

19 Haemolytic Transfusion Reactions (HTR) n=35

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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 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 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 not included (alloimmunisation, and SHOT no longer collects these data).

Key SHOT message

- Patients with sickle cell disease are particularly vulnerable to severe haemolytic transfusion reactions. Laboratory staff should not assume that it is safe to give only Rh/K-matched blood, as antibodies are prone to evanescence and historical antibodies may no longer be detectable serologically. The laboratory should take active steps to seek a transfusion history, and an antibody history if previous transfusion has occurred. For patients in England, Sp-ICE (Specialist Services Electronic Reporting using Sunquest ICE) should also be checked before selecting appropriately phenotyped units and similar shared databases should be checked where available in devolved countries

Number of cases

A total of 35 cases (compared with 59 last year) have been included, 17 acute and 18 delayed (including hyperhaemolysis). The number of delayed reactions is considerably lower than reported in previous years (18 compared with 28).

An additional 5 cases of haemolytic transfusion reaction occurred as the result of errors, and the numbers are included in Chapter 10, Incorrect Blood Components Transfused (IBCT).

Age range and median

There were 5 paediatric cases this year (age range 1 to 15 years). The overall age range was 1 to 88, with a median age of 61 years.

Deaths n=1

There were 2 deaths in total. Both patients had sickle cell disease with hyperhaemolysis following transfusion. In one case the coroner's report ruled out the transfusion as contributory, because the hyperhaemolysis had responded to treatment before the patient deteriorated. The second death was reported as being probably related to the transfusion (imputability 2).

Case 19.1: Death probably related to hyperhaemolysis

A young male patient with sickle cell anaemia received a red cell transfusion in the intensive therapy unit (ITU) in view of hepatic sequestration. Seven days later he had a sudden reduction in his Hb from 85g/L to 45g/L and then a further drop to 31g/L. He had haemoglobinuria, chest pain and had a tachycardia. He was treated with methylprednisolone and intravenous immunoglobulin (IVIg) and further red cell transfusion. While he was being transfused with his first unit he deteriorated, developed chest infiltrates and acidosis. He died of circulatory collapse and respiratory failure some 12 hours later despite maximum support. The coroner's report is awaited.

Major morbidity n=7

The current definition of major morbidity includes 'evidence of intravascular haemolysis, e.g. haemoglobinaemia or haemoglobinuria'; this has caused some confusion, as these signs can also occur with extravascular haemolysis, leading reporters to inappropriately assign major morbidity to HTR where only extravascular haemolysis has occurred. We have reassigned these from major to moderate morbidity and the definition was updated in early 2017 (<https://www.shotuk.org/resources/current-resources/>).

Antibody-mediated intravascular haemolysis, where antibody coated red cells rupture in the bloodstream, is only caused by antibodies that bind complement to the C9 stage, most notably anti-A and anti-B. These reactions are immediate and severe, usually occurring before completion of the unit, and may result in major morbidity or death. Extravascular haemolysis occurs where antibodies do not bind complement (e.g. anti-D) or only bind to C3 (e.g. anti-S), with most of the antibody-coated cells being removed more slowly by the reticuloendothelial system (RES); small amounts of haemoglobin may be released in the plasma, and haemoglobinuria also often occurs, probably due to the RES being overloaded.

There were 2 cases of major morbidity described below, plus an additional 5 cases of hyperhaemolysis in patients with sickle cell disease, described separately in a later section.

Case 19.2: Severe reaction possibly due to exacerbation of autoimmune haemolytic anaemia (AIHA) (imputability 2)

A patient suffered dyspnoea, hypotension, rigors, lower back pain, a feeling of impending doom and loss of consciousness, 5-10 minutes after commencing a second unit of red cells, and was subsequently transferred to ITU. Her Hb fell post transfusion and there was a rise in bilirubin. Pre-transfusion testing showed panagglutinins detected by low ionic strength saline (LISS) indirect antiglobulin test (IAT), and a strongly positive DAT (IgG, IgM and C3d coating), but no underlying alloantibodies. The serological picture did not change post reaction and this is possibly a case of exacerbation of AIHA.

Case 19.3: Life-threatening fall in Hb in a paediatric patient with sickle cell disease (imputability 3)

A child with sickle cell disease was admitted to ITU with acute chest crisis and received a six unit red cell exchange transfusion. Thirteen days later the patient was readmitted with jaundice, limb pain, dark urine and Hb of 32g/L, which fell further to 22g/L. Anti-M and anti-S were identified in both the plasma and eluate. The patient suffered a stroke prior to transfusion of compatible red cells, but recovered quickly following transfusion.

