Haemoglobin Disorders n=57

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Key SHOT messages

- Transfusion remains a key treatment for individuals with haemoglobinopathies, particularly in sickle cell disease (SCD), and this remains complicated by the significant risk of red cell alloimmunisation
- The decision to transfuse in SCD requires careful consideration, taking into account the indications and goals of transfusion and balancing these against the risk of alloimmunisation and haemolytic transfusion reactions
- Patients should be involved in every decision to transfuse and be fully informed of the potential risks and benefits. Patients should be educated on the importance of safe transfusion practice and be issued with a transfusion card highlighting their specific requirements

Abbreviations used in this chapter

ADU	Avoidable, delayed and under/overtransfusion	**IBCT**	Incorrect blood component transfused
BMS	Biomedical scientist	**LIMS**	Laboratory information systems
BSH	British Society of Haematology	**NHSBT**	National Health Service Blood and Transplant
DAT	Direct antiglobulin test	**SCD**	Sickle cell disease
FAHR	Febrile, allergic or hypotensive reactions	**Sp-ICE**	Specialist Services electronic reporting using Sunquest's Integrated Clinical Environment
Hb	Haemoglobin	**SRNM**	Specific requirements not met
HTR	Haemolytic transfusion reactions	**WCT**	Wrong component transfused
IAT	Indirect antiglobulin test		

Recommendations

- Processes should be in place to ensure a detailed transfusion history is obtained in all sickle cell disease (SCD) patients requiring transfusion. It is important that the transfusion history of a patient including antibody status is communicated between clinical and laboratory teams, including any specialist tests from reference laboratories (BSH Davis et al. 2016)
- Individual transfusion decisions in SCD patients can be challenging, and advice from haemoglobinopathy specialists is recommended
- For patients with complex transfusion requirements a multidisciplinary approach is recommended with representation from haemoglobinopathy and transfusion medicine specialists. Where possible a transfusion plan should be agreed in advance of an anticipated transfusion

Action: Hospital transfusion teams, clinical teams looking after patients with haemoglobin disorders, laboratory management

Introduction

There were 57 cases reported this year in patients with SCD or thalassaemia. Of the 43 cases in SCD the most frequently reported event was HTR, occurring in 15 cases, followed by IBCT-SRNM in 14 cases. There were 14 cases reported in patients with thalassaemia which were distributed across the categories with the most common being 4 cases of FAHR.

