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Guideline

GUIDELINES FOR THE USE OF PLATELET TRANSFUSIONS

METHODS

These guidelines are based on many years experience in the use of platelet transfusions by the authors, on searching the literature in MedLine and other databases using appropriate keywords, and a review of the existing guidelines published by expert groups [British Committee for Standards in Haematology (BCSH), 1992; Schiffer *et al,* 2001], including a previous guideline on platelet transfusions (BCSH, 1992) and the recommendations of Consensus Conferences (National Institutes of Health Consensus Conference, 1987; Consensus Conference on Platelet Transfusion, 1998). The section on indications for platelet transfusions was drafted in collaboration with the Haemato-Oncology Task Force of the BCSH.

The authors were selected to encompass a wide range of interests in platelet transfusion therapy, including clinical and laboratory haematology, paediatrics, surgery, anaesthetics and critical care, and nursing.

GRADING OF EVIDENCE AND STRENGTH 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 *Appendix I*.

BACKGROUND

The ready availability of platelet concentrates has undoubtedly made a major contribution to modern clinical practice, in particular, in allowing the development of intensive treatment regimens for haematological and other malignancies (Freireich, 2000).

Considerable advances have been made in platelet transfusion therapy in the last 40 years, but some areas continue to provoke debate, for example, the use of prophylactic platelet transfusions. A number of attempts have been made to achieve a consensus on various aspects of platelet transfusion therapy, including the clinical indications, both in the USA (National Institutes of Health Consensus Conference, 1987; Schiffer *et al,* 2001) and in the UK (BCSH, 1992; Consensus Conference on Platelet Transfusion, 1998). However, lack of objective data have limited the development of evidence-based recommendations, although a number of recent randomized controlled studies have produced useful information in this field.

The use of platelet transfusions continues to increase; there was a 2·3% increase in the demand for platelet concentrates by hospitals in England in 2001–2002 (215 050 adult doses in total) compared with the previous year. Platelet concentrates are expensive, and developments in the collection, processing, storage and administration of platelet transfusions continue to be aimed at increasing their clinical effectiveness and reducing the side-effects associated with their use.

The purpose of these guidelines is to give guidance about the use of platelet transfusions to medical, nursing and technical staff in hospitals responsible for prescribing, administering and providing platelet transfusions. Guidelines for the selection of donors and the preparation of platelet concentrates are described in the Guidelines for the UK Blood Transfusion Services [UK Blood Transfusion Services/National Institute for Biological Standards and Controls (UKBTS/NIBSC), 2002], and will not be addressed in detail in this document.

PREPARATION OF PLATELET CONCENTRATES

Methods

In the UK, platelet concentrates are produced from whole blood using the buffy coat method of preparation, or by plateletpheresis according to agreed guidelines (UKBTS/NIBSC, 2002). Standard requirements for donor selection, and mandatory microbiological testing must be met.

Pooled buffy coat platelet concentrates are derived from four donations of whole blood. The whole blood donation is centrifuged at a relatively high ***g*** force within 8 h of venepuncture, partitioning the platelets into a layer at the interface of the red cells and plasma. The buffy coat is separated using the Optipress system, re-suspended in either plasma or platelet suspension medium (PSM), and subjected to a second, softer, spin which leaves the platelets in suspension above the red cells and leucocytes. Subsequent pooling is performed before the end of the first 24 h from the time of donation. Leucocyte depletion is by filtration using validated methods.

Single-donor apheresis platelet concentrates may be collected by a variety of apheresis systems, using different protocols. Platelet yields may vary, and each procedure or protocol must be fully validated, documented and specifications set accordingly. A single donation procedure may yield one to three therapeutic doses and the donation may be split between two or three bags, depending on counts. Additional

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filtration to achieve leucocyte depletion may be required using some systems.

Recommendations (grade A, level 1 evidence). Pooled platelet concentrates prepared from whole blood and those prepared by plateletpheresis contain approximately the same number of platelets, and comparative studies have shown them to be therapeutically equivalent in terms of post-transfusion platelet increments and haemostatic effectiveness, and their transfusion is associated with a similar incidence of side-effects (Patel *et al*, 1978; Turner *et al*, 1994; Heaton *et al*, 1997; Schiffer *et al*, 2001). It should be noted that a platelet concentrate prepared from the buffy coats from 4 units of whole blood results in a higher donor exposure than a platelet concentrate prepared by plateletpheresis of a single donor.

Quality monitoring

Some red cell serological tests and microbiological screening tests [including nucleic acid amplification technology (NAT) testing for hepatitis C virus (HCV)] are mandatory procedures, and the test results have a direct bearing on whether the final individual components are released or not.

Each component must be visually inspected at each stage of processing and immediately prior to issue. The component is withdrawn if there is evidence of leakage, damage or fault in the container, excessive air, suspicion of microbial contamination, or other contraindications such as platelet clumping, turbidity or abnormal colour change.

Sampling for leucocyte counting must be taken within 48 h of the leucocyte depletion step. The UK specification for leucocyte depletion is that 99% of leucocyte-depleted components tested within the statistical process monitoring (SPM) sampling plan should contain $< 5 \times 10^6$/l leucocytes within 95% confidence limits.

For quality control tests other than leucocyte depletion, the minimum testing frequency is 1% of annual production of each component or 10 of each component type per month, whichever is greater. A minimum of 75% of those components tested must meet the following specified values:

- Volume: usually 150–300 ml for platelet concentrates prepared by apheresis, and 150–450 ml for those prepared from whole blood.
- Platelet count: $> 240 \times 10^9$ per adult dose.
- pH: between 6·4 and 7·4 throughout the shelf-life.

Labelling

The following details must be included on the labels:

- either: platelets, pooled, buffy coat derived, leucocyte-depleted
  or: platelets, apheresis, leucocyte-depleted;
- volume;
- blood component producer's name;
- either: a unique pool or batch number
  or: the donation number of all contributing units
  or: the donation number and, if subdivided, the sub batch number;
- the ABO group;
- the RhD group stated as positive or negative;
- the expiry date;
- the blood pack lot number.

All of the above should be eye readable and in UK Blood Transfusion Services (UKBTS)-approved barcode format.

