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ORIGINAL PAPER

Red-blood-cell alloimmunization and prophylactic antigen matching for transfusion in patients with warm autoantibodies

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Background Warm autoantibodies (WAA) are antibodies that react with an antigen on a patient's own red-blood-cells and can complicate compatibility testing whether or not they cause clinical haemolysis. The goal of this study was to understand the overall prevalence of WAA, the risk of RBC alloimmunization and determine whether RBC selection practices have an impact on alloimmunization.

Materials and methods Records of patients (>1 year of age) with an indirect antibody detection test (IAT) and serologic evidence of WAA over a 10-year-period were included. Eight centres from 5 countries collectively reviewed 1 122 245 patients who had an IAT.

Results Of patients having IAT, 1214 had WAA (0·17%). Transfusion information for 1002 of the patients was available; 631 were transfused after identification of the WAA (63%); of the transfused patients, 390 received prophylactic antigen-matched (PAM) RBCs and 241 did not. Of the 372 patients with WAA who were transfused and had serologic testing 30+ days following transfusion (30–2765 days), 56 developed new RBC alloimmunization (15·1%). Patients who were transfused using a PAM strategy were not protected from new RBC alloimmunization [14·6% (31 of 212 patients) having PAM transfusion approach compared with those not receiving PAM approach (15·6%, 25 of 160 patients, P = 0·8837)].

Conclusions The prevalence of WAA in patients having an IAT is low (<1%). A significant portion of patients with WAA form new RBC alloimmunization (15·1%); however, the use of PAM approach for RBC selection was not found to be protective against new alloimmunization.

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Introduction

Warm autoantibodies (WAA) are IgG phase autoantibodies detected in the plasma of patients [1] and react with antigens on the patient's red-blood-cells (RBCs). These antibodies can be clinically significant causing autoimmune haemolytic anaemia (AIHA), a relatively uncommon clinical diagnosis (1–3 cases per 100 000/year), or can be clinically insignificant and not harmful to the patient [2]. The prevalence of WAA in published accounts is reported to be as high as 17%, depending on the population and approach to immunohematology testing [1,3,4].

The optimal approach to pre-transfusion testing for patients with WAA is not established, hence, practice varies [5]. In the setting of WAA, studies have demonstrated the presence of concurrent alloantibodies in 10–53% of patient specimens tested [6-13]. Given that failure to identify an underlying alloantibody may lead to a haemolytic transfusion reaction (HTR), the transfusion service laboratory must determine whether alloantibodies are present. Most centres (75%) use an autoadsorption procedure (42% would use alloadsorption when needed) to remove the WAA from the patient's plasma and then perform the indirect antiglobulin test (IAT) with adsorbed plasma to detect underlying alloantibodies, while 21% use saline IgG technique [5]. When a patient has been previously transfused, the more technically complex alloadsorption approach should be used [5]. For patients who require repeat transfusions, this approach can lead to the need for successive, labour-intensive and time-consuming adsorption procedures which are not routinely available in hospital-based transfusion services, and therefore, the patient specimen must be sent to a reference laboratory for complete testing, increasing the wait time for transfusion and increasing cost [14].

Red-blood-cell selection is also not standardized in this patient population with some institutions providing more closely antigen-matched units in an attempt to avoid future alloimmunization and haemolytic transfusion reactions, and reduce the number of repeat adsorptions with subsequent testing. Even when laboratory policies to provide antigen-matched units exist, they vary in the extent of the extended matching provided. Further, the actual RBC match for each transfusion event may not reflect local policy given the feasibility of finding antigen negative cells and the urgency of transfusion. In 2015, a survey of transfusion services and immunohematology reference laboratories queried their approaches and policies to practical laboratory questions related to patients with WAA. Of 51 respondents worldwide, 75% and 67% provide prophylactically antigen-matched (PAM) RBCs for transfusion for patients with WAA, with and without a clinical diagnosis of AIHA, respectively, though the degree of antigen matching varies from partial (Rh and Kell antigens) to full extended matching (Rh, Kell, Kidd, Duffy and MNS antigens). The percentage of institutions providing PAM units slightly increased to 76% and 71%, respectively when the patient had a concurrent alloantibody [5]. When utilizing a PAM approach, Shirey et al found that 4·25 adsorption procedures could be avoided per patient [14]. Authors have shown that using antigen-matched units based on genotyping results, in the absence of traditional haemagglutination testing to detect underlying alloantibodies prior to transfusion, provided satisfactory post-transfusion recovery in a small set of patients [15]. Thus, the approach to confirming the absence (or identification) of RBC alloantibodies in patients with WAA is also connected to the approach to RBC unit selection.