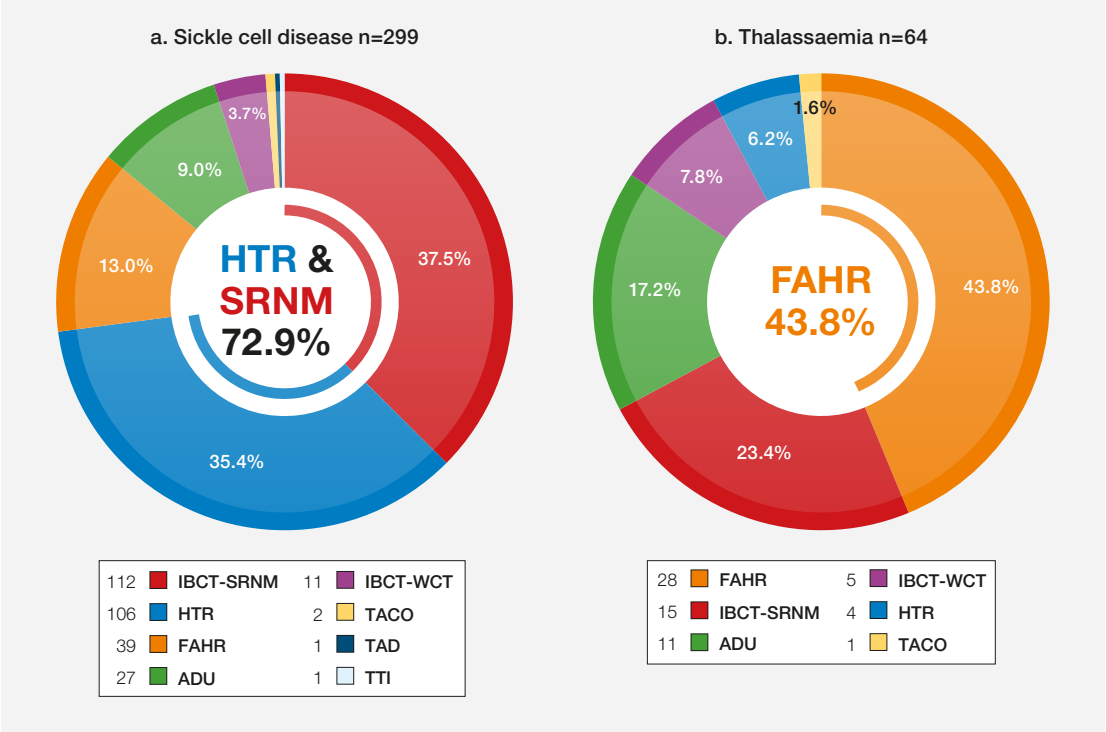
Deaths n=0

There were no deaths related to transfusion in any of the patients with haemoglobin disorders.

Major morbidity n=12

There were 12 cases of major morbidity related to transfusion in this cohort of patients: 10 HTR (9 hyperhaemolysis), 1 IBCT-SRNM and 1 FAHR.

Figure 24.1: Cumulative data for adverse transfusion events in patients with haemoglobin disorders 2010 to 2020



TTI=transfusion-transmitted infection; TAD=transfusion-associated dyspnoea; TACO=transfusion-associated circulatory overload; HTR=haemolytic transfusion reactions; FAHR=febrile, allergic and hypotensive reactions; HSE=handling and storage errors; IBCT-SRNM=incorrect blood component transfused-specific requirements not met; IBCT-WCT=IBCT-wrong component transfused; ADU=avoidable, delayed and under/overtransfusion

Avoidable, delayed and under/overtransfusion (ADU) n=4

There were 3 reports of delayed transfusion; 2 occurred in patients presenting with sickle cell crisis and 1 was for a routine transfusion in a patient with thalassaemia. There was 1 report of overtransfusion for a child with SCD attending for routine transfusion. There were no avoidable transfusions reported this year for patients with haemoglobin disorders.

Case 24.1: Delay due to inappropriate sample rejection

A young male with SCD was admitted with a sickle cell crisis and was deemed to require transfusion. During sample processing, the laboratory inappropriately rejected the group and screen sample. A further sample was requested however the second sample was appropriately rejected due to being incorrect. A senior BMS noticed the original sample was in fact acceptable for processing. These delays resulted in the transfusion being administered over 8 hours after initial bloods were taken. No harm to the patient was reported.

Case 24.2: Infusion pump set up incorrectly

A young female with SCD attended for routine transfusion. The infusion pump was set up incorrectly resulting in overtransfusion. The staff member was not familiar with the local policy and the prescription was not checked. The error occurred during transfusion when the pump was reprogrammed. The patient was reviewed following the incident and no harm to patient was reported as a result of this overtransfusion.

IBCT-specific requirements not met (SRNM) n=15

There were 15 reports of specific requirements not met, 14 of which occurred in patients with SCD and 1 in a thalassaemia patient.

Case 24.3: Failure to merge report from the reference laboratory with historic report on local hospital system

A young female with SCD received a two-unit episodic transfusion. Following transfusion, the laboratory staff noticed there was a discrepancy between the genotyping result available on Sp-ICE and the phenotyping results on the LIMS transfusion record. A sample had been tested by the reference laboratory and the patient found to have Rh variant C and e antigens. These genotyping results had been uploaded to Sp-ICE but the local laboratory had not been informed via a letter. Prior to the discrepancy being noted the patient had received red cells matching the phenotype and subsequently developed anti-C and anti-e.

Red cell genotyping is useful for detecting Rh variants not evident on serological phenotyping. Such specialised tests are only available in certain laboratories and it is therefore important that these results are communicated to the requesting team as well as being available on the national Sp-ICE record.

Case 24.4: SCD patient receives antigen-positive blood despite informing clinical team of his specific requirements

A patient with SCD admitted to a hospital outside his local area with acute pain episode was transfused due to fall in Hb. The patient was aware he had red cell antibodies and asked the medical team to ensure he got appropriate blood. The laboratory team did not see the clinical information on one of two group and antibody screen request forms, indicating the patient had historic alloantibodies, and therefore the patient did not receive antigen-negative units.

This is an interesting case whereby the patient himself was aware of the importance of informing the medical team of his specific requirements for blood and despite this the hospital failed to provide him with appropriate antigen-negative units. Although this was categorised as a laboratory error, the clinical and laboratory teams have a shared responsibility to ensure the patient receives correct blood and, in such cases, where the patient is not known to the local hospital it would be safer for the medical team to talk directly with the laboratory. This further highlights the importance of patient involvement to ensure safe transfusions.

