The reintroduction of nonleukoreduced blood: would patients and clinicians agree?

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With today’s economic uncertainty, hospitals continue to look for new ways to reduce costs in a safe fashion. Some hospitals currently providing only leukoreduced blood have considered providing nonleukoreduced blood components for their patients, presumably assuming that nonleukoreduced blood is less expensive than leukoreduced blood. This commentary examines the safety of the reintroduction of nonleukoreduced blood components in hospitals that previously implemented universal leukoreduction.

Because universal leukoreduction has been in place in most hospitals for almost a decade, many clinicians have never had to weigh the risks and benefits of leukoreduced and nonleukoreduced products, and currently they are not required to decide whether nonleukoreduced components would be seriously detrimental for their patients.

In the past there was debate about whether universal leukoreduction was cost-effective, but the debate did not include a balancing of risks and benefits, because no true risks have been identified (aside from device failures). On the other hand, there is no question that transfusion with nonleukoreduced blood increases risk (defined below) for patients and its reintroduction provides no clinical benefit. The reason to reintroduce these components is to reduce cost.

The decision to reintroduce nonleukoreduced components should involve many stakeholders at the hospital including committees dealing with transfusion practices, the quality of medical care, and risk management, and ultimately the decision should be considered by the medical board. If each of these stakeholders approves the reintroduction of nonleukoreduced blood, the changes to the transfusion medicine formulary must be communicated to the medical staff so that they can understand the medical implications of these actions, which we believe are not justified by the perception of cost reduction. Education and communication would be a key component of any program to introduce nonleukoreduced blood.

Should leukoreduced blood remain the default product? If leukoreduced components are the default, would clinicians specifically order nonleukoreduced blood for any of their patients? It is not likely. To produce a change, nonleukoreduced blood would have to be the default product. How would the clinicians in each subspecialty be educated about the risks of the “new” standard components and participate in the development of new transfusions strategies for patients for whom this new component is not appropriate?

The hospital deciding to switch from universally leukoreduced components to a dual inventory of leukoreduced and nonleukoreduced products should also consider the implications for their patients who may ultimately be transferred to other hospitals for advanced care. Among the patients who may be harmed by receiving nonleukoreduced blood components are those with hematologic malignancies and those in need of organ transplantation. These patients are often treated urgently before diagnosis in one hospital and referred to another for definitive therapy. If the diagnosing hospital reintroduced nonleukoreduced blood, patients with hematologic malignancy or those in need of transplantation may be adversely affected by transfusions that might promote alloimmunization or cytomegalovirus (CMV) seroconversion. Changes in transfusion policy in one hospital can lead to poor patient outcomes in another hospital due to unnecessary exposure to white blood cell (WBC) antigens or cell-associated viruses, even if the patient was transferred in what appeared to be “good condition.”
Reintroduction of nonleukoreduced blood components would increase risks for transfusion recipients in two ways. 1) Risks would increase for all transfused patients. 2) Risks would especially increase for specific subgroups of patients in whom transfusion with nonleukoreduced blood could be life-threatening. The reintroduction of nonleukoreduced blood would not increase the potential harm for this second group if physicians and staff always remembered to request leukoreduced (or CMV-seronegative) blood components and if the transfusion service were 100% accurate in filling such orders. However, the presence of nonleukoreduced as well as leukoreduced components in the hospital inventory creates the potential for incorrectly dispensing a nonleukoreduced product and decreases the likelihood of patients always getting the components they require 100% of the time.8

RISKS FOR ALL PATIENTS

Leukoreduction has been repeatedly shown to prevent most febrile nonhemolytic transfusion reactions (FNHTRs) in multiply transfused patients with a history of FNHTRs.9-11 Many studies have also found that leukoreduction may decrease the incidence and severity of FNHTRs in certain patients without a transfusion history.9-11 Given that it is impossible to predict which patients will develop this reaction during or after transfusion, universal leukoreduction is maintained to best ameliorate this complication. Studies have shown that the reduction in posttransfusion fever can help decrease antibiotic use after transfusion.12,13 Reduction in the number of febrile reactions also decreases the time-consuming transfusion reaction workups performed by the blood bank technicians, diminishes the expensive clinical investigation of symptoms that can mimic sepsis, and decreases the cost and potential clinical complications that result from transfusing a new unit of red blood cells or platelets (PLTs) after a negative clinical and laboratory workup. Avoiding a transfusion reaction that could be easily prevented is important for patients and their families who become very concerned about adverse effects and problems that may seem inconsequential medically but can be very troubling for sick patients in the hospital or outpatient clinic.

