19 Haemolytic Transfusion Reactions (HTR) n=42

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Definition:

Acute haemolytic transfusion reactions (AHTR) are defined as fever and other symptoms/signs of haemolysis within 24 hours of transfusion, confirmed by one or more of the following: a fall in haemoglobin (Hb), rise in lactate dehydrogenase (LDH), positive direct antiglobulin test (DAT), positive crossmatch.

Delayed haemolytic transfusion reactions (DHTR) are defined as fever and other symptoms/signs of haemolysis more than 24 hours after transfusion; confirmed by one or more of the following: a fall in Hb or failure to increment, rise in bilirubin, 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 messages

- Anti-Jk^{a} and anti-Jk^{b} remain the most commonly implicated antibodies in haemolytic transfusion reactions (HTR)
- Hospital transfusion laboratories should ensure that red cell antibodies are managed in the same way as other specific blood requirements. The antibody history must be clearly documented against the patient's record. A national database such as the Specialist Services Electronic Reporting using Sunquest ICE (Sp-ICE) should be used to make this information available in the event of the patient moving between hospitals or other areas of shared care
- Incentives to share the antibody history of the patient need to be supported by patient education to inform the patient of their specific red cell requirements and encourage them to take ownership and alert the clinicians. Clinicians must take responsibility for listening to patients and to act on any information regarding specific blood requirements and take note of any antibody history

Number of cases n=42

A total of 42 cases have been included, 13 acute and 29 delayed reactions (including 6 cases of hyperhaemolysis). The number of delayed reactions reported has increased compared to the previous year (18 delayed transfusion reactions reported in 2016 out of 35 HTR) but is comparable to previous years. Three cases related to emergency transfusions in which antigen-positive blood was transfused due to the clinical urgency with the knowledge that the patient had the antibody.

Age range and median

There was only 1 paediatric case reported (age less than 10 years). The overall age range was <10 to 87, with a median age of 52 years.

Deaths n=1

There was only one patient death attributed to the transfusion. A further two patient deaths were reported but post mortem examinations confirmed that death was due to the underlying conditions and not the transfusion. One death occurred in an acutely unwell patient who was admitted in cardiac failure and post mortem examination confirmed this was the cause of death. The other death was related to complications of sickle cell disease (SCD) and is described under the hyperhaemolysis and major morbidity section.

Major morbidity n=7

There were 7 cases of major morbidity, 6 of which involved hyperhaemolysis syndrome in patients with SCD. In 5/6 cases the symptoms improved following treatment with intravenous immunoglobulin (IVIg) and methylprednisolone.

Hyperhaemolysis and major morbidity

The diagnosis of hyperhaemolysis remains a challenge. Hyperhaemolysis is characterised by more severe haemolysis than DHTR, with haemolysis affecting the transfused red cells and also 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 the purpose of analysing the SHOT data any case reported as hyperhaemolysis by the reporter but in which the serology supports a conclusion of antibody-mediated haemolysis without additional features, the case has been classified as a haemolytic transfusion reaction.

Case 19.1: Death following emergency transfusion of a patient in sickle crisis

A pregnant patient in her 40s with SCD in sickle crisis and symptoms of acute chest syndrome received an urgent red cell exchange transfusion prior to emergency caesarean section. During the transfusion the patient developed symptoms of a transfusion reaction and the transfusion was stopped. The patient had a history of anti-U and possible anti-Jk^a, however due to the emergency nature of the transfusion and the rarity of U-negative, Jk^a-negative red cells, Jk^a-negative units were not selected and units negative to the U antigen only were transfused. The justification given for this was that the presence of anti-Jk^a had not been positively confirmed. The patient developed disseminated intravascular coagulation (DIC) and possible hyperhaemolysis syndrome. At post mortem the death was attributed to acute chest syndrome related to SCD.

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. Case 19.2 was further complicated by the presence of pre-existing alloantibodies and the patient having a confirmed variant Rh phenotype.

