12. Haemolytic Transfusion Reactions (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, confirmed by one or more of: a fall in Hb, rise in LDH, positive DAT and positive crossmatch.
- Delayed reactions are defined as fever and other symptoms/signs of haemolysis more than 24 hours after transfusion; confirmed by one or more of: a fall in Hb or failure of increment, rise in bilirubin, positive DAT and positive crossmatch which was *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	**47**	*Implicated components*		*Mortality/morbidity*	
		Red cells	**46**	Deaths due to transfusion	**0**
		FFP	**0**	Deaths in which reaction was implicated	**0**
		Platelets	**1**	Major morbidity	**8**
		Other (specify)			
		Unknown			

Gender		*Age*		*Emergency vs. routine and core hours vs. out of core hours*		*Where transfusion took place*	
Male	**21**	18 years+	**45**	Emergency	**6**	ED	
Female	**26**	16 years+ to 18 years	**0**	Routine	**37**	Theatre	
Unknown	**0**	1 year+ to 16 years	**2**	Not known	**4**	ITU/NNU/HDU/Recovery	
		28 days+ to 1 year	**0**			Wards	
		Birth to 28 days	**0**	In core hours		Community	
		Unknown	**0**	Out of core hours		Outpatient/day unit	
		Total	**47**	Not known/applicable	**47**	Not known	**47**

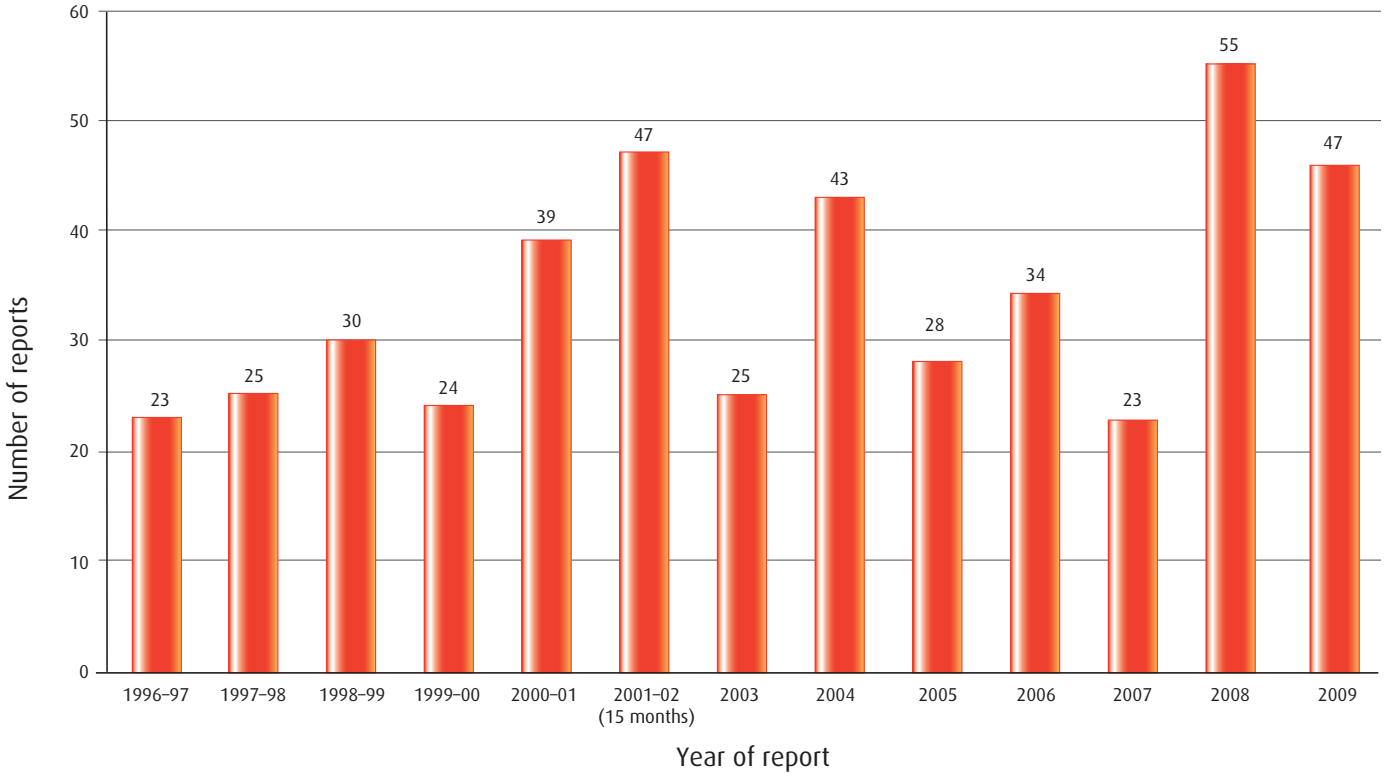
Sixty questionnaires were received; 9 were transferred out, 6 to the IBCT and 3 to ATR; 4 were withdrawn. This section describes the findings from 47 cases: 8 acute and 39 delayed reactions.