The practice of prospective antigen matching for patients with WAA is not only utilized to decrease the need for repeat adsorption procedures but also to improve the safety of the RBC transfusion for a patient who is felt to be at risk for ongoing transfusion support. The rate of patients with WAA and concurrent RBC alloimmunization range widely from publication to publication; 10–53% [6-13,16]. The rate of patients with WAA developing RBC alloimmunization after identification has only been studied in small and single centre studies and is further complicated by the disappearance of alloantibodies over time [17].

Our multicentre study was created to (1) define, in a generalizable way, the prevalence of finding of WAA in samples sent for serological testing, (2) determine the disease associations with WAA, (3) determine the prevalence of RBC alloimmunization in this patient group, (4) assess the incidence of RBC alloimmunization post-WAA identification and (5) estimate the impact of blood product selection on development of alloimmunization when feasible.

Materials & methods

The cohort study was approved by each sites' institutional ethics review board. Chart review was performed on patient records for 10 years between 1 January 2007 and

31 December 2016. Patient records were reviewed if the patient had an antibody detection test (IAT), also called antibody screen and was ≥1 year of age. Patients were excluded if they had a known drug-induced autoantibody, if the patient was taking daratumumab or other anti-CD38 agent, or if the patient had a diagnosis of sickle cell disease (SCD). SCD patients were excluded because of their known high rate of alloimmunization and autoimmunization which would cause bias if included with the patients without SCD [18]. Results of the chart reviews were de-identified at each participating centre and added to a study database for grouped analysis.

The patient records were assessed for the presence of a WAA that met a standardized study definition; WAA detected during IAT testing that was defined as a pan-agglutinin in serum and/or eluate with a positive auto-control and/or anti-IgG DAT across all centres. The laboratory technique used to detect a WAA (tube, gel, solid phase) was not collected because, in practice, the serological method does not determine whether the patient is designated as having a WAA. Blood bank laboratories may use different serological methods (differ from each other and even within one sample) to evaluate in vitro reactivity of antibodies (alloantibodies and autoantibodies) [5]. The study was not designed to measure detection differences in the methods. The blood bank record was assessed for the date of WAA initial detection, patient ABO and Rh blood type (blood type), presence of RBC alloantibodies, date of alloantibody detection, any patient antigen typing results and whether these results were obtained by phenotyping or genotyping, number of RBC transfusions and the most recent serological testing results and dates were also collected. The method of serological detection and enhancement technique was gathered (gel, tube, solid phase), but results were not segregated by method of detection. The genotyping methods were gathered at the site and not the patient level. The following diagnoses that are commonly associated with AIHA were collected from patient records: autoimmune haemolytic anaemia, leukaemia/lymphoma, autoimmune and connective tissues diseases, transplant and transplant type, pregnancy at the time of WAA or none of the above.

The prevalence of WAA detected in the population of patients having an IAT was calculated. The group of patients with WAA was initially divided by initial serological findings; one group with WAA only and one group with WAA identified concurrently with a demonstrable RBC alloantibody because previous studies suggest that previous alloimmunization is associated with additional alloimmunization [19]. Because of the possibility of rapid reappearance of RBC alloantibodies due to amnestic immune system recall, the concurrent detection group included patients with an RBC alloantibody identified before the WAA as well as up to 29 days post-WAA detection date.