Case 19.2: Hyperhaemolysis in patient with variant Rh phenotype and known alloantibodies

A patient with SCD received an elective ten-unit exchange transfusion prior to surgery. The patient was known to have allo anti-Ce, anti-s, anti-K and anti-Jk^b. The patient also had a previously-reported auto anti-e. The patient was genotyped as part of the Blood Service genotyping project for haemoglobinopathy patients and found to have a variant D- and e-genotype. The previously reported auto anti-e was therefore recharacterised as allo anti-e. Due to the unavailability of D- C- E+ c+ e- s-K-Jk^b- red cells the decision was made not to provide e-negative units. The rationale for excluding the anti-e for the purposes of blood selection was that the patient had been transfused e-positive units prior to the identification of the variant e-genotype without symptoms of haemolysis and also that data collected by National Health Service Blood and Transplant (NHSBT) for transfusion of antigen-positive units to patients with variant phenotypes had no reports of haemolysis in e-variant patients with anti-e.

Five days post transfusion the patient developed haemoglobinuria and was readmitted to hospital and required ventilation. The Hb fell from 83g/L to 48g/L and the bilirubin and LDH were raised.

The patient was transfused three units of D+ C- E+ c+ e- s- K- Jk^{b}- red cells. However, monitoring of HbS levels demonstrated that these transfused cells were also haemolysed. No new antibodies were detected on serological investigation and the DAT was positive pre and post transfusion with no change seen in the reaction strength.

Learning point

- Patients with haemoglobinopathies should be monitored for signs and symptoms of haemolysis following transfusion and diagnosis of hyperhaemolysis considered early. It is important that patients are educated when discharged home about signs and symptoms they might develop so they can present early should any of these occur, including signs of haemoglobinuria

Clinical and laboratory signs and symptoms

Acute haemolytic transfusion reactions (AHTR) n=13

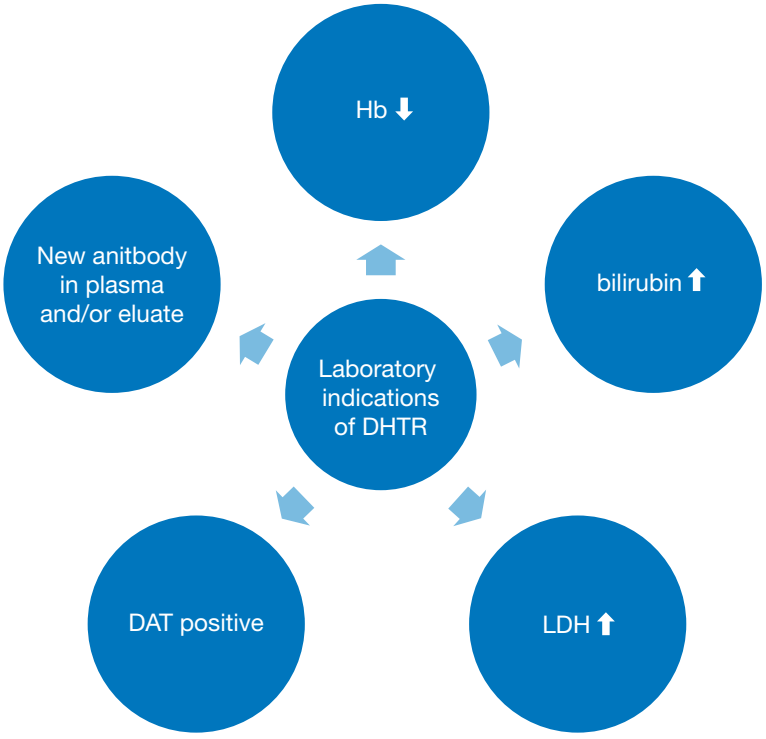
There appears to be no typical set of clinical symptoms associated with an acute haemolytic reaction. In 10/13 (76.9%) of cases the reaction was identified by the patient becoming unwell during transfusion, with the most common symptoms being fever and rigors. Other symptoms included dyspnoea, rash and red/brown urine due to haemoglobinuria.

All reports provided laboratory evidence of haemolysis, with 12/13 patients experiencing an acute transfusion reaction with a raised bilirubin and a fall in Hb.

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

The most commonly reported clinical indications of a DHTR were haemoglobinuria (9 cases) and jaundice (7 cases) with fever and back pain also being reported. However, in 10 cases (43.5%) there were no obvious clinical signs or symptoms associated with the DHTR and the reaction diagnosed by laboratory signs of haemolysis only. The main indicators are shown in Figure 19.1.