In addition, the following statements should appear:

- store at 22°C ± 2°C with continuous gentle agitation;
- always check the patient/component compatibility/identity;
- inspect pack for signs of deterioration or damage;
- risk of adverse reaction/infection.

Storage and shelf life

The storage period depends upon the nature of the container and whether an open or closed system has been used.

- In a closed system, current packs allow storage at 22°C ± 2°C with continual gentle agitation for up to 5 d.
- After suspension in PSM or washing (i.e. an open system), the shelf life is reduced to 24 h, but the component should be used as soon as possible.

Neonatal platelets

Specifications additional to those listed above:

- Components should be free of clinically significant irregular blood group antibodies, including high titre anti-A and anti-B.
- Components should be negative for cytomegalovirus (CMV).
- Components may be prepared by splitting an apheresis platelet pack (often into four), using a closed system.
- Components should contain $> 40 \times 10^9$/l platelets.
- Additional labelling is required: 'platelets for neonatal use'.

Platelets for intrauterine transfusion (IUT)

- These are hyperconcentrated platelet components ($> 2000 \times 10^9$/l) prepared from apheresis platelets with the aim of limiting the volume of the transfusion to the fetus.
- They contain $< 0{\cdot}0025 \times 10^9$/l leucocytes per donation.
- Components should be used within 24 h of completing the apheresis collection.
- Components should be negative for CMV.
- Components must be gamma irradiated (BCSH, 1996).
- Components should contain $> 120 \times 10^9$/l platelets in 60 ml of plasma.
- Additional labelling is required: 'platelets for IUT'.

Gamma irradiation of platelets

The following recommendations are taken from guidelines for the gamma irradiation of blood components (BCSH, 1996):

- Platelet concentrates can be irradiated at any stage during their 5 d shelf life.
- The minimum dose in the irradiation field is 25 Gy, with no part receiving more than 50 Gy.
- Gamma-sensitive labels should be applied to the pack.

- A permanent record of all gamma-irradiated units must be kept.
- All gamma-irradiated components should be identified by an approved overstick label bearing the date of irradiation.

INDICATIONS FOR PLATELET TRANSFUSIONS

Platelet transfusions are indicated for the prevention and treatment of haemorrhage in patients with thrombocytopenia or platelet function defects. Platelet transfusions are not indicated in all causes of thrombocytopenia and may indeed be contraindicated in certain conditions. Thus, the cause of the thrombocytopenia should be established before a decision about the use of platelet transfusion is made. Any decision must also be based on an assessment of risk versus benefit. Risks associated with platelet transfusions include alloimmunization, transmission of infection, allergic reactions and transfusion-related acute lung injury; potential benefits include reducing morbidity associated with minor haemorrhage and reducing morbidity/mortality resulting from major bleeding. There have been several studies since the last BCSH guidelines for platelet transfusions (BCSH, 1992), and these have provided further information to help in this risk–benefit analysis.

Bone marrow failure (due to disease, cytotoxic therapy or irradiation)

Therapeutic platelet transfusions are unequivocally indicated for patients with active bleeding associated with thrombocytopenia, although serious spontaneous haemorrhage due to thrombocytopenia alone is unlikely to occur at platelet counts above 10×10^9/l (Slichter, 1980).

Prophylactic platelet transfusions have become standard practice for patients with bone marrow failure, although there are no recent randomized studies comparing survival and the incidence of haemorrhage in patients receiving prophylactic versus only therapeutic platelet transfusions. Such studies are unlikely to be carried out in the near future. Early studies showed that prophylactic platelet transfusions decreased morbidity, although not mortality, in patients with thrombocytopenia due to bone marrow failure (Roy *et al*, 1973; Higby *et al*, 1974). At that time, a threshold for platelet transfusion of 20×10^9/l was recommended, but this dates from an era when blood cell counters were generally less accurate at low platelet levels, treatment of bacterial sepsis was less effective and aspirin was commonly used as an antipyretic. From recent studies, there is now considerable evidence that the threshold can be lowered safely.

1. Acute leukaemia (excluding promyelocytic leukaemia)

Several studies (Gmur *et al*, 1991; Heckman *et al*, 1997; Rebulla *et al*, 1997; Wandt *et al*, 1998) provide evidence that the threshold for platelet transfusion can be lowered from 20×10^9/l to 10×10^9/l. Gmur *et al* (1991) suggested that the threshold could be reduced further to 5×10^9/l in the absence of fever > 38°C or fresh minor haemorrhage.

2. Acute promyelocytic leukaemia

There are no studies that specifically address the threshold for platelet transfusion in this condition. Gmur *et al* (1991) commented that the presence of coagulopathy necessitated a higher threshold, while Rebulla *et al* (1997) specifically excluded patients with promyelocytic leukaemia from their study. The presence of a coagulopathy would be expected to increase the likelihood of haemorrhage at any given platelet count. As a minimum, the platelet count should be kept above 20×10^9/l in patients who are haemorrhagic.

3. Haemopoietic stem cell transplantation

The risk of mucosal injury is generally higher in bone marrow transplantation than with chemotherapy for acute leukaemia. However, a small number of studies have indicated that the threshold for platelet transfusion can again be safely lowered to 10×10^9/l (Gil-Fernandez *et al*, 1996; Bernstein *et al*, 1998; Nevo *et al*, 1998).

Peripheral blood stem cell transplantation results in a shorter duration of thrombocytopenia than bone marrow transplantation, and it is reasonable to assume that the threshold for platelet transfusion can be the same as for marrow transplantation and acute leukaemia.

4. Chronic stable thrombocytopenia

Patients with chronic and sustained failure of platelet production, for example some patients with myelodysplasia or aplastic anaemia, may remain free of serious haemorrhage with platelet counts consistently below 10×10^9/l or even below 5×10^9/l. Long-term prophylactic platelet transfusions may be best avoided in these patients because of the risk of alloimmunization and platelet refractoriness, and other complications of transfusion. Therapeutic platelet transfusions should be used to treat overt haemorrhage, and such patients may require prophylactic platelet transfusions to prevent recurrent haemorrhage during unstable periods associated with infection or active treatment.

