Safe transfusions in haemopoietic stem cell transplant recipients

SHOT Serious Hazards of Transfusion | The Royal College of Pathologists — Pathology: the science behind the cure | NHS National Blood Transfusion Committee | BSBMTCT British Society of Blood and Marrow Transplantation & Cellular Therapy

The following checklist has been created to reduce errors and optimise safety of transfusions in autologous and allogeneic haemopoietic stem cell transplant (HSCT) recipients and should be used by the transplant centre team as part of every transplant recipient's journey. The blood group changes are only applicable to allogeneic stem cell transplants where ABO and/or D groups are different. This document should be used in conjunction with local policies relating to provision of blood components for HSCT.

Key action point for all HSCT centres: Design a process to incorporate this checklist into your local policy with a procedure describing how to use/ follow it.

The checklist below is based on the emerging themes and weak points identified from the error reports submitted to SHOT and has been approved by the Transfusion Medicine Specialty Advisory Committee of the Royal College of Pathologists, the National Blood Transfusion Committee, the British Society of Blood and Marrow Transplantation & Cellular Therapy, the SHOT Steering Group and the SHOT Working Expert Group. The actions in the checklist below have been grouped according to phases of the patient's transplant journey.

Actions at the transplant centre for every transplant recipient		
Pre-transplant admission		
1	Is a representative from the hospital transfusion team (scientist, clinician, or transfusion practitioner) available to support the transplant planning meetings if advice is needed?	Y/N
2	Does the transplant protocol clearly identify all centres involved in the care of the patient?	Y/N
3	Does the transplant team have the contact details for shared care/referral centre and other teams involved?	Y/N
4	Have samples been taken from both donor and recipient and tested for ABO and D groups, antibody screen, anti-A and anti-B titres by Indirect Antiglobulin Test (IAT) where indicated and direct antiglobulin test (DAT)?	Y/N
5	Has the transplant recipient's baseline CMV status been checked prior to blood transfusions?	Y/N
6	Are all the transfusion specifications (e.g., donor and recipient blood groups in different phases of the transplant and all specific requirements) clearly identified on the transplant protocol?	Y/N
7	Has the copy of the transplant protocol been sent to the transfusion laboratory at transplant centre?	Y/N
8	Has the clinical team received confirmation that the Laboratory Information Management System (LIMS) has been updated to reflect transfusion requirements for the patient?	Y/N
9	Has the transfusion laboratory at the referring hospital been notified about the transplant dates and transfusion requirements with confirmation of receipt?	Y/N
10	Has the patient (and family) been informed/educated about transfusion requirements? Have all relevant Patient Information Leaflets been provided, and discussions documented in patient's clinical notes? *Patients and families/carers need to understand the importance of showing any transfusion cards or transfusion instructions they have received if getting admitted or treated for any reason at a site other than their transplant centre post HSCT.*	Y/N
During transplant admission		
11	Is the transplant protocol with documentation regarding transfusion requirements clearly visible and accessible for nursing staff and clinicians on the wards?	Y/N
12	Is the Safe Transfusion Checklist incorporating administration checklist being applied? Where appropriate is the Transfusion Associated Circulatory Overload (TACO) checklist being used for risk assessment? Monitor patient for any evidence of haemolysis (immediate or delayed) as appropriate.	Y/N
Post-transplant prior to discharge		
13	Are details regarding serious transfusion reactions or events during the transplant admission mentioned in the discharge summary? A copy of the transplant protocol should be attached to the transplant discharge summary. Where feasible, details about the number of transfusions received should be included.	Y/N
Post-transplant follow-up		
14	Does the patient continue to need irradiated blood components and for how long? *This needs to be reviewed by the transplant team periodically based on conditioning regimen, type of transplant, engraftment & immune reconstitution and use of immune suppressants. Any changes must be communicated to the referring hospital team.*	Y/N
15	Have the transfusion laboratories both at transplant centre and referring hospital been notified of any changes to transfusion specific requirements?	Y/N
If the answer is 'no' to any of these, then appropriate actions need to be taken locally to ensure safe transfusions		

Safe transfusions in haemopoietic stem cell transplant recipients

The supporting information below is a summary of recommended transfusion practices in the transplant setting. Links to relevant guidelines and resources are provided. Please note that this does not cover the processing of stem cell products in ABO incompatibility. This information should be used in conjunction with local policies.

