

GUIDELINES

Guidelines on the clinical use of leucocyte-depleted blood components

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Definition: Leucocyte-depleted blood components must contain $<5 \times 10^6$ leucocytes per unit (red cells) or adult therapeutic dose (platelets).

Practical aspects: To achieve residual leucocyte counts of $<5 \times 10^6$, leucocyte-depletion should be carried out under controlled conditions, ideally within 48 h from the collection of the donor unit. The preparation of leucocyte-depleted blood components should be subject to a quality monitoring programme designed to assure 100% compliance.

Indications for leucocyte-depleted blood components

RECOMMENDED

Febrile nonhaemolytic transfusion reactions (FNHTRs)

1 To prevent recurrent FNHTRs after red-cell transfusions, buffy coat-depleted red-cell concentrates should be used, if they are available, or alternatively red-cell concentrates filtered at the bedside.

2 If FNHTRs continue despite these measures, leucocyte-depleted red-cell concentrates should be used.

3 To prevent FNHTRs in patients likely to be dependent on long-term red-cell support, the use of buffy-coat-depleted or bedside filtered red-cell concentrates should be considered from the outset of transfusion support.

4 The routine use of pooled platelets derived from buffy coats is associated with a low incidence of FNHTRs. The use of platelet concentrates leucocyte-depleted prior to storage is recommended for patients with reactions despite the use of such components. Bedside filtration of platelet concentrates is not recommended for the prevention of FNHTRs associated with platelet transfusions.

Reducing graft rejection after haemopoietic cell

transplantation: Patients with severe aplastic anaemia who are potential haemopoietic cell transplant recipients should receive leucocyte-depleted blood components from the beginning of transfusion support. The same might apply to patients with haemoglobinopathies, but more evidence is required before a definite recommendation can be made.

Prevention of transmission of viral infections by blood transfusion: Leucocyte-depletion of blood components is an effective alternative to the use of CMV-seronegative blood components for the prevention of transfusion-transmitted CMV infection to at-risk patients.

Fetal/neonatal transfusions: Leucocyte-depleted blood components should be used for intrauterine transfusions and for all transfusions to infants below 1 year of age.

POSSIBLE

Platelet refractoriness: There is currently no convincing evidence that routine leucocyte-depletion of blood components produces clinical benefits for patients receiving multiple platelet transfusions, although HLA alloimmunization and platelet refractoriness are reduced.

Kidney transplants: Pretransplant blood transfusion may confer some benefit to renal transplant recipients, although some patients will become alloimmunized leading to difficulties in the selection of donor kidneys. Consideration should be given to the leucocyte-depletion of transfusions to renal transplant patients to prevent HLA alloimmunization unless they are part of a deliberate pretransplant immunosuppression protocol.

Immunomodulation: There is insufficient evidence to recommend the routine use of leucocyte-depleted blood components for surgical patients for the prevention of either post-operative infection or tumour recurrence.

Progression of HIV infection: There is insufficient evidence to recommend the use of leucocyte-depleted blood components for reducing the progression of HIV infection.

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NONINDICATIONS. A significant number of recipients of blood components receive a limited number of transfusions over a short period of time, e.g. most general medical and surgical patients. Leucocyte-depletion of blood components is not indicated for these recipients unless there is an additional acceptable indication discussed in one of the other sections in this guideline. Prevention of TA-GvHD is not an indication for leucocyte-depleted

blood components. Gamma-irradiation of blood components is the standard method for avoiding TA-GvHD. There is no need to leucocyte-deplete noncellular blood components such as fresh frozen plasma, cryoprecipitate and blood products prepared from pooled plasma.

Key words: blood transfusion, guidelines, leucocyte-depleted blood.

The presence of leucocytes in blood components is responsible for many of the complications associated with blood transfusion (Bordin *et al.*, 1994). Patients receiving standard red-cell and platelet concentrates receive large numbers of allogeneic leucocytes, which are transfused without any intention of producing clinical benefit. There has been considerable interest in the removal of leucocytes from blood components, and this guideline is primarily intended to provide advice regarding the clinical indications for leucocyte-depleted red-cell and platelet concentrates.

It is important to define what is meant by 'leucocyte-depletion'. Some confusion is caused by the use of rather meaningless terms such as 'leuco-reduced', 'leuco-poor' and even 'leuco-free'. 'Leucocyte-depleted' is the accepted term for red-cell and platelet concentrates, which have been produced by technologies designed to yield low levels of leucocytes, and it has been accurately defined by national and international working groups. A leucocyte-depleted red-cell concentrate is one containing $<5 \times 10^6$ leucocytes per unit, and an adult dose of leucocyte-depleted platelets is one containing $<5 \times 10^6$ leucocytes (UK BTS/NIBSC, 1997).

The situation is further complicated by the increasing introduction in the UK of component processing involving removal of the buffy coat to yield red-cell concentrates and pooled platelet concentrates. These components both contain numbers of leucocytes intermediate between standard and leucocyte-depleted components, and are useful in clinical situations where reduced leucocyte levels but not 'true' leucocyte-depletion is required. The leucocyte levels in the different components are shown in Table 1.

