14. Haemolytic Transfusion Reactions (HTR) and Alloimmunisation

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Definitions

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 lactate dehydrogenase (LDH), positive direct antiglobulin test (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.

Alloimmunisation (optional reporting) is defined as demonstration of clinically significant antibodies post transfusion which were previously absent (as far as is known) and when there are no clinical or laboratory signs of haemolysis.

DATA SUMMARY
Total number of cases: 94

Implicated components		Mortality/morbidity	
Red cells	92	Deaths *probably/likely* due to transfusion	0
FFP	0	Deaths *possibly* due to transfusion	0
Platelets	1	Major morbidity	11
Other (IVIg)	1		
Unknown	0		

Gender		Age		Emergency vs. routine and core hours vs. out of core hours		Where transfusion took place	
Male	35	≥ 18 years	92	Emergency	9	ED	2
Female	59	16 years to <18 years	0	Routine	57	Theatre	6
Not known	0	1 year to <16 years	2	Urgent	22	ITU/NNU/HDU/Recovery	15
		>28 days to <1 year	0	Not known	6	Wards	57
		Birth to ≤28 days	0			Community	2
		Not known	0	In core hours	0	Outpatient / day unit	8
				Out of core hours	0	Not known	4
				Not known/ applicable	94		

Change in definitions for 2012

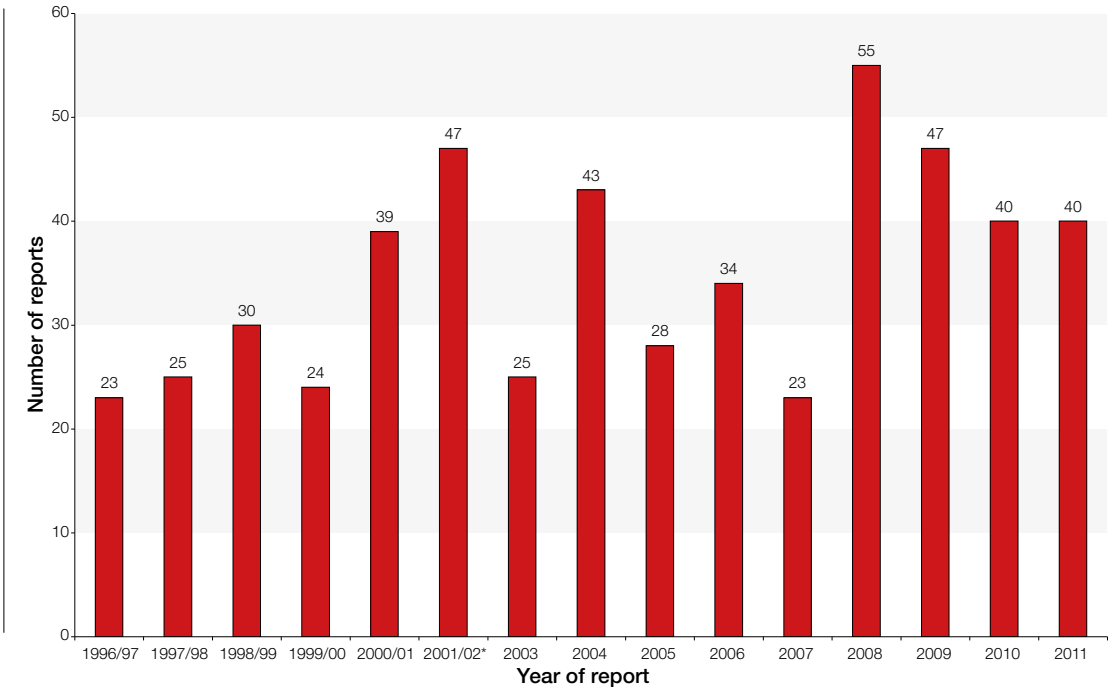
Alloimmunisation is an optional reporting category and a minimum data set is collected. It has become clear from the descriptions given that at least some of the cases had positive DATs and would fall into the current SHOT definition of Delayed Haemolytic Transfusion Reaction (DHTR), and for this reason the 2 categories are being reported in a combined chapter again this year. However, a positive DAT alone without supporting biochemical or clinical signs is not indicative of haemolysis, and therefore, the definition of HTR and alloimmunisation will change in 2012; development of an antibody with or without a positive DAT, but without clinical or biochemical signs of haemolysis will be classed as alloimmunisation.

