CHAPTER 2

METHODS OF LEUKODEPLETION

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SUMMARY

This chapter reviews methods of production of leukocyte-depleted blood components, comments concerning the procedures used in the quality control of these products and a discussion of the proved and potential clinical benefits derived from the transfusion of these products in lieu of conventional white blood cell containing components. The advantages documented for the use of these products include a reduced incidence of nonhemolytic febrile transfusion reactions, a minimized rate of sensitization to HLA antigens and the accompanying immunological refractoriness to platelet transfusions and the provision of and a means to provide "cytomegalovirus" safe blood other than the traditional search for seronegative donors. The benefit of leukodepleted blood products in curtailing transfusion induced HTLV-I transmission, avoiding the immunomodulation which follows the receipt of blood and decreasing the rate of infection and tumor metastases which may be statistically associated with allogeneic blood transfusion are interesting possibilities that require prospective study. During the past three decades the technologies for the production of leukodepleted blood products have evolved from primitive procedures capable of removing less than 90% of the products' native leukocytes to those that currently deplete -4 $\log_{10}$ of the white cells. These techniques include sedimentation, centrifugation, cell washing, red cell freezing followed by deglycerolization, top and bottom component preparation systems and the use of laboratory and bedside filters. Although by definition not a leukocyte-depletion technique, ultraviolet irradiation of platelet concentrate has been recently shown to hold potential for reducing transfusion induced HLA sensitization. As the technologies to remove leukocytes from blood improve, so must the methods to qualify and monitor the production methods and products. At present the lower standard for leukodepleted components has been set at units containing no more than 10^6 white cells (U.S. standard, 5 x 10^6). Clinical studies may change these standards. Prototype filters are capable of now providing product containing as few as 10^3 leukocytes. The virtual elimination of all white cells from

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a blood component could conceivably justify new applications, such as products that lack the potential to elicit graft versus host disease.

The clinical use of leukocyte-depleted blood products (LDBP), specifically red cell (RCC) and platelet concentrates (PC), has dramatically increased in the past 10 years. A recent survey conducted by the College of American Pathologists (1993 CAP Surveys Set J-A) found approximately two-thirds of all facilities provide WBC reduced components to their clinical services and one-third of the responding institutions transfuse more than 10% of their cellular components as LDBP. The survey also confirmed that the majority of WBC reduced products are produced by filtration techniques. Improved efficiency and simplified production account for the increased use of LDBP. Increased use has led to numerous studies which confirm the clinical benefits derived from the use of these products.

INDICATIONS

The most widely published indication for the use of LDBP is for the prevention of non-hemolytic febrile transfusion reactions (NHFTR).[1] The frequency of NHFTR ranges from 0.5% to 5.0% of all RCC transfusions.[2] This number is several orders of magnitude greater for transfusions of PC. Most of reactions are immunologically mediated and represent the clinical manifestation of reactions between allogeneic white blood cell (WBC) borne antigens and alloantibodies formed as a result of previous antigenic exposure. Previously transfused patients and multiparous women experience the majority of such reactions. People with hemoglobinopathies such as B^o thalassemia are among the most consistently transfused patients. Cohorts of these patients are reported to have NHFTR rates in excess of 50% of all transfusions[3,4] (see chapter 6).

A more controversial issue is the use of LDBP to minimize the frequency of the transfusion related Adult Respiratory Distress Syndrome (ARDS).[5] A wide variety of clinical insults has been statistically associated with this syndrome.[6] Among these is the massive transfusion of blood.[7] These products contain microaggregates, particles consisting of WBC and platelets which form in a spontaneous and progressive fashion in stored red cells. The formation of microaggregates is minimized in blood that has been leukodepleted prior to storage. A similar syndrome dubbed "transfusion related acute lung injury" (TRALI) has been described.[8] This problem is caused by the sequestration of the recipient's own WBC in his/her pulmonary vasculature as a result of the infusion of allogeneic plasma containing antibodies directed against cell surface determinants on the recipients cells. For the most part, WBC depletion and the use of LDBP do not prevent this reaction, however, exceptions to this statement and details of the TRALI syndrome are dealt with elsewhere in this text (see chapter 10).

