Review

To filter blood or universal leukoreduction: what is the answer?

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Abstract

The safety of the blood supply has been a concern over the past 20–30 years because of the transmission of infectious diseases. Blood is still routinely tested for viruses, and leukoreduction is an effective strategy to reduce the transmission of cell-associated viruses. Clinically, the benefits of leukoreduction include decreases in transfusion reactions, HLA alloimmunization, infections, fever episodes, and antibiotic use. Although leukoreduction will add cost to a unit of blood, projections indicate that leukoreduced blood will become the standard of care.

Keywords blood transfusion, filtration, leukoreduction

Transfusion medicine has undergone dramatic changes through the centuries. In the early 1900s Karl Landsteiner discovered the ABO blood group system, which allowed blood products to be administered without precipitating immediate severe transfusion reactions. The logistics for collecting and storing blood followed at the time of the onset of World War I, with the introduction of the anticoagulant trisodium citrate to prevent clotting. The mid-20th century was focused on attempts to have adequate blood supply on hand, as operative procedures became technically more complex and medical specialties known to consume large quantities of blood and blood products, such as transplantation, began to emerge. Contamination of the blood supply also was becoming a concern, and in the early 1970s it was recognized that the incidence of hepatitis transmission could be decreased by excluding paid donors. Screening for hepatitis B became standard shortly thereafter. Until 1980, blood donations were only screened for syphilis serology and hepatitis B. Since then, nine new blood tests have been introduced in an attempt to reduce the transmission of HIV-1, HIV-2, hepatitis C, and human T-cell leukemia virus (HTLV)-I and HTLV-II [1]. By 1996, anti-HIV-1 and p24 antigen testing were routinely performed, decreasing the transmission of HIV. Despite these advances, there continues to be major concerns with our blood supply because of bovine spongiform encephalopathy, prion transmission, and unknown pathogens. As we continue into the new millennium, interests are shifting toward technologic advances in pathogen inactivation and modification of the red blood cell (RBC) surface to reduce antigenicity [1].

Leukoreduction is a process in which the white cells, ordinarily present in collected blood components, are intentionally reduced in number. Through the use of centrifugation or filtration, 99.995% leukocyte reduction can be accomplished. Cytomegalovirus (CMV), HTLV-I, and HTLV-II are only transmitted by transfusion of cellular products, and if universal leukoreduction were to be adopted then these viruses would be removed by filtration, and it would no longer be necessary to test for these potential contaminants. Thus, an advantage of leukoreduction is its effectiveness in reducing the transmission of cell-associated viruses, especially CMV, herpesviruses, and Epstein–Barr virus. Leukoreduction filters also bind the *Trypanosoma cruzi* parasite and may decrease the incidence of transfusion-associated Chagas' disease [2]. In 1998, the Blood Products Advisory Committee of the US Food and Drug Administration unanimously voted in favor of universal leukoreduction of blood components, but its members agreed that sufficient evidence-based data were lacking. Thus, both leukoreduced and nonleukoreduced blood components currently remain approved by the Food and Drug Administration. In 1994 and 1997, the percentage

CMV = cytomegalovirus; HTLV = human T-cell leukemia virus; RBC = red blood cell.

Table 1

Advantages of universal leukocyte reduction

Reduction in transfusion reactions; HLA alloimmunization; and CMV, HTLV-I, EBV, HHV-6 and HHV-8 transmission
Improved RBC quality
Reduction in parasite and prion transmission, bacterial sepsis, and acute lung injury
May decrease postoperative abdominal infection, morbidity and mortality in cardiac surgery, and multisystem organ failure
Avoids errors, decreases workload, and simplifies blood bank inventory
No need for a filter, saving time and education

Reproduced with permission from [1]. © 2001, American Society of Clinical Pathologists. CMV, cytomegalovirus; EBV, Epstein–Barr virus; HHV, human herpesvirus; HTLV, human T-cell leukemia virus; RBC, red blood cell.

of blood components transfused in the USA that were leukoreduced were 17.6% and 18.3% and for platelets 16.5% and 15.5%, respectively [3]. Surgical patients and those with gastrointestinal bleeds are the groups most likely to receive nonleukoreduced blood, in part because of the emergent need for blood.

When a unit of blood (approximately 500 ml) is collected, about 2 billion (2×10^9) white cells are present. Even with blood component processing, 90% of these cells remain with the RBCs, primarily as granulocytes; 8% of cells (2 million) remain with platelets as mononuclear cells; and 2% of cells (10 million) remain in an aliquot of fresh frozen plasma. The intent of leukoreduction is to decrease the number of white cells in the aliquot, but even the 0.0005% of cells left after leukoreduction leaves 5000 residual leukocytes. Filtering of the white cells can lead to a 5–10% loss in the number of RBCs recovered per unit. These losses may be justified, however, because they are balanced in part by the improved quality of the filtered RBC unit.

Although it is the most common transfusion reaction, febrile-associated transfusion reaction is due to clerical error and is self-limited. Fatal hemolytic transfusion reaction still occurs in 1 per 500,000 units of blood transfused. The Canadian Blood Service implemented prestorage universal leukoreduction to control febrile reactions [3]. Universal prestorage leukoreduction has resulted in decreased fever episodes and antibiotic use after RBC transfusion, with a reduction in mortality [4]. Suggestions have also been made that transfusion-related acute lung injury may be due to the presence of allogeneic leukocytes in stored RBC products, although most cases of transfusion-related acute lung injury are believed to be due to the passive transfusion of anti-HLA antibodies that react with recipient neutrophils.