To determine the incidence of the development of RBC alloimmunization, the patients who received RBC transfusion after WAA identification were grouped together. These patients were further partitioned to focus on only those who had a serological follow-up in the form of an IAT 30+ days after the RBC transfusion exposure to calculate the number of patients with *new* alloimmunization. Finally, to determine the impact of RBC selection practices, each site was segregated by its RBC selection policy; those that provide prophylactically antigen-matched (PAM) RBC products to patients with WAA or those that do not. A centre was deemed to be using the PAM approach if their policy was to use either partial antigen matching including Rh and K blood group antigens or full extended matching including Rh, Kell, Kidd, Duffy and MNS antigens based on transfusion laboratory policy. Sites could also indicate, at the patient level, whether a patient was assigned to the PAM vs. no PAM approach based on the patient's transfusion requirements and RBC availability. The impact of using PAM to prevent RBC alloimmunization was calculated using chi-square analysis comparing the number of patients with new RBC alloimmunization to those that did not have new RBC alloimmunization. To supplement the chi-square analysis, we ran a multivariable mixed effects regression model to adjust for study centre and potential confounders in the association between PAM and new RBC alloimmunization.

Descriptive statistics were used to summarize the prevalence of WAA in the study population and the RBC transfusion data. Fisher's exact test was for numerical calculations and chi-square for categorical comparisons, such as the presence of new alloimmunization. Patient characteristics were compared between patients with and without new RBC alloimmunization using differences in means and differences in proportions and 95% confidence intervals for continuous and categorical variables, respectively. A multivariable mixed effects logistic regression model, with study centre as a random effect, was conducted to adjust for centre in the association between PAM and new RBC alloimmunization. After removing patients with missing data for AIHA, the final sample size for the model was $n = 328$ patients (from 4 centres). This model also adjusted for potential confounding variables, including sex, AIHA diagnosis, previous alloimmunization and number of RBC units transfused after WAA (age, leukaemia diagnosis, autoimmune disease diagnosis were not significantly associated with the outcome and were not included in the model). The regression model was run in SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). The significance level was set at $P < 0{\cdot}05$ for all analyses.

Results

Eight centres from five countries [USA (3), Brazil (2), United Kingdom (1), Norway (1), Germany (1)] collectively reviewed 1 122 245 patients who had an IAT over the study time period. The prevalence of patients with WAA across all centres was 0·46%, which included 7 hospital-based transfusion services (TS) and one immunohematology reference laboratory (IRL) combined with a TS. Because the IRL was receiving samples from many external facilities, it was enriched for patient samples with WAA that were sent for advanced serological testing. When including only patients tested at a TS, the prevalence of WAA was 0·17%, range 0·01–0·36% (1214 of patients 734 332). The 7 transfusion services all had ≥400 inpatient beds, six centres cited having a laboratory policy to use a PAM approach for RBC unit selection (Table 1). However, when individual patient transfusion histories were reviewed, the institutional policy was not always the adopted practice given difficulty in finding sufficient RBC units meeting the PAM requirements without creating unnecessarily long delays in RBC availability (Table 1). There was a range of 35 587–187 461 patients per centre, the combined IRL and TS submitted 387 913 patients. Complete demographic data were available for patients of six of the seven TS institutions; these 1002 patients with WAA detected from 575 954 patients were grouped together to study (1) the prevalence of RBC alloimmunization, (2) the incidence of RBC alloimmunization and (3) the impact of blood product selection on development of alloimmunization.

Of patients with WAA, 67·9% had WAA alone and 32·1% had WAA with pre-existing/concurrent alloimmunization. Those with WAA alone had a statistically higher risk of having an associated medical diagnosis that is connected with underlying immune system alterations such as AIHA and autoimmune diseases compared to those with pre-existing alloimmunization (Table 2). The patients with WAA and concurrent RBC alloimmunization were more likely to be older (54·9 ± 23·4 vs. 60·8 ± 20·5 years, $P = 0·0001$) and female gender (51·2% vs. 60·2%, $P = 0·0054$), compared to those with WAA alone, respectively. There was no impact of ABO and RhD blood type associated with WAA and alloimmunization.

Six hundred and thirty-one patients with WAA (63·0%) were transfused with at least one RBC unit after identification of the WAA. The patients with WAA and concurrent alloantibody were more likely to receive an RBC transfusion than those with WAA alone, and a greater number of RBC units than those with WAA alone (72·4% vs. 58·5%, $P < 0·00001$) and (17·5 ± 28·1 units vs. 13·8 ± 23·0 units, $P = 0·0676$), respectively. Three hundred and ninety patients were transfused using the PAM approach (259 in the WAA only cohort, 131 in the WAA and concurrent alloantibody cohort) and 241 were transfused with No PAM RBCs (139 in the WAA only cohort, 102 in the WAA and concurrent alloantibody cohort).