Case 24.5: Ambiguity in the diagnosis and indication for transfusion in SCD

A young child with SCD was transfused. The Hb was 71g/L and the indication for transfusion was documented as anaemia. The request form stated '? sickle cell disease'. The laboratory team failed to flag this potential diagnosis and therefore patient did not receive Rh and Kell matched units.

This case highlights a lack of understanding, from both clinical and laboratory teams, of the relevance of SCD in transfusion practice. The patient's baseline Hb was unknown, nor whether there was a clear indication for transfusion, particularly as the requester did not seem to be clear of the diagnosis. Although the diagnosis on the request form was ambiguous, the laboratory team should have contacted the clinical team for clarification if there was any uncertainty to ensure specific requirements were met.

Febrile, allergic or hypotensive reactions (FAHR) n=9

There were 4 reported incidents in children with transfusion-dependent thalassaemia who each developed fever, rigors, and pain in back, chest or loin. All were thought to be non-haemolytic transfusion reactions.

There were 5 reports of non-haemolytic transfusion reaction reported in patients with SCD with symptoms reported include fever, rash, and pain. In all cases there were no reports of serological incompatibility.

IBCT-wrong component transfused (WCT) n=2

Case 24.6: An example of a D-variant leading to difficulties with matching

A young child with sickle cell disease was admitted to a hospital outside of the local area overnight with a sickle crisis and Hb of 51g/L. Blood grouping for D showed a dual population of red cells and the group was misinterpreted as D-positive as the population of D-positive cells looked greater. The D-group could not be easily confirmed with standard phenotyping, however, the BMS thought the patient was D-positive and issued two such units of red blood cells, both of which were D and E-positive. The laboratory policy is that where D-status cannot be determined D-negative red cells are given. The following day the Sp-ICE record was checked, which confirmed the patient to have a D-variant and according to the Blood Service report, and should have received D-, E-, e+ blood. In addition, only one of the two red cell units given was HbS negative. The child was followed up for development of an antibody.

Despite extended Rh matching, alloimmunisation is further complicated by significant genetic heterogenicity in this blood group system in individuals from Black African or African Caribbean ethnic backgrounds. Variant RHD and RHCE alleles can result in altered D, C and e antigen expression which may be incorrectly identified as positive or negative on serological phenotyping. In such cases genotyping is useful to confirm an Rh variant. This may not however, fully negate the risk as the donor could also have an Rh variant that may not be apparent.

Case 24.7: ABO-incompatible transfusion in SCD

A patient group O with SCD was inadvertently administered the blood intended for a different patient. Two units for two different patients were incorrectly checked only against their electronic prescriptions. The nurse set up the blood transfusion for the SCD patient using group A blood that had been collected for the other patient. Following infusion of 3mL of blood the cannula failed causing the pump to alarm and at this point the nurse noticed the wrong blood was being transfused and stopped administration. No adverse outcome to the patient was reported.

In this case the nurse checked the electronic prescription for two units for two different patients at the same time and did not perform checks at the patient's side as recommended. This ABO-incompatible transfusion could have resulted in a serious acute haemolytic transfusion reaction and risk of significant morbidity and death.

Haemolytic transfusion reactions (HTR) n=15

There were 15 incidents of HTR reported, all occurring in patients with SCD. Nine of the cases were reported as hyperhaemolysis, 5 were delayed HTR and 1 was an acute HTR. These cases are analysed in Chapter 19, Haemolytic Transfusion Reactions (HTR).

Case 24.8: Hyperhaemolysis in a child with prior alloimmunisation and an e antigen variant

A child with SCD and a history of alloimmunisation including anti-S, anti-Jk^{b} and e antigen variant was listed for an elective splenectomy and therefore had preoperative transfusion. She presented 2 days following transfusion with flank pain and dark urine. There was a decline in Hb from 104g/L immediately following transfusion to 67g/L. The patient was treated with immunoglobulin and steroid. The DAT was positive and pan-reactive anti-e was demonstrated in the eluate.

This case highlights the difficulties that can arise with Rh variants which can result in patients receiving blood which appears Rh compatible based on serological phenotyping and the patient subsequently

develops red cell alloantibodies. In some cases, an alloantibody may be misdiagnosed as an autoantibody.

