8. Haemolytic Transfusion Reaction (HTR)

Definition

Haemolytic transfusion reactions are split into two categories: acute and delayed. Acute reactions are defined as fever and other symptoms/signs of haemolysis within 24 hours of transfusion; and confirmed by a fall in Hb, rise in lactate dehydrogenase enzyme (LDH), positive DAT and positive crossmatch. Delayed reactions are defined as fever and other symptoms/signs of haemolysis more than 24 hours after transfusion; and confirmed by 1 or more of: a fall in Hb or failure of increment, rise in bilirubin, positive DAT and positive crossmatch not detectable pre-transfusion. Simple serological reactions (development of antibody without positive DAT or evidence of haemolysis) are excluded.

DATA SUMMARY

Total number of cases	**23**	*Implicated components*		*Mortality / morbidity*	
		Red cells	**21**	Deaths due to transfusion	**0**
		FFP	**0**	Deaths in which reaction was contributory	**2**
		Platelets	**2**	Major morbidity	**5**
		Other	**0**		

Gender		*Age*		*Emergency vs. routine Core hours vs. out of core hours*		*Where transfusion took place*	
Male	**8**	<16 years	**1**	Emergency	**7**	A & E	
Female	**15**	<1 year	**0**	Routine	**15**	Theatre	
		<4 weeks	**0**	Not known	**1**	ITU/HDU/recovery	
						Wards	
				In core hours		Community	
				Out of core hours		Other	
				Not known/applicable	**23**	Not known	**23**

Information technology and appropriateness of transfusion (in the opinion of the SHOT reviewer)		
In how many cases was failure or absence of IT a factor?	**0**	
In how many cases was a transfusion possibly unnecessary or inappropriate?	Not known	

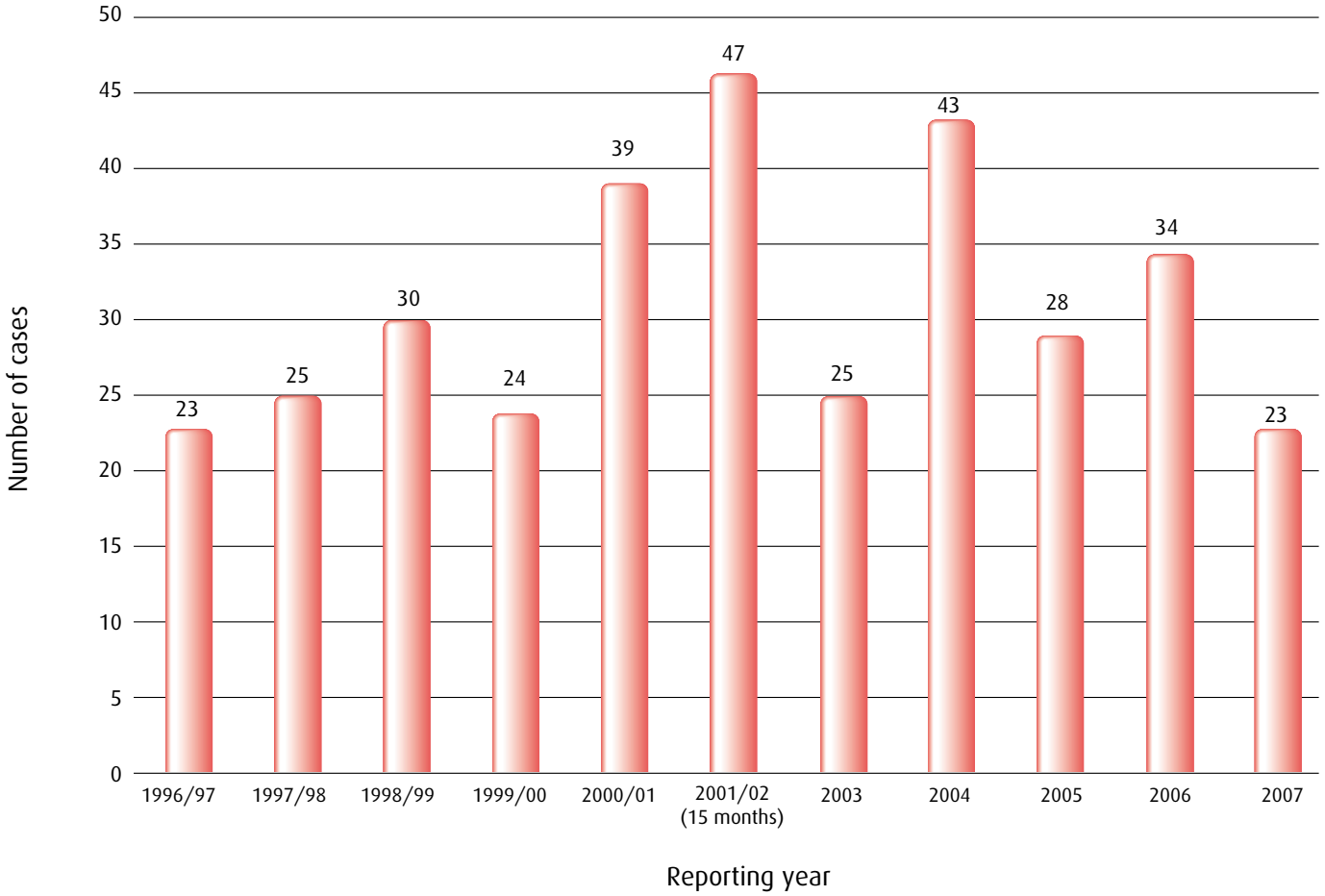
Twenty-seven questionnaires were received; 3 were transferred to the ATR section, and 1 to the IBCT section. This section describes the main findings from 23 completed questionnaires: 3 acute and 20 delayed reactions.

