Haemolytic Transfusion Reactions (HTR) 16

Author: Clare Milkins

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.

This chapter does not include haemolytic reactions resulting from inadvertent ABO-incompatible red cell transfusions, which are described in Chapter 8, Incorrect Blood Components Transfused (IBCT).

DATA SUMMARY
Total number of cases: n=49

Implicated components		Mortality/morbidity	
Red cells	48	Deaths definitely due to transfusion	0
Fresh frozen plasma (FFP)	0	Deaths probably/likely due to transfusion	1
Platelets	1	Deaths possibly due to transfusion	0
Cryoprecipitate	0	Major morbidity	8
Granulocytes	0	Potential for major morbidity (Anti-D or K only)	0
Anti-D Ig	0		
Multiple components	0		
Unknown	0		

Gender		Age		Emergency vs. routine and core hours vs. out of core hours		Where transfusion took place	
Male	17	≥18 years	46	Emergency	8	Emergency Department	4
Female	32	16 years to <18 years	0	Urgent	6	Theatre	3
Not known	0	1 year to <16 years	3	Routine	32	ITU/NNU/HDU/Recovery	7
		>28 days to <1 year	0	Not known	3	Wards	17
		Birth to ≤28 days	0			Delivery Ward	0
		Not known	0	In core hours	0	Postnatal	1
				Out of core hours	0	Medical Assessment Unit	3
				Not known/Not applicable	49	Community	0
						Outpatient/day unit	14
						Hospice	0
						Antenatal Clinic	0
						Other	0
						Unknown	0

(ITU=Intensive therapy unit; NNU=Neonatal unit; HDU=High dependency unit)

Number of cases

A total of 49 cases have been included, 17 acute and 32 delayed reactions.

Age range and median

There were 3 paediatric cases this year (ages 5, 8 and 13 years). The overall age range was 5 to 94 years, with a median age of 59 years.

Deaths n=1

There were 6 deaths in total. In 5 cases the patient died from their underlying disease, but in one case the haemolytic transfusion reaction contributed to the patient's death by triggering a severe sickle cell crisis:

Case 1: Severe sickle cell crisis triggered by DHTR

A patient was treated with a 10 unit exchange transfusion for a sickle chest crisis. He was readmitted 11 days later, unwell and with generalised sickle pain, and reported passing dark urine. The DAT was positive and anti-Jk^{b} and –S were identified in the post-transfusion plasma and eluate. The Hb fell from 98g/L on re-admission to 61g/L by the following day, the bilirubin rose to 674micromol/L and the creatinine rose to 140micromol/L, requiring ITU admission. He later died as a result of liver failure due to an ongoing sickle cell crisis, probably triggered by the delayed transfusion reaction.

Major morbidity n=8

There were 8 cases of major morbidity, 2/8 relating to acute and 6/8 to delayed reactions. Six involved patients with sickle cell disease, with 3/6 due to hyperhaemolysis. Five of 8 patients required ITU admission and 2/8 suffered a life-threatening drop in Hb (one with autoimmune haemolytic anaemia (AIHA) and another with sickle cell disease). The final patient suffered renal failure, requiring renal dialysis, but is since making a gradual recovery.

Clinical and laboratory signs and symptoms

Acute haemolytic transfusion reactions n=17

The most common clinical symptom was fever, reported in 12/17 (70.6%) cases, usually accompanied by rigors. Dyspnoea (6 cases), back or chest pain, and dark urine were the next most commonly reported symptoms (5 cases each). Less common were chills (4 cases), jaundice (3 cases), hypotension, tachycardia, and nausea and vomiting (2 cases each). There were single reports of hypertension, sweating, diarrhoea and myalgia.

An increase in bilirubin and/or a fall in Hb (or no Hb increment) were the usual laboratory signs of haemolysis, in 14 and 13 cases, respectively. The DAT was positive in 9/17 (52.9%) cases and there were 5 reports of a high LDH.

