14 Haemolytic Transfusion Reactions (HTR) n=59

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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 of 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 of increment, rise in bilirubin, incompatible crossmatch not detectable pre transfusion.

NB: Simple serological reactions (development of antibody with or, without a positive DAT but without clinical or laboratory evidence of haemolysis) are summarised in Chapter 27, Alloimmunisation, available in the 2015 Annual SHOT Report: Web Edition. (From January 2016, SHOT is no longer collecting cases of alloimmunisation **apart from new anti-D antibodies found in pregnancy**).

Key SHOT messages

- Patients with sickle cell disease are particularly vulnerable to haemolytic transfusion reactions, often associated with hyperhaemolysis and major morbidity. The clinical picture is often complicated by sickle cell crisis, and clinicians and laboratory staff should be vigilant for any signs of haemolysis following a recent transfusion
- High-titre ABO antibodies from intravenous immunoglobulin (IVIg) and plasma-containing components can cause haemolytic transfusion reactions in non group O recipients. These reactions are usually mild, as they are self-limiting, but vulnerable patients such as neonates, and rarely adult patients receiving high dose IVIg or very large volumes of incompatible plasma can also suffer severe reactions. Where time permits, patients should receive ABO-compatible plasma, or high-titre negative if group O has to be given

Number of cases

59 cases have been included, 24 acute and 35 delayed (including hyperhaemolysis).

Age range and median

There were 6 paediatric cases this year (age range 3 to 13 years), although there were two reports from the same patient. The overall age range was 3 to 91, with a median age of 54.

Deaths n=3

There were 7 deaths in total. Four patients died due to their underlying disease, but in one case the haemolytic transfusion reaction definitely contributed to the patient's death (imputability 3), and in a further two cases, the reaction possibly contributed (imputability 1).

Case 14.1: Death due to anti-Wr^a following electronic issue

An elderly male patient with myelodysplastic syndrome (MDS), chronic obstructive pulmonary disease (COPD) and renal impairment, became hypertensive and complained of severe back and abdominal pain 160mL into the first of a two-unit transfusion, which was immediately stopped. The patient was admitted from outpatients, but continued to deteriorate and died about 12 hours later. Post-transfusion testing showed an elevated LDH (300U/L), increased creatinine (168 to 251micromol/L) and a raised bilirubin (5 to 101micromol/L). The antibody screen was still negative, but a retrospective indirect antiglobulin test (IAT) crossmatch showed the unit to be incompatible and anti-Wr^a was identified in the plasma and in an eluate made from the patient's red cells, and the unit was confirmed as Wr(a+). The post-mortem report supported the diagnosis that death was caused by the transfusion reaction.

Wr^a and risk/benefits of electronic issue

The Wr^a antigen has a frequency of approximately 1 in 1000 in the white population, but anti-Wr^a is a relatively common antibody, often found in patients with other red cell antibodies. Although incompatibility due to anti-Wr^a is a well-recognised cause of haemolytic transfusion reactions and haemolytic disease of the fetus or newborn (HDFN), it has rarely caused severe reactions and a literature search has not found any reports of associated death. In addition to 3 cases this year, there have been 7 cases of AHTR due to anti-Wr^a reported to SHOT in the last three reporting years (2012–2014), one of which resulted in the patient being admitted to the intensive therapy unit (ITU), whilst the other 6 caused minor morbidity only. There were none reported from 2008 to 2011. The increasing number of reports may well be related to the increasing use of electronic issue in the UK (from 42% in 2008 to 67% in 2015 - UK National External Quality Assessment Service (NEQAS) data).

Electronic issue has been widely used in some countries for over 20 years (Butch et al. 1994, Safwenberg et al. 1997), and the benefits are well documented and understood, including: more timely provision of red cells for transfusion, thereby reducing the potential for delays; a reduction in red cell wastage; significant reduction in hands-on work, freeing staff to undertake essential training, competency assessments and other quality improvements.

