High Titre Anti-A/B Testing of Donors within NHS Blood and Transplant (NHSBT)

Purpose

To minimise the risk of causing clinically significant haemolysis due to the presence of high-titre anti-A or anti-B when plasma-rich blood components are transfused to patients of other blood groups.

Method

Review of the literature of cases of haemolytic episodes attributed to the transfusion of high-titre anti-A or anti-B, and of current practice in NHS Blood and Transplant (NHSBT). Recommendations made based on apparent critical titre levels from the literature and operational considerations.

Status

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Introduction

It has long been recognised that, although Group O red cells and platelets may be transfused to patients of any group, rarely the transfusion may be complicated by an acute haemolytic transfusion reaction (AHTR) due to the passive transfer of antibodies to A or B red cells[1,2] (particularly when platelets containing relatively large volumes of plasma are transfused). The majority of reports are of single cases, suggesting that this is a rare complication of transfusion[3-17](Table 1). Five out of the twelve reported cases occurred in children, one of whom received a platelet transfusion from her mother with a fatal outcome[13]. In all cases, there was a significant haemolytic reaction.

An International Forum[18] asked experts from 16 countries what measures if any they took to prevent haemolysis following the transfusion of incompatible apheresis platelets. All countries responding recognised this to be a potential problem and had some measures in place to try to minimise the risk (*Table 2*).

Titration of anti-A/B

In almost all of the case reports (*Table 1*) further investigation of the donor's serum revealed a titre of at least 256 by IAT, and/or 128 haemolysin saline titre at room temperature. Mollison[19] reviews two early studies when group O plasma was deliberately transfused to group A volunteers. These studies found the lowest titres of anti-A to cause haemolysis were 512 and 640, and similar or greater levels than this were found in 40% and 23% of donors respectively.

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It is recognised that such haemolytic reactions may be prevented by screening to detect those donors who have high anti-A or anti-B titres, and ensuring that these components are not transfused to patients of other groups; however there has been very little consensus in the past on the method of screening or the effective cut-off level.

Reported donor anti-A titres implicated in AHTR range from 32 to 16,384 in direct agglutination tests (median, 512), and 32 to 32,000 (median, 4096) in Indirect Antiglobulin Test (IAT)[20]. Some institutions test only for IgM, anti-A/B and others screen for both IgG and IgM. Reported methodology generally involves a haemagglutination test, (IAT) using manual tube, manual gel, semi-automated or automated methods. There is no defined critical titre which will predict *in vivo* haemolysis and the cut-off values in use range from 32 to 200 for IgM anti-A (tube saline) technique and 256 to 512 for IgG anti-A (IAT) (*Table 2*). Although arbitrary, the majority cited the critical high titre haemolysin as cut-off titre of greater than 1:64 for IgM and greater than 1:256 for IgG.[18,21,22] It is clear that there is no recognised standard or universally used method. Josephson et al[22] have studied one hundred samples to quantify anti-A/B IgM and IgG titres. The reported IgM titres which were greater than 32 were: 1:64(18%), 128(6%) and 256(4%); IgG titres greater than 128 were: 1:256(28%), 512(7%), 1024(2%) and 2048 (2%). The Australian Red Cross Blood Service has recently implemented national testing of group O apheresis platelets for high-titre anti-A and anti-B. Low titre is designated as IgM <1:50 dilution (saline tube technique) and IgG < 1:250 (37ºC indirect antiglobulin technique) v pooled A_1 and B cells. Early reports indicated a positivity level of 46% for this combination of tests[23].

Some centres test all apheresis platelets donation and others only test selectively if the product is to be issued as out-of group platelets on demand.

The potential for variation in anti-A/B tests is significant. This results from the use of manual or automated platforms, performance of serial dilution or single predetermined dilution and techniques employed. Therefore it is difficult to compare titre end points in reports coming from different authors/establishments over different time periods using techniques of different sensitivity. Quillen *et al* [24] have recently proposed that “the cut off for classifying high titre depends on the serologic method used and may be customized by the individual facility.”