Case 24.9: Case of further antibody development in a patient with previous alloimmunisation

A young male with SCD and a history of anti-Fy^a underwent an elective exchange transfusion. Twelve days later he presented with fever and abdominal pain and a decline in Hb from 105g/L immediately post transfusion to 78g/L and 55g/L 2 days later. Anti-S was identified post transfusion. The patient made a full recovery.

SCD patients with alloimmunisation are at risk of further antibody development and therefore any subsequent transfusion requires careful consideration.

Case 24.10: A case of poor increment in haemoglobin following blood transfusion

A middle-aged patient with SCD received six units of red blood cells over a 6-day period. The post-transfusion DAT was positive, but antibody screen remained negative. Indications listed for transfusions included sickle cell crisis, anaemia, and poor increment in Hb following blood transfusion. Once a HTR was suspected the patient received steroids and made a full recovery.

Case 24.11: HTR not initially recognised

A middle-aged female with SCD had recently received transfusion for an acute painful episode affecting legs, and then presented with a further painful episode affecting arms. A decline in Hb was noted and a decision was made to further transfuse. This resulted in further decline in Hb to 38g/L and dark urine. The patient was discussed with the regional specialist haemoglobinopathy team and treated with immunoglobulin and steroid for post-transfusion hyperhaemolysis.

In the 2 cases above a poor response to blood transfusion was not initially recognised as a potential HTR and further blood given in both cases resulted in hyperhaemolysis. Following transfusion in SCD, poor increment or decline in Hb should always raise suspicion of a HTR and such cases should be discussed with specialist haemoglobinopathy team as further transfusion may be detrimental.

Case 24.12: Acute HTR in SCD

A middle-aged female with SCD and a history of anti-S had an elective exchange transfusion prior to total hip replacement for avascular necrosis. Within 24 hours of transfusion there was a decline in Hb from 98g/L to 36g/L. Patient's symptoms included dyspnoea, dark urine and jaundice. Anti-Jk^b was subsequently identified.

Alloimmunised SCD patients are at increased risk of HTR. This case highlights the importance of discussing the additional risk of transfusion if required for surgery, which should form part of the discussion on the risks and benefits of surgery so that patients can make a fully informed decision.

Case 24.13: Acute chest syndrome in SCD pregnancy and recurrent hyperhaemolysis

A young female with a history of multiple alloantibodies and previous hyperhaemolysis required a red cell exchange transfusion for acute chest syndrome following a stillbirth. The patient was treated pre-emptively with immunoglobulin and steroids but developed another severe HTR with a decline in Hb to 41g/L, with associated haemoglobinuria and hyperpyrexia. The DAT was positive, but no antibody identified in the eluate.

This case highlights the risk of recurrence of haemolysis following a previous hyperhaemolytic reaction. It is useful to have a multidisciplinary approach for such complex cases including haemoglobinopathy and transfusion medicine representation and to have a pre-emptive transfusion plan.

Conclusion

Despite extended Rh and K matching, patients with SCD remain at risk of alloimmunisation (Coleman et al. 2019). Preventing alloimmunisation must be a priority when managing patients with SCD to reduce the risk of HTR and to avoid future difficulties with blood provision.

The optimum degree of antigen matching remains unclear with international guidance suggesting extended red cell antigen matching (Jk^a, Jk^b, Fy^a, Fy^b, S, s) may provide further protection for alloimmunisation. Red cell genotyping can provide useful information not evidenced on serological phenotyping such as Rh variants and evidence of a GATA mutation (Chou et al. 2020).

A national collaborative termed HAEM-MATCH* has recently been formed, to better define a process of extended matching of patients to donated red cell units for transfusion, to improve outcomes for patients with SCD. The hypothesis is that extended donor and patient antigen typing will enable routine timely and cost-effective, automated extended antigen matching in SCD (and other difficult to transfuse cohorts). Other benefits might include a more efficient donor recruitment strategy, reduced delays to transfusion, reduced risks of alloimmunisation, reduced risk of transfusion reactions and streamlined allocation of units for difficult to match patients.

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For further information please visit http://www.donorhealth-btru.nihr.ac.uk/project/blood-transfusion/

Recommended resources

SHOT Bite No. 15: Hyperhaemolysis
https://www.shotuk.org/resources/current-resources/shot-bites/

HTR and Haemoglobinopathies webinar
https://www.shotuk.org/resources/current-resources/webinars/

References

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Coleman S, Westhoff CM, Friedman DF, et al. Alloimmunization in patients with sickle cell disease and underrecognition of accompanying delayed hemolytic transfusion reactions. Transfusion 2019;**59(7)**:2282-2291.

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