Number of cases

There were 94 cases reported in this chapter, 54 reports of alloimmunisation and 40 reports of HTR.

Of the 40 HTR, there were 6 reports of DHTR with no clinical or laboratory signs of haemolysis, and these are summarised in Table 14.3. The remaining 34 cases of HTR included 10 reported as acute and 24 as delayed, although in at least 2 cases, the patient suffered both acute and delayed reactions.

Figure 14.1 Number of cases of HTR reviewed since 1996



** 2001–2002 figures covered a 15 month period*

Acute haemolytic transfusion reactions (AHTR) n=10 (including 1 that was also DHTR)

Major morbidity n=2

There were 2 cases of major morbidity, both with impaired renal function; one required intensive therapy unit (ITU) admission but recovered, whilst the other died of underlying illness.

Case 1

ITU admission following an acute and delayed HTR

A young female patient with a history of multiple transfusions was admitted with menorrhagia and an Hb of 7.8g/dL, having been transfused 7 days earlier. The bilirubin and creatinine were both raised and the DAT was positive. Anti-Fy^b was identified in addition to a historically known anti-s. Two units of s-, Fy(b-) red cells were transfused. During the 2nd unit, the patient had rigors and difficulty breathing, and the transfusion was stopped. The creatinine continued to rise and the patient was admitted to ITU. The Blood Service reference laboratory confirmed the presence of anti-Fy^b in the plasma and in an eluate. A weak anti-Jk^a was also identified in the plasma by enzyme techniques only. Both units implicated in the acute reaction were Jk(a+), as were at least 2 of the 4 transfused 7 days earlier. The patient remained in ITU for a week, and was discharged with a creatinine of 158 micromol/L.

This appears to be a combination of an acute haemolytic transfusion reaction due to anti-Jk^a, and a delayed reaction due to anti-Fy^b and probably also anti-Jk^a.

Case 2

Patient with an antibody to high frequency antigen requires incompatible red cells in an emergency

An elderly male patient with carcinoma (Ca) colon was admitted with gastrointestinal (GI) bleeding. He was known to have the rare Rh phenotype D--, and anti-Rh17 (anti-Hr_o) in his plasma. He was transfused with 3 units frozen/thawed compatible units but continued to bleed down to a Hb of 5.0g/dL. The decision was taken to transfuse 2 units of incompatible rr K negative red cells, with IVIg and prednisolone cover. The transfusion was uneventful, but signs of haemolysis, including renal impairment, developed a few hours post transfusion and progressed over the next 3 days. The patient was already very unwell and died of his underlying illness.

Learning point

- Additional sensitive techniques are important in elucidating all antibodies present when investigating a haemolytic transfusion reaction.

Delayed haemolytic transfusion reactions (DHTR), n=24

Major morbidity n=9

There were 9 cases of major morbidity, including 5 in patients with sickle cell disease, which were all complicated by hyperhaemolysis and shared care; these are further discussed in the new chapter on haemoglobin disorders (Chapter 23).

In another case a patient's Hb dropped to 3.5 g/dL 11 days post transfusion, although it is not clear how much the patient's underlying condition contributed to this. Another 3 cases resulted in renal impairment, with one patient being admitted to ITU and another dying from their underlying illness.

The case numbers in brackets in some of the vignettes below correlate with those in Table 14.1.

Case 3 (D1)

Delayed and acute reaction to different antibodies

An elderly male patient, with known anti-E+Fy^b was admitted with acute blood loss and transfused on several occasions over a 10 day period. 15 days after admission, the patient was on ITU and bleeding heavily; several units of E-Fy(b-) red cells were incompatible, and patient was transfused with E- K-, Fy^b untyped, serologically compatible red cells. Further samples were sent to the Blood Service reference laboratory, where anti-Fy^b was detected in an eluate, and 6 units of crossmatch compatible, E- K-, Fy(b-) red cells were issued. 4 days later anti-Jk^a was also identified in the plasma. Bilirubin peaked at 80 micromol/L one day later. Creatinine was rising and peaked at 238 micromol/L one day after the transfusion of Fy(b+) red cells. The patient was probably having a delayed HTR due to anti-Jk^a, and possibly an acute HTR due to anti-Fy^b, but given the significant co-morbidities, the clinical team thought it unlikely that the transfusion reaction contributed to the death of the patient a week later.

