Haemolytic Transfusion Reactions (HTR) 17

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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.

DATA SUMMARY
Total number of cases: 42

Implicated components		Mortality/morbidity	
Red cells	42	Deaths due to transfusion	0
FFP	0	Deaths probably/likely due to transfusion	1
Platelets	0	Deaths possibly due to transfusion	0
Cryoprecipitate	0	Major morbidity	9
Granulocytes	0	Potential for major morbidity (Anti-D or K only)	0
Multiple components	0		
Unknown	0		

Gender		Age		Emergency vs. routine and core hours vs. out of core hours		Where transfusion took place	
Male	14	≥18 years	42	Emergency	3	Emergency department	1
Female	28	16 years to <18 years	0	Urgent	13	Theatre	3
Not known	0	1 year to <16 years	0	Routine	25	ITU/NNU/HDU/Recovery	5
		>28 days to <1 year	0	Not known	1	Wards	21
		Birth to ≤28 days	0			Delivery Ward	1
		Not known	0	In core hours	0	Postnatal	1
				Out of core hours	0	Medical Assessment Unit	6
				Not known/Not applicable	42	Community	0
						Outpatient/day unit	4
						Hospice	0
						Antenatal Clinic	0

A total of 42 cases are described, 9 acute and 33 delayed. In addition, 20 cases were reported as HTRs but transferred to other categories, including incorrect blood component transfused (IBCT), specific requirements not met (SRNM), acute transfusion reactions (ATR), alloimmunisation and unclassifiable complications of transfusion (UCT), and another was withdrawn. One of the transferred cases was a death related to a severe acute haemolytic transfusion reaction following high dose intravenous immunoglobulin (IVIg), and this is described fully in Chapter 23 rather than here, as IVIg is a blood product rather than a component. In some cases there is an overlap between SRNM and HTR.

One case was transferred to HTR from SRNM as the patient suffered significant morbidity, so it is included in the numbers for this chapter.

Age range and median

All reports were in adult patients, with an age range of 23 to 88 years and a median of 61.5 years.

Deaths n=1

There was one case where the haemolytic transfusion reaction contributed to the patient's death:

Case 1: Death following a delayed and acute reaction due to anti-Jk^a

An elderly patient with myelodysplastic syndrome (MDS) and persistent sepsis and hypotension became jaundiced and was transferred to the intensive therapy unit (ITU), where she subsequently died. The patient had received a two-unit transfusion 8 days earlier, when no antibodies were detected. Pre-transfusion testing on the current sample, showed panagglutinins by Capture-R®, and anti-Fy^a plus a couple of additional weak reactions by Bio-Rad, with a positive direct antiglobulin test (DAT). The two units issued were crossmatch-compatible Fy(a–). The post-transfusion sample demonstrated anti-Jk^a in addition to anti-Fy^a, but the eluate was non-reactive. The patient's bilirubin rose from 55 to 174 micromol/L post the most recent transfusion and the Hb fell by 20 g/L to the pre-transfusion level.

Jk^a types were not available on any of the units transfused, nor Fy^a types on the initial units transfused. This patient was probably having a delayed haemolytic reaction to anti-Fy^a, anti-Jk^a or both, from the transfusion 8 days earlier, and possibly an acute haemolytic reaction due to anti-Jk^a. Although the delayed reaction could not have been prevented, subsequent transfusion of Jk^a untyped units might have been avoided, and the acute reaction subsequently prevented. If a delayed reaction had been suspected and more extensive serology undertaken, the anti-Jk^a would probably have been identified, by using an enzyme indirect antiglobulin test (IAT) panel and testing an eluate before issuing crossmatch-compatible units. Although the patient was very sick, the reporter felt that the reaction probably contributed to the patient's death.

Learning points

- Anti-Jk^a is often only weakly detectable and more sensitive techniques such as enzyme indirect antiglobulin test (IAT) may be required for detection or identification
- If weak, apparently non-specific reactions are detected, particularly post transfusion, additional techniques should be undertaken to elucidate all the antibodies present. Unless appropriate validated in-house techniques are available, samples will need to be referred to a red cell reference laboratory

Major morbidity n=9

There were 9 cases of major morbidity, 2 relating to acute and 7 to delayed reactions. Overall, 4 involved renal impairment, 3 required ITU admission (including one case of hyperhaemolysis), and two further cases of hyperhaemolysis involved a life-threatening drop in Hb. Five of the 9 were patients with sickle cell disease, which are discussed in further detail in the Haemoglobinopathy chapter (Chapter 28). Three cases of particular interest are described below.

