9. DELAYED TRANSFUSION REACTIONS

Definition
Delayed transfusion reactions are defined in this report as those occurring more than 24 hours following a transfusion of blood or blood components. In practice, these are almost invariably delayed haemolytic reactions due to the development of red cell alloantibodies

This category accounted for 12.7% of non-infectious hazards reported.

34 initial reports were received (32 new) and 30 completed questionnaires were returned. One patient has been excluded as he had no transfusion reaction or detectable antibodies but was reported to SHOT because a historical record of Jka antibody was not taken into account when blood was selected for transfusion. In retrospect this case would, in fact, fall into the IBCT category but has not been included on this occasion. One case which had been carried forward from the previous year was withdrawn because insufficient information could be obtained. 2 questionnaires are outstanding and will be analysed next year. This chapter highlights the main findings from 30 completed questionnaires.

Sex

Males 7
Females 26

Age

Age range 21 - 90 years
Median age 67 years

Timing of Reaction/Diagnosis in relation to previous transfusion

Days post-transfusion	No. of cases
1-5	5
6-10	11
11-15	7
16-20	1
>20	4
Not stated	2

Range 1-75 days
Median 11 days

Reactions Reported

There were 3 deaths in this group of which one was related to the transfusion (Case 19) and 2 were due to the underlying disease. In addition, one patient required renal dialysis but subsequently made a good recovery. The remaining patients suffered minor, or no morbidity.

All reactions were related to the administration of allogeneic red cells but in 3 patients who seemed to have clear-cut haemolytic reactions no antibodies were detected or known from historical transfusion records. In total 34 new antibodies were noted in the 30 patients who suffered a delayed haemolytic transfusion reaction (DHTR), which for the purpose of this report is defined as evidence of haemolysis occurring more than 24 hours post-transfusion, whether or not a new red cell antibody has been identified. Strictly speaking 7 of these reactions were sensitisation episodes only - there was no evidence of haemolysis although 5 cases had a positive DAT. One case was reported because of detection of anti-K 75 days post-transfusion. These cases should probably be regarded as serological reactions, rather than delayed haemolytic transfusion reactions.

Seven patients had pre-transfusion red cell allo-antibodies. In one of these the antibody was not correctly identified and therefore appropriate blood was not selected. In the others, appropriately phenotyped units were selected.

One further patient (Case 24) had a historical record of anti-Jkb which was not communicated to second hospital to which the patient had been transferred. It was not detectable pre-transfusion but was detected 11 days post-transfusion.

Two reports were on 21 year old identical twin sisters with sickle cell disease. One was admitted for red cell exchange because of recent cerebral infarction. The other was admitted one month later with abdominal pain which may have required surgery and so a transfusion was given. In each case the patient developed severe anaemia 1-2 weeks later, reported as "suggestive of hyperhaemolysis syndrome". Serological investigations were negative. It is not known if these patients manifested an appropriate reticulocyte response or whether or not infection-related erythroblastopenia may have played a role. Both patients recovered without sequelae.

Urgency of Transfusion Requirement

In 22 patients the transfusion was said to be routine and in 7 urgent (one not stated). One patient was transfused for recurrent iron deficiency anaemia.

New Post-transfusion Antibodies

Table 16 shows the new post-transfusion antibodies according to antigen specificity and Table 17 gives details of these antibodies for individual patients.

Table 16
New post-transfusion red cell antibodies in 30 patients: according to antigen specificity

Antibody group	Number	Sole antibody
Kidd		
Jka	13[1,2]	7
Jkb	2	1
Duffy		
Fya	2	1
Kell		
K	3	3
Kpb	1[3]	1[3]
Rh		
Cw	1	
c	2	
E	8[4]	3[4]
Lutheran		
Lua	1	
Other		
Yka	1	1

[1] Previously known but not disclosed (1)
[2] Misidentified pre-transfusion (1)
[3] Autoanti-Kpb
[4] enzyme-only antibody pre-transfusion, IAT reactive one week post-transfusion (1)

Table 17
New post-transfusion red cell antibodies in individual patients

ID	Antibody(ies)	Comment
1	K	Pre-transfusion Fya and +ve DAT
2	E + Jka	Pre-transfusion E
3	Fya + Jka	
4	Jka	
5	K	
6	Jka	
7	Jka	
8	E + Cw	
9	Lua	Pre-transfusion E + Kpa + Auto. However, Lua unlikely to have caused fall in Hb
10	Jka	Pre-transfusion K
11	Jka	
12	c + E + Jka	
13	E	Pre-transfusion c, Cw, Fya
14	Jkb	
15	None	DHTR but no antibodies detected
16	Jka	
17	K	
18	E	
19	E	Enzyme-only E pre-transfusion and 4 days post. IAT reactive 7 days post. Died due to renal failure.
20	Jka	
21	E	
22	Jka	Present but mis-interpreted pre-transfusion
23	Yka	Developed auto-immune haemolysis post-transfusion
24	None	Pre-transfusion C + E + DAT +ve. Jkb known historically but not communicated. Not detectable pre-transfusion
25	Jka	
26	Auto-Kpb	Developed auto-immune haemolysis ?"triggered" by transfusion
27	None	?Hyperhaemolysis syndrome/?red cell aplasia in sickle, no antibodies
28	None	?Hyperhaemolysis syndrome/?red cell aplasia (twin of 27), no antibodies
29	Fya	Neg. at 4 days post, positive 11 days post
30	E, c, Jkb	

