

International Forum on Policies and Practice for transfusion of ABO and RhD non-identical platelets: summary

Cardigan, R.; New, H.V.; Estcourt, L.; Zhiburt, E.; Dubey, R.; Bengtsson, J.; ... ; Dunbar, N.

Citation

Cardigan, R., New, H. V., Estcourt, L., Zhiburt, E., Dubey, R., Bengtsson, J., ... Dunbar, N. (2021). International Forum on Policies and Practice for transfusion of ABO and RhD nonidentical platelets: summary. *Vox Sanguinis*, *117*(1), 136-144. doi:10.1111/vox.13129

Version:Publisher's VersionLicense:Licensed under Article 25fa Copyright Act/Law (Amendment Taverne)Downloaded from:https://hdl.handle.net/1887/3566476

Note: To cite this publication please use the final published version (if applicable).

DOI: 10.1111/vox.13129

INTERNATIONAL FORUM

International Forum on Policies and Practice for Transfusion of ABO and RhD Non-Identical Platelets: Summary

Rebecca Cardigan | Helen V. New | Lise Estcourt | Eugene Zhiburt | Rounak Dubey | Jesper Bengtsson | Magnus Jöud | Carlos Castillo | Joan Cid | Miquel Lozano | Dhana Gounder | Peter Flanagan | | Sarah Morley | Gwen Clarke | Dana Devine | Salwa Hindawi | | Aqeel AlOtaibi | Carolina Bonnet Bub | Jose Mauro Kutner | | Toshiyuki Ikeda | Naoko Goto | Hitoshi Okazaki | Magali J. Fontaine | Jeremiah Pasion | Linda Song | Tom Latham | Jean-Louis Kerkhoffs | Masja de Haas | Jaap Jan Zwaginga | Birgit S. Gathof | Katharina Ommer | France Pirenne | Michel Raba | Anne Francois | James Daly | Tanya Powley | Nancy Dunbar

Transfusion of ABO major incompatible platelets (where the recipient has antibodies against the ABO group of the transfused platelets) has been shown to be associated with lower platelet count increments following transfusion [1], although this does not appear to translate to a difference in bleeding outcomes [2]. Transfusion of minor ABO incompatible platelets (where the suspending plasma of the platelet concentrate is not compatible with the ABO group of the recipient's red cells) has been associated with increased risk of haemolytic transfusion reactions. This risk is likely to be lower for platelets stored in platelet additive solution due to the reduced volume of plasma.

Whilst the preference, therefore, is that patients are transfused ABO identical platelets, this is not always possible in emergency situations. Moreover, transfusion of ABO incompatible platelets may also be required to ensure, across the supply chain, that platelets are available when needed without significant wastage of a product with short shelf-life (5–7 days in most countries). For this reason, transfusion of ABO incompatible platelets is not an infrequent occurrence, and thus, many centres have policies in place to mitigate risk to recipients. A previous international survey published in 2010 reported considerable variation in international practice in relation to the transfusion of ABO incompatible platelets [3]. Since that time, platelet production practice has evolved, especially with increased use of platelet additive solution either alone or in combination with pathogen inactivation.

In addition to ABO group, consideration must be given to compatibility of platelets for RhD. Platelets themselves do not express RhD, but are contaminated with a small amount of red cells. The level of red cell contamination is influenced by the method of production, with apheresis platelets reported to contain lower levels than those produced by whole blood [4]. Transfusion of RhD-positive platelets to RhD-negative recipients can result in alloimmunisation, the likelihood of which is related to the type of platelet preparation and factors in the recipient such as immunosuppression [5]. Therefore, many centres have policies to define which recipients should receive RhD-negative platelets. The principal concern is mitigating the risk of alloimmunisation in women of child-bearing potential, potentially leading to haemolytic disease of the foetus and newborn. Where RhD-negative platelets are not available for patients for whom they are indicated, centres may have policies for prophylactic administration of anti-D following transfusion of RhD-positive platelets.

The aim of this International Forum was to assess current international policies for the transfusion of ABO or RhD non-identical, "out of group," platelets in relation to how platelets are produced and tested.

We received responses from 15 centres, with a wide geographical spread. Many respondents were reporting national guidance.

TYPE OF PLATELET COMPONENTS TRANSFUSED

Question 1 Please describe the type of platelets products you supply.

Data are summarized in Table 1.

