A Commentary & Perspective on the Status of Universal Leukocyte Reduction

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Introduction

Blood components (red blood cells, platelets or plasma) destined for transfusion are contaminated with white blood cells (leukocytes) from the donor. While leukocytes are important components of your immune system that can distinguish foreign tissue or molecules from your own, the leukocytes from someone else in your body may be problematic. Reducing the concentration of these cells is known to be of value in select patient populations at high risk for clinical problems caused by foreign leukocytes. Additional evidence suggests that all patients may be at risk for leukocyte-mediated adverse effects. Currently, a controversy exists because it is believed that leukocyte reduction (LR) adds to the cost of patient care. The application of LR to all transfused blood is called Universal Leukocyte Reduction (ULR). ULR is currently the standard of practice in 15 industrialized nations including our neighbor Canada. However, in the US, its progress has slowed as the impact of cost has lead to a reassessment.

Reviewed here are elements of the issues of ULR written for the lay public, hospital administrators, blood banking professionals and physicians or surgeons who prescribe and provide transfusion products. The science and medicine is explained to allow any interested reader to appreciate the nature of the debate and adequate documentation is provided with references for the interested reader to explore relevant issues further. The medical issues represent one important component to the discussion but of equal importance are the political and value-based issues that play a role in creating national public health blood safety policy. These too are addressed. The intent is to not oversimplify the scientific information needed to understand all the issues. This document allows the reader to review those issues in an executive summary format to reach an informed decision on the value of ULR for their hospital, patient, blood center or the patient group they represent as patient advocates.

I. Scope of the Problem

What’s the Problem with Leukocytes in Transfused Blood?

The transfusion of blood and component blood products is a lifesaving and well-accepted therapeutic treatment for a wide variety of patients including trauma and surgery, those with chronic hematological disorders and a host of other medical anomalies.

When a physician prescribes blood products, it is often specific for one of the components of blood such as red cells or platelets or it might be for the coagulation factors present in the plasma or liquid portion of blood. White blood cells or leukocytes comprise one of three cellular elements of blood.

Leukocytes are rarely prescribed for use as a transfusion therapy. However, since leukocytes are present in the source material (whole blood), they come to be distributed between the cellular component blood products in their preparation. Until recently, leukocytes were thought of as innocuous passengers of component blood product preparation. In the 1980s, we came to recognize that, in terms of their frequency of occurrence, the leukocytes of a donor contribute to over 90 percent of all adverse reactions associated with transfusion.

Once recognized for the complications they present, methods were developed to reduce the number of leukocytes present in component blood products, a practice known as leukocyte reduction (LR). LR is often achieved by the filtration of blood. For every unit of whole blood, 1-3 x 10^9 leukocytes may be found. LR is the process of reducing leukocytes below prescribed levels (less than 5 x 10^6 in North America and <1 x 10^6 residual white blood cells per transfused unit is the European specification).
Increasingly, however, the scope of LR has broadened with the greater understanding of the role leukocytes play in mediating adverse reactions to transfusion. This, along with concerns of suspected yet unproven white cell-mediated effects, has served as the impetus to reduce the level of leukocytes present in all red cells and platelet component blood products produced regardless of the underlying medical condition of the intended transfusion recipient, a practice known as universal LR (ULR).

Status of ULR

Over the last several years, many countries have adopted and implemented ULR as shown in Table 1 below. Some countries (including the United Kingdom and Portugal) have specifically adopted ULR to apply the precautionary principle with regard to the theoretical risk of transfusion-associated transmission of variant Creutzfeldt-Jakob disease (vCJD, related to mad cow disease). Many others (such as Germany) have relied on the evidence of benefit in the clinical literature as the reason to make LR available for all patients transfused. In some of these countries (such as Canada), blood safety is paramount and selective uses of interventions such as LR are viewed as safety measures that must be universally applied to all patients.

A number of additional countries are moving toward ULR. These include Sweden, Denmark, Italy, Belgium, New Zealand, Cyprus, Japan and the United Arab Emirates.

In the United States, more than 90 percent of the red cells and platelets processed by the American Red Cross (ARC) are provided to hospitals as LR blood components. The ARC provides about half of the country’s transfused blood products; the other half is made available through independent blood centers (IBC). The IBCs now leukoreduce about 60 percent of their blood products. Together, about 75 percent of all blood products in the US are LR. This may have been, in part, spurred on by the recommendations of both the Blood Products Safety and Availability Committee (BPSAC) to the Department of Health and Human Services (DHHS) and the Blood Products Advisory Committee (BPAC) to the Food and Drug Administration (FDA) in support of ULR. While there is no FDA mandate, the voluntary adoption of ULR has continued, although at a slow pace, since the January 2001 BPSAC meeting.

The continuing adoption of ULR is often delayed or slowed at hospitals because of cost issues and the preferred use of selective LR protocols for patients at risk for adverse effects such as febrile reactions, alloimmunization or transfusion transmitted leukocyte-associated viruses such as cytomegalovirus (CMV). The questions that are likely to be debated by these hospitals include:

• Who should receive blood products containing donor leukocytes?
• When should cost become a deciding factor in providing ULR?
• Who can or should represent the interests of the patient?

To answer these questions, decision-makers must be informed of the evidence concerning ULR and the value of implementation. The next two sections deal with the evidence (section II. on adverse reactions and abrogation with LR) and perceived value (section III. on the determinants of decision-making).

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II. Adverse Reactions to Donor Leukocytes

Many of the confirmed and suspected adverse reactions to transfusion are thought to develop as a consequence of white cells are shown in Table 2 and discussed in detail.

A. Leukocyte-Mediated Adverse Effects of Transfusion Effectively Reduced by Leukoreduction

1. Alloimmunization

The more prevalent of this group of adverse effects of transfusion mediated by leukocytes is alloimmunization or the development of antibodies in the recipient directed against proteins, called human leukocyte antigens (HLA), which are expressed on the surface of donor leukocytes and platelets. Someone requiring chronic platelet transfusion support can, with successive transfusions of blood products containing donor leukocytes, eventually build up a collection of antibodies that destroy the incoming or transfused platelets. Such patients are then said to become refractory to platelets, can no longer be supported by platelet transfusion, and succumb to hemorrhagic death. Alloimmunization is one mechanism by which this condition can develop. LR is known to effectively reduce this adverse reaction to transfusion.6-10

2. Transfusion-transmitted cytomegalovirus (CMV) infection

CMV is in the herpes family of viruses characterized as one that can, after infection, become dormant in the host, a condition referred to as latency. Latent CMV resides in the host’s leukocytes and can be awakened when the host’s immune system is weakened or compromised as can happen when a patient undergoes chemotherapy for treatment of a malignancy. Similarly, a donor who has asymptomatic latent CMV can transmit this infection to a recipient who may be immune compromised. Therefore, hematology or oncology patients might have their own CMV re-activated or they may acquire CMV from a transfusion if the donor was previously exposed to the virus.

Since CMV is a commonly acquired viral infection in the general population (with a probability of 10 percent increase in contracting the disease for every decade of life), those who have CMV and become infected by a different strain are said to be re-infected with CMV. As is true for most viral infections, acquiring CMV will not be particularly distinguishing as such but appear much like any other viral infection in an otherwise healthy person.