Patients

There were 21 male and 26 female patients, with an age range from 4 to 94 years old.

Two patients were under 18 years of age: 2 patients with sickle cell disease (SCD), aged 4 and 7, each of whom suffered a DHTR with anti-Jk^b and anti-S implicated respectively. The latter may have been preventable with better communication between hospitals, but probably also included an element of hyperhaemolysis.

Figure 13
Number of cases of HTR reviewed since 1996



Mortality, Morbidity, and Imputability

Acute haemolytic transfusion reactions (AHTR) *n* = 8

There were no deaths caused, or contributed to, by these transfusion reactions. There were 3 cases of major morbidity; one patient (A4) required ITU admission, while the other 2 (A7, A8) showed signs of deteriorating renal function.

Four reactions were reported as definitely related to the transfusion (imputability 3), 3 probably related (imputability 2), and 1 possibly related (imputability 1).

Delayed haemolytic transfusion reactions (DHTR) *n* = 39

There were 2 patients in this group who died from underlying disease, not related to the transfusion reaction. There were 5 cases of major morbidity. One patient (D10) required dialysis, but made a full recovery. One patient with SCD (D34) required ITU admission following a severe episode of hyperhaemolysis. The other 3 cases showed signs of deteriorating renal function, but did not require dialysis.

Of the remaining 32 cases, 23 patients suffered minor morbidity and 9 had no clinical signs or symptoms. One patient did not even develop a positive DAT, but the case is included in this chapter because of its unusual nature (D39). From 2010, the Dendrite database will accept reports of simple antibody formation without a positive DAT or any other signs or symptoms.

Case D39

Development of multiple red cell antibodies following platelet transfusion

An elderly patient with MDS received a total of 25 adult doses of platelets but no red cells, over a period of approximately a year, and developed anti-c, -E and -A_1, followed by anti-K, -S, -Fy^b, and -Jk^b. There were no clinical or laboratory signs of a haemolytic reaction. The patient finally developed platelet antibodies (anti-HPA-2a) in addition to his red cell antibodies.

Learning point

- Components containing any residual red cells can elicit an immune response.

Timing of reaction in relation to transfusion

AHTR

All the reactions occurred either during the transfusion or soon afterwards, with between 35 mL and the whole unit being transfused.

