Haemolytic Transfusion Reactions (HTR) n=44

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
DAT	Direct antiglobulin test
DHTR	Delayed haemolytic transfusion reactions
EPO	Erythropoietin
Hb	Haemoglobin
HT	High-titre
HTR	Haemolytic transfusion reactions
IV	Intravenous
IVIg	Intravenous immunoglobulin
LDH	Lactate dehydrogenase
Sp-ICE	Specialist Services electronic reporting using Sunquest's Integrated Clinical Environment

Key SHOT messages

- As seen in previous years, cases of hyperhaemolysis remain under-reported. It is important that there is communication between clinical teams and the transfusion laboratory to ensure these cases are reported to SHOT
- Whilst most cases of hyperhaemolysis are seen in patients with sickle cell disease, this can occasionally occur in other patient groups and a low index of suspicion is necessary
- It is important that patients are monitored for signs and symptoms of haemolytic transfusion reactions both during and following the transfusion episode

Recommendations

- Patients must be informed about the risks of transfusion reactions including delayed reactions and know when and how to seek medical help. These discussions should be part of consent pre transfusion

Action: All clinical staff involved in transfusion

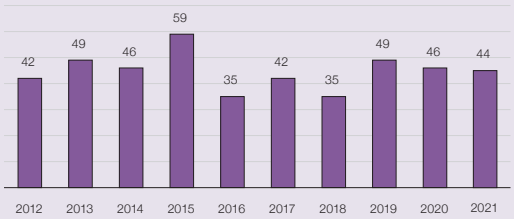
- When submitting reports to SHOT, it is important to record the treatment received by patients with hyperhaemolysis as this remains an evolving field

Action: Haemovigilance reporters

Headline data 2021

Number of reports n=44
Deaths n=1
Major morbidity n=10

HTR reports by year



Demographic data

Male n=11
Female n=33
Adults n=39
Paediatric n=4
Unknown n=1

Blood component data

Red cells n=43
Platelets n=1
Plasma n=0
Multiple components n=0
Other n=0

Number of cases n=44

A total of 44 cases have been included, 14 acute, 23 delayed reactions and 7 cases of hyperhaemolysis. The total number of reactions reported is comparable to 2020 (46 cases) and 2019 (49 cases).

All but 1 reaction occurred following red cell transfusions. One single case followed the transfusion of platelets, and this was also the only case in which the reaction was attributed to ABO antibodies. This case is described in the AHTR section.

Age range and median

The age range was 1 to 92, with a median age of 57. This is shown in Figure 18.1, broken down further by gender. HTR were reported in 4 paediatric patients. In 33/44 (75.0%) of the reactions the patient was female.