The consequences of CMV infection in immune compromised transfusion recipients, however, can be devastating, possibly even fatal. Transfusion-transmitted CMV infection can be reduced to levels seen in patients receiving CMV-screened seronegative blood thereby establishing the clinical utility of LR in averting this adverse effect of transfusion.12-15

Despite this recognized value, some assert the fre...
frequency of occurrence is so low that the value of providing CMV safe blood should be reconsidered.\textsuperscript{16}

Although the importance of leukocyte-mediated cytomegalovirus (CMV) infection in the immunocompromised patient has been appreciated for quite some time,\textsuperscript{17} studies of LR and CMV transmission continue to be reported. Late CMV disease in high risk patients may be as high as 8 percent, and although significantly reduced by providing CMV seronegative or leukoreduced blood products, a small (1-2 percent) risk of transfusion-transmitted CMV infection remains.\textsuperscript{18} This may result from the fact that the level of CMV reduction while quite dramatic with an approximate range of between 100- and 1000-fold using sensitive techniques measuring viral nucleic acid,\textsuperscript{19} removal is not absolute. Contrary to the prevailing view is an isolated study suggesting the abandonment of ULR may be premature.\textsuperscript{20} Some believe a small, but measurable, leukocyte-dependent adverse effect to transfusion remains even after LR prompting the suggestion that filtration manufacturers should develop more efficient filters.\textsuperscript{21}

3. Non-Hemolytic Febrile Transfusion Reactions (NHFTR)

Febrile reactions or fever that sometimes accompany transfusions range from mild to quite severe. Minimally, NHFTR is defined as an increase in body temperature of 1 degree centigrade that occurs within 4 hours from the onset of transfusion. On the opposite end of the spectrum, febrile reactions can become so severe that chills result in stiffening of the muscles, called rigors, and cause intense pain. Although rare, the rigors of NHFTR can cause some patients to refuse lifesaving transfusions. The association between NHFTR and leukocytes present in transfused blood products dates back to the mid 1950s but it was in 1966 when the definitive association between white cells in transfused blood products and fever was reported.\textsuperscript{22} Results continue to support this observation\textsuperscript{23-25} and yet results that are inconsistent with well-established positions continue to appear.\textsuperscript{26}

In addition to confirming the benefit of LR in abrogating alloimmunization, the trial to reduce alloimmunization to platelets (TRAP-study) showed residual white cell levels above the North American standard correlate with transfusion reactions.\textsuperscript{27} Yale-New Haven Hospital undertook a retrospective observational analysis comparing the frequency of adverse reactions after the implementation of ULR. Febrile reactions were significantly reduced by 95 percent for platelets and 47 percent red cells but the incidence of allergic reactions remained unchanged.\textsuperscript{28} In addition, support for LR was strengthened by febrile reactions associated with red cells being reduced from 0.33 percent before LR to 0.19 percent after ULR. Similarly for platelet products, the incidence of febrile reactions were reduced from 0.45 percent to 0.11 percent. Reductions in reactions from both red cells and platelets associated with LR blood were statistically significant.\textsuperscript{29} Similar reports emerged from John Hopkins where, since the advent of ULR at this hospital, the incidence of NHFTRs decreased significantly from 0.57 percent to 0.19 percent.\textsuperscript{30} Even among surgical and trauma patients, who are not perceived to be at particularly high risk of febrile reactions, the incidence of such reactions was significantly lower with LR blood.\textsuperscript{31}

B. Controversies – LR to Abrogate TRIM in Surgical Patients

Transfusion-related immunomodulation (TRIM), the association of transfusion with immune suppression in the patient, has been demonstrated in many recent studies and over a wide spectrum of patient populations. There is no disagreement that transfusions do cause changes in the immune system of a recipient. In the early 1970s, transfusions were used to induce immune suppression in kidney transplant patients in an effort to reduce the frequency of donor organ rejection, thereby increasing the rate of successful engraftment.\textsuperscript{32-34} The practice of blood transfusion continues today as an adjunct to the use of effective immune suppressive drugs.\textsuperscript{35} A dose-dependent relationship between the number of units transfused and the rate of infectious complications, length of hospital stay and even mortality has been reported.
many times and is gaining more attention in the relatively recent literature.\textsuperscript{36-41} That these consequences may be attributable to the leukocytes found in blood products was suggested by laboratory animal work where red blood cells, white cells and plasma were administered separately to groups of animals previously infected with bacteria. Those who were given leukocytes showed the highest rate of mortality and this effect was shown to correlate with the number of white cells transfused.\textsuperscript{42} It is quite natural to assume, from these data, that LR could confer patient benefit by reducing infectious complications. However, this subject has become the seat of controversy when reflecting upon the reviews and opinions provided\textsuperscript{43-58} and perhaps best characterized by Dr. Farrugia\textsuperscript{59} who, when writing on the topic of ULR asserts…

“This measure, which has entered the transfusion environment over the past three years, has divided the blood banking community like few other issues over its history.”

Most of the data related to the TRIM effect in surgery derive from open-heart or cardiac and colorectal surgery.

\textbf{Cardiac Surgery}  

Reports are available to suggest that infectious complications may be reduced in cardiac surgical patients when LR is employed.\textsuperscript{60} Also quite provocative is the observation of van de Watering and colleagues\textsuperscript{61} who showed that mortality is significantly lower in cardiac patients receiving LR blood products. Moreover, in patients receiving multiple transfusions, fewer infections occur when LR blood is transfused.\textsuperscript{60} And in one study in which leukoreduction of allogeneic blood was but one of a variety of LR modes, admittedly a confounding influence, the vast majority of patients so treated showed significant reduction in both hospital length of stay and cost.\textsuperscript{62} Moreover evidence supporting the view that LR of transfused blood alone can confer such benefits has been shown in a recent study for patients receiving LR transfused blood in the face of rising overall costs of care.\textsuperscript{63} A statistical approach allowing for the combined analysis of randomized controlled trials, called meta-analyses, revealed benefit for LR in cardiac surgery.\textsuperscript{64} Not all studies are so supportive\textsuperscript{65-67} and observations like these help fuel the controversy.

\textbf{Colorectal and Hip Surgery}  

In a series of studies, Jensen and co-workers demonstrated substantial reduction in infectious complications when patients were provided LR transfused blood products,\textsuperscript{68-70} a finding corroborated by others\textsuperscript{71} came to the same favorable conclusions for LR.\textsuperscript{72,73} Chang et al\textsuperscript{74} analyzed a database of 1,349 patients undergoing colorectal surgery in 11 Canadian hospitals. The primary outcome was the development of either a postoperative wound infection or intraabdominal sepsis in transfused compared with non-transfused patients. Carson et al\textsuperscript{75} found that in patients undergoing hip surgery that were at least 60 years old and receiving allogeneic blood transfusions, the risk of a serious bacterial infection was 35 percent greater and the risk of pneumonia was 52 percent greater than non-transfused patients. The authors of both studies concluded that allogeneic red cell transfusion was an independent risk factor for the development of postoperative infection in these patients.

It is true that compared with the transfusion of non-LR blood, at least some studies show that infections and tumor recurrence are both decreased by transfusing LR blood. It is also true that not all studies corroborate these findings. Some have suggested there may be a plausible explanation for the results.\textsuperscript{76} Leukocytes begin to die when storage of the blood product begins. The dying leukocytes release factors into the plasma that have demonstrable immune suppressive characteristics. If blood undergoes LR within 2 hours from the time of preparation, the soluble immunosuppressive factors do not accumulate in the blood product following storage. However, if LR occurs after 2 hrs, which is true in the vast majority of settings where LR occurs, the impact upon the accumulation of immunosuppressive agents is unknown. It has been shown that older blood products correlate with more observed
infections. Therefore, if some studies used blood products in which LR occurred later than 2 hrs, there may be some immunosuppressive components not removed by filtration that can offset the benefit of LR. Studies seldom report when LR takes place and this may confound interpretation and a comparison of the available studies.

Furthermore, Hebert et al reported on a large before-and-after ULR implementation study in Canada. There were 6,982 patients in the pre-ULR arm and 7,804 in the post-ULR group. These patients were transfused because of cardiac surgery, hip replacement in orthopedic surgery or were in the ICU after surgery where they were transfused. Hebert reported that one life was saved for every 120 patients receiving at least one unit of LR blood. This very large study was designed by Hebert and colleagues to be generalized to all patients.

TRIM
More recent studies continue to fuel the controversy with results that are sometimes favorable for LR, at times not and still there are new observations that continue to surprise some experienced investigative clinicians. In a study of cardiac valve patients with or without coronary artery bypass grafts, the frequency of infectious complications were significantly lower in patients receiving LR blood products. A multi-centered clinical trial involving 19 hospitals compared gastrointestinal and aneurysm surgical patients provided with blood products that were or were not leukoreduced and showed the latter benefited by having shorter length of hospital stay by 2.4 days and a 30 percent reduction in frequency of multi-organ failure; the latter being a newly reported observation. A cohort controlled study showed a significant reduction in hospital length of stay when cardiac patients were provided leukoreduced blood.