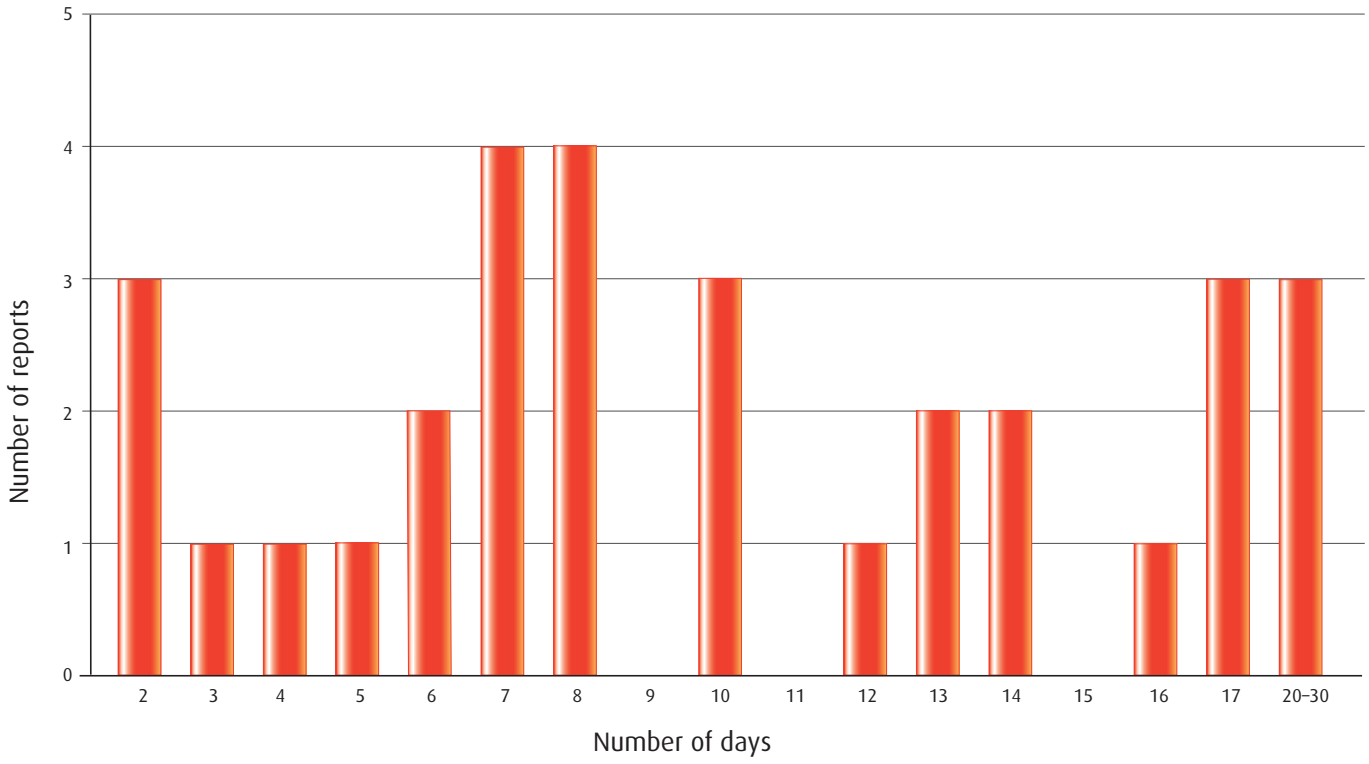
DHTR

Figure 14 shows the reported interval in days between the implicated transfusion and clinical signs or symptoms of a DHTR. The median is 8 days, and the range 2 to 26 days. New antibodies were found between 7 days and 10 weeks after transfusion in the 8 asymptomatic cases.

Serological findings – AHTR *n* = 8

All these cases have good laboratory evidence to support a haemolytic episode. However, these are complex cases and many of the antibody specificities identified are not usually associated with haemolytic transfusion reactions, e.g. Knops, Bg, and weak C^w. In other cases an antibody developed some time after the reaction and it is difficult to draw firm conclusions. Identification of an antibody does not necessarily mean that it is the cause of the reaction, and other causes such as bacterial contamination should also be considered, as should other unidentified or undetectable antibodies.

Figure 14
Interval between administration of implicated transfusion and signs or symptoms of DHTR



Antibody only detectable in eluate

Case A1

A patient with SCD with known anti-D received 2 units of red cells. Ten days later she received a further 4 red cell units over 4 days. At the end of the last unit, she became pyrexial and tachycardic, and haematuria was noted, all thought to be due to sickle cell crisis and medications. Two days later her Hb dropped from 7.4 to 5.0 g/dL. The only antibody detected in the plasma was anti-D, but anti-S was detected in an eluate. The 2 earlier units and 3 of the 4 later units were confirmed to be S positive, including the unit to which the patient reacted. With hindsight, the patient probably suffered a mixture of acute and delayed HTRs due to anti-S.

Delayed detection of antibody

Case A2

An elderly patient required 2 units of red cells postoperatively. She had a 1.6°C rise in temperature during the second unit and the transfusion was stopped. Her Hb fell from 11 to 8.5 g/dL over 6 days, at which point anti-Jk^a was identified. Bilirubin levels began rising and Hb falling within 24 hours of the transfusion, suggesting that this was an AHTR rather than an isolated febrile reaction followed by DHTR.

Case A6

A patient requiring blood for postoperative anaemia had a history of weak, non-specific reactivity by IAT. On this occasion the antibody screen was negative and red cells were compatible by IAT. Approximately three-quarters of the way through the first unit, the patient suffered fever, chills, rigors and dark urine, and the transfusion was stopped. Weak anti-Kn^a/McC^a was confirmed by IBGRL. However, 6 months later anti-Jk^a was identified in addition to the Knops antibody, with no evidence of intervening transfusion. Knops antibodies are not considered to be of clinical significance, but it is not clear whether the AHTR was caused by undetectable anti-Jk^a or something else.