Figure 19.1: Laboratory indications of DHTR



DHTR=delayed haemolytic transfusion reaction; Hb=haemoglobin; DAT=direct antiglobulin test; LDH=lactate dehydrogenase

Antibodies implicated in haemolytic transfusion reactions

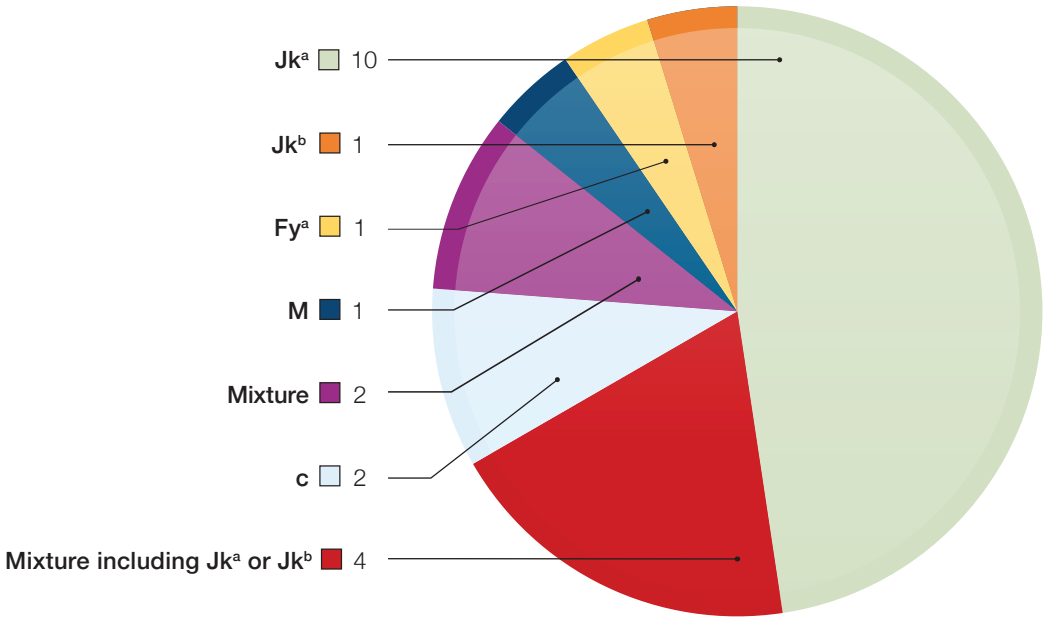


Figure 19.2: Antibodies implicated in DHTR

Antibodies to low frequency antigens where red cells were issued electronically

Antibodies to low frequency antigens were identified in 2 cases of AHTR (anti-Wr^{a} and anti-Co^{b}) and 1 DHTR (anti-Wr^{a}). In all cases the pre-transfusion antibody screen was negative and blood was issued by electronic crossmatch. Pre- and post-transfusion samples were referred to the Blood Service reference laboratory where the antibody was identified in both patient samples and the implicated units confirmed as positive to the corresponding antibody.

The specification for red cell screening cells used for pre-transfusion testing in the UK does not require the inclusion of cells positive for the Kp^{a}, Wr^{a} and Co^{b} antigens. It is therefore not possible to detect these antibodies in a standard antibody screen. The lack of a serological crossmatch step in electronic issue means that the potential to miss low frequency antigens prior to transfusion is a known risk for electronic issue of blood components. However due to the low frequency of these antigens in the donor population the risk of transfusion with an antigen-positive unit remains low.

Reactions associated with antibodies to the Kidd blood group system

In 16/42 cases (38.1%) anti-Jk^{a} or anti-Jk^{b}, either in isolation or combination with other antibodies, was detected in the post-transfusion sample only. Antibodies to the Kidd system were implicated in another 3 cases. In 2 cases antigen-negative blood could not be provided despite the antibody being present due to the emergency nature of the transfusion, and in the 3rd case anti-Jk^{a} had not been fully excluded during an out-of-hours investigation and crossmatch.

Learning point

- Robust methods of recording antibody history against patient's records should be developed and antibody warning cards issued to patients. This should be supported with patient education to empower them to take ownership and inform clinicians that they have specific red cell requirements and clinician education to ensure that they have the understanding to act on this information

Classic delayed HTR

Twenty-three of 29 cases reported as DHTR 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.