Case 2: Major morbidity possibly due to hyperhaemolysis

A patient received 2 units of red cells following a miscarriage. Two weeks later, she was admitted with anaemia and infection. During a second unit of red cells, the patient developed a tachycardia, became febrile and hypertensive, and went on to develop acute renal impairment with a creatinine of 351 micromol/L. The post-transfusion sample was haemolysed and the direct antiglobulin test (DAT) was positive but the antibody screen was negative. The bilirubin rose from normal to 252 micromol/L and the lactate dehydrogenase (LDH) rose to 2248 IU/L. The Hb fell from 68 g/L pre transfusion to 59 g/L post transfusion. Although the patient had human leucocyte antigen (HLA) antibodies, no red cell antibodies were identified by the Blood Service reference laboratory using a whole range of techniques. The conclusion of the reporter is that, although rarely reported other than in patients with sickle cell disease, this is a case of hyperhaemolysis.

Case 3: Major morbidity due to anti-Wr^a

A patient with myelodysplastic syndrome (MDS) had diarrhoea, vomiting and hypotension 100 mL into a red cell transfusion on the day unit, and subsequently became jaundiced. She was moved to resuscitation and then to the intensive therapy unit (ITU). The bilirubin rose from 6 to 29 micromol/L suggesting haemolysis and there was some evidence of disseminated intravascular coagulation (DIC). Anti-Wr^a was identified in the pre- and post-transfusion samples, and the donation was confirmed to be Wr(a+), but the DAT was negative. The units of blood had been issued electronically following a negative antibody screen.

Case 4: Major morbidity not recognised as a delayed haemolytic transfusion reaction (DHTR)

A patient with an Hb of 82 g/L required a pre-operative transfusion. The Blood Service reference laboratory identified anti-Jk^a+S+ce and a positive DAT and provided antigen-negative crossmatch-compatible red cells. The patient spiked a temperature during the transfusion and 2 days later developed signs of haemolysis, including a raised bilirubin and lactate dehydrogenase (LDH) and increasing renal impairment. A transfusion reaction investigation did not demonstrate any additional alloantibodies and the DAT was still 1+ positive, but an eluate was not tested. Although this was initially reported as an acute HTR, it was subsequently concluded that this was not due to red cell immune haemolysis. However, the reporter did not consider that a transfusion given 14 days earlier might have been implicated in the reaction. On that occasion, the DAT was still positive but only anti-Jk^a was detected; both of the transfused units were S positive, and it is likely that this is a case of DHTR due to anti-S.

Learning point

- Delayed haemolytic transfusion reactions commonly occur up to at least 14 days after a transfusion, and the most recent transfusion may not be the cause of a haemolytic reaction. An eluate made from the patient's post-transfusion red cells, might have revealed the presence of the causative antibody, and should have been tested even though the pre-transfusion direct antiglobulin test (DAT) was also positive

Clinical signs and symptoms

Acute haemolytic transfusion reactions n=9

Table 17.1: Details of cases with acute haemolytic reactions

Antibody	Clinical signs	Indicators of haemolysis	Morbidity and imputability
Anti-Jk^a	Hypotension, jaundice	bilirubin↑;Hb↓	ITU admission and death. Probably contributory
Anti-Wr^a	Rigors, fever and hypertension	bilirubin↑;no Hb increment	Probable
Anti-E?	Chills, rigors; hypertension; low O2 sats	bilirubin↑;Hb↓; Hburia; slightly haemolysed plasma	Full recovery. Certain
None (hyperhaemolysis)	Tachycardia, fever, hypertension	bilirubin↑;Hb↓; haemolysed plasma; LDH↑; creatinine↑	Acute renal impairment with full recovery. Certain
Enzyme-only anti-E	Back pain, chest pain, pyrexia, jaundice	bilirubin↑;Hb↓; red urine; LDH↑	Full recovery. Probable
Autoantibody	Pyrexia, nausea, chest pain, rigors	bilirubin↑;Hb did not increment as expected	Full recovery. Probable
Anti-Wr^a	Diarrhoea, vomiting, hypotension, jaundice	bilirubin↑;evidence of DIC	ITU admission with full recovery. Probable
Unspecified antibody to low frequency antigen	Back pain and vomiting	bilirubin↑;	Full recovery. Possible
?auto	Fever	No Hb increment	Full recovery

Delayed haemolytic transfusion reactions n=33

Table 17.2: Serology, laboratory signs and timing of reaction – This table is available in the Annual SHOT Report 2012 Supplement located on the SHOT website, www.shotuk.org under SHOT Annual Reports and Summaries, Report, Summary and Supplement 2012.

