8 Delayed Transfusion Reactions

Definition

Delayed transfusion reactions are defined as those occurring more than 24 hours following a transfusion of blood or blood components. In practice, these are usually delayed haemolytic reactions due to the development of red cell alloantibodies. Simple serological reactions (antibody development without a positive DAT or evidence of haemolysis) are excluded.

Twenty-nine delayed transfusion reaction (DTR) questionnaires were received, one of which was transferred to the Acute Transfusion Reaction chapter.

This chapter describes the main findings from 28 completed questionnaires.

Patients

11 males and 17 females

Ages ranged from 8 to 89

Definition of severity of reaction/ clinical sequelae

Symptoms and signs are divided into 4 categories as follows:

- Group 1 Asymptomatic (with positive DAT only)
- 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

Severity

One patient required ICU admission and subsequently died, but this was thought to be unrelated to the transfusion (Imputability 0).

6 patients were asymptomatic with a positive DAT and antibody development only (Group 1).

22 patients had evidence of increased red cell destruction but without renal impairment:

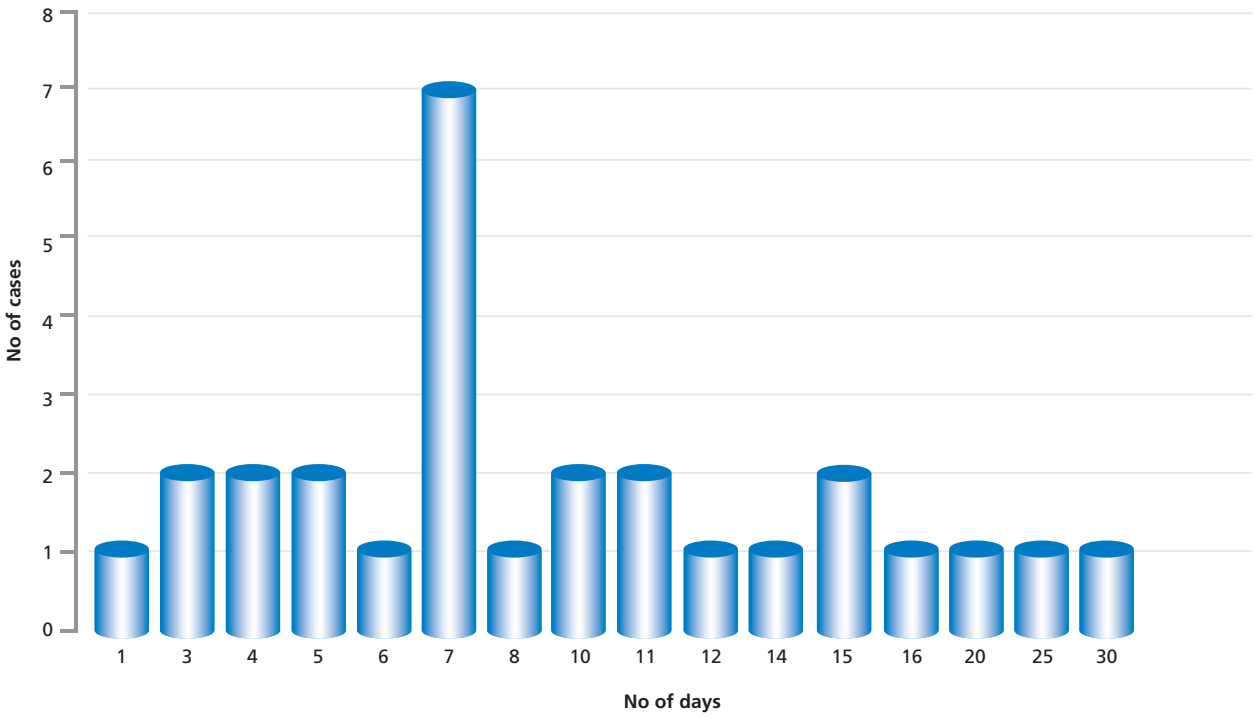
- In 7 cases the only sign was a fall in haemoglobin, with or without a positive DAT and spherocytes (Group 2)
- In 15 cases there was a fall in haemoglobin and a raised plasma bilirubin, although clinically detectable jaundice was only reported in 5 cases (Group 3). One of these patients died (case 9 - see vignette), with no evidence that the death was related to the transfusion and no detectable alloantibody.

