bjh guideline

Position paper on International Collaboration for Transfusion Medicine (ICTM) Guideline 'Red blood cell specifications for patients with hemoglobinopathies: a systematic review and guideline'

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Summary

The International Collaboration for Transfusion Medicine Guidelines (ICTMG) has published guidance on transfusion for haemoglobinopathies. To give a UK perspective on this guidance, each of the recommendations in the ICTMG guideline were reviewed and the applicability for transfusion practice in the UK considered with reference to relevant published British Society for Haematology (BSH) guidelines and national standards . There was much consensus; however, there was disparity surrounding the recommendations for routinely extended matching in those with alloimmunisation.

Keywords: sickle cell disease, thalassaemia, alloimmunisation, crossmatch, genotyping, phenotyping.

The International Collaboration for Transfusion Medicine Guidelines (ICTMG) was established in 2011 and includes international transfusion experts. The group's purpose is to establish evidence-based transfusion medicine guidelines to optimise transfusion care. A systematic review of evidence was performed and used to develop recommendations to assist physicians and transfusion specialists in decision making for optimising choice of red cell units when transfusing patients with haemoglobinopathies (Compernolle *et al.*, 2018).

The British Society for Haematology (BSH) Guidelines committee has four taskforces including the Transfusion Taskforce developing UK guidelines for clinical and laboratory practice. In addition to evidence-based guidelines and good-practice papers, the committee also has agreed to develop position papers supporting the adaptation and adoption of non-UK based guidelines for use in the UK (www.bsh.org.uk). Accordingly, this position paper will explore each of the recommendations in the ICTMG guideline and consider the applicability for transfusion practice in the UK. Reference is also made to relevant published BSH guidelines (British Committee for Standards in Haematology *et al.*, 2013; Davis *et al*, 2017) and national standards (Dick & Rees, ; UK Thalassaemia Society, 2016; NHS England, 2018; Sickle Cell Society, 2018).

Methods

Each of the recommendations in the ICTMG guideline were reviewed and the applicability for transfusion practice in the UK considered with reference to relevant published BSH guidelines (British Committee for Standards in Haematology *et al.*, 2013; Davis *et al.*, 2017) and national standards (Dick & Rees, ; NHS England, 2018; UK Thalassaemia Society, 2016; Sickle Cell Society, 2018).

Results and discussion

ICTMG recommendation 1

Patients with sickle cell disease (SCD) who do not have alloantibodies and who are anticipated to have a transfusion (simple or exchange transfusion) should probably be transfused with CcEe- and K-matched red blood cells (RBCs) to reduce the risk of alloimmunisation (low quality of evidence, weak recommendation). RBCs matched for CcEe and K can be provided by phenotyping or genotyping RBCs. The use of phenotyping or genotyping will depend on the costs of each method in each jurisdiction. Genotyping appears to be more accurate.

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First published online 21 January 2020
doi: 10.1111/bjh.16405

Providing matched RBCs is recommended although patients may not have developed alloantibodies in the past, as there is a potential for alloantibody development with future transfusion.

Phenotyping or genotyping are provided by several centres prior to the first transfusion

This recommendation is in keeping with previous BSH guidance and standards of care in the UK (Dick & Rees, ; Sickle Cell Society, 2018).

Previously published BSH guidance recommends that patients with SCD should receive ABO-, Rh- and Kell-compatible units (Davis *et al.*, 2017). This is of particular importance in SCD where the common Rh phenotypes differ from the donor population.

BSH guidance (British Committee for Standards in Haematology *et al.*, 2013) also recommends that the patient's RBC phenotype or genotype should be known prior to transfusion. There are accruing data on the importance of Rh variants in some patients (Chou *et al.*, 2018) and that genotyping is an effective method for their identification. For patients cared for in England, (which includes the majority of patients with haemoglobin disorders in the UK), genotyping can be provided by NHS Blood and Transplant (NHSBT). Results from tests performed by NHSBT and the International Blood Group Referencing Laboratory (IBGRL) are held on a central NHSBT server (Haematos™) that can be accessed electronically by hospitals served by NHSBT through SpICE™ (https://edilive.nhsbt.nhs.uk/icedesktop/) with advantages for patient care given the lifelong nature of the condition and the mobility of the population. However, phenotyping is cheaper and currently genotyping including variants is only performed at one site: IBGRL, Filton (Bristol, UK). The devolved territories' blood services have their own separate organisational setup and genotyping is not always locally available.

