19 Haemolytic Transfusion Reactions (HTR) n=53

Authors: Tracey Tomlinson and Anicee Danaee

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.

Abbreviations used in this chapter

AHTR	Acute haemolytic transfusion reaction
DAT	Direct antiglobulin test
DHTR	Delayed haemolytic transfusion reaction
ED	Emergency department
EPO	Erythropoietin
Hb	Haemoglobin
HTR	Haemolytic transfusion reaction
ICU	Intensive care unit
IV	Intravenous
IVIg	Intravenous immunoglobulin
LDH	Lactate dehydrogenase
SCD	Sickle cell disease
Sp-ICE	Specialist Services Integrated Clinical Environment

Key SHOT messages

- Avoidable transfusion/s continue to be reported resulting in patient death and major morbidity
- Poor communication contributes to incidents
- While there has been an increase in the number of cases of hyperhaemolysis reported in 2023, it remains under-recognised and under-reported

Recommendations

- Effective communication is vital to maintain transfusion safety, this includes communicating the reasons for, and risks of transfusion to the patient, communication between clinical areas and communication between hospitals

Action: All staff involved in transfusion

- Provide as much information as possible to SHOT when reporting, including the investigations performed, treatment modality and patient outcome

Action: Haemovigilance reporters

- Do not withhold lifesaving transfusion, even if the patient has a history of alloantibodies, and carefully monitor the patient for signs and symptoms of a haemolytic transfusion reaction

Action: Clinical staff involved in transfusion

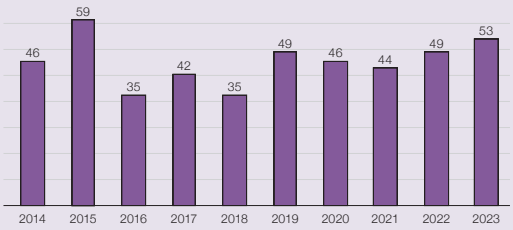
- Laboratory protocols should include a full investigation for HTR which might include referring samples when resources for testing are not available locally

Action: Laboratory staff involved in transfusion

Headline data 2023

Number of reports n=53
Deaths n=2
Major morbidity n=18

HTR reports by year



Demographic data

Male n=22
Female n=31
Adults n=49
Paediatric n=2
Unknown n=2

Blood component data

Red cells n=53
Platelets n=0
Plasma n=0
Multiple components n=0

Introduction

A total of 53 cases have been included, 9 acute, 31 delayed reactions and 13 cases of hyperhaemolysis. The total number of reactions reported is comparable to 2022 (49 cases), 2021 (44 cases) and 2020 (46 cases) but demonstrates a small increasing trend.

All reported cases occurred following red cell transfusions.

Age range and median

The patient's age was not provided in 2 reports (1 male patient and 1 female patient). The age range in the remaining cases was 12 to 95, with a median age of 47. This is shown in Figure 19.1, broken down further by gender. HTR were reported in 2 paediatric patients. In 31/53 (58.5%) of the reactions the patients were female.

