfusion of blood components. However, significant transfusion-associated morbidity and mortality remain a problem. Recent data from various hemovigilance systems worldwide showed that the most common causes of transfusion-associated mortality include transfusion-related acute lung injury (TRALI), ABO hemolytic transfusion events, and bacterial sepsis associated with the transfusion of bacteria present in contaminated blood components (Tables 2, 3). The number of transfusion-associated mortality cases reported annually increased considerably over the past 30 years, which is probably mostly related to increased recognition of such events as being transfusion-associated. As can be seen in both Tables 2 and 3, TRALI has become the most commonly reported cause of transfusion-associated mortality.

The transfusion transmission risk of many pathogens has been greatly reduced by the development of increasingly sensitive screening methods; however, transfusion-transmitted infections still occur. Transfusion-related infections continue to be reported as tests for
many known pathogens are not yet available or not being used.\textsuperscript{18-22} In addition, the ongoing emergence of new agents demonstrates that potential threats to the blood supply will continue to emerge worldwide.

Potential adverse effects associated with the transfusion of blood components containing donor leukocytes and their soluble biological mediators, such as cytokines, are known to have a number of biologic effects associated with transfusion.\textsuperscript{23} Leukocytes with their specific allogenic structure (the HLA class I and class II

### Table 1. Major paradigm shifts in transfusion medicine.

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early 1900</td>
<td>Karl Landsteiner discovers the ABO blood groups and humoral immunity becomes the main paradigm explaining the effects of allogeneic transfusion.\textsuperscript{2}</td>
</tr>
<tr>
<td>1940</td>
<td>Edwin Cohn develops cold ethanol fractionation, the process of breaking down plasma into protein components and products.\textsuperscript{2}</td>
</tr>
<tr>
<td>1950</td>
<td>Carl Walter and W.P. Murphy introduce the plastic bag for blood collection and component preparation, replacing breakable glass bottles with durable plastic bags and most importantly allowing sterile blood component preparation.\textsuperscript{4,5}</td>
</tr>
<tr>
<td>1960 to 1980</td>
<td>Post transfusion viral infections became a major concern affecting the blood recipient, resulting in the development and implementation of effective screening methods to reduce pathogen transmission.\textsuperscript{6,7}</td>
</tr>
<tr>
<td>1990</td>
<td>Leukocyte reduction of blood components are shown to be associated with improved clinical outcome, which lead to the implementation of ULR in many countries.\textsuperscript{8}</td>
</tr>
<tr>
<td>1995 to 2010</td>
<td>Development of pathogen inactivation (reduction) technology to reduce the risk of pathogen transmission by blood components. This will lead to the development of pathogen inactivation technologies to treat the various cellular blood components to further improve blood safety.\textsuperscript{9,10}</td>
</tr>
</tbody>
</table>

ULR = universal leukoreduction

### Table 2. Annual number of transfusion-associated cases reported to the US FDA over the three decades from 1976 to 2005.\textsuperscript{14}

<table>
<thead>
<tr>
<th>Period</th>
<th>Total annual rate</th>
<th>ABO/HTR</th>
<th>TRALI</th>
<th>Bacterial sepsis</th>
<th>Others*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1976 - 1985</td>
<td>25.6</td>
<td>15.8</td>
<td>3.9</td>
<td>2.6</td>
<td>3.3</td>
</tr>
<tr>
<td>1986 - 1995</td>
<td>30.3</td>
<td>15.1</td>
<td>4.4</td>
<td>4.9</td>
<td>5.9</td>
</tr>
<tr>
<td>1996 - 2000</td>
<td>62.6</td>
<td>11.2</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>2001 - 2003</td>
<td>88.3</td>
<td>12.6</td>
<td>14.4</td>
<td>12.5</td>
<td>48.8</td>
</tr>
<tr>
<td>2004</td>
<td>82.0</td>
<td>7.0</td>
<td>21.0</td>
<td>6.0</td>
<td>48.0</td>
</tr>
<tr>
<td>2005</td>
<td>105.0</td>
<td>5.0</td>
<td>30.0</td>
<td>9.0</td>
<td>61.0</td>
</tr>
</tbody>
</table>

*Includes graft-versus-host disease, delayed hemolytic transfusion reactions, transfusion transmitted infections other than bacterial sepsis, anaphylaxis, post-transfusion purpura, transfusion-associated circulatory overload, and others. ABO/HTR=ABO/hemolytic transfusion reaction, TRALI=transfusion-related acute lung injury, NA = data not available.

### Table 3. Transfusion-associated causes of mortality reported to UK Serious Hazards of Transfusion (SHOT) program (1996-2004).\textsuperscript{15}

<table>
<thead>
<tr>
<th>Attributed cause of mortality</th>
<th>Definite</th>
<th>Probable</th>
<th>Possible</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusion related acute lung injury</td>
<td>8</td>
<td>5</td>
<td>23</td>
<td>36</td>
</tr>
<tr>
<td>Incorrect blood component transfused\textsuperscript{7}</td>
<td>6</td>
<td>3</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>Graft-versus-host disease</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Acute transfusion reaction\textsuperscript{7}</td>
<td>2</td>
<td>3</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Transfusion-transmitted infection</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Delayed transfusion reaction</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Post-transfusion purpura</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Total 45 12 43 100

\textsuperscript{7}Patient transfused with component or product that did not meet the appropriate requirement, or was intended for another patient.\textsuperscript{2}Acute transfusion reaction occurring within 24 hours following a transfusion, excluding that due to IBCI.
Table 4. Putative clinical benefits of leukocyte reduction, subdivided as to whether the benefit has been proven by evidence-based guidelines to be relevant clinically, likely relevant clinically, or clinical relevance is unproven.

Proven relevant clinically:
- Reduced frequency and severity of NHFTRs;
- Reduced risk of CMV transmission;
- Reduced risk of HLA-alloimmunization and platelet refractoriness.
- Reduced mortality and organ dysfunction in cardiovascular surgery patients.

Likely clinically relevant:
- Reduced infectious risk associated with immunomodulation (TRIM);
- Reduced direct risk of transfusion-transmission bacteria.

Unproven clinically:
- Avoidance of vCJD transmission.
- Avoidance of HTLV-I/II, EBV etc.
- Reduced risk of GVHD.
- Reduced risk of TRALI.