Definition: leucocyte-depleted blood components must contain $<5 \times 10^6$ leucocytes per unit (red cells) or adult therapeutic dose (platelets)

PRACTICAL ASPECTS OF LEUCOCYTE-DEPLETION OF BLOOD COMPONENTS

Methods

Various techniques have been used for removing leucocytes from blood components including centrifugation

and freeze/thawing, but filtration has been and currently remains the most commonly used technique for leucocyte-depletion of blood components. Apheresis technology, which provides leucocyte-depleted platelet concentrates without any need for filtration or further processing, is now available.

Blood filters have developed in three distinct phases or generations. First-generation filters are 170–240 μm screens, which are part of all red-cell transfusion administration sets for the removal of large clots and particulate debris. Second-generation 40- μm filters were designed to remove microaggregates of fibrin, platelets and leucocytes from red-cell concentrates. These filters reduce the number of leucocytes by one order of magnitude (or log) to $5\text{--}10 \times 10^8$ per unit. Third-generation filters were designed specifically for the removal of 'free' leucocytes. They retain both microaggregates and free cells; see the review by Dzik (1993) for the mechanisms of leucocyte removal by these filters and their design. The number of leucocytes in red-cell and platelet concentrates can be reduced by three orders of magnitude (or 3 logs) to less than 5×10^6 per unit using third-generation filters, and new filters producing even greater leucocyte-depletion are already in routine use.

Filtration can be carried out: (a) at the bedside during the transfusion; (b) in the components processing laboratory. The main issues determining which is preferable are the timing of leucocyte depletion in relation to the biological changes of storage, and the ability to guarantee quality assurance.

Timing of leucocyte-depletion

Leucocyte-depletion within a relatively short time after collection has the advantage that leucocytes are eliminated before they release cytokines, fragments of cell membrane and possibly intracellular viruses, which may not be removed by filtration carried out just prior to transfusion. A relationship has been shown between the age of platelet concentrates and the level of cytokines, such as interleukins-1 and -6 and tumour necrosis factor, and the quantity of leucocyte fragments. Cytokines have been implicated in the pathogenesis of FNHTRs

Table 1. Specifications of red cell and platelet components*

	Red cells		
	Red cells/ Red cells in OAS†	Red cells in OAS, buffy coat removed	Red cells/ Red cells in OAS, leucocyte-depleted
Vol. (mL)	280 ± 60/ 350 ± 70	280 ± 60	locally specified volume ranges§
Hct	0.55–0.75/ 0.50–0.70	0.50–0.70	0.55–0.75 0.50–0.70
WBC per unit	>2 × 10 ⁹	<1.2 × 10 ⁹ †	<5 × 10 ⁶

	Platelets			
	Derived from platelet-rich plasma (PRP)	Platelets, pooled, buffy coat derived (BCD)	Apheresis	Leucocyte- depleted¶
Donors/adult dose	5	4	1	4 or 1
Vol. (mL)	locally defined	locally defined	locally defined	locally defined
Platelets (×10 ¹¹)	>2.75	>2.4	>2.4	>2.4
WBC/dose	<10 ⁹	<10 ⁸ †	<0.8 × 10 ⁹ †	<5 × 10 ⁶

* Derived from UKBTS/NIBSC *Guidelines for the Blood Transfusion Service*, 3rd edn (1997). † The leucocyte levels for buffy-coat-removed red cells, and both BCD and apheresis platelets are often lower than shown. Refer to your supplying Blood Centre for details. ‡ Optimal Additive Solution (SAG-M or equivalent). § Leucocyte-depletion by filtration generally results in the loss of 20–30 mL red cells. ¶ Can be produced from PRP, BCD or apheresis platelets.

particularly after platelet transfusions (see section on FNHTRS below), and there is experimental evidence that leucocyte fragments may play a role in primary HLA alloimmunization (Blajchman *et al.*, 1992).

Standardized procedures are necessary for optimal performance of the filters, but it is difficult to ensure this at the bedside and laboratory-based methods are now favoured (Perkins, 1993; Popovsky, 1996). For maximum confidence in the consistency of the process, filtration carried out as part of component processing offers the possibility of quality monitoring, and of control of the age of the product at the time of filtration.

Filtration is usually performed within 48 h from the collection of the donor unit, but the optimal timing should be validated for each filter. It is sometimes necessary to filter blood, which has been stored for a longer period, just prior to its issue for transfusion, e.g. when selected phenotype units are required.

It has been suggested that leucocyte-depletion should be carried out 6–8 h after collection of blood to allow phagocytosis of any bacteria present in the red-cell or platelet concentrate. However, there is no evidence that

concentrates filtered earlier than this or apheresis units prepared as leucocyte-depleted have an increased risk of bacterial contamination. Appropriate microbiological monitoring should be carried out (UKBTS/NIBSC, 1997).

Quality assurance

The preparation of leucocyte-depleted blood components should be subject to quality assurance, including adequate training of staff and maintenance of standard operating procedures, which control the age of the component, and the temperature and duration of filtration.