Recommendations. On the basis of the above studies, the following guidance is suggested; this advice concurs with the recent Consensus Conference on Platelet Transfusion (1998) and the guidelines of the American Society of Clinical Oncology (Schiffer *et al*, 2001):

- A threshold of 10×10^9/l is as safe as higher levels for patients without additional risk factors. Risk factors include sepsis, concurrent use of antibiotics or other abnormalities of haemostasis (grade A, level Ib).
- For patients without any risk factors, a threshold of 5×10^9/l may be appropriate if there are concerns that alloimmunization could lead to platelet refractoriness (grade B, level IIa). However, accurate counting of low platelet numbers may create difficulties when trying to reduce the threshold below 10×10^9/l.
- A specific threshold for transfusion may not be appropriate for patients with chronic stable thrombocytopenia who are best managed on an individual basis depending on the degree of haemorrhage (grade C, level IV).

Prophylaxis for surgery

There is a lack of evidence to guide therapeutic decisions regarding platelet transfusion to cover surgical procedures, and it is unlikely that comprehensive studies could be carried out because of the large number of variables involved. Some work in this area is reviewed in the guidelines of the American Society of Clinical Oncology (Schiffer *et al,* 2001), and the following guidance is given on the basis of this information and expert opinion.

Recommendations.

- Bone marrow aspiration and biopsy may be performed in patients with severe thrombocytopenia without platelet support, providing that adequate surface pressure is applied (grade C, level IV).
- For lumbar puncture, epidural anaesthesia, gastroscopy and biopsy, insertion of indwelling lines, transbronchial biopsy, liver biopsy, laparotomy or similar procedures, the platelet count should be raised to at least 50×10^9/l (grade B, level III).
- For operations in critical sites such as the brain or eyes, the platelet count should be raised to 100×10^9/l (grade C, level IV).
- It should not be assumed that the platelet count will rise just because platelet transfusions are given, and a preoperative platelet count should be checked to ensure that the above thresholds have been reached.

Platelet function disorders

Patients with platelet function disorders rarely need platelet transfusions. Even patients with severe inherited platelet function disorders such as Glanzmann's thrombasthenia only have sporadic bleeding and may have no bleeding for many years (George *et al*, 1990), although heavy bleeding may occur with the first menstrual period. Negligible or no excessive bleeding can be expected in patients with acquired platelet function disorders as the impairment in platelet function is much less than in Glanzmann's thrombasthenia. However, acquired causes of platelet dysfunction can exacerbate bleeding in patients who already have impaired haemostasis (George & Shattil, 1991).

Recommendations. The following recommendations (grade C, level IV) are for the management of bleeding or for prophylaxis before invasive procedures for patients with a known or suspected platelet function disorder:

- Withdraw drugs known to have antiplatelet activity.
- Correct any underlying condition known to be associated with platelet dysfunction, if possible.
- Correct the haematocrit to $> 0{\cdot}30$ l/l in patients with renal failure, either with the use of recombinant erythropoietin or red cell transfusion.
- Consider the use of DDAVP (1-deamino-8-D-arginine vasopressin, desmopressin) in patients with inherited dysfunction defects, such as storage pool disease.
- Consider the use of DDAVP or cryoprecipitate in patients with uraemia.
- Use platelet transfusions where the above methods are not appropriate or are ineffective.
- The use of human leucocyte antigen (HLA)-matched platelet transfusions were often recommended in the past for the prevention of HLA alloimmunization in patients with inherited platelet function disorders. However, the incidence of HLA alloimmunization with prestorage leucocyte-depleted blood components is low (see below), and it could be argued that it is no longer necessary to use HLA-matched platelet transfusions for non-alloimmunized patients.
- Although platelet therapy may be required in an emergency in Glanzmann's thrombasthenia, the high likelihood of alloimmunization and subsequent platelet refractoriness should be taken into account, and consideration should be given to the use of recombinant factor VIIa, which has been shown to be effective in the management of bleeding and for prophylaxis before surgery in patients with Glanzmann's thrombasthenia (Poon *et al*, 1999).

Massive transfusion

A platelet count of around 50×10^9/l is expected when red cell concentrates equivalent to approximately two blood volumes have been transfused (Hiippala, 1998).

Recommendations (grade C, level IV).

- There is consensus that the platelet count should not be allowed to fall below 50×10^9/l in patients with acute bleeding (BCSH, 1988; Consensus Conference on Platelet Transfusion, 1998; Stainsby *et al,* 2000).
- A higher target level of 100×10^9/l has been recommended for those with multiple trauma or central nervous system injury (Development Task Force of the College of American Pathologists, 1994; Horsey, 1997).

Disseminated intravascular coagulation (DIC)

Platelet transfusions are a part of the management of acute DIC, where there is bleeding associated with thrombocytopenia, in addition to management of the underlying disorder and coagulation factor replacement (BCSH, 1992).

Recommendations (grade C, level IV).

- Frequent estimation of the platelet count and coagulation screening tests should be carried out.
- There is no consensus on a target platelet count, but to aim to maintain the platelet count $> 50 \times 10^9$/l, as in massive blood loss, would seem to be reasonable practice (Consensus Conference on Platelet Transfusion, 1998).
- In chronic DIC, or in the absence of bleeding, platelet transfusions should not be given merely to correct a low platelet count.

Cardiopulmonary bypass

There has been no new published evidence to alter the use of platelet transfusion following cardiopulmonary bypass (CPB) since the last BCSH guideline on platelet transfusion (BCSH, 1992).

Aspirin and other cyclo-oxygenase inhibitors (i.e. non-steroidal anti-inflammatory drugs, such as ibuprofen) cause increased post-surgical bleeding following CPB. Clopidogrel, which acts by antagonizing the pro-aggregatory role of ADP, is a newer drug with profound antiplatelet effects, and it would seem reasonable to withhold both theses classes of drugs in patients attending for elective surgical revascularization. However, increasing numbers of patients present for surgery with acute coronary syndrome and these drugs have an important therapeutic role. Consideration should be given to the use of aprotonin in this group of patients taking these medications.

There is no place for prophylactic transfusion of platelets in patients undergoing CPB; a randomized study of 28 patients found that the administration of a platelet transfusion following CPB did not reduce blood loss or transfusion requirements (Simon *et al*, 1984).