137

(4230410, 2022, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/vox.13129 by University Of Leiden, Wiley Online Library on [08/06/2023]. See

the Terms

and Coi

(http:

on Wiley Online Library for rules

of use; OA articles

are governed by the applicable Creative Commons Licens

In terms of platelet production methods, there was a mix of apheresis and whole blood-derived platelets reported, with a trend towards a higher proportion of platelets produced from whole blood in European Countries as well as New Zealand, Australia, India and Brazil. Most centres (11/15) stored all or part of their platelet supply in PAS or were planning on doing so in the near future. Since the last published survey in 2010 by the BEST group [3], there appears to have been an increase in the use of PAS either alone, or in conjunction with pathogen inactivation. Of the 13 respondents that produce whole blood derived platelets, the majority [6] do so by manual or semi-automated methods (e.g. presses), with 3 using Reveos and 1 (France) using Terumo Automated Centrifuge and Separator (TACSI). Most had similar specifications for platelets for neonatal/infant use as those for adults (Table 1), but in 8/15, these were stated to be provided at smaller volume and/or concentrated. Two responders stated they provide CMV seronegative platelets for this patient group (Spain and UK), and UK guidelines require that this product is free from clinically significant irregular blood group antibodies including high titre anti-A and B. Some countries provide additional mitigations for ABO non-identical transfusions for neonates or children (Table 2).

ABO

Question 2 Do you have national/local clinical polices with respect to transfusion of ABO non-identical platelets? What percentage of platelet transfusions are ABO non-identical? If ABO identical platelets are not available, is priority given to compatibility of ABO group of platelet (avoiding major incompatibility) or suspending plasma with recipients red cells (avoiding minor incompatibility)?

TABLE 1Type of platelets produced

	Type of pla	telets used	Whole blood plate	elets	Storage media used			
Country	Apheresis	Whole blood	Method of processing	No. of donations	Apheresis	Whole blood	Different specification for neonatal/ infant platelets?	
Australia	36%	64%	Semi-automated PRP or BC.	4	60%-70% PAS-E.		Apheresis, smaller volume.	
Brazil	95%	5%	Manual, PRP.	6	Plasma.		No	
Canada	25%	75%	Semi-automated, BC.	4	Plasma.	Plasma (moving to PAS).	No	
England	50%	50%	Manual, BC.	4	Plasma.	65% PAS-E.	Apheresis, smaller volume. CMV neg, micro neg in past two years. Low titre for anti-A/B, negative for clinically significant irregular blood group antibodies.	
France	30% PI	70%	Automated (TACSI) and PI.	5-8	70% PAS-C.		Apheresis, smaller volume. Select the most concentrated packs.	
Germany	70%	30%	Manual BC.	5, moving to 4.	Plasma (moving to PAS).	PAS-C.	No	
India	10%	90% PRP	Manual, PRP.	1	Plasma.		No	
Japan	100%	-	_	-	Plasma.	_	Smaller volume (provided also for small children.	
Netherlands	10%	90%	Semi-automated BC.	5	65% PAS-E.		Smaller volume.	
New Zealand	30%	70%	Manual, BC.	4	60%-70% PAS-E.		Apheresis PC stored in plasma (plan to move to PAS).	
Russia	70%	30%	Manual, BC.	4-5	Plasma or PAS-E.		No, but are usually irradiated.	
Saudi Arabia	10%-20%	80%-90%	Automated (Reveos).	4-6	Plasma.		Smaller volume, ABO compatible.	
Spain	5%	95%	Automated (Reveos).	4-5	Plasma.	65% PAS-C.	CMV neg donors, reduced size pools (from 3 donors).	
Sweden	7%	93%	Automated (Reveos).	4 (3-6)	60%-65% PAS-E.		No, split units from the same donation used for one patient.	
USA	100%	_	80% PI in PAS, 20% non-PI.	_	10% in plasma, 90% in PAS.	_	No	

Abbreviations: BC, Buffy coat; PAS, Platelet additive solution; PI, pathogen inactivation; PRP, Platelet rich plasma.

Question 3 What strategies are taken to mitigate the risk of haemolytic transfusion reactions due to ABO incompatibility and are these dependent upon the type of platelet product?

Data are summarized in Table 2.

138

Most centres (9/15) used national guidelines or policies that describe requirements for ABO matching of platelets and the clinical use of non-identical platelets. Other centres either had local policies or no agreed policy in place. The majority of responses indicated that the preference was to give ABO identical platelets if available, but it was