Sequelae

6 patients were already on ICU, 5 required admission to the ward from outpatients or day care, and at least 5 required further transfusion. Only one was reported as posing a 'risk to life' (case 17).

Figure 8

Time relationship to transfusion



Median = 7 days

Range = 1 to 30 days

Figure 8 shows the interval in days between the implicated transfusion and signs or symptoms of a DHTR. 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 happened to be tested.

There were 3 cases where symptoms were noted within 72 hours of transfusion: in the first (case 2) no earlier recent transfusion was reported and repeat testing of the pre-transfusion sample was not undertaken; in the second (case 12 - see vignette) another transfusion had been given 12 days earlier; in the third (case 27), another 3 transfusions had been given in the preceding 16 days, the most recent of which was 5 days before the DHTR. In both of these latter cases the earlier transfusions were more likely to have been implicated in the DHTR than the reported transfusion.

Serological findings

Kidd antibodies were the most commonly implicated, in 11/28 (39%) of cases, either singly or in conjunction with other specificities. Two patients had no detectable antibodies and are described as vignettes. Table 24 shows the specificity of new antibodies in plasma and eluate, and the number of days post transfusion. Tables 25 and 26 show new specificities by blood group system and severity, respectively.

Table 24

Case number	New antibody (ies) in plasma	Antibodies in Eluate	Comments	No. days post tx
1	Anti-Jk^{b}	No eluate performed		7
2	Anti-Jk^{a}	No eluate performed	Pre-existing anti-E+K. No record of recent transfusion	3
3	Anti-Jk^{a}	No eluate performed	Already in ICU	10
4	Anti-K + E	Anti-E		30
5	None in plasma	Non-specific reactions	Further transfusion required	25
6	Anti-Fy^{a}	No eluate performed		7
7	Anti-Jk^{a} + c	No eluate performed	Required admission	15
8	Anti-S	No eluate performed	Required admission	14
9	None	No eluate performed	Sharp rise in bilirubin. DAT negative. Died unrelated to transfusion	4
10	None in plasma	Anti-Jk^{a}		5
11	Anti-E + Jk^{a}	Anti-E + Jk^{a}		5
12	Anti-S	Anti-S	Also transfusion 12 days previously	1-2
13	Anti-M	No eluate performed	Required admission. History of anti-C+Fy^{a}+S+K+Kp^{a}+Kn^{a}+McC^{a}. DAT negative.	7
14	Anti-Lu^{a} + Jk^{b}	Eluate negative	Required admission	11
15	Anti-S	Anti-S		20
16	Anti-Fy^{a} + E (E enzyme only)	No eluate performed	Already in ICU. Antibody screen weakly positive on retrospective testing.	7
17	M+cold agglutinins	No eluate performed	Already in ICU. Pre-existing anti-K+E. Anti-M previously identified elsewhere.	6
18	Anti-c + E	Anti-E	Required admission and further transfusion	16
19	Anti-C	Eluate negative		10
20	Anti-Fy^{a} + E (E enzyme only)	Anti-Fy^{a}	Already in ICU	11

21	None	Elulate negative	DAT positive but anti-JK[a] subsequently identified at day 11 - 4 days post DHTR	7
22	Anti-Jk[b]	No eluate performed	Pre-existing anti-C+D	4
23	Anti-Fy[a]	Anti-Fy[a]		8
24	No new abs	Anti-Fy[a]	Pre-existing anti-c+E+Fy[a]+Kp[a] Fy(a-) units transfused	7
25	Anti-c + E + Jk[a]	No eluate performed	Further transfusion required	15
26	Anti-Jk[a] + E + Ab to low incidence Ag	No eluate performed	Further transfusion required	12
27	Anti-Fy[a]	Anti-Fy[a]	Already in ICU. Also transfused on 3 occasions during the previous 16 days	3
28	Anti-Fy[a]	No eluate performed	Already in ICU	7

Table 25

New specificities by blood group system

Antibody specificity by blood group system	Number of cases	Sole *new* antibody
Kidd		
Jk[a]	8	4[1]
Jk[b]	3	1
Rh		
C	1	1
E	7	0
c	3	0
Kell		
K	1	0
Duffy		
Fy[a]	6	4
MNSs		
S	3	3
M	2	2[2]
Other		
Lu[a]	1	0
Unspecified low incidence	1	0
Non-specific	1	1[3]