Microvascular bleeding, as indicated by continued oozing from surgical incisions and venous cannulation sites, is the hallmark of platelet-related bleeding. This usually occurs as a consequence of either thrombocytopenia with a reduced platelet count (usually less than 50×10^9/l) or acquired platelet dysfunction. CPB induces a transient reversible platelet dysfunction, the pathophysiology of which is not fully understood. Although the bleeding time is a measure of *in-vivo* platelet function, preoperative measurement has not been shown to be an accurate predictor of those patients who will bleed excessively postoperatively. Similarly, the platelet count following CPB gives no indication of functioning platelets, and an appropriate platelet function test is lacking. The use of the thromboelastograph (TEG) has been found to help the decision-making process about appropriate platelet transfusion in some institutions.

Recommendations.

- Platelets should be readily available in all institutions undertaking cardiac surgery. The same recommendation has been made in relation to the management of ruptured abdominal aortic aneurysms (National Confidential Enquiry into Peri-operative Deaths, 2001) (grade C, level IV).
- The use of platelet transfusion should be reserved for those patients who are experiencing excessive postoperative bleeding and in whom a surgical cause has been excluded (grade A, level Ib).
- The preoperative assessment of patients attending for cardiac surgery should include a thorough review of all medications likely to interfere with platelet function, and in these instances consideration may be given to delaying surgery, the use of appropriate peri-operative pharmacotherapy (aprotonin) or recognition that platelet transfusion may be required. The decision to transfuse platelets in patients following CPB remains a clinical decision based on the evidence of microvascular bleeding in association with excessive post-surgical blood loss (Slichter, 1980) (all grade C, level IV).

Liver transplant surgery

Reduced haemostasis due to a combination of reduced coagulation, enhanced fibrinolysis and thrombocytopenia is found in patients with liver failure. This is exacerbated during liver transplantation as a result of massive transfusion and hyperfibrinolysis, which occurs on reperfusion of the donor liver.

Current practice is to use the TEG to guide the need for platelet transfusion and other blood components (Mallett & Cox, 1992; Hunt, 1998), and this may result in more economical and effective use of blood components (Consensus Conference on Platelet Transfusion, 1998).

Immune thrombocytopenias

1. Autoimmune thrombocytopenia

Recommendations (grade C, level IV).

- Platelet transfusions should be reserved for patients with life-threatening bleeding from the gastrointestinal or genitourinary tracts into the central nervous system or other sites associated with severe thrombocytopenia (BCSH, 2003a).
- A large number of platelet concentrates may be required to achieve haemostasis as a result of reduced survival of the transfused platelets.
- Other therapies such as intravenous methylprednisolone and immunoglobulin should be given at the same time to maximize the chances of stopping the haemorrhage and raising the platelet count.

2. Neonatal alloimmune thrombocytopenia (NAIT)

Recommendations (grade C, level III).

- The optimal approach to the postnatal management of NAIT suspected on clinical grounds is to transfuse compatible platelets as soon as possible, as delay in the provision of effective treatment may result in an increased risk of severe haemorrhage (Letsky & Greaves, 1996). It is not necessary to wait for laboratory confirmation of the diagnosis.
- The transfusion of human platelet antigen (HPA)-1a-negative, HPA-5b-negative platelet concentrates will result in least delay in providing treatment and will be effective in around 95% of cases of NAIT.
- If there is no response to HPA-1a negative, HPA-5b negative platelet concentrates, or if the HPA incompatibility is known to be for HPAs other than HPA-1a or HPA-5b, consideration should be given to the use of a platelet concentrate prepared from the mother. Such concentrates should be gamma irradiated (BCSH, 1996) and washed, in order to minimize the transfusion of maternal platelet alloantibodies that may otherwise prolong the neonatal thrombocytopenia.
- Other approaches to postnatal treatment of NAIT are suboptimal. The 'blind' transfusion of random platelets is unlikely be effective (Murphy & Allen, 1997). There has only been one study of the use of intravenous immunoglobulin for the postnatal management of NAIT; the response rate was 75% and the increase in platelet count

was delayed for 24–48 h, during which time the infant remains at risk of intracranial haemorrhage (Mueller-Eckhardt *et al*, 1989).
- The advice of a fetal medicine unit should be sought in relation to the management of women with a history of NAIT in a previous pregnancy when they are considering further pregnancies.
- Detailed consideration of the antenatal management of NAIT is beyond the scope of this guideline. Recommendations have been provided in a previous BCSH guideline (Letsky & Greaves, 1996).

3. Post-transfusion purpura

No randomized controlled trials of treatment for post-transfusion purpura (PTP) have been carried out. Comparison of various therapeutic measures is complicated because it may be difficult to differentiate a response to treatment from a spontaneous remission in individual patients.

Recommendations (grade C, level III).
- High-dose intravenous immunoglobulin (2 g/kg given over 2 or 5 d) is the current treatment of choice with responses in about 85% of patients; there is often a rapid and prompt increase in the platelet count (Becker *et al*, 1985).
- Platelet transfusions are usually ineffective in raising the platelet count. However, they may be used in an attempt to control severe bleeding in the acute phase, particularly in patients who have recently undergone surgery before there has been a response to high-dose intravenous immunoglobulin, and large doses may be required. There is no evidence that platelet concentrates from HPA-1a-negative platelets are more effective than those from random donors in the acute thrombocytopenic phase, and the dose of platelets may be more important than the type of the donor platelets. There is no evidence to suggest that transfusions in the acute phase prolong the duration or severity of thrombocytopenia.

CONTRAINDICATIONS TO PLATELET TRANSFUSIONS

Thrombotic thrombocytopenic purpura (TTP)

Guidelines on the diagnosis and management of the thrombotic microangiopathic haemolytic anaemias have been published (BCSH, 2003b). Platelet transfusions are contraindicated unless there is life-threatening haemorrhage, as they have been temporarily associated with exacerbation of TTP (Harkness *et al*, 1981; Gordon *et al*, 1987).

