Prevention of HLA Alloimmunization: Role of Leukocyte Depletion and UV-B Irradiation

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HLA alloimmunization is a major cause of the platelet refractory state. The stimulus for HLA alloimmunization is believed to derive from incompatibility between the recipient's lymphocytes and the passenger donor lymphocytes contained in transfused red cells or platelet concentrates. Two techniques to prevent post-transfusion HLA alloimmunization include filtration, which physically removes the donor lymphocytes, and UV-B irradiation, which renders the donor leukocytes biologically inactive. The role of these two techniques in the prevention of HLA alloimmunization is the focus of this review.

Due to the development of blood component therapy and the ready availability of platelet transfusions, thrombocytopenic patients who previously would have suffered a fatal hemorrhage can now be treated. Access to platelet transfusions, for example, permits oncology patients to complete a prescribed course of chemotherapy and in many situations survive for long disease-free periods. The ready availability of platelet concentrates (PC), however, has generated a new concern regarding the development of the platelet refractory state. With this condition, platelet transfusions, which formerly were effective, no longer provide an appropriate post-transfusion platelet count increment. Platelet refractoriness, in general, refers to the inability to obtain an appropriate elevation in platelet count following transfusion. The causes of refractory state are manifold and are listed in Table 1. Of these myriad causes, HLA alloimmunization represents one area which is the current focus of intense biomedical research. The relative contribution of many of the other factors has recently been reviewed [1,2]. The prevention of platelet refractoriness due to HLA alloimmunization will be the subject of this review.

Various guidelines have been developed to aid in determining an appropriate post-transfusion platelet count increment. For adults, one such guideline is to expect a rise in platelet count of 5,000–10,000/µL for every unit of platelets transfused. Such a figure, however, is inappropriate when comparing post-transfusion increments in patients of very small physical stature, such as pediatric patients, with obese or very large adult patients. Accordingly, more complex formulas have been developed. One such formula, a corrected count increment (CCI), is as follows:

Abbreviations: CCI: corrected count increment  PC: platelet concentrates  UV-B: ultraviolet B

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such formula, a corrected count increment (CCI), is as follows:

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\text{CCI} = \frac{\text{Post-transfusion platelet count} - \text{Pre-transfusion platelet count}}{\text{Platelets transfused} \times 10^{11}} \times \text{BSA (m}^2)\]

where BSA = body surface area.

This formula permits comparisons between individuals of different body sizes, as well as between transfusions in which different amounts of platelets were infused.

The etiology of a low post-transfusion platelet count requires clinical investigation. One cause, which has become of increasing importance to physicians, is refractoriness due to HLA alloimmunization. The HLA antigen system includes two classes of molecules: Class I molecules, the HLA-A, -B, and -C loci antigens which are present on leukocytes as well as on platelets, and Class II D locus antigens, including DR, DP, and DQ, which are present only on leukocytes \([3,4]\). According to current theory, primary HLA alloimmunization is a complex process, dependent on recognition of both HLA Class I and Class II antigenic differences \([3,5,6]\). The presence of viable cells bearing Class II antigens such as lymphocytes and antigen-presenting cells is necessary to stimulate primary HLA alloimmunization \([4,7]\) (see Fig. 1). Antigen-presenting cells include monocytes, macrophages, dendritic cells, and B cells. When blood is transfused, the lack of identity between donor and recipient lymphocytes at the Class II (D) locus stimulates the recipient to produce antibody against donor Class I HLA antigens \([4,7]\). This anti-Class I antibody is often responsible for a poor CCI, because Class I HLA antigens are present on platelets. Since it is the incompatibility between recipient and donor leukocytes which initiates the alloimmunization process, platelets can be considered to be "innocent bystanders." Researchers have hypothesized that, since platelets lack Class II antigens and are not the source of the immunogenic stimulus, if ways were found either to remove the Class II-carrying leukocytes physically or to inactivate them, perhaps HLA alloimmunization could be prevented \([5]\). This method will not, however, prevent the formation of platelet-specific alloantibody, which is due to transfusion of incompatible platelet antigens. Although the incidence of refractoriness due to platelet-specific antibody is much smaller, there is active research in this area, too \([8,9,10]\).

