Haemolytic Transfusion Reactions (HTR) n=51

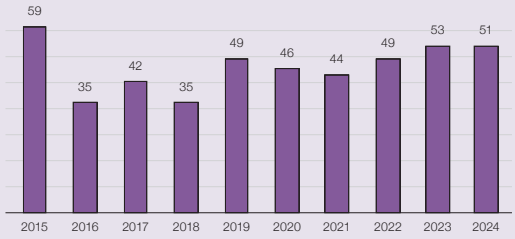
21

Authors: Tracey Tomlinson and Anicee Danaee

Headline data 2024

Number of reports n=51
Deaths n=3
Major morbidity n=14

HTR reports by year



Demographic data

Male n=24
Female n=27
Adults n=45
Paediatric n=6

Blood component data

Red cells n=51
Platelets n=0
Plasma n=0
Multiple components n=0

Key findings:

- The number of HTR cases reported to SHOT each year remain stable
- Antibodies to the Kidd blood group system (anti-Jk^{a} and anti-Jk^{b}) are most commonly implicated in causing delayed HTR
- Most cases of hyperhaemolysis were reported in patients with sickle cell anaemia

Gaps identified:

- Incomplete investigations in patients with suspected HTR
- Direct antiglobulin tests (DAT) and elution studies on the post-transfusion sample are inconsistently performed making it difficult to distinguish between a HTR and haemolysis due to other causes
- Partial information submitted to SHOT makes it difficult to assess the effectiveness of the various treatment options available to manage hyperhaemolysis

Good practice:

- Lifesaving transfusions were provided even in the absence of suitable antigen-negative blood. In urgent clinical situations where suitable components are not available it may be necessary to transfuse red cell units which are positive for a confirmed antibody. Where this occurs the patient must be closely monitored for signs of a HTR

Next steps:

- Adequate and thorough laboratory investigations should be carried out in patients with suspected HTR
- Relevant information should be provided to SHOT to facilitate effective analysis

For all abbreviations and references used, please see the **Glossary** and **Reference list** at the end of the full Annual SHOT Report. Please see the supplementary information on the SHOT website (https://www.shotuk.org/shot-reports/annual-shot-report-2024/).

Definition:

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.

Introduction

A total of 51 cases have been included: 16 acute reactions, 21 delayed reactions and 14 cases of hyperhaemolysis. The total number of reactions reported is comparable to previous years.

All reported cases occurred following red cell transfusions.

The age range of the patients affected was 3 to 83, with a median age of 40. This is shown in Figure 21.1, broken down further by gender. HTR were reported in 6 paediatric patients, which is a slight increase from previous years (2 in 2023 and 5 in 2022). Reactions in female patients accounted for 27/51 (52.9%) of the reactions.

