Haemolytic Transfusion Reactions (HTR) n=49

18

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Definitions:

Acute haemolytic transfusion reactions (AHTR) are characterised by fever, a fall in haemoglobin (Hb), rise in bilirubin and lactate dehydrogenase (LDH) and a positive direct antiglobulin test (DAT). They generally present within 24 hours of transfusion.

Delayed haemolytic transfusion reactions (DHTR), occur more than 24 hours following a transfusion and are associated with a fall in Hb or failure to increment, rise in bilirubin and LDH and an incompatible crossmatch not detectable pre transfusion.

Hyperhaemolysis is characterised by more severe haemolysis than DHTR, with haemolysis affecting the transfused red cells and the patient's own red cells; there is a decrease in Hb to below pre-transfusion levels, which is often associated with a reticulocytopenia. It may be triggered by a new red cell alloantibody, but frequently no new red cell antibody is identified. Hyperhaemolysis can be divided into acute and delayed hyperhaemolysis.

Abbreviations used in this chapter

AHTR	Acute haemolytic transfusion reactions
BSH	British Society for Haematology
DAT	Direct antiglobulin test
DHTR	Delayed haemolytic transfusion reactions
ED	Emergency department
EPO	Erythropoietin
Hb	Haemoglobin
HTR	Haemolytic transfusion reactions
IAT	Indirect antiglobulin test
ICU	Intensive care unit
IV	Intravenous
IVIg	Intravenous immunoglobulin
LDH	Lactate dehydrogenase
NHSBT	National Health Service Blood and Transplant
RCI	Red cell immunohaematology
Sp-ICE	Specialist Services electronic reporting using Sunquest's Integrated Clinical Environment

Key SHOT messages

- Cases of hyperhaemolysis remain under-reported to SHOT
- SHOT continues to receive reports of HTR in sickle cell patients who have records of confirmed red cell antibodies available on national databases such as Sp-ICE

Recommendations

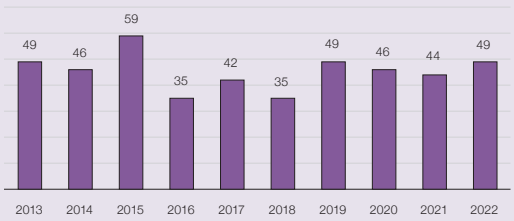
- All staff involved in the transfusion of patients at risk of hyperhaemolysis should be able to recognise, manage and seek specialist help for these cases. They should inform the local transfusion teams of any confirmed cases to facilitate SHOT reporting
- Processes need to be in place to share antibody and transfusion history. This will support safe transfusion, and the investigation and treatment of HTR, in patients who present at different hospitals with symptoms of haemolysis post transfusion

Action: All staff involved in transfusing patients

Headline data 2022

Number of reports n=49
Deaths n=1
Major morbidity n=11

HTR reports by year



Demographic data

Male n=16
Female n=33
Adults n=44
Paediatric n=5

Blood component data

Red cells n=48
Platelets n=0
Plasma n=0
Multiple components n=1
Other n=0

Number of cases n=49

A total of 49 cases have been included, 11 acute, 29 delayed reactions and 9 cases of hyperhaemolysis. The total number of reactions reported is comparable to 2021 (44 cases) and 2020 (46 cases).

All reported cases occurred following red cell transfusions.

Age range and median

The age range was 5 to 80, with a median age of 42. This is shown in Figure 18.1, broken down further by gender. HTR were reported in 5 paediatric patients. Two thirds, 33/49 (67.3%) of the reactions occurred in female patients.

