# 9. DELAYED TRANSFUSION REACTIONS

**Definition**

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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. Excluded from this definition are uncomplicated alloimmunisation episodes which have not resulted in evidence of haemolysis (falling Hb, positive DAT or jaundice) or clinical symptoms. Such reactions are relatively common following red cell transfusions (approximately 1 in 20 transfusions).

This category accounted for 9.8% of non-infectious hazards reported.

28 initial reports were received and 24 completed questionnaires were returned (including one which was initially reported in the previous reporting year). This chapter highlights the main findings from 24 completed questionnaires. One of these cases was a simple serological reaction but, as noted above, reporting of this type of event to SHOT is not required

**Sex**

| | |
|---|---|
| Males | 11 |
| Females | 13 |

**Age**

| | |
|---|---|
| Age range | 33-86 years |
| Median age | 62 years |

**Table 27**
**Timing of Reaction/Diagnosis in relation to previous transfusion**

| Days post-transfusion | No. of cases |
|---|---|
| 1-5 | 1* |
| 6-10 | 14 |
| 11-15 | 4 |
| 16-20 | 1 |
| >20 | 1 |
| Not stated | 3 |

* Case 12, see below

| | |
|---|---|
| Range | 3-30 days |
| Median | 8 days |

## Reactions Reported

There were 2 deaths in this group (cases 7 and 13) which were both due to the underlying disease. In addition, one patient experienced angina secondary to severe anaemia but made a good recovery and a patient who had severe complications following cardiac surgery (case 15) was still recovering at the time of the report. The remaining patients suffered minor, or no morbidity.

All reactions were related to the administration of allogeneic red cells but in 1 patient who seemed to have a clear-cut haemolytic reaction (Case 2) no alloantibodies were implicated. A possible exacerbation of autoimmune haemolysis was suspected. In total 29 new antibodies were noted in the 24 cases.

Six patients had pre-transfusion red cell alloantibodies. A patient with autoimmune haemolytic anaemia (AIHA) who required blood as a matter of urgency (Case 12) was issued with unphenotyped units and was found to have alloanti-E on completion of the antibody identification. This patient showed evidence of a transfusion reaction on day 3.

## Urgency of Transfusion Requirement

In 19 patients the transfusion was said to be routine and in 5 urgent. Most transfusions were for surgery or bleeding. One patient was transfused for iron deficiency anaemia due to gastritis.

## New Post-transfusion Antibodies

Table 28 shows the new post-transfusion antibodies (or antibodies which were later recognised to be present in the pre-transfusion sample) according to antigen specificity and Table 29 gives details of these antibodies for individual patients.

**Table 28**
**New post-transfusion red cell antibodies in 23 patients: according to antigen specificity**

| Antibody group | Number | Sole antibody |
|---|---|---|
| **Kidd** | | |
| Jka | 10 | 6 |
| Jkb | 1 | 1 |
| **Duffy** | | |
| Fya | 3 | 2 |
| **Kell** | | |
| K | 1 | 1 |
| **Rh** | | |
| c | 4 | 2 |
| E | 5 | 2 |
| **SsMN** | | |
| S | 1 | |
| M | 1 | |
| **Other** | | |
| Anti-B[1] | 1 | |
| "private antigen" NOS[2] | 1 | |
| Wra | 1 | 1 |

[1] in liver transplant, donor antibody
[2] Not otherwise specified

**Table 29**
**New post-transfusion red cell antibodies in individual patients**

| ID | Antibody(ies) | Comment |
|---|---|---|
| **1** | Fya | |
| **2** | Nil | ?AIHA, positive DAT and alloanti-E identified pre-transfusion |
| **3** | Fya+Jka+anti-B | liver transplant (O to B), anti-e+S+cold agglutination pre-transplant |
| **4** | Jka | |
| **5** | Jka | |
| **6** | c+E | |
| **7** | E | |
| **8** | K | Serological reaction only |
| **9** | c | |
| **10** | Jka | |
| **11** | Jka | |
| **12** | E | AIHA. Urgency precluded full compatibility testing. Anti-E pre-transfusion |
| **13** | Wra | |
| **14** | Jka | |
| **15** | Jka | |
| **16** | S+M | Anti-C+E+Fya+Jkb+autoanti-D pre-transfusion. Sickle cell disease |
| **17** | Jka | Anti-C+D+E pre-transfusion |
| **18** | ?private antigen | "non-specific antibody" pre-transfusion |
| **19** | Fya | |
| **20** | Jkb | |
| **21** | c+E | Anti-K pre-transfusion |
| **22** | c | Nil detected pre-transfusion. History of HDN (not known initially) |
| **23** | Jka+E | |
| **24** | Jka | Anti-D pre-transfusion. |

## 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 3 patients in this group (cases 5, 8 and 13). Case 13 died of his underlying disease while the other two cases survived without sequelae.