**LEUKOCYTE-REMOVAL FILTERS**

A number of published articles have shown that removal of white cells from blood components prevents, or at least delays, the onset of HLA alloimmunization \([5,11–18]\).
HLA ALLOIMMUNIZATION

FIG. 1. Schematic representation of the molecular interactions that occur between donor monocytes (APC) and recipient T cells during the early stages of immune responsiveness. The various accessory molecules involved in the interaction are also shown. Reproduced with permission of the publisher from [42].

Based on the data presented in these papers, the degree of white cell removal required is at least two to three logs (99.0–99.9 percent). This degree of removal applies to all leukocyte-containing blood components, including platelet concentrates and red blood cells. Units of red blood cells contain up to $10^9$ white cells, and after filtration or washing there are more than $10^7$ white cells still remaining. Based on clinical observations, these remaining white cells are sufficient to stimulate the development of HLA antibody.

Removal of white cells can be achieved by several means, which include centrifugation, with or without cell washing, or the use of blood filtration technology [11]. Centrifugation with buffy coat removal and/or automated cell washing is relatively inefficient, removing at best 1–2 logs of white cells (90–99.0 percent). This percentage of removal, however, still leaves 7–8 logs of white blood cells in the red cell unit, a number which is probably sufficient to stimulate HLA antibody formation. Newly designed third-generation blood filters have been developed which are capable of removing up to 3 logs (99.9 percent) of contaminated leukocytes [19–21].

The first blood filters produced were coarse clot screens, which had pore sizes of 170–260 μm; they were designed primarily to remove clots and debris which formed in blood during storage [22]. These filters are in widespread use due to the FDA and American Association of Blood Banks requirement that, to remove protein coagula and other debris, all blood components be infused through an administration set containing a filter. These filters, however, remove less than 1 log (<90 percent) of the leukocyte aggregates and are unable to remove individual white cells, which are about 8–14 μm in diameter. Second-generation microaggregate filters, both the screen and the depth types, are capable of removing microaggregates (fragments of deteriorated platelets, leukocytes, and fibrin strands) in the size range of 20–120 μm [22]. They can remove up to 1–2 logs (90–97 percent) of the leucocytes from units of red cells most efficiently.
when the blood product is centrifuged and held at 4°C prior to filtration (spin-cool-
fiber technique) [11,23]. Most efficient 3 log (99.9 percent) white cell removal is
achieved, however, only with use of third-generation leucocyte depletion filters.

Third-generation filters employ technology which involves coating the filter fibers
with chemical polymers [19–21]. These polymers impart various surface tension and
adsorption characteristics to the fibers, which make the filtration process highly
efficient in terms of the number of cells removed as well as highly selective in terms of
the specific type of cell removed. Changing the polymer coating on the fiber results in
the ability to remove different numbers as well as different types of cells. One type of
filter will remove both leukocytes and platelets from units of red cells [19], while
another type will selectively remove leukocytes from units of platelet concentrates [20].
If the wrong filter is used, however, the wrong cell may be removed. For example, if one
desires to leukocyte deplete a pool of platelets, filtration of the platelet concentrate pool
through a filter designed to leukocyte deplete red blood cells will result in platelet as
well as white cell removal. Thus, this particular recipient essentially will receive
platelet-poor plasma [21].

As mentioned, various studies have shown that removal of white cells to a level below
10^6 or 10^4 appears to prevent or delay alloimmunization [5,11–18]. Several questions
remain, however. First, the long-term cumulative effects of transfusing third-
generation filtered blood components containing less than 10^3 and 10^4 white cells are
unknown. Perhaps use of these filters merely postpones the onset of HLA alloimmuniza-
tion; further data are needed [5]. Although delay in the onset of alloimmunization is
appropriate in itself, if long-term benefits are not obtainable through use of the filters,
then any advantage from their use may not be balanced by the current $30–$60 cost
per filter.

The indiscriminate use of these third-generation filters cannot be recommended
because many patients may not be helped by the use of such a filter [24]. Multiparous
women, for example, are exposed to paternal HLA antigens at parturition, following
the entry of fetal white cells into maternal circulation; such women are at high risk for
developing HLA alloantibodies [14]. Even these highly efficient white cell depletion
filters thus provide no protection for previously pregnant women patients who have
already been exposed to HLA antigens during the birth of their children, and who may
already have developed HLA alloantibody [14]. If a sufficient number of antigen-

presenting cells were infused during previous blood transfusions that a patient received
prior to the current illness, the patient, again, may already have developed HLA
alloantibodies and would not benefit from the use of white cell depletion filters. Studies
have shown that up to 50 percent of multiply transfused patients will develop HLA
antibodies [5,25–28]. Thus it is possible that many patients may already be HLA
alloimmunized when they present to their physicians. Furthermore, data show that
40–50 percent of patients are non-responders and are unlikely ever to develop HLA
antibodies [29]. A special third-generation leukocyte depletion filter would be unneces-
sary for such patients.