There were 372 patients (59·0% of the transfused patients) with serological follow-up (IAT testing 30+ days post-RBC transfusion). The length of serological follow-up ranged from 30 to 2765 days. Fifty-six patients with WAA had de novo RBC alloimmunization during the study period (15·1%). Patients who were transfused using a PAM strategy were not significantly less likely to have de novo RBC alloimmunization compared with those that did not receive PAM RBCs (14·6% vs. 15·6%, $P = 0·8837$). When the patients were separated into those having WAA only, the PAM strategy was not associated with less new alloimmunization [10·9% (15 of 137 patients having PAM transfusion approach) compared with 13·5% (12 of 89 patients not having PAM approach), $P = 0·6753$] (Fig. 1). When the patients were separated into those having WAA and alloimmunization at time of WAA identification, the PAM strategy was not associated with a decreased likelihood of new alloimmunization [21·3% (16 of 75 patients having PAM transfusion

Table 1 Characteristics of participating hospital-based transfusion services (TS) and immunohematology reference laboratory (IRL).

Centre	Number of Beds	RBC Matching Policy	Method for Patient RBC Antigen Typing	Total WAA Cases	Number of IAT performed	Prevalence of WAA by institution
1	650	Partial (Rh, K)	Phenotype or Genotype	40	19 648	0·20
2	464	Partial (Rh, K)	Genotype	54	35 587	0·15
3	1000	Partial (Rh, K)	Phenotype (genotype if phenotype not valid)	155	81 249	0·19
4*	730	Partial (Rh, K)	Phenotype	214	158 378	0·14
5	1400	Partial (Rh, K)	Rh phenotype until Genotype available	22	163 685	0·01
6	400	None	N/A	51	88 324	0·06
7	795	Partial (Rh, K)	Phenotype	680	187 461	0·36
8*	NA	Full if possible	Phenotype or Genotype	3990	387 913	1·03

*Excluded from demographic and alloimmunization analysis, centre 4 did not have access to detailed patient records and centre 8 is an IRL.

Table 2 Demographic information, blood type and associated diagnoses/transplantation of patients with warm autoantibody (WAA).

Patients with WAA (n = 1002)		WAA only (n = 680)	WAA with concurrent alloantibody (n = 322)	P value
Age (average, years)		54·9 ± 23·4	60·8 ± 20·5	<0·0001*
Female (%)		345 (50·7%)	194 (60·2%)	0·0054*
Blood Type (Note: In the WAA cohort, the blood type for 3 patients was unknown.)	O positive	248 (36·6%)	121 (37·6%)	0·7719
	O negative	42 (6·2%)	21 (6·5%)	0·8893
	A positive	215 (31·8%)	105 (32·6%)	0·7719
	A negative	29 (4·3%)	14 (4·3%)	1·0
	B positive	81 (12·0%)	42 (13·0%)	0·6076
	B negative	14 (2·1%)	4 (1·2%)	0·4521
	AB positive	44 (6·5%)	12 (3·7%)	0·0793
	AB negative	4 (0·6%)	3 (0·9%)	0·6868
Associated Diagnoses (%)				
Autoimmune haemolytic anaemia (AIHA) (n = 583)[a]		162 (27·8)	31 (10·9)	<0·0001*
Autoimmune and connective tissue diseases (CTD)		133 (19·6)	37 (11·5)	0·0015*
Leukaemia/Lymphoma		135 (19·9)	46 (14·3)	0·0348*
History of transplantation (%)				
Solid organ transplant		86 (12·6)	34 (10·6)	0·4046
Haematopoietic stem cell transplant		30 (4·4)	15 (4·7)	0·8710
Pregnancy (%)				
Pregnancy at the time of WAA detection (n = 539 females)[a]		25 (7·2)	1 (0·5)	0·0002*
None (%)				
None (no AIHA, CTD, leukaemia/lymphoma, current pregnancy, transplant)		344 (50·6)	219 (68·0)	<0·0001*