Transfusion support for patients undergoing ABO- or D-mismatched allogeneic haemopoietic stem cell transplant (HSCT)

ABO incompatibility: Around 25-50% of the HLA matched allogeneic transplants are ABO incompatible. ABO matching is not required for a successful HSCT.

Major ABO incompatibility occurs with the presence of anti-A, anti-B or anti-A, B antibodies in the recipient's plasma incompatible with donor red cells, e.g., donor group A, B or AB to group O recipient. In such cases, acute haemolysis at time of stem cell infusion or delayed haemolysis due to production of antibodies by residual host lymphocytes may occur. Red cell aplasia has also been described. The risk for any of these complications depends on the volume of red cells infused and the titre of antibody present.

Minor ABO incompatibility occurs when anti-A, anti-B or anti–A, B antibodies are present in the donor's plasma reactive with the recipient's red cells e.g. donor group O and recipient group A, B or AB. Acute haemolysis at time of marrow infusion caused by anti-A or anti-B in the plasma of the donor product, or a delayed haemolysis of recipient cells due to passenger lymphocyte syndrome can occur.

Major plus minor ("bidirectional") ABO incompatibility is present when both the donor and recipient's plasma have anti-A, anti-B or anti-A, B antibodies reactive with recipient and donor cells respectively e.g., donor group A and recipient group B or vice versa. The risks are as for major and minor mismatches.

Over weeks to months, the recipient develops donor haemopoiesis and immune function, but this depends on several factors.

Table 1: Compatible, major, minor, and bidirectional (both) incompatible HSCT

	Haemopoietic stem cell donor				
Haemopoietic stem cell recipient	**Blood group**	**O**	**A**	**B**	**AB**
	O	Compatible	Major	Major	Major
	A	Minor	Compatible	Bidirectional	Major
	B	Minor	Bidirectional	Compatible	Major
	AB	Minor	Minor	Minor	Compatible

Choice of ABO blood groups for transfusion support:

Pre-transplant (Phase I – period from diagnosis to transplant): Recipient-group red cells and platelets should be given.

Post-transplant immediate phase (Phase II- period from transplant to RBC engraftment): The guidance below applies to the immediate post-transplant period until **all** the following criteria are fulfilled:

1. ABO antibodies to the donor ABO group are undetectable in the 'standard' reverse group and by indirect antiglobulin test using A1 and/or B cells (major ABO incompatibility only).
2. The direct antiglobulin test (DAT) is negative.
3. Conversion to donor group is complete, with no mixed field seen using the patient's cells in standard serological tests with anti-A or anti-B (in practice this can only be demonstrated if there have been no red cell transfusions in the last 3 months).

Major ABO incompatibility:

- For red cells: red cells of recipient's ABO group or group O should be given
- For platelets and fresh frozen plasma (FFP): give platelets and plasma of donor ABO group. Where donor is group AB use group A high-titre negative platelets when the recipient is group A, and group B high-titre negative platelets when the recipient is group B (see Table 2 below)

Minor ABO incompatibility:

- For red cells: red cells of donor ABO group should be given
- For platelets and FFP: give platelets and plasma of recipient ABO group. Where recipient is group AB, group A high titre-negative platelets may be used when the donor is group A, and group B platelets when the donor is group B (see Table 2 below)

Major plus minor ("bidirectional") ABO incompatibility:

- For red cells: red cells of group O should be given
- For platelets and FFP: give group AB plasma and recipient group platelets

Post-transplant after engraftment (Phase III, when all the above criteria are met):
Post engraftment, when ABO antibodies to the donor ABO type are undetectable and the DAT is negative, the donor group may be selected. However, it should be noted that it is increasingly common for multiple cord donations to be used and that each donor cord may be of a different ABO and/or D group. Post-engraftment transfusion management should be decided on a case-by-case basis and will depend on which cord engrafts, in accordance with British Society for Haematology (BSH) guidelines relating to pre-transfusion compatibility procedures in blood transfusion laboratories (Link: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1365-3148.2012.01199.x) .

