Molecular immunohaematology round table discussions at the AABB Annual Meeting, Denver 2013

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Introduction

Six topics were discussed by an international group of transfusion medicine specialists during a 1.5-hour workshop at a conference with strong international attendance in 2013. The molecular immunohaematology concepts addressed may be challenging even for some established professionals in the field of blood group serology[1]. The format of this workshop was similar to that of an international forum held in 2012[2]. The opinion and input from experienced professionals were polled. We provide a summary report of the items discussed and issues raised by the participants.

Organisation of the discussion rounds

Transfusion medicine professionals gathered in the 1.5-hour session "Speed Dating for Molecular Immunohematology Professionals" (n. 9312-TC) on October 14, 2013 at the AABB Annual Meeting and CTTXPO 2013 in Denver, CO, USA. The session was offered to any attendee of the conference and designed using our experience from two similar sessions held in 2011 and 2012, the details of which were described previously[2]: a group of participants at a table met to discuss each topic for 10 minutes with a chaperone representing a single topic; the group stayed while another chaperone joined for the discussion of the next topic. The chaperones, experts in the field and selected prior to the workshop, listened to participants' viewpoints, clarified questions, took notes regarding the points raised and kept the discussion on track. Forty-four individuals registered for the session before the annual meeting and 62 attendees signed up on site; 25 evaluation forms (40%) were returned after the event (Table I).

Table I - Demographics of the participants.

Parameter and characteristics	Replies (n)	Percentage
Level of experience		
1-5 years	6	27%
6-10 years	2	9%
11-19 years	3	14%
20+ years	11	50%
Total	22	100%
*Position**		
Director/manager	6	26%
Supervisor/coordinator	4	17%
Lead/specialist	3	13%
All other replies combined	10	44%
Areas of specialty†		
Patient laboratory testing	7	32%
Molecular testing	4	18%
Education/training	2	9%
Clinical practice/patient care	2	9%
All other replies combined	12	55%
Relevance of content		
Excellent	17	77%
Good	4	18%
Fair	1	5%
Poor	0	0%

* Other replies: physician, resident/fellow/student, technologist/technician (n=2 each); other (n=4).
† Other replies: administration, donor product testing, quality/compliance, other (n=2 each); blood collection, cellular therapy, communication/PR/marketing, regulatory/legal/ethics (n=1 each). Multiple replies possible.
Replies may not sum up to 25, because some fields were not answered on all forms.

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Participants

The transfusion medicine professionals gathered with 12 chaperones and the moderator. There were groups of four to seven participants at nine tables. Participants included physicians, medical technologists, and basic scientists from blood donor centres and hospital-based blood banks (Table I). Several attendees represented blood banking-related industries. The participants hailed from 14 countries, comprising the USA, Canada, Mexico, Venezuela, Brazil, Lebanon, Egypt, Lesotho, Denmark, Austria, Italy, Spain, Thailand and New Zealand. The participants represented a broad range of expertise and experience in serology and molecular testing.

Round table discussions

All participants had the opportunity to give input on the six topics for discussion, designed as a starting point for deliberation and not considered conclusive statements. The six teams of two chaperones each provided the following summaries of their discussion rounds, which represented the views of the participants only.

Discussion 1: "Are SBB education programs in the US adequately preparing technologists for their leadership role in blood group genetics and in the technology underlying molecular testing of blood groups?"

Several participants had completed Specialist in Blood Bank (SBB) training[3], from as recently as 3 years previously to over 20 years ago. The general opinion was that most current programmes are not adequately preparing students for molecular testing, with a very few exceptions. All programmes should provide basic knowledge of blood group molecular genetics. This education in molecular immunohaematology needs to build on what is currently being taught for blood group systems.

The first generation platforms for molecular testing of blood groups are not widely used in institutions with SBB programmes and where such platforms are available financial considerations limit their further use. Currently, the only training technologists in most laboratories are receiving is from vendors of testing platforms. There was discussion on what role the vendors should play in training; most participants thought vendors could and should provide training information beyond performing the assay. Other training suggestions included: live demonstrations, videos, web-based/computer-assisted programmes with animation and case studies.