TABLE 2 Policy and practice for platelet ABO matching

	National or local	% ABO non- identical	Priority given to minor or	Risk mitigation for minor	Frequency of HTR due to ABO
Country	policies?	transfusions	major compatibility	mismatch	incompatible transfusion
Australia	National	Not known	Minor	Storage in PAS. Low-titre for anti-A/B.	No cases since the introduction of anti-A/B testing of donations.
Brazil	National	36%	NR	Low-titre for anti-A/B.	None seen in years but are reportable to HV scheme.
Canada	National	20%	Minor	Low-titre for anti-A/B. Volume reduction.	2 reports since 2017.
England	National	10%–15% likely higher for neonates.	Minor	Low titre for anti-A/B. Pooled platelets in PAS. Avoid group O for non-O patients.	1:625000. None since 2016 - PAS introduced for pooled platelets. No fatalities since testing standardized in 2008.
France	No policy	16% major.	Major	Low-titre for anti-A/B.	Reportable but very rare over past 8 years.
Germany	National	-	Major	Storage in PAS.	13 fatal cases 2000–2017 nationally, 1:600000 platelets.
India	Local	5%	Minor. Avoid group O for latter.	Apheresis platelets, volume reduced if there is time.	None observed at centre last year, but reportable to national HV.
Japan	National	0% apart from HLA matched - 30%.	For HLA matched, minor.	Low-titre for anti-A/B. Washing for HT units or for children. Hospitals can volume reduce.	1:2million PC overall, 1:19108 for HLA matched platelets.
Netherlands	National	5%	Major. Group O RhD neg used in trauma packs	All PC in PAS. Low-titre for anti-A/B anti-A/B for neonates, infrequently volume reduction.	None in 2018.
New Zealand	National	23%	Major	Storage in PAS.	6 reports between 2005–2012 all due to group O PC. None since 2012, PAS introduced 2010–11.
Russia	National	21%	Not stated	Storage in PAS.	NR
Saudi Arabia	Local	20%	Not stated	Volume reduction to 30% for some patients - especially for neonates.	None reported but there is a system to report to national body.
Spain	None	NK	Major - risk of minor reduced by suspension in PAS	Storage in PAS. No testing for anti-A/B.	Not observed in past 30 years, reportable to national HV scheme.
Sweden	Local	22%	Minor but sometimes major.	Storage in PAS for BC PC, apheresis donors tested for anti-A/B. May also wash apheresis PC if from an HLA matched donor with HT antibodies.	Not observed in centre in last 15 years. One case reported to national HV scheme in past 10 years.
USA	Local	42%	Minor	Storage in PAS –OR-volume reduced to 50 ml.	Observed, so considering testing for anti-A/B.

noted that this was not always possible, and this may be particularly the case for specific groups of patients such as neonates. Some blood providers preferentially collect platelets from group O and A donors to aid inventory management and supply, and in this case, group AB and B recipients will be more likely to receive ABO non-identical platelets. If ABO identical platelets are not available, then the preference for prioritizing compatibility of the platelets or plasma that they are suspended in is mixed. Six centres give priority to ensuring the compatibility of plasma with recipients red cells (minor), whereas five preferentially consider the ABO compatibility of the platelets themselves (major). In two centres, it depended on the platelet component. The majority prioritizing minor compatibility indicated that their rationale was that the risk of a haemolytic transfusion reaction was reduced by platelets being suspended in PAS and/or testing to remove high titre units. The proportion of ABO non-identical transfusions (as defined by centres) is typically about 20%. However, ABO incompatible transfusions are a rare event in Japan unless platelets are HLA matched, whereas in the USA. it appears to be more common at over 40%. This is consistent with a recent study in 12 hospitals in the USA demonstrating that 46% of platelet transfusions are ABO non-identical-16% minor incompatible [7]. Some respondents noted that the likelihood of ABO non-identical

transfusion was increased for HLA matched platelets, where HLA matching may take preference over ABO compatibility.

139

In addition to many centres using PAS for all or part of their supply, 6/15 may volume reduce to limit the amount of plasma transfused, and 2 may wash HLA-matched platelets if ABO non-identical. 8/15 have implemented partial or universal testing of anti-A/B for donations destined for platelet production in specific situations including for ABO non-identical transfusions, or for neonates. The method and cut offs used for testing are summarized in Table 3. All the sites that test do so on samples from the donor, apart from the Netherlands who test the final product for neonatal transfusion. There are data from small studies suggesting that the titre of anti-A/B for a given donor are stable over time [8], suggesting that one off testing of donors may be sufficient, but this has not been confirmed in large data sets and many operators (6/7 who responded) still test every donation. Most sites that test do so for IgM only (5/7 where stated), 2 also test IgG. The cut off used to determine whether a donation is "high titre" varies between 1/64 and 1/128 for IgM. It is well known that the methodology for testing affects the titre obtained, and therefore it is difficult to compare across sites [9].

