Haemolytic Transfusion Reactions (HTR) n=35

18

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.

Simple serological reactions (development of antibody with or without a positive DAT but without clinical or laboratory evidence of haemolysis) are defined as alloimmunisation: these data are no longer collected by SHOT.

Key SHOT message

- Hyperhaemolysis is one of the main causes of major morbidity 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

Number of cases n=35

A total of 35 cases have been included, 7 acute and 28 delayed reactions (including 5 cases of hyperhaemolysis). The number of delayed reactions reported is comparable to the number reported the previous year however the total number of reactions reported has reduced. There were 3 cases of acute reactions reported in which antigen-positive blood was transfused with the knowledge that the patient had the antibody. In 2 of these this was due to the clinical urgency requiring the use of emergency O D-negative blood. The third case was the result of a laboratory error.

Age range and median

There were no paediatric cases reported this year (age less than 18 years). The overall age range was 19 to 88, with a median age of 45.

Deaths n=2

In 2 cases, the patient deaths were attributed to the transfusion reactions. Both occurred following episodes of hyperhaemolysis. See Case 18.1 and Case 18.2 for details.

Major morbidity n=4

There were 4 cases reported with major morbidity, and 3 of these were hyperhaemolysis cases. One case was due to the emergency transfusion of Jk^a-positive emergency O D-negative units to a patient with known anti-Jk^a following a postpartum haemorrhage. The patient experienced an acute transfusion

reaction and required ventilation and admission onto the intensive care unit due to renal impairment. The patient made a full recovery.

Hyperhaemolysis and major morbidity

Hyperhaemolysis syndrome has previously only been reported to SHOT in patients with sickle cell disease. However, in 2018, 2 cases were reported in other patient types. In both cases the reaction resulted in patient death.

Case 18.1: Hyperhaemolysis post allogeneic stem cell transplant

A haematology patient with T-cell lymphoma post stem cell transplant developed symptoms consistent with hyperhaemolysis following a four-unit red cell transfusion. The patient was transfused a further five red cell units, but the bilirubin continued to rise and the Hb to fall. The patient developed impaired renal function and died 9 days later.

Case 18.2 Hyperhaemolysis in a patient with Rosai-Dorfman Syndrome

A patient with known Rosai-Dorfman syndrome was admitted with symptomatic anaemia, and a Hb of 24g/L. The patient had previously confirmed autoimmune haemolytic anaemia. The patient was treated with steroids, erythropoietin and rituximab in addition to red cell transfusion. Within 7 hours of transfusion the patient experienced fever, back and chest pain, dyspnoea and haemoglobinuria. The patient's Hb dropped from 81g/L immediately post transfusion to 20g/L, the bilirubin and LDH became raised and spherocytes were detected on the blood film. The patient developed impaired renal function and died 6 days later.

A further 3 cases of hyperhaemolysis were reported in patients with sickle cell disease.

The diagnosis of hyperhaemolysis remains a challenge. 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. Therefore, for analysing the SHOT data cases reported as hyperhaemolysis by the reporter but in which the serology supports a conclusion of antibody mediated haemolysis have been classified as a haemolytic transfusion reaction.

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 3 cases of hyperhaemolysis reported with 'minor morbidity' were upgraded.

Hyperhaemolysis can be divided into acute and delayed hyperhaemolysis. Acute hyperhaemolysis usually occurs within 7 days of transfusion and the DAT is usually negative. Delayed hyperhaemolysis usually occurs more than 7 days post transfusion and the DAT is often positive. In contrast to a classical delayed haemolytic transfusion reaction, in delayed hyperhaemolysis both patient and transfused red cells are haemolysed (Danaee et al. 2015). All of the hyperhaemolysis cases reported to SHOT occurred within 7 days of the transfusion episode and are therefore characterised as acute.

Learning points

- Hyperhaemolysis remains a cause of transfusion-related mortality and major morbidity. Patients with haemoglobinopathies should be monitored for signs and symptoms of haemolysis following transfusions and diagnosis of hyperhaemolysis considered early. It is important that patients are educated about signs and symptoms they might develop when discharged home so they can present early should any of these occur, including signs of haemoglobinuria
- Hyperhaemolysis can also occur in non-haemoglobinopathy patients therefore it is 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 followed up and investigated

Clinical and laboratory signs and symptoms

Acute haemolytic transfusion reactions n=7

There appears to be no typical set of clinical symptoms associated with an acute haemolytic reaction.