Case 4 (D11)

Delayed haemolysis with possible autohaemolysis

Patient with Ca colon and chronic anaemia who presented with Hb 6.7 g/dL was transfused 5 units of red cells over 3 days and discharged with an Hb of 10.3 g/dL. 11 days later the patient represented in A&E with Hb of 3.5 g/dL, positive DAT, raised bilirubin and haemoglobinuria. Samples were sent to the Blood Service reference laboratory and anti-K plus an autoantibody were identified. Four of the 5 units transfused were K positive. The post-reaction Hb was considerably lower than the pre-transfusion Hb, however the initial Hb of 6.7 g/dL was recorded on a point of care testing (POCT) device and was not checked in the laboratory, suggesting that this could have been falsely high, or that there was an element of autohaemolysis involved in addition to immune red cell destruction due to the anti-K.

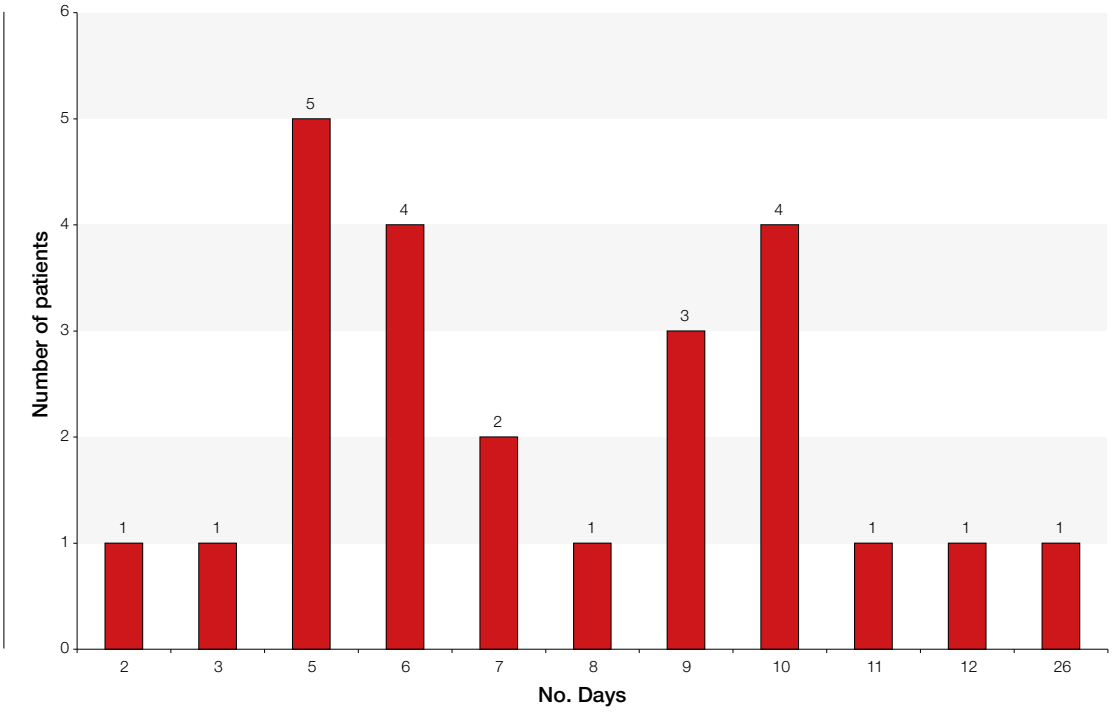
Timing of reaction in relation to the transfusion

AHTR

Eight of the 10 reactions occurred during the transfusion, with a range of 37 to 200mL of red cells being transfused. The other two occurred within 24 hours of the transfusion.

DHTR

Figure 14.2 Interval in days between administration of the implicated transfusion and signs or symptoms of a DHTR



Signs of haemolysis were recorded between 2 and 26 days post transfusion, with a median of 7 days.

Alloimmunisation

Newly detected antibodies were reported between 3 and 410 days following transfusion of between 1 and 6 units of red cells.

Serological findings – AHTR n=10

Nine patients reacted to red cells and 1 probably reacted to platelets.

No causative antibodies were detected in 4 cases and there was no clear explanation for the reaction. Two cases were of low imputability: in one case (Case 5 below), anti-Jk^a had been previously detected in a different hospital and the units transfused were Jk(a+), but there was no evidence that it caused the reaction; in another, the only sign of reaction was jaundice the day after transfusion.