Summary of the causes of the serological findings

Acute

There were three cases where an antibody to a low incidence antigen caused the acute reaction, following transfusion with red cells matched by electronic issue: two anti-Wr^a and one unspecified.

An enzyme-only anti-E caused an acute reaction, following transfusion of 3 units of E positive red cells; there were clear signs of haemolysis, including jaundice, red urine, raised bilirubin and LDH, and a fall in Hb. The patient also suffered back pain, chest pain and pyrexia, and may also have been experiencing a delayed reaction to 2 units of E positive red cells transfused 10 days earlier.

As described earlier, anti-Jk^a was implicated in one case (Case1).

The cause of the remaining reactions is less clear-cut. In one case anti-E was detected post transfusion reaction, but the patient had a reaction a few days later to E negative units, when a weak cold autoantibody was also detected. Further transfusions of E negative red cells given through a blood warmer were tolerated.

No alloantibodies were identified in the remaining cases. One was thought to be due to hyperhaemolysis as described above (Case 2), and another two, to autohaemolysis.

Antibody specificity by blood group system and antigen	No. cases	No. cases where this was the sole new antibody
Kidd		
Jk^a	15	8
Jk^b	5	2
Rh		
E	8	1
c	4	1
C	2	0
C^w	1	0
ce (f)	1	0
Duffy		
Fy^a	4	1
Fy^b	1	1
Fy3	1	1
Kell		
K	4	2
MNS		
M	1	0
S	4	1
U	1	0

Table 17.3: Delayed HTR – specificity of antibody

There were 5 cases where the alloantibodies were not fully identifiable using standard IAT techniques:

Case 5: Transformation from auto to alloantibodies only detectable in different phases

A patient with multiple myeloma had weak panagglutinating autoantibodies by Bio-Rad (but negative in tube), and a 1+ positive DAT (IgA coating only). The Blood Service reference laboratory provided compatible red cells on 4 occasions over the course of 10 days. By this time the DAT was 1+ with anti-IgG and 3+ with anti-IgA. The antibody screen became negative by Bio-Rad, the DAT became more strongly positive, and the hospital provided crossmatch compatible red cells on 3 further occasions. Seventeen days after presentation, the antibody screen was again positive and samples were referred back to the reference laboratory. Anti-Fy^a was detected in the plasma and eluate, anti-Jk^a was detected in the plasma but only by an enzyme indirect antiglobulin test (IAT), and anti-E was detected by enzyme only. The patient only started to have the expected increment in Hb once antigen-negative red cells were transfused.

This case is interesting in that the panagglutinins, which were only detectable in the column technology, disappeared and the IgA coating on the red cells was replaced by IgG and C3d over the course of two weeks. There is no way of knowing for sure, but had an eluate been tested during the time when the DAT first became positive by IgG it might have revealed an alloantibody sooner.

Case 6: Anti-S identifiable only in an eluate

A patient with known anti-Fy^a, presented 10 days post transfusion with signs of haemolysis. The direct antiglobulin test (DAT) showed a mixed field and an enzyme-only anti-D plus ?anti-Jk^a were initially identified in the plasma. However, subsequent testing revealed anti-S in the eluate, and anti-Jk^a was excluded.

Case 7: A range of techniques required

A patient was admitted 7 days post transfusion with jaundice and a low Hb and generally unwell. Anti-Jk^b was identified in the plasma and the DAT was positive. The Blood Service reference laboratory confirmed the presence of anti-Jk^b in the plasma and in an eluate, but also identified an enzyme-only anti-E and anti-S by polybrene IAT.

Case 8: Anti-Jk^a not detectable by IAT

A patient showed signs of haemolysis 4 days post transfusion and the DAT was positive. The Blood Service reference laboratory identified anti-Jk^a in the plasma by enzyme only, as well as an enzyme autoantibody. The eluate was negative.

Case 9: Haemolysis started several days before antibodies detectable by IAT

A very sick patient in critical care received transfusion on 5 occasions over 10 days before the antibody screen became positive and anti-Jk^a, anti-E and anti–M were identified by IAT, and the eluate was weakly positive, probably due to anti-M. However, the patient's bilirubin was rising and had peaked 5 days earlier, and the DAT was noted to be positive 4 days earlier (2+ IgG coating). Retrospective testing demonstrated anti-E by enzyme techniques on the same day that the DAT was noted to be positive.