NHFTRs, non-hemolytic febrile transfusion reactions; CMV, cytomegalovirus; vCJD, variant Creutzfeldt-Jacob disease; GVHD, graft-versus-host disease; TRALI, transfusion-associated acute lung injury.

antigens on their surface) appear to be the main targets of a recipient’s immune system. In addition, some viruses can be transmitted as they exist within leukocytes (i.e. CMV, HHV-8, and HTLV-1/II). Another, not so well characterized effect of transfused leukocytes, is the potential modulating influence on the recipient’s immune system. Leukocyte reduction is typically defined as a blood processing step for reducing the leukocyte content of whole blood, RBCs, or platelet units down to $5 \times 10^6$ (1 $\times 10^6$ in Europe) residual WBCs per unit of component. Universal leukocyte reduction (ULR) is the routine application of the blood-processing step to all units of whole blood, RBCs, and platelets prior to storage in a country or in a blood transfusion service.

To prevent adverse effects of the leukocytes contained in blood components, several methods have been developed to remove leukocytes from the various blood components. Leukocyte reduction procedures can be performed either pre-storage at the blood collection facility, or post-storage either at the hospital transfusion service or at the patient’s bedside. Pre-storage leukocyte reduction of cellular blood components removes donor WBCs before they undergo apoptosis or necrosis and before they release breakdown products or cytokines.

The removal of leukocytes from various blood components can be associated with several improved clinical outcomes (Table 4). These outcomes, subdivided as to whether each benefit has been proven by evidence-based guidelines to be clinically relevant, likely to be clinically relevant, and of unproven benefit (i.e. those that can be considered only of theoretical relevance).

The major disadvantages associated with leukocyte reduction are cost and logistics. The report from the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) published in 1998 concluded that ULR of both platelets and RBCs would add a significant expense to the Canadian health care system, but that leukocyte reduction of all transfused platelets might be cost effective. As a result, leukocyte reduction of all platelets was introduced in Canada during the first quarter of 1998. Leukocyte reduction of RBCs was only introduced subsequently and ULR for all blood products was fully implemented in Canada in July 1999.

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 RBC transfusions 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, there is considerable uncertainty about the proper 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 collections will also likely increase platelet potency of whole blood-derived platelets by negating the 11% filtration effect.

Adverse effects associated with the use of leukocyte reduction filters have been reported. The severe hypotensive reactions to leukocyte reduced blood components have been associated mainly with the transfusion of blood components filtered at the bedside. These reactions are attributed to the generation of bradykinin and possibly other vasodilators, as donor plasma passes over the filter media. Bradykinin generated during filtration has a short half-life and is therefore biologically active only on direct intravenous administration. Blood components that are leukocyte reduced by pre-storage filtration appear not to cause hypotensive reactions and current knowledge indicates that transfusion of these blood components is generally free from complications associated with the use of leukocyte reduction filters. However, recent reports show that hypotensive reactions can occur even with the prestorage leukoreduction of blood products in which a defect in the metabolism of kinins may be a risk factor.

The implementation of ULR has created some new requirements relating to the need to standardize and to quality control the whole process. In our opinion the associated clinical benefits of leukocyte reduction nonetheless far outweigh the adverse features, and in the absence of considerations of cost, most transfusion medicine professionals would readily endorse a policy.
to implement ULR by pre-storage filtration. Others argue that in the absence of adequate data suggesting universal benefit the technology should be applied selectively only to those patients who will clearly benefit from this intervention.\(^{39}\)

In the opinion of the authors, implementation of ULR will improve transfusion safety, which should extend to all patients receiving blood components at the very least for the proven benefits of this intervention. Although patients who have not had a febrile non-hemolytic transfusion reaction (FNHTRs), who are not receiving long-term platelet transfusions, and are not at risk of developing symptomatic CMV disease may derive no immediate benefit from prestorage leukocyte reduction, it is possible that they may accrue tangible benefits in the future. There are also cost savings in resources, time and effort associated with improvements in the efficiency of the transfusion service and nursing personnel, which will further reduce the net community cost.

The current practice of transfusion in Saudi Arabia and other countries around the world is selective leukocyte reduction. This review will thus present an up-to-date review of the clinical issues associated with leukocyte reduction. This review will thus present an up-to-date review of the clinical issues associated with leukocyte reduction. This review will thus present an up-to-date review of the clinical issues associated with leukocyte reduction. This review will thus present an up-to-date review of the clinical issues associated with leukocyte reduction. This review will thus present an up-to-date review of the clinical issues associated with leukocyte reduction.

Evidence-based clinical efficacy of leukoreduction

Evidence-based medicine has been defined as the integration of best research evidence with clinical expertise and patient values. Various classifications of the different types of scientific evidence available, to establish the efficacy of a particular intervention, have been proposed. Table 5 provides such a scheme for assessing the levels of medical and/or scientific evidence and is based on the various publications of Sackett and colleagues.\(^{40}\) Many studies have been done to evaluate the efficacy of leukocyte reduction to prevent or reduce adverse effects caused by leukocytes present in blood components. The following sections review the evidence for various clinical outcomes.

**Non-hemolytic febrile transfusion reactions (NHFTR)**

Historically, NHFTRs were thought to be associated with the presence in the recipient of antibodies to transfused allogeneic leukocytes. NHFTRs, the most common adverse effect of blood transfusions, are thought to be clinical manifestations of allo-immunization.\(^{41}\) The minimum number and type of WBCs needed to generate a post-transfusion NHFTR in an alloimmunized recipient of blood components remains unclear.\(^ {42}\) Over the past decade, however, it has been established that most NHFTRs are due to cytokines present in the transfused blood components, having been elaborated during storage by the leukocytes.\(^ {43}\) Many studies make the point that the timing of filtration is important for reducing the rate of NHFTRs. The age of the blood component is also an accepted risk factor. The older the component is, the greater the likelihood of an adverse reaction. This is particularly the case for platelet concentrates, which are stored at higher temperatures (22±2°C) than RBC units. Thus, a more obvious cause for a transfusion reaction than the number of remaining leukocytes was postulated.\(^ {41,44,45}\)

Since older blood components have greater amounts of cytokines, the accumulation of soluble cytokines released from leukocytes during storage may be the explanation for the higher rate of NHFTRs.\(^ {41,44,46-48}\) It seemed reasonable therefore that pre-storage of blood components would significantly reduce cytokine accumulation during storage. Some clinical trials (not prospective, randomized controlled trials) have demonstrated such effects of pre-storage filtration for RBCs\(^ {48}\) even in previously alloimmunized patients.\(^ {45}\) Many studies

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**Table 5. Levels of scientific evidence that can be used to evaluate the efficacy of various transfusion medicine interventions (modified from Sackett).**\(^ {40}\)