Delayed haemolytic transfusion reactions n=32

In 10/32 (31.3%) reports there were no obvious clinical symptoms associated with the DHTR, which was diagnosed by laboratory signs of haemolysis. Of the remaining 22/32 patients, the most common clinical feature reported was dark urine or jaundice, in 10/22 cases each (45.5%). The next most common presenting feature was fever (9 cases), followed by chest or back pain (8 cases). Other symptoms included dyspnoea, chills and hypotension.

Haemolysis was confirmed in all cases by a fall in Hb or lack of expected Hb increment. A rising bilirubin was reported in 24/32 cases (75.0%). Six patients were reported to have haemoglobinuria, and 15 had a raised LDH. A DAT was undertaken as part of the DHTR investigation in 30/32 cases (93.8%). It was negative in 9 cases, and positive in the remaining 21, with 10 demonstrating IgG coating only, 2 C3d coating only and 9 both.

Serological findings

Acute

There were 3/17 cases again this year where an antibody to a low frequency antigen was likely to have caused the reaction: two anti-Wr^a and one unspecified. One followed transfusion with red cells matched by electronic issue and another by immediate spin. In both cases the DAT was negative but the implicated donation was retrospectively found to be incompatible and there were clear signs of haemolysis, including a fall in Hb and a rise in bilirubin. The third case occurred in a patient with panagglutinins and a positive DAT, where the indirect antiglobulin test (IAT) crossmatch was incompatible, but the presence of alloantibodies had been excluded by the Blood Service reference laboratory. An eluate from the post-transfusion sample showed panagglutinins, but the implicated unit was found to be incompatible using adsorbed plasma. This patient also showed clear signs of haemolysis including jaundice, accompanied by a sharp rise in bilirubin.

Learning point

- Clinical staff need to be vigilant for acute haemolytic reactions and laboratory staff need to be aware of antibody-mediated transfusion reactions caused by antibodies to low frequency antigens, which may not have been detected in electronic or abbreviated crossmatching. This is a known, but accepted small risk of electronic issue and laboratory investigations of suspected haemolytic transfusion reactions should include a retrospective crossmatch

There was one case, where haemolysis may have been caused by an enzyme-only anti-E, but the patient had received fludarabine, which had previously caused a haemolytic episode in the same patient (Case 3).

There was one case of possible anti-Jk^a, although this was unconfirmed when tested by the Blood Service reference laboratory. Another patient developed weak anti-Jk^a+E 24 hours after one transfusion, identified when a further sample was taken following a febrile reaction during a transfusion the next day (Case 4). Anti-Fy3+Kp^a caused a severe acute reaction, requiring ITU admission in a sickle cell patient who already had red cell antibodies, and was probably in combination with a delayed reaction to a transfusion given 7 days previously. There was also one case due to anti-f.

For the first time in 5 years, there was one report of group O platelets causing a mild acute haemolytic episode in a group AB child. The platelets were found retrospectively to have a high-titre of IgG anti-A.

In the remaining 8/17 cases, no red cell alloantibodies were detected, although the patients appeared to have laboratory signs of haemolysis and varying clinical symptoms for which the transfusion was stopped.

Case 2: Major morbidity with no clear cause

A middle aged woman was admitted with a chest infection, for which she was already on antibiotics, and chronic anaemia (Hb 51g/L), a weakly positive DAT (C3 coating only) and panagglutinins by BioRad technique. Whilst being investigated by the Blood Service reference laboratory, she was given a considerable volume of fluid causing her Hb to fall to 40g/L. No antibodies were detected by LISS tube technique and red cells were issued as suitable for transfusion. The patient suffered a severe reaction half way through the second unit, with hypertension, vomiting, dyspnoea, cyanosis and abdominal pain. The post-transfusion plasma appeared haemolysed and she also had haemoglobinuria, with a rising bilirubin and creatinine, although the latter was already raised. She was transferred to the renal unit and required dialysis. Despite extensive investigation, no cause has been established for her anaemia and no red cell antibodies have been detected to explain the haemolytic episode.