Not all studies depict a clear benefit and the outcome of another meta-analysis fuels the controversy surrounding the value of ULR where benefit was afforded only selected patient populations. In contrast, a new meta-analysis of ten studies showed the potential for leukocyte reduction to confer benefit in reducing the risk of post-operative infections. Interestingly, orthopedic and cardiac surgery patients were studied for the rates of infection and duration of hospital stay. Subset analysis revealed orthopedic patients showed significantly fewer infections but the reverse was true for cardiac patients. However the leukoreduced patients were confounded by receiving more units of blood products. Findings like this suggest an influence of blood product volume may have been significant.

C. Benefit of LR Not Well Studied
It is worth noting that other leukocyte-related adverse effects are known to occur but so poorly studied at this time that the effect of LR can only be suggested. However these effects add another dimension of knowledge to the potential adverse effects attributable to leukocytes and make us question just how much evidence is required to render an informed decision.

I. Adult Respiratory Distress Syndrome (ARDS) and Transfusion-Related Acute Lung Injury (TRALI)
These two conditions may be the same or TRALI may be a special case of ARDS. Transfusion-related ARDS has been a well-recognized complication, often leading to an observed opacification of the lung upon x-ray sometimes called ‘white out’ or ‘shock lung.’ Early studies showed that stored blood contained aggregates of blood cells and cellular debris, known as microaggregates. If removed with screen filters, lung function improved. The use of microaggregate reducing filters has become commonplace. TRALI is similar to ARDS in symptoms, and TRALI may be a form of ARDS. When TRALI develops there often, but not always, are anti-leukocyte antibodies present in the donor’s blood directed against the recipient’s white blood cells. Donor antibodies, when presented to the recipient, attack the recipient’s leukocytes causing them to become activated, sticky, sequestered in the lung and effect cellular damage through blocking the smallest
blood vessels of the circulation. These sequestered white cells effect a non-specific release of the caustic agents leukocytes normally possess to fight and dispose of infectious organisms.89 Unless LR can accomplish the removal of antibodies from donor blood, LR cannot be viewed as impacting upon TRALI. However, while antibodies are suspected causal agents of TRALI, it is surprising that infusion of the antibody-containing fraction of blood, called immunoglobulins, is not readily associated with TRALI.90 Only rarely are reactions seen to plasma-derived blood products.90,91 Indeed there is a body of literature to suggest that other adverse effects mediated by the donor white cells can contribute to organ dysfunction and, in the case of the lung, present as ARDS.

Leukocyte-Mediated ’Reperfusion Injury’
In cardiac surgery, for example, it has been shown that a patient’s own white cells harvested in the process of salvaging blood destined to be returned to the patient (and thereby avoid the need for a transfusion of donor blood), there is a well-described ‘reperfusion injury’.92 In fact, there are clinical conditions in which activated white cells contribute to organ dysfunction and these effects can be ameliorated with LR.9394 Therefore, leukocytes present in transfused blood products may very well contribute to organ dysfunction through a non-selective mechanism of organ damage similar to that seen with the reinfusion of salvaged blood; an hypothesis that has not been explored with respect to donor blood. There is evidence for this in pediatric cardiac surgery where donor blood is often added to the heart-lung machine and lung function can be improved if that donor blood is first LR.94

In trauma patients, there is a clear relationship between the number of units of blood transfused and the frequency of infectious complications as reviewed by Tartter.95 He reviews the work of Agarwal et al who identified transfusion as the most significant independent predictor of infection in 5,666 consecutive patients hospitalized at least 3 days at a level 1 trauma center.

TRALI
In summary, an argument can be made for the impact of leukoreduction on TRALI – a rare but potentially fatal transfusion reaction. There are indications that anti-leukocyte antibodies that show activity against the leukocytes of the transfusion recipient can lead to TRALI.96 Other hypotheses exist, and one of these relates to the presence of bioactive lipids which serve to prime the recipients own white cells that, under the right conditions, may develop into a full-blown inflammatory response of the lung.97 The data on the incidence of TRALI in retrospective observational studies has not yet been reported but it might be expected to be lowered by LR. This is due to the rare but documented occasion of recipient antibodies directed against donor leukocytes. However, the idea that donor leukocytes can be primed to turn against one’s own lung tissue, if accurate, opens the door for another related explanation of TRALI. Recent evidence shows storing blood containing donor leukocytes results in the accumulation of soluble factors found in the plasma fraction of the stored blood product that can prime leukocytes.98 In fact, the so-called “two-hit” model of lung injury has been suggested as the pathogenesis of TRALI99 and indeed, pulmonary dysfunction attending cardiac surgery has been simulated by a “two-hit” model in animals.100

2. Graft-Versus-Host-Disease (GVHD)
GVHD is easily understood through an appreciation of the mechanism of immunity. Simply put, leukocytes contribute to fighting off invasion of foreign substances and organisms. Some leukocytes accomplish their task using a property of self-recognition. Anything recognized as foreign is attacked by these leukocytes. It should not be surprising, therefore, that if donor leukocytes are transfused to recipients, each population of leukocytes may look at the other as foreign. In a relatively immune competent individual, there are far more recipient leukocytes than donor white cells and the incoming white cells are usually neutralized. In an immune compromised transfusion recipient, however, the donor white cells are more competent than those present in the recipient. The
donor leukocytes may view the entire recipient as foreign and mount an immune response known as GVHD. The consequences are serious and often fatal in the immunocompromised patient and, for that reason, such patients are provided with gamma-irradiated blood products because such treatment renders leukocytes incapable of reproducing, which is a requirement to manifest GVHD.

Interestingly, immune competent patients are not provided with gamma-irradiated blood because these patients are not viewed as particularly at risk for GVHD. However, although rare, GVHD has been reported in immune competent cardiac surgery and trauma patients. Gamma irradiation is very, but not totally, effective. There are data showing that the dose of leukocytes may be an important determinant of GVHD as well as the dose of irradiation. Therefore, lowering the dose of leukocytes transfused may help and cannot hurt to further reduce the risk of the disease. This is an example of the type of benefit that would never be studied clinically because of the low incidence and consequently enormous expense of conducting the trial.

3. Transfusion-Transmitted Viral Infections

Just as CMV is cell-associated and the well established benefit of LR in abrogating its transmission by transfusion is considered an acceptable indication for LR, other leukocyte-associated viruses exist. Recently it was shown that human T-cell leukemia virus-I (HTLV-I) has been shown to be reduced from blood products and commentary that followed support the view that this may be clinically relevant. In contrast, a trial of LR blood products provided to immunocompromised patients treated for human immunodeficiency virus (HIV) failed to demonstrate statistically significant reduction in the expression of virus as one might expect if LR blood products were not immunosuppressive. Recent observations made by the hemovigilance network in France show that although bacterial contamination was a major cause of morbidity and mortality, it decreased over time and was coincident with the adoption of LR.

D. Implications for the Current Standards: Are they Good Enough?

Although a leukoreduced blood product has definitions in North America and Europe, that does not mean that all patients receiving such products are free of leukocyte-mediated adverse reactions. In fact, there is evidence to suggest that the levels may have to be lower than the current accepted cutoffs of 5 or 1 x 10^6 WBCs/transfused.
unit, particularly in selected patient populations. In the studies cited, neither alloimmunization, transfusion-transmitted CMV nor febrile reactions are totally eliminated by providing leukoreduced blood – there remains a low frequency of these adverse reactions and examples of this continue to emerge in the literature.

Among relatively immune competent patients, there is mounting evidence to suggest the current standard may not provide adequate protection against alloimmunization. For example, now that Canada has been transfusing leukoreduced blood products since 1999, we see more retrospective studies comparing the periods before and after the onset of leukoreduction. Among them is the observation that end-stage renal disease patients destined for kidney transplants may not be provided any benefit related to alloimmunization since the onset of ULR and perhaps the current standards of residual leukocytes may not be low enough. A similar finding was reported in surgical patients and although the sample size was small, results suggest no attenuation of alloimmunization occurred in those patients receiving leukoreduced blood. In a study of 404 cardiac surgical patients, the incidence of alloimmunization among previously non-alloimmunized patients subsequently transfused for surgery did not differ when comparing transfusions that were not leukoreduced with those that were.