There was variable opinion on providing "hands on" experience with the testing, but it was felt that there is definitely a need to know how to interpret molecular results. This knowledge is important as molecular reference laboratories are sending reports to facilities that lack the experience or knowledge to understand the clinical implications. The suggested time needed for molecular training varied from 1 day to several weeks. The longer time period would include "hands on" work and following samples from testing to interpretation (Chaperones: DAW and JMM).

Discussion 2: "For antigens other than ABO, two historical antigen typings should become a standard for red cell unit labeling. If this becomes an accepted standard, which is best or are all equal: A) two phenotypes; B) one phenotype and one genotype; or C) two genotypes?"

Nearly all participants felt that two historical antigen typings would be an acceptable standard for product labelling of non-ABO blood group antigens (Table II). Participants from Canada indicated that a national standard of two historical antigen typings for labelling was already in place, while a participant from Italy mentioned that this practice was also in place at her facility. One individual wondered whether requiring a third historical typing before labelling would be slightly better from the standpoint of donor identification, while another participant recommended consideration of repeat testing. There was also general consensus that if a standard of two historical antigen typings was implemented, then these two typings should be carried out at two separate time points rather than testing performed twice on a single specimen.

Many participants voiced concerns about relying only on historical test results for Rh(D). With developing test platforms and the rare, but clinically significant, possibility for a change in donor phenotype, such as following haematopoietic progenitor cell transplantation[4,5], most participants felt more comfortable with repeat Rh(D) testing at every donation.

There was considerable discussion regarding the optimal approach for determining the expression (or lack thereof) of a donor's non-ABO antigens. A majority of participants who committed to one of the three options felt that the optimal approach to establishing the presence/absence of non-ABO antigens included one serological phenotype and one genotype (option B in Table II). The greater likelihood of identifying discordant results was seen as a favourable feature because they could be addressed and potentially benefit patients' care. Implementing such a standard could encourage reluctant donor centres to "catch up" with genotyping. The participants' thoughts on how to handle discrepant results were explored in the third discussion (see below).

Table II - Potential benefits and drawbacks of three different blood donor typing strategies and participants' preferences.

	Input by the participants*		
Options	*Potential benefits*	*Potential drawbacks*	*Participants (n) †*
a) Two serological phenotypes	Serological testing widely available. Licensed approach to antigen testing	Laborious. Reagents may not be available for all non-ABO antigens.	6
b) One serological phenotype and one genotype	Increased reliability based on two independent methods. Greater potential to identify discordant results. Lagging donor centres may be compelled to upgrade as well, if genotyping is widely implemented.	Increased cost associated with genotyping. Lack of genotyping platforms in some donor centres. Lack of licensure for molecular testing. Potential lack of reimbursement for molecular testing	16
c) Two genotypes	Robust, high-throughput assay. Ability to determine numerous variants and antigens for which antisera are in limited supply or lacking	Genotype may not equal phenotype. Increased cost with potential for lack of reimbursement. Lack of genotyping platforms in some donor centres. Lack of licensure for molecular testing. Potential lack of reimbursement for molecular testing	0
Total			22

*Some input applied to more than one option. The input listed for each option represents the opinions of all participants regardless of whether or not they indicated a preference.
†No multiple replies permitted. Only 22 participants committed a vote to a particular option.

The second most popular approach was testing two phenotypes (option A in Table II). While considered labour intensive and the possible lack of reagents represents a practical limitation, serological testing was ultimately concluded as the only feasible approach available in some countries or regions at this time. These participants also noted that if and when molecular methods are more widely available, option B would likely become their preference (Table II). No participant voted for option C nor did any of the participants feel that the three options were equally valid (Chaperones: CAT and EBK).

Discussion 3: "How should a red cell unit be labeled when the blood group (serologic) phenotype is or appears to be discordant with the (molecular) genotype?"

The groups at six of the nine tables found a consensus from a practical perspective for this general question: they recommended labelling and releasing the red cell unit as antigen positive, without waiting for the discrepancy to be resolved. Two participants suggested withholding the unit until the discrepancy is resolved. One participant recommended labelling as "indeterminate" and one relying on the serological result only.