Quality control to ensure adequate leucocyte-depletion can be carried out by measuring leucocyte counts on every concentrate prior to release for transfusion, but this is labour-intensive. It is equally acceptable to use statistical process control to ensure that the leucocyte-depletion procedure remains within predetermined limits set after initial validation of each filter or other technology (Dumont *et al.*, 1996). An effective quality assurance programme has not yet been devised to demonstrate the

reliable performance of bedside filtration in achieving residual leucocyte levels of $<5 \times 10^6$.

Methods which may be used for counting residual leucocytes in leucocyte-depleted blood components are flow cytometry and large-volume microscopic chambers such as the Nageotte chamber (Rebulla & Dzik, 1994). Automated blood cell counters do not accurately estimate the low levels of leucocytes present in leucocyte-depleted blood components, but can provide the necessary quality control for buffy coat-depleted red-cell concentrates.

Labelling and storage

Red-cell and platelet concentrates may be labelled as 'leucocyte-depleted' when the leucocyte count has been determined to be $<5 \times 10^6$ by one of the methods discussed above. At present, a unit labelled as 'leucocyte-depleted' does not indicate the method used for leucocyte depletion or when it was carried out in relation to the time of donation.

The shelf-life and storage characteristics of leucocyte-depleted blood components do not differ from standard preparations of the same component provided that leucocyte depletion was carried out as a 'closed' procedure, either with an integral filter or with a filter attached using a sterile connecting device.

Recommendations: to achieve residual leucocyte counts of $<5 \times 10^6$, leucocyte depletion should be carried out under controlled conditions, ideally within 48 h from the collection of the donor unit. A quality monitoring programme should be used to confirm, either by counting of individual concentrates or by statistical methods, that each concentrate contains $<5 \times 10^6$ leucocytes.

INDICATIONS FOR LEUCOCYTE-DEPLETED BLOOD COMPONENTS

Febrile nonhaemolytic transfusion reactions (FNHTRs)

FNHTRs have been reported to occur with an incidence of 6.8% after red-cell and 37.5% after platelet transfusions (Heddle *et al.*, 1993). However, the pathogenesis of FNHTRs following red-cell and platelet transfusions are different, and different strategies for prevention are appropriate.

(1) *Associated with red-cell transfusions.* HLA alloimmunization is probably the major cause of severe FNHTR to red cells. However, FNHTRs after red-cell transfusions are not always due to HLA antibodies, and reactions do not always recur. It is only considered necessary to use red-cell concentrates with reduced levels of leucocytes for patients having recurrent

(i.e. two or more consecutive) FNHTRs (Consensus Conference, 1993).

Leucocyte-depletion to $<5 \times 10^6$ leucocytes per unit is not usually necessary to prevent FNHTRs; a reduction in the number of leucocytes to 5×10^8 leucocytes per unit is sufficient in most cases. This can be achieved most cost-effectively using buffy-coat-depleted red-cell concentrates, if they are available, or by filtration at the bedside. Leucocyte-depleted blood components may be reserved for patients in whom FNHTRs persist despite the use of buffy-coat-depleted red-cell concentrates or bedside filtration. Microaggregate ($40 \mu\text{m}$) filtration, sometimes combined with cooling and centrifugation of the blood prior to filtration, can also prevent FNHTRs, but other methods for the prevention of FNHTRs have superseded this technique and it is not recommended.

Leucocyte-depleted red-cell concentrates are effective in the prevention of FNHTRs in patients dependent on long-term transfusion support, e.g. patients with beta-thalassaemia major (Sirchia & Rebulla, 1994). It could be argued that the development of FNHTRs could be awaited before switching to leucocyte-depleted red-cell concentrates, but it is generally agreed that patients requiring long-term red-cell support should receive red-cell concentrates with leucocyte levels $<5 \times 10^8$ to prevent FNHTRs (Consensus Conference, 1993). This level of leucocyte reduction can generally be achieved with buffy-coat-depleted red-cell concentrates. The benefits are best documented for patients with beta-thalassaemia major, but other patient groups requiring long-term red-cell support, such as those with chronic aplastic anaemia, myelodysplasia, sickle cell disease and the anaemia of chronic renal failure (unresponsive to treatment with recombinant erythropoietin), may also benefit (Consensus Conference, 1993; see sections on severe aplastic anaemia and renal transplantation).

(2) *Associated with platelet transfusions.* There is increasing evidence that the major cause of FNHTRs after platelet transfusions is the presence of pyrogenic cytokines released from leucocytes during the 5 days of platelet storage (Muylle *et al.*, 1993). A role for such cytokines or other mediators is supported by the observation that most FNHTRs after platelet transfusions are caused by the transfused plasma (Heddle *et al.*, 1994).

FNHTRs after platelet transfusions are not reliably prevented by bedside filtration of platelet concentrates because of cytokine release during storage (Goodnough *et al.*, 1993). Increases in cytokine levels during storage have not been found in platelet concentrates prepared from pooled buffy coats, in concentrates prepared from platelet-rich plasma and leucocyte-depleted before storage, and in concentrates prepared using modern apheresis technology to contain a low level of

leucocytes (Muylle & Peetermans, 1994; Wadhwa *et al.*, 1996).

