Guidelines for red cell transfusion in urgent situations and when serological compatibility cannot be assured

1. Aim

This document aims to provide guidance on the selection of the most appropriate red cells when the urgency of the need for transfusion dictates that serologically compatible blood will not be available. A cut off for "females of childbearing potential" has been set at fifty years of age rather than 60 years as the potential for an alloimmunised pregnancy after 50 years of age is low and there are screening programs and management strategies in place for this scenario. Senior medical and scientific expertise should be sought as soon as possible and clinical judgement exercised with respect to individual cases.

2. Background

If, when performing compatibility testing, antibodies are found in the recipient against donor red cells, transfusion of the "incompatible" red cells can have a variety of outcomes. Donor red cells that are incompatible with the recipient for ABO blood group antigens are likely to be rapidly destroyed as a result of IgM (and some IgG) antibodies that bind complement and cause intravascular haemolysis, which can result in death in 10-30% of recipients even if identified swiftly and actively managed. ABO incompatible red cell transfusion must therefore be avoided [BCSH 2013 – **ESD121**].

Antibodies against antigens in blood group systems other than ABO have also been described as having caused immunological red cell destruction these include Rhc,C,D,e,E, K/k, Fya/Fyb, Jka/ Jkb, MNSs Lua/Lub and less commonly antibodies against "high frequency" red cell antigens which are typically present on the red cells of >99% of the donor population. These potentially significant antibodies would be expected to be detected by routine compatibility testing performed by hospital and reference laboratories. Non-ABO antibodies typically, though not exclusively, cause delayed extravascular red cell destruction which is less severe than ABO haemolysis and if it is known that incompatible red cells have been transfused the potential adverse effects can be minimised [*Win et al, Trans Med Rev 2010*].

Some red cell antibodies detectable in laboratory tests predictably do not cause reactions or red cell destruction but they can make it difficult to exclude the presence of more significant antibodies [*Daniels et al, Trans Med 2002; Garraty and Petz, Transfusion 2002*].

3. Principles for the transfusion of serologically incompatible red cells

3.1 Basic compatibility testing will not necessarily be completed if red cells are required within 30 minutes.

3.2 Serological testing to identify or exclude significant antibodies may sometimes not be completed within 6 hours if referral on to a reference laboratory is required. In complicated cases this time frame may be even longer.

3.3 In situations such as a flu pandemic, hospital and reference laboratory scientists and transport staff may be less readily available to select, locate, search (especially extended phenotype units) and transport in a timely manner.

3.4 The team looking after the patient should be informed if there may be a delay in the availability of compatible blood and the urgency of any transfusion should be ascertained with specific time frames (e.g. less than 30 minutes, less than 2 hours etc).

3.5 ABO compatible blood would always be selected and the algorithm in figure 1 followed.

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3.6 Even if clinically significant antibodies are present such as anti-c the recipient may suffer no symptoms and no evidence of increased red cell destruction [*Klein and Anstee, Blood Tran Clin Med: 2005*].

3.7 If symptoms do occur and / or there is evidence of increased red cell destruction, the effects can be minimised, particularly if the scientific, medical and nursing team are made aware of this risk early on [*Win et al, Trans Med Rev 2010*].

4. An order of preference for blood selection if urgent transfusion is required before compatible blood is available to minimise the risk of identified or unidentified antibody specificities (see figure 1).

4.1 ABO compatible blood must be supplied (group O if the ABO blood group is not known).

4.2 Avoid antigens that are the target of significant antibodies currently detectable by indirect antiglobulin test (IAT) technique at 37°C.

4.3 Having obtained blood that satisfies 4.1-2, avoid antigens that are the target of antibodies currently detected by enzyme technique only.

4.4 Having successfully achieved 4.1 – 3, supply units that are RhD compatible to females of childbearing potential i.e. females under fifty years of age (men of any age and women >50 are a lower priority for RhD negative red cells if they do not have anti-D antibodies and it may be preferable to avoid historical antibodies in men and older women).