Patients are divided into those presenting with WAA alone and those presenting with WAA and concurrent alloantibody (defined as alloantibody detected before, the same day, or up to 29 days after the WAA was initially detected to include the possibility of evanescent alloantibodies).
HSCT, haematopoietic stem cell transplant.
[a]Indicates different denominator (provided in parentheses) because some sites could not.
*Statistically significant P value < 0·05.

approach) compared with 18·3% (13 of 71 patients not having PAM approach), P = 0·6828]. After adjusting for centre, sex, AIHA diagnosis, previous alloimmunization and number of RBC units transfused after WAA, there was no significant association between PAM and new RBC alloimmunization (OR = 1·46, 95% CI: 0·75–2·86) in patients with WAA who were transfused and had serologic testing 30+ days following transfusion. The length of serological follow-up ranged from 30 to 2765 days.

We assessed the cohort for risk factors for new alloimmunization. Patients with WAA who were female (67·9% vs. 46·8%; AD = 21·0, 95%CI: 7·6–34·4) were more likely to have new alloimmunization compared with those that did not have new alloimmunization following transfusion. Patients who had previous alloimmunization were significantly more likely to have new alloimmunization compared with those that did not have new alloimmunization following transfusion (51·8% vs. 37·0%; AD = 14·8, 95% CI = 0·6–28·9). Those who received PAM were likewise not protected from new alloimmunization (Table 3).

The specificity of the RBC alloantibodies for the patients with WAA who had post-transfusion testing varied; the most frequent were directed at Rh and K blood group antigens. Anti-E was found to be the most common antibody specificity in all patients at all time-points, concurrent and new alloimmunization (Fig. 2, Table 4).

Discussion

This study is the largest known assimilation of laboratory results from patients with WAA. The patients' results were collected from seven centres across the globe. The results serve as a generalizable estimate of the prevalence of WAA in patients having an IAT (0·17%) and indicate that 63% of patients with WAA will need an RBC transfusion after identification of the WAA, most likely due to their illness or other associated reasons (74·3%) and not typically because of immune-mediated haemolysis secondary to the WAA (25·7%).