The routine use of pooled platelets derived from buffy coats is associated with a low rate (3.8%) of FNHTRs (Anderson *et al.*, 1997). For patients having reactions, despite the use of this product, the transfusion of platelet concentrates leucocyte-depleted prior to storage is recommended.

Recommendations

1 For the prevention of recurrent FNHTRs after red-cell transfusions, the use of buffy-coat-depleted red-cell concentrates is recommended, if they are available, or bedside filtered red-cell concentrates if they are not.

2 For patients who continue to have FNHTRs after red-cell transfusions despite the use of buffy-coat-depleted or bedside filtered red-cell concentrates, leucocyte-depletion of red-cell concentrates to $<5 \times 10^6$ leucocytes per unit is recommended.

3 For patients who are likely to be dependent on long-term red-cell support, the use of buffy-coat-depleted or bedside filtered red-cell concentrates should be considered from the outset of transfusion support for the prevention of FNHTRs.

4 The routine use of pooled platelets derived from buffy coats is associated with a low rate of FNHTRs. The use of platelet concentrates leucocyte-depleted prior to storage is recommended for patients with reactions despite the use of such components. Bedside filtration of platelet concentrates is not recommended for the prevention of FNHTRs associated with platelet transfusions.

Platelet refractoriness

(1) *Definition.* Platelet refractoriness is the repeated failure to obtain satisfactory responses to platelet transfusions. It is a common problem in patients receiving multiple transfusions (Slichter, 1990). Various methods are used to assess responses to prophylactic platelet transfusions (BCSH, 1992). In practice, an increase in the patient's platelet count of less than $20 \times 10^9 \text{ L}^{-1}$ at 20–24 h after the transfusion is often used as a simple measure of a poor response (BCSH, 1992).

(2) *Causes.* Many causes of platelet refractoriness have been described, and they can be subdivided into immune mechanisms, most importantly HLA alloimmunization, and nonimmune platelet consumption associated with clinical factors such as fever and/or septicaemia, bleeding disseminated intravascular coagulation and splenomegaly (Slichter, 1990).

Recent evidence suggests that nonimmune platelet consumption may be the most frequent mechanism of platelet refractoriness (Doughty *et al.*, 1994). However,

immune-mediated platelet destruction remains an important and potentially more readily preventable cause, but it follows from these observations that the prevention of HLA alloimmunization will not eliminate platelet refractoriness.

The precise mechanism of HLA alloimmunization remains uncertain. It was postulated that primary HLA alloimmunization was only initiated by intact cells expressing both HLA class I and class II antigens. Such cells include lymphocytes and antigen-presenting cells. Platelets only express HLA class I antigens, providing the rationale for the use of leucocyte-depleted blood components for the prevention of HLA alloimmunization and platelet refractoriness.

(3) *Prevention.* (a) *Leucocyte-depletion of blood components.* The development of HLA alloimmunization is dependent on the dose of leucocytes transfused with the critical level being about 5×10^6 per transfusion (Fisher *et al.*, 1985). The risk of HLA alloimmunization has also been shown to be related to the patient's previous history of blood transfusions and pregnancies. A report of patients with bone marrow failure, mostly with haematological malignancies, supported with red-cell and platelet concentrates leucocyte-depleted before storage found a very low level of HLA alloimmunization (3%) in patients with a negative history of previous transfusions or pregnancies in comparison to a level of 31% in patients who had been previously transfused or pregnant (Novotny *et al.*, 1995).

There is controversy concerning the effectiveness of leucocyte depletion of blood components for the prevention of HLA alloimmunization in patients who may have been sensitized by previous transfusions or pregnancies. In one study, the incidence of HLA immunization in patients with a history of previous pregnancies or transfusions was not reduced by leucocyte depletion of blood components (Sintnicolaas *et al.*, 1995). It is possible that in presensitized patients, the threshold for a secondary immune response may be considerably lower than 5×10^6 leucocytes and only achieved by a much greater degree of leucocyte depletion, but even this may not be sufficient as it is possible that recipient memory B cells may be activated by the HLA class I antigens present on platelets (Claas *et al.*, 1981). However, in contrast to the study of Sintnicolaas *et al.* (1995), the Trial to Reduce Alloimmunization to Platelets (TRAP) (Study Group, 1997) found that leucocyte-depletion of blood components resulted in a reduction in HLA alloimmunization in previously pregnant women from 62% to 32%.

Trials comparing leucocyte-depleted against standard blood components for the prevention of HLA alloimmunization and platelet refractoriness have usually enrolled small numbers of patients. Three of the five prospective

randomized controlled studies failed to show a statistically significant reduction in alloimmunization or platelet refractoriness (reviewed by Hedde, 1994). Moreover, these measures are often taken as surrogate markers for presumed clinical benefits, which remain unproven. Further prospective controlled trials are required to compare costs and clinical outcome in patients who receive leucocyte-depleted vs. standard products. Positive outcomes would include reduced morbidity and mortality due to clinical bleeding, reduced use of red-cell and platelet concentrates and fewer patients requiring HLA-matched or crossmatch-compatible platelet transfusions. The main negative factor is the cost of providing leucocyte-depleted blood components.