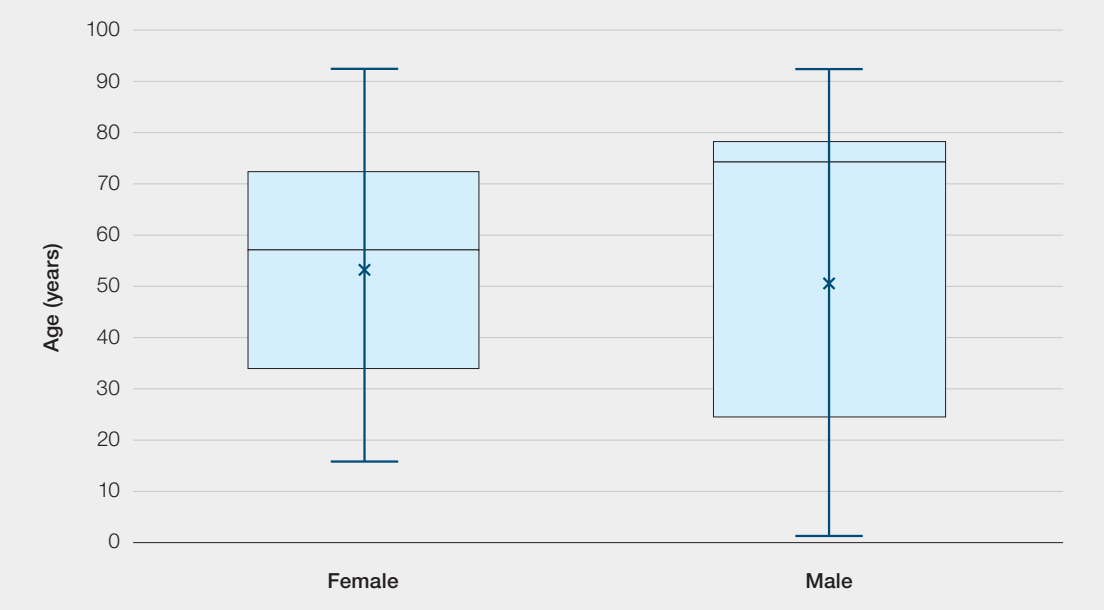


Figure 18.1: Age range in males and females experiencing an HTR

Deaths related to transfusion n=1

There was 1 death in a patient with sickle cell disease that was related to the transfusion reaction. This case is described in Chapter 23, Haemoglobin Disorders.

Major morbidity n=10

There were 10 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 4 cases of hyperhaemolysis reported with 'minor morbidity' were upgraded.

Two patients who had major morbidity following their transfusion reaction died but the death was recorded as being secondary to their underlying medical condition.

Hyperhaemolysis n=7

Five of the hyperhaemolysis cases reported occurred in patients with sickle cell disease. Hyperhaemolysis was also reported in a patient with Diamond-Blackfan anaemia and a patient with myelofibrosis post transplant.

While the majority of hyperhaemolysis is still reported in patients with sickle cell disease, a review of hyperhaemolysis reports from the last 5 years found that 5/30 (16.7%) occurred in patients with other diagnoses (Table 18.1).

Hyperhaemolysis in the last 5 years	
Sickle cell disease	25
Post transplant	2
Diamond-Blackfan anaemia	1
Myelodysplastic syndrome	1
Rosai-Dorfman syndrome	1
Total	**30**

Table 18.1: Diagnoses of patients with hyperhaemolysis reported to SHOT 2017-2021

A lower number of hyperhaemolysis cases were reported to SHOT in 2021 as compared to 2020. It is known that hyperhaemolysis is still under-reported. Staff need to be aware that all such cases should be reported to SHOT to facilitate a better understanding of this condition and identify areas for improvement. It has been reported that patients often undergo repeated episodes of hyperhaemolysis if they continue

to receive transfusions (Madu et al. 2020). Only 1 patient of the 7 cases reported to SHOT in 2021 was recorded as having had previous episodes of hyperhaemolysis.

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). Of the 7 cases reported 2 of the reactions occurred with the first 7 days post transfusion. 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).

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 18.2, which demonstrates that huge variation exists within this field.

Table 18.2: Treatment methods used for hyperhaemolysis cases reported to SHOT in 2020 and 2021

Treatment type	2020	2021
No treatment information provided	1	2
IVIg, IV steroids and EPO	1	2
IVIg and IV steroids	3	2
IVIg only	1	1
IV steroids only	2	-
IVIg and EPO	1	-

Learning points

- Hyperhaemolysis can occur in patients with a variety of diagnoses and should not be dismissed in patients without sickle cell disease
- Hyperhaemolysis continues to be under-reported. Transfusion staff are encouraged to report all cases of hyperhaemolysis to SHOT

Clinical and laboratory signs and symptoms

Acute haemolytic transfusion reactions n=14

There were 13 cases reported where patients received red cells transfusions. Alloantibodies to red cell antibodies were identified in 9 cases. The alloantibodies implicated are shown in Figure 18.2.