Figure 21.1: Age range in males and females experiencing a HTR in 2024

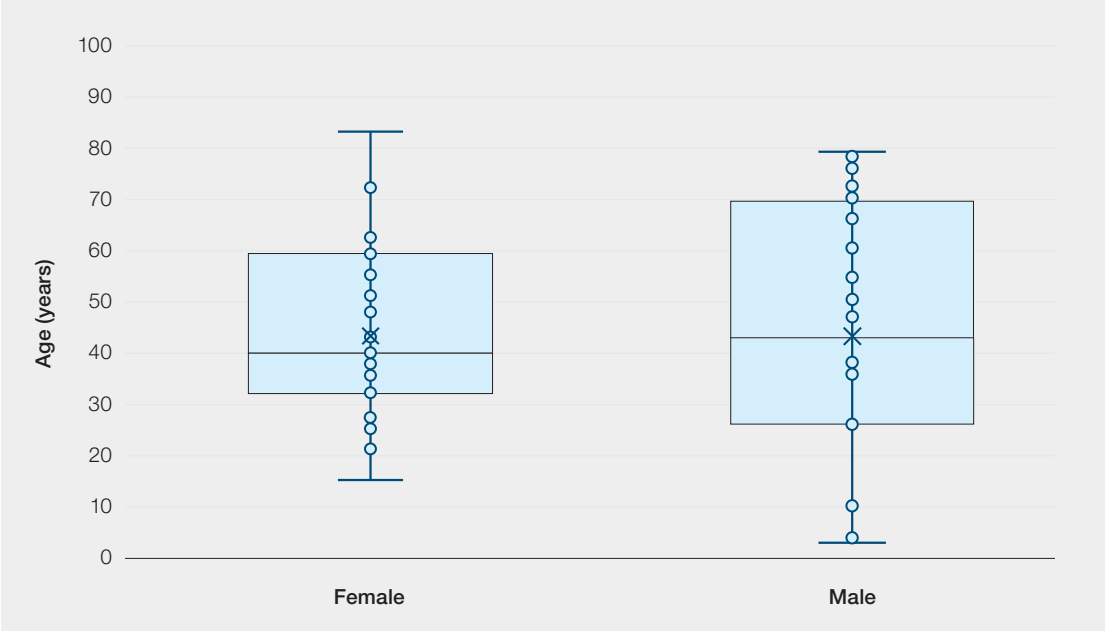


Figure 21.1 is a box and whisker diagram showing the median age and the age range of patients experiencing a HTR reported to SHOT separated by gender. The middle bar in the shaded box indicates the median age, the outer bars of the box represent the upper and lower quartiles. The lines extending from the boxes (whiskers) indicate the lowest and highest values.

Deaths related to transfusion n=3

There were 3 deaths in which the transfusion reaction contributed to the patient death, all in patients with sickle cell anaemia.

Case 21.1: Patient death following an AHTR (imputability 1 – possible)

A patient with a history of multiple red cell antibodies (anti-Co^{b}, -E, -S, -Le^{a} plus an auto and non-specific antibody), reacted to the first unit transfused as part of a routine red cell exchange transfusion to manage the symptoms associated with sickle cell anaemia. During the transfusion, the patient reported feeling unwell with lumbar pain. The transfusion was stopped, and the patient was treated for a suspected transfusion reaction. Serological investigation of the implicated unit demonstrated a positive crossmatch with both the pre- and post-transfusion samples and anti-Co^{b} was identified in the eluate prepared from the patient's red cells. Despite supportive measures, and management in the intensive care unit (ICU), the patient deteriorated and died 5 days later.

Case 21.2: Patient death following hyperhaemolysis (imputability 2 – probable)

A patient presented in hospital with a suspected sickle crisis. They were transfused two units of red cells and discharged home the following day. The patient re-presented 6 days later reporting general weakness and continued pain. The patient's Hb had fallen to below the pre-transfusion level and they exhibited multiple markers of haemolysis. The patient was admitted to the ICU and died 2 days later.

The 3rd case was a death following hyperhaemolysis and is discussed in detail in Chapter 26, Haemoglobin Disorders (Case 26.1).

Major morbidity n=14

SHOT considers that all reported cases of probable hyperhaemolysis, where there is a significant fall in Hb level, should be considered as major morbidity. Following application of this criterion 12 cases of hyperhaemolysis were upgraded from a reported 'minor morbidity' to major morbidity. The remaining 2 cases of major morbidity occurred following DHTR. In both cases the patient had received clinically indicated urgent transfusions and required additional clinical interventions to manage the transfusion reaction.