Learning point

- Haemolytic transfusion reactions due to antibodies directed against low frequency antigens are an acknowledged, but small, risk of omitting the indirect antiglobulin test (IAT) crossmatch, estimated at 1 in 500,000 to 1 in one million transfusions (Garratty 2002). The possibility of this event should always be considered when a patient has an acute haemolytic episode following transfusion, and a retrospective crossmatch should be undertaken to confirm the presence of a red cell antibody, so that the patient can be flagged as being unsuitable for electronic issue, thereby preventing future incompatible transfusions

Case 14.2: AHTR possibly contributed to death – cause of reaction unknown

A patient with MDS became acutely unwell 75mL into a red cell transfusion, immediately following a platelet transfusion. She became acutely short of breath, developed severe rigors and turned blue. She also passed dark urine, and Hb was confirmed in the urine by dipstick. Her Hb fell and bilirubin rose from 29 to 40micromol/L. She was given chlorphenamine, pethidine, hydrocortisone, oxygen and albuterol (Ventolin), and was admitted to critical care but died the next day following a cardiac arrest. Anti-E was identified post transfusion, but this unit and previously transfused units were confirmed as E-negative, as this was not a new antibody. The DAT was positive and anti-E was identified in an eluate made from the patient's post-transfusion red cells. It is possible this was an autoantibody. Anti-Wr^a was also identified post transfusion, but the unit was confirmed as Wr(a-). The cause of death was determined as multiorgan failure and drug-induced myocarditis, however the reporter feels that the transfusion may have contributed.

Case 14.3: DHTR due to anti-Jk^a possibly contributed to death of an already sick patient

An elderly patient was transfused 3 units of red cells in cardiac intensive care over 4 days post heart surgery. Twelve days post surgery this very sick patient developed anti-Jk^a with a positive DAT, increased bilirubin, a fall in Hb, and spherocytes, suggesting a DHTR. Her death was multifactorial, but the reporter believes that the reaction contributed to her critical illness.

Major morbidity n=17

There were 8 cases of major morbidity, with details shown in Table 14.1, plus an additional 9 cases of possible hyperhaemolysis in patients with sickle cell disease, described separately in a later section. Table 14.1 includes a 9th case, which was reported as an incorrect blood component transfused (IBCT), but which caused an acute haemolytic reaction.

Table 14.1 Details of cases of major morbidity

Case type	Antibody/cause	Clinical symptoms	Criteria for major morbidity	Imputability
AHTR	Antibodies to flucloxacillin	Fever, chest pain, hypertension, vomiting, peripheral shutdown, black plasma	Intravascular haemolysis	Probable
AHTR	Not known Known multiple antibodies but Ab screen negative and antigen-negative blood given, DAT positive, no eluate	Rigors, pyrexia, back pain, tachycardia	ITU admission	Probable
AHTR	?E. coli infection with haemolysis exacerbated by transfusion	Pyrexia, fever, chills, hypotension, tachycardia, red plasma, impaired renal function	Required dialysis and ITU admission	Possible
AHTR	Anti-Bg^a with unit Bg(a+)	Rigors, back pain, tachycardia, hypertension	Difficulty breathing requiring O_2 support; required urgent transfer to specialist hospital	Probable
AHTR	Known anti-Fy^a but Fy(a+) emergency O D-negative given	Shock, rigors, hypotension	Required resuscitation and transferred to ITU	Possible
AHTR	?anti-Jk^b, RhCcEe-related antibody; ?exacerbation of AIHA in sickle cell patient	Back pain; dark urine	Required ITU admission	Certain
IBCT/AHTR*	Anti-A in neonate following exchange transfusion with group O SAGM red cells	Collapse, DIC	Intravascular haemolysis; required resuscitation	Possible
DHTR	Anti-U	Flu-like symptoms	Major drop in Hb 90 to 47g/L 6 days post transfusion	Certain
DHTR	Anti-Jk^b	Chest pain, dyspnoea, jaundice	Required ITU admission (already on HDU)	Probable

AIHA=autoimmune haemolytic anaemia; HDU=high dependency unit; ITU=intensive therapy unit; DIC=disseminated intravascular haemolysis; SAGM=saline adenine glucose mannitol

**detailed discussion of this case in Chapter 16, Paediatric Summary*

Clinical and laboratory signs and symptoms

Acute haemolytic transfusion reactions n=24 reactions in 23 patients

There appears to be no typical set of clinical symptoms associated with acute haemolytic reaction; the most commonly reported are shown in Figure 14.1.