The main reported effect of transfusion of ABO major incompatible platelets is a reduction in platelet count increment following

TABLE 3 Methods and cut off used for anti-a/B high-titre testing

Country	What is tested	Test donor or final product	Method, IgM and IgG and cut off used	Tested every donation	Units labelled with titre?
Australia	All donations for platelets and plasma.	Donor	IgM at 1/32 and 1/64 (1:32 shown to be equivalent to 1/128 manual tube method). Apheresis platelet donors positive at 1/64 titred at 1/8000 and if positive deferred from platelet donation.	Yes	No. Labelled as low titre if they test as such.
Brazil	Platelet donors.	Donor	Gel card IgM for anti-A or B, 1/64 used as cut off.	Yes	No. Given on inventory report.
England	All donations.	Donor	Microtitre plate IgM anti-A and B cut off is 1/32 shown as equivalent to 1/128 manual saline tube method.	Yes	No. Labelled as low titre if they test as such.
France	All donations.	Donor	Microtitre saline IgM only >64 cut off.	Yes	No. Labelled with group compatibility.
Japan	Donations for HLA matched platelets if ABO non- identical.	Donor	1/128	Yes	No
Netherlands	Platelets for neonatal use.	Product	Saline tube for IgM, cut off 1/64, must be negative at 1/128.	Yes	No
New Zealand	All donations.	Donor	Micro-titre IgM and IgG using A1B cells. A > 50% reduction of the cell button defined as positive.	Yes	NR
Sweden	Apheresis donors.	Donor	Gel cards. IgM titres ≥64 and IgG titres ≥256 are considered high.	No - once	No. Labelled as high titre or low titre according to cut offs.

transfusion, which appears to be a cumulative effect [1]. This difference is small and does not appear to relate to risk of bleeding [2]. Effects of ABO mismatch on other measures of platelet outcome such as survival are less clear [6]. Some studies suggest that major ABO incompatibility may result in a higher risk of developing HLA or platelet specific antibodies [10] or transfusion reactions [11]. In addition to the development of alloantibodies in the recipient to antigens they lack, the development of immune complexes due to anti-A and/or B present in the recipient with the cognate antigen on donor platelets or soluble antigen has been postulated as a possible mechanism [12, 13].

In the PLADO study, a multi-centre RCT assessing different prophylactic platelet dose regimens, the degree of ABO matching (major or minor) was not associated with any overall difference in platelet alloimmunisation [14] or transfusion related adverse events [15] such as fever, allergic reactions, and tachycardia. There was a trend towards lower risk of febrile reactions in ABO minor mismatched platelets, which the authors attributed to chance. In critically ill children, transfusion of ABO incompatible platelets is not associated with difference in count increments or transfusion reactions [16].

Question 4 Despite steps taken in Question 3, do you observe cases of haemolytic transfusion reactions (HTR) to platelets, are these reported in national hemovigilance schemes and so forth, how frequent are they?

Fatalities associated with a HTR associated with ABO nonidentical platelet transfusion have been reported here and in the literature. In this survey, Germany report 13 fatal cases between 2000 and 2017. In the United States, seven fatal cases have been reported to the FDA between 2007 and 2018 [17]. The responses in this survey suggest that HTR associated with ABO non-identical platelet transfusion are rare events due to the mitigating actions in place although previously many of the centres/countries had reports. The residual risk of a HTR due to ABO non-identical platelet transfusion is estimated as 1:600,000 in Germany, 1:6250,000 in England, and 1:2 million in Japan. Several authors note, as might be expected, that this is more frequent with group O platelets to non-O recipients, due to higher titres of anti-A/B in group O donors.

The relationship between titre level and risk of haemolytic transfusion reactions is not absolute [18]; there are case reports of HTR with platelets that have tested as "low titre" especially in neonatal patients [19]. Additionally, the risk of platelets in additive solution is not zero, in part because for apheresis platelets about 100 ml of plasma from one donor remains in the platelet, and occasionally donors may have very high titres of anti-A/B. In addition to genetic factors that likely influence a donor's level of anti-A/B, environmental factors such as pneumococcal vaccination and pro-biotics have been reported to boost levels in some donors [20-22]. Recent data on a large range of other vaccines suggest that in the main, these have minimal effect [23]. Interestingly to mitigate the risk of very high levels, Australia re-test all donors who test "high titre" using their screening method at a very high titre of 1/8000; any donors testing positive at this level are deferred from platelet donation. Further, pooling and use of PAS would be expected to reduce the risk of HTR to lower than that for apheresis platelets as only a small volume of plasma from each donor will end up in the final product transfused as an example, this is around 20 ml of plasma from each donor in buffy coat platelets in our country (UK). Comprehensive risk modelling using large data sets for PAS platelets and risk of HTR are lacking.

Nonetheless, the responding countries who have implemented routine screening of platelet donors for anti-A/B report that the risk of HTR is now very low based on data from their hemovigilance scheme; this includes large national providers such as the UK, France and Australia. The UK have not observed any fatal cases since the UK-wide standardization of routine testing of anti-A/B, as is also the case for Australia. New Zealand also note that they have not observed any cases of HTR associated with ABO non-identical platelet transfusion since the universal implementation of PAS.

RhD

Question 5 Do you have national/regional clinical polices with respect to transfusion of RhD-negative platelets? For which group(s) of patients are RhD-negative platelets indicated?