Reducing the incidence of alloimmunization to HLA class I antigens is a major indication for the use of LDBP.[9,10] HLA antigens are traditionally divided into class I (A, B and C loci) and class II antigens (D loci). Class I HLA antigens are present on all cells of endothelial derivation, however, the class II antigens are present on dendritic cells, B lymphocytes, monocytes and macrophages. The class I antigen remains the target for antibodies directed against the HLA system. Class I antigens, however, are incapable of eliciting a primary immune response without assistance from those cells bearing class II antigens. In the absence of such cells, antigen presentation does not occur, cytokines are not liberated and the chance of alloimmunization is minimized.[11] Since it is only the WBC in a blood product that express class II antigens, removal of these cells from RCC and PC reduces the rate of alloimmunization and its clinical sequelae; specifically immunological refractoriness to platelet transfusions (see chapter 7).

Viral disease is transmitted by the transfusion of both cellular and acellular allogeneic blood products. Two transfusion transmitted viral infections, however, are mediated solely by the transfusion of infected WBC. Transmission of the cytome-

galovirus (CMV) can be eliminated by reducing the white cell load of the transfused blood product.[12] The incidence of CMV seropositivity exceeds 50% in the USA, as well as in most developed countries. In donors over the age of sixty, seropositivity is as high as 85%.[13] CMV, a Herpes virus, achieves latency following the acute infection. This is an asymptomatic and lifelong period. Past studies prove that the rate of CMV seroconversion in recipients of unscreened blood is dramatically reduced when WBC are removed from the blood product prior to transfusion.[14] It is assumed that similar data prevail for transfusion induced HTLV-1 viral infection, since this virus is also confined to WBC in blood products[15] (see chapter 8).

Immunomodulation, specifically immune suppression, is associated with the transfusion of allogeneic blood. This observation has been capitalized on to enhance renal allograft survival. The mechanism(s) behind this association is not totally understood, however, it is recognized that at least in part, immunosuppression is achieved by the transfusion of leukocyte containing blood components and possibly plasma containing soluble white blood cell antigens.[16] Blajchman et al using an animal model demonstrated that use of LDBP minimizes the ability of allogeneic blood transfusion to enhance malignant tumor growth and metastasis.[17] Individuals exchanged transfused at birth have been shown to retain features of immunosuppression for many years and possibly for their entire lives. This is highly undesirable since loss of immune surveillance has been associated with increased rates of malignancy. Waymack has demonstrated impaired host defense mechanisms in mice following transfusion.[18] In his studies, mice are inflicted with burn wounds that are subsequently colonized with bacteria and the animals are observed for sepsis. The cohort of mice transfused with allogeneic blood experience higher rates of sepsis and death than do their liter mates who are subjected to the same protocol but receive syngeneic transfusions. Many authors, most prominently Jensen,[19] Tartter[20] and Blumberg[21] have proved the clinical importance of these observations. In their studies, data collected from patients recovering from elective surgery prove a definitive correlation between the likelihood of postoperative infection and/or sepsis and the transfusion of allogeneic blood products (see chapter 9).

Based on the foregoing considerations, the use of LDBP is advisable for a significant number of transfusion recipients.[22] In deciding which method(s) should be used to provide LDBP, the maximum allowable concentration of WBC in these products must first be determined. The mean concentration of WBC in units of freshly donated, conventionally anticoagulated whole blood ranges from 2 to 3 x 10^9 leukocytes per 500 mL WBC. Individual units of PC average 1-2 $\log_{10}$ fewer, i.e., the standard random donor pool of platelets contains 10^8 leukocytes. Single donor apheresis platelets collected by 'non-leukocyte depleting technology' also contain an excess of 10^8 leukocytes. It is this concentration of WBC that are responsible for the majority of leukocyte associated adverse transfusion reactions.

It has been conclusively demonstrated that more than 75% of NHFTR are successfully avoided by use of red cell products which contain -1 $\log_{10}$ fewer WBC.[23] This number targets a residual WBC concentration of ~10^8 leukocytes per red cell product. A definitive number to achieve the same goal for PC has not as yet been established. This concentration of leukocytes, 10^8/unit transfused, has been defined as the critical antigenic leukocyte load (CALL),[24] representing the quantity of WBC necessary to elicit symptoms in a host who is already sensitized. The CALL number contrasts with another numerical term, the critical immunogenic leukocyte load (CILL)[25] which is defined as the concentration of WBC required to cause a primary immune response in a previously non-sensitized patient. The CILL is believed to be no higher than 10^6 WBC.[26] Accordingly, a reduction of at least -3 $\log_{10}$ is required to produce blood products that will not initiate such responses.