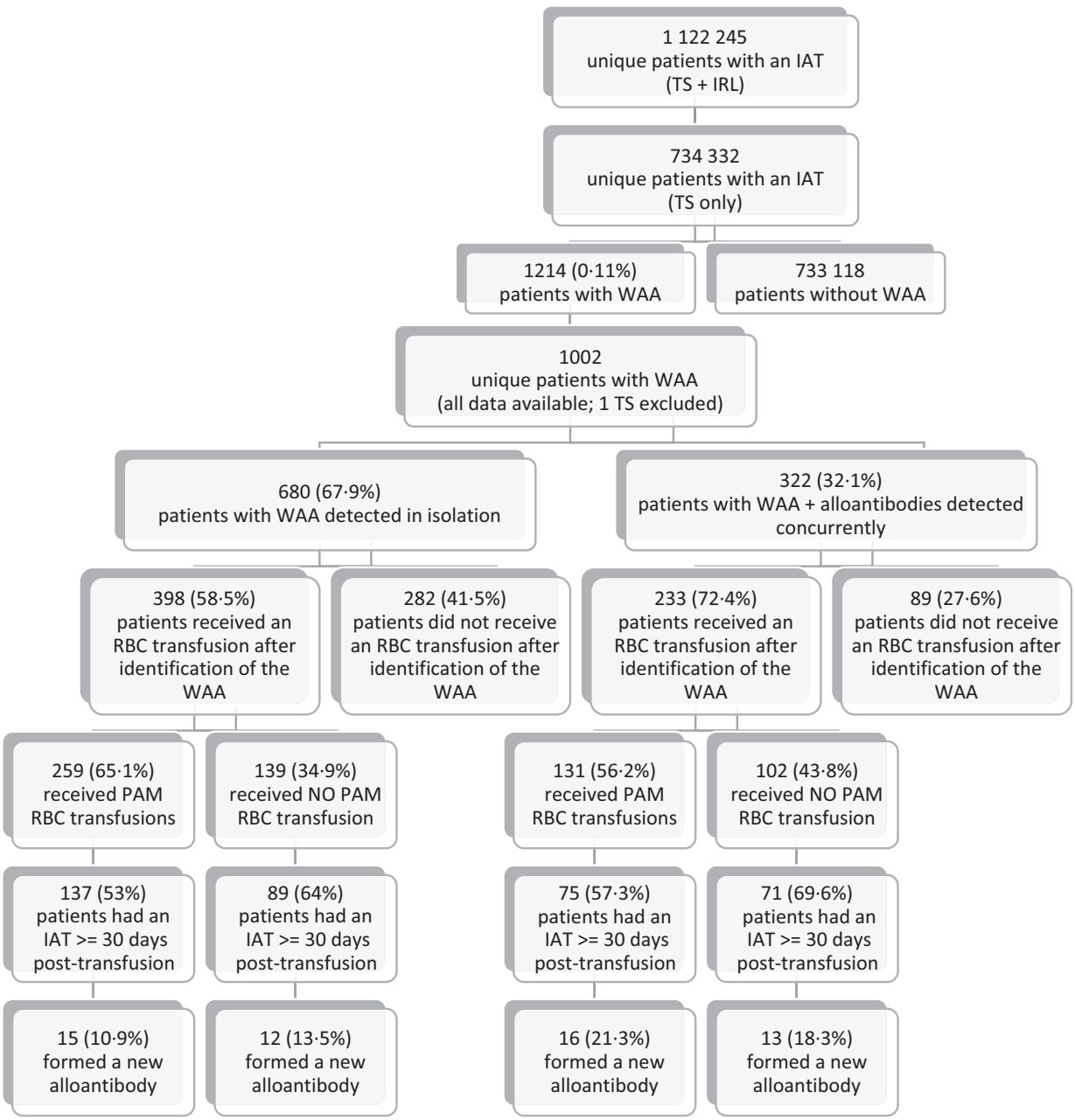

Fig. 1 Patient serological results.

There was an incidence of 15·1% of WAA patients that developed new alloimmunization after RBC transfusion in the study. This suggests that there is significant risk for new RBC alloimmunization in the patient population with WAA, which is higher than the frequency reported in patients without WAA (4·4–10·5%) [20]. A review that included 8 separate studies found a range of 12–40% of patient sera with WAA also contained alloantibodies [5,8-11,16,21,22]. Although these studies were individually smaller (range of 14–263 patients each for a total of 647 patients), they corroborate and support our study's results that show a rate of new alloimmunization in 15·1% of patients with pre-existing WAA. While many centres provide WAA patients with PAM RBCs for transfusion, our patient cohort did not demonstrate a protective effect from new alloimmunization by using PAM transfusion 14·6% vs. 15·6% (P = 0·8837). The lack of impact on the rate of new alloimmunization is likely multifactorial and could be due to the degree of matching, RBC availability, urgency of transfusion, presence/absence of the WAA at

Table 3 Comparison of patient demographic variables as risk factors for new alloimmunization.

	WAA with new alloimmunization (n = 56)	WAA without new alloimmunization (n = 316)	Absolute difference[a] (95% CIs)
Female	38 (67·9%)	148 (46·8%)	21·0 (7·6, 34·4)*
Autoimmune haemolytic anaemia (AIHA)[b]	7 (14·0%)	81 (29·1%)	−15·1 (−26·1, −4·1)*
Autoimmune and connective tissue diseases	8 (14·3%)	51(16·1%)	−1·9 (−11·9, 8·2)
Leukaemia/lymphoma	14 (25·0%)	91 (28·8%)	−3·8 (−16·2, 8·6)
Previous alloantibody (Yes)	29 (51·8%)	117 (37·0%)	14·8 (0·6, 28·9)*
PAM transfusion strategy (Yes)	31 (55·4%)	181 (57·3%)	−1·9 (−16·0, 12·2)
Average RBC units after WAA identification (range)	30·9 (1–192)	20·6 (1–221)	10·3 (−0·8, 21·4)

[a]The absolute difference shows the risk difference for proportions and the mean difference for continuous variables, calculated as the 'new alloimmunization' value minus the 'no new alloimmunization' value.

[b]Data on AIHA were available for 50 of 56 patients with new alloimmunization, and for 278 of 316 patients without new alloimmunization. Percentages were calculated using these totals (50 and 278).

*Statistically significant P value.