The seventh edition of “Guidelines for the Blood Transfusion Services in the United Kingdom”[25] states that “each Blood Establishment should have a testing and issuing policy to avoid the use of high-titre anti-A and / or anti-B in instances where a significant adverse clinical reaction is likely”. It is recommended that a saline agglutination test should give a negative result at a dilution of 1/128 or an equivalent dilution by other techniques.

Manual titration is well recognised to be an imprecise technique. Furthermore, the UK Transfusion Services now rely heavily on automated testing procedures, and it is no longer feasible to perform manual saline titration of IAT tests on all Group O donations. The challenge is to find an automated test (with electronic transmission of results) which can be performed routinely on all donations and which would reliably detect high titre antibodies at a level sensitive enough to prevent haemolysis in all recipients (including neonates), while at the same time not labelling more donors than necessary as “high titre” so that supply of components is compromised.

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In work performed at Leeds for the NHSBT Northern Zone Testing Managers Group (2002) it was shown that tests performed by saline against both A_1B cells, and separate A_1 and B cells showed 31% of donors to be positive at a dilution of 1/32, and 6% at 1/128. Dilutions of 1/40 and 1/100 were then tested on the Olympus PK7200, and 39% and 5% of donors were found to be positive respectively, i.e. very similar to the saline results. They concluded that the techniques were comparable and that testing using a 1/100 dilution on the Olympus was equivalent to a 1/128 titre.

Current testing practice

A national uniform approach to testing for high-titre anti-A and anti-B has been agreed and adopted. A positive control (Alba Bioscience) reactive at 1/128 (or equivalent dilution) by haemagglutination techniques and the negative control 1:64 were introduced in early 2008.

Current IgM testing

Details of the high titre anti-A/-B IgM tests performed by the UK Blood Services:-

Table: High titre anti-A/B tests performed by the UK Blood Services

Blood Service	Test performed on	Dilution used	Donations tested	% HT positive
NHSBT	PK7300	1/85 v A_2B cells	All donations	5-10
NIBTS	Immucor Galileo	1:100 v A_1 & B cells	Whole blood for exchange transfusion of neonates, apheresis platelets & plasma for pooled buffy coat platelets resuspension	31
SNBTS	Glasgow: Olympus PK7200 Edinburgh: Olympus PK7300	1:100 v A_1 & B cells 1:50 v A_1 & B cells	All donations	12 20
WBS	Microplate saline test on Tecan/DUET & BioRad HemOS	1:128 v A_1B cells	Apheresis platelets, male plasma for resuspension of pooled buffy coat derived platelets and donations for neonatal/paediatric use	1-5

Labelling of components

All components (red cells, platelets and frozen components), of all ABO groups, which are found to be negative for high-titre anti-A,B, are labelled as “NEG: HT”. This includes pooled platelets if all constituent donations are negative.

The specification for neonatal components includes the requirement for donations to be high-titre anti-A,B negative. Components labelled as “suitable for neonatal use” are therefore negative for high-titre anti-A,B even though this may not be specifically stated on the label.

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Recommendations

Guidelines for the Blood Transfusion Services in the UK[25] recommend that "There should be a procedure in place to collect and review testing and patient outcome data and to implement changes in policy in the light of continuing clinical experience with the plasma containing blood products issued". Data on acute transfusion reactions is collated by SHOT, and regular review of reports of haemolysis following platelet transfusion should be performed in order to provide feedback on the efficacy of the high titre testing procedure.

A total of 4 cases of (AHTR) due to out of group platelets transfusions were recorded in 2008 SHOT report. SHOT recommended that "Blood services should review the critical titre of 1/128 for screening high titre anti-A and anti-B, and consider whether donations should be screened for IgG in addition to IgM antibodies[26] .

Therefore, the Standing Advisory Committee on Immunohaematology (SAC-IH) have reviewed the SHOT reports (1997-2011) (*table 3*) and have re-evaluated testing of high titre anti-A/B antibodies.

Review of the SHOT report and re-evaluation of testing of high titre anti-AB in NHSBT

SHOT data from 1996/7 to 2011 recorded seventeen cases (*table 3*). Four cases were reported in 2008. No cases were reported in 2009,2010 and one case was reported in 2011.