Case 5

Possible reaction due to undetectable anti-Jk^a known at a previous hospital

A patient with chronic anaemia required urgent transfusion prior to liver surgery. Anti-K,anti-S, and anti-Kp^a were identified. Antigen-negative units were given, but the transfusion was stopped when the patient developed a fever during the 2nd unit. A transfusion history was then obtained from another hospital, where the patient had a record of anti-Jk^a. The bilirubin rose transiently from 23 to 88 micromol/L and the Hb dropped by 2 g/dL. The 2 transfused units were both Jk(a+), but anti-Jk^a was not detectable in a post transfusion sample (confirmed by a reference centre) and the DAT was negative.

It is not clear whether this was a reaction due to undetectable anti-Jk^a or whether the symptoms were due to the patient's underlying liver disorder.

There was one case of an antibody to a high frequency antigen, where incompatible blood was transfused in an emergency, and another of an antibody to a low frequency antigen of undetermined specificity. In one case a cold autoantibody with a high thermal range caused a reaction in the same patient on 2 separate occasions (Case 7 below). One patient with known anti-Fy^{b} received Fy(b+) red cells in an emergency and also had a newly developed but unidentified anti-Jk^{a}.

The 10th patient (see Case 6 below) was group A, post group O/A double cord haemopoietic stem cell transplant (HSCT), who received both group O red cells and platelets, and the reaction was probably due to anti-A from the platelets.

Case 6

Probable anti-A from group O platelets

A patient with acute myeloid leukaemia (AML), blood group A RhD positive, received 2 pools of group O high-titre negative platelets, followed by group O red cells, one year post double cord allograft (one group O and one group A). Within 30 minutes of commencing the red cell transfusion, he developed rigors and fever. The rigors resolved with hydrocortisone and chlorphenamine. His Hb dropped from 9.6 to 4.8 g/dL after transfusion, but was 7.3 g/dL on a sample taken a few hours later, casting some doubt on the validity of the result of 4.8. The bilirubin rose from 2 to 28 micromol/L. The reference laboratory confirmed the ABO group as mixed field A/O, with anti-A detectable in the reverse group, DAT positive (IgG and C3d coating), and no atypical antibodies in the plasma or eluate; however the eluate was not tested against group A cells, as the reference laboratory was unaware of the group O platelet transfusion. The patient was transfused again uneventfully, and was discharged two days later. At the time this was considered to be an acute haemolytic transfusion reaction with no obvious cause; however, retrospective review suggests that this was probably due to passive anti-A from the group O platelets.

Learning points

- Where possible, non-group O plasma components should be selected for recipients of ABO mismatched or mixed haemopoietic stem cell transplant (HSCT) whilst there are circulating group A or B cells.
- Plasma components should be considered as the potential cause of an acute haemolytic transfusion reaction (AHTR) even if the reaction occurs during a subsequent red cell transfusion.

Case 7

Haemolysis due to cold auto-antibody with wide thermal range

A patient with chronic lymphocytic leukaemia (CLL) and anti-C was transfused group A, crossmatch-compatible, antigen-negative units, but the patient had rigors and fever, and haemoglobinuria, and the transfusion was stopped after 150mL. The Blood Service reference laboratory found a cold antibody with undetermined specificity and a positive DAT (complement coating only). Four days later the patient suffered a similar reaction to a unit of group O crossmatch compatible red cells issued by the reference laboratory. Further samples confirmed a cold auto-antibody with a high thermal range. It was recommended that future transfusions should be group A1 and given through a blood warmer.

Learning point

- Cold antibodies with a high thermal range can cause haemolytic transfusion reactions (HTRs) and if the patient is group A or B and has already had an acute HTR, group O blood should be avoided. Consideration should also be given to transfusing blood through a blood warmer in these circumstances.

Serological findings – DHTR

The serology, signs of haemolysis and time intervals are detailed in Table 14.1. The causative antibodies are summarised in Table 14.2.