Heparin-induced thrombocytopenia (HIT)

HIT is a drug-induced immune thrombocytopenia that is frequently associated with severe thrombosis (Warkentin *et al*, 1998). Platelet transfusions should not be administered as acute arterial thrombosis can result (Babcock *et al*, 1976; Cimo *et al*, 1979).

APPROACHES FOR MINIMIZING THE USE OF PLATELET TRANSFUSIONS

1. Lowering of platelet threshold from 20×10^9/l to 10×10^9/l: there is the possibility of further reduction to 5×10^9/l for prophylactic platelet transfusions, but this would require the routine availability of methods for accurate platelet counting.
2. Adherence to agreed policies on platelet use (see above).
3. Local audit of the use of platelet transfusions.
4. Use of tranexamic acid has been shown to reduce the requirement for platelet transfusion during consolidation treatment for acute leukaemia: though in this study platelets were only given on a therapeutic basis rather than prophylactically (Shpilberg *et al*, 1995). Tranexamic acid may be helpful for troublesome local bleeding, e.g. oral haemorrhage, though its use is contraindicated in the presence of haematuria because of the possibility of ureteric clot formation.
5. In thrombocytopenia after chemotherapy or stem cell transplant, the use of cytokine growth factors remains a possibility for the future.
6. Reduction of donor exposure in children (and possibly adults) by the use of split packs of platelets from the same apheresis donation.
7. Correction of concurrent coagulopathy in bleeding thrombocytopenic patients.
8. Pre-operative cessation of aspirin or other antiplatelet therapy whenever possible.
9. Avoidance of formula or prophylactic use of platelets in CPB patients.
10. Intra-operative monitoring of platelet count and TEG with appropriate correction of abnormalities according to an agreed algorithm.
11. Intra-operative use of aprotinin and tranexamic acid.
12. Early return to theatre for surgical bleeding.

BLOOD BANK DOCUMENTATION AND PROCEDURES

The following recommendations are taken with reference to the BCSH guidelines for the administration of blood and blood components and the management of transfused patients (BCSH, 1999).

Generation of the request

The request for platelets should come from the clinician responsible for the patient or their nominated deputy. The request form and the sample for blood grouping (if this has not been carried out previously) must contain full patient identification details, i.e. surname, first name, date of birth, the sex of the patient and a patient identification number, which depending on the circumstances will be a hospital, accident and emergency number or major accident number. Even better would be use of a unique number for patient identification, such as the National Health Service (NHS) number.

The reason for the request should be provided. If the request does not fall within the local agreed guidelines for

platelet ordering, the consultant haematologist in charge of blood bank or their deputy should be notified before the platelet order is accepted.

Hospitals must have a policy for the requesting of special blood requirements, e.g. gamma irradiated, CMV seronegative (BCSH, 1999). In general, it is preferable that any special blood requirements are indicated on the blood transfusion request form each time blood or blood components are requested. Special blood requirements should be stored on the hospital blood bank computer, and hospital blood bank staff should check whether there are any special requirements whenever blood or blood components are requested.

Labelling and documentation

- product label (as described above);
- a patient identification label bearing: surname, forename, date of birth, hospital number, ABO group of patient, RhD group of patient, unique donor number of the pack, date platelets required;
- if indicated, an irradiation label stating date of gamma irradiation;
- if indicated, an HLA- or HPA-matching label;
- if indicated, a label stating that platelets are in PSM/washed with new expiry date/time.

Platelet selection

The following recommendations have been developed with reference to previous guidelines for ABO and RhD incompatibility in relation to platelet transfusions (BCSH, 1992; National Blood Service Transfusion Medicine Clinical Policies Group, 2000), and a recent review of new clinical evidence (Menitove, 2002):

1. ABO compatibility

- Platelet concentrates from donors of the identical ABO group as the patient are the components of choice and should be used as far as is possible (grade B recommendation, level III evidence).
- ABO non-identical platelet transfusions have been associated with poorer platelet count increments in some studies, but this is not usually clinically significant in terms of the haemostatic effectiveness of the platelet transfusion. Administration of ABO non-identical platelets is acceptable transfusion practice (grade C recommendation, level IV evidence), in particular, when platelet concentrates are in short supply, or when HLA-matched platelets are required and the best match is not ABO compatible. The policy of using ABO non-identical platelet concentrates on some occasions may result in less wastage than a policy of exclusive use of ABO compatible platelets, and hospital blood banks may need to do this to manage their stocks of platelet concentrates most efficiently.
- Group O platelets should only be used for group A, B and AB patients if they have been tested and labelled as negative for high-titre anti-A and anti-B (grade B recommendation, level III evidence). It should be noted that there is no generally agreed discriminatory test for high-titre anti-A and anti-B, and there are no precise guidelines for laboratory testing. Hospital blood banks and clinical users of platelet concentrates should be aware of possible haemolysis due to the transfusion of group O platelet concentrates to patients of other ABO groups.
- The transfusion of ABO non-identical platelet concentrates should be considered as a cause of unexplained platelet refractoriness (grade B recommendation, level III evidence).

2. RhD incompatibility

- RhD-negative platelet concentrates should be given, where possible, to RhD-negative patients, particularly to women who have not reached the menopause (grade B recommendation, level III evidence).
- If RhD-positive platelets are transfused to a RhD-negative woman of childbearing potential, it is recommended that anti-D should be given (grade B recommendation, level III evidence). A dose of 250 i.u. anti-D should be sufficient to cover five adult therapeutic doses of RhD-positive platelets within a 6-week period, and it should be given subcutaneously in thrombocytopenic patients.
- It is not necessary to administer anti-D to RhD-negative men or women without childbearing potential who have haematological disorders and receive platelet concentrates from donors who are RhD positive.

3. Gamma irradiation

Data from the first five reports of the Serious Hazards of Transfusion (SHOT) scheme show that transfusion-associated graft-versus-host disease (TA-GVHD) is the most frequent cause of transfusion-associated death (The Serious Hazards of Transfusion Steering Group, 2002). Patients at risk of TA-GVHD should be given gamma-irradiated platelets, according to guidelines for the gamma irradiation of blood components (BCSH, 1996).