The recipient's age was only provided in 12 cases. The majority, 7/12 were paediatric patients (i.e. children under 18 yrs): Ten cases were related to apheresis platelets, six related to pooled platelet product and one after transfusion of 7 aliquots of neonatal platelets.

Anti-A/B titres (either IgM or IgG) were not investigated in 11 cases. Retrospective titrations were only investigated in 6 cases (cases 1, 3, 7,11,12 and 15). In this group, both IgG and IgM antibodies were detected in 4 cases (cases 3, 7,12 and 15). IgG titres were high: the results were 2000,>8192, 2048 and 1024 in cases number 3, 7,12 and 15 respectively. IgM titre of >1024 and 1024 were recorded in cases 7 and 12. It is important to note that these cases had been screened IgM by routine techniques and had been found to be HT negative. SHOT reports demonstrate that implicated platelet components associated with AHTR had anti-A, IgG titre at or above 1024. Other published cases of haemolytic transfusion reactions (HTR) due to anti-A (13 cases) over a 40 year period showed that the implicated components had anti-A titres of 1024 or greater by IAT (range 1024 – 64,000) and/or saline titres of 128 or higher (range 128 – 16,384) (*Table 1*). Known contributing risk factors include small blood volume of the recipient (SHOT report 1996 to 2010) and passive infusion of large cumulative volume of incompatible plasma over time[15] . This was also demonstrated in one of the case reports in SHOT 2008 (case 15). A 14-month-old child (blood group A) received 2 doses of group O HLA matched platelets. The haemoglobin dropped to 6g/dl and investigation confirmed the presence of anti-A, IgM (I:128) and IgG (1:1024). Another potential risk factor is the total number and frequency of issued Group O donor platelets to Non O recipients. This depends on availability, supply and demand of appropriate components.

The actual incidence and risk of AHTR associated with out of group platelets transfusion is not known but has been estimated 1 in 2500 to 1 in 9000 [27,28]. In one institution, within a 3 year period (during which 12,299 apheresis components were transfused) five AHTRs occurred in association with ABO incompatible transfusion[24] .

Case no. 1(1996/7) and case no 7 (2003) were not likely to be due to out of group platelets transfusion. In the former, the HT anti-A was not demonstrated in retrospective testing and it was concluded that autoimmune haemolysis could not be ruled out in that case. In the latter, there was no serological evidence of passive infusion of anti-A antibodies.

In 2008, following recommendations for improving high titre testing in the UK made to the Joint Professional Advisory Committee of the UK Transfusion Services (JPAC) by the SAC-IH and Blood Components, a set of controls, comprising positive and negative standards, has been adopted into routine use.

A positive control (Alba Bioscience) reactive at 1/128 (or equivalent dilution) by haemagglutination techniques and a negative control 1:64 were introduced in early 2008. There have been no reported instances in NHSBT of the screening test failing to pick up the positive control and, indeed, the negative control has on occasion been positive, indicating that the test is working to a higher sensitivity than 1:128. These controls help to ensure a standard process for automated high titre testing on the Olympus Blood Group Analyser.

The scale of out of group platelet transfusion is not known but the total number of platelet units issued in 4 UK Blood Services for 2008/9, 2009/10 and 2010 /11 was 224958, 279260, and 256283 units respectively (*table 4*). It seems to be extremely rare in the UK with existing screening programme (about 1 case per year reported to SHOT). Therefore current test for IgM screen in UK Blood Services (with positive and negative controls introduced in 2008) appears to be working reasonably well and the potential risk seems very low.

Further precautions to reduce the risk of haemolysis

Red cell transfusion

British Committee for Standards in Haematology (BCSH) Guidelines for compatibility procedures in blood transfusion laboratories[29] state that red cells of the same ABO group as the patient should be selected wherever possible. If identical blood is not available for group A or B patients, group O blood should be used, and provided it is in additive solution, it does not need to be tested for high titre haemagglutinins as the volume of residual plasma is too small to cause haemolysis.