All but one report provided laboratory evidence of haemolysis, with the majority of patients having a raised bilirubin and a fall in Hb. There were 9 reports of haemoglobinuria, and 2 severe reactions included haemoglobinaemia, suggesting intravascular haemolysis.

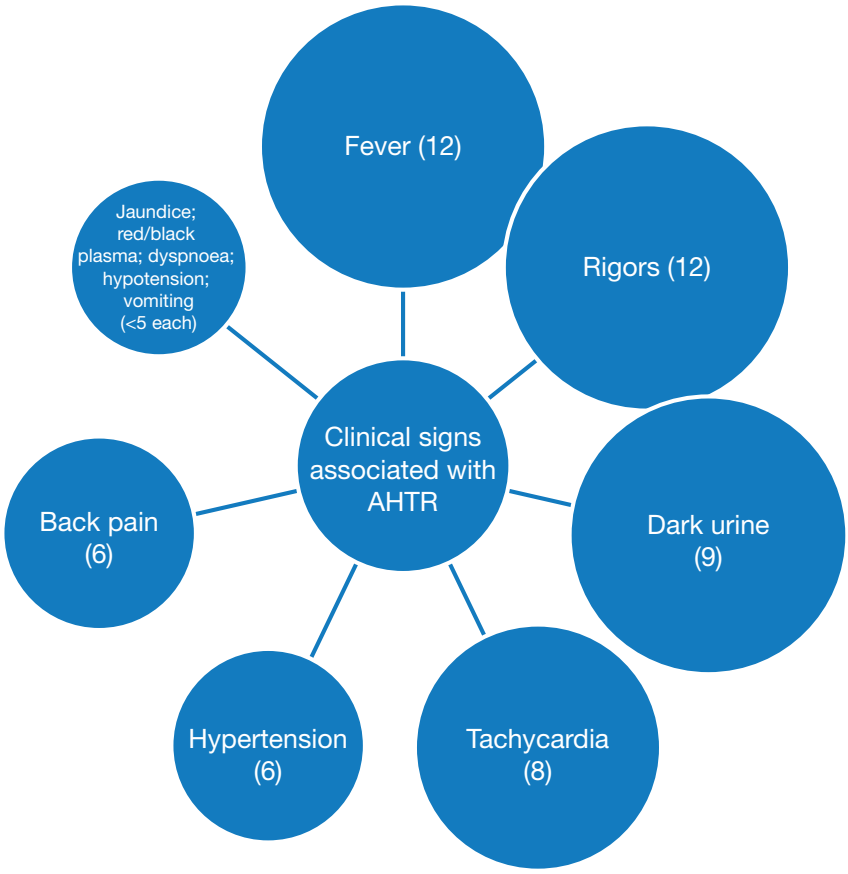

Figure 14.1: Clinical signs associated with AHTR

Delayed haemolytic transfusion reactions n=26 (excluding potential cases of hyperhaemolysis)

Seven patients had jaundice and/or dark urine. In the remaining 19/26 cases (73.1%) there were no obvious clinical symptoms associated with the DHTR, which was diagnosed by laboratory signs of haemolysis. The main indicators are shown in Figure 14.2.