The criteria for diagnosing HLA alloimmunization rest on the finding of a positive
test for HLA antibody. No one test, however, is sufficiently sensitive. Accordingly, a
negative finding with one type of assay does not rule out the possibility that HLA
antibody might actually be present. Most experts agree, therefore, that several types of
HLA antibody assays should be performed and found to be negative before HLA
alloimmunization is eliminated as a cause for a poor post-transfusion CCI.
The exact number of white cells necessary to trigger the immune response is not known. As more studies are performed evaluating the role of leukocyte depletion filters, a clearer picture will emerge regarding the role of leukocyte removal in prevention of HLA alloimmunization. Even if every white cell could be removed from every unit of platelet concentrate and red blood cells, however, platelet refractoriness would still exist because many of the causes of poor post-transfusion platelet count increments (Table 1) are not related to HLA antibody at all but to the myriad of other factors mentioned previously [1,2].

**UV-B IRRADIATION**

Another type of technology that may prevent or delay the onset of HLA alloimmunization in transfused patients is the use of UV-B (ultraviolet B) irradiation [30-32]. Instead of removing the Class II antigen-containing leukocytes as filters do, UV-B irradiation appears to inactivate Class II molecules present on donor antigen-presenting cells, thus inhibiting recipient recognition of the transfused donor cells as being foreign. This process of UV-B irradiation is adequate for inactivation of leukocytes in units of platelet concentrate. Because hemoglobin absorbs light in the UV-B spectral range, however, effective UV-B irradiation of the white cells present in full units of red cell products cannot be achieved with existing technology. The UV-B cannot penetrate farther than a few millimeters into the red cells; thus, most of the unit fails to receive any radiation. To radiate whole blood effectively, a thin layer of blood is needed, and the cross-sectional diameter of the layer of blood to be UV irradiated should not exceed several millimeters. Thus, for full units of whole blood or red cell products, third-generation filters still must be used to remove the leukocytes physically.

Two published studies have shown in dog models that transfusions of UV-irradiated blood products do not stimulate HLA alloimmunization [33,34]. Deeg et al. [33], using a donor dog, transfused whole blood which was exposed to UV light in a dosage of 1.35 J/cm². The blood to be transfused was placed in a sterile petri dish and then exposed to the ultraviolet source. Since small aliquots of blood were used, the UV radiation adequately penetrated the blood and thus effectively irradiated any contained white cells. The recipient dogs were given three transfusions of UV-treated blood followed by a bone marrow graft from the DLA-identical transfusion donor dog. All recipient dogs so treated achieved sustained engraftment. For the control group, however, sham exposure of the donor dog blood to visible light failed to prevent alloimmunization, and all control dogs rejected their grafts.

Slichter et al. [34], in a study of the immunosuppressive effects of UV irradiation of platelet concentrates, provided weekly UV-irradiated platelet transfusions from a single random donor dog to a recipient dog. After eight weekly transfusions, of the 12 recipient dogs studied, 92 percent (11) remained non-immunized. In the control group, however, of the dogs who received eight weekly transfusions of non-UV-irradiated platelet concentrates, only 14 percent were non-immunized at the end of the eight weeks. Thus, UV irradiation of donor platelets was markedly successful in preventing alloimmunization. Furthermore, two-thirds (67 percent) of the non-alloimmunized dogs who had previously received UV-irradiated platelets remained un-immunized after receiving an additional eight non-UV-irradiated transfusions from their same donors; this fact suggests the induction of a state of tolerance. This result raises concerns, however, regarding the possible paralysis of the patient’s immune system, making the recipient of UV-irradiated blood components susceptible to infections with
a variety of bacterial, viral, or fungal agents. Animals receiving UV-irradiated blood products, however, can make antibody to sheep red blood cells as well as to various bacteria; thus their immune systems are not totally paralyzed following use of UV-irradiated blood products.