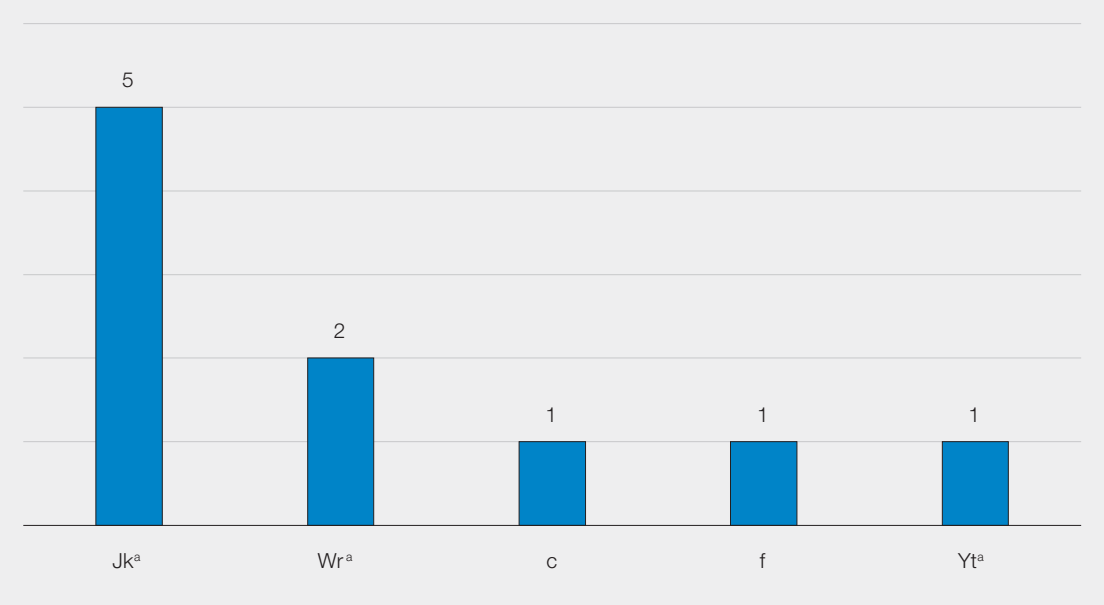


Figure 18.2: Alloantibodies reported in AHTR in 2021

There were 3 cases involving antibodies to low incidence red cell antigens: 2 due to anti-Wr^a and 1 due to anti-Kp^a. In both anti-Wr^a cases, the antibody screen had been negative, and the red cells issued by electronic issue. The post-transfusion antibody screen was also negative and the anti-Wr^a antibodies were only identified during the serological investigation following a positive repeat IAT crossmatch against the implicated unit. These cases demonstrate the importance of repeat testing against the implicated unit as part of the serological investigation of a transfusion reaction. This will allow the detection of antibodies to low incidence red cell antigens which are not expressed on the screening cells and not detectable in pre-transfusion testing or electronic crossmatching.

Reports of acute transfusion reactions emphasise the need to monitor patients closely during transfusion. This is especially important as in many cases the patients may be showing symptoms because of their underlying condition which may make the identification of a reaction more difficult.

In 2021 there was 1 AHTR due to the transfusion of non-ABO identical platelets to a patient. The last incidence of a HTR due to ABO antibodies was reported in 2016 and was also following a platelet transfusion.

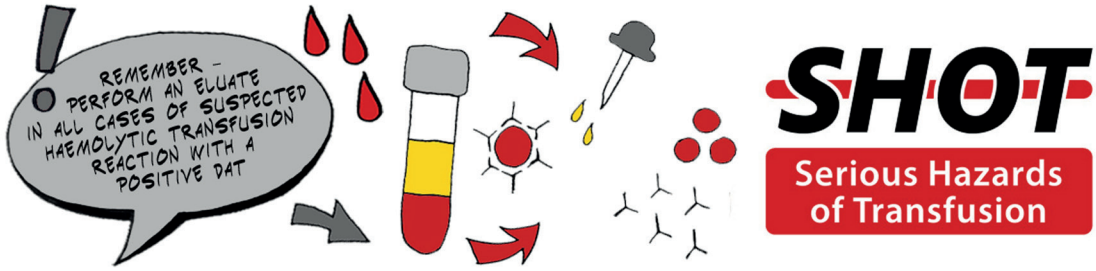
Case 18.1: Reaction due to anti-B in platelet unit

An infant with blood group AB was transfused with group A platelets. The platelets were labelled 'not for neonatal transfusion' and were not HT-negative. The patient also received a group AB red cell top up. A reaction was reported 8 hours following transfusion with an increase in the patient's bilirubin, and no Hb increment was observed following the red cell transfusion. Following investigation, it was identified that the issuing BMS in the laboratory had been focused on whether the 'not for neonatal transfusion' label was applicable to a patient >1 year of age and failed to consider the need for a HT-negative unit. Information regarding the anti-B titre in the transfused component was not available.