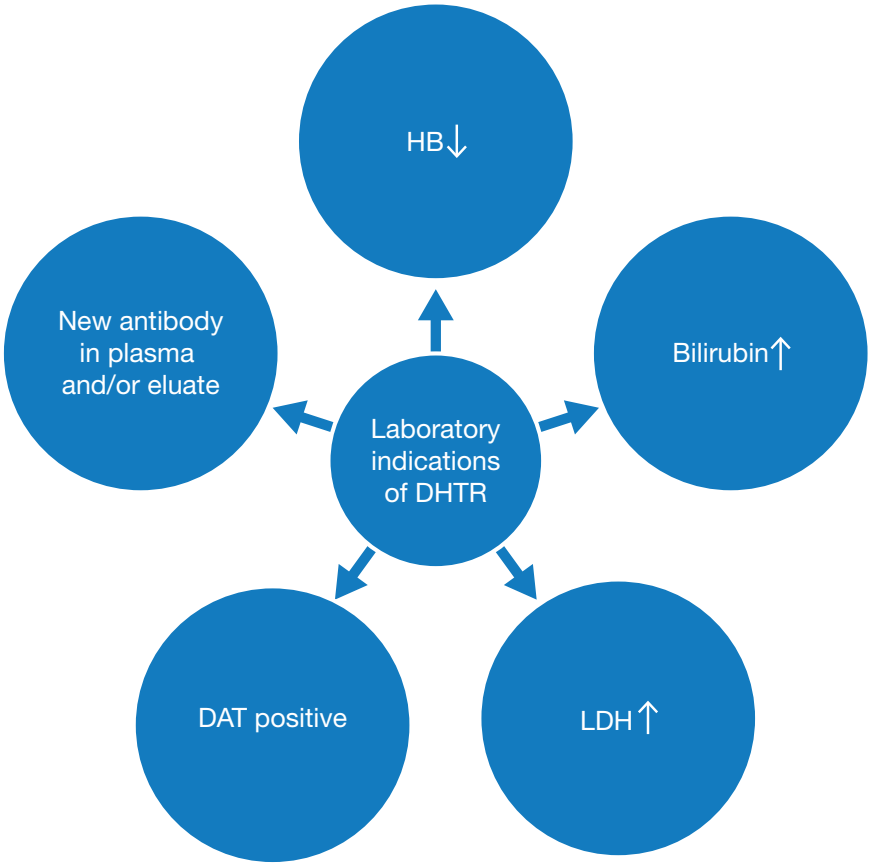

Figure 14.2: Laboratory indications of DHTR

Serological findings

Acute n=24 reactions in 23 patients

Antibodies to low frequency antigens

There were three cases of anti-Wr^a reported in 2015. All were confirmed retrospectively as incompatible with the implicated donation. One patient died as a result of the incompatible transfusion, and this has been described earlier (Case 14.1).

Antibodies known about pre transfusion (1 emergency; 1 error)

Emergency O D-negative red cells were transfused in 1 urgent case where the patient was known to have anti-Fy^a, and the transfused unit was Fy(a+).

Another patient with known anti-K+Fy^a had a rigor and spiked a temperature during the transfusion of one of the selected units, which was noted retrospectively to be unlabelled for K, and was in fact K+. Pre-transfusion testing was undertaken by an experienced biomedical scientist (BMS) in a pressured situation. There were several errors involved, including not noting that the unit was not labelled as K-negative and not investigating or excluding an incompatible crossmatch from transfusion.

Kidd (Jk antigen)/Rh antibodies cause 3 serious haemolytic reactions

Anti-Jk^a was responsible for 2 quite serious haemolytic reactions, in which both patients passed dark urine and became jaundiced. One was a newly developing antibody following a transfusion 2 days earlier, and was detectable in a new sample tested just after a Jk(a+) unit had been transfused. The other was probably identifiable in the pre-transfusion sample, but a doubtful reaction brought forward for review was repeated and found to be negative by the analyser the second time round. Retrospective review showed weak positive reactions by eye.

A third case involved Rh and Kidd antibodies in a patient with sickle cell disease and is described in the section on sickle cell patients.

Passive ABO antibodies causing acute and delayed reactions

Unusually, one group AB adult patient suffered rigors and passed dark urine during the transfusion of a group A apheresis platelet unit (not labelled as high-titre negative), which was retrospectively found to have high-titre anti-B (>512). The patient had a positive DAT post transfusion (C3d coating), but no eluate was undertaken, as there was no in-house method set up for this test.