Another view has emerged from animal model studies. Data suggest that in the immune competent animal, there is an ability to mount an immune or alloimmunization response when receiving foreign protein processed by recipient leukocytes. This mechanism is normally masked by the donor leukocyte-mediated mechanism of alloimmunization. However, in the immune competent recipient of a leukoreduced blood product, this alternative mechanism may be operative and lead to alloimmunization. Therefore, evidence for more aggressive leukoreduction is touted by some and others suggest that in the immune competent patient aggressive leukoreduction may require further study.

Despite the myriad considerations to contemplate, the clinical studies have prompted Professor van de Watering to point to the benefits of universal leukoreduction as being important, but rare. Some patients we cannot predict will be spared death, infectious complications and multiple organ dysfunction syndrome (a manifestation of septic shock). A few patients will benefit from preventing alloimmunization; a value they will appreciate should they become donor organ recipients. So clinical benefit is not the issue but rather how many will receive such benefits and is this worth the money?

In summary, when taken together LR confers accepted benefit in reducing alloimmunization, CMV, NHFTR, and may reduce infections in surgical patients and tumor recurrence in those undergoing surgery for solid organ tumor removal. With this in mind, how can such a collection of information become so emotionally charged that it would prompt a number of hospital blood bank medical directors to petition the medical community against adopting ULR while 15 countries have decided the exact opposite and embraced ULR? Finally, there are well-established leukocyte mediated effects where the data suggest LR may be of help but will likely never see the controlled clinical trials needed to unequivocally support the positions taken. The conflict appears to be centered about money and politics, the apparent determinants of the decision-making process.
III. Determinants of Decision Making

Policy decisions are made with recommendations of experts as a guide that is buffered by other considerations, not the least of which is cost. This section will review key elements that may be applied to a decision for or against the adoption of ULR in the US. Three elements of the debate are:

A. Expert Medical Opinion: Clinical Efficacy vs Cost-Effectiveness

The scientific and medical foundation has been presented with contrasting medical opinions as discussed below, and may now be appreciated. We have already recognized the controversy around ULR; however, if cost were not an issue, there is nearly unanimous agreement that ULR should be adopted. Therefore, cost considerations are influencing medical opinions concerning the implementation of ULR.

Some feel the added cost of blood is about $40 per unit with 15 million red cells and platelet products transfused annually totaling $600 million added to the national health care budget. Others argue that ULR is being accomplished now and that the incremental increase in cost is far less than projected (perhaps $120 million). Others still argue the small cost savings demonstrated in studies, if real, translate to billions of dollars in savings. Cost data, unfortunately, are quite variable and while studies show a modest savings, the variability in cost makes it nearly impossible to demonstrate statistical significance with the numbers of patients studied.

Moreover, the Department of Health and Human Services budgeted and spent over $425 billion dollars in 2001 making the incremental cost increase for ULR, at the highest estimate, only 0.14 percent. Looked at another way, of the $2.1 trillion budgeted for 2003, 18 percent or $378 billion is in Medicare and Medicaid expenses. Again, at the highest estimate, ULR represents only 0.16 percent of this expenditure. Lack of commitment in government funding in the form of reimbursement through Medicare and Medicaid is, perhaps, the most significant political barrier to the adoption of ULR in the US. It has been stated by experts, Vamvakas, Dzik and Blajchman, that..."In the absence of considerations of cost, there is both scientific and medical consensus that leukocyte reduction is appropriate medical practice," so how much of a role can and should cost play in this issue of blood safety? Clearly cost-effectiveness has not been unequivocally demonstrated to favor ULR but the positions are reviewed to assist the reader in formulating an opinion on the relative merits of each point of view presented.

B. Logistics

Implementing ULR, in the absence of a federal mandate, requires adoption by the American Red Cross (ARC), which is responsible for providing half the nation’s blood supply, as well as independent blood centers represented in part by America’s Blood Centers (ABC), and endorsement of the American Association of Blood Banks (AABB) where hospital blood bank Medical Directors have a significant voice. To accomplish ULR there are both advantages (such as limiting the variety of inventory) and disadvantages (necessitating training and physical space accommodations) that influence the decision-making process. Perhaps most significant of all is that LR blood intended to be received by patients will be available. Dual inventories are problematic and there is a risk of not having LR blood available when needed.

C. Informed Consent – Patient Advocacy

As a patient, considerable trust is held in the physician responsible for patient care, as it should be. However, when the medical community is divided as it is concerning ULR, what voice do patients have through the process of informed consent?
Center for Biologics Evaluation and Research (CBER) of the Food and Drug Administration (FDA). The patients at greatest risk are the multiply-transfused hematology/oncology patients and those with chronic anemia and a few particularly sensitive patients that may fall in other groups. The use of red cells across patient populations has been described (Joseph M. Sweeney, MD, Associate Professor of Medicine, Brown University and Medical Director, Blood Banks at the Miriam, Rhode Island and Roger Williams Hospitals in Providence, Rhode Island – personal communication) and is shown in Figure 1. Those high risk patients comprise from 18-31 percent of the total suggesting selective LR may be correctly applied to only a fraction of the entire transfusion-receiving patient population and excludes at least 50 percent including those requiring transfusions associated with surgery.

![Figure 1. Distribution of packed red cell transfusions across patient groups](image)

**What is the Cost of ULR?**

Estimating the cost of ULR has become controversial in itself. Dr. AuBuchon repeatedly stated at the University HealthCare Consortium (UHC) Technology Assessment Symposium on ULR that the annual cost of ULR in the US would be about half a billion dollars. The AABB estimates the potential cost in three different ways, each with varying results.

- Based on figures derived from the Canadian Coordinating Office for Health Technology Assessment (CCOHT; an assessment used in 1993 to determine the potential costs of ULR for Canada), estimates put the cost of ULR implementation in the US at about $400 million.
- Using figures from the British government, estimates of cost are $672 million per year.
- Whereas, James MacPherson, Chief Executive Officer of ABC, also speaking at the UHC Technology Assessment Symposium, estimates that ULR will add about 20 to 25 percent cost for each unit of blood for a cost increase in the neighborhood of $300 million annually.

**Will ULR Really Cost $600 Million?**

Clearly in selected patient populations, some studies show benefit, whereas others do not. This prompted Dzik et al to study ULR in 2,780 patients and reported no statistically significant reduction in the cost of care or length of hospital stay. Heddle notes in her editorial in the same issue of *Transfusion* that it is not clear that length of stay chosen as a surrogate endpoint in the Dzik trial is the appropriate assessment of ULR. In her view, given that LR is one of the few medical interventions that carries no risk, the policy decision tool whether or not to use ULR should be based on benefit versus cost.

Other points of the Dzik study are relevant to the conclusions drawn. The study was confined to those patients to whom LR blood is not normally provided, that is, not the whole population of transfusion recipients. Dzik and co-workers conclude that because of this outcome ULR should not be implemented in the US and further clinical trials are warranted. It is possible to raise legitimate concerns about the conclusions drawn.
First, patients who are clearly indicated to receive LR blood were excluded from the study, so this trial was not of ULR but rather limited to patients who do not normally receive LR blood. The implication of this maneuver is to discount the cost savings that accrue from the use of LR blood in patients where savings are very likely to be observed.

Secondly, the two groups received different blood products beyond the LR intervention. Control patients received pooled platelets from random donors whereas the LR group was provided with single donor platelets. Also, the control group received packed red cells that were stored significantly fewer days than those given to the LR group. Aged blood is known to be associated with a higher rate of infectious complications.

Finally, the measure of cost was estimated by simply adding $30 per unit to those receiving LR units. There was no indication that the cost differences between pooled random donor, which is about half the price of single donor platelets, was accounted for and this could artificially raise the cost of care for the LR group. These limitations notwithstanding, the LR group median was $300 lower than controls and the average was about $800 lower. Although the study was designed to be able to detect a 15 percent reduction in cost (about $4500), $800 is what was observed and that represents closer to 5 percent. Therefore, the study was not adequately sized to detect this difference.

In the same issue of *Transfusion*, Volkova and colleagues failed to document a statistically significant cost savings with LR. However, their conclusions differed from Dzik and co-workers reflecting the bias that exists over this controversial issue. They conclude that... "The benefit of an all WBC-reduced blood supply for patients requiring transfusion would be many. A policy of selective WBC reduction for only certain groups of patients could not be expected to achieve the same level of protection for the entire population of patients who receive transfusion." Others argue that since ULR is in an advanced stage of adoption in the US, most of the estimated cost is being covered already and the incremental increase is more likely to be about $120 million or just a fraction of 1 percent of the health care costs of the country.