The risk of haemolysis due to passively transfused anti-A and anti-B is small but present and should be considered in any situation in which relatively large volumes of incompatible plasma are transfused (including platelet components). Between 2015-2021, there have been 2 cases reported to SHOT, both were due to ABO unmatched platelet transfusions in children. The case prior to the one described here was reported in 2016 where passive anti-A from a HT-negative unit of group O apheresis platelets which caused an acute reaction and haemolysis in a paediatric patient. The patient had a fall in Hb (of 22g/L) and a rise in bilirubin, with spherocytes noted on the blood film. Anti-A was confirmed in the plasma and eluate (Bolton-Maggs et al. 2017). There have been no reports in adults in the recent years. It is important to also recognise that although testing for high-titre ABO antibodies in blood donors may reduce the risk of HTR in 'out of group transfusion', it cannot be eliminated through this route. Group O platelets can cause HTR even when tested and labelled negative for high titre haemolysis. These should only be used for non-group O patients (particularly paediatric patients) as a last resort.

Learning points

- Investigation of acute transfusion reactions should include a serological crossmatch against the implicated units to facilitate the identification of antibodies directed to low incidence red cell antigens that are not routinely present in screening cells. Local processes should therefore be in place to ensure that the unit is available for a full serological investigation to take place
- The risk of haemolysis due to passively transfused anti-A and anti-B is small but present and should be considered in any situation in which relatively large volumes of incompatible plasma are transfused (including platelet components). It is important to also recognise that although testing for high-titre ABO antibodies in blood donors may reduce the risk of HTR in 'out of group transfusion', it cannot be eliminated through this route



Delayed haemolytic transfusion reactions n=23

No clinical symptoms of a transfusion reaction were reported in 9/23 DHTR cases submitted to SHOT. This remains comparable to previous years.

Antibodies were detected in 22/23 of the DHTR reported and in 20 of these cases, alloantibodies were detected in the patient's plasma post-transfusion that were not detected pre transfusion.

In every DHTR case in which the patient's bilirubin and Hb were provided, at least one of these indices was impacted and 14/23 patients diagnosed with a DHTR had exhibited both an increase in bilirubin and a drop in Hb.

The identification of a new antibody post transfusion, along with a rise in bilirubin and lack of Hb increment indicates a delayed transfusion reaction. It is important that all patients with DHTR are followed up appropriately, educated about the red cell antibodies and informed about risks with future transfusions.

Case 18.2: Investigations post transfusion identifying DHTR and prompting patient follow up

An anaemic patient was transfused two units of red cells as an outpatient. Two weeks later the patient attended for a routine check-up. DAT was positive, a new anti-Jk^a was identified and eluted from her red cells. In addition, her Hb had dropped to 64g/L from a pre-transfusion level of 78g/L with a rise in bilirubin and LDH. The transfusion laboratory recommended that the patient was monitored for a delayed transfusion reaction. A letter was sent to the patient asking her to attend the GP surgery for further blood tests at which point the patient reported that she had been feeling unwell following the transfusion and her Hb had dropped further to 49g/L.

Identification of HTR in patients

HTR is a serious complication that can occur after a blood transfusion. The identification of a reaction can be difficult as the classical symptoms often mimic symptoms of the patient's underlying diagnosis (for example, temperature increase or low Hb). It is important that all healthcare professionals involved in transfusions are aware of the signs and symptoms of transfusion reactions and take relevant actions in a timely manner. These must be investigated appropriately and reported to SHOT.

As delayed reactions typically occur after the patient has been discharged, patients need to be aware of the danger signs and know when and how to seek medical help. Appropriate post-transfusion advice must be provided to all patients.

Learning points

- 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

Antibodies implicated in HTR

Anti-Jk^{a} continues to be the most frequent antibody specificity implicated in HTR and was detected in 13/44 cases. The antibody specificities reported are shown in Figure 18.3. In 7/44 the patient had multiple red cell antibodies in the post-transfusion sample.