Figure 18.1: Age range in males and females experiencing an HTR

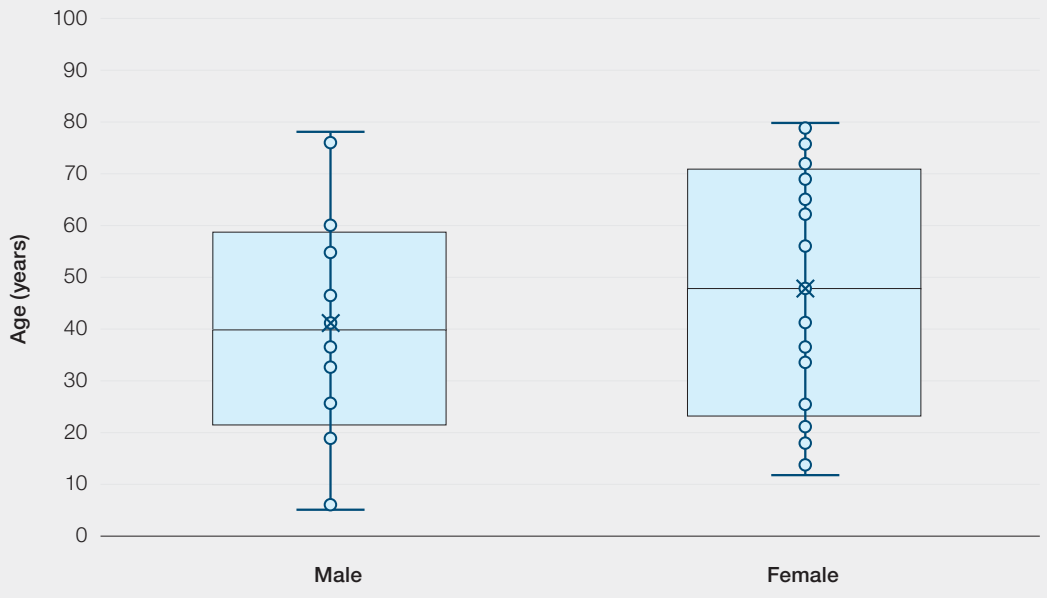


Figure 18.1 is a box and whisker diagram showing the median age and the age range of patients experiencing a HTR reported to SHOT separated by gender. The middle bar in the shaded box indicates the median age, the outer bars of the box represent the upper and lower quartiles. The lines extending from the boxes (whiskers) indicate the lowest and highest values.

Deaths related to transfusion n=1

There was 1 death in a sickle cell patient attributed to the transfusion reaction (imputability 2, probable). This was a young female patient in her 20s who was admitted with suspected sickle crisis and was subsequently diagnosed with hyperhaemolysis. The patient was admitted to ICU where they rapidly deteriorated.

Major morbidity n=11

There were 11 cases reported in which the patient suffered major morbidity. SHOT considers that all reported cases of probable hyperhaemolysis, where there is a significant fall in Hb, should be considered as major morbidity. Following application of this criterion 8 cases of hyperhaemolysis reported with 'minor morbidity' were upgraded.

Hyperhaemolysis n=9

The majority of hyperhaemolysis cases reported (8/9) occurred in patients with sickle cell anaemia. One further case of hyperhaemolysis was reported in a patient with non-Hodgkin lymphoma in their 70s.

While the number of hyperhaemolysis cases reported was comparable to previous years, it is strongly suspected that hyperhaemolysis is still under-reported to SHOT. This is partially attributed to the fact that hyperhaemolysis can be difficult to diagnose with symptoms showing many similarities to DHTR and vaso-occlusive crisis (Adkins et al. 2020). In contrast to other HTR, hyperhaemolysis has been reported to be accompanied by a decrease in the patient's absolute reticulocyte count and an increase in the ferritin level (Win et al. 2019).

Hyperhaemolysis can be either acute or delayed. Acute hyperhaemolysis occurs within 7 days of transfusion and the DAT is usually negative. Delayed hyperhaemolysis occurs more than 7 days post transfusion and the DAT is often positive.

In contrast to a classical DHTR, in delayed hyperhaemolysis both patient and transfused red cells are haemolysed (Danaee et al. 2015). Three cases reported the reactions occurred within the first 7 days post transfusion. Of these, 1 patient was DAT-positive in both the pre-transfusion and post-transfusion samples however this was the patient with non-Hodgkin lymphoma and these patients are often DAT-positive.

Treatment in hyperhaemolysis

There are no published recommendations on the treatment of hyperhaemolysis. There is paucity of published randomised clinical trials in the effectiveness of the available interventions, however, eculizumab has been licensed to treat ongoing brisk haemolysis (NHS England 2020). Since 2020 SHOT has requested reporters to provide information on how these patients were managed. Generally, patients are treated with a combination of IVIg, steroids and EPO. A summary of the treatment methods reported is provided in Table 18.1, which demonstrates that huge variation exists within this field.