Patients

8 males and 15 females.
Ages ranged from 10 to 89 years.

One report relates to a patient <16 years: a 10-year-old girl suffered an AHTR following an ABO-incompatible platelet transfusion (Case A2).

Figure 7
Number of cases of HTR analysed since 1996
[Cases in this section were referred to as delayed transfusion reactions until 2006]



Mortality, morbidity, and imputability

Acute (n = 3)

There was one clear case of major morbidity relating to intravascular haemolysis following ABO-incompatible platelet transfusion (Case A1 – imputability 3): the patient made a full recovery. A second case was less clear-cut – this appeared to be intravascular haemolysis due to anti-A, but was not proven (Case A2 – imputability 1). The third suffered only minor morbidity (imputability 3).

Delayed (n = 20)

There were four deaths in this group – two were reported as definitely unrelated to the DHTR, whereas the other two were reported as possibly contributory – see Cases D15 and D20. The reactions were reported as probably related (imputability 2) in 3 cases and as possibly related (imputability 1) in 1 case.

Three patients suffered major morbidity: 1 had deteriorating renal function requiring dialysis and admission to ITU. However, diagnosis was complicated by the acute clinical picture (imputability 2 – see Case D2). The second (imputability 3 – see Case D7) dramatically dropped her Hb from 8.5 g/dL to the pre-transfusion level of 3.6 g/dL, 5–6 days post transfusion of 6 units of red cells. The third (imputability 2 – see Case D15), dropped her Hb way below the pre-transfusion level of 7.0 g/dL to 2.7g/dL – this might have been a case of hyperhaemolysis, but could also have been a developing AIHA; this patient subsequently died and has been included in the previous paragraph.

The remaining 14 patients suffered minor or no morbidity. In 7 cases the reaction was reported as probably related (imputability 2) to the transfusion, and in 6 cases definitely related (imputability 3). One case was less clear (imputability 1) – the patient was readmitted 58 days after transfusion, with several new red cell antibodies and a 4g drop in Hb, thought to be excessive for the amount of blood loss. However, the DAT was negative and transfused red cells remained in the circulation.