A retrospective study of patients with acute leukaemia suggested that leucocyte-depletion of blood components had a beneficial effect on haemopoietic recovery after chemotherapy, use of blood components, occurrence of serious infections and relapse-free survival (Oksanen & Elonen, 1993), but these effects have not been found by others (Copplestone *et al.*, 1995). A cost-effectiveness analysis suggested that the use of leucocyte-depleted blood components would not increase the cost of transfusion support in patients with acute leukaemia (Balducci *et al.*, 1993), but the assumptions on which this conclusion was based were criticized (Perkins, 1993).

These studies emphasize the need for large randomized controlled studies of the benefits of prevention of platelet refractoriness by leucocyte-depletion of blood components and its cost-effectiveness. In the United States, the large multicentre TRAP study (1997) compared the incidence of platelet refractoriness due to HLA alloimmunization in a control group receiving pooled PRP-derived platelet concentrates and three other groups of patients with acute myeloblastic leukaemia, given (1) pooled PRP-derived platelet concentrates irradiated with ultraviolet-B light, (2) leucocyte-depleted pooled PRP-derived platelet concentrates and (3) leucocyte-depleted apheresis platelet concentrates during remission induction therapy. The study showed a significant reduction in HLA alloimmunization and platelet refractoriness in the three treatment groups compared to the control group. However, the incidence of major bleeding was <1% in all groups, and the study failed to demonstrate any clear clinical benefits in the treatment groups.

(b) Irradiation of platelet concentrates with ultraviolet-B light. Available evidence suggests that inactivation of specialized potent antigen-presenting cells such as dendritic cells by irradiation with ultraviolet-B light may prevent recipient alloimmunization (Pamphilon & Blundell, 1992). In two recent clinical transfusion studies using platelet concentrates irradiated with ultraviolet-B light, alloimmunization was reduced, but the reduction

was not statistically significant (Andreu *et al.*, 1993; Blundell *et al.*, 1996). The TRAP study (1997) demonstrated a significant reduction in HLA alloimmunization and platelet refractoriness compared to the control group but there was no clear clinical benefit.

Recommendation: there is currently no convincing evidence that routine leucocyte-depletion of blood components produces clinical benefits for patients receiving multiple platelet transfusions, although HLA alloimmunization and platelet refractoriness may be reduced

Prevention of transmission of viral infections by blood transfusion

(1) Cytomegalovirus (CMV). Transfusion-transmitted CMV infection may cause significant morbidity and mortality in immunocompromised CMV-seronegative patients. The use of blood components from CMV-seronegative donors has been the standard method for the prevention of transmission of CMV by blood transfusion (see reviews by Sayers *et al.*, 1992; Hillyer *et al.*, 1994; Goldman & Delage, 1995). Patients for whom the risk of transfusion-transmitted CMV infection is well established include CMV-seronegative pregnant women, premature infants (<1.2 kg) born to CMV-seronegative women, CMV-seronegative recipients of allogeneic bone marrow transplants from CMV-seronegative donors and CMV-seronegative patients with the acquired immunodeficiency syndrome (Sayers *et al.*, 1992).

The use of CMV-seronegative blood components has been shown to reduce the incidence of CMV infection in at-risk groups to a level of about 1–3%, but transfusion-transmitted CMV infection is not completely prevented (Hillyer *et al.*, 1994; Goldman & Delage, 1995). This incomplete prevention of transmission of CMV may be due to the occasional failure to detect low-level antibodies, the loss of antibodies in previously infected donors and the transfusion of components prepared from recently infected donors.

CMV is transmitted by leucocytes, and there has been interest in the potential for leucocyte-depletion of blood components to prevent CMV transmission. A number of studies found that leucocyte-depletion of blood components was successful in preventing transfusion-transmitted CMV infection in neonates, acute leukaemia and bone marrow transplant patients (Hillyer *et al.*, 1994; Goldman & Delage, 1995). Furthermore, a recent prospective randomized study found that leucocyte-depletion using bedside filtration was as effective as the use of CMV-seronegative blood components in bone marrow transplant patients (Bowden *et al.*, 1995). However, in view of concerns about the quality control of leucocyte-depletion carried out by bedside filtration, blood components

leucocyte-depleted under controlled, validated conditions are to be recommended in preference to bedside filtration as a substitute for CMV-seronegative blood components.

Recommendations: leucocyte-depletion of blood components is an effective alternative to the use of CMV-seronegative blood components for the prevention of transfusion-transmitted CMV infection to at-risk patients. Whether leucocyte-depleted or CMV-seronegative blood components are used in individual patients depends on factors such as the cost and availability of each type of blood component, and whether leucocyte-depleted blood components will be used anyway to prevent another complication of blood transfusion

(2) *Human T-cell leukaemia/lymphoma virus type I and type II (HTLV-I and -II)*. HTLV-I and -II target T lymphocytes, and are solely transmitted by cellular blood components (reviewed by Sandler *et al.*, 1991). The minimum infective dose of lymphocytes is unknown, but there are epidemiological and experimental data to suggest that it might be very low. There is no clinical or laboratory evidence that leucocyte-depletion of blood components to currently achievable levels will significantly protect against HTLV infection.