Hyperhaemolysis n=14

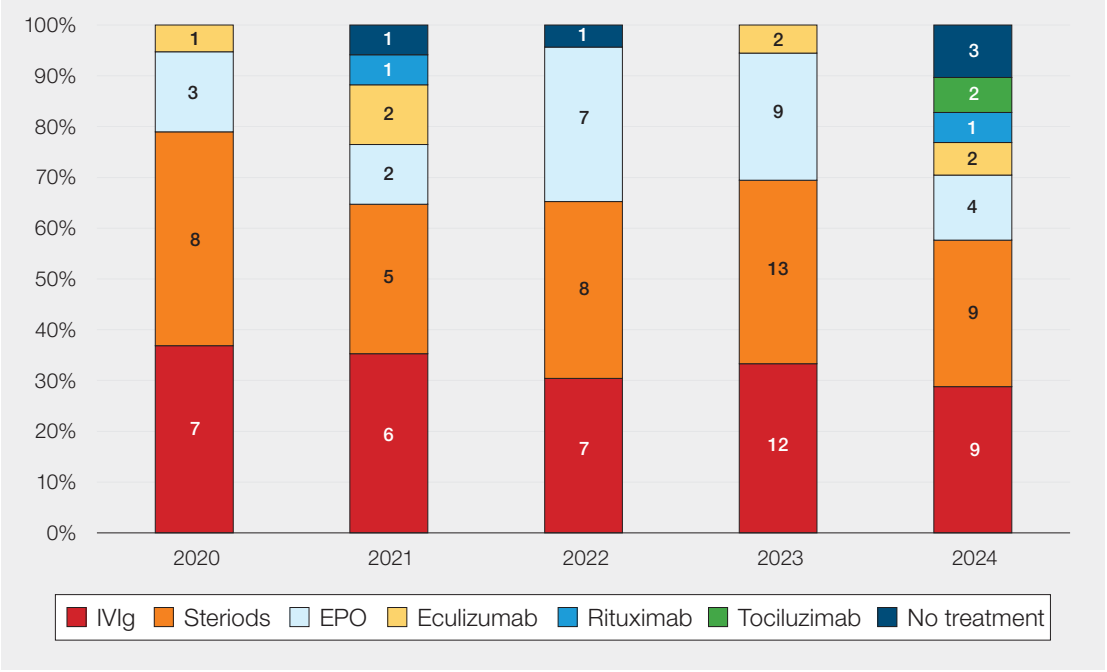
Eleven hyperhaemolysis cases reported occurred in patients with sickle cell anaemia. The remaining 3 cases occurred in a single patient with severe immunodeficiency who experienced multiple reactions over a 10-day period (see Case 25.9 in Chapter 25, Paediatric Cases).

Hyperhaemolysis can be divided into acute and delayed hyperhaemolysis. 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). Seven cases reported the reactions occurred within the first 7 days post transfusion.

Treatment in hyperhaemolysis

SHOT has been requesting information on treatment modalities used to manage hyperhaemolysis since 2020. The aim is to provide a better understanding of practice nationally, improve and share knowledge. Eculizumab has been licensed to treat ongoing brisk haemolysis (NHSE, 2020) and was reported as being used in 2 cases in 2024. There was 1 additional case in which rituximab was given to treat the hyperhaemolysis. SHOT data shows that patients are generally treated with a combination of intravenous immunoglobulin (IVIg), steroids and erythropoietin (EPO). Figure 21.2 illustrates the treatments used in the management of hyperhaemolysis cases reported to SHOT 2020-2024. In 2 cases, tocilizumab was used to treat hyperhaemolysis and has been included in the figure. It is important to note that combinations of different treatments are often used to manage hyperhaemolysis, with no clear trends. Further details can be found in the supplementary material of this chapter.

Figure 21.2: Treatments used to manage hyperhaemolysis (2020-2024)