Delayed haemolytic transfusion reactions n=23 (excluding cases of hyperhaemolysis)

No clinical symptoms of a transfusion reaction were reported in 10/23 delayed haemolytic transfusion reaction cases submitted to SHOT. Where clinical symptoms were reported, fever and haemoglobinuria occurred the most frequently. The clinical symptoms that were observed are shown in Figure 18.1.

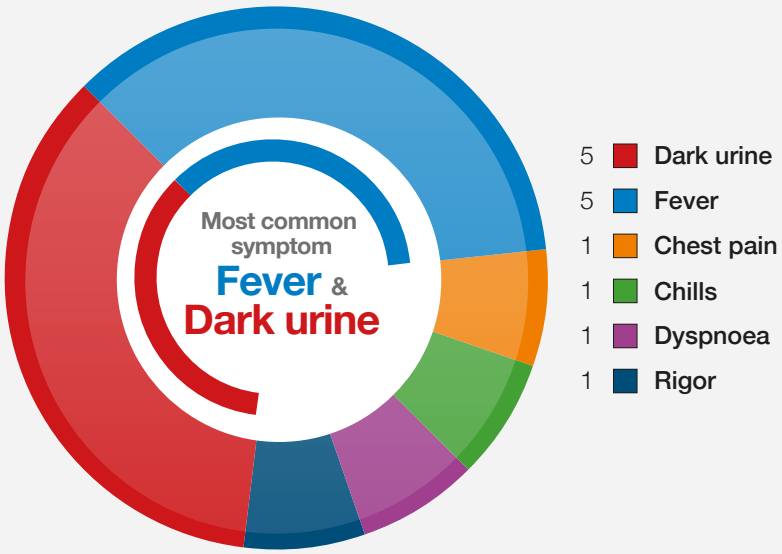


Figure 18.1: Clinical symptoms associated with DHTR

Delayed haemolytic transfusion reactions were more frequently diagnosed based on the laboratory indications. The main indicators and frequency reported are shown in Figure 18.2.

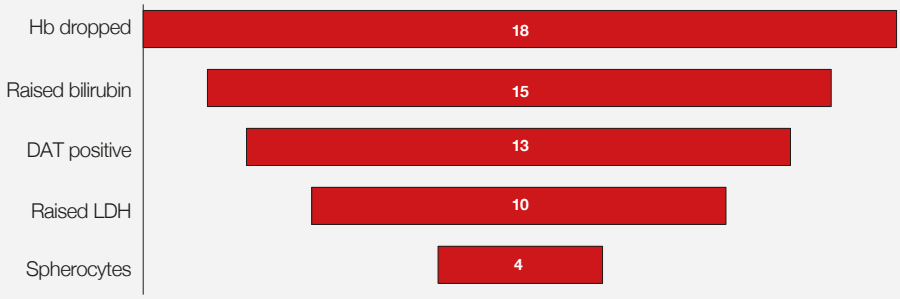


Figure 18.2: Laboratory indications detected in DHTR

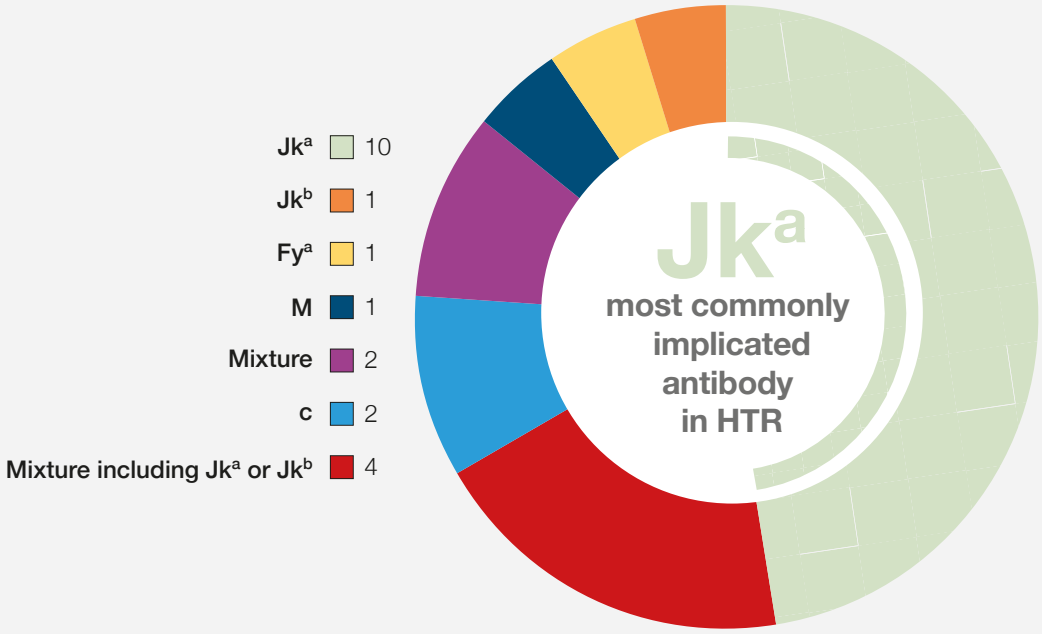
DAT=direct antiglobulin test; Hb=haemoglobin; LDH=lactate dehydrogenase