Clinical sequelae

Symptoms and signs could be divided into 4 categories as follows:

- Group 1 Asymptomatic (± positive direct antiglobulin test (DAT) ± spherocytes)
- Group 2 Falling haemoglobin (↓Hb)/positive DAT/spherocytes (2 of these parameters)
- Group 3 ↓Hb + jaundice ± positive DAT ± spherocytes
- Group 4 As group 3 + renal impairment

Group 1
There were 6 patients in this group (cases 4, 5, 10, 11, 17, 21). All survived without sequelae.

Group 2
There were 10 patients in this group (cases 1, 2, 8, 14, 16, 25, 26, 27, 28, 30) of whom 9 survived without sequelae and 1 had to have planned surgery delayed due to the reaction.

Group 3
There were 11 patients in this group (cases 3, 6, 7, 12, 13, 15, 18, 22, 23, 24, 29) of whom 6 survived without sequelae, 2 died from unrelated causes, 1 experienced slowing of recovery from previous renal failure and 2 experienced ongoing fatigue and jaundice. In addition, one patient (case 29), who was already recovering from renal failure at the time of her reaction, was felt to have acquired more prolonged renal support than anticipated as a result of the transfusion reaction, but subsequently made a good recovery.

Group 4
There were 3 patients in this group (cases 9, 19, 20) of whom 1 died due to the transfusion reaction (case 19), 1 required readmission to hospital because of failure to cope secondary to her anaemia and the third survived without sequelae.

The above results are detailed in Table 18

Table 18
Grouping of cases by clinical sequelae of DHTR

Group 1		Group 2		Group 3		Group 4	
ID	**Antibody**	**ID**	**Antibody**	**ID**	**Antibody**	**ID**	**Antibody**
4	Jka	1	K	3	Fya + Jka	9	Lua + AIHA
5	K	2	E + Jka	6	Jka	19	E (enzyme)
10	Jka	8	E + Cw	7	Jka	20	Jka
11	Jka	14	Jkb	12	c + E + Jka		
17	K	16	Jka	13	E		
21	E	25	Jka	15	None		
		26	AIHA (Kpb)	18	E		
		27	None	22	Jka		
		28	None	23	Yka + AIHA		
		30	E, c, Jkb	24	Jkb		
				29	Fya		

Analysis of serological information

Antibody screening

Table 19 gives information on the serological methods used for antibody screening in the 30 reported cases.

Table 19
Summary of serological methods used for antibody screening

Screening Method	2 cell screen	3 cell screen	4 cell screen	Total
Tube LISS IAT	1	3		4
Column IAT	7	14		21
Solid Phase	1		2	3
Not done				1
Not known				1
Total	**9**	**17**	**2**	**30**

This table shows a preponderance of column technology for antibody screening in these cases. However, this is in keeping with NEQAS (Blood Transfusion Laboratory Practice) data which showed that 75.3% of NEQAS participants were using column technology for antibody screening in July 1998. Detailed assessment of the techniques used (serum:cell ratios, incubation times etc) was not carried out. In two instances a "rapid" rather than "routine" technique was employed. In 18 cases the pre-

transfusion sample was re-investigated and yielded the same results other than in one case in which an anti-Jka, present pre-transfusion, had not been appropriately identified.

At least 9 different suppliers of antibody screening cells were reported. There was no association between the cell supplier and apparent or possible non-detection of pre-existing antibodies.

Details of some unusual serological cases are given below:

- *Case 9 This 90 year old female received a transfusion for the anaemia of chronic disease. She had had many previous transfusions. Pre-transfusion she was noted to have anti-E, Kpa and autoantibodies reacting by LISS IAT and manual polybrene. The DAT was positive (IgG). Four days post-transfusion she developed jaundice with a falling Hb and renal impairment. Anti-Lua was noted in the post-transfusion sample in addition to the previously identified antibodies. It was felt unlikely that the anti-Lua had caused the degree of anaemia noted and this patient has probably experienced an exacerbation of auto-immune haemolytic anaemia.*

- *Case 19 A 68 year old female with multiple myeloma and a history of transfusion one month previously developed jaundice, falling Hb, haemoglobinuria and anuria 1-2 days following transfusion of two units of red cells. A pre-transfusion sample and a 4 day post-transfusion sample, screened by LISS IAT tube techniques and a 2 cell panel showed no antibody. However, testing of both samples by papain technique showed the presence of an anti-E in both samples. Repeat testing at 7 days post-transfusion showed that the antibody was now IAT reactive. Both transfused units were R2r. The patient developed renal failure and died as a result of this reaction. Death from the underlying myeloma was NOT expected at this point in the patient's care.*