Case 8 (D17)

Anti-Jk^a detected by more sensitive techniques

An elderly male patient with myelodysplastic syndrome (MDS) was seen at a routine outpatient appointment with Hb 5.3 g/dL. Patient was D negative with anti-D and positive DAT. Samples were sent to the Blood Service reference laboratory where anti-Jk^a was also identified by enzyme indirect antiglobulin test (IAT) only. Anti-D and anti-Jk^a were both detected in an eluate. The patient had been transfused at a different hospital 26 days earlier where he had undergone surgery for an aortic aneurysm repair, without the laboratory being informed that the patient had MDS, and should therefore have received RhD negative red cells.

Learning points

- More sensitive techniques might be required to detect all causative antibodies following an haemolytic transfusion reaction (HTR).
- An eluate is an essential part of an investigation into a haemolytic transfusion reaction, at least when the direct antiglobulin test (DAT) is positive.
- Full clinical details should be provided so that the laboratory can provide the most appropriate components.

Case 9 (D20)

Haemolysis due to anti-A from IVIg

A patient with a severe autoimmune inflammatory skin condition, blood group A, was treated over 4 days in outpatients with high-dose IVIg. He was admitted 5 days later with signs of severe haemolysis, including haemoglobinuria, a raised bilirubin and a massive fall in Hb, from 15.3 to 8.5 g/dL, requiring transfusion of 2 units of group O red cells. The DAT was positive, but no anti-A was detected in the eluate. The titre of anti-A in the batch of IVIg was 4 by direct agglutination at room temperature, but 1024 by IAT at 37°C. This was reported as major morbidity, presumably due to the huge fall in Hb; however, even though the haemolysis was due to anti-A, the time-frame suggests that this was relatively slow extravascular haemolysis, rather than acute intravascular haemolysis, and it does not therefore meet the SHOT definition of major morbidity.

Strictly speaking, this case is not reportable to SHOT, as IVIg is classed as a medicinal product, and reactions are reportable to the Medicines and Healthcare products Regulatory Agency (MHRA) under the 'Yellow Card Scheme'. However, because the product caused such a severe haemolytic reaction due to anti-A, it fits well with this chapter and provides a good opportunity to make some learning points.

Learning points

- Large volume transfusion of IVIg can cause significant haemolysis in non-group O recipients, particularly where the patient has an underlying inflammatory condition.
- When severe haemolysis occurs in group A, B, or AB patients, it may be necessary to stop the IVIg therapy and transfuse group O red cells. A different batch of IVIg should be considered for subsequent therapy.
- A mechanism should be put in place to monitor patients for signs of haemolysis post high-dose IVIg therapy.

Table 14.1 Serology, laboratory signs and timing of reaction DHTR

Case number	New antibody (ies) in plasma	Antibodies in eluate	Comments	Days post transfusion
D1	Jk^a	Fy^b	Hb↓; bilirubin↑; creatinine↑. Known anti-E+Fy^b - ; Also acute HTR - non-typed red cells issued in emergency; died unrelated.	5
D2	c	Not done	Hb↓; bilirubin↑; fever, back pain, chills.	5
D3	Fy^a	Fy^a	bilirubin↑; renal impairment; dark urine.	11
D4	Jk^a	Not done	bilirubin↑; Hburia; chills & rigors; DAT C3d coating only.	10
D5	(E, C^w)	No specificity	Fever, Hb↓; bilirubin↑. Anti-E+C^w present pre-transfusion but not detected. Units E neg, C^w untyped.	6
D6	Auto anti-D, (C, Fy^a)	Non reactive	Hb↓; bilirubin↑; Hburia; creatinine↑. SCD - ? hyperhaemolysis	8
D7	K, Jk^b	Not done	bilirubin↑; dark urine; creatinine↑.	10
D8	Jk^b, S	Jk^b, S	SCD Hb↓↓↓; bilirubin↑; known anti-E; also historical anti-Jk^b + S.	9
D9	K, auto	Not done	Hb↓; bilirubin↑.	12
D10	E, c, K	E	Hb↓; bilirubin↑; Hburia	
D11	K	Non reactive	Hb↓↓↓; bilirubin↑.	10
D12	None	Not done	SCD; hyperhaemolysis; DAT negative.	6
D13	Fy^a	Non reactive	SCD; hyperhaemolysis; DAT negative.	6 + acute
D14	Jk^a	Not done	Hb↓.	1-2 days
D15	Jk^a	Jk^a	Hb↓; bilirubin↑.	5
D16	Jk^a	Not done	Hb↓; bilirubin↑; DAT negative	3
D17	D, Jk^a	D Jk^a	Hb↓.	26
D18	E, C^w, Jk^b, Lu^a, C	Not done	SCD; Hb↓; bilirubin↑; creatinine↑; DAT negative.	7
D19	E	Not done	Hb↓; DAT not done.	7
D20	Passive anti-A	Non reactive against O cells	Hb↓↓↓; bilirubin↑; dark urine; IVIg.	5
D21	Jk^b, C	Jk^b	Hb↓; LDH↑; Known anti-Fy^a.	6
D22	Jk^b	Not done	Hb↓; bilirubin↑; dark urine.	10
D23	Fy^a	Fy^a	Hb↓; bilirubin↑.	9
D24	Anti-c (enzyme only)	Not done	Hb↓; bilirubin↑; dark urine. Chest pain soon after transfusion but AHTR not considered. DAT negative.	9

