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, a rise in lactate dehydrogenase (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, a 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	**58**	*Implicated components*		*Mortality/morbidity*	
		Red cells	**58**	Deaths due to transfusion	**1**
		FFP	**0**	Deaths *probably/likely* due to transfusion	**0**
		Platelets	**0**	Deaths *possibly* due to transfusion	**0**
		Other (granulocyte)	**0**	Major morbidity	**2**
		Unknown	**0**		

Gender		*Age*		*Emergency vs. routine and core hours vs. out of core hours*		*Where transfusion took place*	
Male	**19**	≥18 years	**57**	Emergency	**13**	A&E	**2**
Female	**38**	16 years to <18 years	**0**	Routine	**43**	Theatre	**9**
Not known	**1**	1 year to <16 years	**1**	Not known	**2**	ITU/NNU/HDU/recovery	**7**
		>28 days to <1 year	**0**				
		Birth to ≤28 days	**0**	In core hours	**45**	Wards	**36**
		Not known	**0**	Out of core hours	**9**	Community	**0**
		Total	**58**	Not known	**4**	Outpatient/day unit	**3**
						Not known	**1**

Alloimmunisation

This is the first year that SHOT has collected data from cases in the category of alloimmunisation.

Definition

Alloimmunisation occurs when, after a transfusion, there is demonstration of clinically significant antibodies against RBCs that were previously absent (as far as is known) and when there are no clinical or laboratory signs of haemolysis. This term is categorised as a delayed serological transfusion reaction (DSTR) by the ISBT.

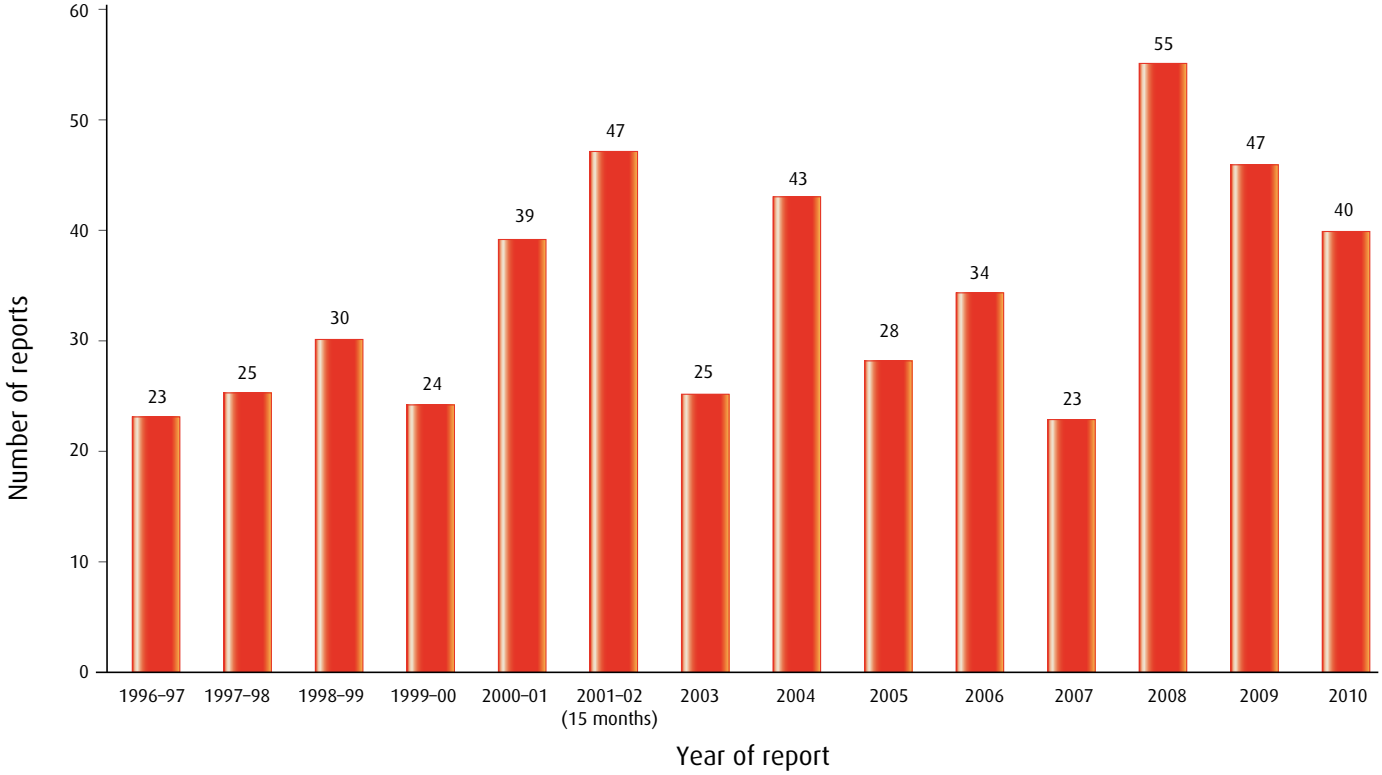
Development of an antibody with positive DAT or development of haemolysis should be reported in the HTR category.