A second patient (group AB) had a delayed haemolytic reaction following the last of 5 daily injections of high dose intravenous immunoglobulin (IVIg). Five days after the last dose, the patient was admitted with breathing difficulties and his Hb had dropped from 152 to 96g/L, and he reported having passed pink urine. He died suddenly at home 11 days later, but at this point the Hb was 120g/L with a negative DAT and his death was considered unrelated to the HTR.

A third patient was a neonate with ABO haemolytic disease of the newborn, who suffered what appeared to be a severe intravascular haemolytic episode, collapse and DIC following exchange transfusion with 320mL of group O SAGM red cells (this was an error in ordering and has been reported in the IBCT-WCT category), which was retrospectively shown to have a high-titre of IgM anti-A (1 in 512 by saline test). This complex case is described in detail in Chapter 16, Paediatric Summary.

Antibodies not usually associated with haemolytic transfusion reactions

There were 5 cases (related to 4 patients) where anti-Lu^a, -Bg^a and -Sd^a were implicated, although 3 were of low imputability. More information can be found in the supplementary information on the SHOT website www.shotuk.org.

Reactions probably not associated with red cell alloantibodies

One patient suffered a severe intravascular haemolytic episode (black plasma) with fever, chest pain, hypertension and peripheral shutdown. The reference laboratory identified antibodies to flucloxacillin in the plasma and eluate, and an enzyme-only anti-e in the plasma.

Another suffered a severe haemolytic episode, also involving what appeared to be intravascular haemolysis, and required dialysis and ITU admission. No red cell antibodies were detected and it is possible that this was an *Escherichia coli* infection with haemolysis exacerbated by transfusion.

There were 3 cases that were likely to have been exacerbation of autoimmune haemolysis, and another 5 where no cause was found. One of the latter cases did have a positive DAT with anti-Jk^a in the plasma and eluate, which could have been autoantibody, or alloantibody from a possible previous transfusion in another country.

A second case with cause unknown was a patient with complex historical antibodies (not currently detectable) and a positive DAT who required ITU admission following fever, rigors, tachycardia, back pain and a seizure during a (fully phenotyped) red cell transfusion. Although the antibody screen was still negative post transfusion, samples were not referred for more sensitive testing nor was an eluate tested.

Learning points

- Exacerbation of autohaemolysis is a recognised effect of transfusion, and should be taken into account when transfusing patients with autoantibodies. New autoantibodies can also be stimulated by transfusion (Young et al. 2004, Petz and Garratty 2004)
- It is advisable to use more sensitive techniques (and test an eluate if the direct antiglobulin test (DAT) is positive) where no antibodies are detected in the antibody screen following a haemolytic transfusion reaction