It is quite possible that the patient was having a DHTR several days before the antibody screen became positive. The patient was very sick with signs of DIC and multiorgan failure and a DHTR was not considered as a possible cause of the positive DAT. Had an eluate and more sensitive techniques been used when the DAT became positive, the developing antibodies might have been identified earlier, and antigen-negative blood provided.

Learning points

- When new alloantibodies are developing in response to a transfusion, they are sometimes only detectable in an eluate made from the patient's red cells, because the available antibody is all attached to the transfused antigen-positive red cells
- Kidd antibodies and other newly developing antibodies may only be weakly detectable, and more sensitive techniques are required to ensure that all specificities have been identified. This may require referral to a red cell reference laboratory

Direct antiglobulin tests (DAT) and eluates

Overall, an eluate made from the patient's red cells was tested as part of the investigation in 19/33 (57.6%) cases of delayed HTRs. In 9/19 cases a specific antibody was identified, including one case where the antibody was only identified in the eluate and not the plasma. The majority were undertaken by a Blood Service reference laboratory. In 1/33 case it was not possible to establish whether an eluate had been performed or not.

Of the 13/33 cases where an eluate was not tested, the DAT was negative in 3 cases, in 2 cases was positive with anti-C3d only, and there were insufficient cells available in another. There seems to be some difference in practice between Blood Service reference laboratories regarding the use of eluates, depending on whether the DAT is positive for IgG and on the strength of reaction. Eluates should definitely have been tested in the remaining 7/13 cases. There were 3 instances where a sample was referred to the Blood Service reference laboratory for antibody investigation, but no indication was given that the patient had been recently transfused and that this was part of an HTR investigation (including one case where the DAT was negative). In a further 3 cases, in-house testing did not include an eluate and samples were not referred for further testing. There were 2/7 cases where the DAT was positive with anti-IgG (weakly in one case), but the reference laboratory did not test an eluate.

Learning point

- A positive direct antiglobulin test in a post-transfusion patient should be investigated and an eluate made and tested, as this may be the only way to identify the causative antibody

Timing of reaction

Acute

Four of the reactions occurred during transfusion of red cells, and 5 within 24 hours of transfusion.

Delayed

The delayed reactions were detected between 2 and 35 days of transfusion, with a median of 9 days. In some cases the patient received transfusion over several days and it is not clear which red cell unit was implicated in the reaction; where this is the case the shorter time period has been used in Figure 17.1 and to calculate the median.