Laboratory investigation of haemolytic transfusion reactions

In 7/35 (20.2%) haemolytic reactions reported, no eluate had been tested despite the patient developing a positive DAT post transfusion. In transfusion reactions, red cell antibodies may be identified in the eluate which are not detectable in the plasma. This is due to the free antibody binding to the corresponding antigen on the transfused cells. Elution tests to identify these antibodies can help confirm the specificity of the individual antibodies implicated in the reaction.

Antibodies implicated in haemolytic transfusion reactions

Figure 18.3: Antibodies implicated in DHTR



Learning point

- In cases where there is evidence of red cell haemolysis, elution studies should be included in transfusion reaction investigations as these can help reveal antibody specificities not detectable in the free plasma and can provide confirmation of the specificity of antibodies implicated in the transfusion

HTR due to preformed antibodies

There were 17/23 (73.9%) cases reported as DHTR which followed the classic pattern of a negative antibody screen on the pre-transfusion sample and the identification of an alloantibody in the post-transfusion sample. A further 2/7 AHTR had a negative antibody screen reported in the pre-transfusion sample and anti-Jk^a detected in the post-transfusion sample. However, on repeat testing of the pre-transfusion sample, the antibody was detectable in the 2 acute cases.

Case 18.3: Antibody detectable pre transfusion in eluate

The patient was admitted for laparotomy for a small bowel obstruction. Fully automated pre-transfusion testing was performed, and a negative antibody screen result obtained using the Ortho AutoVue Innova. Blood was crossmatched by electronic issue. During the transfusion the patient's heart rate increased and their temperature rose by 2°C. The transfusion was stopped, and a transfusion reaction investigation requested. As part of the investigation the antibody screen on the pre-transfusion sample was repeated as negative, however a DAT was also performed on this sample. The DAT was positive and anti-Jk^a was detected in the eluate. Anti-Jk^a was also detected in the post-transfusion sample and in an eluate performed from this sample. One of the units transfused was confirmed as Jk^a-positive.

Case 18.4: Discrepant pre-transfusion results obtained using automated analysers

Blood was issued by electronic crossmatch following a negative antibody screen result using the Ortho AutoVue analyser. Ninety minutes post transfusion the patient experienced rigor, back pain and fever. Samples were sent to the laboratory for investigation of a transfusion reaction. Pre- and post-transfusion samples were tested on a second Ortho AutoVue analyser. They both gave positive reactions and anti-Jk^{a} was subsequently identified. This was reported to the analyser manufacturer for investigation. Following testing of the antibody titre it was concluded that the antibody was at a level that was below the minimum level for detection.

Learning point

- Patient databases such as Specialist Services electronic reporting using Sunquest's Integrated Clinical Environment (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

References

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

Patel A. (2008) Management of sickle cell disease. Beware of transfusions and hyperhaemolysis. *BMJ* 2008;**337**:a1874.

Petz LD, Garratty G. (2004) Blood Transfusion in AIHAs. In Immune Haemolytic Anaemias, 2nd edition, 2004:pp 375-400, Churchill Livingstone, New York.

Win N, New H, Lee E, et al. (2008) Hyperhaemolysis syndrome in sickle cell disease case report and literature review. *Transfusion* 2008;**48**:1231-1237. https://onlinelibrary.wiley.com/doi/full/10.1111/j.1537-2995.2008.01693.x [accessed 31 May 2019].

Woodcock BE, Walker S, Adams K, et al. (1993) Haemolytic transfusion-successful attenuation with methylprednisolone and high dose immunoglobulin. *Clin Lab Haematol* 1993;**15(1)**:59-61.

Young P, Uzieblo A, Trulock E, et al. (2004) Autoantibody formation after alloimmunisation: are blood transfusion a risk factor for autoimmune haemolytic anaemia? *Transfusion* 2004;**44**:67-72. https://onlinelibrary.wiley.com/doi/full/10.1046/j.0041-1132.2003.00589.x [accessed 31 May 2019].