Case 3: Acute haemolytic reaction in patient with enzyme-only anti-E and a history of haemolysis with fludarabine

An elderly patient with Waldenstrom's macroglobulinemia on fludarabine became cyanosed and dyspnoeic, and his oxygen saturation fell at the end of a 2 unit red cell transfusion. The bilirubin rose from 14 to 91micromol/L, the Hb fell quickly back to the pre-transfusion level and the patient had haemoglobinuria. The DAT was negative and the only red cell antibody to be detected was an enzyme-only anti-E. The reporters have also considered that this could be a case of fludarabine-related haemolytic anaemia, as this is a recognised phenomenon and the patient's Hb had been noted to drop following a previous dose of fludarabine.

Learning point

- Fludarabine has been associated with episodes of autoimmune haemolytic anaemia and could contribute to a confusing picture when the patient has also been transfused [55]

Case 4: Anti-Jk^a not immediately identified

A young male patient on extracorporeal membrane oxygenation therapy (ECMO), was given one unit of red cells without any problem. However, 180mL into a second unit of red cells the following day, the patient had a rise in temperature and the transfusion was stopped. The antibody screen was negative pre transfusion but weakly positive on the post-transfusion sample. The DAT had become weakly positive, with C3 coating only, and the bilirubin rose from 17 to 32micromol/L. No antibody was identified but 2 units of E-K- units were issued. Three days later, anti-E+Jk^a were clearly identified and the DAT was more strongly positive (again C3 coating only). Another 5 days later, spherocytes were noticed on the blood film, the bilirubin was rising again and the DAT was now mixed field positive with both C3 and IgG coating, but the eluate was negative. The patient may have been suffering from a mild delayed HTR in addition to the acute HTR.

It is possible that the anti-Jk^a (and maybe the anti-E) could have been identified when the antibody screen was weakly positive, by using more sensitive techniques such as an antiglobulin test using enzyme treated cells or by testing serum rather than plasma.

Learning point

- Kidd antibodies are often weak, complement-binding and difficult to identify. More sensitive techniques, such as an enzyme antiglobulin test, and/or a serum sample may be required for conclusive identification

Case 5: Acute reaction in a sickle cell patient with a history of hyperhaemolysis

A patient with sickle cell disease, and a history of hyperhaemolysis at another hospital, had fever, rigors, chest pain and dyspnoea during the second unit of a transfusion. The Hb rose from 38g/L to 48gL post transfusion, but began to fall again next day. The bilirubin increased from 95 to 143micromol/L and there was a slight rise in the absolute reticulocyte count. The pre and post DAT were positive but the antibody screen was negative on both samples. The reporter queried whether this was an episode of hyperhaemolysis.

This is not typical of hyperhaemolysis as the reaction occurred during the transfusion and there was no evidence that the Hb dropped to below pre-transfusion levels. However, the patient had a clear haemolytic episode with no evidence of alloantibodies. This patient is usually given IVIg cover when transfused at his local hospital but IVIg was not given on this occasion.

Case 6: Mild haemolysis following transfusion of group O platelets to a group AB child

A young child, group AB, received group O, cytomegalovirus (CMV) negative, irradiated, high-titre (HT) negative platelets, post chemotherapy. Two hours later the patient developed fever, chills and rigors during a group A red cell transfusion. The post-transfusion DAT was positive and anti-A was

eluted from the red cells. There were no other red cell antibodies detected. The platelets were retrospectively confirmed as having an IgM titre of 128 but an IgG titre of 2048. In future, this hospital plans to give group A platelets to non group O paediatric patients.

Learning point

- Group O platelets can cause haemolysis in non group O recipients, even when labelled as 'High-titre negative'. Paediatric patients are especially vulnerable, and where possible, (non group O recipients) should be given group specific or group A platelets in preference to group O

Delayed haemolytic transfusion reactions

No antibodies were detected in 8 patients with sickle cell disease (further details are shown in Table 16.2). The antibodies from the remaining cases are summarised in Table 16.1. Further details can be found in a Table on the website in the Annual SHOT Report 2013 Supplement, www.shotuk.org under SHOT Annual Report and Summaries, Report, Summary and Supplement 2013.