(3) *Other viral infections*. Leucocyte-depletion of blood components is not an option for preventing transmission of viruses present in plasma, including HIV 1 and 2, hepatitis B and C and parvovirus B19.

Immunomodulation

Ever since observations were made of the favourable effect of transfusion on survival of subsequent renal allografts, the basis of transfusion-induced immunomodulation has been the subject of debate. Many investigators have attempted to examine the influence of transfusion on putative clinical effects of immunomodulation, such as post-operative infection and tumour recurrence, but the findings have been conflicting. It has often been assumed that allogeneic leucocytes are required for this effect, but there are very few studies in which leucocyte-depleted blood has been formally compared with standard components.

(1) *Post-operative infection*. In a study of colorectal cancer patients, the post-operative infection rate was increased in patients receiving whole blood transfusions compared to nontransfused patients, but patients receiving leucocyte-depleted red-cell concentrates had the same incidence of infection as nontransfused patients (Jensen *et al.*, 1992). However, there were conflicting results from two randomized studies comparing post-operative infection rates in patients receiving leucocyte-depleted or

buffy-coat-depleted red-cell concentrates; one study found no difference (Houbiers *et al.*, 1994) and one found a significantly lower incidence in the patients receiving leucocyte-depleted blood (Jensen *et al.*, 1996).

A recent analysis of trials in this area, albeit before publication of the study by Jensen *et al.* (1996), concluded that any transfusion effect on infection was small, and that leucocyte-depletion did not confer any convincing benefit over other components (Vamvakas, 1996). Further analysis, including the study of Jensen *et al.* (1996), agreed that no definite conclusion could be made at the present time (Blajchman, 1997).

(2) *Cancer recurrence*. Retrospective observational studies of cancer patients are conflicting as to whether tumour-free survival is influenced by transfusion, with almost equal numbers for and against the hypothesis (Vamvakas & Moore, 1993). There was no difference in tumour-free survival when leucocyte-depleted and buffy-coat-depleted red-cell concentrates were compared in patients with colonic cancer (Houbiers *et al.*, 1994).

In acute myeloblastic leukaemia, an improved relapse-free survival was found in one study of patients receiving leucocyte-depleted blood components (Oksanen & Elonen, 1993), but other studies have not demonstrated such a beneficial effect (Coppstone *et al.*, 1995).

Recommendation: there is insufficient evidence to recommend the routine use of leucocyte-depleted blood components for surgical patients for the prevention of either post-operative infection or tumour recurrence

Reactivation of latent viral infections

(1) *CMV*. Herpes viruses such as CMV cause latent infection and may become reactivated after an immunological stimulus such as transfusion or co-culture with allogeneic cells (Olding *et al.*, 1975). This may be relevant in pregnancy where blood transfusion might reactivate maternal CMV infection which could be transmitted to the fetus with potentially serious clinical sequelae (Sayers *et al.*, 1992).

In addition to the use of CMV-seronegative or leucocyte-depleted blood components to prevent transmission of CMV to CMV-seronegative pregnant women (see section on prevention of CMV transmission), it could be argued that CMV-seropositive pregnant women should receive leucocyte-depleted blood components to prevent reactivation of latent CMV infection although there are no published data suggesting that reactivation of CMV infection due to allogeneic transfusion is a major problem. One possible way of combining these two recommendations would be to use leucocyte-depleted blood components for all transfusions to women during

pregnancy, and this would standardize transfusion practice for all women during pregnancy. An alternative standard approach, which is less expensive, is the use of CMV-seronegative blood components for all transfusions to pregnant women, both CMV-seronegative and CMV-seropositive.

Recommendation: leucocyte-depleted blood components may be used as an alternative to CMV-seronegative blood components to prevent transfusion-transmitted CMV infection to CMV-seronegative women during pregnancy. To standardize transfusion practice for all pregnant women, consideration could be given to the use of leucocyte-depleted blood components or CMV-seronegative blood components for all transfusions in pregnancy

(2) *HIV*. Increased HIV secretion may be induced in HIV-infected cells *in vitro* by allogeneic leucocytes but not red cells, platelets and plasma (Busch *et al.*, 1992). Two retrospective studies provided evidence that transfused patients with HIV infection have a worse outcome than nontransfused patients (Vamvakas & Kaplan, 1993; Sloand *et al.*, 1994). While some centres already use leucocyte-depleted blood components to avoid any possible additive immunosuppressive effect of transfusion in patients with HIV infection, further evidence from prospective studies is needed before a definite recommendation can be made. A multicentre randomized trial of standard and leucocyte-depleted blood components in HIV-infected patients is in progress in the United States – The Viral Activation Transfusion Study (VATS) (Busch *et al.*, 1996).