Figure 19.1: Age range in males and females experiencing a HTR in 2023

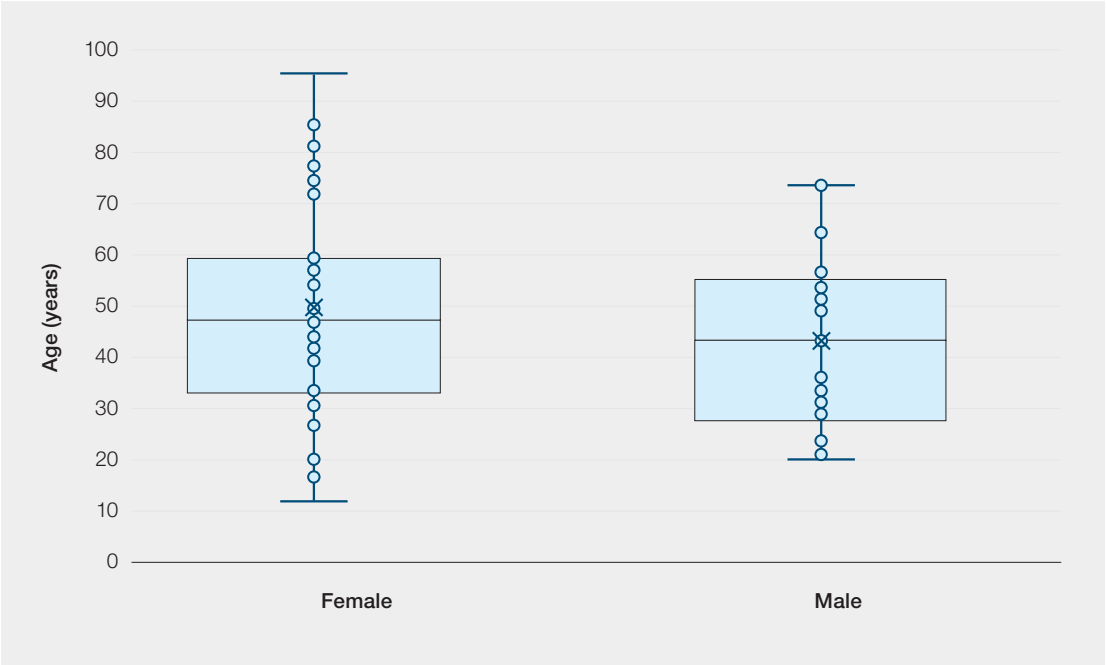


Figure 19.1 is a box and whisker diagram showing the median age and the age range of patients experiencing a HTR reported to SHOT separated by gender. The middle bar in the shaded box indicates the median age, the outer bars of the box represent the upper and lower quartiles. The lines extending from the boxes (whiskers) indicate the lowest and highest values.

Deaths related to transfusion n=2

Two deaths related to the transfusion reactions were reported (imputability 2). Both reactions occurred in patients with SCD.

Case 19.1: Fatal haemolytic transfusion reaction following unnecessary elective exchange transfusion

A patient with SCD was scheduled for an exchange transfusion in advance of elective surgery. The patient was informed that the surgery had been cancelled and despite this being communicated to the patient in advance of the transfusion, this information was not communicated to the haematology team and the exchange transfusion went ahead. Five days later the patient presented at the ED with severe pain and symptoms consistent with a delayed HTR. The patient later collapsed and suffered a cardiac arrest.

Case 19.2: Death attributed to hyperhaemolysis with delays in treatment

A patient with SCD and an existing heart condition presented to haematology outpatients with severe pain 5 days post transfusion. The patient did not have an appointment and was told to go to ED where they were admitted for suspected hyperhaemolysis and transferred to the ICU. The patient was treated with IVIg, methylprednisolone and eculizumab and was showing signs of recovery when they suffered cardiac arrest and died.

Major morbidity n=18

There were 18 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 6 cases of hyperhaemolysis reported with 'minor morbidity' were upgraded.

Hyperhaemolysis n=13

All 13 hyperhaemolysis cases reported occurred in patients with SCD. While the majority of hyperhaemolysis cases continue to be reported in this patient group, hyperhaemolysis does occur in other patient groups as shown in Table 19.1.

Clinical condition	Acute reaction	Delayed reaction	Total
SCD	26	21	**47**
T-cell lymphoma	1	0	**1**
Dosai-Dorfman syndrome	1	0	**1**
Myelodysplastic syndrome	0	1	**1**
Diamond-Blackfan anaemia	0	1	**1**
Myelofibrosis post transplant	1	0	**1**
Non-Hodgkin lymphoma	1	0	**1**
Total	**30**	**23**	**53**

Table 19.1: Hyperhaemolysis cases reported between 2017 and 2023

While the number of hyperhaemolysis cases reported in 2023 was comparable to previous years, it is suspected that hyperhaemolysis is still under-reported. 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).

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). Six cases reported the reactions occurred within the first 7 days post transfusion.

Treatment in hyperhaemolysis

SHOT started requesting information on the treatment used to manage patients experiencing hyperhaemolysis in 2020. The aim is to provide a better understanding of practice nationally and improve and share knowledge. Eculizumab has been licensed to treat ongoing brisk haemolysis (NHSE, 2020) and was reported as being used in 1 case. SHOT data shows that patients are generally treated with a combination of IVIg, IV steroids and EPO. A summary of the treatment methods reported is provided in Figure 19.2. This demonstrates a move towards more aggressive treatment regimens with 12/13 (92.3%) patients receiving two or more different treatments in 2023.