Table 16.1 Delayed – specificity of antibody

Antibody specificity by blood group system and antigen	Number of cases	Number of cases where this was the sole new antibody
Kidd		
Jk^a	9	7
Jk^b	5	2
Rh		
E	1	1
c (±E)	4	3
C	1	1
e	1	1
Fy		
Fy^a	2	2
Kell		
K	1	0
MNS		
M	1	1
S	2	1
s	1	0

Case 7: Unrecognised DHTR at home

An elderly woman with myelodysplastic syndrome received 2 units of red cells on the haematology day unit with no ill effect. Eight days later she experienced loin pain and passed black urine, which continued for 5 days. The primary care team prescribed antibiotics, but did not take a urine sample or report this to the haematologist. It was not until 3 weeks later, when the patient returned to the day unit for an appointment that a DHTR (due to anti-c) was diagnosed.

Learning point

- Primary care teams should be aware of the symptoms of a delayed haemolytic transfusion reaction (DHTR), and instigate appropriate investigations

Case 8: Anti-Jk^b could have been identified in the pre-transfusion eluate

A young patient with sickle cell disease was admitted with a painful crisis; the patient grouped as a D variant, with anti-C+D in the plasma. The Hb was 57g/L and 2 units of red cells were transfused. Six days later the Hb had fallen to 60g/L and a further 2 units of red cells were transfused. The patient was readmitted 13 days later with a Hb of 57g/L, the antibody screen was positive, anti-C+D was again identified and 2 units of CDE, K negative red cells were issued as crossmatch compatible. The following day, an antibody panel was performed on a new sample and anti-Jk^b was also identified. The DAT was positive pre and post transfusion and anti-Jk^b was eluted from both the pre- and post-transfusion samples. All 6 units were confirmed as Jk(b+).

Learning point

- The possibility of a delayed haemolytic transfusion reaction (DHTR) should always be considered when the patient's Hb drops within 2 weeks of a transfusion – in this case a direct antiglobulin test (DAT) should be undertaken, followed by an eluate if the DAT is positive

Haemolytic reactions in patients with sickle cell disease

HTRs were reported in 16 patients with sickle cell disease. There were no red cell antibodies detected in 9 of these; hyperhaemolysis was indicated in at least six cases. Table 16.2 shows more details of these cases.

Table 16.2: HTRs in patients with sickle cell disease

Reaction type	Cause	Clinical signs	Morbidity	Additional comments
Acute	Unknown	Fever, rigors, chest pain, dyspnoea	Minor	History of HHTR*
Acute & delayed	Anti-Fy3+Kp^a	Chest pain, dyspnoea	Major: ITU admission	May have required ITU admission due to sickle cell crisis
Delayed 10 days	Anti-Jk^b	None noted in report	Minor	
Delayed 9 days	Anti-Jk^b	Fever and generally unwell	Minor	
Delayed 8 days	HHTR	None noted in report	Minor	
Delayed 7 days	HHTR	Back pain, fever & chills	Major: Hb fell to 34g/L	Previous episodes of HHTR and methyl prednisolone cover given
Delayed 6 days	?HHTR	Jaundice	Minor	Complicated by sickle cell crisis
Delayed 17 days	HHTR	Fever	Major: ITU admission	
Delayed 10 days	HHTR	Fever & chills	Major: ITU admission	
Delayed 8 days	HHTR	Fever, rigors & back pain	Minor	
Delayed 8 days	Anti-S	Back pain	Minor	
Delayed 8 days	Anti-Jk^b+Le^a	Dark urine	Minor	Patient under shared care between 4 hospitals and transfusion history not always available
Delayed 11 days	Anti-Jk^b+S	Fever, chills, back & chest pain, jaundice, restlessness, dyspnoea & dark urine	Major: ITU admission and death	Sickle cell crisis ongoing in the liver
Delayed 23 days	Unknown	Fever, chest pain, dyspnoea & red urine	Minor	
Delayed 16 days	Anti-Jk^b+s	None noted in report	Major: ITU admission	
Delayed 5 days	Unknown	Fever, back pain, chest pain/ discomfort, dyspnoea/difficulty breathing, dark urine & jaundice	Major: ITU readmission	