Achieving a reduction in the incidence of transfusion associated CMV infection by use of LDBP is possible as demonstrated by work published by Bowden et al.[27] These authors found that it is necessary for this purpose to use blood products which are leukodepleted by approximately -3$\log_{10}$ of their native WBC. The effect of leukodepletion on transfusion induced immunomodulation in humans has not been proved, however, previously cited work published by Blajchman and colleagues[17] in animal models, again suggests a minimal -3$\log_{10}$ depletion of WBC in transfused products.

These data create a strong bias in favor of defining a LDBP as a component which is minimally depleted of its original WBC concentration by -3 $\log_{10}$ (99.9%), resulting in a residual quantity of leukocytes no greater than 1-5 x 10^6 cells. The assurance that any technique used to produce LDBP yields components at this level of depletion is a demanding task. Monitoring the results of historical leukocyte depleting procedures which were comparatively inefficient was easily performed with the assistance of automated cell counters and low volume hemocytometers. These procedures yield precise and accurate data for WBC reductions of 90% or less. However, technologies which remove -3 $\log_{10}$ or more of WBC from blood products defy monitoring by conventional cell counting techniques.[28] Low volume chamber counts are inaccurate at a level of 10 cells/μL, due to a lack of precision in this range. The automated blood cell counters lose linearity below 100 cells/μL. Of promise is the use of fluorescence-activated cell sorters. Preliminary studies suggest these instruments are capable of monitoring a WBC reduction as great as -6 $\log_{10}$.[29] Gaining in popularity is use of chambers with volumes of 50 μL, such as the Nageotte chamber, a procedure recommended by the Biomedical Excellence for Safer Transfusion (BEST) party of the International Society of Blood Transfusion. These chambers accurately monitor concentrations of leukocytes at levels which approximate 1 cell/μL (see chapter 3).

There are seven procedures that are or have been employed to remove WBC from either RCC, PC or both. These include sedimentation, centrifugation, cell washing, freeze-thaw deglycerolization, laboratory filtration, bedside filtration and the use of the "top and bottom" system of component preparation. Additionally, ultraviolet (UV) irradiation of platelet concentrates (PC) and the use of apheresis procedures which yield PC with low residual WBC contamination must be added to the list of techniques which hold potential for reducing some of the risks associated with the transfusion of homologous leukocytes (Table 2.1).

SEDIMENTATION

Red cells remain suspended in physiological diluents for an indefinite period a result of the negatively charged cells' inability to form rouleaux. Rouleaux formation is a prerequisite to sedimentation. The red cell charge at the level of sheer is defined as the zeta potential and must be overcome if rouleaux are to form and sedimentation is to occur.[30] Zeta potentials can be minimized by the addition of bipolar, macromolecules to the blood product. These compounds such as dextran, polyvinylpyrrolidone and hydroxyethyl starch, reduce the repulsive forces between the red cells, thereby facilitating the process of sedimentation.[31] Formed elements in whole blood sediment in respect to their individual densities. The result is their separation into visibly distinct layers of red cells, white cells/platelets and plasma. Obviously these layers are merely enriched for the various components and the procedure resists any attempt at process control. The features which accounted for the previous popularity of the sedimentation technique were the need for minimal supplies and no capital equipment. The procedure causes a small loss of red cells, approximately 5%, and a single volume sedimentation roughly results in an 80% reduction of WBC.[32] The results can be enhanced by use of a double sedimentation procedure which requires two to three hours and removes 95% (-1.5 $\log_{10}$) of the native leukocyte load.[33]

Table 2.1. Techniques which result in leukocyte attenuation of red cell products

Technique	WBC Removal %(Log_{10})	Red Cell Loss	Comments
Sedimentation			
- single	80% (~0.9 Log_{10})	5%	Obsolete
- double	95% (~1.5 Log_{10})	15%	
Centrifugation	70-80% (0.9 Log_{10})	15%	Widespread use worldwide
Washed Red Cells	70-95% (0.8-1.5 Log_{10})	15%	Useful if plasma removal required
Frozen-Thawed Washed Red Cells	95% (~1.5 Log_{10})	20%	Expensive, Time consuming
Laboratory Filtration	99-99.99% (2-4 Log_{10})	5-10%	
Bedside Filtration:			
Microaggregate	85-95% (0.9-1.5 Log_{10})	5-15%	
Leukoabsorbent	99-99.99% (2-4 Log_{10})		
UV Irradiation	N/A	N/A	Unproven
Top and Bottom Systems	~80%	15%	

Sedimentation is a time consuming procedure which is performed by "open processing." Its product falls short of the target value of 10^6 residual leukocytes. Its time demanding requirements and shortcomings have made this technique obsolete.