Nearly all those responding (12/13) prioritized the use of RhDnegative platelets for RhD-negative women of child-bearing potential, the definition of which, where given, varied between 45 and 55 years of age (Table 4). Several of these national policies also included RhDnegative children in this category. Policies for other RhD-negative patients varied. Japan does not have a national policy due to the low (<0.5%) frequency of RhD-negative individuals in the population. Russia does not take RhD into consideration when transfusing platelets.

Question 6 If RhD-negative platelets are not available for the above patients what mitigation steps are taken to reduce the risk of alloimmunisation if RhD-positive platelets are transfused?

In 10/15 if RhD-positive platelets are transfused to a RhD-negative females of child-bearing potential (as defined by their policy), then anti-D prophylaxis is routinely given/recommended. In a further 3/15, anti-D may be given at the discretion of the treating physician. Only New Zealand routinely use anti-D for male children in this situation. Interestingly, both New Zealand and France take into account the clinical status of the patient in the decision to administer prophylactic anti-D: this may not necessarily be given if patients are immunosuppressed. In addition to the volume of red cells transfused, recipient factors are thought to contribute to the likelihood of alloimmunisation to RhD. In healthy volunteers, even small doses of RhD-positive red cells are near certain (80%) to induce alloantibody formation in RhDnegative individuals [24]. However, the reported frequency of alloimmunisation when RhD-positive platelets are transfused to RhDnegative patients is reported to be relatively low at approximately 1.5% [25]. The latter study was a large multi-centre study that included all indications for platelet transfusion, as such a significant proportion of recipients were immunosuppressed either through treatment or pathology.





TABLE 4 Policy and practice for RhD matching

	National/ local	Patients for whom RhD neg indicated	Assessment of red cell	
Country	policies	& policy, if not available	contamination (cut off applied)	Is alloimmunisation to RhD reported?
Australia	National	RhD-neg females of CBP. Anti-D unless immunosuppressed.	Visual–colour chart (1 ml red cells).	No. HV system captures alloimmunisation post-transfusion.
Brazil	National	RhD-neg females <45y. Anti-D.	Visual	Yes. Reportable to HV scheme.
Canada	Local	RhD-neg females <45y. May be extended to all children in some sites. Anti-D for women <45y, boys at physician discretion.	Visual – colour chart.	Yes. Reporting is voluntary.
England	National	RhD-neg females of CBP. RhD- negative boys <18, pre-existing anti-D antibodies, and transfusion- dependant adults. Anti-D for women of CBP.	Visual – colour chart ~4 x 10 ⁹ RBC/L.	No. Anti-D in women of CBP reportable to HV scheme. No cases in past 10 years.
France	Local	RhD-neg females <50y. Anti-D unless immunosuppressed.	Visual	Yes. Recommended to test 1–4 months after RhD incompatible transfusion.
Germany	National	RhD-neg women of CBP. Children <14y. Anti-D.	FBC and QC by flow cytometry (3 \times 10 9 RBC/L).	No
India	Local	RhD-neg women of CBP if available. Anti-D at discretion of treating physician	Visual (0.5 ml or 5 \times 10%).	No
Japan	None	RhD-neg patients, may use anti-D in rare cases of RhD pos to RhD-neg women of CBP, but use is off label.	Annual QC 10 per year.	None reported in last decade.
Netherlands	National	RhD-neg females <45. Anti-D except for <3 months old.	Visual (6 \times 10 ⁹ RBC/L).	Yes to national HV scheme.
New Zealand	National	RhD-neg females <55. Other RhD-neg patients if available. Anti-D for females <55 and male children. Underlying condition/treatment considered in risk of alloimmunisation.	No routine testing but data from studies.	No. 2y analysis where RhD pos given to RhD-neg patients without anti-D showed 1.4% alloimmunisation.
Russia	None	D, C, c, E, e, and K are not taken into acco concentrates obtained by apheresis o pathogen-reduced platelet.	No	
Saudi Arabia	Local	All RhD-neg patients but especially females of CBP. Anti-D.	Visual colour chart (>2 ml red cells)	Reportable to local HV scheme, not all hospitals will have this.
Spain	Local	RhD-neg women of CBP, anti-D for females<50.	Visual + QC of PC by flow cytometry	No, but as most recipients also on chronic red cell support should be picked up in pre-transfusion testing.
Sweden	Local	All RhD-neg patients. For women of CBP and children RhD pos must be approved by a physician. For trauma/major bleeding, RhD pos may be used regardless of group/ age/sex of recipient. Anti-D for women of CBP and children.	Visual	No Risk considered low

Question 7 Do you routinely assess the level of red cell contamination of platelets?

