Purpose

To ensure that NHSBT provides consistent advice to transplant units and hospital blood banks regarding selection of the ABO/Rh group of blood components for recipients of ABO/Rh mismatched allogeneic stem cell transplants.

Definitions

PBSC – Peripheral blood stem cell
Allo-HSCT – Allogeneic haematopoietic stem cell transplant
Major incompatibility – The recipient plasma contains antibodies against an antigen on the donor's cells
Minor incompatibility – The donor plasma contains antibodies against an antigen on the recipient's cells
Major mismatch – The recipient can form antibodies against an antigen on the donor's cells
Minor mismatch – The donor can form antibodies against an antigen on the recipient's cells
Bi-directional incompatibility – The donor and recipient plasma both contain antibodies against an antigen on the recipient's and donor's cells respectively (i.e. both major and minor incompatibility)
GvHD – Graft versus Host Disease
EBMT - European Society for Blood and Marrow Transplantation

Changes in this version

Section 3 (Pre-transplant investigations):
- Full Rh and K type should be completed pre-transplant
- Donor phenotyping should be completed where the recipient has an antibody of clinical significance

Section 4: Definition of transplant phases
- Reverse grouping may not fully convert to donor type in minor/bi-directional ABO incompatible transplant
- Added serological definition of graft failure/rejection

Section 5: Blood component selection
- Clarified component selection in graft rejection/failure and when to switch from pre-engraftment selection to recipient type selection

Section 6 (ABO selection):
- Clarified statement on alternatives where AB platelets would be required

Section 7 (RhD):
- Used the term mismatch instead of incompatibility to reference the fact that most D-negative recipients/donors will not have anti-D
- Clarified the criteria for considering D-positive components in major RhD mismatch (now more restrictive)

Section 8 (RhCE):
- New section

Table 2:
- Switched recipient and donor columns to match EBMT format – the table remains in the same order and the advice unchanged

Applicable Documents

SPN 251 – SCI policy for processing of stem cell products in ABO/Rh mismatched allogeneic stem cell transplants
SPN 214 – The clinical significance of blood group alloantibodies and the supply of blood for transfusions
INF 178 – High titre anti-A/B testing of donors within NHS Blood and Transplant (NHSBT)

1. BACKGROUND

Approximately 40-50% of allo-HSCTs are ABO-mismatched(1). While stem cell transplantation across the ABO barrier is possible, a collection of immuno-haematological problems can occur such as immediate and delayed haemolysis, pure red cell aplasia (PRCA), and delayed transfusion independence(2). The prevalence of these conditions depends on numerous factors, including the type of mismatch (major/minor/bi-directional), the stem cell source (PBSC, bone marrow, cord), the relationship between recipient and donor (matched-related, haplo-identical, matched-unrelated), antibody titre, graft manipulation techniques (T-cell-, red cell-, plasma-depletion) and recipient preparation (conditioning regimen, use of immunoadsorption)(2–4).

The impact of ABO-incompatibility on transplant outcomes remains an area of active investigation. A recent large retrospective study by the EBMT's transplant complications working party, analysing data from 30,487 patients, has provided some clarity. Although ABO mismatch was previously thought to slightly reduce overall survival – possibly due to rare cases of fatal immune-mediated haemolysis – the EBMT data showed no significant association between ABO-compatibility and overall survival, non-relapse mortality, progression free survival, or relapse incidence(5).

Prior studies investigating the effect of ABO-incompatibility on graft failure rates were either inconclusive, complicated by confounding HLA-mismatches, or found significance on univariate but not multivariate analysis(6). In contrast, the EBMT analysis found a modest but statistically significant increase in non-engraftment rates in major and bi-directional mismatches (HR 1.04, p=0.021; HR 1.09, p=0.003)(5).

Most literature agrees that ABO incompatibility does not affect chronic GvHD incidence or severity. While some earlier reports suggested a higher risk of acute GvHD with minor or bi-directional mismatches(6), this is not supported by the EBMT findings. Interestingly, the EBMT study found a lower rate of severe acute GvHD in major mismatches, though the reason remains unclear. Proposed explanations include the use of increased immunosuppressive strategies in these cases, or a possible modulatory effect of recipient anti-A/B antibodies on donor lymphocytes(5).

Overall, while major ABO mismatch modestly impacts non-engraftment rates, the EBMT study described outcome differences as subtle. As such, EBMT have recommended that ABO-compatibility should not be a key determinant in donor selection.

This policy provides guidance on the appropriate investigations before and after transplant, potential complications and the selection of appropriate blood components. This policy does not cover the processing of stem cell products, nor recipient preparation techniques in ABO incompatibility; this is detailed in a separate SCI policy in SPN251.