CENTRIFUGATION

World-wide, the most common technique used for the production of leukodepleted blood products is centrifugation. This yields a product referred to as "buffy coat" poor red cell concentrate. The centrifugal process is influenced and limited by most of the factors that govern the sedimentation process. Centrifugation relies on an increase in gravitational force instead of the use of macromolecules to enhance rouleaux formation. Like sedimentation, it visibly segregates the various blood components from one another. The popularity of blood component production makes the separation of blood by centrifugation a readily available and desirable adjunct. Removal of the buffy coat imposes little burden beyond the routine procedure. In some laboratories, the ability to sell the buffy coat to commercial firms for the production of interferons serves as a source of revenue. The technique is simple, performed within a closed-bag multiple pack system, and does not prematurely accelerate the expiration date of the processed unit. In spite of all of these desirable features, the technique produces a LDBP with a WBC residual too high to provide the majority of previously cited clinical advantages. At best, only 70-80% of the native leukocytes are removed from a unit of red cells by the centrifugation and buffy coat extraction process. Poorer results are obtained if the process is applied to platelet concentrates. Twenty percent of the red cells are lost during this procedure, which ultimately exposes the recipient to a greater number of donor products.[34] As with products produced by the sedimentation procedure, buffy coat reduced blood requires further processing to serve as a true LDBP.

RED BLOOD CELL WASHING

Automated red blood cell washers employ the same principles described for centrifugation, adding the dimension of a continuous introduction of physiological saline wash fluid. The technique is a "spin-off" from technology developed to remove cryopreservatives from red cell concentrates stored by freezing. The centrifugation process is carried out in uniquely shaped bowls

or containers designed to allow the various blood components to be removed at will in order of their specific densities. This is accomplished by a "spill over" effect through ports that are strategically positioned in the container. One outstanding feature of the cell washing procedures is its ability to remove the majority of plasma from a unit of whole blood or concentrate. The efficiency of this method approaches a plasma removal of 95%.[35] The removal of WBC is less dramatic. Depending on the protocol and equipment used, the range of leukocyte depletion varies from 70-95%, and red cell loss approximates 15%.[36] The technique is time consuming and despite the automated procedure requires the operator's total attention. Since the anticoagulant/nutritive solution is removed from the product and the system is exposed to the environment, the shelf-life of the product is reduced to 24 hours. Use of this procedure currently has few advocates and has been replaced by the logistical ease and effectiveness of filtration procedures.

FROZEN-THAWED WASHED RED BLOOD CELLS

Until the availability of filtration procedures which are discussed in following sections, the "industrial standard" for leukocyte depleted red cell products was accepted as frozen deglycerolized red cells. Leukocyte depleted platelet concentrate had no similar standard prior to the advent of filters, since the deglycerolization procedure is not applicable to PC. To preserve red blood cells by freezing it is first necessary to add a cryoprotective agent to the concentrate. This agent is generally glycerol. The cryoprotectant is avidly taken up by the red cells, displacing the majority of their intracellular water in the process. The cryoprotectant is not effectively incorporated by WBC and platelets and these cells maintain their normal state of hydration.[37] Formation of intracellular ice crystals during the freezing process causes the WBC and platelet membranes to rupture and form stromal debris. The centrifugation-saline wash procedure which is used to remove the glycerol from the thawed product, first aggregates the stroma and then removes it. The efficiency of this technique in removing WBC and platelets from red cell concentrate averages -1.5 $\log_{10}$ (95%).[38] Some concern has been raised regarding the unremoved stroma and its potential to be immunogenic.[39] For the most part, this is a mute point since the level to which the WBC themselves are reduced by the procedure does not fulfill the CILL criterion. The technique continues to be used for the preservation of red cells of rare phenotypes which can be stored in frozen state for as long as 10 years prior to use.