** HHTR = Hyperhaemolyic transfusion reaction*

Eluates

Eluates were prepared and tested in the majority of cases: 22/32 (68.8%) DHTRs and 8/9 (88.9%) AHTRs (in the 9/17 cases where the DAT was positive). The eluate was helpful in 14/22 (63.6%) DHTR investigations by revealing specific antibody. In one case (Case 8), anti-Jk^{b} was only detectable in the eluate. The eluate only revealed a specific antibody in 2 of the AHTR cases (anti-A and anti-Kp^{a}).

There were 4 cases where the DAT was positive, but no eluate was tested, even though at least one of the investigations was undertaken by a Blood Service reference laboratory.

Timing of reaction

Acute

Twelve of the acute reactions occurred during the transfusion, 3 within 2 hours and 2 within 7 hours of transfusion.

Delayed

The delayed reactions were detected between 2 and 23 days post transfusion with a median of 8.5 days as shown in Figure 16.1.

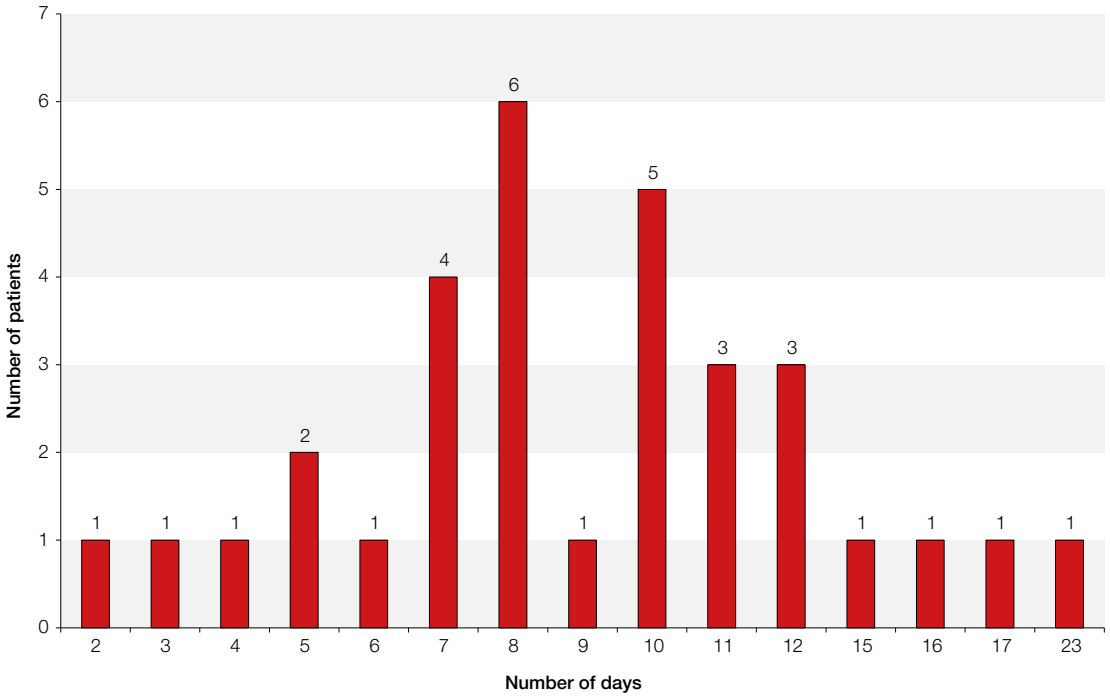

Figure 16.1: Number of days between transfusion and detection of DHTR

Technology and retrospective testing

Retrospective retesting of the pre-transfusion sample was undertaken in 6/32 (18.8%) cases of DHTR. The same result was obtained in all 6 cases; however, retesting was undertaken using the same techniques in 4 cases and by the same individual in one case; in only 2 cases was the testing confirmed by a reference laboratory. The majority of the time the sample had been discarded by the time the reaction was recognised.