4.5 Having fulfilled 4.1-4, avoid historical but currently undetectable antibodies.

4.6 Once 4.1-5 have been completed, consider supplying blood that is compatible for cCeE and K despite the absence of current or historical antibodies of these specificities if the patient is likely to require chronic transfusion [*Seltsam et al, Transfusion: 2003*].

4.7 Based upon the frequency and severity of historic reports of reactions to incompatible transfusions the following order of antigen negative selection should be used if selecting blood that is not fully compatible. The antigens in brackets are high frequency antigens (HFA) which in practice in urgent situations are likely to be unavoidable and hence relegated to the "HFA" position in the order of selection [*Seltsam et al, Transfusion 2003*]
D>c>C>E>e>K(k)>Jk$^{a/b}$>Fy$^{a/b}$ > S/s(U)> M>N>HFAs.

4.8 If packs expressing the phenotype of the red cells are not available the blood establishment may supply lists of historical red cell phenotype which can be referred to for additional confirmatory testing where possible in the hospital laboratory and an IAT crossmatch.

4.9 If antigen negative units are not available and time allows there may be some benefit in selecting heterozygous antigen positive units rather than homozygous ones (e.g. K+k+ if the recipient has anti-k).

4.10 It is important to note that antibodies that show strong reactivity by IAT may be more active *in vivo* than if the same antibody showed weaker reactions. Where possible 'serologically least incompatible' units should be selected. Some of the antibodies are extremely rare and little or nothing is known about their clinical significance [*Daniels et al, Trans Med 2002*]. Absence of evidence of clinical significance does not mean that a transfusion of 'incompatible' blood will be uneventful.

5. Management of patients who have been / are being transfused with red cells expressing the antigen(s) against which they have antibodies.

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5.1 The most senior transfusion laboratory scientist and the NHSBT consultant on duty should be informed. NHSBT consultant should liaise with Hospital haematologist to review the case and to be involved in the management of the index case. Consultant Haematologist should inform and discuss the following advice (follow steps 5.2 to 5.8 below) to the medical/surgical team directly caring for the patient.

5.2 The team looking after the patient should ensure that the patient remains adequately hydrated but not fluid overloaded with monitoring of fluid intake and output.

5.3 Baseline and serial monitoring for evidence of haemolysis and its complications should be undertaken including a dipstick urine for Hb, a full blood count, reticulocyte count, bilirubin, LDH, haptoglobin, Urea and electrolytes and coagulation.

5.4 The patient should be informed of the potential of haemolysis and the risk of not receiving blood.

5.5 Transfusion should be given with IV methylprednisolone 1g cover (provided there is no contraindication for steroids). It is readily available and easy to administer, if not alternative IV steroids should be used such as hydrocortisone, which is stocked on most wards. Dose conversion for steriods (1g methyl-prednisolone is equivalent of 1250 mg of prednis(ol)one. Hydrocortisone 200mg is equivalent of 50mg prednis(ol)one.

Least incompatible blood should be transfused with extra caution (with sequential transfusion of 20 and 50 ml and then the entire unit of incompatible RBC). Pulse, BP, temperature should be monitored closely. It is preferable to give blood transfusion during the day working hours.

Serial monitoring for evidence of haemolysis and its complications should be undertaken. If transfusion reaction is suspected, transfusion should be discontinued and advice sought from the Consultant Haematologist and transfusion laboratory.

5.6 Where appropriate, strategies for ameliorating the immunological responses such as the use of intravenous immunoglobulin (IVIG) should be considered [*Kohan et al, Vox Sang 1994; Woodcock et al, Clin Lab Haem 1993].* Recent studies have shown that the provision of IVIG and steroids may correct anaemia and prevent both the acute haemolytic transfusion reaction and delayed haemolytic transfusion reaction for transfusion with incompatible red cell units in urgent clinical situations [*Win et al, Transfusion 2018; Win et al, Transfusion 2019*].

5.7 Clinical advice may only be given to hospitals by an NHSBT consultant, who should discuss the case with the hospital consultant haematologist who will further liaise with the clinical team. The decision to provide IVIG may be made at the discretion of the hospital haematologist/clinicians.