A potential, yet controversial, benefit of leukoreduction involves decreased transfusion-related immunomodulation. Transfusion-related immunomodulation is most likely caused by the down regulation of the immune system and/or the inflammatory response by donor WBCs after allogeneic blood transfusion. Some studies report modest benefits after leukoreduction including decreased postsurgical infection and/or mortality rates,14,15 while others report no improvement in these rates.16-20 Less controversial benefits include a decrease in posttransfusion febrile episodes and leukocytosis, which may subsequently lead to decreased antibiotic use.14,15 The potential detrimental effects of unnecessary antibiotic use or the possible progression of infection as a result of transfusion with nonleukoreduced blood in certain patient populations should be further elucidated before the reintroduction of these products.

A recent study has shown that leukoreduction may help diminish the detrimental effects of the storage lesion.21 Prolonged storage times may lead to an increase in cytokines and other products released from deteriorating WBCs, which may increase the magnitude of the potential detrimental effects of long storage times on the recipient. This is a controversial point and current evidence is not conclusive. Massively transfused trauma patients tend to receive a significant amount of blood stored for more than 14 days. Given that trauma patients do not currently fit into a category of patients that must receive leukoreduced products, these patients may be in the group that hospitals target to receive nonleukoreduced products. Again, given the potential benefit of leukoreduction on the storage lesion, how would hospitals justify transfusing nonleukoreduced components to trauma patients? Further studies must be performed to confirm or disprove the findings regarding the storage lesion.

In theory, the transmission of intracellular viruses should decrease when leukoreduced products are given. Transfusion transmission of viruses such as human T-lymphotropic virus-1 (a very rare complication) has been shown to decrease with optimal leukoreduction and this prestorage process may help to decrease the risk of transmission, especially during the serologic window period.22 Avoiding CMV seroconversion from transfusion of nonleukoreduced blood may also be important in the event that the patient requires a transplant or immunosuppressive therapy in the future.

The pathogenesis of certain rare disorders, posttransfusion purpura and transfusion-associated graft-versus-host disease (TA-GVHD), involves recipient exposure to donor PLTs and donor T cells, respectively, both of which are essentially removed during the leukoreduction process. Data from the United Kingdom SHOT study suggests that universal leukoreduction has resulted in a consistent decrease in reporting of posttransfusion purpura and TA-GVHD.23 Further studies are needed to help confirm these findings, especially if hospitals are considering the reintroduction of nonleukoreduced products into the community. Although patients at known risk for TA-GVHD should continue to receive irradiated blood products, there is probably some benefit to patients not known to be at risk from receiving leukoreduced blood components.
**RISKS FOR PATIENT SUBGROUPS**

**Patients who may need organ transplantation**

The risks of receiving nonleukoreduced components can affect certain subgroups of patients severely. Patients exposed to blood components contaminated with WBCs may become alloimmunized to HLA antigens that might jeopardize a future transplant. Transplantation may not have been a consideration at the time of these earlier transfusions and, therefore, there may not have been sufficient concern about future alloimmunization. Nevertheless, countless dollars are spent screening patients on transplant lists for antibodies to HLA antigens. The more reactive the patients’ plasma, the longer they may have to wait for an organ. In some cases, broadly reactive alloantibodies induced by transfusions can make transplants very difficult if not impossible.

**Patients with leukemia**

Many studies have shown that transfusion with leukoreduced products decreases the incidence of HLA alloimmunization and the rate of PLT refractoriness in certain patient populations. Patients who require chronic transfusions are at risk for alloimmunization, and thus transfusion with nonleukoreduced blood is generally considered potentially harmful. With publication of the TRAP trial, the evidence for leukoreduction to decrease HLA alloimmunization and PLT refractoriness in patients with leukemia is overwhelming. It is impossible to predict which patients will require leukoreduced products in the future. Once a patient becomes refractory, testing for and finding HLA-matched or crossmatch-compatible PLTs is time consuming, costly, and often ineffective. The way to avoid increasing the risk for chronically transfused patients and help minimize the number of patients who become refractory is to always provide leukoreduced blood products.