Platelet transfusion

Even with uniform testing to prevent “high-titre” donations from being transfused to patients of blood groups other than O, there will still be a potential risk if large volumes of “low titre” plasma are transfused. This may be particularly likely in instances such as large volumes of double-dose HLA matched platelets being transfused daily to an individual, or where children are repeatedly transfused with adult doses of apheresis platelets.

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Pooled platelets theoretically pose a lesser risk; for a pool to be labelled “high titre negative”, all of the donations in that pool must have been found to be of low titre.

Clinicians should be made aware of the potential for haemolysis in these circumstances. The Transfusion Medicine Clinical Policies Group document on ABO and RhD Compatibility in relation to Platelet Transfusions[30] provides the relevant information:-

- Platelet concentrates from donors of the same ABO group as the patient are the components of choice.
- Platelet recovery of both major and minor ABO incompatible platelet transfusions may be impaired to some extent, but this is not usually clinically significant.
- A more important consideration concerning donor ABO antibodies is the avoidance of acute haemolysis, which may occur after ABO-incompatible platelet transfusions, typically with transfusions of high titre anti-A to A_1 recipients. This problem has been particularly apparent in small children receiving apheresis platelet concentrates, which contain large volumes of plasma from single donors. It is preferable to use Group A platelets for Group B patients and vice versa rather than Group O if ABO identical platelets are not available. If these are also not available then Group O may be used, but in either case platelets should be selected which are labelled as high-titre negative as above.

Plasma Transfusion

Plasma components should preferably be ABO identical. If this is not possible, for example because of supply shortage when large volumes are required, they should always be ABO compatible i.e. group O plasma should only be given to group O recipients[31].

It is even more critical that plasma for transfusion to neonates should be ABO compatible because of the increased risk of haemolysis due to their low plasma volume.

Conclusion

The risk of haemolysis due to passively transfused anti-A and anti-B is small but present, and should be considered in any situation in which relatively large volumes of incompatible plasma are transfused (including platelet components).

It is important to recognise that, although testing for high titre ABO antibodies in blood donors may reduce the risk of HTR in ‘out of group transfusion’, it cannot be entirely eliminated through this route.

Group O platelets can cause HTR even when tested and labelled negative for high-titre haemolysin. They should only be used for non-group O patients (particularly paediatric patients) as a last resort.

- Improving the safety of the supply of platelet components by identifying donations with high titre anti-A, or -B would require a test which balances the need to identify the donors with the highest titre without causing an operationally unsustainable proportion of the donor population to be excluded from out-of-group transfusion.

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- A study by the Welsh Blood Service (WBS personal communication) has identified that there is a poor correlation between anti A/B IgM and IgG titres. Anti-IgG screening titre of 1024 would identify approximately the highest 5% of the donor population (by IAT using A_1B cells). There is currently no screening by IAT for IgG anti-A/B antibodies in UK and none of the UK transfusion services currently operates equipment which could achieve such a high dilution in an automated manner. Manual testing is not considered appropriate by UK Testing laboratories. There is no plan to introduce testing IgG for HT screen at present.

- A review of SHOT reports (1997-2011) shows that AHTR due to out of group platelets transfusion is extremely rare (less than one case per year). There has been one case report since 2008. Therefore the current test for IgM screening in UK Blood Services (with positive and negative controls introduced in 2008) appears to be working reasonably well and the potential risk seems very low.

- Group O red cells in additive solution do not need to be tested for high titre haemagglutinins when transfused into patients who are not group O as the volume of residual plasma is too small to cause haemolysis.

- Any suspected instance of haemolysis should be reported to the local Blood Centre, SABRE and SHOT so that further investigation can be performed and the effectiveness of the current testing regime for IgM can be monitored.

