Haemolytic Transfusion Reactions (HTR) n=46

19

Authors: Tracey Tomlinson and Anicee Danaee

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.

Key SHOT messages

- Monitoring the key markers of haemolysis pre and post transfusion is important to allow the identification and classification of haemolytic transfusion reactions
- Reporters should include all relevant clinical and laboratory details when reporting cases with hyperhaemolysis. This will help improve understanding of the management of this complex syndrome
- Monitoring the patient's reticulocyte and ferritin levels can help to distinguish hyperhaemolysis from other haemolytic transfusion reactions

Abbreviations used in this chapter

AHTR	Acute haemolytic transfusion reactions	**HTR**	Haemolytic transfusion reactions
BSH	British Society for Haematology	**IV**	Intravenous
DAT	Direct antiglobulin test	**IVIg**	Intravenous immunoglobulin
DHTR	Delayed haemolytic transfusion reactions	**LDH**	Lactate dehydrogenase
EPO	Erythropoietin	**Sp-ICE**	Specialist Services electronic reporting using Sunquest's Integrated Clinical Environment
Hb	Haemoglobin	**TACO**	Transfusion-associated circulatory overload

Recommendations

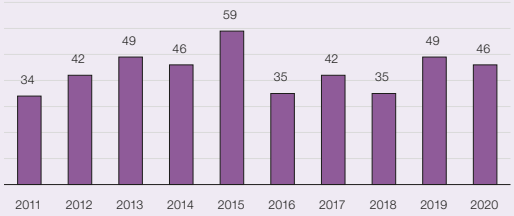
- Controls should be in place to ensure compliance with British Society for Haematology (BSH) guidelines relating to management of transfusions in patients with sickle cell disease and thalassaemia including pre-transfusion compatibility procedures in blood transfusion (BSH Milkins et al. 2013). Local hospital transfusion policies and procedures should reflect these guidelines
- 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)

Action: Hospital transfusion teams, hospital transfusion committees, laboratory management

Headline data 2020

Number of reports n=46
Deaths n=0
Major morbidity n=12

HTR reports by year



Demographic data

Male n=21
Female n=25
Adults n=43
Paediatric n=3

Blood component data

Red cells n=46
Platelets n=0
Plasma n=0
Multiple Components n=0
Other n=0

Number of cases n=46

A total of 46 cases have been included, 12 acute, 25 delayed reactions and 9 cases of hyperhaemolysis. The total number of cases is comparable to the 49 cases reported in 2019, however it must be noted that the total numbers of transfusions occurring in 2020 was reduced due to a decrease in elective procedures during the COVID-19 pandemic.

One HTR case resulted from emergency transfusion of antigen-positive blood due to clinical need for immediate transfusion.

In 1 case of acute HTR, the patient also experienced TACO and this is included and discussed in more detail in Chapter 18b, Transfusion-Associated Circulatory Overload (TACO).

Age range and median

The age range was 8 to 95, with a median age of 57. This is shown in Figure 19.1, broken down further by patient gender. HTR were reported in 3 paediatric patients.