A minimum data set is collected, but it was clear from the descriptions given that at least some of the cases reported as alloimmunisation had positive DATs and would currently fall into the SHOT definition of DHTR. For this reason the two categories of DHTR and alloimmunisation have been combined for this year's report. All 18 cases reported as alloimmunisation, plus a further 7 cases reported as DHTR with no clinical or laboratory signs of haemolysis, are summarised in Table 41.

Haemolytic transfusion reactions

There were a further 27 cases reported as DHTRs and 6 as AHTRs, giving a total of 58 cases in this chapter.

Figure 10
Number of cases of HTR reviewed since 1996



NB The graph does not include the 18 cases of alloimmunisation reported in 2010.

Mortality and morbidity

Acute haemolytic transfusion reactions (AHTR) *n* = 6

A paediatric patient with sickle cell disease died as a direct result of hyperhaemolysis following transfusion (imputability 3). The hyperhaemolysis episode was noted 13 days post transfusion and was exacerbated by a further transfusion. The remaining 5 cases of AHTR suffered minor morbidity only.

Case 1

Death due to hyperhaemolysis

A paediatric patient with sickle cell disease had an Hb of 8.1 g/dL and received 1 unit transfusion prior to a tonsillectomy. Thirteen days later she was admitted unwell with an Hb of 5.4 g/dL. Following a further 2 units of red cells, she deteriorated and her repeat Hb was 4.8 g/dL. She was transferred to a paediatric ITU at a specialist centre, but on arrival through A&E received a unit of flying squad group O RhD negative red cells. Hyperhaemolysis was suspected and she received IVIg and methylprednisolone. Although her Hb was initially 6.6 g/dL following receipt of the unit of flying squad, within 6 hours it had fallen to 3.8 g/dL and she had developed multi-organ failure (MOF) and acute respiratory distress syndrome (ARDS). The patient died the same day.

Learning point

- Hyperhaemolysis is an uncommon but well-documented serious complication of transfusion in sickle cell disease in which there is destruction of both autologous and transfused red cells. If possible, further transfusion should be avoided since this may exacerbate the haemolysis and lead to a protracted course or even death. The use of IVIg and/or steroids should be considered as a means of correcting the anaemia.

Delayed haemolytic transfusion reactions (DHTRs), including alloimmunisation *n* = 52

Two cases met the definition of major morbidity: 1 required admission to HDU 5 days post transfusion and another had impaired renal function 12 days post transfusion. Both reactions were clearly related to the transfusion and both patients made full recoveries.

The remaining 25 cases of DHTR suffered minor morbidity only. A further 25 cases, including those reported in the alloimmunisation category, had no clinical or laboratory signs of haemolysis, except for a positive DAT in some cases.