Up to 30% of platelet transfusions lead to a febrile reaction; however, this may be secondary to the release of platelet-specific chemokines rather than the chemokines released by contaminating leukocytes. In a multicenter study conducted in patients with leukemia and sponsored by the US National Institutes of Health, a difference in platelet refractoriness did not lead to clinical differences. On the other hand, the American Society of Clinical Oncology found level I grade A evidence, and recommended that only leukoreduced products be used in patients with acute myeloid leukemia. This is because alloimmunization against histocompatibility antigens occurs in many recipients of multiple random donor platelet transfusions, and is the most important long-term complication of platelet transfusion [5].

Leukoreduction may occur in two forms: prestorage filtration or poststorage filtration. The most common form used in Europe and the USA is prestorage leukoreduction, which removes leukocytes before they can contribute to the storage lesion (RBCs) or transfusion reactions (platelets/RBCs). The process allows the opportunity for better quality control, has not been associated with acute hypotensive episodes, and eliminates the need for transfusion services to manage filter inventories and for nursing staff to maintain multiple blood administration protocols. Table 1 lists the advantages of universal leukocyte reduction. Prestorage leukoreduction not only decreases the incidence of certain virus transmissions but also eliminates the delay associated with filtering blood in a patient who requires blood to be administered urgently. Only one type of filter is needed, allowing standardization to occur, obviating the need to train technicians and nurses on the procedure, and eliminating the clotting of filters during a transfusion.

One advantage that poststorage filtration may have is that the filter used with transfusion administration may remove undesired substances that accumulate during storage. No studies to date have shown benefits from this type of filtration. Table 2 summarizes the disadvantages of leukoreduction.

A study of elective orthopedic surgery patients confirmed the presence of T-cell-mediated immunity after allogeneic transfusion. With buffy coat depleted or white blood cell filtered RBCs, alloantigen-induced T-cell proliferation was significantly reduced [6]. However, in a group of patients with advanced HIV infection, in which T-cell immunity is important, leukoreduction provided no clinical benefit with respect to HIV, CMV, or cytokine activation [7].

Table 2

Disadvantages of leukoreduction

Cost	$600 million/year in USA
	In Rhode Island, prestorage leukoreduction implementation cost $1,466,250 (extrapolating to $319 million across the whole of the USA)
Logistics	2% loss of red blood cells
	Platelet loss of 11% due to trapping

Six studies [8–13] suggested that leukoreduction is beneficial in preventing postoperative complications in patients undergoing surgery, but two studies [14,15] showed no benefit. Because of issues regarding study design, data analysis, and other factors, these findings are still a subject of debate. There are no data indicating that patients undergoing abdominal surgery will benefit. On the other hand, two studies [12,13] were published that reported evidence of improvement in morbidity and mortality. One large study [13] found a 50% decrease in the mortality rate and a decrease in postoperative infection as a secondary end-point in patients undergoing cardiac surgery receiving leukoreduced blood.

The largest prospective randomized study of leukoreduction [16] enrolled 2780 patients, and documented no differences in the outcome measures studied, including in-hospital mortality, hospital length of stay, intensive care unit length of stay, postoperative length of stay, antibiotic usage, and readmission rate. Subgroup analyses based on age, sex, amount of blood transfused, and category of surgical procedure showed no effect of leukocyte reduction. Patients who received leukocyte-reduced blood exhibited a lower incidence of febrile reactions ($P = 0.06$). In that important study no beneficial effect from leukocyte reduction was demonstrated.

A recent meta-analysis [17] reviewed all randomized controlled trials evaluating leukocyte-reduced transfusions and mortality. There was no association between transfusion and mortality across 14 trials reporting on short-term mortality (summary odds ratio 1.20, 95% confidence interval 0.87–1.65) or across three trials reporting on long-term mortality (summary odds ratio 0.87, 95% confidence interval 0.64–1.19). Subgroup analysis suggested an association between non-leukocyte-reduced blood transfusion and increased short-term mortality in cardiac surgery patients.

No prospective randomized studies have yet investigated whether leukoreduction of blood is associated with improved outcome in critically ill patients specifically.

Leukoreduction of blood can add approximately $100 to the cost of a unit of blood. In the State of Rhode Island, with a population of 1 million, the cost of leukoreduction is US$1,466,250 [18]. Extrapolating this figure to universal leukoreduction in the entire USA yields an annual cost of around $319 million, but this does not take into account the above-mentioned cost savings associated with reduced time, resources, and effort (Table 2).

Emerging scientific and clinical evidence demonstrates that leukoreduction technology is an effective means to reduce the risk for three complications of transfusions [19]: HLA alloimmunization, CMV transmission, and recurrent febrile nonhemolytic transfusion reactions. Notwithstanding the ongoing debate on the merits versus the disadvantages of universal leukoreduction, most projections indicate that within the next few years all blood in the USA will be leukoreduced.

Competing interests

None declared.

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