<table>
<thead>
<tr>
<th>Level</th>
<th>Scientific Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Data from RCTs that are sufficiently large to give clear cut results, with only a small risk of an error. This level of evidence includes meta-analysis from such RCTs.</td>
</tr>
<tr>
<td>2</td>
<td>Data from small RCTs that give uncertain results and that may have a moderate to high risk of error. This level of evidence includes meta-analysis from such RCTs.</td>
</tr>
<tr>
<td>3</td>
<td>Nonrandomized cohort observational studies that use concurrent cohort data.</td>
</tr>
<tr>
<td>4</td>
<td>Nonrandomized cohort observational studies that use historical cohort data.</td>
</tr>
<tr>
<td>5</td>
<td>Case series that use data from uncontrolled observations; or that represent unsubstantiated “expert” opinion.</td>
</tr>
</tbody>
</table>
published after 1990 have addressed the incidence of febrile reactions in the context of leukocyte filtration (Table 6).26 All studies achieved a level of leukoreduction of <5 × 10^6 leukocytes in the transfused blood component.26

Until recently the role of leukoreduction in ameliorating the rate of NHFTRs had not been clearly established. Several recent publications show clearly that leukoreduction is associated with a significant reduction in the NHFTR rate (level 1 evidence) (Table 7).26 The NHFTR rate following RBC transfusion was shown to be reduced by approximately 50%, from 0.35% to 0.18%.50-52 Similarly, the pre-storage leukoreduction of platelets, which is generally associated with an approximate frequency of a 30% rate of NHFTRs, has been shown to be reduced significantly by trans fus ing pre-storage leukocyte reduced platelets.50,51,53

**Pathogen transmission**

**Viruses.** Leukoreduction is a known effective strategy for reducing the risk of the transmission of cell-associated viruses. The most prominent among these are the herpes viruses, particularly CMV, also known as human herpes virus (HHV) 5.34-40 CMV is transmitted by the leukocytes present in transfused blood components. To acquire CMV from a blood donor, a blood transfusion recipient must be exposed to donor WBCs that are latently infected with CMV. CMV then must be reactivated and the cell must survive long enough in the host to release infectious virus particles.41 Several patient populations are at risk for serious morbidity as a result of transfusion-associated CMV infection (TA-CMV), including low birth weight infants, some oncology patients, allogeneic bone marrow transplant recipients, but most particularly immunosuppressed patients. Early studies of TA-CMV indicate that the prevalence of post-transfusion CMV, without employing any pre-

**Table 6.** Incidence of non-hemolytic febrile transfusion reaction (per transfusion, excluding allergic and other reaction) (modified from CCOHTA).26

<table>
<thead>
<tr>
<th>Study</th>
<th>Pre-storage filtration</th>
<th>Post-storage filtration</th>
<th>No filtration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Platelets</td>
<td>RBC</td>
<td>Platelets</td>
</tr>
<tr>
<td>Federowicz et al (1996)</td>
<td>1.7%</td>
<td>1/119</td>
<td>1.1%</td>
</tr>
<tr>
<td></td>
<td>59/3405</td>
<td></td>
<td>60/5412</td>
</tr>
<tr>
<td>Dzieczkowski et al (1995)</td>
<td>1.6%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>82/5197</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heddle et al (1993)</td>
<td>NA</td>
<td>NA</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muir et al (1994)</td>
<td>0.9%</td>
<td>NA</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>2/222</td>
<td></td>
<td>14/280</td>
</tr>
</tbody>
</table>

+++ apheresis platelets, FNHTR only; ++ = pooled platelets, all reactions; +++ = sensitized hematological patients, apheresis platelets. NA = Not available

**Table 7.** Reports describing non-hemolytic febrile transfusion reactions (NHFTR) rate reduction associated with the pre-stage leukoreduction (LR) of RBCs and platelets.26

<table>
<thead>
<tr>
<th>Study</th>
<th>NHFTR rate reduction associated with LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>For RBCs</td>
<td></td>
</tr>
<tr>
<td>Paglino et al</td>
<td>0.34% to 0.18%</td>
</tr>
<tr>
<td>Yazer et al</td>
<td>0.33% to 0.19%</td>
</tr>
<tr>
<td>King et al</td>
<td>0.37% to 0.19%</td>
</tr>
<tr>
<td>For Platelets</td>
<td></td>
</tr>
<tr>
<td>Heddle et al</td>
<td>21.3% to 12.3%*</td>
</tr>
<tr>
<td></td>
<td>4.1% to 1.6%*</td>
</tr>
<tr>
<td>Paglino et al</td>
<td>2.18% to 0.11%</td>
</tr>
<tr>
<td>Yazer et al</td>
<td>0.45% to 0.11%</td>
</tr>
</tbody>
</table>

*Comparing NHFTR rate reduction of platelets from which supernatant plasma was removed with that seen with pre-storage LR platelets. **All NHFTR. *Severe NHFTR.
allogeneic transfusions in these patients will reduce this post-transfusion CMV risk to approximately 1.3%.\textsuperscript{58}

In comparison, a recent study has shown that the use of pre-storage leukoreduced RBCs or platelet transfusions can reduce the risk of post-transfusion CMV to approximately 2.5%.\textsuperscript{65} Over the years there have been a large number of studies examining strategies to prevent TA-CMV. Interpretation of some of these studies is difficult as many were not randomized, failed to use a control group, used historical controls, or were retrospective.\textsuperscript{57}

Nonetheless, the balance of the evidence from the available clinical studies suggests that acceptable CMV safety can be achieved by pre-storage leukoreduction. Although it is likely that leukoreduced blood components are effective in reducing the risk of TA-CMV, there is insufficient evidence at this time to firmly recommend the discontinuation of CMV testing even in the face of ULR.\textsuperscript{66} Considerable debate thus exists as to whether leukoreduction and the use of serologically negative CMV allogeneic transfusion can be considered equivalent. A recent (2001) Canadian consensus conference that has examined this issue in detail recommended that high-risk patients (i.e. allogeneic bone marrow transplant patients) receive leukoreduced blood products that are also seronegative for CMV.\textsuperscript{61}

A recent study provides strong evidence (level 2 evidence) that human herpes virus 8 (HHV-8) can be transmitted by allogeneic transfusion, particularly in high prevalence geographic regions.\textsuperscript{69} Based on the experience with CMV, it is likely that pre-storage leukocyte reduction may prevent the transmission of HHV-8 due to its WBCs associated nature. HHV-8 can cause a lifelong infection, with periodic reactivations, during which virus may circulate in peripheral blood WBCs and be transmissible through transfusion (level 5 evidence).\textsuperscript{68}