The exact mechanism of UV-B inactivation is unclear. Some believe it relates to interference with movement of calcium in the cell membrane [32]. Initially it had been thought that the protective effect was related to the loss or shedding of Class II antigens from the donor APC induced by the UV-B irradiation. This concept has been challenged by other investigators, however, and definitive studies are lacking [5,35]. Recent work implicates loss of ICAM-1 from the surface of APC monocytes following UV-B irradiation [36]. ICAM-1 is an accessory adhesive molecule involved in stabilization of the donor APC and recipient T-cell complex [36]. Human clinical trials are currently being performed to evaluate the ability of UV-B irradiation to prevent onset of alloimmunization; there are insufficient data at present to reach conclusions. It is likely, however, that parous women will need to be studied separately to ensure that the lack of development of HLA antibody in these patients is not due to their being "non-responders" who would not have made antibody [29].

Another area of UV-B research involves irradiation of bone marrow. In an attempt to prevent graft-versus-host disease, scientists are evaluating the effect of UV-B radiation on bone marrow. Published data show that UV-B light can be used to inactivate bone marrow T lymphocytes selectively, while sparing hematopoietic precur-
sor cells [37]. Further clinical studies are in progress.

Another problem related to the use of UV-B irradiation of platelet concentrate concerns the ability to store such concentrates. Platelet concentrates can be stored for up to 120 hours (five days) at 20–24°C with continuous gentle agitation. If UV-B irradiation is to be most useful in modern transfusion medicine, it would be desirable to be able to store the irradiated platelets prior to transfusion. This procedure would allow for ease of handling by blood centers or major hospitals which must supply products to other institutions that may not have the facilities to UV-B irradiate platelet concen-
tracts. Several studies have been published, one by Pamphilon et al. [31] showing that, following a low dose of UV-B irradiation (300 mJ/cm²), platelets appeared to store well over five days. Another study by Snyder et al. [38], showed that, at a higher dose (10,000 mJ/cm²), while there were no significant adverse changes seen after 48 hours of storage, when platelets had been stored for four days after having been UV-B irradiated, significant changes in platelet storage characteristics were observed. These changes included a sharp decline in morphology and osmotic recovery scores, a loss of surface immunoreactive GP Ib, and a change in 2D-PAGE patterns of solubilized whole platelets. Thus, dose effects appear to play a role in maintenance of platelet integrity during storage after UV-B irradiation. Lastly, Andreu et al. [39] published the finding that UV-B irradiation at energy levels below 3 J/cm² did not impair platelet function.

Prevention of HLA alloimmunization by the use of third-generation filters or UV-B irradiation appears feasible. There are many refractory patients who are not alloimmu-
nized, however (refer to Table 1), and physicians and other health care personnel must remember that unqualified claims, implying that use of a filter or an irradiation technique will prevent refractoriness in all patients, are exaggerated. Such claims can refer only to individuals who are not yet alloimmunized and even then only to the possible ability to prevent or merely to delay the onset of HLA antibody formation. It
should not be misconstrued to mean that these techniques will be of benefit to patients with any of the many other causes of platelet refractoriness outlined in Table 1. The distinction between refractoriness to platelet transfusion and HLA alloimmunization as one cause of refractoriness must be remembered.

One last area of controversy associated with prevention of HLA alloimmunization is the loss of a possible graft-versus-leukemia effect following the use of leukocyte-poor blood components. Tucker et al. [40] raised concerns that the use of leukocyte-poor blood components to prevent HLA alloimmunization could also prevent a so-called "graft-versus-leukemia" effect. This theory states that lymphocytes which are contained in red cell or platelet transfusions may be useful in fighting the residual leukemia in the recipient in the form of graft-versus-host (leukemia) disease. Removal of the white cells may inhibit this reaction, thus decreasing rates of remission and survival of recipients of such blood components. More information is needed before one can decide whether this idea is a valid concern. Evidence for an antileukemic effect of bone marrow transplantation not explained by the associated high-dose chemotherapy and/or radiotherapy has recently been published by Horowitz et al. [41].

CONCLUSIONS

This review has addressed an area of transfusion medicine practice which is involved with the development of the immune response. Modulation of the immune response by removal of white cells or by inactivation of various antigens on the white cells which play a key role in initiation of the immune response in an area of active research. Achieving and maintaining an appropriate post-transfusion corrected count increment by prevention of HLA alloimmunization is an important goal. Even though the prevention of HLA alloimmunization will not completely eliminate the refractory state, it will, to a large degree, make medical care for patients requiring platelet transfusions more efficient and more effective.

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