Timing of reaction in relation to the transfusion

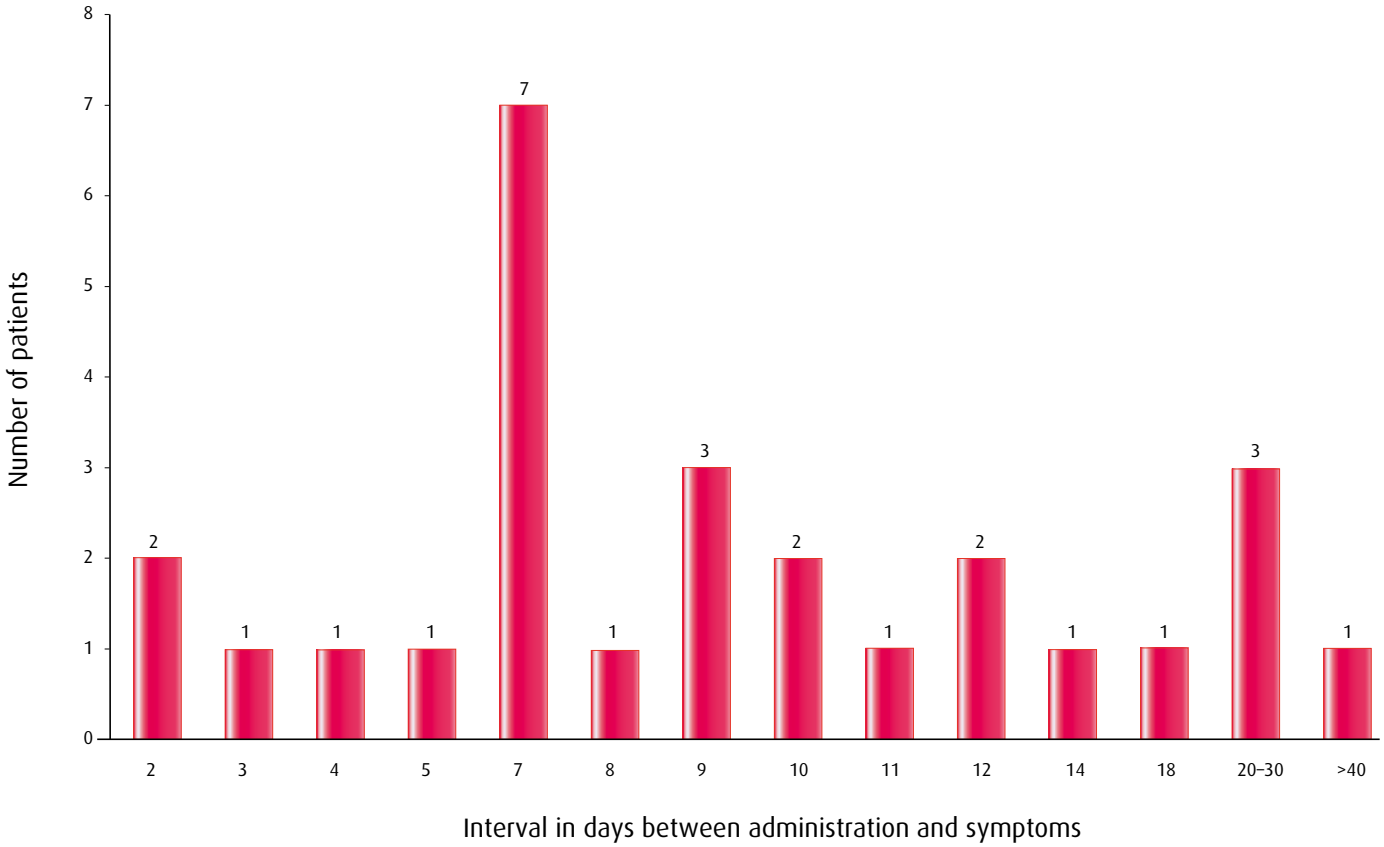
AHTR

Excluding the patient who died due to hyperhaemolysis, 4 of the reactions occurred during the transfusion, which was stopped on the advice of a doctor, and 1 occurred shortly after the transfusion was finished.

DHTR

Figure 11 shows the reported interval in days between the implicated transfusion and the clinical signs of a DHTR. The median time interval was 9 days, with a range of 2 to 41. New antibodies were found between 4 days and 3 months after transfusion in the 25 asymptomatic cases.

Figure 11
Interval in days between administration of the implicated transfusion and signs or symptoms of a DHTR



Serological findings – AHTR *n* = 6

This year no reactions were reported due to ABO incompatible platelet transfusion – all reactions were associated with red cell transfusions.

No alloantibodies were detected in the plasma of the patient who died following hyperhaemolysis. Anti-Jk^{a} was associated in 2 cases, including 1 where it was only detectable post transfusion in an eluate. In 1 case, an antibody to a low frequency antigen was suspected, in another anti-Co^{b} was missed in the IAT crossmatch and in the last case no specificity was assigned.