For other viruses such as Epstein-Barr virus (EBV), human T-cell lymphotrophic virus type I and II (HTLV I and II), no conclusive studies exist that demonstrate a similar efficacy of virus removal by leukoreduction as seen for CMV. Some experimental in vitro studies indicate a significant reduction of HTLV I virus from blood components by pre-storage leukoreduction but the prevention of clinical HTLV I infections with leukoreduction in humans has not been proven.\textsuperscript{69} Nonetheless, it is reasonable to assume that leukoreduction adds more safety to transfusion of blood components, since not all HTLV I infected donors express HTLV I antibodies.\textsuperscript{70}

**Bacterial/protozoal infections.** Bacterial contamination of blood components can result in a severe complication of allogeneic blood transfusion in recipients. The risk of contaminated pooled platelet transfusion has been estimated to be as high as 2% (asymptomatic cases) since platelet concentrates are stored at room temperature (a temperature that facilitates bacterial growth) to preserve their viability and function.\textsuperscript{71-73} Asymptomatic bacteremias and/or infections in a donor and the ability of *Yersinia enterocolitica* to grow at low temperatures in an iron-rich environment such as in stored RBC components makes *Y enterocolitica* the most commonly encountered serious bacterial contaminant associated with RBC transfusion.\textsuperscript{74,75} Several studies have demonstrated that the bacterial overgrowth of blood components by *Y enterocolitica* in inoculated into blood components under experimental conditions is diminished or prevented by pre-storage leukoreduction, after a room temperature holding period.\textsuperscript{75,76} One way of reducing the risk of bacterial contamination in platelet concentrates is to reduce the level of leukocytes present. Filtration to remove leukocytes does not prevent bacterial growth, although it can reduce the level of bacterial contamination for some organisms. This process is not effective against some species of bacteria (for example, *S epidermidis*). This method, therefore, does not provide full protection against the risk of bacterial contamination, but has been shown to significantly reduce the risk of transfusion-associated sepsis.\textsuperscript{77}

The mechanisms by which leukoreduction removes bacteria are complex and several possibilities have been proposed, based on experimental data. First, bacteria are phagocyted during the proposed 8-hour storage of blood at ambient temperatures and then removed with the leukocytes upon leukoreduction. Secondly, bacteria are adsorbed directly by the filter matrix or indirectly by binding to leukocytes and platelets or on activated complement components, which are removed by negatively charged filters.\textsuperscript{78}

Recent data from the Hemovigilance Network in France clearly indicates that the bacterial sepsis rate, as the percentage of all transfusion event rates, was significantly reduced (1.7% versus 3.8%) following the implementation of ULR in France compared with before the implementation of ULR (Table 8).\textsuperscript{79} Of particular relevance is the fact that 1 in 3000 cellular blood components have been shown to contain bacteria.\textsuperscript{77}

The risk of the transmission of *Trypanosoma cruzi*, the causative agent of Chagas’ disease, which is common in South America, but rare in other parts of the world, was shown to be decreased by leukoreduction, in an experimental study in susceptible mice.\textsuperscript{80}

**Variant Creutzfeldt-Jacob Disease transmission (vCJD).** vCJD is a major concern of the transfusion medicine
community, because infectivity can be detected in the lymphoreticular system as well as in blood.51 Evidence from an immunodeficient animal model of scrapie suggests that host lymphocytes and/or follicular dendritic cells play a role in peripheral neuroinvasions.52,53 The abnormal prion protein PrPSc of vCJD has been detected in lymph nodes, tonsillar tissue, spleen and the appendix in clinical cases of vCJD.64 Animal studies have shown that B lymphocytes might play a key role in disease transmission.65 In several countries, particularly in western Europe, ULR was instituted over the past 6 years in an attempt to reduce the theoretical risk of vCJD transmission via transfusion of allogeneic blood and blood components.66,67 Four cases of probable transfusion transmission of vCJD infection have recently been diagnosed in patients in the United Kingdom. All four cases had received transfusions of non-leukoreduced RBCs between 1996 and 1999 from donors who developed symptoms of vCJD after blood donation. These four cases of vCJD infection associated with blood transfusion increases the level of concern about the possible risk of vCJD transmission between humans by blood transfusion, although much remains unknown. This concern reinforces the importance of the existing precautions that have been introduced to reduce the risk of transmission of vCJD infection by blood and blood components.68 Blood screening assays are currently under development but are not yet ready for application.69 A recent study by Gregory et al, in a hamster model of blood-born transmissible spongiform encephalopathy (TSE) transmission, showed that filtration leukoreduction was associated with a reduced risk of TSE infection (from 48.1% to 31.5%).70 The authors of this study showed that filtration leukoreduction was associated with reduced TSE infectivity, but that this intervention was not sufficient to remove all TSE infectivity.71 Specific prion reduction filters for RBCs offer the possibility of a further substantial reduction in vCJD infectivity and in the overall risk of vCJD transmission. However, concerns persist about how best to assess the efficacy of these technologies, since current assays are not sufficiently sensitive to detect infectivity in the blood of patients with clinical vCJD.72

### Table 8. Occurrence of transfusion incident report (TIR) before and after implementation of universal leukocyte reduction in France.73

<table>
<thead>
<tr>
<th>Before universal WBC reduction</th>
<th>After universal WBC reduction</th>
<th>Variation</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>%</td>
<td>Number</td>
<td>%</td>
</tr>
<tr>
<td>RBCs transfused</td>
<td>3 124 649</td>
<td>3 053 807</td>
<td>-71</td>
</tr>
<tr>
<td>HLA antibodies and NHFTR</td>
<td>112</td>
<td>6</td>
<td>33</td>
</tr>
<tr>
<td>Isolated NHFTR</td>
<td>615</td>
<td>32.9</td>
<td>363</td>
</tr>
<tr>
<td>Bacterial contamination</td>
<td>71</td>
<td>3.8</td>
<td>24</td>
</tr>
<tr>
<td>Anaphylactoid</td>
<td>266</td>
<td>14.2</td>
<td>224</td>
</tr>
<tr>
<td>Hemolytic reactions (excluding ABO &amp; D)</td>
<td>26</td>
<td>1.4</td>
<td>23</td>
</tr>
<tr>
<td>D incompatibility</td>
<td>12</td>
<td>0.6</td>
<td>11</td>
</tr>
<tr>
<td>ABO incompatibility</td>
<td>30</td>
<td>1.6</td>
<td>33</td>
</tr>
</tbody>
</table>

Analysis of RBCs transfusion 18 months before and after implementation of universal WBC reduction shows as expected no significant impact on anaphylactoid reactions, ABO and D incompatibility and hemolytic reactions due to other RBC antibodies. Conversely, there is dramatic reduction of TIRs related to HLA immunization, non-hemolytic febrile transfusion reactions (NHFTR) and bacterial contamination.71 Comparison of rates (i.e. 1408/3 053 087 vs. 1872/3 124 649) using the chi-square test.