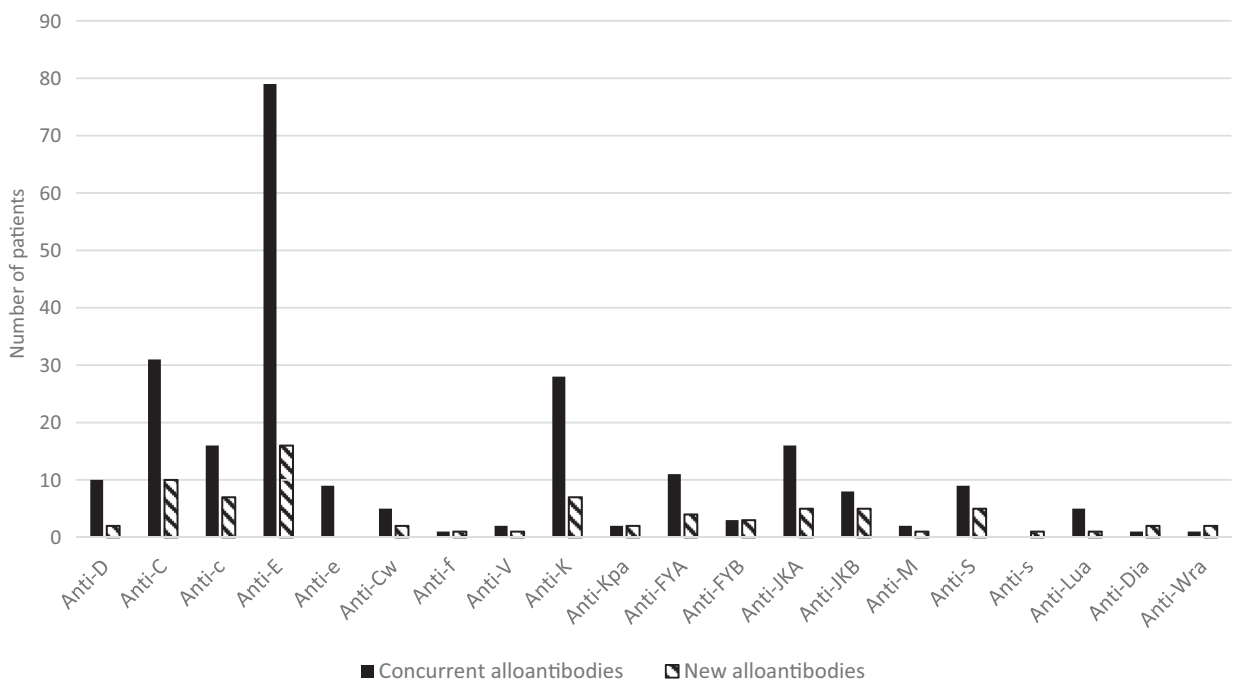

Fig. 2 RBC alloantibody specificities for patients with WAA, RBC transfusion after WAA detection and serologic follow-up at least 30 days following RBC transfusion (n = 372 patients)*. *Several antibody specificities were detected concurrently, but not as new antibodies: Jsa (1 patient), Bga (1 patient), Coa (1 patient), Lea (2 patients) and Leb (1 patient).

the time of transfusion and patients receiving care at another institution which did not provide PAM RBC units. Further, given these logistical and operational constraints, it is not possible to pinpoint which RBC exposure gave rise to each antibody, which would require prospective study. This weakness is especially evident in the fact that the most common antibody was anti-E, such that finding antigen-matched/negative RBC unit should not be difficult. Past exposure to foreign RBCs either due to transfusion or pregnancy may have also been the trigger for alloimmunization.

There were a number of differences seen with patients with WAA who had previous alloimmunization at the start of the study. For instance, they were older and predominantly female. Further, patients with pre-existing RBC alloimmunization may have had an underlying

Table 4 Number of patients who formed RBC alloantibody specificities, pre- and post-WAA identification for patients (n = 56) who formed new alloantibodies after the RBC transfusion.