At least 1 patient required a further transfusion as a result of the DHTR.

Laboratory signs of haemolysis

Many patients showed laboratory signs of haemolysis without any clinical signs being noted. The laboratory signs are often complicated by the underlying disease, and are defined as follows:

- Group 1 (3 patients) Positive DAT only
- Group 2 (7 patients) Falling haemoglobin(↓Hb)/positive DAT/spherocytes (2 of these parameters)
- Group 3 (9 patients) ↓Hb + jaundice ± positive DAT ± spherocytes
- Group 4 (1 patient) As group 3 + renal impairment

Timing of reaction in relation to transfusion

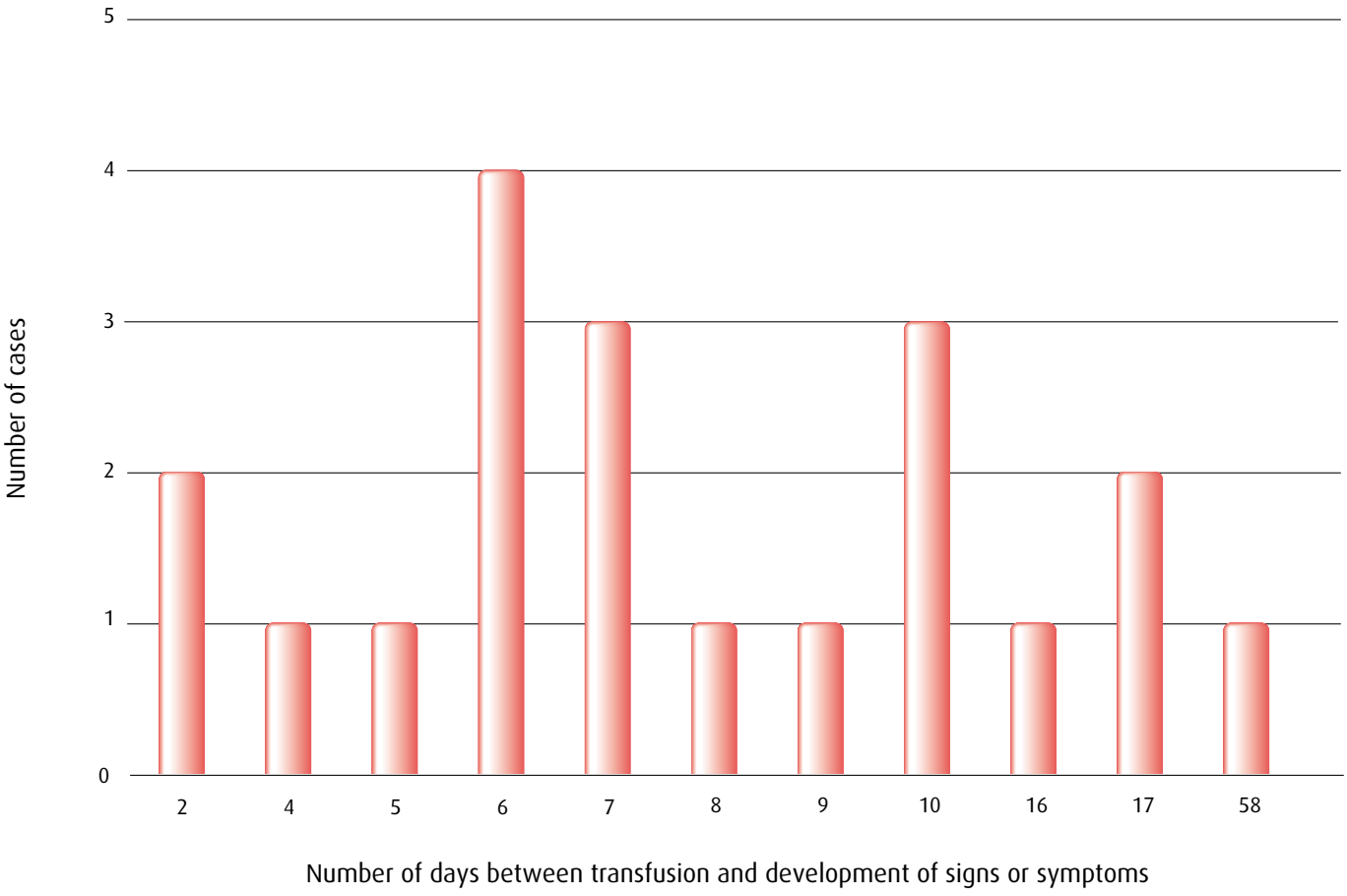
Acute

2 reactions occurred during the transfusion, and 1 immediately post transfusion.

Delayed

Figure 8 shows the reported interval in days between the implicated transfusion and signs or symptoms of a DHTR.

Figure 8
Time interval between HTR and transfusion



Median = 7 days
Range = 2 to 58 days

The intervals given are necessarily those when the signs or symptoms were first noted. In asymptomatic cases this relates to the number of days that elapsed before a repeat sample was received for group and screen, or crossmatching. There were 2 cases where symptoms were noted within 48 hours of transfusion: 1 of these patients also received a previous transfusion 7 days before the onset of laboratory signs, which was more likely to have been implicated in the DHTR than the reported transfusion (see Case D6); the other was a case of possible hyperhaemolysis (see Case D15).

Serological findings

Acute reactions

Two reactions were due to anti-A from mismatched platelets, 1 apheresis platelet donation and 1 derived from pooled buffy coats. Both were tested and found negative for high-titre anti-A and anti-B prior to issue; however the buffy coat unit was retrospectively found to be positive for high-titre anti-A. The third case involved weak anti-Fy^a retrospectively identified in the pre-transfusion sample; in this latter case there was insufficient laboratory testing to confirm haemolysis. Table 24 shows details.