In case of graft rejection, the selected red cells should remain compatible with both the patient and donor until complete reversion to the original recipient ABO and D type. Then provision of all components must revert to recipient-type red cells and platelets.

Table 2: Selecting appropriate blood groups for recipients of ABO mismatched stem cell transplants

	Donor	Recipient	Phase I: All components	Phase II and Phase III				
				Red cells	Platelets		FFP	
					First choice	Second choices**	First choice	Second choices
Major ABO incompatibility	A	O	Recipient	O	A	AB*, B, O	A	AB
	B	O	Recipient	O	B	AB*, A, O	B	AB
	AB	O	Recipient	O	AB*	A, B, O	AB	-
	AB	A	Recipient	A, O	AB*	A, B, O	AB	-
	AB	B	Recipient	B, O	AB*	B, A, O	AB	-
Minor ABO incompatibility	O	A	Recipient	O	A	AB*, B, O	A	AB
	O	B	Recipient	O	B	AB*, A, O	B	AB
	O	AB	Recipient	O	A	A, B, O	AB	-
	A	AB	Recipient	A, O	A	A, B, O	AB	-
	B	AB	Recipient	B, O	B	B, A, O	AB	-
Bi-directional ABO incompatibility	A	B	Recipient	O	B	B, A, O	AB	-
	B	A	Recipient	O	A	A, B, O	AB	-

*Due to the population distribution of group AB and its value as a universal plasma donor, stocks may be limited
**Choices are listed in the order of preference and high titre negative platelets should be selected where available to reduce the risk of haemolysis
The various phases (I,II and II) are explained in the text preceding this table

This table is based on the guidance in the ESH-EBMT handbook (https://www.ebmt.org/sites/default/files/2019-01/2019_Book_TheEBMTHandbook.pdf).

D matching: Incompatibility between donor and recipient for the D red cell antigen occurs commonly in the setting of allogeneic HSCT.

- Major Rh incompatibility exists where a donor is D-positive and a recipient D-negative. Minor Rh incompatibility occurs where a donor is D-negative, and the recipient is D-positive
- In cases of minor Rh incompatibility delayed haemolysis can occur due to donor lymphocyte-derived anti-D. The risk is higher if the donor has been previously sensitised to the D antigen and in recipients of non-D-selected peripheral blood stem cells
- Pre-transplant: recipient-type red cells and platelets should be given
- Post-transplant:
    - HSCT recipients should receive D-negative red cells and platelets except when both the HSC donor and recipient are D-positive
    - Major RhD incompatibility: D-negative blood components to be given until D-positive red cells are detected. Thereafter can receive D-positive components
    - Minor RhD incompatibility: D-negative blood components should be given indefinitely
- Please note that BSH guidelines (https://onlinelibrary.wiley.com/doi/full/10.1111/j.1365-3148.2012.01199.x) state that when either the recipient or donor is D-negative, D-negative red cells should be selected. Refer to local policies when making these decisions and consult local transfusion experts

Safe transfusions in haemopoietic stem cell transplant recipients

Other antigens:

- If a transplant recipient has other clinically significant red cell alloantibodies detectable at the time of transplantation, the donor should be phenotyped for the relevant blood group antigen and the donor marrow should be red cell depleted where indicated. If advice is required, discuss with a transplant or red cell immunohaematology consultant
- Immune haemolysis following HSCT caused by alloantibodies directed against the Kidd, MNSs and Kell antigen systems have all been described and the haemolysis can be severe if several alloantibodies are simultaneously involved