In all reported cases of DHTR the period between transfusion and identification of the reaction meant that it was not possible to repeat testing on the pre-transfusion sample or repeat compatibility testing against the implicated units. It can therefore be difficult to confirm imputability. However, in 5 cases it was possible to confirm from Blood Service records that the transfused unit was antigen-positive for the implicated antigen.

Case 19.3: DHTR due to anti-c

A patient receiving chemotherapy was transfused two units of red cells issued by electronic crossmatch following a negative antibody screen using a fully automated system. The following week the patient returned to hospital with discoloured urine and anaemia. The patient's bilirubin had risen from 10 to 40micromol/L and her Hb had dropped from 102g/L to 88g/L. The antibody screen on the new samples was positive and anti-c was identified. The transfused units were confirmed as c-antigen positive.

Case 19.4: DHTR due to anti-Fy^a

A renal patient with history of a negative antibody screen was transfused two units of red cells. Eleven days later the patient returned for their next routine appointment. Investigation of the samples taken during this admission found that anti-Fy^a was now detectable in the plasma. Anti-Fy^a was also eluted from the patient's red cells. The patient had reported no clinical symptoms but laboratory tests indicated the Hb had not incremented following the transfusion and she had now developed a positive DAT.

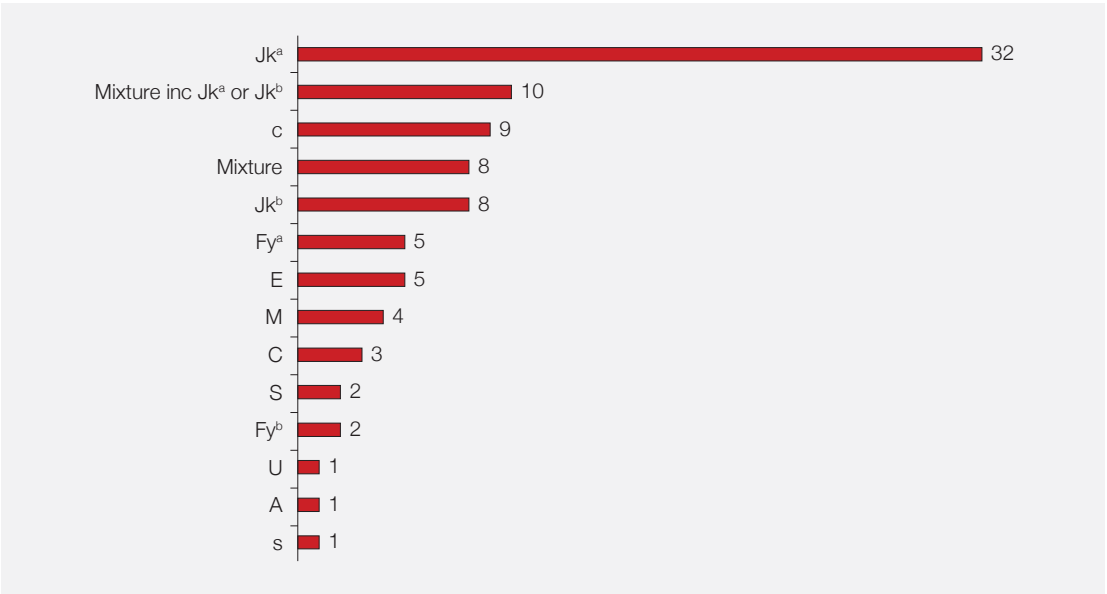
Delayed HTR is the main cause of HTR and many are only detected by careful analysis of laboratory results.

Review of antibodies implicated in DHTR

Figure 19.3 summarises the antibodies implicated in DHTR reports over the last 5 years. No data on antibody mixtures were available for 2013 and 2014.

Anti-Jk^a and anti-Jk^b remain the antibodies most commonly implicated in haemolytic transfusion reactions. This is probably due to the known tendency for the levels of these antibodies to fall to undetectable levels after the initial immunisation event. It is therefore important that when detected, the presence of the antibody is recorded against the patient's antibody record and a blood group warning card issued to patient.

