AUGUST 2023 VOL. 44 No. 3 Pages 102 - 151 AUSTRALIAN JOURNAL OF MEDICAL SCIENCE

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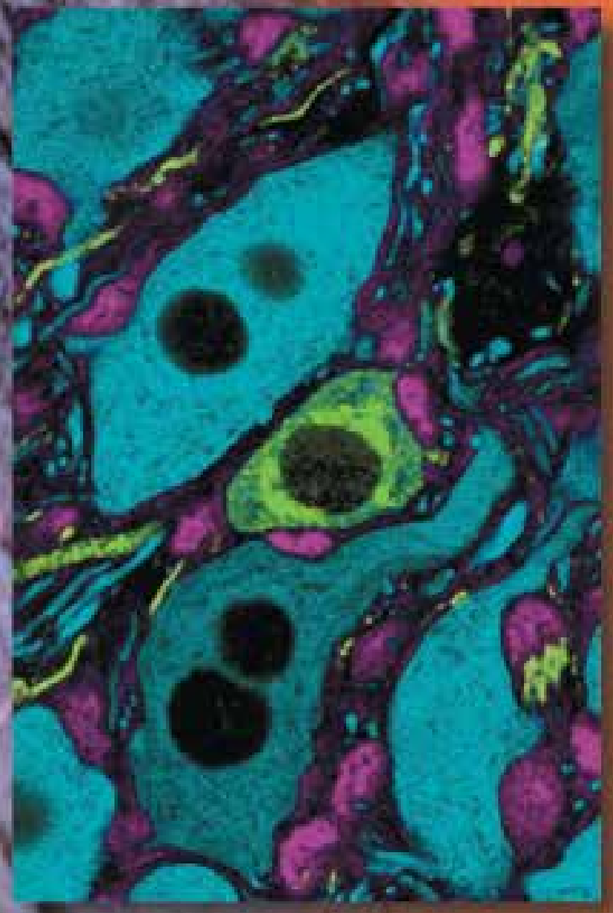
AUSTRALIAN JOURNAL OF Medical Science