2. Risks of Major/Minor/Bi-directional ABO incompatible transplants

2.1 Major ABO incompatibility

2.1.1 *Definition:* Major incompatibility exists when a novel blood group antigen from a donor is transfused into a recipient with the corresponding blood group antibodies. This is most frequently seen when a group O recipient receives a transplant from a non-O donor, but also occurs when group A or B recipients receive transplants from an AB donor.

2.1.2 *Risks:* The main complications of major ABO incompatible transplantation are immediate haemolysis at the time of graft infusion, delayed red cell engraftment, and pure red cell aplasia(2,7–9). The risk of immediate haemolysis is dependent on the number of red cells in the graft and the strength of the recipient's antibodies(1) (both of which can be manipulated) and is covered in more detail in SPN251. Major ABO-incompatible transplants are associated with an average of 10 days delay in RBC transfusion independence over ABO-compatible transplants, with this effect being further compounded through reduced intensity conditioning, with the combination of major-ABO mismatch and non-myeloablative conditioning delaying RBC transfusion independence for up to 1-2 months(10). In pure red cell aplasia, graft-directed isohaemagglutinins from persistent recipient plasma cells disrupt normal early erythroid maturation, due to interactions with the ABO antigens on early colony forming erythroid progenitors(2,3,7).

2.2 Minor ABO incompatibility

2.2.1 *Definition:* Minor incompatibility exists when the donor's plasma contains antibodies (anti-A, anti-B, or anti-A,B) to the A or B antigens expressed on the recipient red cells. This is most frequently seen when a non-O recipient receives a transplant from an O donor, but also occurs when group AB recipients receive transplants from an A or B donor.

2.2.2 *Risks:* The two most significant complications of minor ABO incompatible transplantation are both related to haemolysis. Immediate haemolysis can occur at the time of infusion due to pre-formed antibodies in the donor graft plasma, while delayed haemolysis – typically starting between days 5 and 15 – can result from graft-derived lymphocytes producing the same antibodies post-transplant; the phenomenon known as passenger lymphocyte syndrome(2,7).

2.3 Bi-directional ABO incompatibility

2.3.1 In bi-directional ABO incompatibility both a major and minor incompatibility exist, and the patient is at risk of complications related to both types of incompatibility.

3. INVESTIGATIONS

Pre-transplant: Samples from both donor and recipient for:
ABO, Rh, K typing and antibody screen
Anti-A and anti-B titres by IAT – when clinically indicated (see SPN251)
Direct antiglobulin test (DAT)
Extended donor red cell phenotyping – where the recipient antibody screen is positive for a clinically significant antibody (see SPN214)

Post-transplant: Monitor for haemolysis – immediate and delayed as appropriate

4. Definitions of Transplant Phases

4.1 Pre-transplant (Phase I)
Prior to the start of the induction regimen.

4.2 Pre-engraftment (Phase II)
From the start of induction regimen until 'complete engraftment'. Complete engraftment is defined by meeting the three criteria below:

1. Complete conversion of forward group to the donor group – i.e. no mixed field reaction using standard serological tests (in practice this may only be demonstrable if there have been no red cell transfusions in the last 3 months).
2. The direct antiglobulin test is negative using polyspecific AHG.
3. Antibodies to the donor ABO group are undetectable using standard reverse grouping techniques.

It should be noted that in minor and bi-directional ABO incompatibility, the reverse group may not fully convert to the anticipated donor group, due to the presence of A and B antigens on recipient non-haematological tissues causing immune tolerance(11); this does not preclude classification as complete engraftment, as long as the above criteria are met.

4.3 Post-engraftment (Phase III)
When the criteria for 'complete engraftment' have been met (see 4.2).

4.4 Graft failure (Phase IV)
Loss of the criteria for complete engraftment after previously meeting the criteria
OR
Graft failure as defined by transplant clinician.

5. Blood Component Selection

5.1 Pre-transplant (Phase I)
Use components compatible with the recipient typing.

5.2 Pre-engraftment (Phase II)
Discussed in section 6-9 below.

5.3 Post-engraftment (Phase III)
Use components compatible with the donor typing.

5.4 Graft failure/rejection (Phase IV)
Graft failure should be confirmed with the transplant consultant in charge of the patient's care.
Use pre-engraftment (Phase II) rules (see section 6), until donor cells no longer detectable.
Once donor cells no longer detectable on forward group, revert to recipient matched components.

6. Pre-Engraftment (Phase II) ABO Selection (All blood components)

6.1 Major ABO Incompatibility

RBCs/Granulocytes – Recipient ABO group or group O

Platelets/FFP/Cryoprecipitate – Donor group

- Provision of AB platelets may deplete stocks. Where the donor is AB, the below substitutions should be used:
  - Group A HT negative for A recipients
  - Group B HT negative for B recipients
  - Group A or B, HT negative for O recipients

6.2 Minor ABO Incompatibility

RBCs/Granulocytes – Donor ABO group or group O

Platelets/FFP/Cryoprecipitate – Recipient group

- Provision of AB platelets may deplete stocks. Where the recipient is AB, the below substitutions should be used:
  - Group A HT negative for A donors
  - Group B HT negative for B donors
  - Group A or B, HT negative for O donors

6.3 Bidirectional ABO Incompatibility

RBCs/Granulocytes – Group O

FFP/Cryoprecipitate – Group AB

Platelets – Recipient group

7. Pre-Engraftment (Phase II) RhD Selection (RBCs/Granulocytes/Platelets)

7.1 Major RhD Mismatch – Recipient RhD negative, Donor RhD positive

- RhD negative **until complete engraftment**
- RhD positive components can be considered during phase II (pre-engraftment) if:
  - Recipient does not have anti-D **and**
  - Donor RhD positive cells detectable **and**
  - Supply of RhD negative components is challenging

7.2 Minor RhD Mismatch – Recipient RhD positive, Donor RhD negative

- RhD negative **indefinitely**

8. Pre-Engraftment (Phase II) RhCE Selection (RBCs)

8.1 Donor **and** Recipient RhD positive

- Components compatible with **recipient RhCE** type should be selected

8.2 Donor **or** Recipient RhD negative

- Select **rr** RBCs
  - The use of rr blood is required to protect rare blood supplies (e.g. r'r')
  - In the presence of anti-c or anti-e, blood provision should be discussed with an NHSBT consultant

The EBMT advises choosing blood compatible with both the recipient and donor Rh typing, with a preference for matching the recipient's typing if compatibility with both is not possible. However, given the added complexity, the potential use of rare blood types, and the fact that donor RhCcEe types are often not available, NHSBT has not recommended this approach at present (appendix 1).

9. Other Blood Group Systems (RBCs)

If the recipient and/or donor is K-, then K- blood should be selected using the principles outlined in section 7.

If a transplant recipient has other clinically significant red cell alloantibodies (SPN214) detectable at the time of transplantation, the donor should be phenotyped/genotyped for the relevant blood group antigen and graft/donor techniques (SPN251) should be discussed with a transplant or red cell immunohaematology consultant.

Table 1: Component selection during pre-engraftment (Phase II)

			RBC/Granulocytes	Platelets	FFP/Cryoprecipitate	
ABO incompatibility classification	Recipient	Donor	Choice	1st choice	1st choice	2nd choice
Major	O	A	O	A	A	AB
	O	B	O	B	B	AB
	O	AB	O	A or B†	AB	-
	A	AB	A/O	A†	AB	-
	B	AB	B/O	B†	AB	-
Minor	A	O	O	A	A	AB
	B	O	O	B	B	AB
	AB	O	O	A or B†	AB	-
	AB	A	A/O	A†	AB	-
	AB	B	B/O	B†	AB	-
Bi-directional	A	B	O	A†	AB	-
	B	A	O	B†	AB	-

†AB platelets are serologically ideal in these combinations; however, their limited availability restricts their feasibility as first choice.

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Appendix 1:

Table 2: Ideal RhCE selection for common D+ donor/recipient pairs

Donor / **Recipient**	R_1r or R_1R_0 or R_0r' D, C, c, e	R_1R_1 or R_1r' D, C, e	R_1R_2, R_1r'', R_2r', R_zr, R_0R_z, R_0r^y D, C, c, E, e	R_2r, R_2R_0, or R_0r'' D, c, E, e	R_2R_2 or R2r'' D, c, E	R_0R_0 or R_0r D, c, e
R_1r, R_1R_0, or R_0r' D, C, c, e	E-	c-, E-	E-	C-, E-	**C-, E-**	C-, E-
R_1R_1 or R_1r' D, C, e	c-, E-	c-, E-	c-, E-	**c-, E-**	**c-, E-**	**c-, E-**
R_1R_2, R_1r'', R_2r', R_zr, R_0R_z, R_0r^y D, C, c, E, e	E-	c-, E-	-	C-	C-, e-	C-, E-
R_2r, R_2R_0, or R_0r'' D, c, E, e	C-, E-	**C-, E-**	C-	C-	C-, e-	C-, E-
R_2R_2 or R2r'' D, c, E	**C-, e-**	**C-, e-**	C-, e-	C-, e-	C-, e-	**C-, e-**
R_0R_0 or R_0r D, c, e	C-, E-	**C-, E-**	C-, E-	C-, E-	**C-, E-**	C-, E-

Underlined specifications indicate recipient-determined requirements and take precedence over non-underlined donor-determined requirements

Bold text indicates donor/recipient pairs where RhCcEe requirements conflict – recipient requirements have been prioritised