15 Haemolytic Transfusion Reactions (HTR) n=46

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Definition:

Acute haemolytic transfusion reactions (AHTRs) 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 (DHTRs) 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) may be reported in the Alloimmunisation category.

Note that for the purposes of the European Union (EU) legislation, serious adverse reactions (SAR) are defined as any reactions in patients that are 'life-threatening, disabling or incapacitating, or which result in or prolong hospitalisation or morbidity.' These must be reported to the Medicines and Healthcare products Regulatory Agency (MHRA) (a legal requirement).

The following HTR are included in this requirement: 'immunological haemolysis due to ABO incompatibility' (reported in Chapter 9 Incorrect Blood Component Transfused (IBCT)), and 'immunological haemolysis due to other alloantibody' reported in this chapter.

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
- There were no clinical symptoms associated with delayed haemolytic transfusion reactions in 50% of reported cases, making it the responsibility of transfusion laboratory staff to recognise laboratory signs that a reaction may have occurred. Laboratory staff should consider the possibility of a haemolytic transfusion reaction if there are any laboratory signs of haemolysis, development of new antibodies, or equivocal serological reactions within 4 weeks of a transfusion. Investigation should include a DAT, an eluate, and testing using additional techniques, e.g. enzyme or enzyme indirect antiglobulin test (IAT) panels, before further transfusions are given, unless the urgency of the transfusion requires concessionary release
- There is a huge variety of clinical symptoms associated with acute haemolytic reactions, and haemolysis may not be easy to confirm, particularly when the transfusion has been stopped after the transfusion of a small volume. Pre-transfusion serology should be repeated with a new sample, and an IAT crossmatch should be included where the red cells were provided by electronic issue. Investigation should include a DAT, and an eluate if the DAT is positive or if the serological picture is different from the original testing

- Anti-A or anti-B present in high dose intravenous immunoglobulin (IVIg) has been implicated in HTRs in non group O patients. Although these are usually mild reactions that may go unnoticed, rarely, the haemolysis can be severe, resulting in major morbidity. Blood transfusion laboratories should be made aware that patients are receiving high dose IVIg so that they can be vigilant for signs of haemolysis. All complications of IVIg infusion should be reported to the MHRA via the yellow card reporting system, although transfusion-related reactions should also be reported to SHOT

Number of cases

A total of 46 cases have been included, 18 acute and 28 delayed reactions.

Age range and median

There was one paediatric case this year (age 8 years). The overall age range was 8 to 97, with a median age of 64 years.

Deaths n=1

There were 3 deaths in total. In 2 cases the patient died due to their underlying disease, but in one case the haemolytic transfusion reaction definitely contributed to the patient's death (imputability 3).

Case 1: AHTR in very sick patient contributes to death

A patient was admitted to the intensive therapy unit (ITU) with drug-induced pneumonitis. The Blood Service reference laboratory reported allo anti-C plus strongly reactive autoantibodies, with a positive DAT, and provided R_2R_2 (cDE/cDE) K-negative red cells as suitable for transfusion. The first unit was transfused with IVIg and steroid cover, but 30 minutes after completion, the patient became agitated, flushed, tachypnoeic and wheezy, and developed haemoglobinuria, but then settled. Four and a half hours after completion of the unit, the patient deteriorated with decreased urine output; she suffered a cardiac arrest during intubation and died two hours later. Post transfusion her plasma was grossly haemolysed and the bilirubin had risen from 16 to 71micromol/L. The post mortem report cited the primary cause of death as multi-organ failure, HTR and pulmonary fibrosis, with a secondary cause of ischaemic heart disease. The contribution of the HTR to the patient's death was confirmed by the coroner. The most likely explanation for the HTR is exacerbation of the autoantibody by transfusion.

Major morbidity n=5

There were 5 cases of major morbidity. Three involved patients with sickle cell disease, two due to confirmed and one potential hyperhaemolysis, involving life-threatening falls in Hb, with one requiring ITU admission. One patient developed multiple antibodies 6 days post massive transfusion and required ITU admission, and another developed renal impairment following development of anti-Jk^a (Case 2).

