Universal Leukocyte Reduction of Blood Transfusions

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(See the article by Cervia et al. on pages 1008–13)

In this issue of Clinical Infectious Diseases, Cervia et al. [1] review the evidence that removal of leukocytes from transfused blood by adherence filtration ("leukocyte reduction" [LR]) reduces the likelihood of infectious complications in recipients. Despite being employed by Pall, a manufacturer of LR filters, the authors present a moderate and balanced review of the issues, some of which have been extremely contentious. Their article delineates why LR is the greatest advance in transfusion medicine of the past half-century, along with infectious disease testing, and that LR is perhaps even more important than infectious disease testing if a reduction in short-term transfusion recipient morbidity and mortality is the criterion employed. Most of the complications prevented by infectious disease testing (e.g., HIV-1 infection and hepatitis C) cause morbidity and mortality some years or decades after transfusions, whereas most of those prevented by LR include common causes of morbidity and mortality (e.g., postoperative infection and multiple-organ failure syndromes) during the current hospital admission.

In the first half of the 20th century, the main challenges to transfusion therapy were finding techniques for maintaining cellular function during storage and avoiding immunologic incompatibility between donor and recipient. In the second half of the 20th century, the challenge was to make transfusion safer by avoiding transmission of viral agents, such as hepatitis B and C viruses and HIV. These problems were largely overcome and are among the most important advances in modern medical care, and they represent the triumph of collaborative research by immunologists, hematologists, epidemiologists, infectious diseases physicians, and microbiologists, among others.

The 21st century's dawning finds transfusion therapy facing newer and more subtle challenges. The efficacy of transfusions—particularly transfusions of stored RBCs—appears, as currently practiced, to be considerably less than had been assumed, particularly in the critical care setting [2]. Previously unknown or uncommon infectious agents, such as prions, protozoa, and bacteria, have become a source of continuing concern, leading to research into pathogen inactivation or reduction using chemicals, such as psoralens [3] or riboflavin [4]. It has also become apparent that transfusion is very much like a temporary organ transplantation and that it has profound immunologic effects on host defenses, sometimes with favorable and sometimes with unfavorable clinical consequences [5, 6]. Examples include reduced solid-organ allograft rejection in patients who have undergone transfusions and increased postoperative infections and multiple-organ failure in surgical patients who have undergone transfusions. It appears that some of the immunologic effects that reduce allograft rejection impair host defenses against microbial organisms, as occurs with some of the immunosuppressant drugs in clinical use. Thus, the new challenges are to improve the clinical efficacy of transfusions while reducing their immunologic adverse effects.

LR, which removes ~99.9% of the allogeneic WBCs from donor blood before transfusion, is a strategy for ameliorating the infectious and immunomodulatory effects of transfusions. It is relatively simple, essentially risk free, and relatively inexpensive, increasing the costs of a $200 unit of RBCs by perhaps 10%–15%. Almost all physicians accept the data that LR reduces the risk of nonhemolytic febrile transfusion reactions; reduces alloimmunization to HLA-A and HLA-B antigens, which can cause platelet transfusion refractoriness, acute lung injury, and organ allograft rejection; and reduces transmission of WBC-associated viruses, such as cytomegalovirus [7]. These benefits alone are compelling clinical arguments for transfusing only blood that has undergone LR to all patients who require transfusions, even if the patients are not currently immunosuppressed, receiving platelet transfusions, or on allograft waiting lists. All patients
may find themselves in those categories in the near or distant future; in particular, this is the case for children and younger adults.

It may be short-sighted to consider only the immediate consequences of complications of transfusion. For example, transmitting cytomegalovirus by transfusion to a young woman transfused due to hemorrhagic complications of an ectopic pregnancy may lead to fetal morbidity and mortality due to cytomegalovirus in a subsequent pregnancy years later. Sensitizing a young man, via transfusions for blunt trauma in an auto accident, to HLA-A, HLA-B, or neutrophil antigens may compromise his care if he later develops a disease requiring myeloablative chemotherapy or, should he later donate blood, render him more likely to cause transfusion-related acute lung injury in a transfusion recipient. These potentially catastrophic long-term complications of transfusion therapy largely can be abrogated by use of blood transfusions that have been subjected to LR. A recent report suggests that the uniformly fatal—albeit rare—transfusion complication of graft-versus-host disease may be largely preventable by universal LR [8].

On the basis of randomized trials, it has been found that patients receiving transfusions that have not undergone LR for surgery have a 50% higher rate of postoperative infection, compared with those who received transfusions subjected to LR [9]. Infections are the most common cause of morbidity, increased length of hospital stay, and mortality in surgical patients. Because there are so many other benefits and no risks, other than a modest cost increase, one might assume that universal LR of the blood supply is now a “no brainer” in terms of reducing morbidity, mortality, and costs. But that has not been the case. Despite the fact that 2 major federal advisory committees recommended universal LR of the blood supply (the US Food and Drug Administration Blood Products Advisory Committee in 1998 [10] and the Department of Health and Human Services Advisory Committee on Blood Safety and Availability in 2001 [11]), no action has been taken, and there is no national policy of any sort. This major public health oversight resulted from flawed reviews and meta-analyses. It is penny-wise and pound foolish.

What data exist suggest that LR of transfusions is that rarest of therapeutic advances that prevents suffering, illness, and death, yet saves money [12]. The rationale for not implementing universal LR has been that individual physicians should decide whether their patients require transfusions that have undergone LR. Because 80% of transfusions are now subjected to LR, the cost of implementing universal LR in the United States is probably only on the order of $50,000,000–$100,000,000 annually, maximally. Universal LR would no doubt result in easier-to-maintain inventories of the various ABO and Rh blood types, with less chance of serious errors.

Even in patients who are not undergoing surgery, there is nothing good that will come of patients needlessly being alloimmunized to HLA antigens, experiencing febrile reactions, or becoming infected with cytomegalovirus. We advise, on the basis of information in the review by Cervia et al. [1] and of our own experience and research, that all treating physicians should insist on administering LR transfusions to all of their patients and at all times. This will require that their hospital’s blood supply consist only of blood that has undergone LR. Anything less is suboptimal medical care, will cause needless harm to patients in the short and long term, and will, in the final analysis, cost their hospital and the health care system nationally more money than implementation of universal LR.

We hope that the US Food and Drug Administration and voluntary organizations, such as the AABB, the American Hospital Association, the Joint Commission, and clinical specialty groups, will mandate universal LR of all transfusions, so that the United States can join most of the rest of developed world and reverse one of the most serious public health policy errors in the history of transfusion therapy in the United States.

Acknowledgments

Potential conflicts of interest. J.M.H. has worked as a consultant for Gambro. N.B. has received recent research funding from Gambro; has worked as a consultant for Gambro, Fenwal (Baxter), and Bayer; and has been on the speakers’ bureau for Pall, Gambro, and Fenwal (Baxter).

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