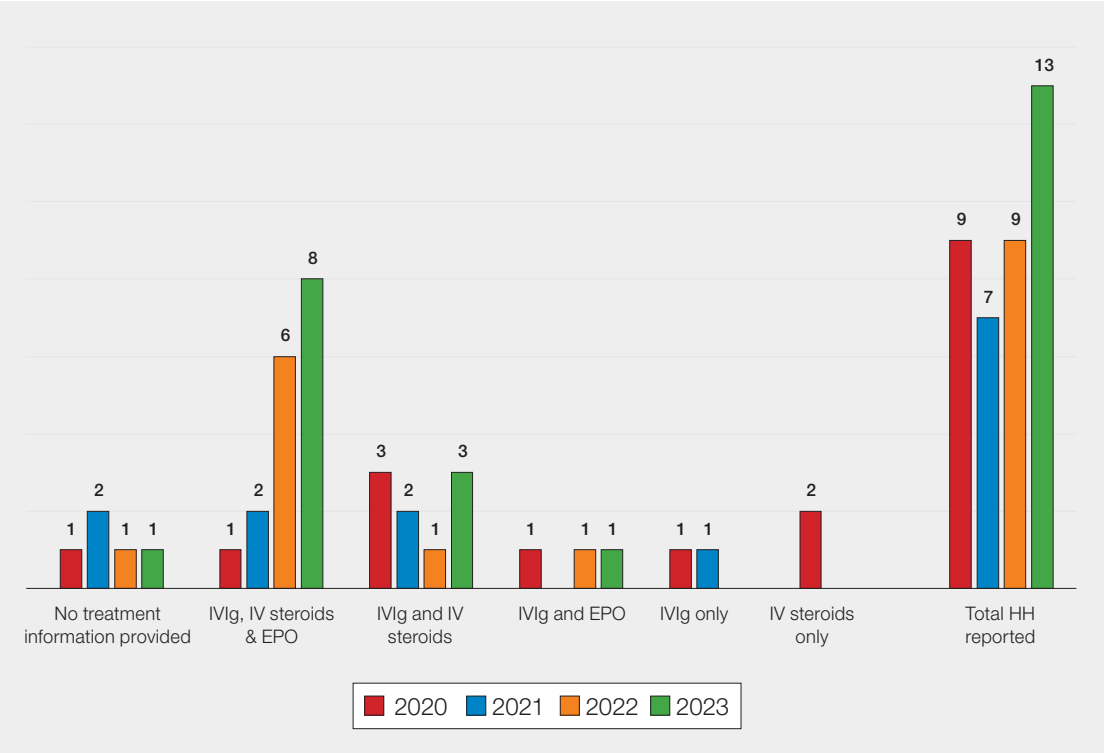


Figure 19.2: Treatments used to manage hyperhaemolysis

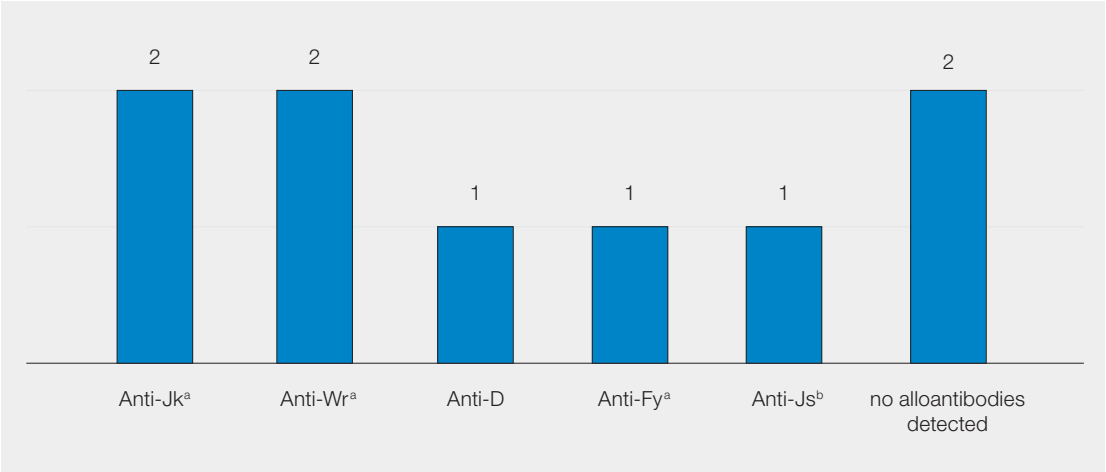
EPO=erythropoietin; HH=hyperhaemolysis; IV=intravenous; IVIg=intravenous immunoglobulin

Clinical and laboratory signs and symptoms

Acute haemolytic transfusion reactions n=9

Alloantibodies to red cell antigens were identified in 7 of the 9 AHTR cases reported. The alloantibodies implicated are shown in Figure 19.3.