Case 2: Anti-Jk^a of donor origin post haemopoietic stem cell transplant (HSCT)

A patient with acute myeloid leukaemia (AML) was 9/12 post HSCT, with graft versus host disease (GvHD) and receiving regular transfusions. Within an hour of starting the first unit, the patient developed rigors and back pain, was hypotensive and passed red urine. The pre-transfusion Hb of 69g/L fell to 43g/L post reaction, suggesting haemolysis of the patient's circulating red cells in addition to those just transfused. The patient had received 7 units of red cells during the previous 9 days. Weak anti-Jk^a was identified in the post-transfusion sample (stronger one week later) in addition to the anti-E already identified. The patient was Jk(a+) pre transplant, but the donor was Jk(a-), confirming that the antibody was of donor origin. The DAT was negative pre transfusion but became positive, suggesting an acute HTR to the current red cell unit, but involving destruction of the previously transfused cells in addition. The patient's renal function had started to deteriorate the day before the current transfusion, and this was thought to be related to ongoing haemolysis of previously transfused Jk(a+) red cells.

Clinical and laboratory signs and symptoms

Acute haemolytic transfusion reactions n=18

There appears to be no typical set of clinical symptoms associated with acute haemolytic reactions, although the most commonly reported signs were fever (n=8), rigors (n=7), dark urine (n=7) and back pain (n=6), in different combinations. Other less commonly reported signs were hypotension (n=2), nausea/vomiting (n=2), and one each of hypertension, dyspnoea, flushing and jaundice.

Seven patients had clinical signs of a reaction during the transfusion, which was subsequently stopped, and the unit returned to the laboratory. One of these had fever and rigors, but showed no clinical or laboratory signs of haemolysis. It is not clear whether the anti-Wr^a subsequently identified was the cause of the reaction, or whether this was coincidental, although the implicated donation was confirmed to be Wr(a+) and retrospectively incompatible.

Two patients with red cell antibodies received emergency O D-negative red cells, and another, crossmatch compatible red cells before testing was complete. None showed any signs of a clinical reaction, but two did show laboratory signs of mild haemolysis. In the third case, treatment was withdrawn, and no further laboratory tests were undertaken, so a haemolytic transfusion reaction could not be confirmed.

The remaining 8 patients showed clinical signs of a transfusion reaction within 24 hours of completion of the transfusion.

Blood samples were taken for investigation in all cases, and urine samples collected from patients who had passed dark urine.

Delayed haemolytic transfusion reactions n=28

In 14/28 cases (50%) there were no obvious clinical symptoms associated with the DHTR, which was diagnosed by laboratory signs of haemolysis.

Of the remaining 14 patients, the most common clinical features reported were dark urine and/or jaundice, in 12/14 cases (85.7%). Fever, back pain, chest pain and dyspnoea were also reported clinical features in a minority of patients.

Haemolysis was confirmed in the majority of cases, 25/28 (89.3%), by a fall in Hb or lack of expected Hb increment. In 2 cases a transient rise in bilirubin (with or without a raised LDH) was the only indication of a mild haemolytic reaction. The final case involved high dose IVIg, given to a group A patient, which may or may not have caused a haemolytic reaction, described below.

Case 3: High dose IVIg potentially causes an HTR

A patient with chronic myeloid leukaemia (CML), blood loss and sepsis required urgent transfusion. 5/6 units were incompatible and emergency O D-negative red cells were issued. The DAT was positive, and anti-A reacting only with A_1 cells was identified in the plasma and eluted from the patient's red cells. A batch of IVIg given 4 days earlier, was identified as the source and in-house testing revealed a titre of 256 against A_1 cells in IgG cards. The patient had a raised bilirubin and did not appear to show an increment in Hb, but was septic with multiple problems including ascites and blood loss. It was felt by the reporter that the anti-A from the IVIg may have contributed to the patient's worsening clinical condition.