The typing should be done prior to the first transfusion and if possible at the first set of bloods in the haematology clinic, but for those who have missed this, and have been transfused in the last three months, then genotyping is the preferred method particularly if there is alloimmunisation. Note, phenotyping is currently the preferred method for ABO grouping.

ICTMG recommendation 2

Patients with SCD who have one or more clinically significant alloantibodies should be transfused with antigen-negative blood to the corresponding antigen(s) alloantibody(-bodies) if feasible (low quality of evidence, strong recommendation). Consideration should be given to inform individuals of their alloantibodies by for example providing them with cards/letters that can be presented at each hospitalisation to ensure they receive antigen-negative RBCs.

This recommendation is predominantly in keeping with previous BSH guidance and standards of care in the UK.

Previously published BSH guidance on compatibility (British Committee for Standards in Haematology *et al.*, 2013) recommends that red cells provided for transfusion should be antigen-negative for some alloantibodies, but for others cross-match-compatible units are acceptable e.g. Anti-M not active at 37°C, anti-Kpa. BSH guidance on transfusion in SCD (Davis *et al.*, 2017) is in agreement with the ICTMG guidance and recommends that if there are clinically significant red cell antibodies (current or historical) then the red cells selected should be negative for the corresponding antigens.

The UK Serious Hazards of Transfusion (SHOT) Haemovigilance scheme highlights the importance of communication pathways required in ensuring that patients with haemoglobinopathy do receive blood based on their special requirements. The reports indicate risks of potential adverse consequences including failure to give antigen-matched blood for "evanescent" or historical antibodies where these special requirements have been missed due to breakdown in communication.

ICTMG and BSH guidances are in concordance in regard to the fact that patients should be informed regarding their antibody status and given a card to notify healthcare workers of their antibody status. The ICTMG states that this card/letter should be presented at each hospitalisation. It is worth emphasising that this should in fact be presented at each contact with healthcare professionals as transfusions are often required in the outpatient or daycare setting. The issue with transcribing errors on such cards has not been resolved nationally, nor has the issue of keeping this information contemporaneous and therefore there needs to be very careful governance surrounding issuing of cards/letters and ensuring these are kept up to date.

ICTMG recommendation 3

Patients with SCD who have one or more alloantibodies should probably be transfused with CcEe-, K-, Fy^a-, Fy^b-, Jk^a-, Jk^b-, Ss-matched RBCs to reduce the risk of alloimmunisation if feasible and if matching does not cause undue delays that adversely affect patient care (low quality of evidence, weak recommendation).

This is not currently in any UK guidance and is not concordant with current BSH advice.

This recommendation recognises that those with some antibodies often have a predilection to form further antibodies, making them progressively more difficult to transfuse. The evidence is weak, and the recommendation does use the word "feasible". Here the feasibility in the UK needs to be explored further. Many adults in the UK who are on long-term transfusions for SCD are treated on automated exchange where the regimen can vary from four to eight weekly and need 8–14 units a time, depending on the parameters set and the size of the patient. The donor population in England is ~98% Caucasian, therefore until we start fully genotyping these donors, matching large quantities of blood for these antigens routinely

whilst theoretically optimal is not feasible. Priority must be given to the provision of antigen-negative blood for patients with pre-existing alloimmunisation to minimise the risk of delayed haemolytic transfusion reactions. Routinely requesting blood to be matched extended beyond Rh and K antigens and the antigens to which they have developed an antibody, would place considerable demands on Blood Services that are unlikely to be fulfilled and may risk the patient having their transfusion delayed or less units being available for their transfusion. This could result in patient harm. In this scenario, the hypothetical advantage of more closely matched blood would be greatly offset by the transfusion being postponed or less blood being available such that haematological targets are not met. Therefore, such requests should be made only in exceptional circumstances and considered on a case-by-case basis through discussion and agreement between the Consultant Haematologist responsible for the patient and the Specialist Red Cell Immunohaematology team. Specific and complex transfusion requirements for patients should also be discussed at Network Multidisciplinary team meetings with the Haemoglobinopathy Coordinating Centre as per the new NHS England structure (2018), and devolved countries should have their own network arrangements. As with all transfusion, consultation with the patient (and family for children) is also important. Blood services are continuing to strive towards increased donation from black and minority ethnic (BAME) donors. As these efforts bear fruit and with the possible wider application of whole-genome sequencing of donors and patients informing blood provision in a precision transfusion model, the feasibility of applying more stringent matching criteria should be evaluated and guidance could be amended.