**Neonates and patients who are severely immunocompromised**

There is little disagreement that leukoreduction decreases transfusion-transmitted CMV. Evidence strongly suggests that leukoreduction is equally effective as CMV serologically negative blood at reducing transfusion-transmitted CMV infection. However, some clinicians request CMV-negative and leukoreduced units for their patients who are at the greatest risk for transfusion-transmitted CMV infection. Although the need for both filtration and testing for seriously ill patients remains controversial, most clinicians would probably agree that the number of patients who might benefit from receiving both tested and filtered blood is likely smaller than the number of patients who would be adequately treated with either filtered blood or CMV-tested negative blood. In addition, we can be certain that having nonleukoreduced CMV-untested units stored in a hospital blood bank greatly increases the chance that an immunocompromised adult patient or a neonate will receive a potentially life-threatening component in error.

**Patients who undergo cardiac surgery**

Many studies have reported benefits of leukoreduction for certain cardiac surgery patients. Myocardial ischemia may enhance neutrophil activation and may thus lead to reperfusion injury after restoration of blood flow after heart surgery. In both heart transplant and cardiac bypass patients, leukoreduced blood has been shown to decrease biochemical markers of myocardial damage. Leukoreduction may be associated with decreased hospital stay, decreased in-hospital mortality (demonstrated by randomized clinical trials), a reduction in postoperative mortality, improved cardiac function, and potentially decreased peri- and postoperative infection after cardiac surgical procedures. Although there are studies that support only limited benefits from leukoreduction and do not demonstrate reduced length of stay, there is considerable evidence to support the avoidance of nonleukoreduced products in cardiac patients. These patients are undergoing costly procedures with inherently high morbidity and mortality and lengthy recovery periods. Attempting to minimize potential complications and hospital stay through leukoreduction may prove to be a cost-effective process that also improves patient outcome. Whether the positive effects of leukoreduction also apply to other surgical groups with large blood needs will require further research.

**SUMMARY**

Universal leukoreduction is a cornerstone of modern, high-quality transfusion therapy and a reasonable means to avert the consequences of failing to identify those who currently need leukoreduced products and those who will need these products but have not yet been identified. It should be considered best practice to provide leukoreduced blood to all patients, removing any risk that a patient will be harmed if nonleukoreduced blood is stored and subsequently transfused inappropriately. Given the numerous studies that support leukoreduction as a means to decrease current and future risks to patients, it is troubling to introduce nonleukoreduced blood components as a measure to control costs. Before leukoreduction was universal, there was debate about which indications for leukoreduced products were the strongest and which were most cost-effective. Now that leukoreduction is nearly universal and patients are experiencing its benefits, the reintroduction of nonleukoreduced blood forces the
discuss the issue of which patient groups should be exposed to the higher risks of receiving nonleukoreduced components.

Even if one sets aside the key issue of increased risk, how effective is nonleukoreduction as a cost control measure? A study that examined giving leukoreduced versus nonleukoreduced blood to cardiac surgery patients found that leukoreduced blood may be cost saving or at least cost neutral in certain settings. The cost of maintaining dual inventories, ensuring that only appropriate patients receive nonleukoreduced blood, investigating a source for fever after transfusion, extended stays in the intensive care unit or hospital as a result of transfusion reactions, the cost and time of managing patients refractory to PLT transfusion, or those who cannot receive organ transplants due to alloimmunization could outweigh the cost of leukoreduction.

More than 85% of the blood transfused in the United States is prestorage leukoreduced, and more than 80% of institutions in the United States have implemented universal leukoreduction. The FDA’s Blood Products Advisory Committee and the HHS Blood Safety and Availability Committee recommended universal leukoreduction at a time when the incremental cost of manufacturing a leukoreduced component was probably relatively higher than it is today.

If the information comparing leukoreduced and nonleukoreduced blood components is shared openly with the physician staff, it seems unlikely that there would be willingness to transfuse an inferior component, knowing that a safer component has been the standard for years and remains readily available in the hospital. There is no guarantee that the reintroduction of nonleukoreduced products will save money, and more important, there are better and safer means to attempt to decrease costs in the hospital without compromising the quality of patient care.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES


