Provision of Red Cell Transfusion Support for Transfusion Dependent Patients

1.0 Definition

Transfusion dependent patients are those who require frequent and long-term transfusion support to sustain life. Such patients may have been diagnosed with one of the following conditions:

- thalassemia syndromes
- severe aplastic anaemia (SAA)
- sickle cell disease (SCD)
- myelodysplastic syndromes (MDS)
- other congenital or acquired chronic anaemias

2.0 General

In addition to the potential complications of red blood cell (RBC) transfusions common to all recipients, there are special problems that are unique in transfusion dependent patients who are on chronic transfusion support.

In this document, policies for red cell transfusion support and the principles on which they are based are discussed. The purpose of this document is to establish uniform policies for the benefit of medical and scientific staff who may be involved in giving advice on serological problems and on the optimal use of red cells. Clinical management of complications such as iron overload, hyperhaemolysis in SCD etc are not dealt with herein, nor does the document include the selection of blood for patients who may require frequent transfusions for a limited period but are not expected to require lifelong red cell replacement. Hence this policy does not apply to those unlikely to require lifelong transfusions, e.g. leukaemia patients undergoing chemotherapy.

The aim of good transfusion practice in transfusion dependent patients is to:

- minimise the risk of alloimmunization to RBC antigens
- ensure maximum survival of transfused red cells
- ensure the presence of optimal number of RBCs per unit transfused

3.0 Special problems

3.1 Alloimmunization to red cell antigens.

Due to the diversity of RBC antigens among different individuals, multi-transfused patients are likely to be exposed to many allogeneic RBC antigens. Exposure to foreign RBC antigens is more likely when there are differences in ethnicity between the blood donor population and the recipients[1], such as in SCD patients receiving blood from Caucasian donors.

Up to about 30% of transfusion dependent haemoglobinopathy patients are reported to develop RBC antibodies,[1-3] most of which are within the Rh and Kell systems.[4,5] There is a significant reduction in alloimmunisation rate (dropped from 3% to 0.5% per unit) by providing blood matched for Rh (CcDEe) and K antigens.[6] These antigen matching protocols have been associated with reduced alloimmunisation rate and decreased incidence of haemolytic transfusion reactions in patients with SCD.[7] Similar recommendation (providing Rh and K matched units) was made in patients with Thalassemia.[8]

Since 1997, blood banks in the UK have adopted the policy of providing blood matched for Rh (CcDEe) and K antigens, in addition to ABO matching for patients with sickle cell disease and thalassemia.

3.2 Difficulty in assigning antibody specificity

Some patients, especially those with multiple RBC alloantibodies, show reactions in serological tests for which antibody specificity cannot be assigned. Selecting suitable blood for these patients is extremely difficult. In such situations, the only option is to select units that match the patient's phenotype / genotype, as clinically relevant. This is possible only if the full phenotype of the patient has been determined before initiating the transfusion programme. Serological typing is simple, quick and could be undertaken by NHSBT Red Cell Immunohaematology (RCI) laboratories. If however, the patient has already been transfused, has a positive autologous control, Direct Antiglobulin Test (DAT) or is on a therapeutic monoclonal antibody (TMAb), genotyping for blood group antigens is available from most RCI laboratories.

3.3 Donations from individuals with sickle cell trait (HbAS genotype)

The main goals of transfusion in SCD patients are to reduce the HbS level and/or to elevate the Hb. The former would not be achieved effectively if the unit transfused was from an HbAS donor. Therefore, only RBC units that are screened and found to be negative for HbS should be used for transfusion to SCD patients.

Provision of Red Cell Transfusion Support for Transfusion Dependent Patients

4.0 Recommendations

4.1 Extended RBC phenotyping / genotyping

Perform extended RBC phenotyping serologically prior to initiating the transfusion regime. Patients should be tested for the following RBC antigens: C, c, D, E, e, M, N, S, s, K, k, Fy^a, Fy^b, Jk^a and Jk^b.

Patients who are S-, s- should have their U antigen status determined.

For haemoglobinopathy patients, if extended genotyping is required then samples should be referred to the International Blood Group Reference Laboratory (IBGRL) in Filton, for molecular typing for the following blood group antigens:
RhD, C, c, E, e, (including common RhD, C and e variants), V, VS, hr^B , hr^S , K/k, Kp^a /Kp^b, Js^a /Js^b, Do^a /Do^b, Fy^a /Fy^b, Jk^a /Jk^b, M/N, S/s, U-, U_{var}

In all other transfusion dependent patient groups, if the patient has a positive autologous control, DAT, has been recently transfused, is on a therapeutic monoclonal antibody (TMAb) such as an anti-CD38 or anti-CD47 treatment regimen and phenotyping is not possible, please send a 6ml EDTA blood sample to the local NHSBT RCI laboratory for molecular typing.

4.2 RBC antigen matching

Select ABO and K compatible red cell units that are also matched for D, C, E, c, e, for example when the patient is:

R_o – select preferably R_o. rr only if Ro unavailable
R_1r – select E neg
R_1R_1 – select R_1R_1
R_2R_2 – select R_2R_2
R_2r – select C neg

If clinically significant RBC antibodies are present, select antigen negative units and issue blood compatible in the crossmatch by IAT according to national guidelines.[9]

NB In addition to selecting Rh/K matched units, matching for Fy(a-b-) or U- is not required unless Duffy antibodies or anti-U are present. Nevertheless, some centres have “extended matching” protocols aiming to match Duffy, Kidd, MNS and Lewis antigens for SCD patients whenever possible.[10]

Provision of Red Cell Transfusion Support for Transfusion Dependent Patients

4.3 Selection of RBC units.

For patients with SCD, all units selected must be negative for HbS. Units tested for HbS and found negative are marked '**HbS Neg**' on the pack label. If the only suitable donations are not tested previously, the NHSBT Donation Testing laboratory should undertake HbS testing and, if necessary, will release the index units under concession.

4.4 Age of RBC units.

4.4.1 For all patients with haemoglobinopathies

Ideally, red cell units selected for transfusion dependent patients who require frequent transfusions should be less than 2 weeks old to ensure maximum possible survival in the patient's circulation. On some occasions, this may not be possible. In such situations, freshest available suitable units may be transfused.

4.4.2 For patients with SCD

Where possible, red cell survival post-transfusion should be maximised by selection of 'fresh' red cells. Red cells should be ideally less than 10 days for top-up transfusions and less than 7-days old for exchange transfusion,[11, 13] but this may not be possible where the patient has multiple red cell alloantibodies. In such situations freshest available suitable units may be transfused.

5.0 Paroxysmal nocturnal haemoglobinuria:

These patients have an increased sensitivity to complement mediated lysis. In the past washed cells were provided but there is evidence that leucodepleted red cells in SAG-M are suitable and have been shown not to increase haemolysis.[12]. Therefore, washed cells are not required.

Provision of Red Cell Transfusion Support for Transfusion Dependent Patients

References

1. Yazdanbakhsh K, Ware R, Noizat-Pirenne F. Red blood cell alloimmunization in sickle cell disease: pathophysiology, risk factors, and transfusion management. *Blood* 2012, **120**: 528-537.

2. Rosse WF, Gallagher D, Kinney TR, Castro O, Dosik H, Moohr J, Wang W, Levy PS. Transfusion and alloimmunization in sickle cell disease. The Cooperative Study of Sickle Cell Disease. *Blood*, 1990 Oct 1; **76**(7): 1431-1437.

3. Vichinsky E, Neumayr L., Trimble S, Giardina PJ, et al. Transfusion complications in thalassemia patients: a report from the Centers for Disease Control and Prevention. *Transfusion* 2014, **54**: 972-981.

4. Mijovic A, Perera G J, Thein S L. Red blood cell alloimmunization in sickle cell disease – prevalence and trends: A single centre cross-sectional study from United Kingdom. *Transfusion* 2013, **53**: 3279-80.

5. Redman M, Regan F, Contreras M. A prospective study of the incidence of red cell alloimmunisation following transfusion. *Vox Sang* 1996; **71**(4): 216-220.

6. Vichinsky EP, Luban NLC, Wright E, Olivieri N, et al. Prospective RBC phenotype matching in a stroke-prevention trial in sickle cell anemia: a multicenter transfusion trial. *Transfusion* 2001; **41**:1086-1092.

7. Treml A, King K E. Red Blood cell alloimmunization: lessons from sickle cell disease. *Transfusion* 2013; **53**: 692-695.

8. Spanos T, Karageorga M, Ladis V, Peristeri J, et al. Red cell alloantibodies in patients with thalassemia. *Vox Sang* 1990; **58**(1): 50-55.

9. Milkins, C. and Berryman, J., 2013. British Committee for Standards in Haematology: guidelines for pre-transfusion compatibility procedures in blood transfusion laboratories. *Transfus Med*, **23**, pp.3-35.

10. La Salle-Williams M, Nuss R, Le T et al. Extended red blood cell antigen matching for transfusions in sickle cell disease: a review of 14-year experience from a single centre. *Transfusion* 2011; **51**: 1732-1739.

11. United Kingdom Blood Services Handbook of Transfusion Medicine 5th edition. Editor: D Norfolk. TSO 2013.

12. Sherman SP, Taswell HF. The need for transfusion of saline-washed red blood cells to patients with paroxysmal nocturnal hemoglobinuria: a myth (abstract). *Transfusion* 1977; **17**: 683.

13. Davis, B.A., Allard, S., Qureshi, A., Porter, J.B., Pancham, S., Win, N., Cho, G., Ryan, K. and British Committee for Standards in Haematology, 2017. Guidelines on red cell transfusion in sickle cell disease. Part I: principles and laboratory aspects. *British journal of haematology*, **176**(2), p.179.