LABORATORY FILTRATION

The current widespread use of LDBP is directly related to the commercial production of efficient leukocyte depletion filters. These filters have evolved through multiple generations of improved function and currently are capable of producing a unit of red cells, pooled platelet concentrate or single donor apheresis platelets which contain fewer than 500,000 WBC. In fact, newly developed experimental filters are capable of producing LDBP with a total leukocyte content below 5,000 cells. Clearly the filtration method is the only procedure which produces products which consistently meet the defined criterion for leukodepleted blood. Filters are available in two configurations, those suitable for production of LDBP in the laboratory and those intended for use at the bedside during transfusion. The removal of WBC by filtration depends on the selective adsorption characteristics of the medium employed. It is also influenced by the medium's critical surface tension. Currently available filters are composed of cellulose acetate, cotton wool and polyester fiber. Cellulose acetate adsorbs polymorphonuclear leukocytes more tenaciously than lymphocytes.[40,41] Up to 25% of the red blood cell mass may be lost with the cellulose acetate filters. As with centrifugation, this loss can ultimately increase the recipient's exposure to the number of allogeneic donor products transfused. Cotton

wool filters and polyester fibers adsorb mononuclear cells and granulocytes with the same degree of efficiency.[42] Proprietary geometry and fiber modifications are essential to the function of the filters. The older cotton wool and cellulose acetate filters effectively reduce the WBC concentration of blood products by approximately -2 $\log_{10}$, whereas some of the polyester filters function at a level of -4 $\log_{10}$.[43] A newly available product incorporates a polyester red cell depletion filter as an integral component of the collection system (Leukotrap RC System, Cutter/Miles West Haven, CT), which eliminates the need to sterile-dock the device to the container.

BEDSIDE FILTRATION

The removal of leukocytes from blood products by the use of bedside filters began with the use of devices designed to remove microaggregates from stored blood. As previously stated, microaggregates are particles composed of platelets and WBC which form in a spontaneous and progressive fashion in stored red blood cells.[44,45] It follows therefore, that a technique that maximizes microaggregate formation and removal, effectively produces a LDBP. Centrifugation of refrigerated blood increases the mass and frequency of these aggregates. However, these particles are friable and easily broken apart. An additional period of refrigeration increases the cohesive strength of the particles and prevents their disruption by filtration.[46] This phenomenon is possibly the result of the incorporation of fibronectin into the aggregates. The entire technique of centrifugation, refrigeration and microaggregate filtration is referred to as "spin, cool and filter" (SCF). The WBC removal efficacy of the technique does not exceed -1.5 $\log_{10}$ and preferentially removes granulocytes. However, SCF proved that bedside leukocyte depletion of blood was feasible and desirable. Such proof ultimately led to the development of specific leukocyte depleting filters. Currently, the leukocyte depleting filters available for bedside use in the U.S. are composed of polyester fibers. Cellulose acetate filters are available in other countries. The most efficient polyester filters remove -4 $\log_{10}$ WBC from blood products, leaving a residual cell concentration of 10^5 leukocytes in the RCC or PC component.[47] The average final WBC concentration of units of blood filtered at the bedside approximates 5 WBC/μL. Unlike the SCF method, bedside filters require no special processing of the unit and are not influenced by the age of the blood.

The mechanism(s) which allows fibers made of cellulose acetate, cotton wool and polyester to selectively remove WBC from blood components is not known. All of the available devices are depth filters whose function traditionally involves adsorption phenomena. Steneker and her colleagues[48] (see chapter 4) using direct visualization techniques conclude that red cell leukodepletion filters remove lymphocytes and monocytes by direct interception, i.e., capturing them within the pores of the fiber matrix. On the other hand the authors conclude that granulocyte depletion is dependent on platelets first being adsorbed to the fiber which allows for a platelet-granulocyte interaction. The mechanism cited by these authors for the binding of granulocytes to platelets involves calcium dependent phenomena which presumbly are minimized in a unit of chelated RCC or PC. Callaberts et al[49] using leukocyte depleting platelet filters concluded that platelet retention did not correlate with WBC retention. A major problem with the quantitative data in both studies involves the WBC counting procedures employed. Both groups used methods known to be imprecise and inaccurate at the cell concentrations which were detected.[50]