Uncertain cause of reaction

Case A3

A patient with SCD and a history of multiple antibodies (anti-E, -Fy3, -Jk^b, -McC^a and anti-HI), was issued with red cells suitable for transfusion. After 60 mL had been transfused, she suffered fever, headache, loin pain, jaundice and dark urine. No further red cell alloantibodies were identified.

Case A4

A patient with anti-K, -C, enzyme-only auto-anti-e and a positive DAT was transfused with crossmatch compatible red cells. Towards the end of the unit, the patient developed a fever, dyspnoea and laboratory signs of haemolysis, and was admitted to ITU. No further antibodies were identified and it was thought that the transfusion exacerbated auto-immune haemolysis. A DHTR due to anti-C from transfusions 11–15 days earlier cannot be excluded.

Case A7

A patient with chronic anaemia became pyrexial after the third unit of red cells; this was followed by haemoglobinuria and deteriorating renal function. Anti-E and a pan-reactive autoantibody were identified in the post-transfusion sample only, by enzyme techniques only. The anti-E gradually became detectable by IAT and the DAT became weakly positive; however, an eluate was negative. All 3 units transfused were E negative. Transfusion of E negative blood a few days later caused a similar reaction. The patient's Hb increased following treatment with high dose steroids. It is not clear whether this reaction was due to an undetectable alloantibody, autoantibody, or something else.

Case A8

A patient with known anti-E and a non-specific cold antibody received 3 units of red cells compatible by NISS IAT. At the end of the third unit the patient developed fever, dark urine and jaundice. There was a rise in bilirubin, and a 2.0 g/dL fall in Hb. Anti-E and weak anti-C^w were identified in the post-transfusion sample, and retrospectively in the pre-transfusion sample using DiaMed and PEG IAT. An eluate revealed weak anti-C^w and the first unit was confirmed as C^w positive. However, the patient had a positive DAT before transfusion (IgG coating), was on high dose antibiotics, and had hypersplenism. The haemolysis continued for some time after the transfusion, and the patient required no further transfusion post splenectomy. The reporter concluded that the haemolysis was unlikely to have been due to the anti-C^w.

HLA antibodies apparent cause of AHTR

Case A5

Having been transfused 100 mL for symptomatic anaemia, a patient suffered nausea, vomiting, rigors, fever, abdominal and knee pain, tachycardia and hypotension. Her O_2 saturation fell to 90%. She required resuscitation with O_2 and fluids. Immediate symptoms were followed by signs of haemolysis. Pre- and post-transfusion antibody screens were negative and blood was issued electronically. Although the DAT was positive (IgG coating) on both the pre- and post-transfusion samples, an eluate was non-reactive. Anti-C and a pan-reactive autoantibody were detected using a 2 stage enzyme; a retrospective IAT crossmatch was initially incompatible, but the antibody was not identified. Three weeks later a further incompatible unit was found. Further testing showed the patient's plasma to be positive against HLA A28, B7 and B17 (Bg^c, Bg^a, Bg^b, respectively). The implicated donor was typed as HLA-B57 (a subgroup of B17); the serological incompatibility was not confirmed by IBGRL, but a CDC crossmatch was positive. Although the serological picture is not clear, this appears to be an acute haemolytic transfusion reaction due to Bg antibodies.

Learning points

- The patient's clinical condition can obscure the diagnosis of an acute haemolytic reaction.
- Testing an eluate is an important part of investigating an HTR.
- Presence of an alloantibody does not prove cause and effect.

Serological findings – DHTR *n* = 39

Kidd (Jk) and Rh alloantibodies were the most common, present in 18/39 and 19/39 (46 and 49%) cases respectively, either singly or in combination with other specificities.

Table 39 shows details of the serology, laboratory signs and time interval by case, and Table 40 shows the specificity of new antibodies detected post transfusion, by blood group system.

