

**GUIDELINES FOR THE MANAGEMENT OF PLATELET
TRANSFUSION REFRACTORINESS**

Purposes

To define and recommend policies and procedures for the provision of optimal transfusion support for patient's refractory to unselected platelet components.

Method

Recommendations are based on review of the literature and a review of currently accepted practice. The definitions of the types of evidence and the grading of recommendations used in this document originate from the US Agency for Health Care Policy and Research and are provided in the Appendix.

Consultation

NBS Transfusion Medicine Clinical Policies Group
NBS Transfusion Medicine Clinical Policies H&I Sub-group

Status

Original document approved by the NBS Transfusion Medicine Clinical Policies Group on 18th February 2002.

Summary

Platelet transfusion refractoriness may result from immune or non-immune platelet destruction. In patient's refractory to platelet transfusion the identification of those with transfusion failure due to HLA alloantibodies is important since provision of HLA-matched platelet components may result in improved transfusion responses (Grade C, level IV). The identification of patients with other allo- and (rarely) autoantibodies is equally important since matching for HPA, increasing the transfused dose or discontinuing transfusion may be appropriate strategies for improving responses to platelet transfusions (Grade C, level IV). An algorithm for identifying and managing platelet refractoriness has been developed from a review of the literature and currently accepted practice (Grade C, level IV).

1 Background

Alloimmunisation is defined as the development of anti-HLA Class I antibodies or HPA antibodies or both¹. Refractoriness is the failure to obtain satisfactory responses to transfusions of unselected platelet components. A proportion of patients with alloimmunisation become refractory¹. In a large multi-centre study of 530 patients with acute myeloid leukaemia and without HLA antibodies at presentation (TRAP Study) the incidence of alloimmunisation, refractoriness and refractoriness resulting from alloimmunisation were 45%, 16% and 13% respectively². The incidence of alloimmunisation is reported to be as high as 50%. Non-immune mechanisms (see below) are an important cause of refractoriness and have been shown to cause transfusion failure in at least 80% of patients in some series³. The impact of leucodepletion, universally applied to cellular blood components in the UK since November 1999, has been shown to reduce the incidence of alloimmunisation to 10 - 25%, this is largely because of women who were exposed to HLA alloantigens in pregnancy^{4,5,6}.

Various methods are used to assess responses to platelet transfusions. If the patient is bleeding, clinical response is an important indication of the effectiveness of the transfusion. The response to a prophylactic platelet transfusion is assessed by measuring the increase in platelet count after the transfusion. Various formulae have been used to correct for the variation in response dependent on the patient's size and the number of platelets transfused; these include *platelet recovery* and *corrected count increment*. However, in practice, an increase in the patient's platelet count of $<10 \times 10^9/L$ at between 1 and 24 hours after the transfusion can be used as a simple measure of poor response.

2 Aetiology

2.1 Causes of platelet refractoriness can be subdivided into *immune* mechanisms, most importantly HLA alloimmunisation, and *non-immune platelet consumption*. The latter is the most frequent mechanism of platelet refractoriness, usually associated with sepsis^{1,3}.

Immune

Platelet alloantibodies
HLA
HPA
Other antibodies
Platelet autoantibodies
Drug-dependent platelet antibodies
ABO
Immune complexes

Non-immune

Infection and its treatment, especially amphotericin B
Splenomegaly
Disseminated intravascular coagulation (DIC)
Bleeding