Clinicians prescribing the IVIG should be aware of the potential side effect of IVIG (see foot note adverse effects of IVIG) and should also inform the patient.

Dose: IVIG 1-2 g/kg over 2 to 5 days, given with IV steroids (500 to 1000mg) either prior to or within 24 hrs of 'incompatible' transfusion [Win, 2018; Win, 2019]

Please note (low dose IVIG 0.4g/kg is associated with fewer adverse reactions compared to high dose 1g/kg).

5.8 The transfusion should be given at the slowest rate consistent with the clinical condition and the patient observed closely throughout.

5.9 If haemolytic transfusion reactions develop:

i) Stop transfusion immediately, review the nature of the reaction and if time permits reinvestigate the case.

ii) For urgent clinical situations it is the discretion of the clinical team to make a decision to continue transfusion. If need further transfusion, issue least incompatible blood, monitor and consider additional dose of IVIG and steroids (additional IVIG 0.4g/day for next 3-4 days if not contraindicated and not exceeding maximum total dose of 2g/kg) and IV methylpred 1G the next day. Also monitor renal function: consider Dopamine infusion if indicated [*Woodcock et al, Clin Lab Haem 1993; Win et al, Trans Med Rev 2010; Win et al, Transfusion 2018*].

6. Urgent clinical situation:

6.1 Occasionally, clinical urgency requires that blood must be transfused before the antibody has been identified or before a tentative identification has been confirmed. Under these circumstances, ABO compatible, RhD K matched, serologically least incompatible blood should be transfused with extra caution. The decision to issue ABO compatible, RhD matched, least incompatible blood should be made on the balance of risk of severe haemorrhage (anaemia, urgent requirement), versus a haemolytic transfusion reaction with potential complications including renal failure.

6.2 As discussed above, strategies for ameliorating the immunological response, such as the use of intravenous immunoglobulin and high dose steroids, should be considered (follow steps 5.2 to 5.9 above).

7. Adverse effects of IVIG therapy

7.1 Although IVIG is generally considered a safe treatment; adverse reactions ranging from mild and self-limited to severe have been reported. Infusion of IVIG has been associated with a) renal toxicity b) thromboembolic events (TEE) [*BNF 2013; Funk et al, Vox Sang 2013; Williams et al, US Pharm 2010*] and c) haemolytic reactions.

a) Acute renal failure is a rare complication: the risk factors are those with pre-existing renal impairment, diabetes mellitus, age greater than 65 yrs, dehydration, paraproteinemia and concomitant use of nephrotoxic drugs. All patients should have their renal function monitored during the use of IVIG and discontinuation of treatment should be considered if indicated (Note: IVIG products containing sucrose as a stabiliser accounted for most reported cases of renal failure).

b) Pre-existing risk factors for TEE (advance age, hypertension, diabetes mellitus, history of vascular disease or thrombotic episodes): TEE appears to be rare (reported 0 -0.83 cases per 1000 kg IVIG distributed) [*Funk et al, Vox Sang 2013*].

c) IVIG administration may result in mild haemolytic reactions, usually due to the presence of anti-A or anti-B isoagglutinins. These blood group antibodies often result in a slight degree of haemolysis, mild hyperbilirubinemia, and a positive DAT. These events are usually subclinical. Very rarely significant haemolysis may occur with a fall in hemoglobin of 1 to 5 g/dL (more common in blood group A recipient). *Daw et al [Transfusion 2008]* recognised 16 cases of clinically significant haemolysis among 1000 IVIG-treated adults (1.6%). The decrease in haemoglobin was from 0.8 to 5.2 g/dl and the haemolysis was recorded after the administration of larger doses of IVIG (cumulative dose of IVIG was 50 to 350 g). Haemolysis associated with the administration of IVIG was observed from 12 hrs to 10 days after the first dose of IVIG and it has been recommended to monitor the Hb level 48 to 72 hr after IVIG infusion [*Khawaji et al, Clin Journal Amer. Soc. Nephrology 2009*].