This at first appeared to be a case of hyperhaemolysis as the Hb fell to a much lower level than the pre-transfusion Hb. However, destruction of all transfused red cells following a large volume exchange transfusion can clearly result in the same picture.

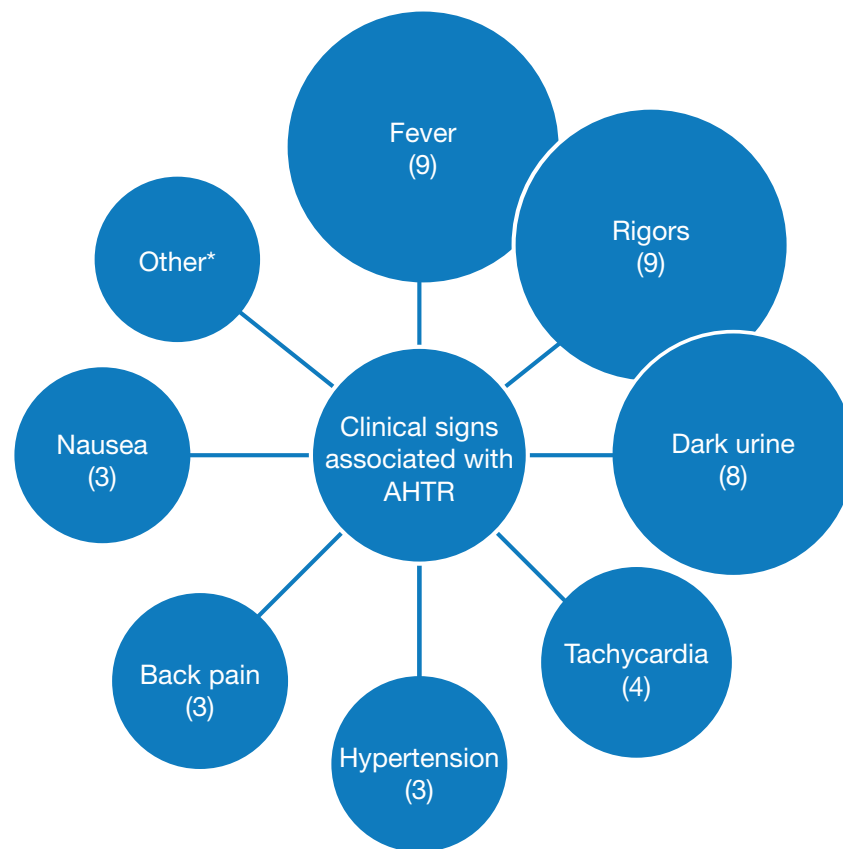
Clinical and laboratory signs and symptoms

Acute haemolytic transfusion reactions n=17

There appears to be no typical set of clinical symptoms associated with acute haemolytic reactions – the most commonly reported signs are shown in Figure 19.1, with the top three the same as last year.

All reports provided laboratory evidence of haemolysis, with the vast majority of patients having a raised bilirubin and a fall in Hb. There were also 6 reports of haemoglobinuria.

Figure 19.1:
Clinical signs
associated with
AHTR



*Other=jaundice; dyspnoea; hypotension; chest pain; elevated respirations; chills (<3 each)

Delayed haemolytic transfusion reactions n=12 (excluding potential cases of hyperhaemolysis)

Seven patients had jaundice and/or dark urine; dyspnoea was also reported in a single case and limb pain in another. In the remaining 5/12 cases (41.7%) there were no obvious clinical symptoms associated with the DHTR, which was diagnosed by laboratory signs of haemolysis. These signs include a fall in Hb, increase in bilirubin and LDH, a positive DAT and the finding of a new antibody in the plasma and/or eluate.

Serological findings

AHTR n=17

Antibodies to low frequency antigens where red cells were electronically issued (one certain, one probable and two possible) n=4

In one case anti-Wr^a definitely caused an AHTR following electronic issue of red cells. The patient suffered fever, rigors and vomiting and had an elevated bilirubin; the IAT crossmatch was incompatible and anti-Wr^a was found in the plasma and eluate. In a second case, the patient had fever, rigors, tachycardia, hypertension and a sharp rise in bilirubin; although the retrospective IAT crossmatch was incompatible, the DAT was negative and the antibody specificity was not identified. In a third case, the patient had dyspnoea and hypertension, with an increased bilirubin, and although the post-transfusion DAT became transiently positive, no further investigation was undertaken to confirm that the cause of the apparent AHTR was an antibody to a low frequency antigen. In the fourth case, the patient had fever, rigors and chest pain and passed dark urine at home a few hours post transfusion. The post-

transfusion plasma looked haemolysed, she had a rise in bilirubin and her Hb fell to the pre-transfusion level. The DAT was negative, no antibodies were found and the plasma was negative against a panel of low frequency antigens. However, the donations were not available for retrospective IAT crossmatch.