**How Large Should a Proper Cost Study be?**

Studies of cost, like clinical or scientific endpoints, require an estimate of the effect size or magnitude of the response as well as an estimate of the inherent variability of the data. Clinical trials, in which cost was measured, often show a reduction of hundreds to more than one thousand dollars per patient with LR. If a few reasonable assumptions are made, it is possible to determine the sample size of a definitive cost-effectiveness study. Assume that the cost of patient care is $20,000; this is reasonable and supported in the literature. Also assume the variability or dispersion of the data about the mean is comparable to the average cost itself; this too is supported by the literature. Then the sample size can be estimated using a statistical approach called power analysis. Power analysis applied to Dzik’s study shows over 10,000 patients were required to establish statistical significance to the savings suggested by the difference between the average values of the two groups studied. That turns out to be about a 5 percent effect size and the study was powered to show only effect sizes greater than 15 percent. If patient costs average over $20,000 and it could be established that patient costs were significantly reduced by only $800, then the savings to the health care economy could be $800 times 15 million transfusions or $12 billion, an amount close to the estimate provided by Blumberg and colleagues in their recent study.

**Who Will do the Definitive Cost Study?**

Since many US hospitals are already using LR for all cellular blood components, it is unlikely such a definitive trial on postoperative infection or mortality would ever be done and certainly not within the next 3 to 5 years. The proponents of ULR believe that the entire body of available evidence for the benefits of ULR needs to be considered including known benefits, suspected but unproven...
benefits and the vast knowledge about the role leukocytes play in the manifestation of inflammation and inflammatory diseases. The results of new studies, such as that of Hebert and co-workers\(^1\) on its statement of risk to patients, should be considered. Also to be considered is the point that Vamvakas\(^6\) identified with a meta-analysis that the type of blood transfused in the US as standard red cells may pose a greater risk than the buffy coat depleted red cell product with its lower leukocyte burden often transfused in Europe as a standard product. In so doing, the experience of institutional practice becomes important. There are retrospective or look back studies being performed in Canada since the 1999 implementation of ULR (Hebert – presented at the AABB 2002). Cost analyses will likely follow as publications are appearing that serve to substantiate the need for, and appropriateness of, before and after studies.\(^*\) Retrospective studies are, and will likely always be, criticized because they fail to consider the effect of a change in the practice of medicine that occurs over time.

Prospective randomized trials of the impact of ULR on the rate of infectious complications or reduction in costs will be formidable challenges. This is because of the large number of patients that will be required to establish clinically important and statistically significant effects. Power analysis, an accepted statistical approach, allows for estimates of the required size of the patient population in order to establish a given effect size. An effect size might be the percent reduction in the incidence of infectious complications (Figure 2A) or it might be the reduction in the cost of care of patients (Figure 2B). With each some assumptions need to be made: Where the current level of infectious complications lies among control patients is required to model the impact of reducing infectious complications rates and the higher the starting point, the fewer patients required to establish statistical significance. Considering costs, and the high variability in the data reflected by the standard deviation, a large sample size is required to establish a given effect size. Hence, both figures show clearly that meaningful clinical impact may require tens of thousands of patients – a trial that is not likely to be undertaken any time soon.

In the absence of data such studies could provide, many rely on the experience of others. **Local Experience Supports Cost-Effective Implementation of ULR**

Actual ULR costs from hospitals, large and small, primary and tertiary care, and academic medical centers across the US as well as costs from other nations that have already implemented ULR are available for the asking. These institutions have...
demonstrated a very different cost picture than that depicted in the published literature. The move for some US hospitals to 100 percent pre-storage filtration has been cost neutral and, for others, resulted in substantial cost savings. The following provides examples of some of the real life strategies and experiences of implementing 100 percent LR in a cost-effective manner.

- Riverview Hospital, a 156-bed community hospital in Noblesville, Indiana has been 100 percent LR for some time now. Using a Value Analysis Process where a variety of functions and departments within the hospital that previously performed separately, joined together as a team to analyze patient outcomes and quality of care relating to cost. There is no doubt it will cost money to universally leukoreduce, but cost savings achieved in other areas would make ULR feasible. That is how we funded it at Yale.

  Edward L. Snyder, MD, Professor of Laboratory Medicine, Yale University School of Medicine

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- Yale-New Haven Hospital, a major academic medical center with a 900-bed tertiary care facility, implemented 100 percent pre-storage filtration in 1999. The initial upfront cost for 100 percent red blood cell filtration was $280,000 and the 100 percent filtration of platelets was cost neutral. The hospital anticipates that costs will continue to decrease, as ULR becomes the standard of care all across the US and could possibly reach the point where filtration pays for itself with savings from clinical benefits to patients.

- Vanderbilt University Medical Center, a large academic medical institution in Tennessee, was one of the first academic medical centers to expand the use of LR blood products to all patients. They achieved 100 percent filtration in a cost neutral way. Starting with 100 percent filtration of platelets, which allowed for a shift from single donor pools to random donor pools. Vanderbilt was able to save enough money to cover the cost of LR of the entire blood supply for all patients.

- Summit Medical Center, a 204-bed medical and surgical facility in Tennessee, conducted a study to determine whether the cost benefit ratio of LR justified the hospital's conversion to 100 percent. The study of transfused patients undergoing orthopedic surgery, colorectal surgery, patients with GI bleeding and patients with simple pneumonia and pleurisy found that patients who received LR blood had a decreased length of hospital stay, recovered faster and used fewer hospital resources. This resulted in $1.8 million savings in annual hospital charges. For every dollar spent on LR, $29 in hospital charges was saved. The savings found in using filtered blood with just Medicare patients paid for the cost of LR for all patients.

- Carraway Methodist Medical Center, a 617-bed teaching hospital and level 1 trauma center in Birmingham, Alabama, conducted an implementation study comparing LR and non-LR blood transfusion in both cardiac and colorectal surgical patients. The study found a 5-day reduction in average length of stay for colorectal surgical patients (from 16 days to 11 days) and a greater than 3-day reduction in average length of stay for cardiac surgery patients (from 12.89 to 9.65 days) associated with LR blood transfusion. In just an 11-month period, this length of stay reduction results in a cost savings of over $2.65 million. This return on investment allowed Carraway to alter its standard of practice to provide LR blood for all patients that require a blood transfusion.

- In Canada, the cost of ULR in practice has been in the range of $35 to $40 million Canadian (roughly $25 million US), a dramatic decrease from the original CCOHT estimate.
Should cost even be a factor in determining implementation of ULR as a blood safety measure?

The critics say the cost of ULR is prohibitive and the money would be better used for other transfusion practices. The economics of ULR do not provide sufficient cost benefit and its implementation, based on the finite resources available to hospitals, could place hospital transfusion services in financial jeopardy.

The proponents of ULR say that blood safety measures, such as ULR, should not be subject to economic or cost benefit analyses. And that the estimates of cost used by the critics are highly speculative because they do not take into consideration the fact that 75 percent of the US blood supply is already LR. Nor do they take into consideration the documented life experiences of hospitals that have moved to 100 percent filtration, some of which have been able to implement in a cost neutral way and others with cost savings.

The proponents of ULR believe that cost is driving the debate and that if there were appropriate reimbursement for inpatient blood transfusions (where a majority of transfusions take place), similar to that which the government has recently designated for outpatient blood transfusions, the debate on ULR would cease.

Removing cost as a consideration, nearly all medical experts agree, LR is what they want for themselves.

The sentiments expressed by the experts appear reasonably well aligned on the side of ULR.