- Is this information on the label or shared with hospitals that use the platelets?
- By what method and what is the upper limit considered acceptable to issue platelets?
- Virtually all responding participants (12/15) perform a visual inspection of platelets and have a colour chart to prevent those

grossly contaminated with red cells being issued, but the cut offs used vary. The American Association of Blood Bank guidelines are followed by two respondents, which state that if platelets appear to contain ≥ 2 ml of residual red cells, making the component appear pink to salmon in colour, compatibility testing with the recipient's plasma is required [26]. India and Australia use a cut off of 0.5 ml and 1 ml, respectively, whereas Germany, England, and the Netherlands use cut offs that equate to 3, 4, and 6×10^9 RBC/L, respectively. Spain and Germany are the only respondents that routinely accurately measure the red cell contamination of platelets by flow cytometry.

Curiously, there are no European guidelines for routine quality control of red cell contamination of platelets, whereas guidelines state that prior to freezing, fresh frozen plasma should contain $<6 \times 10^9$ RBC/L [27]. This is somewhat surprising as the risk of alloimmunisation caused by RhD incompatible plasma is lower than that of platelets. First, levels of red cells in plasma prior to freezing are lower than in platelet concentrates, and second, red cell stroma following thawing is considered likely less immunogenic than intact red cells [24]. Consequently, in some jurisdictions, frozen-thawed plasma is transfused irrespective of RhD group.

For platelets, it is unclear what minimum number of red cells is likely to result in the formation of anti-D when RhD-positive platelets are transfused to RhD-negative recipients. Small volumes of pure red cells of 0.5 ml or above are known to result in 80% of healthy volunteers developing anti-D, 20% being non-responders [28]. Before the advent of current antibody production techniques, this was used as a method of harvesting anti-D for purification and therapeutic use. The minimum quantity of red cells required to result in anti-D formation following transfusion is frequently quoted as being 30 µl of pure red cells based on a study from 1970 [29]. However, in this latter study, volunteers were actually given 10 µl of red cells on three occasions, 2 weeks apart and thus the number of RBC that may cause primary sensitisation may be lower than cited. Thirty microliters of pure red cells is equivalent to approximately 0.8 $\times 10^9$ RBC/L in the volume of a unit of platelets and much lower than most centres' cut off for the acceptable levels of RBC in a unit of platelets described here.

Additionally, as well as intact red cells, platelets contain red cell microparticles that retain RhD antigens, the number of which varies by product type [30, 31]. However, red cell microparticles are not usually assessed by most methods that measure intact red cells. Intact red cells are known to be generally present at lower levels in apheresis compared to whole blood derived platelets [4, 32]. Contaminating red cell levels in buffy-coat derived platelets have been demonstrated to be substantially lower in platelets prepared using automated TACSI method compared to semi-automated [33]. Interestingly, France was the only respondent that routinely used TACSI to produce their whole blood derived platelets (70% of their supply), yet the rate of alloimmunisation for D mismatched platelets observed (1%) appears to be similar to other studies [25]. Conversely, factors in the recipient such as immunosuppression, as well as the frequency and amount of platelets transfused might all influence how many red cells will elicit a response.

Question 8 Do the answers to Questions 5 and 6 apply to all types of platelet, or does this depend on the level of red cell contamination?

All responding sites applied policies for RhD-negative platelet provision and mitigation of alloimmunisation to RhD irrespective of the type of platelets or red cell contamination.

Question 9 Do you have a system for routinely capturing cases of alloimmunisation to RhD due to platelet transfusions, in haemovigilance schemes for example?

5/15 respondents mention some form of reporting scheme where such cases may be captured. In addition, one country has recommendations on testing 1–4 months following RhD incompatible transfusion, and one has done a two-year analysis where RhD-positive platelets were given to RhD recipients without anti-D, showing 1.4% rate of alloimmunisation.

CONCLUSIONS

In summary, this international forum highlights some of the different approaches currently taken to provide ABO and RhD compatible platelets. It was notable that there was a significant difference in whether respondents prioritize major or minor ABO compatibility of platelets. This probably reflects the uncertainties with regards to the clinical consequences of ABO incompatible platelet transfusion. Approximately half of respondents prioritized the ABO group of the platelets themselves, indicating that the rationale was that the risk of a HTR due to minor incompatibility was reduced by the use of PAS and/or testing for high titre anti-A/B. This appears to be a shift in thinking with blood providers moving to platelets in PAS/introduction of testing. The risk of a HTR due to ABO incompatible platelets was estimated as being between 1:600,000 to 1:2 million, and several respondents noted that no fatal cases had been observed since the introduction of routine testing for high titre anti-A/B. Risk assessments based on large data sets are needed to fully understand how much PAS reduces the risk of HTR from ABO minor incompatible platelet transfusion.