Table 39
Serology, laboratory signs and timing of reaction

Case no.	New antibody(ies) in plasma	Antibodies in eluate	Comments	Days post transfusion
1	K	Not performed	Hb↓ bilirubin↑; dark urine	7
2	C	None	Hb↓ bilirubin↑ creatinine↑	8
3	Jk^a	Not performed	bilirubin↑	17
4	K, c	Not performed	Hb↓ bilirubin↑ dyspnoea, hypotension	13
5	Jk^a	Jk^a	No signs or symptoms	14
6	Jk^a, K, warm auto	Jk^a	Hb↓	3
7	Jk^b	No specificity	Hb↓ bilirubin↑; fever during transfusion; known anti-K	10
8	K	Not performed	No signs or symptoms; died unrelated	7
9	C, E, auto-D	E	Hb↓ bilirubin↑. Normal D gene confirmed – presumably auto anti-D	13
10	Jk^a, E	Not performed	Hb↓ bilirubin↑↑; dyspnoea, hypotension, fever	10
11	E	E	No signs or symptoms; prob. primary response	10 weeks
12	Jk^a	None	bilirubin↑, poor Hb increment	16–18
13	D	Not performed	bilirubin↑	5–8
14	Jk^a	Not performed	Hb↓ bilirubin↑	17
15	c	Not performed	Hb↓	14
16	C	Not performed	no Hb increment. Known anti-Jk^a	?26
17	c	c	Hb↓ Hburia (?UTI)	4
18	Lu^a	Jk^a	No signs or symptoms	54
19	Jk^b	None	Hb↓ bilirubin↑ creatinine↑; known anti-c	7
20	Jk^a	Jk^a	Hb↓	22
21	Fy^a	Not performed	Hb↓ bilirubin↑	6
22	Jk^a	Jk^a	Hb↓	10
23	C, E	None	No Hb increment	??
24	Jk^a	Not performed	No signs or symptoms	10
25	Jk^b	Jk^b	Hb↓ bilirubin↑	23
26	Jk^a, C^w, auto	Jk^a + panagg	Hb↓ bilirubin↑	6
27	c	Not performed	Hb↓ bilirubin↑ LDH↑; known anti-E	17
28	E+K	K	No signs or symptoms	16
29	Jk^a	Jk^a	Hb↓	8
30	None	None	Hb↓ Hburia, methaem	7
31	E	E	bilirubin↑ creatinine↑	2–3
32	S (detected previously elsewhere)	Not performed	Hb↓↓ bilirubin↑; known anti-M (+S); also ?hyperhaemolysis	1–2
33	K	K	No signs or symptoms	74
34	Fy^a, Fy3, S	Not performed	Hb↓↓ dark urine, LDH↓, ?hyperhaemolysis	7
35	S, Jk^b	S+Jk^b	No signs or symptoms. Known anti-E	12–14
36	Fy3	Inconclusive	Hb↓↓ bilirubin↑↑ dark urine. Known anti-Fy^a+Jk^b+M. SCD	2
37	Jk^b	Jk^b M	Hb↓↓ bilirubin↑↑ Hburia	8
38	D	D	No signs or symptoms	28
39	E, c, A_1, K, S, Fy^b, Jk^b	None	No signs or symptoms; platelet transfusions only	? 2 months

Serological techniques used – DHTRs only

Antibody screening was undertaken using a variety of automated systems, broadly representative of those used routinely in the UK. Of those answering the question, 19 undertook an IAT crossmatch (7 of these had a positive antibody screen), 3 an immediate spin, and 14 electronic issue.

Use of eluates

In 24/39 (62%) of cases an eluate was made from the patient's post-transfusion red cells and tested for antibody. This is similar to last year (63%). Of these eluates, 17 were performed in reference laboratories and 6 in-house (one unknown). In 16 cases (67%) a specific antibody(ies) was identified. In 1 case (D18), anti-Jk^{a} was detectable only in the eluate.

Retrospective testing findings

Retrospective testing of the pre-transfusion sample was undertaken in house in 7 (18%) cases: the same results were obtained in all 7 cases. However, in 4/7, no different or additional testing was undertaken, and none was confirmed by a reference centre. In most cases the pre-transfusion sample had been discarded, even though in 2 cases the reaction occurred within 3 days of transfusion.

DHTR cases

Case D34

Major morbidity in patient with sickle cell disease

A female patient with SCD and a history of transfusion but no alloantibodies had an 8 unit red cell exchange. Seven days later she returned to the ED with several signs of severe haemolysis, her Hb having fallen from 10.4 g/dL to 4.2 g/dL. The reporter queries an element of hyperhaemolysis as well as DHTR. The DAT was strongly positive with IgG coating, and anti-Fy^{a}, -Fy3 and -S were identified in the plasma, but no eluate was performed. The patient required ITU admission but made a full recovery. As a result of this reaction, the hospital is changing its transfusion policy for patients with SCD, to give Fy(a-) red cells to Fy(a-) individuals.