Three specific scenarios were presented and discussed in more detail. (i) A donor types as D antigen negative in routine serology and as *RHD* gene positive in a polymerase chain reaction. The primary recommendation of the groups at seven tables was to resolve the issue, usually by repeating the serological test. If this approach fails, the groups at four tables recommended releasing the red cell unit as Rh(D) positive while the group at one table recommended releasing it as Rh(D) negative. Some participants recommended deferring the donor from future red cell donation because of anticipated problems in the confirmatory testing at transfusing institutions. (ii) A donor carries the *(C)cde*^{s}-allele known to express an atypical C antigen. The groups at seven tables suggested labelling the red cell unit as "C positive". The groups at three tables suggested retaining this valuable information in a database and utilizing blood collections from this donor for specific patients; the participants recognised that *(C)cde*^{s} expresses a partial C antigen, which may be the preferred unit for patients with the same haplotype and an anti-C. (iii) A donor was historically characterised by serology as negative for an antigen of high prevalence, such as Lu^{b}, and is now found to be a compound heterozygote including one standard allele with a mutation of unknown impact, such as a missense mutation. No group reached a consensus on this complex situation that will be encountered more frequently in genotyping of large numbers of donors. About half of the participants recommended retaining the unit as a rare inventory for patients in special need of such units and the other half recommended discarding the unit (Chaperones: FFW and FNP).

Discussion 4: "Which antigen(s), other than ABO and D, should be prophylactically matched for red cell transfusions to girls and women of childbearing age?"

Several factors were considered to influence a decision for prophylactic matching. The key factor was the prevalence of haemoglobinopathies, such as thalassaemia, sickle cell disease, myelodysplastic syndrome, and other conditions necessitating frequent transfusions, as certain countries may not have a high enough proportion of these patients to warrant a policy for prophylactically matching all transfusions in girls and women.

The majority of participants recommended that antigen-matched blood should be reserved for patients who have developed antibodies, because most patients will not develop any antibody[6]. Following formation of at least one antibody, some participants would prophylactically match for the C, E and K1 (Kell) antigens[7]. Although anti-K1 was considered a serious problem causing haemolytic disease of the foetus and newborn (HDFN), prophylactic matching of the K1 antigen caused much discussion. Short of a universal agreement among the participants, it was widely accepted that the K1 antigen should be prophylactically matched for girls and women of childbearing age. Some participants also recommended K1-negative blood units for all chronically transfused patients.

The feasibility of prophylactic matching was discussed from the perspectives of cost, turnaround time for phenotyping, and availability of inventory. Responses differed according to affiliation and country of origin. Participants from blood agencies and hospitals were concerned about the increased cost of such blood units, which could slow the adoption of the policy or prevent it from becoming a standard. The turnaround time for phenotyping was not considered a limitation by the industry but concerned hospitals without ready access to matched blood units. For instance in the USA, individuals affiliated with industry considered prophylactic matching was feasible and felt it could be rapidly provided. Centralised databases were favoured to identify suitable blood units and distribute available inventory (Chaperones: NS and SW).

Discussion 5: "*Routine* genotyping in the prenatal clinic could prevent the exposure of RhIG to women who express those weak D types that do not pose a risk of making anti-D. What are the reasons for the failure to universally adopt this procedure?"

The polling of the participants revealed a number of reasons for the slow adoption of a policy change (Table III). More than 80% of the participants reported a reason for the failure to adopt the new procedure and only seven participants abstained from identifying any such reason. A clear majority of the participants traced the failure of universal adoption to the obstetricians, who may not be aware of the benefits to their patients offered by the available molecular immunohaematology technologies. The cost, with lack of reimbursement, was the second most relevant reason. No participant raised the lack of Food and Drug Administration approval or the need for send-out tests as a primary reason for lack of adoption. Screening for molecular weak D types in an effort to limit RhIG administration is already practised in some form at the institutions of participants from Austria, Denmark, Italy and Québec/Canada, but not at any institution of the USA participants (Chaperones: GS and MD).

Table III - Reasons for the failure to universally adopt weak D genotyping in Rh(D) negative mothers from the perspective of immunohaematologists.

Primary reason	Participants (n) *
Lack of sufficient knowledge about this novel topic	
Among obstetricians	19
Among transfusion medicine physicians	1
Unsure about cost reimbursement	7
Reluctance to abandon a tried and true practice	5
RhIG in current practice	
Not universally applied to weak D	4
Not standard of care for weak D	3
Risk of RhIG is perceived to be small	3
Unsure/abstain	7
Total	49

*No multiple replies permitted.