UV IRRADIATION

By definition, UV irradiation of blood products is not a leukodepletion technique. However, it may hold promise for reducing the alloimmunization and immunological refractoriness associated with the transfusion of platelet products. Lindahl-Kiessling and Safwenberg originally reported that UV irradiated WBC did not

proliferate nor stimulate allogeneic responder cells in mixed lymphocyte cultures.[51] Subsequently, the clinical correlate of this effect was demonstrated by exposing skin to UV irradiation. The ability of Langerhan's cells to function as antigen-presenting-cells is blocked[52] in irradiated skin and graft survival is prolonged.[53] Studies in canine models have demonstrated that UV irradiation can be used successfully to block transfusion-induced bone morrow graft rejection[54] and refractoriness to random donor platelet transfusions.[55] Few trials have been published using UV treated blood components in people. However, existing feasibility studies suggest that irradiation protocols and plastic storage containers can be formulated to provide adequate function of the UV modified product.[56] Factors such as energy source, wavelength and storage time appear to be key determinants in the viability and function of the treated product.[57] Enthusiasm for the routine use of UV irradiated blood products must be tempered by their currently unproved efficacy, the requirement that they be irradiated in containers with specific light transmission characteristics, and the difficulty involved in effectively irradiating red cell products. Questions have also been raised regarding the ability of UV irradiation to activate latent viruses[58] and concern remains about its mutagenic potential.[59]

The mechanism(s) involved in the process which allows UV light to inactivate antigen presentation and lymphocyte response has not been elucidated. Among the possible candidates are loss of Ia antigen due to shedding,[60] interference with the internalization and re-expression of HLA antigens by antigen presenting cells,[61] alteration of the dendritic cells ability to mobilize calcium and cytokines[54] and a reduction in the surface expression of the intracellular adhesion molecule ICAM-1.[57]

LEUKOCYTE DEPLETED APHERESIS PLATELETS

Alternative technologies such as apheresis procedures which harvest platelets with a reduced concentration of WBC are available. The WBC content of single donor platelets (SDP) harvested by apheresis is determined by a variety of factors such as the equipment and protocol, the type and amount of anticoagulant used and whether a "single or double arm" harvesting technique is employed.[62] As a consequence, the concentration of white blood cells in SDP has been reported to range from 0-28 x 10^6 (Baxter CS-3000 with and without the TNX6 chamber),[63] to 2.6-16 x 10^6 (Cobe Spectra)[64,65] and even as high as 210-400 x 10^6 (Haemonetics V50).[66,67] By extrapolating from the data in the cited studies, it is apparent that the V50 and CS-3000 without the TNX6 chamber fail to provide leukodepleted SDP within the recommended concentration of WBC. The Spectra and CS-3000 Plus fail to meet this criterion 15% of the time. Clinical studies as to their efficacy are lacking and extrapolated from other methodologies. It remains advisable to filter these products at the present time.

TOP AND BOTTOM SYSTEM

In 1988, Hogman and colleagues described the use of a modified blood collection bag which has outlet ports on both ends, the top and bottom.[68] Although this container has not gained popularity in North America, it is in use in Europe. The two ports allow for the simultaneous expression of plasma from above and red cells from below, after the whole blood is centrifuged. This leaves the buffy coat behind in the original container from which platelet concentrate can be made by use of a clamp device. A modification of the original procedure was evaluated by Pietersz et al[69] who found that the WBC concentration in RCC produced by this method was roughly one-fifth that of conventionally prepared RCC but still averaged 1.4 x 10^8, two logs greater than the leukocyte depletion target suggested by the Council of Europe. On the other hand, the concentration of WBC in platelet concentrates was three times greater in "top and bottom" prepared components than in the conventionally prepared product.

CONCLUSIONS

1. It is clear that most of the procedures previously used to provide leukocyte-depleted blood products had little clinical benefit other than reduction of the NHFTR. Intensive therapeutic protocols and transplantation procedures require LDBP which contain the least WBC residual possible.
2. Filtration is currently the only method that consistently achieves the target value of 10^6 residual WBC in leukodepleted blood components.
3. Leukodepleted PC obtained by apheresis procedures can only be used when a commitment to quality control all products by a qualified counting procedure has been made.
4. Qualified counting procedures include the use of Nageotte chambers and flow cytometry techniques.
5. UV irradiation of blood products has yet to be proved a useful clinical adjunct.
6. The clinical benefits derived from the use of adequately leukodepleted blood products include reductions in the rate of NHFTR, CMV seroconversion and alloimmunization.
7. The utility of leukodepleted components in influencing transfusion induced immunomodulation and GVHD has yet to be proved.

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