It is essential that hospitals have procedures to ensure that patients in these categories receive gamma-irradiated blood components. Difficulties have been experienced in doing this in the past for patients being treated on a shared-care basis, or for later clinical events in patients requiring gamma-irradiated blood indefinitely. The National Blood Service Transfusion Medicine Clinical Policies Group has prepared an information leaflet and card for this purpose that has been approved by the BCSH; they are available from National Blood Service Hospital Issue Departments.

Recommendations (all grade C, level IV). Blood components for the categories of patients identified in previous BCSH guidelines (BCSH, 1996) should be gamma irradiated. Patients requiring gamma-irradiated blood should be given an information leaflet and card, and their need for gamma-irradiated blood should be stored in blood bank records.

4. CMV-seronegative platelets

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 (Sayers *et al*, 1992). The majority view at a recent Consensus Conference was that CMV-seronegative (and leucocyte-depleted) blood was indicated for CMV-seronegative pregnant women, intrauterine transfusions and CMV-seronegative allogeneic haemopoietic stem cell transplant recipients; CMV-seronegative blood was considered to be probably indicated for patients undergoing solid organ transplants, CMV-seronegative patients with conditions likely to require allogeneic haemopoietic stem cell transplantation and CMV-seronegative patients with HIV infection (Lapaucis *et al,* 2001).

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 is probably as a result of 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.

There has been interest and controversy over the potential for leucocyte depletion of blood components to prevent CMV transmission (BCSH, 1998; Pamphilon *et al*, 1999). A number of studies found that leucocyte depletion of blood components was successful in preventing transfusion-transmitted CMV infection in neonates, and acute leukaemia and bone marrow transplant patients (reviewed in Hillyer *et al*, 1994; Goldman & Delage, 1995; Pamphilon *et al*, 1999). Furthermore, a prospective randomized study claimed 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), although the authors' interpretation of the results has been controversial and not universally accepted. A recent observational study found no difference in transfusion-acquired CMV in allogeneic stem cell transplant patients receiving prestorage leucocyte-depleted platelet concentrates compared with CMV-seronegative platelet concentrates (Ronghe *et al,* 2002).

Recommendations (all grade C, level IV).

- All intrauterine and neonatal transfusions must be CMV seronegative, in addition to being leucocyte depleted (BCSH, 1997).
- Other patients at risk of primary CMV infection or CMV reactivation may be given blood components which are both leucocyte depleted and CMV seronegative, at the discretion of the physician in charge of the patient.

5. Management of red cell T-antigen activation

Red cell T-antigen activation due to reduced sialic acid residues on the red cell membrane can be detected in up to 1 in 180 blood donors, and more frequently in neonates with necrotizing enterocolitis and in children with other bacterial infections. Although some case reports have suggested an association between T activation and haemolysis, a definite causal relationship has not been established (Crookston *et al,* 2000; Eder & Manno, 2001; Ramasethu & Luban, 2001).

There is debate about the need to use washed blood components and low anti-T fresh-frozen plasma for the management of patients with T activation (Crookston *et al,* 2000; Eder & Manno, 2001; Ramasethu & Luban, 2001). Any perceived benefit of washing platelets to remove anti-T in plasma must be balanced against the delay in transfusion due to the time needed for the procedure, the loss of platelets during the process and the effect of washing on the haemostatic effect of platelets.

ADMINISTRATION

When platelets are given prophylactically to adults, it is recommended that one adult therapeutic dose is given. This should increase the platelet level by at least 20×10^9/l, providing that the patient is not refractory. When platelets are given therapeutically to treat active bleeding, a larger dose of platelets may be indicated; the dose and frequency of administration depends on the individual circumstances, and it is not possible to give general advice.

The following recommendations are all grade C, level IV:

Inspection of the unit

- Platelet concentrates should be inspected by hospital blood bank staff prior to issue, with particular attention to: the integrity of the pack, checking for leaks at the ports and the seams; and evidence of unusual colour or turbidity which might suggest bacterial contamination.
- It is good practice for the staff administering the unit to check it in a similar way before its administration, and to return it to the hospital blood bank if any abnormalities are found (BCSH, 1999).

Duration of the transfusion

It is recommended that a platelet concentrate is administered over a 30 min period (BCSH, 1992, 1999). In the paediatric setting, this approximates to a rate of 20–30 ml/kg/h.

Calculation of dose

- One platelet concentrate is usually given to most adult patients.
- In small children (< 20 kg), 10–15 ml/kg up to the adult dose of one platelet concentrate is used; in older children, an adult dose of platelets should be used.
- The dose of platelets ($\times 10^9$) can be calculated in more detail, if required, from the desired platelet increment (PI), the patient's blood volume in litres (BV, estimated by multiplying the patient's body surface area by 2·5, or 70 ml/kg in an adult) and a correction factor (F) of 0·67 to allow for pooling of approximately 33% of transfused platelets in the spleen, using the following formula:

$$\text{Dose} = \text{PI} \times \text{BV} \times \text{F}^{-1}$$

For example, if a platelet increment of 40×10^9/l is required for a patient with a blood volume of 5 l, a dose of 300×10^9, i.e. 3×10^{11} is required. Information such as the average number and range of platelets in platelet

concentrates should be available to clinical users and hospital blood banks.

Giving sets/filters

- Platelet concentrates should be transfused through a standard blood or platelet administration set.
- Platelet concentrates should not be transfused through giving sets that have been used for blood (BCSH, 1999).
- A screen filter is required for the giving of platelets via a syringe in the setting of neonatal or fetal transfusion.

Monitoring during the transfusion

- The patient should be informed about possible complications of transfusion, and the importance of reporting any adverse effects.
- Visual observation of the patient is often the best way of assessing patients during transfusion (BCSH, 1999).
- It is recommended that baseline observations (pulse, temperature and blood pressure) should be made prior to commencing the transfusion of platelet concentrates, and that pulse and temperature are measured and recorded 15 min after the start of each transfusion (BCSH, 1999).
- Pulse, temperature and blood pressure should be repeated at the end of the transfusion.

MANAGEMENT OF ADVERSE EFFECTS

Some examples of transfusion reactions and their management are provided in the BCSH guideline on the administration of blood and the management of transfused patients (BCSH, 1999).