Figure 19.3: Alloantibodies reported in AHTR in 2023



There were 2 cases reported in which no alloantibodies were detected. In 1 case the patient had a strongly active warm autoantibody. In the other case the antibody screen was negative in both the pre- and post-transfusion samples. The DAT was positive post transfusion but unfortunately an eluate was not performed.

In 4 cases, antigen-positive red cells were transfused urgently following advice from specialist transfusion medical staff.

The remaining case involved the presence of an anti-Js^{b} antibody.

Case 19.3: Acute haemolytic transfusion reaction in a patient with known anti-Js^{b}

A patient with a history of anti-Js^{b} was scheduled for major surgery with a high expected blood loss. Js^{b} antigen-negative blood is rare, with 100% of caucasians being Js^{b}-positive (Reid, et al., 2012) however two Js^{b}-negative units were provided from the Blood Service frozen blood bank and issued to the patient. Some additional 'best matched' Js^{b} untyped units were also crossmatched on standby in case of major blood loss which were placed in the theatre blood refrigerator in error. During the surgery a one-unit top-up transfusion was prescribed. One unit of the 'best matched' red cells was taken and transfused despite the compatible Js^{b}-negative units being available for transfusion. The patient immediately started to exhibit symptoms of an acute transfusion reaction but recovered fully following appropriate management.

Learning points

- 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 using concessionary release. An example form is outlined in the BSH 2013 guideline, appendix 9 (Milkins, et al., 2013)
- Where patients have complex blood requirements, the transfusion plan should clearly define blood availability and use

Delayed haemolytic transfusion reactions n=31

No clinical symptoms of a transfusion reaction were reported in 8/31 DHTR cases submitted to SHOT and in all 31 cases a lack of sustained Hb increment following transfusion was described.

Antibodies were detected in 28/31 of the DHTR reported and in 25 of these cases, alloantibodies were detected in the post-transfusion plasma that were not detected pre transfusion. In 5 of these cases, the antibody specificity implicated had been previously reported on Sp-ICE. One case involved the transfusion of antigen-positive emergency O D-negative red cells in an emergency.

Antibodies to the Kidd blood group system remain the most frequently implicated antibodies in DHTR however in contrast to previous years, in 2023, there were more cases due to anti-Jk^{b} than anti-Jk^{a} (Figure 19.4).

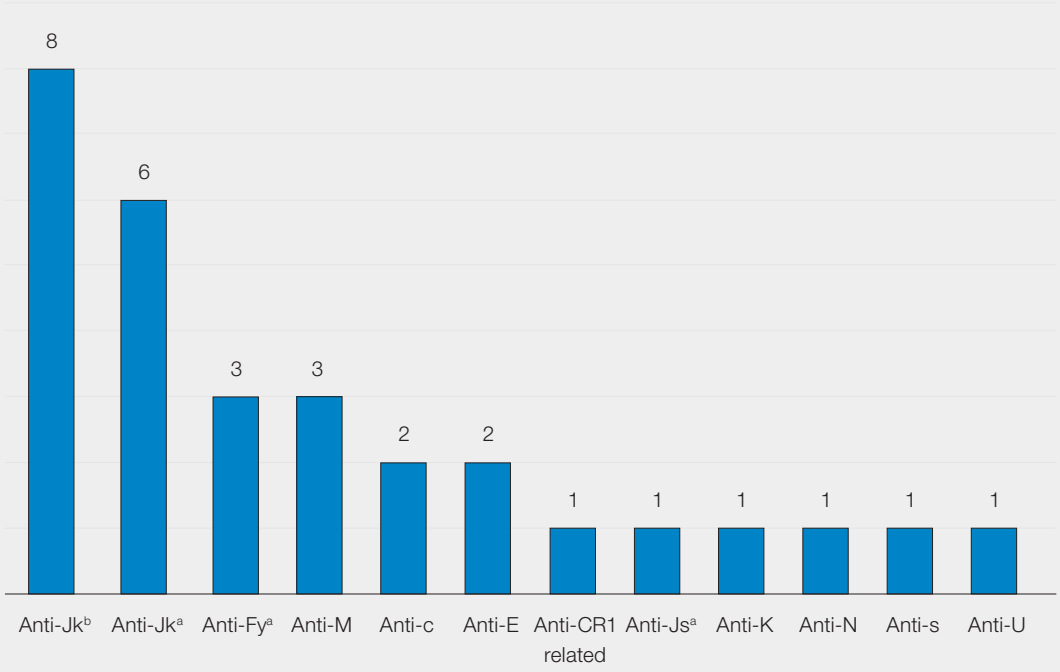
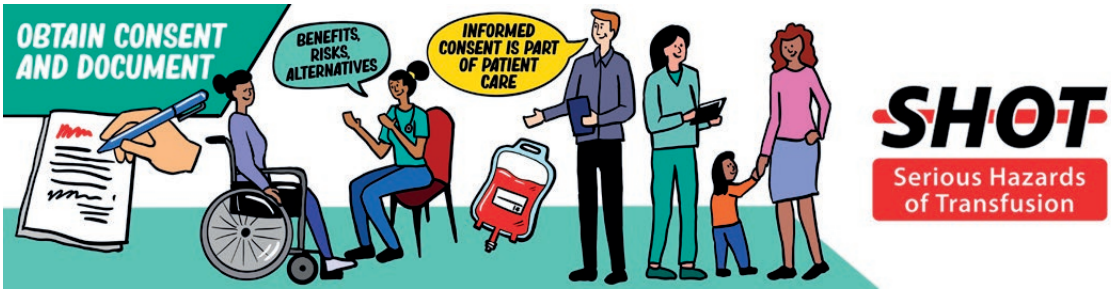