1 - one detected only 4 days post DHTR and one detected in eluate only
2 - one also developed cold agglutinins
3 - in eluate only

Table 26

Antibody specificity by severity definition, where antibodies in brackets relate to pre-existing specificities

Group 1		Group 2		Group 3					
Case No.	**Ab specificity**	**Case No.**	**Ab specificity**	**Case No.**	**Ab specificity**	**Case No.**	**Ab specificity**	**Case No.**	**Ab specificity**
15	S	1	Jk^a	2	Jk^a (E+K)	10	Jk^a (eluate only)	22	Jk^b (C+D)
18	c+E	4	K+E	3	Jk^a	12	S	24	None (multiple) Fy^a in eluate
19	C	7	c+Jk^a	5	Non spec	13	M (multiple)	26	Jk^a+E
23	Fy^a	11	E+Jk^a	6	Fy^a	14	Lu^a+Jk^b		
27	Fy^a	16	Fy^a+enz E	8	S	17	M + cold aggs (K+E)		
28	Fy^a	25	c+E+Jk^a	9	None	21	Jk^a (4 days post DHTR		

Use of plasma/serum

In 27 cases plasma was used (96%) for pre-transfusion (one not stated); 23 also used plasma for post transfusion testing (5 not stated).

Serological Techniques Used

These broadly reflected those used in clinical practice.

One BioVue user used an inappropriate cell:plasma ratio and one low-ionic-strength-solution (LISS) tube suspension user used too high a cell concentration and an inappropriate plasma:cell ratio. However, in neither of these cases is there any evidence that the causative antibody was missed in the pre-transfusion sample.

Use of eluates

Only 14 (50%) stated that an eluate made from the patient's post transfusion red cells was tested for antibody, though a further 4 did not answer the question. 10 were performed by reference labs and 4 in-house. In 10 cases a specific antibody(ies) was identified, and in one case this was the only way of identifying the anti-Jk^a, since the antibody was not detected in the plasma. In 3 cases the eluate was negative, and in one non-specific reactions were observed; in this latter case, no free antibody was detectable in the plasma. In 4 cases the eluate demonstrated a single specificity where a mixture of new antibodies was present in the plasma, including one case of anti-c+E, where only anti-E was demonstrable in the eluate.

Retrospective testing findings

Retrospective testing of the pre-transfusion sample was undertaken in 13 (46%) cases; the same result as in the original (pre-transfusion) testing was obtained in 11 of these. In one of the other 2 cases (case 16), the antibody screen was found to be weakly positive on retrospective testing using the same DiaMed IAT technique, although the reporter did not state whether the anti-Fy^a was actually identified; this followed an earlier transfusion within the previous two weeks. In the second case (case 13 - see vignette) some weak reactivity against 2 panel cells was noted in a sample from a patient with multiple other antibodies, but no specificity could be assigned; identification in this patient was complicated by Knops/McCoy activity.

Clinical management and review

15 (54%) of cases were referred to the Blood Centre Reference Laboratory and 25 (89%) to the HTC. Twelve of these were reported to both.

Vignettes

No antibodies detected - no clear evidence of a DHTR (imputability 1)

Case 5

A 34 year old female patient with post-operative bleeding required 3 units of red cells. 26 days later her DAT was strongly positive (IgG) and spherocytes were noted on her blood film. Samples were referred to the blood service red cell reference laboratory, but no antibodies were detected in the plasma, and an eluate made from the patient's red cells showed no specificity. The Hb dropped by 3g/dL between day 25 and day 27, with a small rise in bilirubin, but no signs of bleeding. She required a further transfusion, which was followed by a similar drop in Hb over the next 48 hours. During this time she also became pyrexial, and Candida was detected in the blood cultures. The patient was subsequently transfused with R_1R_1 K- red cells, although the presence of transfused red cells made her phenotype impossible to determine; her Hb then remained stable.