**Group 2**
There were 5 patients in this group (cases 1, 2, 7, 14 and 17) of whom 3 survived without sequelae, one developed angina (case 2) and one (case 7) died of her underlying disease.

**Group 3**
There were 15 patients in this group (cases 3, 4, 6, 9, 10, 11, 12, 16, 18, 19, 20, 21, 22, 23 and 24) all of whom survived without sequelae.

**Group 4**
There was only one patient in this group (case 15) who suffered multiple problems following cardiac surgery, probably exacerbated by the haemolysis, but who was recovering at the time of the report.

The above results are detailed in Table 30

**Table 30**
**Grouping of cases by clinical sequelae of DHTR**

| Group 1 | | Group 2 | | Group 3 | | Group 4 | |
|---|---|---|---|---|---|---|---|
| **ID** | **Antibody** | **ID** | **Antibody** | **ID** | **Antibody** | **ID** | **Antibody** |
| 5 | Jka | 1 | Fya | 3 | Fya+Jka+anti-B | 15 | Jka |
| 8 | K | 2 | Nil | 4 | Jka | | |
| 13 | Wra | 7 | E | 6 | c+E | | |
| | | 14 | Jka | 9 | c | | |
| | | 17 | Jka | 10 | Jka | | |
| | | | | 11 | Jka | | |
| | | | | 12 | E | | |
| | | | | 16 | S+M | | |
| | | | | 18 | ?to private Ag | | |
| | | | | 19 | Fya | | |
| | | | | 20 | Jkb | | |
| | | | | 21 | c+E | | |
| | | | | 22 | c | | |
| | | | | 23 | Jka+E | | |
| | | | | 24 | Jka | | |

## Analysis of serological information

### Antibody screening

Table 31 gives information on the serological methods used for antibody screening in the 24 reported cases.

**Table 31**
**Summary of serological methods used for antibody screening**

| Screening Method | 2 cell screen | 3 cell screen | Total |
|---|---|---|---|
| **Tube LISS IAT** | 1 | | 1 |
| **Column IAT** | 9 | 13 | 22 |
| **Solid Phase** | 2 | | 2 |
| **Liquid Microplate** | | 1 | 1 |
| **Total**[1] | **12** | **14** | **26** |

[1] *two respondents recorded more than one technique in the antibody screen questions*

This table shows a marked preponderance in the use of column technology for antibody screening in these cases. This is in keeping with the national trend towards increasing use of column technology as shown in the National External Quality Assurance Scheme (NEQAS) for Blood Transfusion Laboratory Practice (BTLP). Antibody screening cells from a large number of suppliers were used with this technology and it is not possible to say if the cells used were always optimal for the column technology selected.

Results were analysed to determine whether or not a 2-cell screen was more likely to be associated with an initially negative antibody screen. This was not the case. 5/12 patients screened using a 2-cell screen had a negative screen compared to 11/14 tested using a 3-cell screen (in 1 case, details were not given). However, as 2-cell screens are more likely to miss antibodies of $C^w$, $Lu^a$ or $Kp^a$ specificities, none of which were implicated in these events, this result is perhaps not surprising.

In 14 cases the pre-transfusion sample was retested and gave the same result in 13 cases. The exception was the patient with anti-Wra which could not have been detected with the screening cells used but which was revealed on further investigation.