### Alloimmunization and platelet refractoriness

Alloimmunization is defined as a recipient immune response against antigens on tissue from a genetically dissimilar donor. The direct allo-recognition pathway occurs when recipient T-helper cells directly interact with class II molecules encoded by the major histocompatibility complex (MHC) on donor antigen-presenting cells (APCs). This pathway is the strongest known stimulator of immunity and the one targeted for removal by leukoreduction strategies.73 The reduction in alloimmunization is a well documented beneficial effect of using leukoreduced blood component transfusions, and is especially important for repeatedly transfused patients and transplant recipients.74-76 Table 9 provides a cumulative meta-analysis of seven randomized, controlled trials which clearly showed that the relative risk of HLA alloimmunization can be reduced considerably through the use of leukoreduced blood components (level 1 evidence). In the years 1983 to 1995 there were seven reports whose cumulative relative risk reduction with the use of leukoreduced allogenic blood components was 0.32, with 95% confidence intervals of 0.18...
to 0.56. These seven studies involved a total of only 418 patients. In 1997, the TRAP study which examined the relative risk of HLA alloimmunization and platelet refractoriness in 400 patients provided level 1 evidence (a large randomized controlled trial) that the relative risk of HLA alloimmunization and platelet refractoriness with the use of leukoreduced blood components was statistically significant. The cumulative relative risk reduction of HLA immunization for all the published studies, following the use of leukoreduced blood components, was recently estimated to be 0.30 (95% confidence intervals; 0.20 to 0.46).

A recent retrospective analysis of 13,902 platelet transfusions in 617 Canadian patients undergoing chemotherapy for acute leukemia or stem cell transplantation before (n=315) and after (n=302) the introduction of ULR showed a significant reduction in alloimmunization (19% to 7%, P < .001) and in alloimmune platelet refractoriness (14% to 4%, P < .001). Alloimmunization and alloimmune refractoriness in 318 patients who were previously pregnant and/or transfused were also reduced after ULR (P = .23 and P = .005, respectively).

### Table 9. Cumulative meta-analysis of randomized, controlled trials on the efficacy of leukoreduction in preventing HLA alloimmunization

<table>
<thead>
<tr>
<th>Study</th>
<th>Publication Year</th>
<th>Cumulative sample size (study n)</th>
<th>Cumulative relative risk (RR) of HLA alloimmunization (95% Confidence Intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schiffer et al</td>
<td>1983</td>
<td>56 (56)</td>
<td>0.35 (0.10–0.16)</td>
</tr>
<tr>
<td>Sniecinski et al</td>
<td>1988</td>
<td>96 (40)</td>
<td>0.32 (0.17–0.60)</td>
</tr>
<tr>
<td>Andreu et al</td>
<td>1988</td>
<td>165 (69)</td>
<td>0.26 (0.16–0.49)</td>
</tr>
<tr>
<td>Kooy et al</td>
<td>1991</td>
<td>218 (53)</td>
<td>0.21 (0.12–0.35)</td>
</tr>
<tr>
<td>Oksanen et al</td>
<td>1991</td>
<td>249 (31)</td>
<td>0.23 (0.13–0.38)</td>
</tr>
<tr>
<td>Williamson et al</td>
<td>1994</td>
<td>372 (123)</td>
<td>0.27 (0.16–0.46)</td>
</tr>
<tr>
<td>Sintnicolas et al</td>
<td>1995</td>
<td>418 (46)</td>
<td>0.32 (0.18–0.56)</td>
</tr>
<tr>
<td>TRAP</td>
<td>1997</td>
<td>818 (400)</td>
<td>0.30 (0.20–0.46)</td>
</tr>
</tbody>
</table>

**Transfusion-related immunomodulation (TRIM)**

Most animal studies using whole blood transfusion have found immunosuppressive-like responses in recipients, primarily due to the leukocyte content of the donor blood. Moreover, evidence from a variety of sources indicates that allogenic blood transfusion (ABT) enhances the survival of renal allografts, and may increase the recurrence rate of resected malignancies, increase the incidence of postoperative bacterial infections, reduce the recurrence rate of Crohn’s disease, and reduce the risk of recurrent spontaneous abortion. This clinical syndrome, whose mechanisms still remain to be defined, has been referred to in the transfusion medicine literature as transfusion-related immunomodulation (TRIM). The hypothesis of homogeneity was rejected across the 12 trials (P < .01 for the Q-test statistic). When the results were combined under conditions of heterogeneity, the effect of the WBC-containing allogenic blood transfusion on postoperative infection did not quite attain statistical significance (summary OR = 1.24; 95% CI, 0.98 – 1.56; P > .05). Four of these trials showed an increased association between allogenic blood transfusion and postoperative infection, but the others did not (Figure 1).

One possible explanation for the lack of consistency among the trials is that the TRIM effect may in fact be quite small (i.e. less than 10%). Vamvakas and Blajchman have postulated that to detect a 5% to 10% reduction in the risk of postoperative infection, a randomized trial enrolling 10,000 to 20,000 subjects would be required. Such a study has not been done and is unlikely to be done in the foreseeable future.

There is also evidence that the use of leukoreduced blood components is associated with improvement in morbidity and mortality in cardiac surgery. A randomized trial involving a large series of patients in whom the mortality rate was 50% less in patients receiving leukoreduced blood also reported a significantly lower postoperative infection rate. The findings of
this large study suggest that leukoreduction should be applied for all patients undergoing cardiac surgery in order to improve patient outcome. Figure 2 shows the summary odds ratio of short-term mortality in recipients of non-leukocyte reduced versus leukocyte-reduced allogeneic RBCs, from 5 randomized, controlled trials conducted in cardiac surgery. When the 5 trials were studied in a meta-analysis, WBC-containing allogeneic blood transfusion was associated with a 72% increase in postoperative mortality (summary OR=0.99; 95% CI, 0.73-1.33; P>.05) compared to patients receiving leukoreduced allogeneic blood.127

A prospective randomized study by Alexiou et al reported that leukoreduction reduces the numbers of circulating activated leukocytes and pulmonary inflammations during cardiopulmonary bypass (CPB).128 Improved lung function and reduced mechanical ventilation requirements also have been reported following the use of leukoreduction in patients having abnormal preoperative pulmonary function.129-131 Recently two meta-analyses of 10 randomized, controlled trials evaluated the efficacy and effectiveness of RBC leukoreduction and demonstrated that patients who were transfused leukoreduced RBCs might benefit from a decrease in postoperative infections. A decrease in mortality may have been realized if more patients had been enrolled in the various randomized trials.132