Table 24
Acute reactions – serology and symptoms and laboratory signs

Case number	Antibody(ies) in plasma	Clinical symptoms	Laboratory evidence	Comments
A1	Anti-A	Fever, rigors, nausea, vomiting	Hb↓; bilirubin↑; DAT pos (C3 coating only; eluate non-reactive)	Group O buffy coat platelets – high-titre anti-A identified
A2	Anti-A	Generally unwell	Hb↓; bilirubin↑; DAT pos (C3 coating only; eluate not performed)	Group O apheresis platelets
A3	Anti-Fy^a	Fever, head and chest pain, hypotension, tachycardia, cyanosis	Hb; weak anti-Fy^a identified; DAT negative	Known anti-Ce + -e

Case A1

A 17-year-old group A D negative male with ALL and a platelet count of 3 x 10^9/L, was given 1 unit of buffy coat derived O D negative platelets – the reason for the supply of group O rather than group A platelets by the blood service is not clear. During the transfusion the patient suffered from dramatic and prolonged rigors, nausea and vomiting, and the transfusion was discontinued. Laboratory tests indicated a sharp rise in bilirubin from 40 µmol/L to 109 µmol/L, and a fall in Hb from 7.1 to 4.9 g/dL. The patient fully recovered from the reaction. All 4 constituent donations had tested negative for high-titre anti-A and anti-B by routine automated testing prior to issue. Retrospective testing showed that 1 of the donations had a high-titre IgM anti-A of 1 in 1,024 and the same donor had previously tested positive for high-titre anti-A in 3 of 8 donations.

Case A2

A 10-year-old female with ALL was transfused with 1 unit of group O apheresis platelets, because no group A platelets were available. During the transfusion the patient became unwell, but no specific details are known. Laboratory tests indicated a sharp rise in bilirubin from 40µmol/L to 102 µmol/L, and a fall in Hb from 10.2 to 8.2 g/dL. The donation was tested and found negative for high-titre anti-A. The patient fully recovered from the reaction. Subsequent donations from the same donor have all tested negative for high-titre anti-A.