For RhD, most respondents prioritized RhD-negative platelet provision for RhD-negative females of child-bearing potential, and most either gave or recommended the use of prophylactic anti-D if RhDpositive platelets were transfused to this group. Only two respondents considered whether recipients were immunosuppressed in the decision to give prophylactic anti-D, as these patients are less likely to form alloantibodies to mis-matched platelets. Most respondents visually assess the level of red cell contamination of platelets, with varying cut offs for maximal acceptable levels. However, these are all above the level likely to be capable of causing alloimmunisation to RhD in RhD-negative individuals who are immunocompetent. Studies assessing whether a reduction in intact red cells and/or microparticles will reduce the risk of alloimmunisation are needed to fully understand whether such an approach may be beneficial.

ORCID

 Rounak Dubey
 https://orcid.org/0000-0002-9467-5759

 Magnus Jöud
 https://orcid.org/0000-0002-4734-0040

 Joan Cid
 https://orcid.org/0000-0001-5445-4508

 Miquel Lozano
 https://orcid.org/0000-0003-2593-833X

 Peter Flanagan
 https://orcid.org/0000-0001-5270-3910

 Gwen Clarke
 https://orcid.org/0000-0001-7738-3378

 Salwa Hindawi
 https://orcid.org/0000-0003-3804-5434

 Jose Mauro Kutner
 https://orcid.org/0000-0003-3784-6731

REFERENCES

- Triulzi DJ, Assmann SF, Strauss RG, Ness PM, Hess JR, Kaufman RM, et al. The impact of platelet transfusion characteristics on posttransfusion platelet increments and clinical bleeding in patients with hypoproliferative thrombocytopenia. Blood. 2012;119:5553–62.
- Slichter SJ, Kaufman RM, Assmann SF, McCullough J, Triulzi DJ, Strauss RG, et al. Dose of prophylactic platelet transfusions and prevention of hemorrhage. N Engl J Med. 2010;362:600–13.
- Lozano M, Heddle N, Williamson LM, Wang G, AuBuchon JP, Dumont LJ, et al. Practices associated with ABO-incompatible platelet transfusions: a BEST collaborative international survey: PLATELET TRANSFUSION AND ABO INCOMPATIBILITY. Transfusion 2010;50:1743-8.
- Culibrk B, Stone E, Levin E, Weiss S, Serrano K, Devine DV. Application of the ADVIA cerebrospinal fluid assay to count residual red blood cells in blood components: automated counting of residual red blood cells. Vox Sang. 2012;103:186–93.
- Cid J, Yazer MH, Lozano M. Platelet transfusion and respecting patient D type. Curr Opin Hematol. 2015;22:540–6.
- Shehata N, Tinmouth A, Naglie G, Freedman J, Wilson K. ABOidentical versus nonidentical platelet transfusion: a systematic review. Transfusion 2009;49:2442–53.
- Gottschall J, Wu Y, Triulzi D, Kleinman S, Strauss R, Zimrin AB, et al. The epidemiology of platelet transfusions: an analysis of platelet use at 12 US hospitals. Transfusion 2020;60:46–53.
- Sprogøe U, Yazer MH, Rasmussen MH, Antonsen B, Bistrup C, Assing K. Minimal variation in anti-a and -B titers among healthy volunteers over time: implications for the use of out-of-group blood components. J Trauma Acute Care Surg. 2017;82:S87–90.
- Harm SK, Yazer MH, Bub CB, Cohn CS, Jacob EK, Kutner JM, et al. Seasonal variability is not observed in the rates of high anti-a and anti-B titers in plasma, apheresis platelet, and whole blood units tested by different methods. Transfusion 2019;59:762–7.
- Carr R, Hutton JL, Jenkins JA, Lucas GF, Amphlett NW. Transfusion of ABO-mismatched platelets leads to early platelet refractoriness. Br J Haematol. 1990;75:408–13.
- Malvik N, Leon J, Schlueter AJ, Wu C, Knudson CM. ABOincompatible platelets are associated with increased transfusion reaction rates. Transfusion 2020;60:285–93.
- 12. Blumberg N, Refaai M, Heal J. ABO matching of platelet transfusions "start making sense". Blood Transfus. 2015;13:347–50.
- Zaffuto BJ, Conley GW, Connolly GC, Henrichs KF, Francis CW, Heal JM, et al. ABO-immune complex formation and impact on platelet function, red cell structural integrity and haemostasis: an *in vitro* model of ABO non-identical transfusion. Vox Sang. 2016; 110:219-26.
- Hess JR, Trachtenberg FL, Assmann SF, Triulzi DJ, Kaufman RM, Strauss RG, et al. Clinical and laboratory correlates of platelet alloimmunization and refractoriness in the PLADO trial. Vox Sang. 2016;111:281–91.

 Kaufman RM, Assmann SF, Triulzi DJ, Strauss RG, Ness P, Granger S, et al. Transfusion-related adverse events in the platelet dose study: PLT transfusion adverse events. Transfusion 2015;55:144–53.