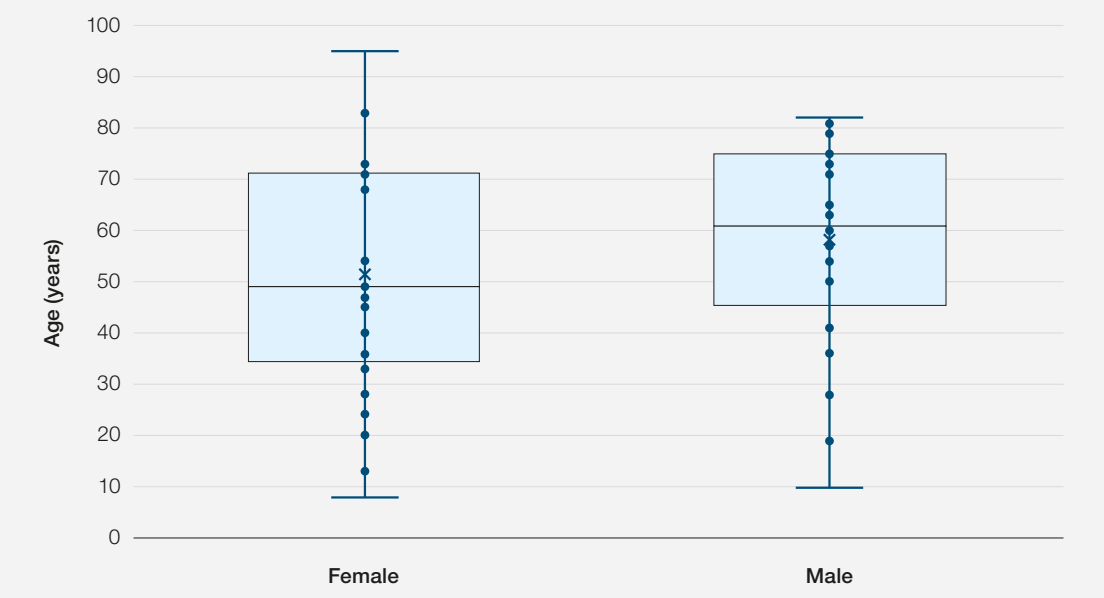


Figure 19.1: Age range in males and females experiencing a HTR

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 n=0

There were no patient deaths reported resulting from haemolytic transfusion reactions.

Major morbidity n=12

There were 12 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 all cases of hyperhaemolysis reported with 'minor morbidity' were reclassified.

Hyperhaemolysis n=9

Nine cases of hyperhaemolysis syndrome were reported which is a significant increase from previous years (4 were reported in 2019). All these cases were reported in patients with sickle cell anaemia, and each patient made a full recovery. It is likely that this increase in reports is related to an increase in awareness of hyperhaemolysis syndrome amongst clinical teams leading to better diagnosis, treatment and haemovigilance reporting. However, it is likely that hyperhaemolysis is still under-reported. Ongoing education is required to ensure that all cases are submitted to SHOT.

Historically it has been difficult to distinguish hyperhaemolysis from other HTR. 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). In 2020 SHOT started collecting data on these results. The patient's pre-transfusion and post-transfusion reticulocyte level was provided in 5/9 reports and in all 5 cases the reticulocyte count did drop. Unfortunately, the pre- and post-transfusion ferritin results were only provided in 1/9 reports however this did show a dramatic increase from 46 to 540ng/mL. If a pre-transfusion ferritin level is not available serial monitoring with steep increases in ferritin combined with falling Hb and a drop in reticulocyte count will help support the diagnosis of hyperhaemolysis syndrome.

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). Of the 9 cases reported 7 of the reactions occurred within the first 7 days post transfusion.

Treatment of hyperhaemolysis

Various treatment protocols for management of hyperhaemolysis have been suggested including the use of IVIg, steroids and EPO. There have been no published randomised trials in the effectiveness of these however eculizumab has been licensed to treat ongoing brisk haemolysis (NHS England 2020). The treatment methods used in the 9 hyperhaemolysis cases reported in 2020 is summarised in Table 19.1.

Table 19.1: Summary of treatment protocols used

Treatment type given	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
IVIG	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No
IV Steroids	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes
EPO	Yes	No	No	No	No	No	Yes	No	No