Recommendations (all grade C, level IV).

- Hospitals should have policies for the management and reporting of adverse events following transfusion, including reporting to SHOT.
- If a transfusion reaction is suspected, the transfusion should be stopped immediately. A member of the medical staff should be contacted immediately, and the patients' temperature, pulse and blood pressure recorded (BCSH, 1999).
- Further management depends on the type and severity of the reaction.
- Premedication with hydrocortisone and/or chlorpheniramine should not be used routinely before platelet transfusions (BCSH, 1992).

RESPONSE TO PLATELET TRANSFUSIONS

Monitoring of the response

Responses to platelet transfusions should be monitored as they will serve as a guide to further platelet supportive care, although there is no evidence that monitoring and acting on the results of responses to platelet transfusions decreases the incidence of bleeding events (Schiffer *et al,* 2001).

If the platelet transfusion was given because the patient was bleeding, the clinical response is the most important indication of the effectiveness of the transfusion.

Responses to a prophylactic platelet transfusion should be assessed by measuring the increase in the platelet count following the transfusion. Various formulas have been used to correct for the variation in the increment of the platelet count, depending on the patient's size and the number of platelets transfused, including:

1. Platelet recovery

The percentage platelet recovery (R) is calculated from the platelet increment ($\times 10^9$/l) (PI), the blood volume (BV) in litres and the platelet dose transfused ($\times 10^9$) (PD):

$$R\ (\%) = PI \times BV \times PD^{-1} \times 100$$

2. Corrected count increment

The corrected count increment ($\times 10^9$/l) (CCI) is calculated from the corrected count increment (PI), the body surface area of the patient in square metres (BSA) and the dose of platelets transfused ($\times 10^{11}$) (PD):

$$CCI = PI \times BSA \times PD^{-1}$$

A successful transfusion may produce a platelet recovery of about 67% in a stable patient, but the minimum platelet recovery to define a successful transfusion is considered as > 30% at 1 h post transfusion and > 20% at 20–24 h, or a CCI of $> 7{\cdot}5 \times 10^9$/l at 1 h and $> 4{\cdot}5 \times 10^9$/l at 20–24 h.

Although the use of these formulas for calculating responses to platelet transfusions are considered to be essential to provide consistency for platelet transfusion studies, their use is not feasible for routine practice because the platelet content of each platelet concentrate is not provided. In practice, a poor response to a prophylactic platelet transfusion can be defined as failure to raise the platelet count above the 'trigger' platelet count for the transfusion (Schiffer *et al,* 2001). In addition, it is inconvenient to measure 1-h post-transfusion platelet counts in non-bleeding hospitalized patients. It is reasonable to assess responses to platelet transfusions using the platelet count taken on the morning after the platelet transfusion. For outpatients, responses to platelet transfusions can be assessed using a platelet count taken 10 min after the transfusion, which produces identical results to platelet counts taken 1 h after the transfusion (O'Connell *et al*, 1988).

PLATELET REFRACTORINESS

Platelet refractoriness is defined as the repeated failure to obtain satisfactory responses to platelet transfusions. Some patients may have a poor response to one platelet transfusion and good responses to subsequent transfusions, and a diagnosis of platelet refractoriness should only be made after a poor response to two or more platelet transfusions.

Causes of platelet refractoriness

There are many causes of repeated poor responses to platelet transfusions, and they can be subdivided into immune and non-immune. The main immune cause is HLA alloimmunization, which occurs predominantly in women with a history

of pregnancy. Other immune causes include HPA alloimmunization, ABO incompatibility, platelet autoantibodies and drug-related platelet antibodies (Novotny, 1999).

Alloimmune platelet refractoriness is mainly caused by HLA antibodies, but its incidence has declined as a result of leucocyte depletion of blood components, and more aggressive treatment for patients with haematological malignancies and other cancers (Brand, 2001). Platelet refractoriness is now mainly due to shortened platelet survival associated with non-immune clinical factors, such as infection (including its treatment with antibiotics and antifungal drugs), DIC and splenomegaly (Bishop *et al*, 1988; Doughty *et al*, 1994). The incidence of HLA alloimmunization varies with the type of blood components transfused, the patient's underlying condition, and the previous history of pregnancy and transfusion. For example, HLA alloimmunization is more frequent in patients with aplastic anaemia than in patients with acute leukaemia (Holohan *et al*, 1981). The Trial to Reduce Alloimmunization to Platelets Study Group (1997) found that, in patients with acute myeloblastic leukaemia receiving non-leucocyte-depleted blood components, the incidence of HLA alloimmunization was 33% in those who had never been pregnant and 62% in those who had been pregnant; in patients receiving leucocyte-depleted blood components, it was 9% and 32% respectively.

Investigation of refractoriness

If platelet refractoriness occurs, a clinical assessment should be made for clinical factors likely to be associated with non-immune platelet consumption. If there are no obvious clinical factors present, an immune mechanism should be suspected and tests for HLA antibodies carried out (see *Appendix II*).

Broadly reactive and strong HLA antibodies, as detected by the lymphocytotoxicity test (LCT), almost always cause platelet refractoriness, but the LCT is not a sensitive test and will not detect non-cytotoxic HLA antibodies that may cause platelet refractoriness. The monoclonal-antibody-specific immobilization of platelet antigens (MAIPA) assay has been shown to be superior to the LCT (Kiefel *et al,* 2001; Kurz *et al,* 2001), but is very difficult to use for the management of transfusion-dependent patients and a screening test for non-cytotoxic HLA antibodies is preferable (Brand, 2001). A suitable combination of tests for the initial screening for both cytotoxic and non-cytotoxic HLA antibodies in patients with suspected alloimmune platelet refractoriness would be the LCT with either the lymphocyte or platelet immunofluorescence test or an enzyme-linked immunosorbent-assay-based method.

HPA antibodies are rare (0–2%) in the absence of HLA antibodies and do not always cause platelet refractoriness. It is not necessary to test for HPA antibodies during the initial serological investigation of platelet refractoriness.