Case 2

Reaction possibly due to an antibody to a low frequency antigen

A patient was being transfused following a PPH. The transfusion was stopped when the patient showed signs of fever, chills, rigors and tachycardia. There was no evidence of haemolysis. However, the implicated unit (originally released by EI), was found to be incompatible on retrospective crossmatch; the antibody screen, DAT and eluate were all negative, and an antibody to a low frequency antigen was suspected.

Case 3

Reaction possibly due to enzyme-only anti-Jk^{a}

The patient twice spiked a temperature during a transfusion for chronic anaemia before it was stopped. Anti-Jk^{a} was detected retrospectively in the pre-transfusion sample by enzyme technique only, and the unit was confirmed as Jk(a+); the DAT was positive pre and post transfusion, but an eluate was non-reactive and there was no evidence of haemolysis.

These two cases demonstrate how difficult it is to classify ATRs where antibodies are detected retrospectively, but the transfusion is stopped early and no evidence of haemolysis is noted. It is not possible to be sure whether the antibodies are the cause of the reaction or coincidentally present.

Case 4

Anti-Jk^{a} only detectable in an eluate

A patient suffered fever and rigors and became hypertensive shortly after a transfusion for chronic anaemia. The post-transfusion DAT was positive and anti-Jk^{a} was detected in an eluate made from the patient's red cells but not in the plasma. The Hb fell back to the pre-transfusion level within 4 days of the transfusion.

Case 5

Anti-Co^{b} missed in crossmatch

A patient requiring transfusion for chronic anaemia had anti-E, anti-Co^{b} and an autoantibody, plus previously detected anti-Jk^{a}, -C^{w} and -Lu^{a}. The Blood Service provided 3 units of crossmatch compatible E-, C^{w} -, Jk(a-) red cells. During transfusion of the second unit, the patient had dyspnoea, headache and chills, and the transfusion was stopped; subsequently, signs of haemolysis were noted, including a fall in Hb and a raised bilirubin. Retrospective testing found 2 of the 3 units to be Co(b+) and incompatible in the IAT crossmatch. Policy at the time was to issue crossmatch compatible units rather than Co^{b} type, due to limited availability of a Co^{b} typing reagent. Anti-Co^{b} reagent was actually available at the time and the policy has since been changed to phenotype units for Co^{b} whenever possible.

Case 6

No specificity identified

A patient with anti-D, -C, -E, -K, -Jk^{a} and -M was provided with 3 units of antigen negative, crossmatch compatible red cells for chronic anaemia. During the third unit, the patient suffered fever, back pain and vomiting, and the transfusion was stopped; subsequently signs of haemolysis were noted, including a fall in Hb and a raised bilirubin. Retrospective crossmatching gave the same result, and an eluate gave weak non-specific reactions. The International Blood Group Reference Laboratory (IBGRL) confirmed the antibodies previously identified, plus further positive reactions, with no specificity assigned.

Learning point

- If a typing reagent is available, antigen-negative units should be provided for patients with anti-Co^{b}, since serological crossmatching is more prone to error.

Serological findings – DHTR

A total of 44 new antibodies were identified in 27 patients. Kidd and Rh alloantibodies were again the most common, present in 15/27 (56%) and 13/27 (48%) cases, respectively. Multiple specificities were identified in 43% of cases.