Recommendation: in patients with HIV infection, there is insufficient evidence to recommend the use of leucocyte-depleted blood components for the prevention of the reactivation of CMV infection or the progression of HIV infection.

Avoidance of sensitization to transplantation antigens in potential transplant recipients

Sensitization to transplantation antigens by preceding blood transfusions has been shown to have an adverse effect in patients with aplastic anaemia undergoing bone marrow transplantation and in renal transplant patients. Sensitization to transplantation antigens can potentially be prevented by leucocyte-depletion of pretransplant transfusions, and this issue will be discussed in the following section on the use of leucocyte-depleted blood components in specific patient groups.

Use of leucocyte-depleted blood components in some specific patient groups not already considered

(1) *Severe aplastic anaemia*. Preceding blood transfusions have been found to increase the risk of graft rejection in patients with aplastic anaemia (Anasetti *et al.*, 1986). This led to the practice of avoiding pretransplant transfusions, particularly from the marrow donor and other family members. Studies in an animal model showed that leucocyte depletion of pretransplant transfusions significantly reduced the incidence of graft rejection (Storb *et al.*, 1979), although these results have not been confirmed in human studies.

Recommendation: patients with severe aplastic anaemia who are potential haemopoietic cell transplant recipients should receive leucocyte-depleted blood components from the beginning of transfusion support to minimize the risk of graft rejection.

(2) *Haemopoietic cell transplantation for patients with haematological malignancies*. Graft rejection following haemopoietic cell transplantation is less of a problem in patients with haematological malignancies compared with those with aplastic anaemia. There is no evidence that prevention of sensitization to transplantation antigens is important in patients with acute leukaemia who are potential recipients of allogeneic transplants, although it has been recommended that family member transfusions are avoided (Slichter, 1988).

Recommendation: leucocyte-depleted blood components are not indicated for patients undergoing transplantation for haematological malignancies, other than as a substitute for CMV-seronegative blood components for patients who are CMV-seronegative and who are potential recipients of an allogeneic transplant

(3) *Haemoglobinopathies*. Patients with beta-thalassaemia major and patients with sickle cell anaemia requiring long-term transfusion support should receive leucocyte-depleted blood components to prevent FNHTRs (see section on FNHTRs). A recent study found allograft rejection in 4/22 patients undergoing bone marrow transplantation for sickle cell disease (Walters *et al.*, 1996). This high level of graft rejection could be due to transfusion-induced alloimmunization, which could potentially be prevented by leucocyte depletion of pretransplant transfusions as in aplastic anaemia.

Recommendation: buffy-coat-depleted or bedside filtered red-cell concentrates are recommended for the prevention of FNHTRs in patients with haemoglobinopathies requiring long-term transfusion support. Consideration

could be given to the use of leucocyte-depleted blood components for patients with sickle cell disease or beta-thalassaemia major who are potential candidates for haemopoietic cell transplantation to reduce the risk of graft rejection

(4) *Solid organ transplant recipients.* (a) *Kidney transplants.* A number of factors affect graft survival, including the underlying renal disease, the age, sex and race of the patient, the immunosuppressive drug regimen employed, the degree of HLA mismatching and the use of pretransplant blood transfusions (Blajchman & Singal, 1989). Opelz *et al.* (1973) reported that graft survival was better in transfused patients irrespective of matching for HLA-A, B or DR antigens. The mechanism of the 'transfusion effect' was poorly understood, but seemed to be due to transfused leucocytes.

The transfusion effect became less apparent following the introduction of cyclosporin for post-graft immunosuppression and improved patient management in the 1980s, although multicentre studies continue to show that transfused patients have a better outcome than nontransfused patients (Opelz *et al.*, 1997). However, many centres have switched their attention to the prevention of HLA alloimmunization caused by pretransplant transfusions, by using recombinant erythropoietin to avoid the need for transfusions and by the use of leucocyte-depleted blood components if transfusions are necessary. One attempt to preserve the immunosuppressive effect of transfusion without causing alloimmunization has involved careful selection of the donor of the transfused blood so that there is a common HLA haplotype or shared HLA-DR and HLA-B antigens (Lagaaij *et al.*, 1989; van Twuyver *et al.*, 1990).

Recommendation: pretransplant blood transfusion may confer some benefit to renal transplant recipients, although some patients will become alloimmunized leading to difficulties in the selection of donor kidneys. Consideration should be given to the leucocyte-depletion of transfusions to renal transplant patients to prevent HLA alloimmunization unless they are part of a deliberate pretransplant immunosuppression protocol. The additional advantage of the routine use of leucocyte-depleted blood components is that there is no need to provide CMV-seronegative blood components for CMV-seronegative patients whose kidney donors are also CMV-seronegative.

(b) *Liver transplants.* Unlike allogeneic haemopoietic cell or renal transplantation, liver transplantation does not appear to require HLA matching or lymphocyte cross-matching before transplantation (Nusbacher, 1991),

although there have been recent reports of a poorer outcome with positive lymphocyte cross-matches (Takaya *et al.*, 1992; Katz *et al.*, 1994).