Learning point

- Passive anti-A from high dose intravenous immunoglobulin (IVIg) is not an uncommon cause of an incompatible crossmatch in non group O patients, although it rarely causes a severe haemolytic reaction. Group O red cell transfusions should be considered until anti-A is no longer detectable as should a different batch of IVIg, where the patient suffers a haemolytic episode (Padmore 2012)

Haemoglobinuria was reported in five patients who were noted to have passed dark urine, and 13 had a raised LDH. A DAT was undertaken as part of the DHTR investigation in all cases. It was negative in 4 cases, and positive in the remaining 24, with 13 demonstrating IgG coating only, one C3d coating only, 8 both, and two not stated.

Serological findings

Acute n=18

There were four cases this year where an antibody to a low frequency antigen was likely to have caused the reaction: three anti-Wr^a and one unspecified. All were confirmed to be retrospectively incompatible with the implicated donation. In one case there was no evidence of haemolysis, and only mild haemolysis in the others.

Learning point

- Haemolytic transfusion reactions due to antibodies directed against low frequency antigens are a small but acceptable risk of omitting the indirect antiglobulin test (IAT) crossmatch. 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

Emergency O D-negative red cells were transfused in 2 urgent cases, where the patient was retrospectively found to have a red cell antibody, incompatible with the transfused units (one each of anti-e and anti-Fy^a).

There were 6 cases where each patient had an alloantibody identified post transfusion, which had not been detected pre transfusion: anti-Jk^a (Case 2), anti-f (detectable pre transfusion using a different analyser in Case 8), anti-E (clearly identifiable by enzyme and by IAT with a different panel of red cells in Case 4), anti-M (detected one week later in a sickle cell patient), anti-C^w, and enzyme-only anti-C.

In the remaining six cases, no red cell alloantibodies were detected. Four clear haemolytic episodes were likely due to autohaemolysis exacerbated by the transfusion. This included the patient who died (Case 1, described earlier). There was no explanation for the other 2 cases, but there was significant haemolysis in both patients, with one reported to have had similar episodes with subsequent transfusions.

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)

Case 4: Weak anti-E not identified prior to urgent transfusion due to a reagent failure and no enzyme panel

A patient was admitted with an upper gastrointestinal (GI) bleed and Hb 59g/L. Six units of red cells were requested as an emergency. The patient was O D-positive with a positive antibody screen and 2/6 units were incompatible by IAT. The antibody identification (ID) panel was negative as was the DAT. The 4 compatible units were transfused under concessionary release. Meanwhile, a sample was sent to the Blood Service red cell reference laboratory, where anti-E was identified clearly by enzyme and with the R_2R_2 cell (cDE/cDE) by IAT. Two of the transfused units were confirmed to be E+. Antibody identification was repeated with a new panel of cells, and a positive reaction was found by IAT with the R_2R_2 cell. The reagent failure was reported to the manufacturer. The next day, the bilirubin was slightly raised, from 6 to 31micromol/L and the LDH had increased from 285 to 400U/L. Bloods taken 12 days later showed that the Hb had remained stable, the LDH was 800U/L, the DAT was positive and anti-E was detected more strongly, but an eluate was not tested. The laboratory is considering the introduction of an enzyme panel.

Learning point

- Many antibodies reactions are enhanced by using enzyme techniques, and the British Committee for Standards in Haematology (BCSH) guidelines recommend that a panel of enzyme treated cells is available (BCSH Milkins et al. 2013)

Delayed n=28

No alloantibodies were detected in 5 patients with sickle cell disease (further details are given later).

Kidd antibodies were the most commonly implicated in the remaining reactions, being identified in 13/23 (56.5%) of cases, 8 where it was the sole specificity. Rh antibodies were the second most commonly identified, in 11 cases (47.8%), followed by Duffy and MNS (5 cases each). Kell antibodies were only implicated in 3 cases. Further details can be found in a table on the SHOT website, www.shotuk.org under SHOT Annual Reports and Summaries.