Ronald A. Sacher, MD, Director of Hoxworth Blood Center at the University of Cincinnati, despite his questions about long-term effects of LR on immunomodulation, admits: “If you asked me what type of blood transfusion I want (for myself), I’d say LR.” He also knows that in discussing public policy considerations Vamvakas, Dzik and Blajchman note that in the absence of cost there is medical and scientific consensus that leukocyte reduction is appropriate medical practice.37

Edward L. Snyder, MD, Professor of Laboratory Medicine, Yale University School of Medicine and Director of Blood Transfusion Services at Yale-New Haven Hospital in Connecticut, argues that physicians need to look at the cost issue differently. He contends: “Some physicians, in an attempt to control cost, resort to making the point that there are not enough data to establish the value of ULR. There is no doubt it will cost money to universally leukoreduce, but cost savings achieved in other areas would make ULR feasible. That is how we funded it at Yale.”39

Dr. Jay Epstein, MD, Director of the FDA’s Office of Blood Research and Review, and Stephen D. Nightingale, MD, former Executive Secretary, ISAC, Office of Public Health and Science, Department of Health and Human Services, echoed this position stating that there is a need to separate the scientific and the economic debates.41

Ann Neff, MD, Assistant Professor of Pathology and Medicine at Vanderbilt University Medical Center in Nashville, Tennessee, sums up this position in her comments about the decision of Vanderbilt to move to 100 percent LR. Vanderbilt is one of the first academic medical centers in the US to implement ULR for all patients. “Prior to the decision for Vanderbilt to convert to a 100 percent LR blood supply, I realized that if I or a member of my family required a transfusion, I would prefer it to be LR. Why should I not work to provide that same level of quality for all the patients served by our Transfusion Service?” she said.411

Dr. Jay Epstein, Director of FDA’s Office of Blood Research and Review, stated at the April 26, 2000 HSAC meeting that the “FDA remains convinced at a scientific level that ULR is an improvement in blood safety and purity.”415 At the same meeting, Jong-Hoon Lee, MD, Chief of the FDA’s Blood and Plasma Branch of the CBER, in a presentation and comments to the HSAC committee, noted that LR was an increase in product purity identifying LR as blood GMP. He also noted at that time the FDA was in favor of implementing ULR.415

“Removing cost as a consideration, nearly all medical experts agree, LR is what they want for themselves.”

Ann Neff, MD, Assistant Professor of Pathology and Medicine at Vanderbilt University Medical Center

“I realized that if I or a member of my family required a transfusion, I would prefer it to be LR. Why should I not work to provide that same level of quality for all the patients served by our Transfusion Service?”

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Furthermore, in his presentation at the UHC Technology Assessment Symposium on October 24, 2000, Dr. Lee noted the importance of the known clinical benefits of pre-storage LR (NHFTR, CMV transmission, HLA alloimmunization) and stated FDA’s support for ULR by raising the following points:

- “Why tolerate fevers before being recognized?”
- “HLA alloimmunization, always a future concern”
- “Decrease use of bedside filters”
- “Precautionary measure”

There are some obvious reasons to support ULR and these include:

- White cells are a contaminant and never intended for transfusion — In the scientific case for ULR, the clinical benefits of reduction of NHFTR, alloimmunization and transfusion associated transmission of CMV are clear and unquestioned benefits that should be available to all patients who receive a blood transfusion. As Harvey Klein, MD, Department of Transfusion Medicine, National Institutes of Health, simply stated in an editorial in *The Journal of the American Society of Hematology,* as early as October 1992, “Peripheral blood leukocytes were not designed for blood transfusion. Nevertheless, current transfusion practice exposes patients to large numbers of allogeneic white blood cells. Blood quality relies upon the removal of recognized impurities. Even as evidence mounts that passenger leukocytes may be detrimental to an increasing number of recipients, practical technology for removing these cellular impurities has emerged. We have the ability to remove them now.”

- Some feel you cannot put a price on safety — James P. Aubuchon, MD, Professor of Pathology and Medicine, Dartmouth-Hitchcock Medical Center in New Hampshire, commented at a meeting of the AABB, that health care (including blood) is now regarded as a purchasable commodity just like a car or a boat or a bicycle. Paul Haas, Ph. D., Professor of Economics, Bowling Green State University, and panelist on Health and Human Service’s (HHS) Blood Safety and Advisory Committee (BSAC), stated that supply and demand economics cannot be applied to blood and blood safety because everyone should have access to safe blood. He also stated at the same BSAC meeting that the blood banking industry does not have the reputation to allow it to make decisions about blood safety and ULR based on cost, considering its historical record. The scientific uncertainty about the cost benefit ratio was one of the issues in delaying implementation of appropriate blood safety precautions and measures during the advent of the AIDS epidemic.

- LR does no harm — There were some early reports of a drop in blood pressure associated with the use of LR using blood filters at the bedside or point of transfusion. The proposed mechanism of blood activation by the foreign surfaces of the filter appeared to manifest in patients on drugs called ACE inhibitors used in cardiac patients. Cardiac patients are candidates for ACE inhibitors and coincidentally are prone to the hypotensive effects of bradykinin even in the absence of any transfusions. ULR reduces the likelihood of these effects because filtration occurs at the time of blood product preparation and not at the point of transfusion allowing sufficient time for degradation of the suspected hypotensive agent, bradykinin. In addition, red-eye reportedly developed rarely and was associated with one brand of filter. In general, the medical community does not view the use of this technology as problematic.

- It is not justifiable to provide a safer blood product to some and not all — There are significant problems with selective transfusion protocols as many patients who meet criteria for a selective protocol, such as LR, are not recognized. Additionally, the proponents believe there is no justification to subject any patient to a transfusion reaction when there is technology available that reduces the frequency of such a reaction. Current medical practice cannot reliably determine which patients will get such a reaction and places patients in possible jeopardy for any future transfusions they might
receive. The proponents note the irony that
many of the critics of ULR admit they would opt
for LR blood for themselves or their families,
even if they were not one of the patient groups
designated to receive filtered blood. In sum-
mation, it is not justifiable to provide a safer
blood product to some and not all.

- Are we asking more of ULR than we have
  of any other treatment? Dr. Joe Sweeney
  (Medical Director, Blood Banks at the Miriam,
  Rhode Island and Roger Williams Hospitals)
  wonders why the cost-effectiveness measures
  that are being applied to ULR are different from
  the criteria applied to other blood safety mea-
sures. Vamvakas, Dzik and Blajchman note in
discussing the case for ULR, “...only a small
fraction of therapeutic decisions made in health-
care are supported by results of double-blind
(randomized control trials) RCTs and very few
managerial or health care policy decisions and
few conclusions as to the cause and natural
history of disease can be supported by such evi-
dence...” In practice, most cause-and-effect rela-
tionships are based on results of methods other
than RCTs.47

These same authors also noted in their chapter
that, “In the absence of the considerations of cost,
there is both scientific and medical consensus
that leukocyte reduction is appropriate medical
practice.”47

Examples in the literature of adopted clinical prac-
tice in the absence of randomized controlled tri-
als are easy to find.

- More is spent on defibrillators - At the
  recent AABB (55th Annual Meeting, Orlando, FL,
  October 2002) Hebert reported on a large pre-
  and post-ULR implementation study in Canada
  with 6,982 patients in the group prior to imple-
  menting ULR and 7,800 post-ULR. These patients
  were transfused because of cardiac surgery, hip
  replacement in orthopedic surgery or were in
  the ICU after surgery and given transfusions.
  Hebert reported that one life was saved for
every 120 patients receiving at least one unit
of LR blood. If one assesses the cost-effective-
ness based upon cost per life-year gained, treat-
ment for 120 patients with LR approximates
$6,120 ($30/transfusion x 2 transfusions/patient x
120 patients). These results can be contrast-
ed with other interventions such as cardio-
defibrillators that save lives at a cost of $78,400
per life-year gained.152

- More is spent on blood screening - Linda
  A. Chambers, MD, Senior Medical Office,
  Biomedical Services of the ARC, which pro-
  vides half of the nation’s blood supply, fur-
  thered this argument in her presentation at the
  University Health System Consortium (UHC)
  Technology Assessment Symposium.153 She said
  that cost benefit and QALY (quality adjusted life-
  year) figures are irrelevant when dealing with
  safety. LR is a product safety enhancement and
  safety enhancements in blood are made regard-
less of cost. She noted it is the same type of safe-
ty enhancement as donor-screening tests that
are not optional, not within the scope of ‘med-
ical practice,’ performed as part of manufac-
turing and are done for all patients and all
transfusions. She argued that there is prece-
dent that fits the historic experience of bring-
ing in other blood safety measures regardless
of cost such as p24 testing, (nucleic acid test-
ing) NAT, deferral of travelers to Great Britain
and the (hepatitis C virus) HCV look back.