The results of a retrospective before/after study following the institution of ULR in Canada compared cardiac surgery, hip fracture repair, and intensive care unit patients and found decreased mortality, fewer fever episodes, and subsequent use of antibiotics in high-risk patients (Table 10).133 Subsequent reduced length of hospital stay and cost of hospital care may be an additional financial benefit.134,135

TRIM and cancer. A higher rate of tumor growth and recurrence with allogenic transfusion and lower rates with leukoreduced ones have been reported in a number of experimental animal model studies.136,137 Approximately 90 observational studies in man have examined the effect of TRIM on tumor growth promotion.138 Of these, 33 (30 observational and 3 randomized, controlled trials) have been in patients with a colorectal malignancy; 14 in patients with a head and neck malignancy; 10 in patients with a breast malignancy; 8 in patients with a gastric malignancy and 8 in
**Summary**

The odds ratio (OR) of short-term mortality in recipients of non-WBC-reduced versus WBC-reduced allogeneic RBCs, is shown. These ORs are calculated from intention-to-treat analysis. The figure also shows the summary ORs of short-term mortality across the depicted RCTs, as calculated from a meta-analysis.\textsuperscript{110,119,121-123}

**Figure 2:** Randomized controlled trials (RCTs) conducted in cardiac surgery investigating the association of WBC-containing allogeneic blood transfusion with short-term (up to 3 months post transfusion) mortality from all causes.\textsuperscript{127} The odds ratio (OR) of short-term mortality in recipients of non-WBC-reduced versus WBC-reduced allogeneic RBCs, is shown. These ORs are calculated from intention-to-treat analysis. The figure also shows the summary ORs of short-term mortality across the depicted RCTs, as calculated from a meta-analysis.\textsuperscript{110,119,121-123}

**Table 10.** Before-after study evaluating the effect of the implementation of universal leukoreduction on various primary and secondary outcomes in 14,786 patients.\textsuperscript{79}

<table>
<thead>
<tr>
<th></th>
<th>Leukoreduction (%) (n=7804)</th>
<th>Non-leukoreduction (%) (n=6983)</th>
<th>Odds ratio (95% confidence interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>6.19</td>
<td>7.03</td>
<td>0.87 (0.76-1.00)</td>
<td>.04</td>
</tr>
<tr>
<td>Suspected infections</td>
<td>12.7</td>
<td>13.9</td>
<td>0.91 (0.83-1.00)</td>
<td>.05</td>
</tr>
<tr>
<td>Confirmed infections</td>
<td>10.1</td>
<td>10.7</td>
<td>0.93 (0.84-1.04)</td>
<td>.21</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>9.6</td>
<td>10.1</td>
<td>0.94 (0.84-1.05)</td>
<td>.30</td>
</tr>
<tr>
<td>Hemodynamic failure</td>
<td>1.9</td>
<td>1.9</td>
<td>1.02 (0.80-1.13)</td>
<td>.93</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1.0</td>
<td>1.1</td>
<td>0.93 (0.67-1.30)</td>
<td>.72</td>
</tr>
<tr>
<td>Fever</td>
<td>22.5</td>
<td>24.7</td>
<td>0.88 (0.82-0.95)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Antibiotic use</td>
<td>14.8</td>
<td>16.4</td>
<td>0.89 (0.81-0.97)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Transfusion reactions</td>
<td>0.46</td>
<td>0.64</td>
<td>0.71 (0.45-1.13)</td>
<td>.16</td>
</tr>
</tbody>
</table>
patients with a lung malignancy. Approximately 50% of the available observational studies (level 3 evidence) indicate that patients having allogeneic transfusions (compared with those not having such transfusions) had a higher incidence of cancer recurrence or death as a result of cancer recurrence as well as a shorter overall survival after the cancer resection operation.138-141

The three randomized, controlled trials in colorectal cancer patients that compared the incidence of cancer recurrence in recipients of buffy coat-reduced allogeneic RBCs with that of recipients of control blood, showed no statistical difference in the incidence of cancer recurrence.106,109,116 The randomized, controlled trials in humans are thus still inconclusive. This may be due to the lack of homogeneity among the studies, the difference in blood component preparation used (buffy coat method versus leukofiltration), multicenter versus single center trials and the type of data analysis by investigators (multivariate versus univariate). Studies in a rabbit allogeneic transfusion tumor growth model clearly indicated that buffy coat reduction was associated with a significant reduction in pulmonary tumor nodule formation.142,143

Transfusion-associated graft-versus-host-disease (TA-GVHD)

TA-GVHD is an infrequent, although almost uniformly fatal complication of blood transfusion, caused by a proliferation of T-cell lymphocytes derived from the donor. Patients with cell-mediated immunodeficiency are at particular risk for TA-GVHD. Another risk group includes patients who have an HLA genotype that is haploidentical with that of the donor.144 No studies exist investigating the efficacy of leukoreduction for the prevention of TA-GVHD. There are only single case reports and animal studies.145 These reports conclude that the minimum threshold of transfused lymphocytes which prevents the development of TA-GVHD cannot currently be defined.146-148 A very recent report describes a reduction in reports of TA-GVHD to the United Kingdom Serious Hazards Of Transfusion Program (UK SHOT) since the introduction of ULR in the UK (11 reports of GVHD associated with non-leukoreduced blood components, and only two with the use of leukoreduced blood components). This low rate has occurred with the use of a combination of ULR and the provision of gamma-irradiated blood components for patients at risk.149 The gamma-irradiation of blood components has been demonstrated as the best current technology to reduce the risk of TA-GVHD.150 In any event, most patients who need gamma-irradiated blood components as well. Both measures simultaneously applied in order to prevent TA-GVHD will result in the increased safety of allogeneic transfusions. Another approach might be the use of pathogen inactivation.151 This report also describes a reduction in cases of post-transfusion purpura (PTP) following the introduction of ULR (mean number of reports/year before ULR 10.3; post ULR 2.3).149

Transfusion-related acute lung injury (TRALI)

TRALI is a severe, often fatal, and complex complication of transfusion. TRALI has become the most common cause of transfusion-associated mortality reported to both the United States Food and Drug Administration (US FDA) and UK SHOT14,15,151 Although the pathophysiology of TRALI is not well understood,152 several mechanisms for TRALI have been postulated: Popovsky’s immune-mediated model,153 in which donor antibodies and less frequently recipient antibodies causing an immune reaction targeting leukocyte antigens and Silliman’s two-hit model.154 In the latter model, the first hit is a physiological insult that activates pulmonary endothelium and promotes priming, resulting in the adhesion of neutrophils, (sepsis and trauma). The second hit is an event that activates the neutrophils, causing the release of biological active mediators present in the blood components.155 If Silliman’s model is valid, pre-storage leukocyte filtration and the use of younger blood components in at-risk patients should reduce the incidence of TRALI. Leukoreduction reduces biologically active mediators associated with prolonged storage,154-158 but whether leukoreduction can reduce the incidence of TRALI is not currently known.