Treatment type	2020	2021	2022
No treatment information provided	1	2	1
IVIg, IV Steroids & EPO	1	2	6
IVIg and IV Steroids	3	2	1
IVIg only	1	1	-
IV Steroids only	2	-	-
IVIg and EPO	1	-	1

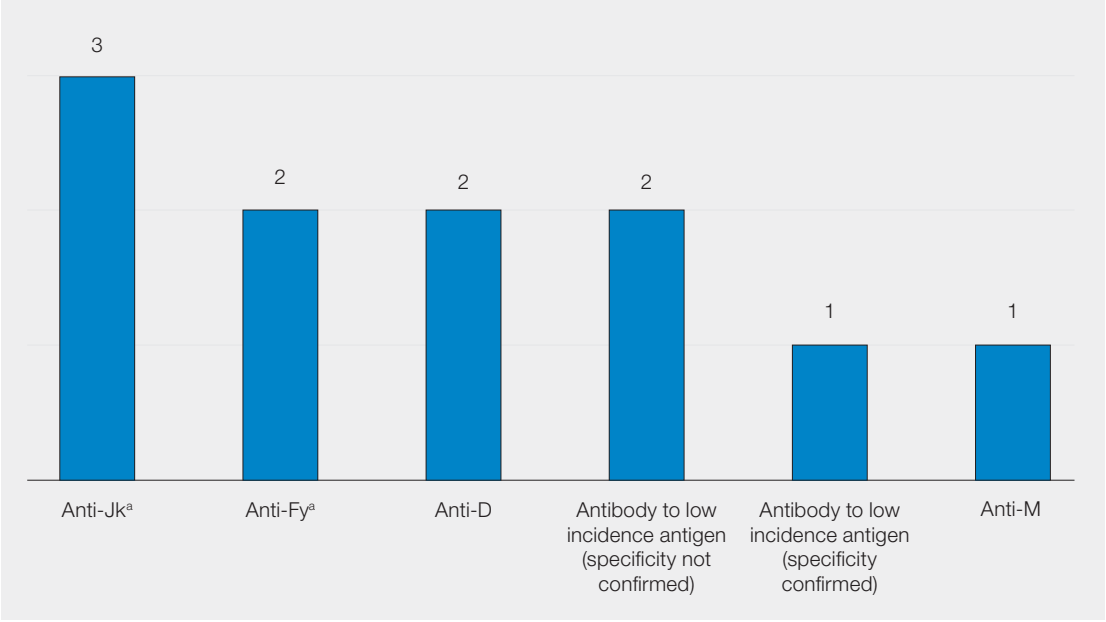
Table 18.1: Treatment methods used for hyperhaemolysis cases reported to SHOT 2020-2022

Clinical and laboratory signs and symptoms

Acute haemolytic transfusion reactions n=11

There were 11 cases reported. Alloantibodies to red cell antibodies were identified in all 11 cases. The alloantibodies implicated as shown in Figure 18.2.

Figure 18.2: Alloantibodies reported in AHTR in 2022



In 9 cases the implicated antibody was not detected in the pre-transfusion sample.

In 3 cases the patient received urgent transfusion of antigen-positive blood with the agreement of the transfusion medics. All 3 patients made a full recovery. It is important that lifesaving transfusion is not withheld due to a history of alloantibodies. In urgent clinical situations where suitable antigen-negative blood is not available it may be necessary to transfuse blood which is positive for a confirmed antibody. This decision must be made on an individual basis and in conjunction with concessionary release procedures (BSH Milkins et al. 2013).

Symptoms of fever, rigors and chills were reported in 8/11 AHTR, with symptoms of dyspnoea, tachycardia and hypertension also being reported at the time of the transfusion. In 5/11 cases, patients also reported dark urine.

Learning point

- Lifesaving transfusion should not be withheld in urgent clinical situations for patients with a history of alloantibodies. In such instances where suitable antigen-negative blood is not available, it may be necessary to transfuse blood components which are positive for a confirmed antibody. These decisions must be made only after liaising with specialist transfusion staff and balancing the risks versus benefits for the patient

Delayed haemolytic transfusion reactions n=29

No clinical symptoms of a transfusion reaction were reported in 7/29 DHTR cases submitted to SHOT and in all 29 cases a lack of sustained Hb increment following transfusion was described.