Learning point

- If a patient has an acute haemolytic transfusion reaction with no obvious cause, unless an antibody to a low frequency antigen has been ruled out as the cause, e.g. by a retrospectively compatible indirect antiglobulin test (IAT) crossmatch, the patient's record should be flagged as unsuitable for electronic issue (EI)



Case 19.4: Kidd antibodies identified but relation to the reaction is unclear (1)

A 19-year-old female patient with apparently no previous transfusions suffered chills, rigors and nausea during the third unit of red cells, which was stopped. She had a weak pan-reactive antibody and a strong positive DAT (IgG and C3d) pre transfusion, but anti-Jk^a was identified in addition to the panreactivity in the post-transfusion plasma sample, and the DAT was more strongly positive. There was no evidence of alloantibody in the eluate and the units were Jk(a-). It was thought that the haemolytic episode may have been caused by cold agglutinins following transfusion of cold red cells.

Case 19.5: Kidd antibodies identified but relation to the reaction is unclear (2)

A regularly transfused patient with anti-E and anti-Ch/Rg, received two E-negative red cell units uneventfully. Twenty four days later she was admitted with acute bleeding, a Hb of 52g/L and a positive DAT (1+), and anti-C^w was also identified. Transfusion was stopped after one unit when the patient became febrile, dyspnoeic and hypotensive; the LDH was raised, and spherocytes were noted on the blood film. A new sample demonstrated the same antibodies as before in the plasma but also a stronger positive DAT (3+) and anti-Jk^a in the eluate. The Jk^a status of the units transfused 24 days earlier was unknown but the one transfused during the current transfusion was Jk(a-). The next day, a new sample was sent to the Blood Centre reference laboratory but on this occasion the eluate was negative.

Learning point

- If there is evidence of a haemolytic transfusion reaction, an eluate should be tested as part of the investigation. Occasionally a new alloantibody will be detectable in the eluate but not in the plasma



Case 19.6: Anti-E possibly present in the pre-transfusion sample

Towards completion of a second unit of red cells, a patient developed fever, rigors and passed red urine. He had a rise in bilirubin and no Hb increment. The DAT was negative, but anti-E was identified in the post-transfusion plasma and at least one of the red cell units was confirmed as E-positive. Retrospective testing of the pre-transfusion sample showed some weak reactions by enzyme technique that were suggestive of anti-E. The patient had also been transfused 17 days earlier, and it is probable that the anti-E was developing in response to this earlier transfusion.

Case 19.7: Passive ABO antibodies

There was one case of passive anti-A from a high-titre (HT) negative unit of group O apheresis platelets, causing an acute reaction and haemolysis in a paediatric patient (weight 22.5kg). The patient had a fall in Hb (of 22g/L) and a rise in bilirubin, with spherocytes noted on the blood film; anti-A was confirmed in the plasma and eluate. It is not known whether the HT testing was repeated.

Reactions probably not associated with red cell alloantibodies

There were three cases that were likely to have been exacerbation of autoimmune haemolysis, and another six where no cause was found.

Case 19.8: Probable autohaemolysis following haemopoietic stem cell transplant (HSCT) (imputability 2)

Five months prior to this transfusion a group O D-positive child with acute lymphoblastic leukaemia (ALL) received a HSCT from a group A D-negative donor, and had developed weak anti-D. Two hours into a group O D-negative red cell transfusion, the patient developed a rash all over her abdomen, torso, face and hands; she had an increased heart rate, developed back pain and passed dark red urine. Haemolysis was confirmed by a fall in Hb and a sharp rise in bilirubin (21 to 117micromol/L). The DAT became positive post transfusion and although the eluate was positive by IAT, no specificity was determined. The patient had similar reactions during subsequent transfusions with phenotyped matched red cells, but following treatment with IVIg tolerated further transfusions well.

Additional cases reported as IBCT more details are available in Chapter 10, Incorrect Blood Components Transfused (IBCT)

There were two ABO-incompatible transfusions associated with acute haemolysis: the first (due to collection and administration of the wrong unit, Case 10.5) resulted in a life-threatening AHTR; in the second case (due to wrong blood in tube, Case 10.4), the patient had mild loin pain and 'haematuria' for 24 hours.

A neonate with haemolytic disease of the fetus and newborn (HDFN) due to anti-D suffered prolonged haemolysis following exchange transfusion with D-positive red cells (Case 10.1).

A patient with known anti-S suffered a haemolytic episode following transfusion with S-positive red cells (Case 10.2).