Learning points

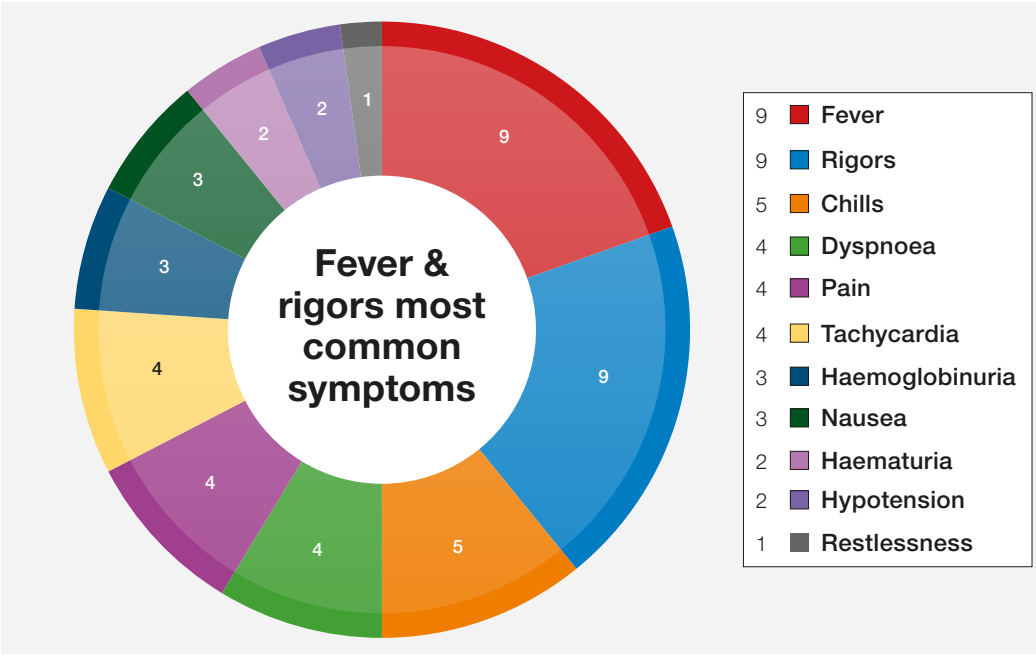
- Hyperhaemolysis can be accompanied by a drop in the patient's absolute reticulocyte levels
- Monitoring of the patient's reticulocyte and ferritin levels can be helpful in distinguishing hyperhaemolysis from other haemolytic transfusion reactions
- All cases of hyperhaemolysis should be considered as major morbidity

Clinical and laboratory signs and symptoms

Acute haemolytic transfusion reactions n=12

The clinical symptoms reported in AHTR are shown in Figure 19.2.

Figure 19.2: Clinical symptoms reported in AHTR



Delayed haemolytic transfusion reactions n=25 (excluding potential cases of hyperhaemolysis)

No clinical symptoms of a transfusion reaction were reported in 11/25 (44.0%) delayed haemolytic transfusion reaction cases submitted to SHOT. This remains comparable to previous years.

Most delayed haemolytic transfusion reactions were initially identified due to a lack of Hb increment following transfusion (13/25, 52.0%) or the development of a positive DAT (12/25, 48.0%).

Laboratory investigation of HTR

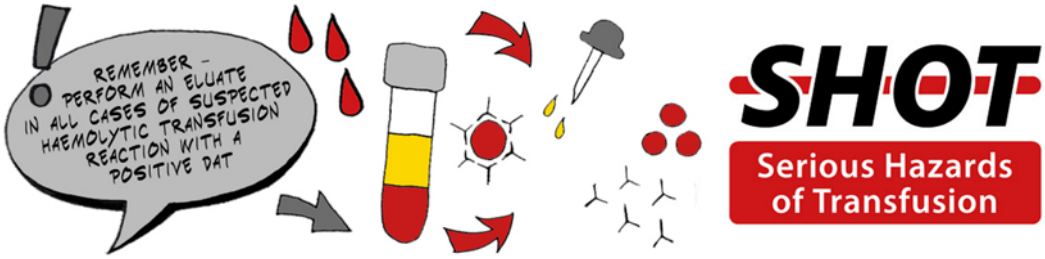
This year the diagnosis of HTR was complicated by a lack of availability of pre- and post-transfusion testing results. Reporters had noted that this was in response to the COVID-19 pandemic and it most often related to the pre-transfusion chemistry results. Additionally, 2/46 (4.3%) reports stated that no post-transfusion DAT had been performed and a further 11/46 (23.9%) provided no post-transfusion serology results.

Case 19.1: HTR investigation prompted by a failure in Hb increment post transfusion

A patient with B cell lymphoma was transfused to treat chronic anaemia. A non-specific antibody was reported in the pre-transfusion antibody investigation and two units of crossmatch-compatible red cells were issued. The patient did not show any clinical symptoms of HTR except that they failed to show the expected increment in Hb post transfusion. Repeat samples were sent to the transfusion laboratory. The post-transfusion DAT was positive and anti-Jk^a was identified in the plasma. The pre-transfusion serology was reviewed, and it was concluded that the pre-transfusion sample also showed evidence of anti-Jk^a.

Learning point

- A lack of the expected increment in haemoglobin or the development of a positive direct antiglobulin test (DAT) post transfusion can be the first indication of a haemolytic transfusion reaction



Antibodies implicated in HTR

Anti-Jk^a continues to be the most frequent antibody specificity implicated in HTR. The antibody specificities reported are shown in Figure 19.3.