	PAM transfusion strategy (n = 31)		No PAM transfusion strategy (n = 25)	
Antigen specificity	Pre-existing/concurrent alloimmunization	New alloimmunization	Pre-existing/concurrent alloimmunization	New alloimmunization
D	1	0	1	2
C	3	6	4	4
c	2	4	3	3
E	8	5	4	11
e	0	0	0	0
f	0	1	0	0
Cw	1	2	0	0
V	0	1	0	0
K	1	4	3	3
Kp^a	1	2	0	0
Fy^a	4	2	0	2
Fy^b	0	1	1	2
Jk^a	1	2	1	3
Jk^b	3	3	0	2
M	1	0	0	1
S	2	3	1	2
s	0	1	0	0
Lu^a	1	1	0	0
Di^a	0	2	0	0
Wr^a	0	1	0	1

diagnosis that required ongoing RBC transfusion due to their underlying illness or exposure to foreign RBCs through past pregnancies. We also found these patients were more heavily transfused (before WAA identification; average of 7·0 vs. 2·7 units in patients without a pre-existing alloantibody). Those patients with WAA without previous alloimmunization were more likely to have AIHA, autoimmune diseases or leukaemia/lymphoma.

The study found that in patients with WAA, female gender and a diagnosis of AIHA were significant associations with new alloimmunization. The gender difference may be due to exposure to foreign red-blood-cells during previous pregnancy. In a large cohort study, alloimmunization was found to be more common in females (2·38%) than males (1·68%, $P \leq 0{\cdot}0001$) [23]. AIHA can be precipitated by previous viral infection and autoimmune diseases, both of which can be associated with loss of immune tolerance [24]. A study of alloantibodies in a cohort of patients with autoimmune disease found that autoantibodies appeared to have IgG and IgM classes of antibodies, suggestive active immune activity, and may cross-react with similar epitopes in other patients with alloantibodies to Kell and Lutheran [24,25]. Thus, a hypothesis could be that in patients with a diagnosis of AIHA or suspected AIHA, the PAM approach should be used instead of using PAM for all patients with WAA, given the possibility that the underlying mechanism for WAA alone appears to be tilted towards disease association.

Our study also demonstrated that previous alloimmunization was significantly associated with new antibody formation in patients with pre-existing WAA (51·8% vs. 37·0%; AD = 14·8, 95%CI = 0·6–28·9). Higgins and Sloan found that in a large cohort of transfused patients, 13% form antibodies and then subsequently have a 30% chance of developing new alloantibodies thereafter [19]. The authors suggest that although factors such as inflammatory state and number of transfusions may play a role in alloimmunization development, these are not sufficient factors to alone cause alloimmunization without a 'yet-to-be fully characterized' genetic predisposition. Thus, the idea of using PAM after the first alloantibody is detected may be advantageous to prevent additional alloimmunization. Other authors use this approach in the sickle cell disease (SCD) population based on their institutional experience [26]. Further, Kacker and colleagues suggest that waiting until after the first alloimmunization event is cost-effective with over $80 000 of financial savings over 10 years compared to matching for all patients with SCD regardless of risk factors [27].

The results of this study did not include assessing the number of adsorption procedures or other serological assessments that were used (or avoided) by using PAM. In a study of 20 patients, Shirey and colleagues found that using PAM transfusion approach with WAA can help to avoid 4·25 adsorption procedures per patient, whereas the patients who were not receiving PAM required 4·9 adsorption procedures per patient [14]. When the PAM approach is employed, it does not protect from patients receiving a non-antigen-matched transfusion at a different centre or if an antibody falls below the threshold of detection, which can occur up to 4–6 months after detection [17,28,29]. Shirey and colleagues did not find new alloimmunization using the PAM approach; however, it took place during 1 year of time, making it difficult to compare to our study which had a longer serological follow-up.

No matter the approach chosen for serological evaluation and RBC product selection for patients with WAA, the laboratory steps require skills and resources. Our study provides a comprehensive assessment of the prevalence of WAA in the population of patients who have an antibody screen. We also show that RBC alloimmunization is fairly common in the patients with WAA. The associated risk factors appear to have been previously identified and supported by others. As blood bank inventories increase the percentage of antigen-typed units available, it may become more feasible for the PAM approach to be widely adopted [30]. The choice on how to apply the PAM approach should be informed by the patient-related factors, such as AIHA and possibly previous alloimmunization. Future studies into the biological differences in WAA found alone and those found with concomitant alloimmunization may provide insight into the immune system pathways that lead to the development of WAA in patients.

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Conflict of interest

None identified.

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