Discussion 6: "All transfusion recipients should ultimately be red cell genotyped to prevent alloimmunization through "dry" matched transfusions. What are the reasons to support or to limit this statement?"

Several reasons were cited by the participants as to why "dry" matched transfusions should or should not be used to prevent alloimmunisation (Table IV). All participants were familiar with the concept of molecular-based matching ("dry" matching) by genotype without attempting to determine the blood group phenotype[8]. Many participants suggested that "dry" matching at this time should be limited to defined groups of patients and certain antigens. Specifically, patients needing chronic transfusion, such as those with haematological or sickle cell disease (SCD), were considered to benefit from this approach.

Patients with SCD often descended from sub-Saharan populations, where many variants of RHD and RHCE antigens or phenotypes, such as U− and Fy(a−b−), are prevalent. For such patients, red cell genotyping was generally accepted as helpful in detecting clinically relevant blood group variants and "dry" matched transfusions were regarded as possibly beneficial in

Table IV - Rationales, when considering "dry" matched transfusions.

Pros	Cons
Chronically transfused patients will benefit.	Costs and reimbursement are not defined.
Some patients with autoantibodies will benefit.	Commercial platforms have not been approved by the Food and Drug Administration.
Red cells can be matched for antigens, when no commercial reagents are available today.	Null phenotypes of blood group continue to be detected and are a concern.
The concept lends itself to automation.	ABO genotyping will not be available for some time.

preventing alloimmunisation. Participants from three centres reported that they already genotype donors of African origin and SCD patients routinely and "dry" match transfusions of their SCD patients.

Several participants regarded the turn-around-time as a limitation to red cell genotyping in the setting of patients' care. It is not an alternative to fast serological typing in emergency situations. For elective transfusions participants readily considered red cell genotyping. Cost effectiveness and reimbursement issues concerned most. Questions were raised concerning how many blood group systems should be "dry" matched and which blood donors should be genotyped. It was felt that extended matching may require larger inventories than exist today, increasing costs through outdating. Several participants wondered whether donation centres could provide all genotype information available for a blood unit and at what additional fee. A few participants noted that the majority of transfused patients do not develop antibodies. One participant reported on positive experience with the serological approach to selection and cross-matching of red cells in chronically transfused patients (Chaperones: CW and LC).

Comments by the authors

The round table discussions represented a global cross-section of immunohaematology experience among individuals with diverse professional backgrounds (Table I). Here we summarise and comment on the participants' input.

Discussion 1

The general opinion was that most of the currently sixteen accredited SBB programmes in the USA[3] are not adequately preparing students for molecular immunohaematology. This contrasts sharply with the perceived need for knowledge and experience to understand the clinical implications. However, at least three SBB students received an AABB-Fenwal Scholarship Award for molecular immunohaematology projects in 2004[9], 2011[10] and 2013[11] and other such SBB projects were published[12,13]. Training the trainers in the USA and elsewhere[14] will be a key to a wider implementation of molecular immunohaematology in SBB programmes and beyond.

Discussion 2

There was a general consensus among the immunohaematology practitioners that two historical antigen typings would be an acceptable standard for red cell product labelling of blood group antigens other than ABO and Rh(D). This procedure has been standard practice in many countries, such as Canada, German-speaking and Scandinavian countries, Israel and Australia, but not in the USA, the UK, China or New Zealand[15]. Reliable donor identification, required for using historical data, is apparently considered possible in many countries. The optimal approach for antigen typing was expected from a combination of at least one phenotype and one genotype (option B in Table II), although this was not reported by any participant as a standard practice at this time. The majority of participants did not commit to one of the three options, which may reflect limited experience and an interest to learn more about the genotyping option; they were not convinced that the currently mandated approach (option A in Table II) is the best option for patients' care.

Discussion 3

When a new technique is introduced to confirm parameters of record, discrepant results will occur. A strategy should be in place to intercept and resolve discrepancies. As expected, most participants opted for a cautionary approach and erring on the accepted "safe side", such as labelling a red cell unit as antigen positive or quarantining the unit until further testing resolved the discrepancy. Based on previous experience with introducing new techniques in a blood centre, several participants anticipated problems in the hospital and opted for pragmatic approaches. The exclusion of donors from further red cell donation may be unwarranted and cause the loss of precious units with rare phenotypes.