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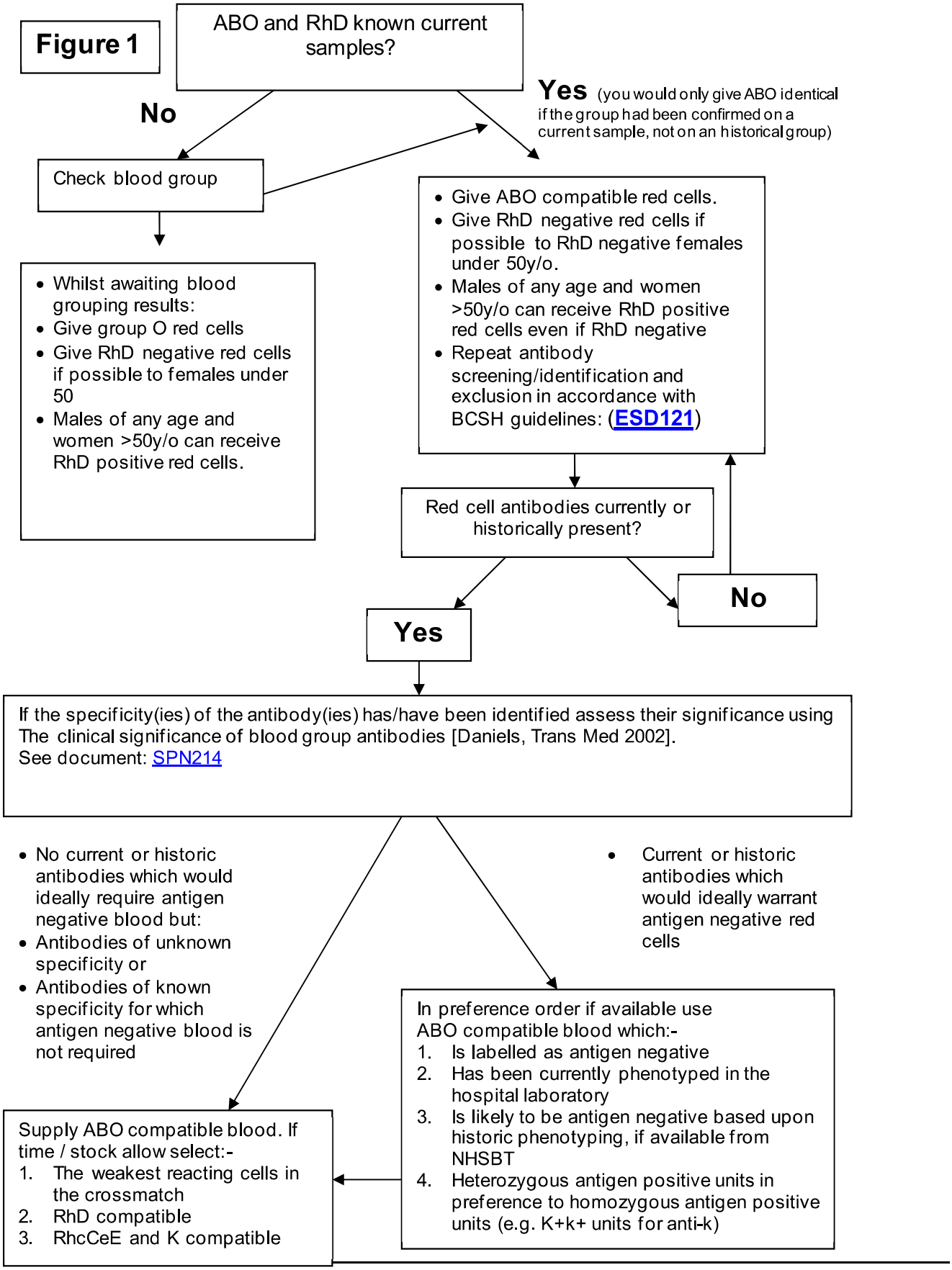
Figure 1



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