These platelet transfusions occurred towards the end of 2006, and since then the National Blood Service (NBS) testing strategy has been revised to identify a higher percentage of donations as high-titre positive. New control reagents have also been produced in the interim and are now in routine use by the UK Blood Services.

Case A3

A 56-year-old female with ovarian cancer and known anti-Ce + e, required a 2 unit transfusion for anaemia. At the end of the second unit the patient developed a fever, head and chest pain, tachycardia and hypotension. Weak anti-Fy^a was identified retrospectively in the pre-transfusion sample by a reference laboratory. The Hb fell from 9.4 g/dL immediately post transfusion to 8.2 g/dL the next day, but the DAT was negative and no other tests were undertaken to confirm that this was a haemolytic reaction. A similar reaction was noted during a transfusion a year before. The patient clearly had a reaction to the red cell transfusion but the only evidence that this was haemolytic was a drop in Hb (imputability 1).

Learning points

- Group O platelets can cause acute haemolytic reactions even when tested and labelled negative for high-titre haemolysins. They should only be used for non-group O patients (particularly paediatric patients) as a last resort, and should not be kept by hospitals as stock.
- Acute reactions are often difficult to classify, particularly when laboratory tests are not undertaken, and when the patient is seriously ill.

Delayed reactions

Kidd antibodies were the most commonly implicated, in 11/20 (55%) of cases, either singly or in conjunction with other specificities. Table 25 shows the specificity of new antibodies detected post transfusion, by blood group system.

Table 25
Delayed reactions – serology and time after transfusion

Case no.	New antibody (ies) in plasma	Antibodies in eluate	Comments	No. days post tx
D1	Anti- Jk^b + enz anti-C	Anti-Jk^b	Bilirubin ↑; Hb ↓ Death unrelated	8
D2	Anti-Jk^a	Anti-Jk^a	Bilirubin↑; LDH ↑; Hb↓ creatinine↑ Reqd dialysis and ITU admission	7
D3	Anti-Jk^a	Anti-Jk^a	Pre-existing anti-E; Bilirubin↑; Hb ↓	16
D4	Anti-Jk^a + e	No eluate performed	Jaundice	6
D5	Anti-C (+Fy^a)	Anti-Fy^a + C	3 units incompatible blood tx in emergency; bilirubin↑	10
D6	Anti-Fy^a + HTLA + ? anti-f	Anti-Fy^a	No Hb increment; sample too old Death unrelated	2 - 10
D7	Anti-Jk^b + Lu^b	No eluate performed	Pre-existing anti-K+C; Bilirubin ↑; Hb↓	6
D8	Anti-C+S	Eluate negative	Jaundice and ↑bilirubin but varices; no Hb increment, but bleeding	10
D9	Anti-Jk^b	No eluate performed	Hb↓	10
D10	Anti-C+K+Kp^a+Lu^a	No eluate performed (DAT negative)	Hb fell 4g over 58 days	58
D11	Anti-Jk^b + S + M + unidentified antibodies	No eluate performed (DAT negative)	Pre-existing anti-Le^{a+b} SCD; Hb↓; haemoglobinuria	17
D12	Anti-Jk^a	Eluate negative	Pre-existing anti-Fy^a + enz anti-C^w bilirubin↑; haemoglobinuria	5
D13	Anti-Jk^b + D	No eluate performed (DAT negative)	Hb↓	4
D14	Anti-D	No eluate performed	Bilirubin↑; Hb↓; spherocytes; further transfusion required	7
D15	None ? Hyperhaemolysis	No eluate performed	Pre-existing anti-E+K; bilirubin↑; Hb↓ Death probably unrelated	2
D16	Anti-Fy^a	Anti-Fy^a	Jaundice; bilirubin↑; Hb↓- but liver trauma	9
D17	Anti-E (enzyme only)	Anti-E	No signs or symptoms	17
D18	Weak reaction – specificity not identified	Anti-Fy^a	No signs or symptoms	7
D19	Anti-Jk^a	Anti-Jk^a	No signs or symptoms	6 – 8
D20	Anti-Jk^a	Anti-Jk^a	Bilirubin↑; no Hb increment; Death probably unrelated	6