The following 2 cases demonstrate the need for transfusion laboratories to consider that weak or unexpected reactions in the antibody screen or crossmatch may be due to developing antibodies from an earlier transfusion, and that the patient may already be undergoing a haemolytic transfusion reaction.

Case 5: Weak antibody missed pre transfusion

A patient with AML (transfused 5 days previously) had a positive antibody screen by Capture and a positive DAT, but the identification panel using manual techniques was inconclusive. The patient received a routine transfusion with crossmatch-compatible red cells, while a sample was referred to the Blood Service reference laboratory where anti-E was identified by BioRad IAT and anti-c by enzyme only. No eluate was undertaken on this sample as it was thought by the reference laboratory to be a pre-transfusion sample. The next day, the patient had a slight rise in bilirubin and the Hb dropped from 97g/L immediately post transfusion to 90g/L. A further sample was referred to the reference laboratory 2-3 weeks later, which showed anti-c now detectable by IAT, but the eluate was negative. The anti-c+E were presumably developing following the earlier transfusion, and it is not clear whether the mild HTR was due to the earlier or later of the 2 transfusions.

Case 6: Weak anti-Jk^a might have been detected in an eluate pre transfusion

A patient with acute blood loss and Hb 75g/L had a positive antibody screen; anti-C plus an enzyme non-specific antibody were identified, and one of four C-negative units crossmatched was incompatible by IAT. The patient had also been transfused 3 weeks earlier, when non-specific reactions by IAT and enzyme panagglutinins had been noted. The patient was transfused with two units of C-negative, K-negative red cells, compatible by IAT. Meanwhile a sample was sent to the Blood Service reference laboratory for investigation of a suspected antibody to a low frequency antigen. The reference laboratory identified anti-Jk^a in addition to the anti-C and enzyme panagglutinins. The anti-Jk^a was only reacting with some but not all Jk(a+b-) cells in the plasma by IAT but was clearly identifiable in an eluate made from the patient's red cells, as was the anti-C. The DAT was positive, and both antibodies were presumably developing in response to the transfusion 3 weeks earlier. It is not clear whether either of the two recently transfused units were Jk(a+), but when the Hb was next measured 5 days later, there had been no increment. The patient may have been having a delayed transfusion reaction to the earlier transfusion and a more acute reaction to the recent transfusion.

Learning point

- Weak or unexpected positive reactions, in a recently transfused patient, should be investigated by more sensitive techniques, such as enzyme or enzyme indirect antiglobulin test (IAT) before further transfusion, if the clinical situation allows. An eluate should also be tested, since any IgG antibody on the transfused red cells, may be reactive more strongly, or in some cases, only in the eluate

Haemolytic reactions in patients with sickle cell disease

HTRs were reported in 11 patients with sickle cell disease, 2 acute and 9 delayed.

One acute reaction occurred in a patient who had known alloantibodies and warm autoantibodies; no further alloantibodies were detected post transfusion and this is likely to be a case of exacerbation of autoimmune haemolysis. The other acute reaction was unusual in that the bilirubin was raised, the Hb did not increment, and the DAT became positive post transfusion, but no antibodies were detectable in the plasma or eluate until one week later, when anti-M was identified.

The newly appointed hyperhaemolysis review panel confirmed four cases of hyperhaemolysis with the clinicians using the 'post-transfusion hyperhaemolysis referral and follow-up form', and these cases were subsequently reported to SHOT in the usual way. The reaction was first reported between 6 and 8 days post transfusion, and in each case the Hb continued to fall to several g/L below pre-transfusion levels. No alloantibodies were detected in 3 of these cases. The 4th case is more complicated as the patient was transfused 4 units of red cells on holiday in a different country 7 days before presenting at hospital in the UK, with severe anaemia (38g/L), pain, fever and nausea. Following further transfusion, the Hb fell to 26g/L and she was treated with IVIg and methylprednisolone, and was moved to the high dependency unit (HDU). Anti-S+Jk^{b} were present on admission, and anti-Fy^{a}, anti-M plus a pan-reactive autoantibody were identified post transfusion. The low Hb and a low reticulocyte count, confirmed this as hyperhaemolysis.