Table 14.2 Summary of cases by antibody specificity

Antibody specificity by blood group system	No. cases	Sole new antibody
Kidd		
Jk^a	6	5
Jk^b	5	1
Rh		
D	2	1
C	3	0
E	4	1
c	3	0
C^w	2	0
Kell		
K	4	2
Duffy		
Fy^a	4	3
MNSs		
S	1	0
Other		
Lu^a	1	0
Total	**35**	**13**

Table 14.3 New antibodies with or without positive Direct Antiglobulin Test but with no clinical or laboratory signs of haemolysis (alloimmunisation)

Specificity	No. cases
Jk^a	14
E	8
Mixture including Rh	7
c+/- E	6
K	5
Fy^a	5
e+/-C	4
Jk^b	2
Lu^a	2
Mixture Rh and Kidd	2
M	1
C^w	1
Kp^a	1
Mixture including Kidd	1
Mixture other	1
TOTAL	**60**

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

The DAT was positive in 19/24 (79%) cases of DHTR, negative in 4 cases, and not undertaken in one case. The DAT was positive in 7/10 (70%) cases of AHTR.

Eluates were undertaken in 12/24 (50%) cases, including 2 cases where the DAT was reported to be positive with C3d coating only. Of the cases where an eluate was not tested, 4 of these had a negative DAT, and one was positive due to C3d coating only. In another case, the reference laboratory did not prepare an eluate because the DAT was also positive pre-transfusion and the hospital did not mention that the referral was part of an investigation into an HTR.

The serology was confirmed by a reference laboratory in 16/24 (67%) cases of DHTR and in 9/10 cases (90%) of AHTR.

COMMENTARY

Anti-Jk^a is the single most common specificity implicated in both acute and delayed reactions and in the alloimmunisation group.

Eluates were only undertaken in 50% of DHTR cases, which is the same as last year; however, the reference laboratories generally do not prepare eluates unless the DAT is positive with IgG coating. Reference laboratories also need to be made aware that they are investigating a transfusion reaction.

Patients with sickle cell disease were, once again, overrepresented in the DHTR cohort, and all suffered major morbidity. These cases have also been discussed in a separate chapter on haemoglobin disorders (Chapter 23).

The severe haemolytic episode following treatment with IVIg is an interesting case. Most episodes of haemolysis due to IVIg are mild and probably often go unnoticed. Rare cases of severe haemolysis have been reported with high doses of IVIg (more than 100g over 2-4 days or 1 to 2 g/Kg), and are more likely where the ABO haemagglutinin titre is >16[55]. It has also been suggested that the newer liquid products have higher titres of anti-A/B than the lyophilised products[56]. Patients with an underlying inflammatory state appear to be at greater risk[57]. ABO haemagglutinins are not removed during manufacture of IVIg, but the European Pharmacopoeia recommends that they should not be detectable at a titre of 64[58]. It is recommended that IVIg recipients be monitored for clinical signs and symptoms of haemolysis[59]. Several strategies have been suggested by the above authors for managing patients who have severe HTRs: if transfusion is required, use group O red cells; titre the causative batch of IVIg and select a different batch with a lower titre.

Recommendations

- Plasma components should be considered as the potential cause of an acute haemolytic transfusion reaction (AHTR) even if the reaction occurs during a subsequent red cell transfusion.

  Action: Hospital Transfusion Teams (HTTs)

- If platelets are thought to be the cause of an AHTR, this must be reported to the Blood Service for further investigation, whether or not they are labelled as high-titre negative.

  Action: HTTs

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