Delayed (excluding potential hyperhaemolysis) n=26

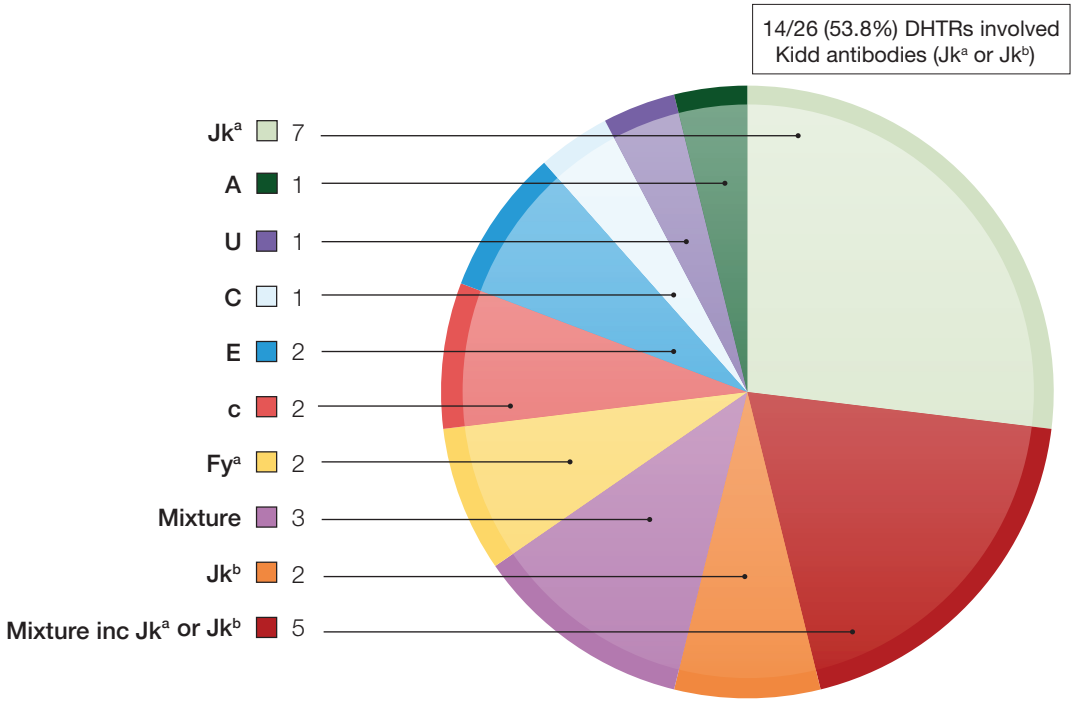

Figure 14.3: Specificities involved in the DHTRs

Haemolytic reactions in patients with sickle cell disease

HTR were reported in 11 patients with sickle cell disease, 9 delayed (all potential cases of hyperhaemolysis) and 2 acute reactions. This is the same number of cases as reported last year.

Acute

One pregnant patient, with known anti-E+Fy^a, had a serious acute haemolytic episode during a red cell transfusion at delivery, resulting in ITU admission. She was found to have developed a new anti-Jk^b, an Rh CcEe-related antibody (compatible with -D-/-D- cells), anti-Le(a+b), and an auto panreactive antibody. It is not clear which of these antibodies was responsible for this serious reaction.

The second patient had known anti-Fy^a and a panreactive autoantibody. The patient had fever and rigors during a transfusion and was found to have anti-Lu^a post transfusion, but there was no evidence of haemolysis provided and it is not clear whether the implicated unit was Lu(a+).

Potential hyperhaemolysis

Some of these cases were reported as minor morbidity and others as major morbidity. However, the reported reductions in Hb were very similar in all cases. SHOT considers that all reported cases of probable hyperhaemolysis where there is a significant fall in Hb should be considered as major morbidity.

The review panel confirmed two cases with the clinicians using the 'post-transfusion hyperhaemolysis referral and follow-up form', before these were reported to SHOT. In addition, there were 5 probable and 2 possible cases.

In 5 cases there were no new alloantibodies, and post-transfusion Hb levels fell to between 36 and 45g/L, with one patient requiring ITU support. Four haemolytic episodes occurred between 4 and 7 days, which is classic timing for cases where no alloantibodies are implicated, and these have been referred to as 'acute' (Win et al. 2008) The 5th case was atypical in that the Hb fell from 63 to 39g/L within 24 hours of admission, 18 days post transfusion.

The other 4 patients developed new red cell antibodies, but in all cases the post-transfusion Hb was lower than the pre-transfusion Hb suggesting destruction of the patient's own cells in addition to any antibody-coated transfused cells. These reactions occurred 7-10 days post transfusion, fitting the classic definition of 'delayed' hyperhaemolysis (Win et al. 2008). One of these patients already had anti-C+S+Kp^a, plus a pan-reactive autoantibody, and developed anti-Fy^a, -Fy3 and -Jk^b post transfusion. The patient's Hb fell to 41g/L which was below the pre-transfusion level, but did not show any other signs of haemolysis, and it is possible that this could have been a more classic DHTR and/or exacerbation of AIHA.

Timing of reactions

Acute

The majority (13/24) of reactions occurred during the transfusion, which was discontinued in all but one case. 4 occurred within 2 hours of the transfusion and the remaining 7 within 24 hours.

Delayed

The delayed reactions were detected between 2 and 18 days post transfusion with a median of 8 days. In some cases, the exact time period was unclear as the patients had received several transfusions over a number of days.

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