No serological cause for the reaction was detected in 4 of the 44 cases reported in 2021. Of these, 2/4 were in patients experiencing hyperhaemolysis. In all cases however, the patient experienced clinical symptoms of a HTR, and their laboratory results indicated haemolysis with an increased bilirubin, increased LDH and reduction in Hb, supporting this diagnosis.

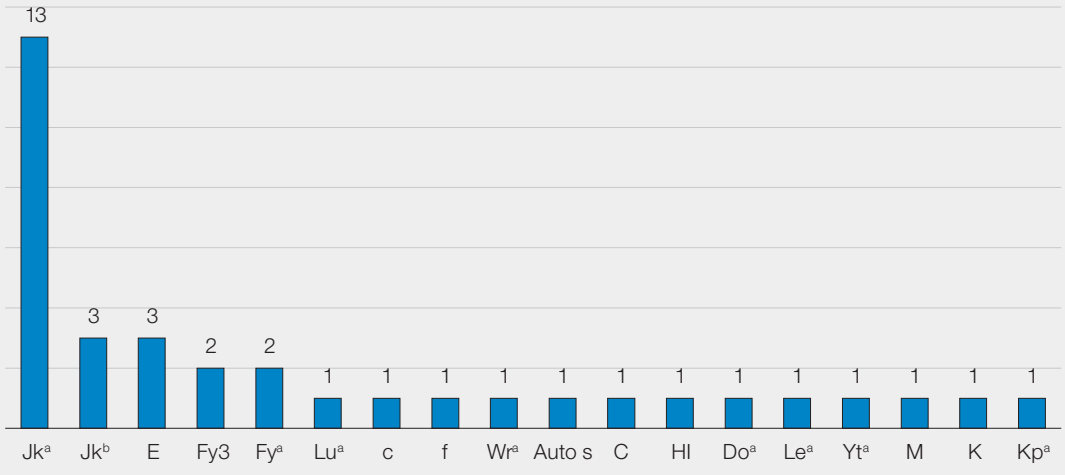


Figure 18.3: Antibody specificities implicated in HTR

Learning points

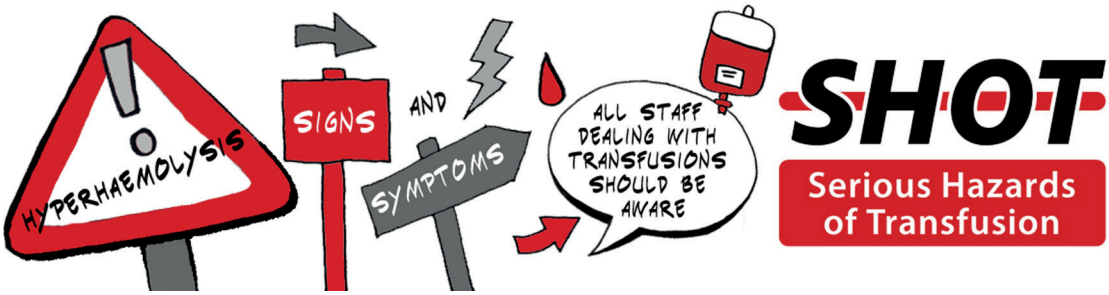
- Patients/carers should be asked if they are aware that they have any red cell antibodies as part of the pre-transfusion process. Any information obtained should be relayed by the clinical teams to the transfusion laboratory staff
- Patient databases such as Sp-ICE can provide vital antibody history 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

Conclusion

Red cell transfusions are lifesaving for patients with severe anaemia and/or bleeding and are generally safe. Haemolytic transfusion reactions most often occur when there is immunologic incompatibility between a transfusion recipient and the red blood cells from the blood donor. The main determinants of severity, site of haemolysis (intravascular or extravascular), and timing are the specific red cell antigens, and the nature and titre of alloantibodies present at the time of transfusion. 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. Hyperhaemolysis is one of the main causes of major morbidity and mortality reported in haemolytic transfusion reactions. Hyperhaemolysis is usually reported in patients with haemoglobinopathies, however it has also been observed in non-haemoglobinopathy patients. It is therefore important that all clinicians involved in the transfusion process have an awareness of the signs and symptoms of hyperhaemolysis and that any suspected cases are investigated and managed appropriately.

Recommended resource

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



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