Irradiation requirements (from the 2020 BSH guidelines on the use of irradiated blood components): https://doi.org/10.1111/bjh.17015)

Allogeneic HSCT:

- All recipients (adult and paediatric) of allogeneic HSCT should receive irradiated blood components from the time of initiation of conditioning chemo/radiotherapy. The recommendation applies for all conditions where HSCT is indicated regardless of the underlying diagnosis
- Irradiated components should be continued until **all** the following criteria are met:
  1. >6 months have elapsed since the transplant date
  2. The lymphocyte count is >1·0 × 10^9/L
  3. The patient is free of active chronic Graft versus Host Disease (GvHD)
  4. The patient is off all immunosuppression
- If chronic GvHD is present or continued immunosuppressive treatment is required, irradiated blood components should be given indefinitely
- Treatment with irradiated blood components should continue indefinitely if this is required based on transplant conditioning, underlying disease or previous treatment, e.g. previous diagnosis of Hodgkin's lymphoma or previous purine analogue treatment
- Allogeneic cellular blood components transfused to bone marrow and peripheral blood stem cell donors of all ages within 7 days prior to or during the harvest should also be irradiated

Autologous stem cell transplantation (ASCT):

- Patients (adult and paediatric) undergoing bone marrow or peripheral blood stem cell collections for future autologous re-infusion should receive irradiated cellular blood components for 7 days prior to and during the bone marrow/stem cell harvest to prevent the collection of viable allogeneic T lymphocytes, which can potentially withstand cryopreservation
- All patients undergoing ASCT irrespective of underlying diagnosis or indication for this treatment should receive irradiated cellular blood components from initiation of conditioning chemo/radiotherapy until 3 months post-transplant (6 months if total body irradiation was used in conditioning) unless conditioning, disease or previous treatment determine indefinite duration, for e.g. previous diagnosis of Hodgkin's lymphoma or previous purine analogue treatment

Cytomegalovirus (CMV) requirements for blood components in HSCT recipients (from SaBTO guidance)
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/215125/dh_133086.pdf

- All patients in whom HSCT is considered as a potential treatment option must have baseline CMV testing performed as blood transfusions can result in false positive tests due to passive transfer of antibodies
- CMV-negative components are not required irrespective of serological status of donor and recipient for HSCT except for granulocytes. Leucodepleted blood components suffice for adults and children post haemopoietic stem cell transplantation for all patient groups including CMV-seronegative donor/seronegative recipients- this however does not apply for granulocytes as they cannot be leucodepleted. ***Local practices may differ so please refer to local policies and transplant teams should liaise with the Transfusion Consultants in making this decision. This again should be clearly documented on the transplant protocol***
  - Except granulocytes, all blood components issued in the UK are leucodepleted. The UK specification for leucodepletion is that more than 90% of leucocyte-depleted components from relevant processes should have less than 1 × 10^6 leucocytes and more than 99% of components should contain less than 5 × 10^6 leucocytes, both with 95% confidence https://www.transfusionguidelines.org/red-book/chapter-7-specifications-for-blood-components/7-1-leucocyte-depletion
  - Granulocytes for CMV-negative HSCT recipients should be CMV-negative (granulocytes cannot be leucodepleted). Any decision to transfuse CMV-positive or unscreened granulocytes will have to be made after consultation with a senior transplant physician if the urgency to treat the underlying condition outweighs the risks of potentially developing CMV infection
- Patients requiring transfusions who may require a transplant in the future may also safely be transfused with leucodepleted products (e.g., seronegative leukaemia or thalassaemia patients)
- CMV PCR monitoring should be considered for all patients (even CMV negative/negative patients) to allow early detection of any possible CMV infection (whether transfusion transmitted or otherwise acquired)