ICTMG recommendation 4

Patients with thalassemia syndromes who do not have alloantibodies and who require RBC transfusion should probably be transfused with CEK matched RBCs to reduce the risk of alloimmunisation (low quality of evidence, weak recommendation).

RBCs matched for CcEe and K can be provided by phenotyping or genotyping RBCs. The use of phenotyping or genotyping will depend on the costs of each method in each jurisdiction. Genotyping appears to be more accurate.

Providing matched RBCs is recommended although patients may not have developed alloantibodies in the past as there is a potential for alloantibody development with future transfusion.

This recommendation is in keeping with previous BSH guidance (British Committee for Standards in Haematology *et al.*, 2013) and standards of care in the UK (UK Thalassaemia Society, 2016).

The genotyping and phenotyping comment for thalassaemia should be the same as for SCD (see comments on recommendation 1).

ICTMG recommendation 5

Patients with thalassemia syndromes who have one or more clinically significant alloantibodies should be transfused with antigen-negative blood to the corresponding antigen(s) if feasible (low quality of evidence, strong recommendation).

Consideration should be given to inform individuals of their alloantibodies by for example providing them with cards/letters that can be presented at each hospitalisation to ensure they received antigen-negative RBCs.

The ICTMG recommendation is largely in agreement with BSH guidance (UK Thalassaemia Society, 2016; British Committee for Standards in Haematology *et al.*, 2013); however, again semantically for some alloantibodies, crossmatch-compatible blood is sufficient (e.g. anti-M not active at 37°C).

The advice for informing those about antibody status is the same for thalassaemia as for SCD (see comments on recommendation 3).

ICTMG recommendation 6

Patients with thalassemia syndromes who have one or more alloantibodies should probably be transfused with CcEe-, K-, Fy^a-, Fy^b-, Jk^a-, Jk^b-, Ss-matched RBCs to reduce the risk of alloimmunisation if feasible and if matching does not cause undue delays that adversely affect patient care (low quality of evidence, weak recommendation).

This is not in the current UK guidance and is not concordant with current BSH advice.

Alloimmunisation in this patient cohort is often historical and often against Rh and Kell antigens and due to transfusion prior to introduction of guidance for Rh and Kell matching or for *ad hoc* transfusions performed away from specialist centres when the team transfusing was unaware of the thalassaemia status or the transfusion guidance for thalassaemia. Development of further antibodies for those with transfusion-dependent thalassaemia is rare (Trompeter *et al.*, 2015) particularly compared to the sickle cell cohort and it would be difficult to demonstrate such matching would confer an advantage to the patients. Therefore, the recommendation from ICTMG is not currently applicable in the UK on a regular basis. Such requests should be made only in exceptional circumstances and considered on a case-by-case basis through discussion with the Red Cell Immunohaematology consultant and the consultant looking after the patient as well as discussed at the Network Multidisciplinary team meeting with the Haemoglobinopathy Coordinating Centre. Once again, as with all transfusion, consultation with the patient (and family for children) is also important. Blood services are continuing to strive towards increased donation from BAME donors. As these efforts bear fruit and with the possible wider application of whole-genome sequencing of donors and patients informing blood provision in a precision transfusion model, the feasibility of applying

more stringent matching criteria should be evaluated and guidance could be amended.

Other comments. "Thalassaemia syndromes" is used throughout the document and is not defined although it is accepted that even if it were, the nature of thalassaemia would require inclusion of a wide variety of genotypes. Most of the references understandably draw on papers on transfusion-dependent or -independent (usually beta) thalassaemia; however, this has been extrapolated to all forms (seemingly) in the document. It does seem reasonable, given the paucity of data, to extrapolate this to all those with transfusion-dependent and -independent thalassaemias.

There is no mention of age of blood and that HbS-negative units should be used in the ICTMG guidance. BSH and other UK guidance should stand (UK Thalassaemia Society, 2016; Sickle Cell Society, 2018), although more work needs to be done to underpin the age of blood recommendation for these patient cohorts.

Acknowledgements

This work has been reviewed by the Transfusion Task Force and Executive Committee of the British Society of Haematology Guidelines Committee.

Author contributions

ST wrote the paper, EM and SR edited the paper.

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