Clinical and laboratory signs and symptoms

Acute haemolytic transfusion reactions n=16

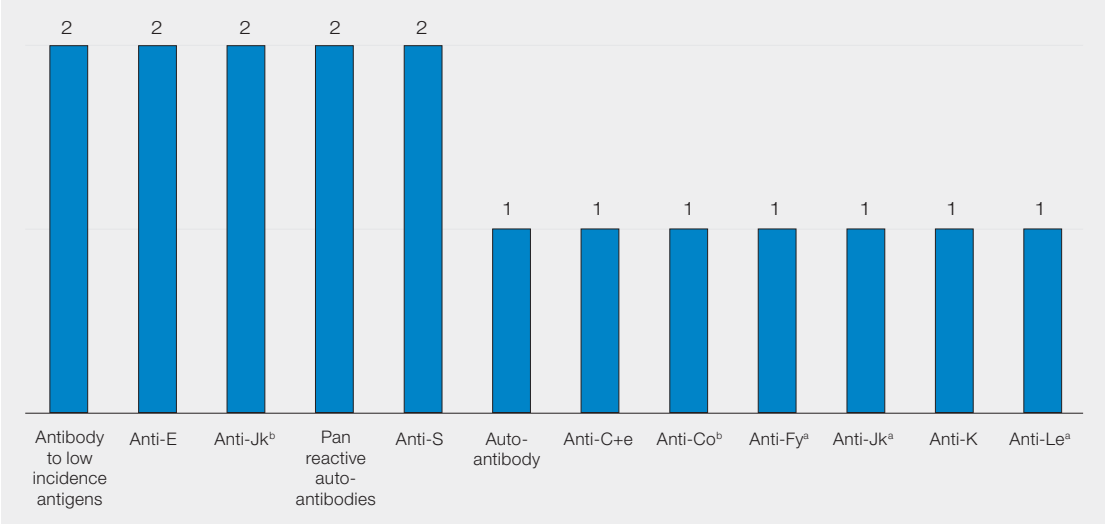
Clinical symptoms of a transfusion reaction were observed in 15/16 reports. Alloantibodies to red cell antigens were identified in 12 of the 16 AHTR cases reported. The alloantibodies implicated are shown in Figure 21.3.

In 2 cases where no alloantibodies were detected, a strongly active pan-reactive warm autoantibody was detected. A further case had an auto anti-D and auto anti-C.

In 3 AHTR cases, the patients received urgent transfusion of antigen-positive red cell components with input from consultants with transfusion expertise. 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 (SHOT, 2025c).

There were 3 reactions attributed to antibodies to low incidence antigens (1 anti-Wr^{a} and 2 unidentified). However, reactions to these antibodies remain rare.

Figure 21.3: Antibodies implicated in AHTR in 2024



Delayed haemolytic transfusion reactions n=21

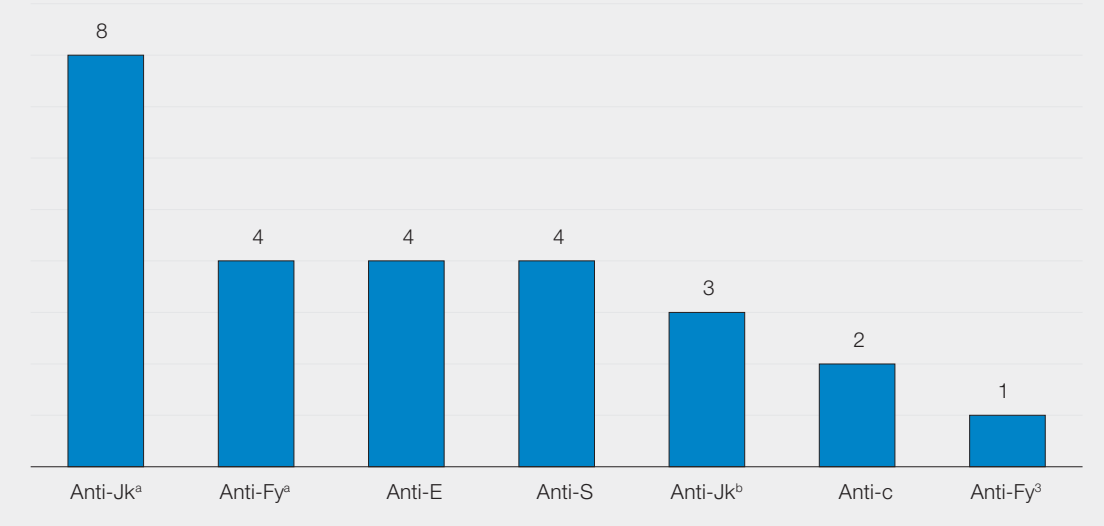
No clinical symptoms of a transfusion reaction were reported in 10/21 DHTR cases submitted to SHOT but in all cases a lack of sustained Hb increment following transfusion was described.