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Table 1. Reported cases of haemolysis due to anti-A/B

First author and Ref	Year of publication	Recipient Group	Donor Group	Implicated antibody	Component transfused	Reaction	~ A/B titre	Age of recipient
Keidan [9]	1966	A	O	A	Grp O whole blood	Severe haemolytic leading to acute renal failure	H/L 128 agglut. 256	4 yrs
Zoes [14]	1977	A int B	O	anti-A_1	10 units recovered platelets	Severe haemolytic. Free haemoglobin in serum & ↑ bilirubin	256 (pool of all donations)	44 yrs
Inwood [8]	1978	A	O	anti-A	Almost whole unit of red cells (~ 95 ml plasma)	Haemolytic with haemoglobulinaemia & haemoglobinuria	8192	31 yrs
McLeod [11]	1982	A	O	anti-A	2 units recovered platelets	Significant haemolytic Hb 14 → 8	Both donors 10240 (IAT) H/L titre 32 + 64	45 yrs
Conway [5]	1984	A	O	anti-A	Apheresis platelets	Haemolytic → DIC (Donor was sister) Required haemodialysis	8192 (saline)	15 yrs
Pierce [13]	1985	A B	O O	anti-A anti-B	Apheresis platelets 1 Gp O recovered platelet in pool with 5 Gp B	Severe haemolytic → (Donor was mother) DIC & death Hb 11.5 → 5.7 No acute reaction Hb 14.3 → 8.2 in 7 days No haemoglobinaemia	32000 (IAT) (Weak pos in saline at RT) 256 (IAT)	2½ yrs 58 yrs
Ferguson [6]	1988	A	O	anti-A	Recovered platelets x1	Acute haemolytic, red serum & urine, back pain. Hb ↓ 2.6 g/dl in 5 hrs.	> 4000 (IAT) 256 (RT)	66 yrs
Reis [29]	1989	B	O	anti-B	Apheresis platelets	Haemolytic. Hb 11.3 → 5.2	4096 (IAT)	56 yrs
Murphy [12]	1990	A	O	anti-A	HLA-matched platelets (448 ml)	Severe haemolysis, Hb 11.4 → 6.0 g/dl, acute renal failure	256 (sal) 1024 (IAT)	30 yrs
Boothe [3]	1995	B	O	anti-B	O cells resuspended in AB plasma	Severe haemolytic, temp ↑, haemoglobinuria. (Neonatal exchange transfusion)	16384 (sal) > 64,000 (IAT)	6 days
Duguid [4]	1996	A	O	anti-A	Platelets	Infant undergoing cardiac surgery. No acute reaction. Hb 13.6 → 9.1 at 48 hrs	3200 (IAT)	5 weeks
Mair [10]	1998	A	O	anti-A	Apheresis platelets	Severe haemolytic. Hb 8.4 → 5.8 in 24 hrs.	128 (sal)	28 yrs
Barjas-Castro [16]	2003	A	O	anti-A	Red cells (approx. 55 mL plasma)	Fever, back pain, haemoglobinaemia, Hb 6.9 → 6.8 in 24 hours after 1 unit transfusion	1024 (sal)	38 yrs
Sapatnekar [17]	2005	A	O	anti-A	Apheresis platelets	Shock, severe intravasc haemolysis Hb 12 → 8.1 (after 2 units of O red cells)	2048 (sal) 16384 (IAT)	2 yrs
Sadani [15]	2006	A	O	anti-A	Apheresis platelets x 3	Haemoglobinuria and jaundice. Hb 7.7 → 3.9. Renal failure	640 (IAT) IgG alone 1280.	65 yrs

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Table 2: Strategies for screening apheresis platelet donors for high-titre isogglutinins[5]

Country	Screen Donors	Method	Critical Titre	% Donors
United States[84,90,91]	No (2%)[90]	Tube, gel	1:50-1:200	3-28%
England[89]	Yes	Automated Tube	1:100 1:128	3-10%
Scotland[87]	Yes		1:50	
Italy[89]	Yes	Gel IAT	1:64 1:256	
Germany[89]	Yes	Tube, saline	1:64	5%
Czech Rupublic[89]	Yes	Tube, saline	1:64	
Norway[89]	Yes	IAT	1:250	
Sweden[89]	Yes	Tube, saline IAT	1:100 1:400	
Switzerland[89]	Yes	Hemolysis	1:16	
Finland[89]	Yes	Tube, saline	1:32	5.7%
Japan[89]	Yes	IAT	1:512	