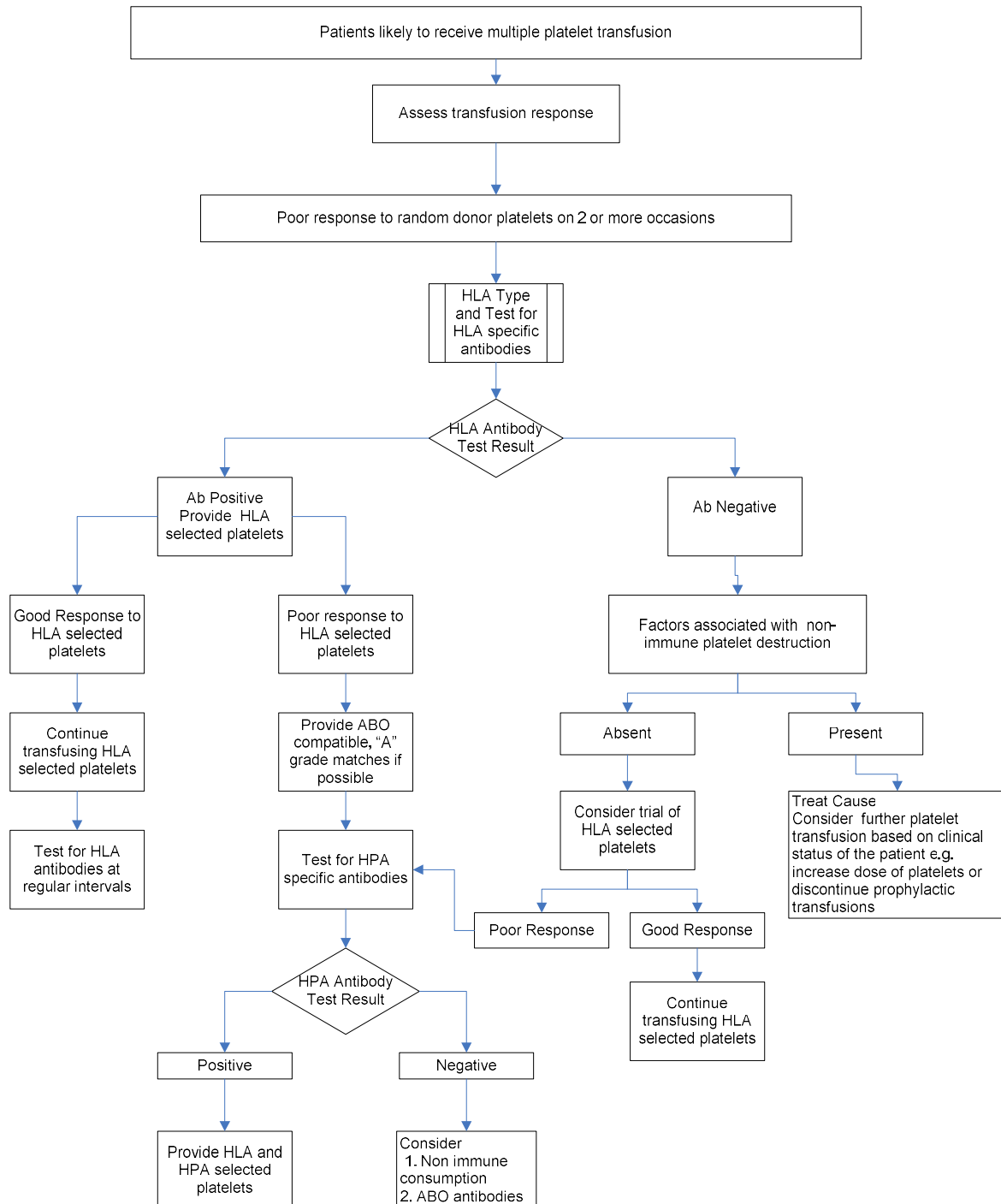
2.2 Primary HLA alloimmunisation appears to be initiated by intact cells expressing both HLA class I and class II antigens such as lymphocytes and antigen-presenting cells. Platelets only express HLA class I antigens and leucocyte-depleted blood components causes primary HLA alloimmunisation in $<3\%$ of recipients⁵. Studies show that leucodepletion is best performed at the time of component preparation. Secondary HLA alloimmunisation does not require the presence of HLA class II antigens and may occur in patients who have been pregnant or previously transfused with non-leucocyte-depleted blood components.

3 Investigation and management

3.1 All patients who receive multiple platelet transfusions should have the platelet count estimated on the day after transfusion on a regular basis. If platelet refractoriness occurs, the following algorithm can be used for the investigation and management.

3.1 continued ..