In the vast majority of cases, 41/45 (91.1%), pre-transfusion antibody screening was undertaken using full automation (4 gave no answer), with a range of IAT technology, reflecting what would be expected based on standard practice data collected through United Kingdom National External Quality Assessment Service (UK NEQAS) questionnaires.

Learning point

- BCSH guidelines for pre-transfusion compatibility testing [19] advise that a pre-transfusion sample should be retained for at least 3 days post transfusion and that it is useful to keep plasma available for 7–14 days post transfusion for investigation of delayed transfusion reactions

COMMENTARY

- Kidd antibodies were once again implicated in the majority of the DHTRs where there was an antibody present 14/24 (58.3%). These antibodies can be weak and difficult to detect or identify, but often become clear when an enzyme antiglobulin test is used. If the hospital transfusion laboratory does not have a validated enzyme-IAT technique, samples may require referral to a Blood Service reference laboratory. Kidd antibodies usually bind complement and may also be easier to identify in a serum rather than a plasma sample. British Committee for Standards in Haematology (BCSH) guidelines recommend that a clotted sample is requested in addition to an EDTA sample for investigation of suspected HTRs [19]
- For the second year running, 3 AHTRs were due to antibodies to low frequency antigens, not present on screening cells. This is a small, but acceptable risk of electronic issue
- There were 8 cases reported as AHTRs where no alloantibodies were detected, and a further 2 where the presence of an alloantibody was dubious. All these patients had clinical reactions during or shortly after the transfusion, with clear laboratory signs of haemolysis. The cause of these reactions is not clear, and in at least 2 cases the only laboratory indication of haemolysis was a rise in bilirubin, which does not necessarily indicate immune haemolysis. Transfusion of red cells at the end of their shelf life has been shown to be associated with a rise in bilirubin levels (with no significant change in Hb, haptoglobin or LDH), peaking at 4 hours post transfusion and returning to normal after 24 hours [56]. Mechanical haemolysis may also occur following rapid resuscitation techniques using red cells under pressure through narrow access, both venous and intraosseous [57]. A similar picture has previously been seen in haemodialysis due to kinking of dialysis lines [58]. Clinical teams should report any suspected episodes of haemolysis associated with rapid resuscitation, in both the hospital and pre-hospital space, providing details of the equipment and techniques used
- HTRs were reported in 16 patients with sickle cell disease, representing nearly a third of all cases. Five of these were associated with major morbidity, and in one case contributed to the patient's death. These patients are known to have a higher incidence of alloimmunisation than the patient population as a whole, often develop multiple antibodies, and frequently have shared care. In one case this year, the patient was attending 4 different hospitals, making it more difficult to track the transfusion and antibody history (see also Chapter 26, Summary of Transfusion Complications in Patients with Haemoglobin Disorders)
- Hyperhaemolyic transfusion reactions (HHTR) were implicated in at least 6 patients with sickle cell disease. These are not always easy to distinguish from classic DHTRs, as alloantibodies may also be present, although this year, only one had detectable alloantibodies. In HHTRs the post-transfusion Hb is lower than the pre-transfusion Hb, indicating haemolysis of both patient and donor red cells. Serial Hb and HbS levels are helpful in confirming the diagnosis of HHTR. For further discussion, see Chapter 26 Summary of Transfusion Complications in Patients with Haemoglobin Disorders

Recommendations

- A clotted sample should be requested for investigation of suspected haemolytic transfusion reaction (HTR) to allow identification of weak complement binding antibodies, particularly anti-Jk^{a} and anti-Jk^{b}

Action: Transfusion Laboratory Managers

- Hospital transfusion laboratories should actively seek an antibody history when a sickle cell patient requires transfusion, using the NHS Blood & Transplant (NHSBT) Sp-ICE system where available (Specialist Services Electronic Reporting using Sunquest ICE)

Action: Transfusion Laboratory Managers

Recommendations still active from previous years are available in the 2013 Annual SHOT Report Supplement located on the SHOT website, www.shotuk.org under SHOT Annual Reports and Summaries, Report, Summary and Supplement 2013.