Table 39
Serology, laboratory signs and timing of reaction

Case number*	New antibody (ies) in plasma	Antibodies in eluate	Comments	Days post transfusion
1	M+S+?	Not done	Dark urine; jaundice; Hb↓; bilirubin↑; known anti-c	8
2	Jk^{a}	Jk^{a}, M	Poor/absent increment in Hb; spherocytes	7
3	E, Jk^{a}	DAT negative; no eluate	Fever; headache; patient 'felt off'; bilirubin↑; Hb↓	16
4	C+Jk^{b}	DAT positive C3; no eluate	Bilirubin↑; Hb↓; LDH↑; haemoglobinuria; known anti-E+S DHTR followed by AHTR	14
5	E+K+Jk^{b}	Not done	Hb↓; bilirubin↑↑	9
6	Jk^{a}	Jk^{a}	Hb↓; DAT positive IgG+C3	7
7	K+E+ enz-only c	Not done	Hb↓ but chronic anaemia; bilirubin rising but still normal	41
8	E	Not done	Hb↓; spherocytes	27
9	E	Not done	Hb↓↓; bilirubin↑↑	25
10	E	Not done	Hb↓	20
11	Jk^{b}	Not done	Hb↓; bilirubin↑↑; haemoglobinuria; SCD with known anti-Jk^{b} from 2003 from another hospital	7
12	E+Lu^{b}+auto	E+Lu^{b}+auto	Hb↓↓; bilirubin↑↑; spherocytes; fever, chest pain	10
13	Jk^{a} +Lu^{a}	Not done	Hb↓; bilirubin↑	14
14	Fy^{a}	Fy^{a}	Known anti-E+K; Hb↓	5–7
15	E+c+Fy^{a}	Not done	DAT positive pre and post transfusion Hb↓, but chronic anaemia	11
16	Jk^{a}	Not done	Hb↓; bilirubin↑; creatinine↑	12
17	Jk^{a} + E	Not done	Hb↓; bilirubin↑; LDH↑	7
18	E	Not done	No Hb increment	4
19	Jk^{a}	Not done	Slight rise in bilirubin; death unrelated	4 or 10
20	Jk^{a}	Jk^{a}	Hb↓	10
21	Jk^{b} + Fy^{b}	Auto anti-C	Hb↓; bilirubin↑; dark urine; spherocytes; known anti-c+M	9
22	D	D	Poor Hb increment; spherocytes	7
23	Jk^{a}	Not done	Hb↓; bilirubin↑	7
24	S, Fy^{a}, N, ?	S+ Fy^{a}	Hb↓↓; bilirubin↑↑; haemoglobinaemia; admitted to HDU; known anti-E+Cw+K+Lea+?	5–9
25	Jk^{a} + Fy^{a}	Jk^{a} + Fy^{a}	Hb↓; bilirubin↑; spherocytes	3
26	E	E	Hb↓ but acute bleeding	11
27	Jk^{b}	Not done	Hb↓; bilirubin↑; haemoglobinaemia; spherocytes	10

The case numbers in this table do not correspond to those used in the case studies.
SCD, sickle cell disease.

Table 40
Summary of the cases by antibody specificity

Antibody specificity by blood group system	No. of cases	Sole new antibody
Kidd		
Jk^a	10	5
Jk^b	5	3
Rh		
D	1	1
C	1	0
E	11	5
c	2	0
Kell		
K	2	0
Duffy		
Fy^a	4	1
Fy^b	1	0
MNSs		
M	2*	0
N	1	0
S	2	0
Other		
Lu^a	1	0
Lu^b	1	0
Total	**44**	**15**

** One example of anti-M identifed in eluate only.*

There were 35 cases showing no evidence of haemolysis, 7 reported as DHTR and 15 as alloimmunisation. These cases are summarised in Table 41.

Table 41
New antibodies with or without positive DAT but no clinical or laboratory signs of haemolysis

Specificity	No. of cases
K	3
Jk^a	7
Jk^b	3
Fy^b	1
Lu^a	1
M	2
D	1
E	2
c	2
C+D+E	1
$C+Jk^a+S$	1
$K+Jk^a$	1

Direct antiglobulin tests (DATs), use of eluates and referral to a Blood Service reference laboratory

The DAT was positive in 24 cases and negative in 1; 12 went on to test an eluate, including 1 who stated that a DAT had not been undertaken. Although 8 reporters did not answer either question, this appears to represent a decrease from last year in the number of investigations that included an eluate. Antibody identification was undertaken or confirmed by a reference laboratory in 20/34 cases and it is possible that additional testing, including an eluate, was undertaken by the reference laboratory without the reporter being aware. In 2 cases, 1 acute and 1 delayed, an antibody was only detectable in the eluate.

Learning point

- Testing an eluate is an important part of investigating an HTR, and may be the only way of identifying any or all of the antibodies present.