Current international status of ULR

Internationally, 19 countries (Table 11) have implemented ULR as part of their blood safety policy. Several other countries are also currently moving toward implementing ULR, including Sweden, Denmark, Italy, Belgium, Cyprus and Japan.159 The motivation to implement ULR varies from one country to another. Some countries, including the United Kingdom and Portugal, decided to adopt ULR in an effort to comply with the precautionary principle concerning the theoretical risk of TA-vCJD.160 This decision was taken because of evidence that indicated that the pathogenic prion, the causative agent of vCJD, was associated with B-lymphocytes. The precautionary principle calls for reducing potential serious risks to public health even if cause and effect relationships are not fully established scientifically. Other countries, such as Germany and Canada, have relied on the evidence of clinical benefit in other
clinical areas to justify the adoption of ULR for all transfused patients. In some countries, such as Canada, blood safety is considered paramount, and the use of safer blood components, such as those that are leukocyte reduced cannot be restricted and must be applied to all patients.\textsuperscript{163}

The adoption of ULR in the United States has been delayed primarily because of economic issues, leading to the approach of selective leukocyte reduction protocols for patients thought to be at greatest risk for adverse effects associated with the presence of leukocytes in blood components. The selective patient populations include those who are immunocompromised or chronically transfused. The well-established leukocyte mediated reactions include febrile reactions (fever), alloimmunization and its clinically significant consequence known as platelet refractoriness, and transfusion transmitted leukocyte associated viruses such as CMV. The differences in practice, belief, and opinion on how best to spend money for blood components has formed the basis for the controversy in the United States over ULR. Both the FDA blood product advisory committee (BPAC) in 1998 and the blood safety and availability (BSAC) in 2001 recommended ULR for the United States blood supply.\textsuperscript{162,163}

Both the additional cost of ULR and the controversy over the available clinical evidence to support the use of leukoreduction for all patients has delayed implementation of ULR in the United States, despite the BPAC and BSAC recommendations. In fact, the ULR debate has become so politicized that it has become one of the most divisive issues in the history of US transfusion medicine. In 2005, approximately 65% to 70% of the blood supply was leukocyte reduced in the US.\textsuperscript{161} It is important to note in this context that many centers and hospitals in the US provide ULR blood components.

At present ULR is practiced in only approximately 20 countries. The main reason for not implementing ULR universally appears to be financial. Other reasons include the opinion that there is not yet sufficient evidence to justify adopting the policy of ULR.\textsuperscript{164,165}

**International experience**

Hebert et al\textsuperscript{135} evaluated clinical outcomes after the adoption of ULR in Canada by conducting a retrospective before and after cohort study in 23 academic and community hospitals (n=14,786). Although an increased risk of nosocomial infections was not demonstrated in this trial, in-hospital mortality was found to be significantly lower (P=.04) following the introduction of ULR in Canada.\textsuperscript{166} The authors of this study indicate that assuming a 7% mortality rate in the control period, the decreased odds of death based on these results would translate to one life saved for every 120 patients who received leukocyte reduced blood as opposed to non-leukoreduced blood. This observation, according to the authors, was consistent among all subgroups and throughout the range of blood exposures. In addition, this study also found that ULR was associated with a decreased frequency of febrile episodes and subsequent use of antibiotics.\textsuperscript{113}

Fergusson et al\textsuperscript{166} evaluated the clinical outcome following implementation of a ULR program in premature infants admitted to neonatal intensive care units (NICUs) by conducting a retrospective before and after study in three Canadian tertiary care NICUs from January 1998 to December 2000. Thus study demonstrated no significant reduction in NICU mortality or bacteraemia, but reported an improvement in several clinical outcomes in premature infants requiring RBC transfusions (Table 12).\textsuperscript{166} The authors therefore recommended the adoption of ULR in the care of all low

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**Table 11. Countries that have mandated universal leukocyte reduction as a matter of public blood safety policy.**

<table>
<thead>
<tr>
<th>Country</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>April 1998</td>
</tr>
<tr>
<td>Canada</td>
<td>July 1998 (platelets only)</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>December 1998</td>
</tr>
<tr>
<td>Austria</td>
<td>January 1999</td>
</tr>
<tr>
<td>Eire (Southern Ireland)</td>
<td>January 1999</td>
</tr>
<tr>
<td>Canada</td>
<td>July 1998, ULR</td>
</tr>
<tr>
<td>Wales</td>
<td>August 1999</td>
</tr>
<tr>
<td>Scotland</td>
<td>August 1999</td>
</tr>
<tr>
<td>Switzerland</td>
<td>September 1999</td>
</tr>
<tr>
<td>England</td>
<td>October 1999</td>
</tr>
<tr>
<td>Northern Ireland</td>
<td>October 1999</td>
</tr>
<tr>
<td>Malta</td>
<td>January 2001</td>
</tr>
<tr>
<td>Spain (Portugal)</td>
<td>May 2001</td>
</tr>
<tr>
<td>New Zealand</td>
<td>June 2001</td>
</tr>
<tr>
<td>United Arab Emirates</td>
<td>July 2001</td>
</tr>
<tr>
<td>Germany</td>
<td>October 2001</td>
</tr>
<tr>
<td>Qatar</td>
<td>January 2002</td>
</tr>
<tr>
<td>Holland</td>
<td>January 2002</td>
</tr>
<tr>
<td>Norway</td>
<td>January 2002</td>
</tr>
<tr>
<td>Finland</td>
<td>November 2002</td>
</tr>
</tbody>
</table>

ULR—Universal leukocyte reduction, platelets and RBCs.
Table 12. Outcomes and odds ratios among 515 premature infants who underwent transfusion before and after implementation of ULR in Canada.\textsuperscript{166}

<table>
<thead>
<tr>
<th>Outcomes\textsuperscript{a}</th>
<th>Odds Ratio (95% confidence interval)\textsuperscript{†}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-leukoreduction period</td>
</tr>
<tr>
<td><strong>Primary outcomes</strong></td>
<td></td>
</tr>
<tr>
<td>Bacteremia</td>
<td>79 (29.6)</td>
</tr>
<tr>
<td>Mortality</td>
<td>45 (16.8)</td>
</tr>
<tr>
<td><strong>Major NICU morbidities</strong></td>
<td></td>
</tr>
<tr>
<td>Retinopathy of prematurity</td>
<td>130 (59.1)</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>141 (52.6)</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>32 (12.5)</td>
</tr>
<tr>
<td>Grade 3 or 4 IVH</td>
<td>45 (17.4)</td>
</tr>
<tr>
<td>Any major NICU morbidity\textsuperscript{b}</td>
<td>207 (83.5)</td>
</tr>
</tbody>
</table>