Table 26
DHTRs – new specificities by blood group system

Antibody specificity by blood group system	Number of cases	Sole *new* antibody
Kidd Jk^{a} Jk^{b}	6 5	5 1
Rh D C E e ?f	2 4 (1 enzyme only) 1 (enzyme only) 1 1	1 1
Kell K Kp^{a}	1 1	
Duffy Fy^{a}	4	2
MNSs S M	2 1	
Other Lu^{a} Lu^{b} HTLA	1 1 1	

Serology – DHTRs only

Table 27 shows the technology used for antibody screening by IAT.

Table 27
IAT technology used for antibody screening

IAT screening technology	Number of cases	By automation
DiaMed	7	6
BioVue	9	6
Solid phase	3	3
Liquid phase microplate	1	0

For pre-transfusion testing, plasma was used in 16 of the 20 cases, serum was used in 2, and 2 were not stated.

An IAT crossmatch was undertaken in 10 cases (7 had antibodies present pre-transfusion, and 1 was retrospective), immediate spin was undertaken in 2 cases, and electronic issue (EI) in 8. This is likely to be representative of techniques being used routinely, although available data are incomplete. In 2005, 26% of UK laboratories were routinely using electronic issue, and data provided by a proportion of UK laboratories for the National Transfusion Laboratory Collaborative telephone survey suggest that this is now much higher. The data also suggest that an even higher proportion of transfusions are given based on EI, as it is the higher throughput laboratories that are more likely to be using full automation and EI.

Use of eluates

In 12/20 cases (60%) an eluate made from the patient's post-transfusion red cells was tested for antibody – this has increased from 35% last year; 8/12 were performed in reference labs and 4 in-house. In 10 cases specific antibody(ies) was identified.

Retrospective testing findings

Retrospective testing of the pre-transfusion sample was undertaken in house in 10 (50%) cases; 2 were referred directly to the reference centre, and another 5 were confirmed by a reference centre.

Clinical management and review

Twenty-one (91%) of cases were referred to the HTC, and 13 (57%) to the Transfusion Centre Reference Laboratory.

Delayed haemolytic transfusion reactions (DHTR)

Case D2

A 36-year-old male with antiphospholipid syndrome and peripheral vascular disease required massive transfusion (> 30 units of red cells) following rupture of the iliac artery during a stenting procedure. Ten days later the patient showed clinical and laboratory signs of a severe DHTR, though the clinical picture was complicated by the acute clinical condition. The patient suffered from dyspnoea, jaundice, falling Hb and deteriorating renal function, requiring dialysis. The DAT was positive and anti-Jk^a was identified in the post-transfusion plasma, and in an eluate made from the patient's red cells.

Case D5

A 56-year-old male admitted with a ruptured aortic aneurysm received an emergency transfusion of 2 units O D negative and 6 units of ABO/D matched red cells. Retrospective serology revealed anti-Fy^a, and 3 of the transfused units were found to be incompatible. A further 14 units of Fy(a-) red cells were transfused over a 4 day period. Ten days after admission the patient was febrile and jaundiced, and the bilirubin rose to 150 µmol/mL. The NBS reference laboratory identified anti-C in addition to anti-Fy^a (anti-E could not be excluded); the DAT was positive (both IgG and C3 coating) and an eluate made from the patient's red cells contained both anti-Fy^a and anti-C. The patient made a full recovery.

This case above is interesting as, although incompatible blood was transfused and anti-Fy^a was eluted from the transfused red cells, no signs of a transfusion reaction were noted until day 10.