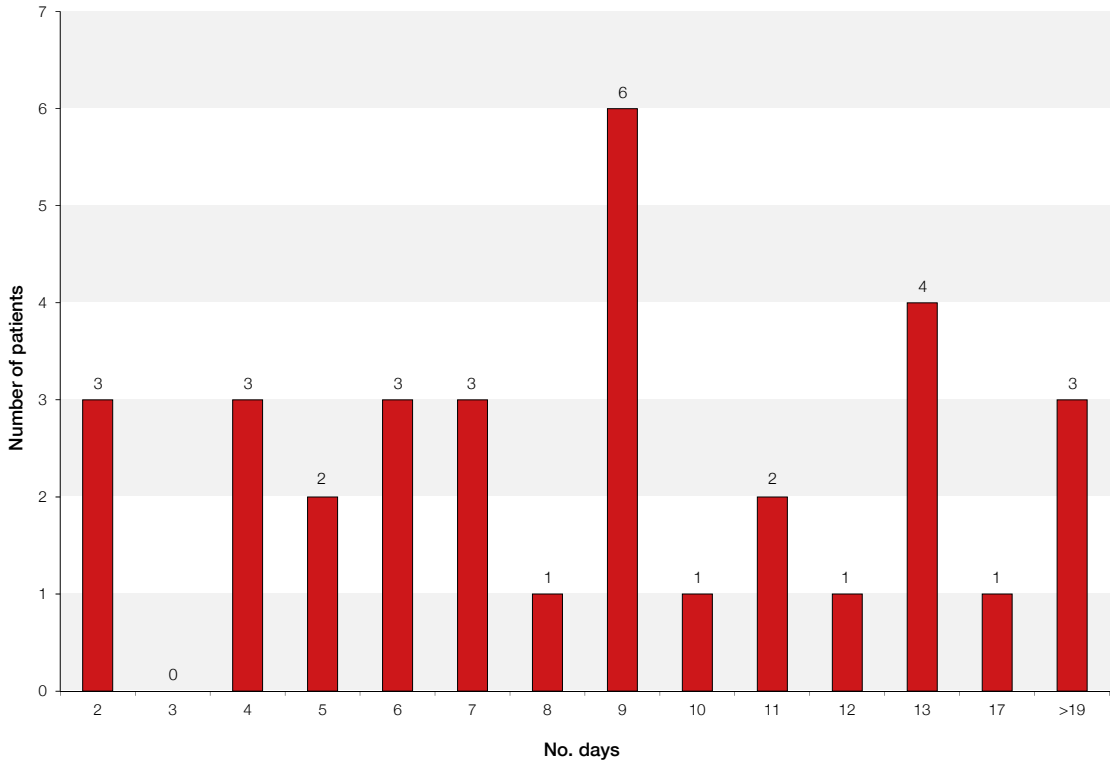

Figure 17.1: Time between transfusion and recognition of the reaction

Technology used and retrospective testing

Pre-transfusion testing was undertaken using automated techniques in 35/38 cases (92.1%) across the range of different IAT technologies. Electronic issue was used in 15/29 (51.7%) of cases where the antibody screen was negative and the question was answered when reporting to SHOT. This pattern reflects what would be expected based on standard practice data collected through United Kingdom National External Quality Assessment Service (UK NEQAS) questionnaires.

Retrospective testing of the pre-transfusion sample was undertaken in 12/33 cases of DHTR (36.4%) as the pre-transfusion sample was unavailable in the majority of cases. Reporters stated that in 3/12 cases they obtained different results retrospectively but no details were provided.

COMMENTARY

The majority of DHTRs are not preventable because the antibody is not detectable in the pre-transfusion sample. However, better communications between different hospitals and between hospitals and Blood Service reference laboratories could help identify patients with known antibodies which are no longer detectable, and thereby prevent some HTRs. Hospital laboratories are encouraged to participate in NHSBT's new Sp-ICE initiative to share information on patients' antibodies.

Signs of an HTR can be overlooked, particularly in very sick patients, and laboratory indicators of haemolysis should be looked for when a recently transfused patient develops a positive DAT or apparent non-specific reactions by IAT. Where signs of haemolysis are apparent, full investigation of weak reactions, using additional and more sensitive techniques, could help prevent both acute and further DHTRs.

Kidd antibodies are once again the most commonly implicated specificity in DHTRs, accounting for 10/18 (55.6%) of cases where a single new antibody was the cause of the reaction. Kidd antibodies are often difficult to identify, sometimes only reacting with cells bearing homozygous expression of the antigen, or by a more sensitive technique, such as an IAT using enzyme-treated cells.

This year, there were 3 cases of acute haemolytic reactions in patients with antibodies to low incidence antigens, not detected because the antigen is not present on the screening cells, and blood is provided by electronic issue. This is a known, but accepted small risk of electronic issue.

Sickle cell patients were once again overrepresented in the DHTR cases, with 7 cases reported, 5 of whom suffered major morbidity. Two of these could have been prevented had appropriately phenotyped blood been selected and there is further discussion of these cases in the Haemoglobinopathy chapter (Chapter 28).

An eluate made from the patient's post transfusion red cells was tested for antibodies in 19/33 DHTR cases; this represents 65% of those cases where the DAT was positive and there were sufficient cells for testing. Again, there was one case this year, where the causative antibody was only identifable in the eluate, demonstrating how important it is to include this test as part of the investigation of an HTR. There were 3 cases where the reference laboratory did not test an eluate because they were unaware that the patient had been recently transfused. British Committee for Standards in Haematology (BCSH) guidelines recommend that an eluate is tested for the presence of specific antibodies in all patients with a positive DAT who have been transfused within the previous month[35].

Recommendation

- Hospital transfusion laboratories should ensure that an eluate is tested as part of the investigation of a haemolytic transfusion reaction (HTR); this may necessitate referring samples to a red cell reference laboratory

Action: Hospital Transfusion Laboratory Managers

Recommendations from previous years are available in the Annual SHOT Report 2012 Supplement located on the SHOT website, www.shotuk.org under SHOT Annual Reports and Summaries, Report, Summary and Supplement 2012.