Antibodies to the Kidd blood group system remain the most frequently implicated antibodies in DHTR (Figure 21.4).

Case 21.3: DHTR due to anti-Jk^a

A positive antibody screen was detected prior to transfusion. Antibody identification was performed by the reference laboratory but the antibody was mistakenly identified as anti-K. K-negative units were crossmatched and transfused, however the patient later showed symptoms of a delayed transfusion reaction. On investigation of the cause of the reaction, it was identified that the antibody detected pre transfusion was actually an anti-Jk^a.

Figure 21.4: Antibodies implicated in DHTR in 2024



In 8/21 DHTR cases, the patient had multiple red cell antibodies detected post transfusion. In cases where an eluate was performed, detection of an antibody in the eluate was considered as evidence of that specificity being the cause of the reaction. Elution studies and DAT tests are considered a key test in the diagnosis of a HTR. This can help distinguish between a true HTR and cases in which the observed clinical features and laboratory results are indicative of the patient's underlying condition. DAT was performed on the post-transfusion sample in all cases, however an eluate was not reported in 6/21 DHTR and 5/16 AHTR. Relevant diagnostic workup is vital to correctly diagnose and report transfusion reactions.

Mitigating the risk of HTR

HTR, when they occur, can be very distressing to both patients and the treating clinical teams. Whilst it is impossible to prevent all HTR, the risk can be mitigated by robust pre-transfusion procedures which includes determining if the patient has a history of red cell antibodies. This is especially true for DHTR, which are often caused by previously identified red cell antibodies dropping to undetectable levels in the pre-transfusion antibody screen. Issuing antibody cards to patients with red cell antibodies has been used to inform patients and alert clinical teams. The effectiveness of these depends on the patient showing the card to their healthcare professional prior to transfusion testing and for this information to be relayed to the blood transfusion laboratory. Another method is the use of national antibody databases, such as Specialist Services Integrated Clinical Environment (Sp-ICE), however these are not interfaced with laboratory computer systems and therefore add an additional step to the pre-transfusion process, which is often omitted. Further work is therefore required to address this issue. Alternative methods to share important safety information including the presence of red cell antibodies need to be investigated, for example, by including it on the electronic patient record.

Conclusion

Diagnosis of a HTR can be difficult as many of the classically associated clinical symptoms can also be seen in a number of clinical conditions for which a transfusion is prescribed. In these cases, changes in the results of laboratory tests can be instrumental in providing evidence to confirm a suspected transfusion reaction. Examples include the Hb falling below pre-transfusion levels, the development of a positive DAT in HTR and reticulocyte levels falling in hyperhaemolysis. It is therefore vital that robust laboratory testing is performed when a HTR is suspected.

Providing all relevant details in incident reports submitted to SHOT including results from laboratory investigations supports better understanding, effective analysis and meaningful learning to improve transfusion safety. The SHOT team contacts the reporter to request this information when this is not provided. Over recent years, SHOT has seen a gradual decline in this information being provided within reports. This makes it increasingly difficult for SHOT working experts to distinguish the true reactions and has a negative impact on the quality of the haemovigilance data available for analysis.

Preventing, identifying, treating and reporting HTR requires careful co-ordination, collaboration and communication between multiple clinical and laboratory teams.

Recommended resources

SHOT Bite No. 8: Massive haemorrhage – delayed transfusion
https://www.shotuk.org/resources/shot-bite-no-8/

SHOT Bite No. 15: Hyperhaemolysis
https://www.shotuk.org/resources/shot-bite-no-15/

SHOT Bite No. 31: The role of Sp-ICE in preventing Haemolytic Transfusion Reactions (HTR)
https://www.shotuk.org/resources/shot-bite-no-31/