- MRI provides better images than CT scans
  but costs twice as much – where is the
cost justification? Only a small fraction of
therapeutic decisions made in health care are
supported by the results of double-blind RCTs
and very few health care policy decisions and
few conclusions as to cause and effect can be
supported by such evidence. Joseph D. Sweeney,
MD, Associate Professor of Medicine, Brown
University, and Medical Director of three Rhode
Island hospital blood banks, offered examples
in his comments to CAP Today about the use
of magnetic resonance imaging (MRI) which
provides better images than CT scans but costs
twice as much. But there are no RCTs sup-
...only a small
fraction of
therapeutic
decisions
made in
healthcare
are supported by
deresults of
double-blind
(randomized control trials) RCTs..."
porting improved patient outcomes with the use of MRI vs. CT. Another similarity can be found with the implementation of nucleic acid testing (NAT) of blood for HIV, where it cannot be proven that it makes a material difference but is being implemented without the degree of opposition found in the ULR debate. Laurence A. Sherman, MD, JD, retired Professor of Pathology at Northwestern University, Chicago, cites another example with the institution of HTLV-1 testing of blood when there was limited data about its relationship to disease and frequency in the donor population, and no RCTs demonstrating outcome.

B. Logistics

ULR Leads to Current Good Manufacturing Practice (cGMP)

According to the ARC, ULR is a safety enhancement and not a part of medical practice any more than donor screening is an option or part of medical practice. Jong-Hoon Lee, MD, Chief of the FDA Blood and Plasma Branch, CBER, said at the March 2000 conference on the Clinical and Molecular Basis of Transfusion Induced Immunomodulation, (Washington, DC) “…LR is increasingly being regarded as blood GMP rather than as the practice of medicine. Insufficient reimbursement, not necessarily excessive cost, remains the primary obstacle against the rapid implementation of ULR as a new blood GMP standard. “154

Are We mortgaging a Patient’s Future Without ULR?

This raises the question as to why should any patient needing a blood transfusion be subjected to a potential NHFT or to possible transmission of CMV when the technology is available to prevent or minimize these risks? From the perspective of one physician, denying a young male or female LR blood because there is no indication may be mortgaging his or her future. This patient could become ill later in life and present for cancer treatment already alloimmunized because of the transfusions they received when they were younger. Women who have given birth to children are already one step closer to alloimmunization, and giving them a transfusion of non-LR blood brings them even closer to the risk of alloimmunization to future transfusions, if needed. As Edward L. Snyder, MD, Professor of Laboratory Medicine, Yale University School of Medicine, and Director of Blood Transfusion Services at Yale-New Haven Hospital in Connecticut, remarked in a recent interview with the publication CAP Today, “It’s similar, in my perspective, to not giving a person a tetanus shot now because they’re not likely to run into a rusty nail.”

Dual Inventories Run the Risk of Mistaken or Unintentional Transfusions

Paul M. Ness, MD, past President of the AABB and Director, Transfusion Medicine at Johns Hopkins Medical Institution, notes that there are significant problems with selective transfusion protocols. He says there are documented examples of patients who met criteria for selective protocols, such as LR, who were not recognized. He explains that there can be multiple reasons for this including:

• Physicians do not recognize the requirement.
• Patients are transfused at different sites.
• The patient location in the hospital is not always predictive.
• Computerized databases are often incomplete.
• Hospital blood bank staff may miss a patient in need especially with fewer transfusion specialists and the centralization of transfusion services.

Dr. Ness also suggests it would be very difficult and perhaps legally indefensible to define a subgroup of patients who would qualify for an expensive component (such as LR components) limiting its availability for other patients who could benefit.

Another logistic benefit to ULR is the assurance that patients requiring blood products that minimize the risk of CMV will be assured of having them when needed.

“It’s similar, in my perspective, to not giving a person a tetanus shot now because they’re not likely to run into a rusty nail."
Edward L. Snyder, MD, Professor of Laboratory Medicine, Yale University School of Medicine
Hidden Savings of ULR by Omitting Dual Inventory, CMV Testing

Further cost savings with ULR may also potentially be found in reducing the need for serologic testing for CMV. The alternative to LR blood is to screen donor blood products for the absence of antibodies directed against CMV and declaring the product to be CMV seronegative. This product is becoming more and more difficult to find. Since it has been shown that LR can significantly reduce the risk of CMV transmission, comparable to and, some medical experts believe, possibly better than CMV seronegative blood, LR can obviate the need for and hence the cost of CMV screening. Numerous hospitals across the US that have converted to 100 percent filtration have been able to eliminate the cost of testing for CMV and the associated costs of managing multiple parallel inventories while reducing the number of outdated blood products.

C. Informed Consent

Who Should be Making the Determination of Patient Risk in a Blood Transfusion?

Allowing the patient to make an informed choice about the blood transfusion they may require is the same as the process that might be conducted for any clinical treatment that may carry potential risks as well as benefits. Domen and Smith in their chapter - Confidentiality and Informed Consent Issues in Transfusion Medicine in Ethical Issues in Transfusion Medicine identify the patient rights movement as the empowering force moving patients to be participants in clinical decisions about their medical treatment.155 In the past physicians made authoritative decisions based on the patient’s best interests. As Somerville notes in the same text,156 this would be an example of what she identifies as blind trust. “Trust me because I know what is best for you and will act in your best interests.” While physicians may certainly have the best of intentions, keeping the decision making process closed to patients has largely become a practice of the past. In the Institute of Medicine (IOM) report from 1995 on HIV and the Blood Supply: An Analysis of Crisis Decision-making, it was noted that the assumptions about medical decision making in which patients played a relatively passive role led to failures to disclose completely the risks and did not enable individuals to make informed decisions for themselves.157

In the current debate on the use of ULR in the U.S., the voice that is not heard is that of the patient. What is the process to inform the patient about the option of leukocyte reduction for their transfusion? Are patients made aware of this type of blood component and given a choice? For the patient to make an informed choice, what should be disclosed about LR?

What is the Standard of Care?

As Schiff and Barber note in Informed Consent for Blood Transfusion, “Traditionally, a physician’s duty to provide informed consent has been measured by a professional standard of care.158 Under this analysis, physicians are required to provide information about the risks associated with the proposed medical treatment that physicians consider to be ‘material’. Or what a reasonable physician would disclose under similar conditions when discussing the potential need for transfusions with a patient.

Given that 15 countries have adopted ULR, with 8 more in the review process and the US is implementing to the extent of 75 percent, does ULR constitute a standard of care? This issue has not been challenged legally, as might be expected in HIV-related mortality; however, as the consequences of leukocyte-mediated morbidity becomes more widely understood, we may see this issue in the informed consent for transfusions. Informed consent for transfusions is increasingly discussed in the literature.159-161

The critics of ULR believe the decision to provide filtered blood is the practice of medicine and it is up to the physician to make the determination on who should or should not receive it, based on medical guidelines.160 The decision to use filtered blood should not be mandated by the blood banking industry. Given this position, do those who...
favor this position believe that the patient should have no voice in whether or not they receive a blood product that is LR.

Would the American public believe it to be just or equitable that the FDA and the BSAC characterize LR blood as a safer, purer product in their recommendations and comments and not make it available to all who require transfusion? Would the American public find selective protocols that may well miss patients who should receive LR blood because of inadequate education of physicians and hospital processes prone to error acceptable? This is unlikely, but then the American public is not hearing about this in the media.

When the BSAC committee was evaluating ULR at their January 2001 meeting, one of the members took an informal poll, asking the committee members whether they would want LR blood for themselves or loved ones that might require a transfusion. With one exception, all committee members acknowledged that LR blood would be their preference. As we know this committee recommended that ULR be adopted as soon as is feasible in 2001.162

**Informed Consent**

In 1995 the Joint Commission on Accreditation of Healthcare Organizations added the requirement for informed consent for blood transfusion to its standards for hospital accreditation. According to Sazama, in her overview of informed consent in *Informed Consent for Blood Transfusion*, all hospitals that transfuse blood and blood components as well as the physicians ordering the use of those components should have a clear understanding of the process of informed consent for blood transfusion at that institution. This should include a description of the recommended treatment or procedure, a description of the risks and benefits, a description of alternatives, the results of no treatment and the probability of success of the treatment and any possible problems that might be encountered. This practice is more aligned with the current partnership model for medical decision making with both the physician and the patient as active participants. This represents what Somerville identifies as "earned trust." "Trust me because I have shown that you can trust me."156

In the chapter Alternatives to Transfusion of Allogeneic Blood Components, Linda Chambers, MD, writes on alternatives to transfusion identifying LR as one of the alternatives in component preparation. She concludes: "Obtaining informed consent for transfusion should include a discussion of the alternatives to, and within, the planned therapy." This may include LR, particularly where selective protocols are practiced.