Another patient showed a similar pattern of results to the first 3 cases, with a Hb lower than the pre-transfusion level, and no alloantibodies; this case was not referred to the review panel at the time of the reaction, and insufficient details are available to confirm whether or not this is a further case of hyperhaemolysis.

Three patients with sickle cell disease suffered minor morbidity as the result of classic delayed HTRs due to red cell alloantibodies (anti-E (Case 7), anti-S, and multiple specificities).

The final patient is more difficult to classify. She had a haemolytic episode 14 days post transfusion, with fever and back pain, red plasma, dark urine, a raised bilirubin and Hb 10g/L lower than immediately post transfusion, but although the DAT was positive, no alloantibodies were detected in the plasma or eluate.

Case 7: Incorrect historic phenotype leads to DHTR due to anti-E

A patient with sickle cell disease was exchange transfused with R_2R_2 (cDE/cDE) red cells based on an incorrect historical phenotype undertaken in 1984. 18 days later, the patient had back pain, rigors and dark urine, the bilirubin was raised and the Hb was 40g/L lower than it had been post exchange; the DAT was positive and anti-E was identified in the plasma, although the eluate was negative. The patient had been suffering from several recent sickle cell crises, but did appear to be suffering from a DHTR as well. The laboratory has subsequently changed its policy to undertake a second Rh phenotype where there has been no recent transfusion activity.

Eluates

An eluate was tested in 21/28 cases of DHTR, and revealed a specific antibody in 13/21. The eluate was negative in 6 cases, had non-specific reactions in one case and no result was stated in another. Anti-E was identified in the eluate in one case where the DAT was negative. An eluate was not tested in 7 cases, 3 were cases of hyperhaemolysis where no alloantibody was present and the DAT was negative. The other 4 all had alloantibodies identified and a positive DAT. Two of these were referred to Blood Service reference laboratories - in one of these, an eluate had been undertaken recently revealing panreactive antibodies, so it was not considered helpful to repeat the test, as any alloantibodies would be masked by autoantibody; in the second of these, the reference laboratory should have prepared an eluate, but overlooked the test. The other 2 cases without testing of an eluate were not referred to a reference laboratory.

Timing of reaction

Delayed

The delayed reactions were detected between 2 and 40 days post transfusion with a median of 7 days. However, there were three further cases where the time period was unclear as the patients had received several transfusions over a number of days. Details are available on the SHOT website, www.shotuk.org under SHOT Annual Reports and Summaries.

Role of serological techniques

In 2 cases the reporter noted that the IAT method failed to detect the implicated antibodies.

Case 8: Weak antibody detected retrospectively on different analyser

A patient was transfused following a negative antibody screen on the Immucor Echo analyser, and subsequent electronic issue. She developed fever, hypertension and back pain after the first unit, triggering repeat serological testing. Post-transfusion investigation revealed anti-f in the pre-transfusion sample using the Immucor Galileo analyser and also by manual DiaMed technique, but not on the Echo. The conclusion, following investigation by the manufacturer, was that this antibody was at the threshold for detection and the analyser was working as expected.

Case 9: Weak antibody reacts differently by different technologies

A patient had a positive antibody screen using the Immucor Neo analyser, but gave non-specific results in the panel. Units were crossmatched and found compatible by DiaMed. Two days post transfusion, the patient had chest pain and dyspnoea, a raised bilirubin and a positive DAT, anti-Jk^a was identified. The hospital is moving towards crossmatching by the Immucor Neo.

Learning points

- Different indirect antiglobulin test (IAT) technologies have different sensitivities and it is unlikely that any single technology will be the best at detecting all weak antibodies
- Kidd antibodies are often difficult to detect and it is worth considering testing a serum sample and/or using an enzyme antiglobulin test where the antibody screen is weakly positive but no specific alloantibody can be identified

References

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