Figure 19.3: Antibodies implicated in DHTR 2013-2017



Shared care

Case 19.5: Failure to identify previous antibody history available in a patient treated across multiple hospitals

Anti-C and anti-S were confirmed in a patient in 2000 by the Blood Service and a report and antibody warning card for the patient issued to the referring hospital (Hospital 1). In 2015 the same patient was seen in Hospital 2 and samples referred to the International Blood Group Reference Laboratory (IBGRL) for red cell genotyping. In February 2017 the patient was seen in Hospital 3 and another sample was sent to the IBGRL for genotyping. At this time both the report from 2000 and the genotype report from 2015 were available on Sp-ICE.

In May 2017 the patient was seen at a 4th hospital (Hospital 4). Samples were again referred to the Blood Service reference laboratory and this time anti-Lu^{a} and anti-Fy^{a} were detected. A report was issued to Hospital 4 stating the new antibodies and also the previously detected anti-C and anti-S. A new antibody card for the patient, listing all four antibody specificities was sent with the report. This new report was also uploaded to Sp-ICE.

In July 2017 the patient presented again to Hospital 1. An antibody screen was performed and found negative and ABO, Rh and K group-matched blood was issued. Approximately 5 days later, the patient was admitted to a 5th hospital (Hospital 5) with symptoms of a HTR including an acute drop in Hb and positive DAT.

Learning points

- It is important that resources such as Specialist Services Electronic Reporting using Sunquest ICE (Sp-ICE) are used to identify previously detected antibodies prior to transfusion, especially when patient care is being provided by multiple hospitals
- Patients should also be informed of the risks associated with changing their care provider and empowered to inform clinicians of their red cell requirements

Emergency transfusion

Three cases of HTR were reported following transfusion of antigen-positive red cells in an emergency.

Emergency transfusion to treat major haemorrhage is vital to avoid hypovolaemic shock and its consequences allowing the patient to survive long enough for clinicians to treat the cause of the blood loss (NPSA 2010). It is therefore important to remember that it is often lifesaving. In these cases, the risk of an adverse reaction is outweighed by the need to support the patient over the initial phase allowing treatment to take place.

Case 19.6: Transfusion of emergency O D-negative red cells

A patient suffered a major gastrointestinal arterial bleed and required immediate transfusion. The two emergency O D-negative units were taken from the hospital transfusion laboratory refrigerator and a further three uncrossmatched group O units were provided. Subsequent testing of the pre-transfusion sample identified anti-Jk^{b} in the patient's plasma. Three of the units issued were confirmed to be positive for the Jk^{b} antigen. The patient developed fever and jaundice and laboratory tests confirmed haemoglobinuria, raised bilirubin, raised LDH, a rapid drop in Hb and positive DAT. The patient recovered and survived.

Case 19.7: Issue of 'best match' in major haemorrhage

A major haemorrhage alert was called on a bleeding patient with cholecystitis and the emergency O D-negative units were collected. Part of the first unit was transfused before the transfusion laboratory staff were able to inform the clinical area that the patient had a history of anti-E, anti-Fy^{a} and anti-Jk^{a}. On discussion with the consultant haematologist it was agreed to crossmatch two E-negative Fy^{a}-negative, Jk^{a}-untyped units as no suitable Jk^{a}-negative units were available in the hospital transfusion

laboratory. These units were subsequently confirmed as Jk^a-positive. The patient did not suffer any clinical symptoms of a HTR but laboratory tests showed a positive DAT and rapid fall in Hb. The patient recovered and survived.

The third case has been described above (Case 19.1).

Learning points

- It is important that lifesaving transfusion is not withheld due to a history of alloantibodies. However, in such cases the patient should be carefully monitored, both during and after transfusion for signs of a haemolytic transfusion reaction
- The Blood Service recommends that where the antibody screen is positive or the patient has known antibodies for which compatible blood is not readily available, ABO, full Rh and K-matched blood may be given, with intravenous (IV) methylprednisolone 1g and/or IV immunoglobulin (IVIg) cover if required. 80% of patient antibodies are within the Rh and K systems (Win et al. 2018)
- Discuss with a clinical haematologist regarding the need for methylprednisolone and/or IVIg and monitoring (including urine output) for delayed haemolytic transfusion reactions (Win et al. 2008, Win et al. 2018, Woodcock et al. 1993)

Reactions probably not associated with red cell alloantibodies (low imputability)

Similar to last year there were 2 cases that were likely to have been exacerbation of autoimmune haemolysis, 1 case where the clinical and serological symptoms could be associated with the patient's underlying condition and another 3 where no cause was found.

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