Case D32

A 7-year-old patient with SCD and a historical record of anti-M, not currently detectable, was transfused with 2 units of M negative red cells (Rh and K matched). The Hb fell from 8.6 g/dL immediately post transfusion to 4.1 g/dL 48 hours later, 1 g/dL lower than the pre-transfusion Hb of 5.1 g/dL. Other signs of haemolysis were dark urine, and rising bilirubin and LDH. The patient was transferred to a second hospital which the patient had attended 2 months earlier, when anti-S had been identified in addition to anti-M. One of the units transfused had been S positive, and the patient was found to have a positive DAT, though an eluate was non-reactive. Anti-S and anti-M became detectable 3 days post transfusion. This appears to be a case of HTR due to anti-S combined with hyperhaemolysis.

Learning points

- 'New' patients with sickle cell disease are likely to have been tested and possibly transfused elsewhere. They are at higher than average risk of developing red cell antibodies and hospitals should actively seek a transfusion and antibody history.
- Where care is shared between hospitals there should be a system for communicating important serological information between sites.

Case D30

No specificity identified

A woman required an emergency transfusion of 5 units of red cells and 2 units FFP at delivery. Nine days later her DAT was weakly positive, Hb had fallen by 3 g/dL, haptoglobins became undetectable and LDH was raised. The blood service identified weak anti-C by enzyme techniques only and obtained a strong reaction with a single panel cell, but were unable to identify a specificity. The patient had received a massive transfusion at delivery several years earlier.

Table 40
DHTRs – New specificities by blood group system

Antibody specificity by blood group system	No. cases	Sole *new* antibody
Kidd		
Jk^a	12	8
Jk^b	6	4
Rh		
C	4	
E	7	2
c	5	2
D	2	3
C^w	1	2
Auto anti-D	1	
Kell		
K	7	3
Duffy		
Fy^a	2	1
Fy^b	1	
Fy3	2	1
MNSs		
S	4	1
M	1	
Other		
Lu^a	1	
A_1	1	

COMMENTARY

- Antibodies not commonly associated with haemolytic transfusion reactions were identified in several patients following AHTRs. It is likely in some cases that these antibodies were not responsible for the reaction.
- Patients with sickle cell disease are once again prominent in both AHTR and DHTR cases. These patients are particularly vulnerable to haemolytic reactions as they have a higher incidence of sensitisation, are prone to episodes of hyperhaemolysis and have clinical symptoms which can mask HTRs. In addition they often move between different treatment centres. As the result of a serious DHTR, one centre has changed its policy to routinely provide Fy(a-) blood to Fy(a-) patients with SCD.
- HLA antibodies (Bg) were apparently the cause of a severe AHTR. Although Bg antibodies are usually benign, there have been a few associated cases of HTR reported in the literature.[35,36]
- In 3 cases (one acute, and 2 delayed), an antibody specificity was identified in an eluate made from the patient's post-transfusion red cells which had not been detected in the plasma. This highlights the vital role played by this test in the investigation of an HTR.

RECOMMENDATIONS

There are no new recommendations this year; however, previous recommendations remain relevant and those in the table below are pertinent to this year's report. The second, recommending a national register of patients with antibodies, is now redirected to the newly formed IT subgroup of the NBTC and its counterparts in Scotland, Wales and Northern Ireland.

Previous recommendations relevant to this year's report

Year first made	Recommendation	Target	Progress
2008	Prior to transfusion, an antibody history and a transfusion history should be actively sought for previously unknown patients with sickle cell disease. This must include contacting the local blood service reference laboratory as well as any other hospitals the patient has attended.	**Hospital blood transfusion laboratories**	The Shared Care document is now nationally available and can be used for patients with sickle cell disease. www.sicklecellsociety.org/pdf/CareBook.pdf
2008	A national register of patients with antibodies, linked between the red cell reference laboratories, should be considered.	**UK blood services**	For 2010 this task is directed to the newly formed IT subgroup of the NBTC.
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 63% of cases this year and last year, compared with 35% in 2006 and 50% in 2005, suggesting sustained 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).