Recommendation: leucocyte-depleted blood components are not indicated, apart from as a substitute for CMV-seronegative blood components for CMV-seronegative patients whose donors are also CMV-seronegative

(c) *Heart transplants.* Graft survival is significantly influenced by HLA compatibility (Opelz & Wujciak, 1994). Evidence is increasing in support of prospective HLA matching, including lymphocyte cross-matching in sensitized patients, in order to select well-matched recipients for cardiac transplantation (Morris, 1994). There is no information about the possible benefit of preventing HLA alloimmunization by leucocyte-depletion of pretransplant transfusions.

Recommendation: leucocyte-depleted blood components are not indicated, apart from as a substitute for CMV-seronegative blood components for CMV-seronegative patients whose donors are also CMV-seronegative

(5) *Fetal/neonatal transfusions.* Fetal/neonatal transfusions often consist of relatively fresh blood containing viable leucocytes. There is consequently a high risk of transmission of leucocyte-associated viruses such as CMV, which was considered in the BCSH recommendations on the transfusion of infants and neonates (BCSH, 1994). There is also a theoretical risk of immunosuppression, for which the fetus/neonate may be at particular risk because of physiological immune incompetence, and HLA alloimmunization, which can occur in multiply transfused infants. The presence of fresh, viable lymphocytes may cause transfusion-associated graft-vs.-host disease (TA-GvHD), which can be prevented by gamma-irradiation of blood components according to BCSH recommendations (BCSH, 1996).

Intrauterine transfusion of cellular blood components was included in the recommended indications for leucocyte-depletion of blood components (Consensus Conference, 1993) on the grounds of the potential long-term benefits and the limited costs of such a recommendation. The same approach could be taken for transfusions of both red-cell and platelet concentrates to neonates. While it could be argued that definitive proof benefit should be awaited in the perinatal group of patients, the potential to avoid theoretical long-term sequelae already exists without a great increase in costs. Another Working Party recommended that leucocyte-depleted blood components should be used for infants below 3 months of age (Danish Society of Clinical Immunology, 1996), and the Department of Health has recently recommended that all

transfusions to neonates and infants under 1 year of age should be leucocyte-depleted.

Recommendations: leucocyte-depleted blood components should be used for intrauterine transfusions and for all transfusions to infants below 1 year of age

Nonindications for leucocyte-depleted blood components

1 A significant number of recipients of blood components receive a limited number of transfusions over a short period of time. These recipients include a large proportion of surgical patients, as well as medical and other groups of patients. Leucocyte-depletion of blood components is not appropriate in these recipients unless there is an additional acceptable indication discussed in one of the previous sections in this guideline.

2 Prevention of TA-GvHD is not an indication for leucocyte-depleted blood components. Gamma-irradiation of blood components is the standard method for avoiding TA-GvHD (BCSH, 1996).

3 Transfusion-related acute lung injury (TRALI) is a rare complication of blood transfusion, in which the patient has a severe reaction characterized by chills, fever, cough and dyspnoea (Popovsky *et al.*, 1992). The chest X-ray shows perihilar and lower lobe nodular shadowing. It is believed to be due to preformed leucocyte antibodies in the plasma of the donors, most of whom are multiparous. Leucocyte depletion of blood components would not be expected to prevent TRALI.

4 Fresh frozen plasma, cryoprecipitate and blood products prepared from pooled plasma are prepared to ensure minimum cellular contamination and are virtually free of cellular material. There is no indication to leucocyte-deplete these blood components and products.

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ADDENDUM ON VARIANT CREUTZFELDT-JAKOB DISEASE (vCJD)

Classical Creutzfeldt–Jakob disease (CJD) is a rare disease with an annual incidence of approximately 1 case/million population. Most cases are spontaneous or familial, with iatrogenic cases associated with the use of pituitary-derived hormones, transplants of dura mater or cornea, or contaminated neurosurgical instruments. There is no epidemiological evidence that classical CJD can be transmitted via blood components. However, individuals at particular risk of classical CJD are excluded from blood donation.

vCJD was first identified in 1996, and is thought to have arisen from the ingestion of beef products contaminated with the agent responsible for BSE in cattle. Over

20 cases have been identified to date, clinically distinct from classical CJD. For example, the abnormal prion-related protein (PrP) can be found in the tonsils and the spleen of patients with vCJD, but not in those with classical CJD. This raises the theoretical possibility that circulating lymphocytes might harbour the agent responsible for vCJD, leading to concerns that the disease could be transmitted via blood transfusion. Recent data have also highlighted the role of lymphocytes in the transport of the abnormal prion protein to the nervous system. However, no data are available on the likely transmissibility of vCJD by blood transfusion.

At the time of production of these guidelines, a risk assessment of vCJD in relation to transfusion is ongoing at Department of Health level. This includes consideration of the possible benefits of leucocyte-depletion of all blood components (including plasma for fractionation). Until this exercise is completed, or until new scientific data become available, the Blood Transfusion Task Force considers that these guidelines represent the current state of knowledge regarding the overall clinical benefits of leucocyte-depletion of blood components.