To resolve a discrepancy the repetition of serology was commonly recommended. Few participants opted for the molecular characterisation of the underlying allele, although this is in many instances the only way to resolve the discrepancy. Some participants opted to ignore the molecular data altogether and to label the unit based on the licensed serological method; this may be perceived as the mandatory approach in some jurisdictions, particularly the USA, but forgoes the opportunities offered by genotyping to improve patients' care.

Discussion 4

The need to prevent HDFN by prophylactic matching in girls and women of childbearing age and the antigenic potency of K1 were well recognised. Cost considerations and the lack of suitable informatics support to identify antigen-matched blood were considered impediments to a wide implementation of such prophylactic matching. Apart from the D antigen, the antigens K1, E and G (a combined specificity of D and C) occur most frequently in pregnant women with alloantibodies[16,17]. These data explained the choice by many participants to prophylactically match C, E and K antigens following alloimmunisation. However, this choice does not reflect the antigen potency of c, C^w and Lu^a, which are known to be more immunogenic than C, as previously estimated in male transfusion recipients[18].

Discussion 5

RhIG is generally administered to all Rh(D) negative women during pregnancy and after the birth of a Rh(D) positive baby. Depending on the serological technique, a weak D phenotype may be missed, often purposefully, and the mother typed as Rh(D) negative; RhIG may also be administered to women regardless of her recognised weak D phenotype[19,20]. Evidence has been gathered that many mothers with a weak D phenotype do not benefit from RhIG and weak D genotyping can specifically detect such mothers[21].

The perceived small risk of RhIG and the reluctance to change a tried practice were pointed out by eight participants (Table III), because RhIG has an excellent safety record for decades in the USA, although not everywhere in the past 50 years. Withholding RhIG is a recommended practice in the USA, as pointed out by seven participants, and the right strategy for mothers with the common weak D phenotypes, but not for most mothers with less common weak D phenotypes. Only molecular immunohaematology can discriminate the two groups who do or do not benefit from RhIG and resolve the proper indication to administer or withhold RhIG[19,22]. There may be direct costs to administering RhIG, besides the cost of the product itself, and also "indirect" costs, such as discomfort and adverse effects, associated with any unnecessary RhIG administration.

Discussion 6

Costs and lack of reimbursement were the primary concerns of many participants (Table IV), who would readily apply red cell genotyping to prevent alloimmunisation through "dry" matched transfusions, if funding were available. Modes for reimbursement are in place in many health care systems and are becoming implemented in the USA as well. Further development of red cell genotyping might reduce both the costs of genotyping and the turn-around-time[23]. A wider application of this technology might facilitate such progress by economies of scale.

Conclusion

This international forum documented the breadth of knowledge regarding six current topics, as well as the acceptance and concerns among a large and varied international group of transfusion medicine specialists. These topics, with questions limited to areas of interest, may be valuable for other professional gatherings, such as Obstetrics and Gynaecology as well as Haematology. Collating such information is essential for the developing arena of molecular immunohaematology, as the perception of experienced specialists will be critical in shaping the adoption of this new technology in our field.

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Authorship contributions

WAF and GAD designed the topic statements and organised the session. The six teams of two chaperones, who volunteered to participate, each wrote the summaries of their discussion rounds. GAD moderated the session; and WAF compiled and wrote the report.

Conflict of interest disclosure

FFW receives royalties for RHD genotyping. GAD is a beneficiary of blood group genotyping patents in European countries. JMM is an employee of Grifols Diagnostic. LC is on the Transfusion Advisory Board of Grifols. MD received travel support from BioArray/Immucor. WAF receives royalties and holds intellectual property rights for RHD genotyping applications. The remaining authors do not have conflicts of interest relevant to this article.

Statement of disclaimer

The views expressed do not necessarily represent the view of the National Institutes of Health, the Department of Health and Human Services, or the U.S. Federal Government.

At the time of the meeting, none of the molecular immunohematology assays for blood group genotyping

had been approved by the US Food and Drug Administration (FDA). When used for patient care the tests come under the authority of the Clinical Laboratory Improvement Amendments (CLIA) and are categorised as tests of either "high" or "moderate" complexity.

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