Case D6

A 70-year-old female with an ischaemic transverse colon and sepsis, received 3 units of red cells during a hemicolectomy. Five days later a new sample was received for further crossmatching as the postoperative Hb was 6.8 g/dL. One unit of red cells was transfused, on each of 3 successive days, starting on the day after the sample was taken. Two days later the patient became jaundiced and the Hb had dropped back to 6.1 g/dL. The patient was on ITU with multi-organ failure, making a diagnosis of DHTR complicated. The DAT was positive and the post-transfusion plasma contained anti-Fy^a, which was also eluted from the red cells. The NBS reference laboratory also identified a possible anti-f and an HTLA antibody. It is not known which of the units were Fy(a+). The patient died on ITU but this was unrelated to the DHTR.

A procedural review identified that a new sample should have been requested after the first of the 3 units transfused postoperatively, because the patient had been transfused 6 days earlier.

Case D7

A 62-year-old female was admitted with an Hb of 3.5 g/dL and referred to a haematologist. She produced an old BTS card stating that she had anti-K + anti-C, and was transfused with 5 units of phenotyped red cells. Six days later her Hb fell dramatically from the post-transfusion level of 8.5 g/dL back down to 3.6 g/dL, with no evidence of bleeding. The bilirubin increased from 22 to 83 µmol/mL. Anti-Jk^b and anti-Lu^b were identified in both the plasma and an eluate. The patient made a full recovery.

Case D15

A 63-year-old female was admitted through ED, with dehydration, confusion and renal impairment. She had been transfused 6 days previously and had known anti-E+K and a positive DAT (IgG and C3 coating). E-K- units were all found to be incompatible using a BioVue technique, but the reference laboratory reported no antibodies using different techniques. She was transfused with a further 3 units of E-K- red cells for symptomatic anaemia. Over the next 2-3 days her Hb dropped from 7.0 g/dL pre-transfusion to 2.7 g/dL, her bilirubin rose from 14 µmol/L to 69 µmol/L, and the plasma showed haemolysis. No further antibodies were identified by the reference laboratory and the DAT was equally positive pre- and post-transfusion. A further 8 units of red cells were transfused over the next 4 days, and the patient was started on IVIg, but died before a full diagnosis could be made. It is unclear whether the haemolysis was due to a developing AIHA or hyperhaemolysis as a result of the transfusion.

Case D20

An 89-year-old male with myeloproliferative disease required 2 units of red cells for top-up transfusion. He had received a transfusion 6 days previously. A new sample was taken 2 days before the implicated transfusion. The antibody screen was positive, anti-K identified, and 2 units of K- blood were given. During transfusion of 1 of the units the patient became febrile, had an increase in heart rate and difficulty breathing, and the transfusion was stopped; however, the reaction was not reported to the transfusion team until 2 days later. The bilirubin rose from 15 to 50 µmol/L and the Hb dropped from 7.1 g/dL pre-transfusion to 6.1 g/dL over the 5 days following transfusion. However, the reporter feels that these factors could have been due to developing disease. A sample taken 2 days after transfusion was DAT positive and anti-K again identified. Weak anti-Jk^{a}, reacting only by a sensitive enzyme antiglobulin test, was identified by the reference laboratory in both the pre- and post-transfusion plasma samples and eluates. The patient died, but this was thought to be unlikely to be related to the transfusion (imputability 1).

Although a reaction occurred during transfusion, it was thought likely that the patient was suffering from a delayed reaction to the earlier transfusion.

Learning points

- If a patient has been transfused within the last 3-14 days, a fresh sample should be taken within 24 hours of the next transfusion, in line with BCSH guidelines[16].
- Kidd antibodies are often difficult to detect, and more sensitive techniques may be required to confirm the identification.
- Transfusion reactions should be reported the transfusion team immediately, so that appropriate investigations can be undertaken.

COMMENTARY

- Group O apheresis and on this occasion pooled platelets, which tested negative for high-titre haemolysins, have once again caused haemolytic reactions, although in 1 case retrospective testing confirmed that 1 of the donors was high-titre positive. There have been 11 previous reports to SHOT of group O platelets causing ATRs in group A or B recipients – 4/7 (57%) have occurred in paediatric patients (in 4 cases the age was not recorded), and in 8/11 cases apheresis platelets were implicated.