Case 9

An 84 year old female patient received 12 units of red cells over an 8 day period for rectal bleeding. 3 days after the most recent transfusion, she became jaundiced and was suffering from acute respiratory distress syndrome (ARDS); her bilirubin rose from 20 to 127 µmol/L and reached a peak of 231 2 days later. The Hb also fell, but it is unclear whether this was due to bleeding or the transfusion or both. She received a further 2 units 9 days later and once again her bilirubin rose from 167 to 291µmol/L. A DAT was not performed until 8 days later when it was negative. The patient was subsequently admitted to ICU and died, but this was thought to be unrelated to the transfusion.

Difficult to classify

Case 10

A 75 year old female patient received 3 units of red cells for an inferior mesenteric artery bleed. A group and save sample tested 3 days previously gave a positive antibody screen and a positive DAT (both IgG and complement coating). The sample was referred to the blood service red cell reference laboratory 2 days later, where anti-Jk^a was eluted from the patient's red cells, although no plasma antibody was detected. It is not clear why non-phenotyped blood was issued based on an empirical crossmatch. The patient did not get the expected increment in Hb and had a raised bilirubin 5 days after transfusion; however, the reporter indicated that these signs were indistinguishable from those due to multiple disease factors.

This case is difficult to classify: the anti-Jk^a presumably developed as a result of a transfusion given 14 to 28 days previously and was clearly present in the pre-transfusion sample. Whether the blood was transfused without Jk^a typing, due to a lack of communication or a misunderstanding is not clear. It is also unclear which symptoms were due to a transfusion reaction and which were due to disease. This could therefore equally be classified as an acute transfusion reaction or an IBCT.

Case 12

A 7 year old female patient with sickle cell disease was admitted with a painful crisis and a Hb of 6.6g/dL. The antibody screen was negative and she was transfused with a unit of red cells. 12 days later she was re-admitted, again with painful crisis. Her Hb was initially 8.5g/dL but on repeat was found to be only 4.5g/dL. The antibody screen was negative, and although the DAT was weakly positive (due to both IgG and complement coating), this was not investigated until 3 days later because it was a Friday night. She again received one unit of red cells. Over the following 2 days, dark urine was noted and laboratory tests indicated that she had no increment in Hb and a raised bilirubin; a DHTR was suspected. Anti-S was identified post transfusion and was eluted from the patient's red cells. Both red cell units were found to be S positive. The patient recovered quickly.

This case was reported as a DHTR occurring 1-2 days post the second transfusion. However, the timing and the pre-transfusion DAT, suggest that this is more likely to be a combination of a DHTR due to the transfusion given 12 days previously and an acute haemolytic transfusion reaction (AHTR) following the 2nd transfusion of S positive blood. The picture is also complicated by the sickle cell crisis.

More unusual/interesting cases

Case 13

A 69 year old woman with a myeloproliferative disorder and a history of multiple red cell transfusions, was known to have anti-K+Kp^a+S+C+Fy^a+Kn^a/McC^a, although only the anti-K and -Kp^a had been recently detectable. On this occasion the pre-transfusion sample showed further reactions and the sample was sent to the reference laboratory for further investigation and crossmatching. The reference laboratory found anti-Kn^a and McC^a, but no convincing evidence of new antibodies and provided 3 units of crossmatched blood, 2 of which were transfused 4 days later. Seven days post transfusion the patient developed left upper quadrant pain, progressive splenomegaly and jaundice, and her Hb dropped. The reference laboratory was sent a post-transfusion sample on which it made an immediate verbal report of anti-M; both transfused units were subsequently confirmed as M positive. Five days later another transfusion was required and M negative blood was supplied. After 200mL of the first unit, the patient developed fever and rigors, and passed dark urine, requiring admission from the day ward. Spherocytes and hyperbilirubinaemia were later noted. The DAT was negative following both transfusions and no eluates were performed. Bacterial contamination of the unit was excluded and the cause of the acute reaction was not established. The acute reaction has also been reported in the ATR chapter (case 1).

This is an unusual case; the anti-M was reported to have been weak (2+) and the DAT was negative, so would be an unusual cause of a DHTR; however there appears to be no obvious alternative cause. Anti-M has been excluded as a cause of the AHTR since the latter units transfused were M negative.

Case 2

A 72 year old female patient was bleeding following over-anticoagulation with Warfarin, and required a 3 unit red cell transfusion The pretransfusion antibody screen was positive and anti-E+K was identified in the plasma using a BioVue IAT and 2-stage enzyme technique; crossmatch compatible, antigen negative blood was transfused. 3 days later the patient passed dark urine and became jaundiced. Laboratory investigations demonstrated a raised bilirubin, a falling Hb and spherocytes. Anti-Jk^a in addition to anti-E and -K was identified in the plasma, and the DAT was positive, due to both IgG and complement coating. No eluate was performed and the pre-transfusion sample was no longer available for testing.