Learning point

- 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)

DHTR (excluding potential hyperhaemolysis) n=12

Table 19.1:
Specificities
involved in the
DHTR

Antibody	Number
Anti-Jk ^a	3
Mixture including Kidd	1
Other mixture	3
Anti-C, -Fy ^b , -c	1 each
None	2
Total	12

In addition, there was one ABO-incompatible transfusion due to wrong blood in tube that resulted in a haemolytic reaction and renal impairment, not noted until 14 days following a four unit red cell transfusion. More details can be found in Chapter 10, Incorrect Blood Components Transfused (IBCT), Case 10.3.

Haemolytic reactions in patients with sickle cell disease n=8

HTR were reported in 8 patients with sickle cell disease, all delayed.

Potential hyperhaemolysis n=6

This group included 6 cases with 2 deaths. Some were reported as minor morbidity and others as major morbidity. However, the reported reductions in Hb were very similar in all but one case. SHOT considers that all reported cases of probable hyperhaemolysis should be considered as major morbidity where there is a significant fall in Hb. The cases are detailed in Table 19.2.

Classic DHTR n=2

Two severe DHTR occurred in patients with sickle cell disease. One was unavoidable and is described earlier in the section on major morbidity (Case 19.3).

The other could have been prevented as the patient had a history of red cell antibodies which were known but undetectable at the time of transfusion (Case 19.9).

Case 19.9: Avoidable DHTR following transfusion of antigen-positive red cells

The patient received an eight unit red cell exchange transfusion at hospital A (prior to surgery at hospital B) with red cells matched only for Rh and K. She was admitted to hospital B 6 days later, very unwell, with fever, jaundice, black urine and a falling Hb. Hospital B had a historical record of anti-E+S+Fy^a+Fy^b+Fy3 for this patient and confirmed that several of the units used in the exchange were antigen positive; anti-Fy^a+Fy3 were identified in the plasma and eluate.

There were two opportunities for the patient history to be available to hospital A: the laboratory in hospital A could have requested the history from either hospital B or from Sp-ICE; the laboratory in hospital B could have actively informed the laboratory in hospital A as they were aware that the exchange transfusion would take place there.

Case	Serology	Clinical & laboratory signs	Morbidity	No. days post transfusion	Additional comments	Imputability of reaction to the transfusion
HH1	No antibodies; DAT positive (IgG+C3d); eluate negative	Fever; haemoglobinuria; bilirubin↑; Hb↓↓	Major: impaired renal function (creatinine 63 to 184 micromol/L) Hb fell to 41g/L	6	Treated with steroids and IVIg	Probable
HH2	Anti-E+S+c and positive DAT pre transfusion; anti-N in eluate	Fever; jaundice; pain; nausea; bilirubin↑; Hb↓↓; LDH↑	Major: Hb fell to 33g/L	6	Treated with steroids	Possible
HH3	No new antibodies; anti-C+Jk ^b pre transfusion; probable anti-N between transfusions	bilirubin↑; Hb↓↓	Major: Hb fell to 42g/L	2 - 14	Transfused on 3 occasions within 3 weeks; treated with steroids	Probable
HH4	Known anti-Jk ^b +S; no new antibodies	Chest pain; dark urine, jaundice; bilirubin↑; Hb↓↓; LDH↑↑(8180U/L)	Major: Hb fell to 41g/L	5	Treated with IVIg and steroids; death not related to transfusion	Certain
HH5	No antibodies	Tachycardia; hypoxia; haemoglobinuria;	Death probably related to HH; Hb fell to 31g/L	7	Treated with IVIg and steroids	Certain
HH6	Known anti-E+Jk ^b +Kp ^a , DAT1+; no new antibodies	Fever, jaundice, dark urine; Hb↓ LDH↑	Moderate: Hb fell to 58g/L	6	3 unit transfusion; treated with IVIg and steroids	Probable

Table 19.2:
Cases of hyperhaemolysis (HH) in patients with sickle cell disease

Timing of reactions

Acute

The majority (9/17) of reactions occurred during the transfusion which was discontinued in all but one case, where the symptoms were not fully recognised until a fifth unit had been transfused. Four occurred within two hours of the transfusion and the remaining four within 24 hours. The suspected unit was returned to the laboratory for investigation in 12/17 cases; in 4/17 cases, the reaction occurred after completion of the transfusion (or was not recognised until after completion of the transfusion), so the empty bag had presumably been discarded. There was one case where the reaction occurred during the transfusion, and the transfusion was stopped, but the bag not returned.

Delayed

The delayed reactions were detected between 3 and 15 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.

References

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

Young P, Uzieblo A et al. (2004) **Autoantibody formation after alloimmunisation: are blood transfusion a risk factor for autoimmune haemolytic anaemia?** Transfusion 44, 67-72