**Details of some unusual serological cases are given below:**

- *Case 3 This 47 year old old male patient, Group B, received a liver transplant from a Group O donor (anti-B titre 1/4). Pre-transfusion testing showed anti-e, S and cold agglutinins but a unit of cross-match compatible, S+ve blood was transfused before investigations were complete. Ten days post-transplant a falling Hb, raised bilirubin and positive DAT were noted. Serological testing showed anti-Fya, Jka and anti-B in addition to his previously known antibodies. The anti-B was presumably of donor origin while the other antibodies are likely to have been produced by the recipient. The reaction noted may have been due to any (or all) of the four antibodies - anti-B, S, Fya or Jka.*

- *Case 16 This 33 year old old male patient with sickle cell disease received 5 units as an exchange transfusion prior to surgical debridement. Five days later he was noted to be jaundiced, with no rise in the Hb and HbS level of 98% suggesting that any transfused units had been destroyed. Pre-transfusion he was shown to have anti-C, E, Fya, Jkb and autoanti-D but subsequent testing showed the presence of anti-S and anti-M in addition. It is possible that these had been responsible for the apparent destruction of the transfused units and may have been present, but missed, at the time of initial testing. Repeat testing of the pre-transfusion sample was not performed*

- *Case 22 This 48 year old old female patient received 4 units of red cells for a bleeding duodenal ulcer. At readmission, 8 days later, she was noted to have dark urine, jaundice, low Hb and back pain. Anti-c was found in a sample drawn at readmission but the pre-transfusion sample was not available for retesting. The patient advised that her last child had been affected by HDN but this history was not ascertained at the time of first admission.*

## Cross-matching

### Interval between drawing cross-match sample and transfusion

The interval between sampling and transfusion is shown below for 24 reports

| Interval between sampling and transfusion (hrs) | No. of cases |
|---|---|
| 0-47 | 17 |
| 48-71 | 3 |
| 72-96 | 1 |
| >96 | 1 |
| Not known | 2 |

In general, the timing of pre-transfusion samples was in keeping with the national guidelines[17]. In one case (Case 24) the time between drawing the sample and transfusion appeared to be inappropriately long (>96 hrs) in view of the history of recent (within 14 days) transfusion.

- *Case 24 This 34 year old female patient was transfused on 2 occasions in one week for anaemia due to liver disease and splenomegaly. Anti-D was noted at the time of the first of these transfusions. Six days later a further transfusion was given, matched against a sample drawn more than 4 days before. Jaundice, anaemia and a positive DAT developed. The patient was subsequently shown to have developed anti-Jka.*

**Cross-matching methods used**

The methods used for cross-matching are shown below in Table 32:

**Table 32**
**Cross-matching methods**

| Method | No. of cases |
|---|---|
| Electronic issue | |
| Immediate spin | 8 |
| LISS IAT Tube | 6 |
| Column | 9 |
| Not known | 1 |
| **Total** | **24** |

There was no evidence of inappropriate use of the Immediate Spin cross-match. All patients with a positive antibody screen had blood matched by IAT methods.

## Reporting to Blood Centres and Hospital Transfusion Committees

19/24 (79%) cases were reported to the Hospital Transfusion Committee while only 11 (46%) were reported to the local Blood Centres. The involvement of the Hospital Transfusion Committee has increased from last year which presumably reflects the increased availability of these committees and greater awareness of their role. It is presumed that the local Blood Centres would have been notified if assistance was required in antibody identification or sourcing of subsequent units of compatible blood.

## COMMENTARY

- As in earlier SHOT reports the antibodies responsible for the DHTRs were consistent with those reported in the literature with a preponderance of Kidd - 11/29(41%) of all antibodies, 11/24 (46%) of patients.

- Kidd antibodies, undetectable by current methods, remain the major cause of delayed haemolytic transfusion reactions

- In 1 case (Case 22) the existence of an alloantibody was known historically but not reported to the hospital laboratory. The antibody was not detectable on pre-transfusion testing and, unfortunately there was no sample available for retesting.

- In 3 additional cases it appears that the antibody could have been detected in the pre-transfusion sample (Cases 12, 13 and 16). However, in one case clinical urgency precluded the completion of full testing (Case 12), one implicated antigen would not normally be expressed on screening cells (Case 13 - anti-Wra) and in the third case (Case 16) the presence of two additional antibodies (S+M) may have been missed in a patient with multiple antibodies.

## RECOMMENDATIONS

- **Transfusions for iron deficiency anaemia (or other medically treatable causes) should be avoided if possible, both because of the risk of primary immunisation and also because of the risk of inducing a secondary immune response with haemolysis. BCSH guidelines on the appropriate use of red cells are in press.**

- **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 sought from all relevant sources (including the patient) and acted upon.**

- **Development of screening techniques in order to improve the detection of extremely low levels of Kidd antibodies should be considered by serologists and manufacturers of screening systems.**

- **Information for patients who may be transfused should include the fact that antibody development is possible and unavoidable.**