- In all cases but 2 (where an answer was given), plasma rather than serum was used for both pre- and post-transfusion investigations. It is known that weak complement binding antibodies, e.g. some examples of anti-Kidd, may be missed when using plasma, unless more sensitive techniques are used, e.g. enzyme IAT.

- This year 60% of investigations included testing an eluate made from the patient's red cells, compared with only 35% last year. Where a mixture of antibodies is present, an eluate may help to distinguish which specificity(ies) is more likely to be implicated in a haemolytic reaction. Furthermore, the implicated antibody may be present only in an eluate. Identification of all specificities present is essential if further haemolytic reactions are to be prevented.

RECOMMENDATIONS

There are no new recommendations this year; however, previous recommendations remain relevant and the first 5 are pertinent to this year's cases.

Year first made	Recommendation	Target	Progress
2005	All cases of suspected AHTR and DHTR should be appropriately investigated, and ideally referred to a reference laboratory. Referring hospitals should make it clear to reference laboratories that they are investigating an HTR to ensure that timely, appropriate tests are undertaken. Clinical details should be completed on the request forms and the donation numbers of the units transfused should be included, so that their phenotype can be determined	**Hospital blood transfusion laboratories, Blood Service reference laboratories and the NBTC Transfusion Laboratory Managers' Working Group**	BCSH guidelines for investigation and management of transfusion reactions are in progress
2005	Reference laboratories should ensure that investigation of DHTRs includes testing an eluate made from the patient's red cells when the DAT is positive	**Blood Service reference laboratories**	Eluates were undertaken in 60% of cases this year compared with 35% in 2006 and 50% in 2005; however, numbers are too small to draw any conclusions
2005	Pre-transfusion testing on patients who have been recently transfused and require further transfusion should be carried out in accordance with BCSH Guidelines[16] relating to the timing of the samples	**Hospital blood transfusion laboratories and the NBTC Transfusion Laboratory Managers Working Group**	This recommendation was made in Guidelines for Compatibility Procedures in Transusion Laboratories, BCSH (2004)[16]
2003	There is a need for a review, co-ordinated by a professional national body, of how long specimens should be kept post-transfusion. The review needs to consider the relative risks and benefits of storing specimens beyond the time that they are suitable for use in further crossmatching tests	**BBTS and BCSH**	During 2008 this issue will be addressed by the writing group for the revised BCSH guidelines for compatibility procedures in blood transfusion laboratories
2001/02	Investigation of a suspected HTR should include retesting of the pre-transfusion sample (where still available) by different or more sensitive techniques. Consideration should also be given to requesting clotted samples for investigation of suspected HTRs and using polyspecific AHG. These actions may involve referral to a reference centre	**Hospital blood transfusion laboratories and the NBTC Transfusion Laboratory Managers Working Group**	BCSH guidelines for investigation and management of transfusion reactions are in progress
2001/02	Consideration should be given to issuing antibody cards or similar information to all patients with clinically significant red cell antibodies. These should be accompanied by patient information leaflets, explaining the significance of the antibody and impressing that the card should be shown in the event of a hospital admission or being crossmatched for surgery. Laboratories should be informed when patients carrying antibody cards are admitted	**The CMO's NBTC and its counterparts in Scotland, Wales, and Northern Ireland**	This recommendation was made in the BCSH Guidelines (BCSH, 2004)[16]
2000/01	Group identical platelets should be selected whenever possible, with group O being the last choice for non-group O recipients. Blood Services should stock higher levels of non-group O platelets	**Hospital blood transfusion laboratories, Blood Service Issue departments and the NBTC Transfusion Laboratory Managers Working Group**	'Amendments and Corrections' to the BCSH guidelines 'Transfusion Guidelines for neonates and older children' clarifies these recommendations (2004)