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Table 3: Reported cases of haemolysis (SHOT) due to anti-A/B: 1996 - 2011

	SHOT /year	Recipient Group	Donor Group	Implicated Antibody	Component transfused all labelled as high titre Neg	Reaction	- A/B titre	Age of recipient
1.	1996/1997	A	O		Pooled platelets		Tested HT Neg	Not given
2.	1997/1998	A	O	Anti-A eluted from RBC	2 x Apheresis platelets		HT not investigated	55 yrs
3.	1998/1999	A	O	DAT post	Apheresis platelet	Evidence of haemolysis	IgM HT Neg - IgG 1:20,000	36 yrs
	1999/2000	No Report						
4.	2000/2001	A	O		Pooled platelet	No details provided (haemolytic reaction). Age: not given. Issued as group A, not readily available.		
5.		A	O		Pooled platelet			
6.		A	O		Apheresis platelet			
	2001/2002	No Report						
7.	2003	A	O	Anti-A	Apheresis platelet	Haemolysis within 24 hrs	IgM 1:1024 IgG > 1:8192	31 yrs
8.	2003	A	O	Anti-A Anti-A eluted from RBC	Neonatal platelets (7 aliquots)	Haemolysis within 24 hrs Hb 3.16 g/dL	Titre not Investigated	3 mths
	2004/2005	No Report						
9.	2006	A	O	Anti-A Anti-A eluted from RBC	Apheresis platelets	Bilirubin 16 to 94 (day 1) to 210 (day 2)	Titre not investigated	11 mths
10.		AB	O	Anti-A	Apheresis platelets	Bilirubin 11 to 62 Hb dropped from 6.7 to 6.1	Titre not investigated	5 yrs
11.	2007	A	O	Anti-A in plasma	Apheresis platelets	Bilirubin increased from 40 to 102 Hb dropped from 10.2 to 8.2	Donation was tested and found (-) for high titre anti-A	10 yrs
12.		A	O	Anti-A in plasma	Pooled platelets	Bilirubin raised from 40 to 109 Hb dropped from 7.1 to 4.9	Retrospective testing showed 1 donation IgM 1:1024 IgG 2048	17 yrs
13.	2008	A	O	DAT Neg Eluate: Non-reactive	Apheresis platelets + 2 group A RBC	Bilirubin raised from 28 to 237 Hb remained 8.2	No anti-A in plasma	71 yrs
14.		A	O	DAT Positive Anti-A eluted from RBC Anti-A in plasma	Pooled platelets	Bilirubin raised from 23 to 88	Titre not investigated	7 yrs
15.		A	O	DAT Positive Anti-A eluted from RBC Anti-A in plasma	HLA matched platelet 2 dose same donor	Hb dropped to 6g	IgM 1:128 IgG 1024	1 yr 2 mths
16.		A	O	DAT Positive Anti-A eluted from RBC Anti-A in plasma	HLA matched Platelet + 2 RBC (group A)		Titre not investigated	76 yrs
	Please see no.17 overleaf							

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	SHOT / year	Recipient Group	Donor Group	Implicated Antibody	Component transfused all labelled as high titre Neg	Reaction	- A/B titre	Age of recipient
17.	2011	A/O (mixed field)	O	DAT Positive No eluate study Post double cord allograft (O and A) Blood Group mixed field O/A	Hb dropped from 9.6 to 4.8	Bilirubin raised from 2 to 28	Anti-A in reverse grouping - titre not investigated	Not provided
	Note:	**Case 17: The case was initially considered to be an AHTR with no obvious cause, hence titre studies were not investigated.**						

Table 4: Total number of platelets issued (Pooled+apheresis: adult+ paediatric packs) among 4 UK Blood Services

Year	NHSBT	SNBTS	WBS	NIBTS	Total
2008/09	185000	24000	8834	7124	224958
2009/10	236000	28000	8524	6736	279260
2010/11	245000	25000	8821	7462	256283

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