- *Case 23 This 65 year old female was transfused for haemorrhage from a wound haematoma. Pre-transfusion testing showed no auto- or alloantibodies. Ten days post-transfusion she developed cramps, a raised bilirubin, falling Hb and a positive DAT (IgG). Investigation of post-transfusion sample showed the presence of anti-Yka and an autoantibody. Anti-Yka is not generally thought to be clinically significant. It was proposed that the transfusion may have stimulated an autoimmune haemolytic anaemia.*

In five cases the transfusion reaction occurred within 5 days of transfusion. This is perhaps the most interesting group in terms of possible “missed” antibodies. Three of this group had 2 or 3 antibodies detected in the pre-transfusion sample and each of these patients developed evident jaundice within 5 days of transfusion. In each case the presence of 2-3 antibodies was identified using only a single panel of cells. Two labs used both IAT and papain techniques while one used an IAT technique only.

- *Case 24 A 33 year old previously transfused male with AIDS and a lymphoma was identified as O RhD positive with anti-C + E. This would be an unusual combination in a Rh positive patient. These two antibodies were identified using a single 10 cell panel and a single column technology. He developed jaundice and falling Hb 3 days post-transfusion. Post-transfusion investigation revealed only anti- C + E but it was noted that anti-Jkb had been previously detected at the hospital which transferred the patient. The post-transfusion antibody identification was again performed using a single panel of cells and a single technique.*

- *Case 13 A 42 year old female with post-surgical bleeding had the presence of anti-c, Fya and Cw noted in the early 1980s. On this occasion these antibodies were “confirmed” using a single 11-cell panel by IAT and papain column agglutination techniques. The patient developed jaundice and anaemia 2-3 days post-transfusion and the post-transfusion sample was referred to the local transfusion centre where the presence of an additional anti-E was noted. This is unusual in that it would be expected that a patient with anti-c would have received R_1R_1 units (this detail was not clarified by the questionnaire). It is therefore not clear how the anti-E had arisen unless an R_1R_Z unit was administered.*

Cross-matching

Interval between drawing cross-match sample and transfusion

The interval between cross-matching and sampling is shown below for 30 reports

Interval between cross-matching and sampling (hrs)	No. of cases
0-47	23
48-71	2
72-96	2
>96	0
Not known	3

Cross-matching methods used

The methods used for cross-matching are shown below:

Method	No. of cases
Electronic cross-match	2
Immediate spin	3
LISS IAT Tube	8
Column	16
Not known	1
Total	**30**

In general, the timing of pre-transfusion samples was in keeping with the national guidelines[4]. It was not always possible to ascertain from the questionnaire the timing of an earlier transfusion and the implicated transfusion.

Reporting to Blood Centres and Hospital Transfusion Committees

Only 16/30(52%) of cases were reported to the local Blood Centre and 19/30 (62%) were reported to the Hospital Transfusion Committee. It is presumed that reporting hospitals felt that the local Blood Centre had nothing additional to contribute to the case and that there were no implications for recipients of other components from the same donor.

COMMENTARY

- In general there is little evidence of poor laboratory practice with the majority of DHTRs apparently occurring as the result of the development of new antibodies which could not have been detected or predicted pre-transfusion. However, in the cases in which early post-transfusion reactions occurred there is evidence that antibodies may have been present in some cases and "masked" by other antibodies in the sample.

- As in earlier SHOT reports the antibodies responsible for the DHTRs were consistent with those reported in the literature[10] with a preponderance of Kidd 14/34 (41%) of all antibodies, 14/30 (45%) of patients.

- In 7 cases there was no evidence of any haemolysis and patients were reported because of the later detection of new antibodies. This included one case detected to have anti-K 75 days post-transfusion. It is not the intention of SHOT to collect reports on allo-immunisation in the absence of other manifestations of DHTR although there may be occasions (e.g. development of anti-D in a young female patient) in which a report to SHOT is appropriate.

- In 2 cases the presence of an anti-Kidd was known historically but either not communicated to the receiving hospital or retrieved from Blood Bank records. The antibody was not detectable on pre-transfusion testing.

- An enzyme-only anti-E was felt to be implicated in a fatal transfusion reaction. Enzyme-only antibodies are not generally felt to be clinically significant and therefore this case is both unusual and worrying. The reaction pattern of the antibody evolved over the week post-transfusion, becoming reactive by both enzyme and IAT techniques.

RECOMMENDATIONS

- Laboratories should ensure that any antibodies which may be masked by a detected antibody(ies) have been excluded by the use of additional panels and techniques (e.g. enzyme-treated cells).

- Historical transfusion details should be communicated by referring hospitals and retrieved from previous transfusion records, where available.

- Nursing and medical staff should ask patients whether or not they carry a red cell antibody card at the time of drawing blood for pre-transfusion testing. However, it is currently not routine practice in all areas to issue these cards and their value in improving transfusion safety has not been formally assessed.

- For laboratories who may feel that alternative technologies may have been able to detect an implicated antibody in the pre-transfusion sample the National External Quality Assurance Scheme (Blood Transfusion Laboratory Practice) can offer a range of technologies which may not be available locally.