Alloantibodies were detected in 27/29 of the DHTR reported and in 21 of these cases, alloantibodies were detected in the post-transfusion plasma that were not detected pre transfusion.

Anti-Jk^{a} remains the most frequently implicated antibody in DHTR (Figure 18.3).

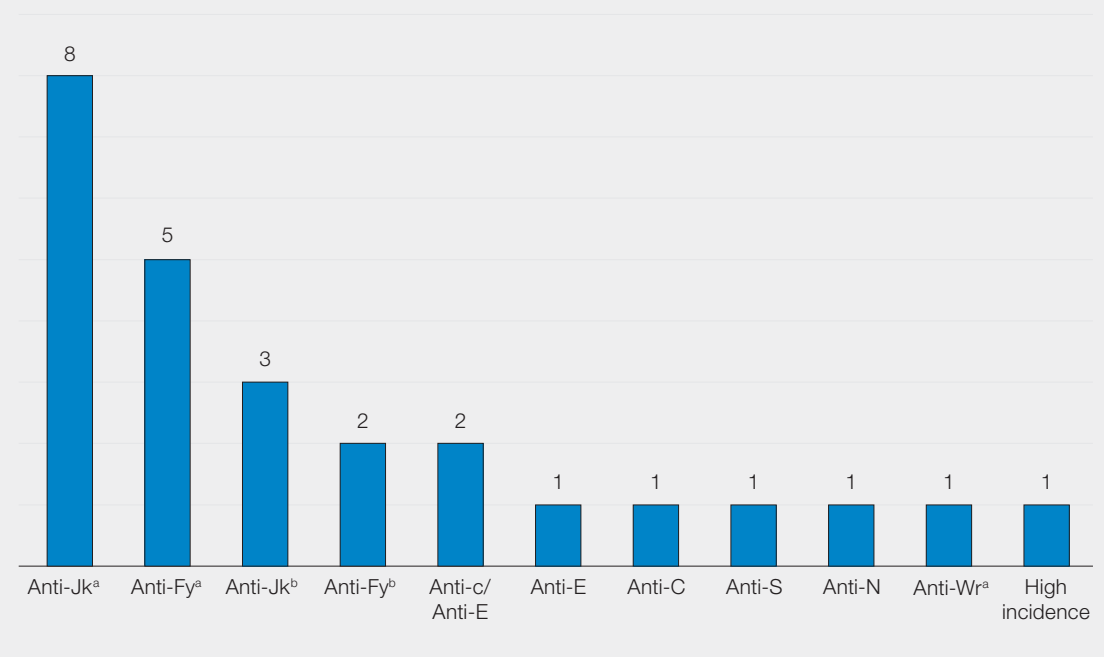


Figure 18.3: Antibody specificities implicated in DHTR

DHTR in shared care patients

In contrast to previous years, 6 cases were reported in which the patient had received the transfusion at a different hospital to the one that they presented to with symptoms of HTR. In all cases the investigation of the reaction was complicated by difficulties in obtaining details of the patient's history and pre-transfusion serology results.

Case 18.1: Diagnosis of DHTR delayed due to supply of incorrect transfusion history

A patient presented at the ED feeling unwell and experiencing thigh pain and pyrexia. The patient reported receiving a recent transfusion but when the previous hospital was contacted, they stated that the patient had only received plasma products. Laboratory results were suggestive of haemolysis with a high bilirubin, raised LDH, positive DAT and haemoglobinuria. An anti-E antibody was detected in the group and screen sample. The patient's Hb dropped to 60g/L overnight. The transfusion practitioner at the previous hospital later confirmed that the patient had received four units of red cells in her last transfusion episode at the hospital of which at least one was confirmed as positive for the E antigen.