Abbreviations: IVH, intraventricular hemorrhage; NICU, neonatal intensive care unit; ULR, universal leukoreduction. \textsuperscript{†} All outcomes data are expressed as No. (%). Denominators vary from 268 and 241 because of missing data. \textsuperscript{‡} Odds ratios of less than 1.00 indicate a beneficial effect of leukoreduction. \textsuperscript{†} All multivariate models included site, admission status (outborn/inborn), gestational age, sex, birth weight, mode of delivery, antenatal steroids, volume transfused, apgar score at 5 minutes, score for Neonatal Acute Physiology on day 1, any cardiovascular pressor on day 1, continuous positive airway pressure, (0, 1-10, 11-25, or >25 days), influenza season (December-March), mechanical ventilation on day 1, high-frequency ventilation on day 1, supplemental oxygen support on day 1, steroids on day 1, umbilical catheter, and percutaneous catheter. \textsuperscript{§} Including retinopathy of prematurity, bronchopulmonary dysplasia, necrotizing enterocolitis, and grade 3 or 4 IVH.

birth weight infants requiring RBC transfusions.

Another before and after study (n=2095), conducted in the United Kingdom by Llewelyn et al\textsuperscript{167} examined 11 hospitals with patients undergoing cardiac bypass surgery or total hip and/or knee replacement and found no impact of ULR on postoperative infections, as reported in the Canadian study, but this study was considerably smaller than the Canadian study (n=2095 versus n=14786).

Yazer et al\textsuperscript{51}, Paglino et al\textsuperscript{50} and King et al\textsuperscript{52} demonstrated that hospitals moving from a selective protocol to ULR had a significantly reduced rate of fevers associated with RBC and platelet transfusions. These fevers occurred in patients who would have been unlikely to receive leukocyte reduced blood with a selective protocol. The difficulty in conducting such studies will increase over time because there are few European countries that do not currently use ULR and because approximately 70% of the blood in the United States is already leukocyte reduced. Finding study sites which will also have a parallel and appropriate control arm to receive non-leukocyte reduced blood is becoming increasingly difficult.

Conclusions

The ongoing development of safer transfusion options for use in the care of patients has created many controversies for the field of transfusion medicine. In the debate concerning the implementation of ULR, some experts believe that the clinical benefit for ULR has been shown for many potential recipients who suggest therefore that this technology be applied universally, as the only downside is cost.\textsuperscript{168} Others argue that in the absence of data suggesting universal benefit, the technology should be applied only selectively to patients who will clearly benefit.\textsuperscript{165}

All the data presented in this review clearly indicate that leukoreduction is associated with a reduced risk to patients for some clinical indications, but not for others. In some instances the available evidence is quite strong, but in others the evidence for instituting ULR is not as strong. It is nonetheless clear that ULR does reduce the risk and severity of NHFTRs (level 1 evidence), the risk of CMV transmission (level 1 evidence), and is associated with a reduced risk of HLA alloimmunization and platelet refractoriness (level 1 evidence). A causal relationship between allogeneic blood transfusions and cancer recurrence seems to be indicated by the observational studies (level 3 evidence) reported between 1985 and 2000 but not by the available randomized, controlled trials in colorectal cancer patients (level 1 evidence). Specifically, the three available randomized, controlled trials provide no indication that perioperative allogeneic blood transfusion causes an increase in cancer recurrence or death as a result of cancer recurrence. Relevant experimental animal studies nonetheless indicate that allogeneic blood transfusions enhance tumor growth promotion in animal models. Concerning
whether leukoreduction is associated with a decreased incidence of preoperative mortality and postoperative infections, there is evidence, particularly in patients undergoing cardiac surgery,\textsuperscript{125} that the use of leukoreduced blood components is associated with a decreased risk for bacterial infection (level 1 evidence); reduces the risk of multi-organ dysfunction (level 3 evidence); and most importantly leukoreduction significantly reduces the risk of mortality (level 1 evidence in cardiac surgery patients).\textsuperscript{125,127}

Some have noted that there are significant problems with the use of selective transfusion protocols. One problem involves the selection of a patient who might meet the criteria for the selective use of leukoreduction, but who is not being recognized. Such patients thus do not get the best blood component and thus will not benefit from this intervention. This could result from physician ignorance, incomplete hospital databases, or patients undergoing allogeneic transfusions at sites where leukoreduced blood components are not provided.\textsuperscript{169}

What about female patients with multiple pregnancies? Transfusion with non-leukocyte reduced blood will likely further alloimmunize them. Does this then represent the mortgaging of their medical future? For example, if certain treatments might be required by such patients, such as kidney allograft transplantation, or the need for chemotherapy to manage a malignancy for which transfusion therapy support might be required?\textsuperscript{166}

It seems illogical to support laboratory-based programs of quality management to reduce the errors and accidents affecting blood transfusion recipients without recognizing that selective transfusion programs are a major source of error. Thus, the implementation of good manufacturing practices and quality initiatives in blood centers and transfusion services will be inherently incomplete until they can assure that transfusion requirements can be met without error.\textsuperscript{170}

In discussing public policy considerations, Vanvakis, Dzik and Blajchman stated the following: “In the absence of considerations of cost, there is both scientific and medical consensus that leukocyte reduction is appropriate medical practice. The WBCs are not a component of blood generally intended to be transfused and they can be viewed as undesirable. Furthermore, leukoreduction is almost entirely risk free at least in most situations.”\textsuperscript{170}

Blajchman ended his 1999 editorial by quoting Sir Anthony Bradford Hill,\textsuperscript{168} the father of randomized controlled trials: “All scientific work is incomplete, whether it is observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. This does not confer on us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time.”\textsuperscript{171}

If zero risk is the goal of transfusion medicine, the legacy from the HIV/HCV experience over the last two decades dictates that all risks should be considered and the resources allocated for each according to priority goals. As important as the direct financial cost is the possibility of re-direction of resources away from risks that have already been documented. In this regard it is important to note that most early manufacturing interventions or changes in practice in transfusion medicine were not introduced based on quality of evidence! Moreover ULR should also be seen as an important processing step that will contribute to improving the safety and purity of blood components. In addition, it can also be seen as an important but necessary preliminary processing step both resulting in safer products for transfusion recipients, but also one that will be required in anticipation of the next new paradigm in transfusion medicine: pathogen inactivation (see Table 1).\textsuperscript{172}

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