Figure 19.4: Alloantibodies implicated in DHTR in 2023

Unnecessary transfusions

There were 2 HTR reported in 2023 in patients whose transfusions were not indicated by current guidelines. One of these cases resulted in a patient death and has been described earlier in this chapter. The other transfusion was for a patient with iron deficiency.

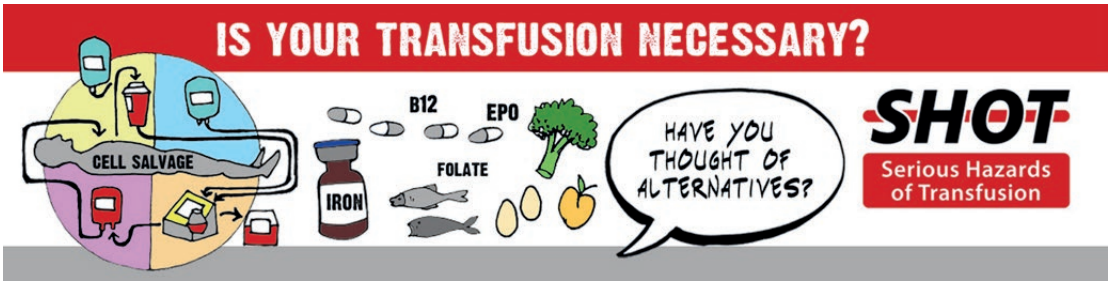
There was 1 further case reported in which the reason for transfusion and patient consent was not recorded in the patients notes and therefore the appropriateness of the transfusion cannot be assessed.



While the safety of transfusion continues to improve, it must be remembered that it is not without risks. Care should be taken to ensure that transfusions are only given where indicated and supported by published guidelines.

Learning point

- Transfusions should only be given where indicated and supported by published guidelines



Quality of data

Two potential cases had to be rejected due to insufficient information being available in the report to allow confirmation. Further cases which were included had key information missing from the report that limited the analysis of these cases. Examples of missing information included patient age, underlying clinical condition, reason for transfusion and the outcome of the laboratory investigations performed.

Conclusion

HTR continue to be a cause of transfusion-associated reactions and it is important that both clinical teams and patients are educated in the signs and symptoms of a HTR to allow their prompt management.

Many HTR, especially DHTR, are largely preventable and local protocols should be in place to reduce the risk, including the use of patient databases such as Sp-ICE, to identify historical antibody information.

All HTR should be reported to SHOT with as much information as possible provided to facilitate a better understanding of gaps in management and inform recommendations to improve safety.

Recommended resources

SHOT Bite No. 8: Massive Haemorrhage Delays
SHOT Bite No. 15: Hyperhaemolysis
SHOT Bite No. 31: Sp-ICE
https://www.shotuk.org/resources/current-resources/shot-bites/

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