Case 18.2: Clinical notes stated patient history not available on a haemoglobinopathy patient

Anti-S was detected in an initial sample and three units of S-negative red cells were issued by IAT crossmatch. The patient was being monitored as having a high risk for hyperhaemolysis when classical symptoms indicative of a DHTR were reported, including a falling Hb, high bilirubin, raised LDH, positive DAT and haemoglobinuria. The post-transfusion sample was DAT-positive and anti-Jk^{b} plus another possible IAT-reactive antibody were detected in addition to the anti-S. Samples were referred to the reference laboratory who confirmed they had previously investigated this patient in 2015 when they confirmed the presence of anti-Jk^{b}. This result was available on Sp-ICE. Investigation into the reaction by the hospital found that the patient had a clinical note on record stating that the ward had attempted to obtain the patients previous history, but this had not been available.

The hospital had no process in place to check patients on Sp-ICE and are looking at improving this process following this incident.

Sp-ICE was launched by NHSBT in November 2013 as a national database of patient antibody data. Initially RCI reports from 2011 were migrated to Sp-ICE but a later project uploaded reports from referrals from 31st October 2006 onwards. In 2016 the usefulness of Sp-ICE or similar national databases was discussed with a key SHOT recommendation that hospitals should take active steps to check these databases for those patients at high risk of experiencing transfusion reactions such as those with sickle cell anaemia. This recommendation was repeated in 2017, 2018, 2019 and 2021. However, each year SHOT continues to receive reports of HTR in sickle cell patients who have confirmed antibody history available on Sp-ICE. While Sp-ICE seems to be a helpful tool in helping to prevent DHTR often challenges in the blood transfusion laboratory make it difficult to use the database.

Rejected reports

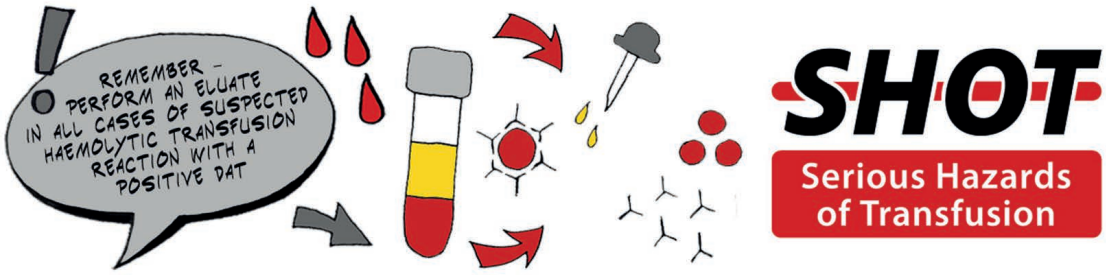
Three reports were submitted due to the detection of a new antibody specificity post transfusion, but with no detectable signs of haemolysis or other changes in the patient's serology e.g., development of a positive DAT. These cases were therefore considered as primary sensitisation to a new antibody rather than an HTR. SHOT stopped collecting data on sensitisation events in 2015, however diagnosis of HTR remains challenging and therefore the SHOT team can be contacted for advice if the reporter is unsure on whether a case is reportable to SHOT or not.

Learning point

- Identification of a new antibody without any clinical or laboratory signs of haemolysis is not indicative of HTR

Conclusion

HTR are recognised as an important cause of transfusion-associated reactions and may be subclinical, mild, or fatal. DHTR and hyperhaemolysis continue to pose diagnostic and therapeutic challenges. HTR are largely preventable and adherence to established protocols for prompt identification and timely management, as well as reporting them, remain the cornerstone of management of HTR. Patient databases such as Sp-ICE can provide vital antibody history for antibodies where the level has dropped below the detectable titre. Hospitals should have local polices to decide which patients to check on Sp-ICE or equivalent databases in the UK. All patients with laboratory evidence of haemolysis should be evaluated and followed up clinically. Procedures for investigation of transfusion reactions should be compliant with the BSH guidelines covering investigation and management of acute transfusion reactions (BSH Tinegate et al. 2012). Patients receiving transfusions should be educated about the signs and symptoms of transfusion reactions and know when and how to seek medical help.



Recommended resources

SHOT Bite No. 8: Massive Haemorrhage Delays
SHOT Bite No. 15: Hyperhaemolysis
https://www.shotuk.org/resources/current-resources/shot-bites/

References

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