Although 3 days is a shorter interval than is classically expected for a DHTR, this patient had no recent history of transfusion and there was no indication of anti-Jk^a in the pre-transfusion sample, even using a 2-stage enzyme technique.

Case 17

A 16 year old male patient required a transfusion in ICU following emergency surgery. Anti-E+K were identified in his plasma and one unit of antigen negative, crossmatch compatible blood was transfused. 6 days later he passed dark urine and became jaundiced. Laboratory investigations demonstrated a raised bilirubin and a falling Hb; the DAT was positive due to both IgG and complement coating and anti-M plus a non-specific cold autoagglutinin were detected in the plasma and confirmed by a reference laboratory. An eluate was not performed. Retrospective testing of the pre-transfusion plasma using the same DiaMed IAT technique confirmed that only anti-E and anti-K were detectable pre-transfusion. Anti-M had apparently been identified by a different hospital 2 months previously, but this information was not available until after the patient had been transfused.

Case 24

An 84 year old male patient with myelodysplasia and a history of transfusion (> 3 months previously) required several units of red cells over a 2 day period, following a total hip replacement. The patient was known to have anti-c+E+Fy^a+Kp^a, and crossmatch compatible antigen negative blood was transfused. 7 days later it was noted that the patient had increased reticulocytes and a raised bilirubin. The reference laboratory confirmed that the DAT was positive due to IgG coating, but that no new antibodies were detectable. Anti-Fy^a was identified in an eluate made from the patient's red cells, despite all the transfused units apparently being confirmed as Fy(a-).

COMMENTARY

- According to the literature, DHTRs caused by anti-M are rare. Anti-M was found in two cases of DHTR this year, with clinical signs of red cell destruction in both cases; i.e. dark urine, falling Hb and raised bilirubin 6 to 7 days post transfusion. Both of these cases had complex serology, with pre-existing alloantibodies, and in one case newly developed cold agglutinins. Unfortunately in neither case was extensive investigation undertaken to prove whether or not anti-M was responsible for the red cell destruction. It is particularly difficult to draw any conclusions in case 17, since there were no details available regarding the patient's underlying diagnosis, the DAT was positive for complement as well as IgG and anti-M does not bind complement, and the transfused unit was not typed for M. There have been 5 cases in previous SHOT reports where anti-M has been identified as a new specificity; in 4 of these, additional specificities were also identified, but there is no record of eluates being performed.
- In all cases (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.
- In 3 cases DHTRs were reported to have occurred within 72 hours of the implicated transfusion. However, in 2 of these, earlier transfusions were more likely to have been implicated in the reaction.
- Only 50% of investigations included testing an eluate made from the patient's red cells. 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 only be present in an eluate, as in case 10. Identification of all specificities present is essential if further haemolytic reactions are to be prevented.
- As in previous years, communication problems have contributed to DHTRs, where information about previously known antibodies has not been available at the time of a subsequent transfusion.

RECOMMENDATIONS

- 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 a DHTR 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. Reference laboratories should ensure that investigation of DHTRs includes testing an eluate made from the patient's red cells when the DAT is positive.

  Action: Hospital blood transfusion laboratories and reference laboratories

- Inconclusive antibody screens should be investigated prior to transfusion and results confirmed with a reference laboratory if necessary.

  Action: Hospital blood transfusion laboratories

- Investigation of a suspected DHTR 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 DHTRs and using polyspecific antihuman globulin (AHG). These actions may involve referral to a reference centre.

  Action: Hospital blood transfusion laboratories.

- Hospitals and reference laboratories should be encouraged to publish case reports of DHTRs, after appropriate investigations have been undertaken, and where the implicated antibody is not recognised as a common cause of such reactions.

  Action: Hospital blood transfusion laboratories and reference laboratories.

- In line with recommendations made in the BCSH Guidelines,[21] 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.

  Action: The CMO's NBTC and its counterparts in Scotland, Wales, and Northern Ireland.

- 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.

  Action: BBTS and BCSH.