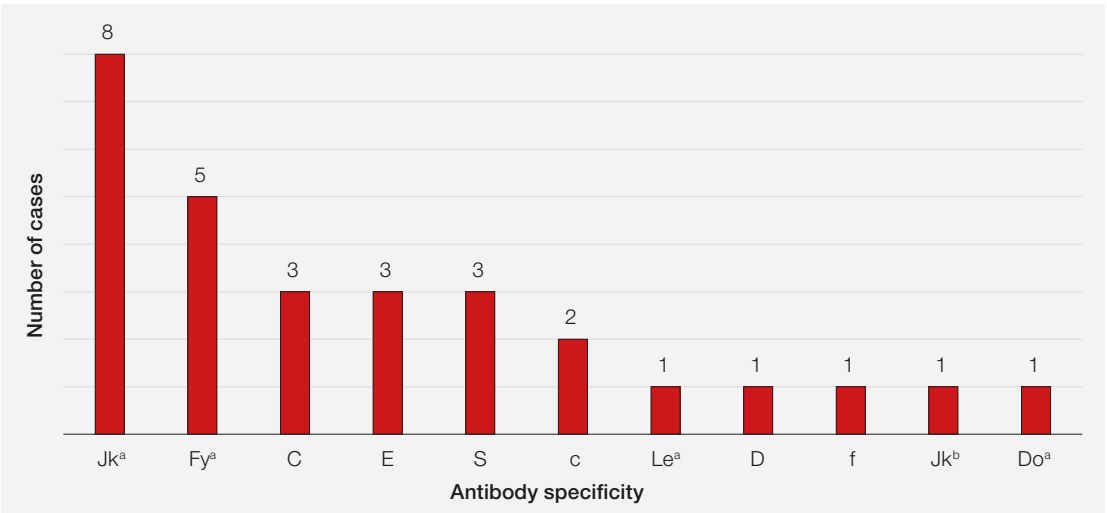


Figure 19.3: Antibody specificities implicated in HTR

In 21/25 (84.0%) cases of DHTR antibodies were detected in the post-transfusion sample which were not detectable in the pre-transfusion sample.

Two cases were reported in which information on the presence of the antibody was available on Sp-ICE at the time of pre-transfusion testing. In another case, a patient with sickle cell anaemia experienced a reaction caused by anti-C and anti-E which could have been avoided if extended Rh matched red cells had been selected in compliance with BSH (BSH Milkins et al. 2013) and local hospital guidelines.

Case 19.2: Failure to issue extended Rh matched units

A young patient with sickle cell anaemia received an exchange transfusion in 2014 without being tested for an extended phenotype. In 2020 the patient was given another exchange transfusion. The patient had the Ro (D+C-c+E-e+) phenotype however the units transfused were only matched for ABO and K type. Following transfusion, the patient showed signs of haemoglobinuria, jaundice and a falling Hb and anti-C and anti-E were detected in the post-transfusion sample.

Learning points

- All individuals involved in the transfusion process must be aware of the need to share information pertinent to the patient's transfusion requirements including details of their underlying diagnosis and antibody history
- Patients should be informed when clinically significant antibodies are detected. This is especially important in multi-transfused patients, and in shared care
- Where possible, patients should be asked whether they have antibodies as part of the pre-transfusion process and any information obtained relayed to the transfusion laboratory and acted on
- Transfusion databases (such as Specialist Services electronic reporting using Sunquest's Integrated Clinical Environment (Sp-ICE)) can provide vital information in cases where antibody levels have dropped below the detectable titre. Hospitals should have local policies to decide which patients to check on transfusion databases

Recommended resource

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

HTR Webinar 2021
https://www.shotuk.org/resources/current-resources/webinars/

References

BSH Milkins C, Berryman J, Cantwell C, et al. Guidelines for pre-transfusion compatibility procedures in blood transfusion laboratories. Transfus Med 2013;**23(1)**:3-35. http://onlinelibrary.wiley.com/doi/10.1111/j.1365-3148.2012.01199.x/full [accessed 25 March 2021].

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Danaee A, Inusa B, Howard J, et al. Hyperhaemolysis in patients with hemoglobinopathies: a single-center experience and review of the literature. *Transfus Med Rev* 2015;**29(4)**:220-230.

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