Management of platelet refractoriness

If HLA antibodies are detected on initial serological screening, HLA-matched platelet transfusions should be used (see *Appendix II*). The use of HLA-matched platelet transfusions can also be justified if there has not been time to carry out serological testing or if the screening has only included the LCT, in particular when the platelet refractoriness is associated with bleeding (Brand, 2001). HLA-matched platelet transfusions are not indicated when full serological testing has failed to detect HLA antibodies. Further consideration should be given to the presence of non-immune clinical factors and, if they still appear to be absent, then testing for HPA antibodies should be undertaken.

Responses to HLA-matched platelet transfusions should be carefully monitored, ideally with post-transfusion platelet counts both 1 h and 20–24 h post transfusion. If there are improved responses, HLA-matched platelet transfusions should continue to be used for further transfusions. If there are poor responses to HLA-matched platelet transfusions, the reasons should be sought, including HLA incompatibility (which is most likely to occur in patients with unusual HLA types with few well-matched donors), non-immune platelet consumption, and HPA and ABO incompatibility. Further serological investigations, including testing for HPA antibodies, may be indicated at this stage to differentiate between these possibilities. Depending on the results of these investigations, the appropriate management could be the use of ABO-identical or HPA-matched platelet concentrates if the specificity of the HPA antibodies can be identified. Platelet crossmatching may be helpful in some patients with non-specific HPA antibodies.

The management of patients with HLA and/or HPA alloimmunization with no compatible donors may be very difficult. There is no evidence that alloimmunized patients benefit from incompatible platelet transfusions that do not produce an increase in the platelet count, and prophylactic platelet support should be discontinued. If bleeding occurs, platelet transfusions from random donors or the best-matched donors, despite being incompatible, may reduce the severity of haemorrhage, although larger doses of platelets may be required. Other management approaches for severe alloimmune refractoriness, such as the use of high-dose intravenous immunoglobulin, splenectomy and plasma exchange, have not been shown to be effective (Schiffer *et al,* 2001).

The management of patients with non-immune platelet consumption is similarly problematic. The usual practice is to continue with daily platelet transfusions as prophylactic platelet support, but it is not known whether this approach is effective, or whether platelet transfusions should be discontinued or the dose of platelets increased.

Recommendations.

- Responses to platelet transfusions should be monitored by assessing the effect on bleeding, if it is present, and by measuring the platelet count after all transfusions (grade C, level IV evidence).
- Platelet refractoriness should only be diagnosed after poor responses to two or more platelet transfusions. It may result from immune or non-immune platelet destruction.
- In patients refractory to platelet transfusion, the identification of those with transfusion failure due to HLA antibodies is important as provision of HLA-matched platelet components may result in improved transfusion responses (grade B, level III evidence).

- The identification of other causes of refractoriness is important as matching for HPA, increasing the transfused dose or discontinuing transfusion may be appropriate (grade C, level IV evidence).
- An algorithm for identifying and managing platelet refractoriness has been developed from a review of the literature and currently accepted practice (see *Appendix II*).

AUDIT

These guidelines are presented as a standard against which platelet transfusion practice can be audited. Audit topics might include the appropriate use of platelet transfusions, including the use of special components such as gamma-irradiated and CMV-seronegative platelets, the management of platelet refractoriness and the documentation of platelet transfusions in clinical records.

DISCLAIMER

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors nor the publishers can accept any legal responsibility or liability for any errors or omissions that may have been made.

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Keywords: guidelines, platelets, transfusion, clinical use.

APPENDIX I

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 randomized controlled trials.
Ib	Evidence obtained from at least one randomized controlled trial.
IIa	Evidence obtained from at least one well-designed controlled study without randomization.
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 randomized 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 randomized 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)

APPENDIX 2

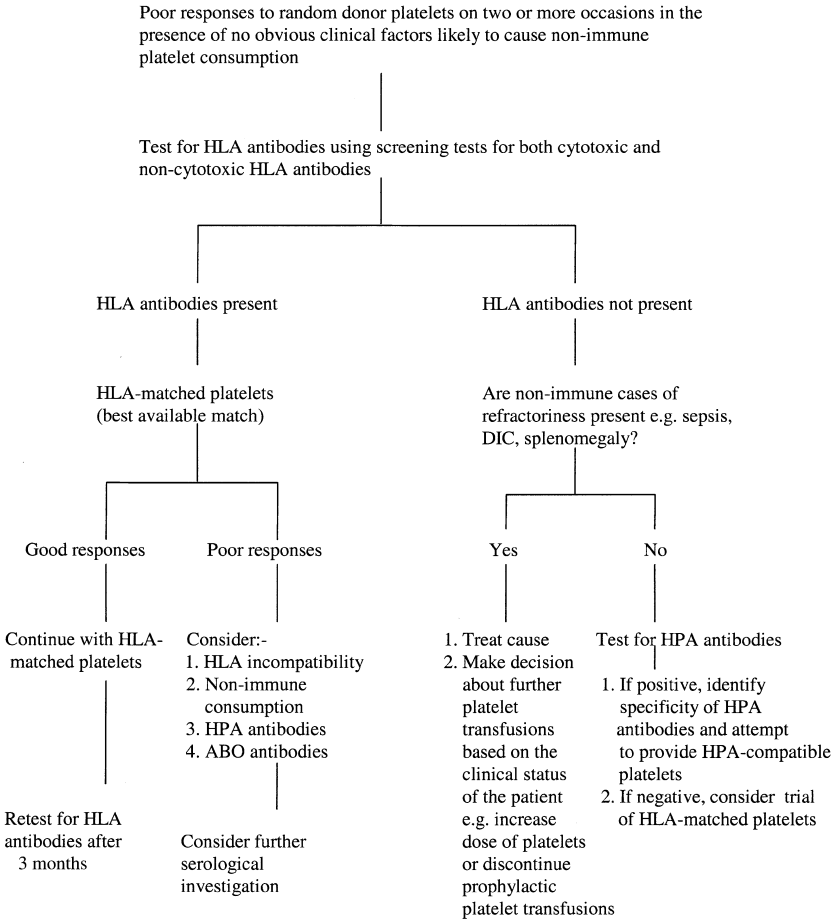

Fig 1. Algorithm for the investigation and management of patients refractory to platelet transfusions. Modified from algorithm developed by Phekoo *et al* (1997).