Even when opinions differ among physicians on the standard of care, as they do on the topic of ULR or where LR should be applied, physicians may wish to disclose this to their patients to assure their knowledge in agreeing to using a particular intervention or not using it. As Sazama notes, "for informed consent to withstand legal scrutiny, physicians in doubt should err on the side of overdisclosure."160

The physicians who are advocating the use of selective protocols provide another view. Some of these physicians believe that the decision of whether or not to provide a blood component, as LR is the practice of medicine, therefore, in their reasoning the choice should be made by the physician. It is not clear how this view fits with the use of informed consent for blood transfusion nor does it necessarily align with the views expressed in the AABB published book on informed consent. While there is little actual input on the views of patients on this topic, several patient advocacy organizations publicly endorsed ULR at the January 2001 BSAC Meeting. These included the Committee of Ten Thousand, the National Hemophilia Foundation, the Hemophilia Federation of America and the Immune Deficiency Foundation.162

Where is the patient’s voice in this debate and what communication about LR should the patient have? If ULR is an incremental improvement in the safety and quality of cellular blood components with little to no risk, is a failure to act or to inform patients of this option’s availability appropriate?
Summary of Positions on ULR

Dr. Morris A. Blajchman, Professor, Hematology, McMaster University who voted "yes" to ULR in an editorial in Transfusion, 1999, echoed this and provided the reasons for his support, still true today, as follows:

• It is unlikely that further definitive prospective randomized controlled trials (RCTs) on TRIM will be forthcoming.
• The available RCTs have considered a question of little relevance to North America and have produced contradictory findings with regard to TRIM. In North America, the white cell burden is about three times higher than that found in the European buffy-coat removed red blood cells.
• The preponderance of other available evidence, including the beneficial effect of allogeneic white blood cells in prolonging renal allograft survival and in preventing recurrent abortions.
• The evidence from animal models of tumor recurrence and postoperative infection.
• Recent observational studies support the hypothesis of a deleterious allogeneic transfusion effect.48

The evidence for ULR begins with the three classical uses for NHFTR, alloimmunization and CMV. Indeed, some proponents of ULR say that evidence is sufficient to extend the benefit to all transfusion recipients and denounce the selective use of LR.

Others are paralyzed by the controversy over LR and TRIM and the lack of RCTs supporting a benefit for ULR. There is little doubt that TRIM exists and many examples of published studies showing the value of LR in reducing infectious complications, hospital length of stay and associated costs as well as the observed reduction in mortality are difficult to ignore. The anecdotal information show large and small hospitals have examined the question of cost-effectiveness and concluded that without in their institutions, ULR is either cost-neutral or generates revenue.

Finally, the scientific documentation of leukocyte-mediated components of inflammation, unresolved ARDS and the transmission of leukocyte-associated viral infections are all reasonable constructs that suggest additional benefit may be provided to all patients with the adoption of ULR.

The United Kingdom, based upon the politically charged issue of mad cow disease and the potential for transfusion-transmission of vCJD, has used the meager information that prions, the infectious agents, were shown to be associated with a subpopulation of white cells and this may have been pivotal to their implementation of ULR. Most recognize that this was a political reaction to a particularly trying time but that is not the case for the remaining European countries who have adopted ULR based upon the same information available to us and reviewed here.

Clearly, the overriding objection is cost. The cost issue is so pervasive that it makes reasonable arguments difficult to accept. It is true that 75 percent of the cost of ULR is already being spent and that the incremental increase spread across the 6,000 hospital in the US is about $120 million or $20,000 per hospital each year; this is less than one-tenth of 1 percent of the nation’s health care expenditure.

The following statements lend further support for the adoption of ULR.

• Leukocytes are not an intended component of the transfusion product
• Leukocytes are known to do harm
• Experts agree nearly unanimously that if they had to receive a transfusion they prefer it to be a LR product
• LR does no harm
• We are asking more of ULR than we have of far more expensive medical practices that have been adopted
The value to be gained from ULR include more consistent blood products conforming to current Good Manufacturing Practice and the logistic advantages that accrue by avoiding dual inventories.

ULR avoids mortgaging a young patient’s future by reducing the risk of alloimmunization in a person who may one day find himself/herself in the position of requiring chronic platelet transfusion support.

ULR assures that patients requiring LR transfused blood will receive it since everyone will.

ULR avoids the potentially litigious nature of white-cell mediated morbidity and issues of informed consent that grow more realistic as the clinical consequences of leukocytes become more widely recognized.

No matter how the discussion of ULR was brought to the forefront, it is a discussion whose time has come. As the clinical evidence of the benefits of LR became more apparent, countries around the world have made the decision for ULR. Some of these, specifically the United Kingdom and Portugal, have done so as a precautionary measure against the theoretical risk of the transmission of vCJD via transfusion. But most other countries, including Canada, Austria and Germany, have moved to ULR strictly on clinical grounds. Our northermmost neighbor Canada implemented 100 percent filtration of blood products in 1999. Graham Sher, MD, Vice President Medical, Scientific & Clinical Management of the Canadian Blood Service, emphasized that this decision was based on the clinical evidence at hand, not on the theoretical consideration of transfusion-transmitted CJD. As for zero-risk, it is clear that our blood supply is not risk free and the advent of ULR will not make it risk free either. For example, there remain pathogens, both viral and bacterial, that can still be transmitted in a blood transfusion as well as new and emerging threats. ULR is just one step, albeit an important step, to help make one of the world’s safest blood supplies even safer. We may never reach a zero-risk blood supply but using the technology of filtration we can significantly help minimize some of the risks. And the public can be assured that whichever hospital or provider they go to, they will be provided with the safest blood available today.

Dr. Morris Blajchman in his 1999 editorial quoting from a lecture Sir Anthony Bradford Hill (father of the randomized controlled trial) gave late in his career reminded us that…

“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.”

Should you find yourself in the unfortunate position of having to receive a transfusion and you think it should be leukocyte reduced, then you are a proponent of ULR. You therefore should aspire the call of Sir Anthony Bradford Hill and take the action that the information to date appears to demand and prescribe, provide or recommend LR blood products.
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<th>Table of Abbreviations</th>
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<td>Ambulatory Patient Code</td>
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<td>America's Blood Centers</td>
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<td>American Red Cross</td>
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<td>Blood Products Advisory Committee</td>
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<td>Blood Safety and Availability Advisory Committee</td>
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<td>Canadian Coordinating Office for Health Technology</td>
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<tr>
<td>Center for Biologics Evaluation and Research (a highly sensitive diagnostic tool relying on an x-ray beam. It produces an X-rayed cross-section of the tissue scanned)</td>
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<td>Computed Axial Tomography</td>
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<td>Creutzfeldt-Jakob Disease</td>
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<td>Cytomegalovirus</td>
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<tr>
<td>Department of Health and Human Services</td>
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<td>Food and Drug Administration</td>
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<tr>
<td>Health Care Finance Administration</td>
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<tr>
<td>Institute of Medicine</td>
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<tr>
<td>Leukocyte Reduction or Leukocyte Reduced (according to context of use)</td>
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<tr>
<td>Magnetic Resonance Imaging</td>
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<td>Non-hemolytic Febrile Transfusion Reactions</td>
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<td>Nucleic Acid Testing</td>
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<td>Quality Adjusted Life Year</td>
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<td>Randomized Controlled Trials</td>
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<td>Transfusion Related Immunomodulation</td>
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<td>Transfusion Requirements in Critical Care Study™</td>
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<td>Universal Leukocyte Reduction</td>
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<td>University Health System Consortium</td>
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<td>Variant CJD</td>
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