- Nellis ME, Goel R, Karam O, Cushing MM, Davis PJ, Steiner ME, et al. Effects of ABO matching of platelet transfusions in critically ill children*. Pediatr Crit Care Med. 2019;20:e61–9.
- Food & Drug Administration. Transfusion/Donation Fatalities [Internet]. [cited 2021 Feb 2]. US Food and Drug Administration. Transfusion/Donation Fatalities. https://www.fda.gov/vaccines-blood-biologics/report-problemcenter-biologics-evaluation-research/transfusiondonation-fatalities
- Karafin MS, Blagg L, Tobian AAR, King KE, Ness PM, Savage WJ. ABO antibody titers are not predictive of hemolytic reactions due to plasma-incompatible platelet transfusions: high-titer plasmaincompatible AP transfusions. Transfusion 2012;52:2087-93.
- 19. Serious Hazards of Transfusion Annual Reports 1996–2019 [Internet]. [cited 2021 Feb 2]. https://www.shotuk.org/shot-reports/
- Noël A. Anti-A isoagglutinins and pneumococcal vaccine. Lancet. 1981;318:687–8.
- Wolfram W, KMT S, Binder CJ, Eibl-Musil N, Wolf HM, Fischer MB. Pneumococcal polysaccharide vaccination elicits IgG anti-a/B blood group antibodies in healthy individuals and patients with type I diabetes mellitus. Front Immunol [Internet]. 2016;7 [cited 2021 Feb 5]:493.
- Daniel-Johnson J, Leitman S, Klein H, Alter H, Lee-Stroka A, Scheinberg P, et al. Probiotic-associated high-titer anti-B in a group a platelet donor as a cause of severe hemolytic transfusion reactions. Transfusion 2009;49:1845–9.
- Berséus O. Effects on the anti-ABO titers of military blood donors from a predeployment vaccination program. J Trauma Acute Care Surg. 2017;82:S91–5.
- 24. Klein A. Mollison's blood transfusion in clinical medicine. 12th ed. Hoboken, New Jersey: Wiley-Blackwell; 2014.
- Cid J, Lozano M, Ziman A, West KA, O'Brien KL, Murphy MF, et al. Low frequency of anti-D alloimmunization following D+ platelet transfusion: the anti-D Alloimmunization after D-incompatible platelet transfusions (ADAPT) study. Br J Haematol. 2015;168:598-603.
- 26. Standards for blood banks and transfusion services. 32nd ed. Bethesda, Maryland: AABB publishing; 2020.
- Guide to the preparation, use and quality Assurance of Blood Components. 20th ed. Strasbourg, France: Council of Europe Publishing; 2020.
- Gunson HH, Stratton F, Cooper DG, Rawlinson VI. Primary immunization of Rh-negative volunteers. BMJ. 1970;1:593–5.
- Jakobowicz R, Williams L, Silberman F. Immunization of Rh-negative volunteers by repeated injections of very small amounts of Rhpositive blood. Vox Sang. 1972;23:376–81.
- Thibault L, de Grandmont MJ, Cayer M-P, Dussault N, Jacques A, Ducas E, et al. Rhesus D antigenic determinants on residual red blood cells in apheresis and Buffy coat platelet concentrates. Transfus Med Hemother. 2020;47:129–34.
- Victoria E, Branks M, Masouredis S. Immunoreactivity of the rho(D) antigen in cytoskeleton-free vesicles. Transfusion 1987;27: 32–5.
- Santana JM, Dumont LJ. A flow cytometric method for detection and enumeration of low-level, residual red blood cells in platelets and mononuclear cell products. Transfusion (Paris). 2006;46: 966–72.
- Cavagnetto C, Blanco RA, McKenna H, Willmott L, Aydogdu E, Akinyemi N, et al. Residual red cells in blood components: a multisite study of fully automated enumeration using a hematology analyzer. Transfusion 2020, published ahead of print. https://doi.org/10. 1111/trf.16196

143

Guest Editors Rebecca Cardigan NHS Blood & Transplant, Cambridge, UK Email: rebecca.cardigan@nhsbt.nhs.uk

Helen V. New NHS Blood & Transplant, London, UK Email: Helen.new@nhsbt.nhs.uk

Lise Estcourt NHS Blood & Transplant, Oxford, UK Email: lise.estcourt@nhsbt.nhs.uk International Forum Editor Nancy Dunbar Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA Email: Nancy.M.Dunbar@hitchcock.org

How to cite this article: Cardigan R, New HV, Estcourt L, Zhiburt E, Dubey R, Bengtsson J, et al. International Forum on Policies and Practice for Transfusion of ABO and RhD Non-Identical Platelets: Summary. Vox Sang. 2022;117:136–144.