Investigation of Immune Refractoriness to Platelet Transfusion



¹Note that patients with inherited thrombocytopathies e.g. Glanzmann's disease or Bernard Soulier Syndrome, may bleed when the platelet count is normal or near normal. They should, therefore, receive platelet transfusions as clinically indicated to treat bleeding and not on the basis of platelet count. However, alternatives to maintain haemostasis should be considered at first because of the risk of GPIIb/IIIa or GPIb/IX/V isoimmunisation. Platelet transfusion should be HLA-matched from diagnosis and ABO compatible, wherever possible, to minimise the risk of HLA alloimmunisation

3.2

Type of HLA match	Number of compatible HLA – A & B antigens	Number of mismatched HLA A & B antigens
A	4	0
B1	3	1
B2	2	2
B3	1	3
B4	0	4

3.3 HLA epitope matching

Specific regions of polymorphism in HLA molecules determine the nature of public and private HLA epitopes. Matching at the epitope level, based around either the characterization of short sequences of amino acids from linear or discontinuous regions of the HLA molecules, may be more relevant for assessing HLA compatibility between patients and donors and the effect of donor-specific HLA antibodies. This approach of epitope matching can result to more efficient matching particularly for highly sensitized patients.

4 Samples required

Request that 6 ml clotted blood plus 6 ml EDTA if HLA type is required is sent to the local blood centre. Samples will then be transferred to the appropriate H&I testing laboratories.

5 Blood Centre Management of platelet refractoriness

5.1 There should be regular meetings in the NHSBT H&I laboratories including senior clinical staff to discuss and agree ongoing provision of matched platelets. The selection HLA matched platelets will be performed by trained H&I scientific staff.

5.2 It is important that there is regular contact between individual NHSBT centres and hospitals to discuss requests, provide clinical information including follow-up data such as platelet increments to the NHSBT H&I laboratories. In each centre or group of functionally linked centres an NHSBT H&I Consultant Clinical Scientist will take responsibility for ensuring that essential data is provided to and discussed with the H&I laboratories.

5.3 All irradiated prior to issue⁷.

6 On-call arrangements

Requests for provision of HLA matched platelets outside normal working hours should be discussed with and approved by the National Consultant Clinical Scientist on-call.

Please consult the NHSBT H&I user guide (INF136) for details regarding provision of HLA and HPA-selected platelet components.

References

1. Murphy MF, Waters AH (1990). Platelet transfusions: The problem of refractoriness. *Blood Reviews*, **4**, 16-24.
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4. Williamson LM, Wimperis JZ, Williamson P, Copplestone JA, Gooi HC, Morgenstern GR, Norfolk DR. (1994). Bedside filtration of blood products in the prevention of HLA alloimmunization - a prospective randomized study. *Blood*, **83**, 3028-3035.
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6. Williamson LM (2000). Leucocyte depletion of the blood supply - how will patients benefit? *Br J Haemat*, **110**, 256-272.
7. BCSH Blood Transfusion Task Force (1996). Guidelines on gamma irradiation of blood components for the prevention of transfusion-associated graft-versus-host disease. *Transfusion Medicine*, **6**, 261-271.
8. CJ Brown & CV Navarrete (2011) Clinical relevance of HLA system in blood transfusion. *Vox Sang*, **101**, 93-105.
9. Marsh JCW, Stanworth SJ, Pankhurst L, Kallon D, Gilbertson A, Pigden C, Deary AJ, Mora AS, Brown J, Laing E, Choo CJ, Hodge RL, Llewelyn C, Harding K, Sage D, Mijovic A, Mufti GJ, Navarrete CV, Brown CJ. An epitope-based diagnostic approach to identify HLA matched platelets for transfusion in alloimmunised patients: a non-inferiority randomised trial. *Blood* (2021) 137 (3): 310–322.

Appendix

Key to evidence statements and grades of recommendations

The definitions of the types of evidence and the grading of recommendations used in this guideline originate from the US Agency for Health Care Policy and Research and are set out in the following tables.

STATEMENTS OF EVIDENCE

- Ia Evidence obtained from meta-analysis of randomised controlled trials.
- Ib Evidence obtained from at least one randomised controlled trial.
- IIa Evidence obtained from at least one well-designed controlled study without randomisation.
- IIb Evidence obtained from at least one other type of well-designed quasi-experimental study.
- III Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
- IV Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

GRADES OF RECOMMENDATIONS

- A Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation.**
(Evidence levels Ia, Ib)
- B Requires the availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.**
(Evidence levels IIa, IIb, III)
- C Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality.**
(Evidence level IV)