Case 7

A classic DHTR followed by a preventable AHTR

A patient with anti-E+S required a 2-unit red cell transfusion perioperatively. Fourteen days later, the Hb had fallen by 2 g/dL, the bilirubin had risen from 6 to 26 and the LDH had risen from 294 to 4590. A panel showed anti-E+S plus a further unidentified antibody; the DAT was negative. Two units of E-S- crossmatch compatible red cells were given. During the second unit, 'blood' was noted in the catheter bag and the transfusion was stopped. Anti-Jk^{b} was identified using a different panel and a review showed that this specificity could not be excluded in the pre-transfusion panel. Samples tested 2 days later by a reference laboratory confirmed a weakly positive DAT and the presence of anti-C and -Jk^{b} in addition to E+S; both units were confirmed as C+, Jk(b+). Although the transfusion was stopped, there was no clinical or laboratory evidence of haemolysis, apart from the 'blood' in the catheter bag.

This appears to be a case of classic DHTR possibly followed by an AHTR, the latter being preventable. The laboratory has changed its protocol relating to antibody identification and now refers samples to the Blood Service reference laboratory if antibodies cannot be excluded.

Learning point

- Systematic exclusion of all antibodies of likely clinical significance is an essential part of the antibody identification process and may necessitate the use of further red cells or techniques.

Case 8

Symptoms of DHTR attributed to sickle cell crisis

A patient with HbSC was transfused 2 units of red cells post emergency Caesarean section. Ten days later she presented with an Hb of 6.7 g/dL, fever, hypoxia and pain due to presumed sickle cell crisis. The patient underwent an exchange transfusion (ET) of 6 units of red cells but still had fever, pain and dyspnoea, causing her Hb to drop below pre-transfusion levels and with evidence of haemolysis noted on a blood film. A transfusion reaction investigation was not undertaken until several days later because all the symptoms were attributed to sickle cell crisis. The DAT was positive with anti-Jk^{a} detectable in the eluate on the pre- and post-exchange samples. Four out of the 6 units used for the ET were Jk(a+). The anti-Jk^{a} became detectable in the plasma after a couple of days.

Had this been diagnosed as a DHTR sooner, the 6-unit exchange may have been unnecessary and any red cells transfused could have been typed for Jk^{a}.

Learning point

- A DHTR should be considered as a diagnosis in patients with sickle cell disease presenting with crisis up to 14 days post transfusion.

Case 9

A known antibody from a different hospital, no longer detectable, causes a DHTR

Seven days after a 6-unit ET, a patient with sickle cell disease had a falling Hb, a rising bilirubin and haemoglobinuria. The DAT was positive and anti-Jk^b was identified in the plasma; however, an eluate was not tested. Subsequent investigation revealed that anti-Jk^b had been identified in 2003 at a different hospital. This laboratory has since changed its policy to issue red cell antibody cards to all patients with newly identified antibodies and to acquire a transfusion history for patients on long-term transfusion support.

COMMENTARY

Patients with sickle cell disease were again the subject of acute and delayed transfusion reactions. One patient died following an episode of post-transfusion hyperhaemolysis; another probably had a DHTR that was overlooked because all of the symptoms were attributed to sickle crisis and further transfusion of antigen-positive red cells could have been avoided; a third could have avoided a DHTR if a transfusion history had been known or if the patient had been carrying an antibody card. A distinction between a sickle crisis and immune haemolysis can be difficult but is aided by serial Hbs, reticulocyte counts, HbS/A% and urinary Hb high-performance liquid chromatography (HPLC).

There is not always any laboratory evidence of haemolysis in the cases reported as AHTRs, although red cell antibodies were detected in all cases. It is difficult to be sure about the relationship between the reaction and the antibody.

This is the first year that data relating to simple alloimmunisation have been collected. There was a clear overlap between the cases reported as DHTR and those reported as alloimmunisation. The definitions may have to be reviewed for future years.

In 3 cases (1 acute and 2 delayed) an antibody was only detectable in an eluate made from the patient's red cells. This is a recurring theme, but despite this an eluate was not tested in the majority of cases.

Recommendations

- Clinicians looking after patients with sickle cell disease should be aware that symptoms of a sickle cell crisis occurring up to 14 days post transfusion could be due to a DHTR, and should send samples for serological investigation.

  Action: HTCs

- Clinicians should be aware of the existence of hyperhaemolysis in sickle cell disease in which the Hb drops to levels lower than pre transfusion. Urine Hb HPLC can be useful to demonstrate the presence of both HbS and HbA and advice on the use of IVIg and/or steroids should be sought from a specialist unit or the Blood Service.

  Action: HTCs

For active recommendations and an update on their progress, please refer to the SHOT website.