2023



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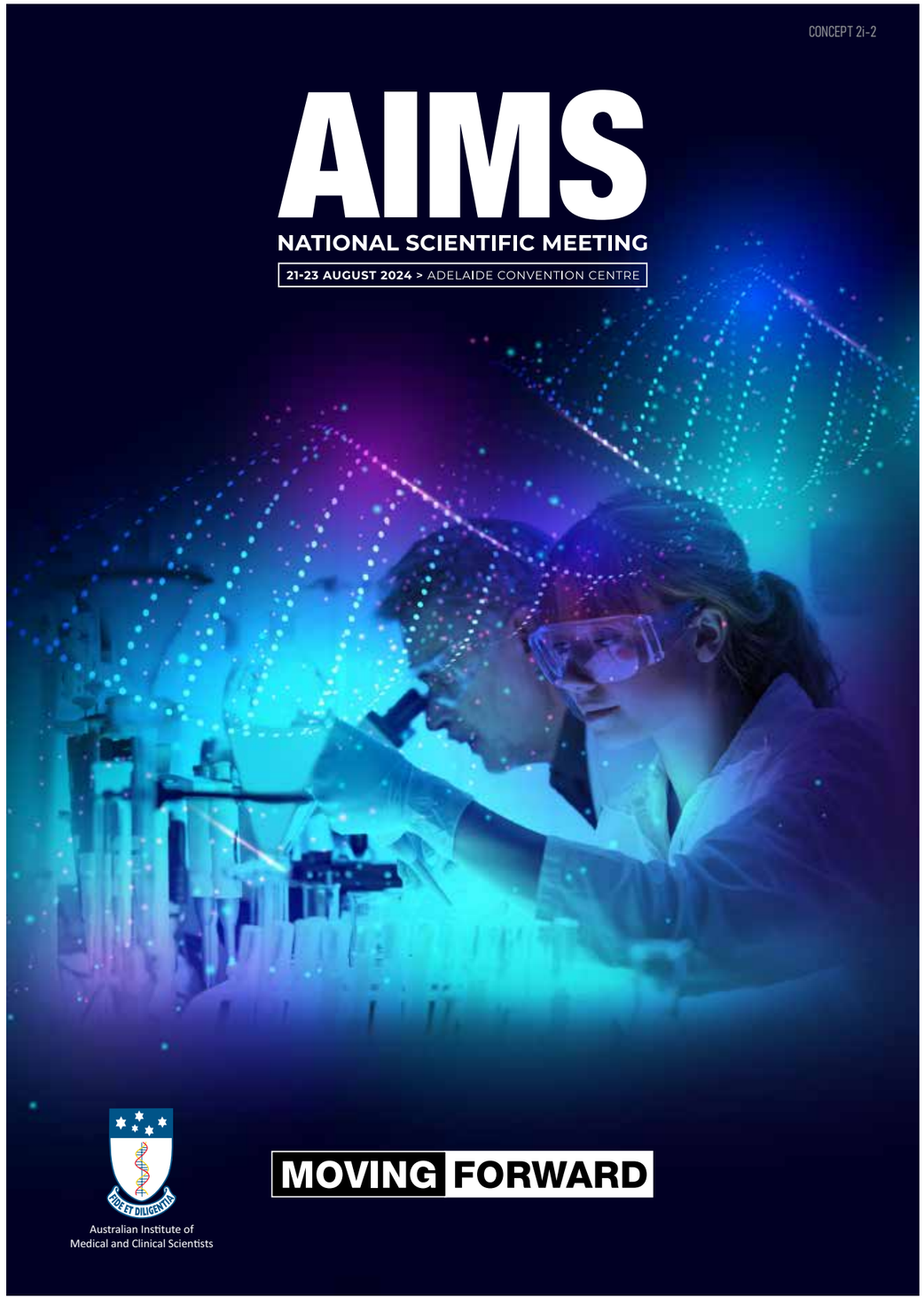
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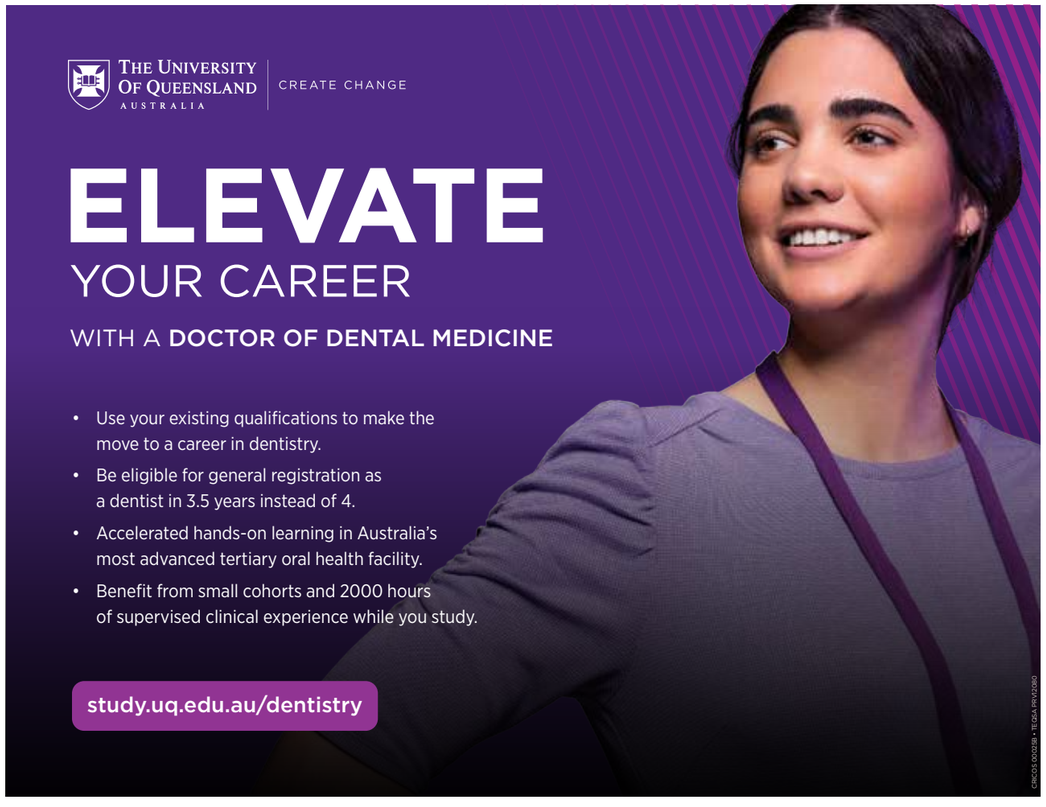
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Design, formatting and management: AIMS National Office
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Website: www.aims.org.au
Telephone: 61 7 3876 2988
Address: PO Box 1911 Milton Qld 4064 Australia

The Australian Journal of Medical Science is the official publication of the Australian Institute of Medical and Clinical Scientists (AIMS).

Circulation 1500 per issue. The Journal is circulated to members in pathology laboratories, universities and research institutes throughout Australia and overseas.

Annual subscription rates are available from AIMS National Office.

Article reprints may be organised on request from AIMS National Office.

Advertising rates are available from AIMS National Office.

Abstraction of the Australian Journal of Medical Science is through the following serial catalogue listings: Australasian Medical Index, Chemical Abstracts, and EMBASE/Excerpta Medica.

The Australian Journal of Medical Science is included on the Australian Research Council ERA 2018 Journal List.

ISSN 1038-1643

Printed by Westminster Eagle Eye Printing, PO Box 161, Paddington Qld 4064.

Design Cover and layout design by Kim Brown, 23 Denman St Exeter SA 5019 kimbo@internode.on.net. Cover photograph courtesy of Prof Ian Gibbins, Flinders Medical Centre, Adelaide.

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Instructions to authors *are available on the AIMS website: www.aims.org.au*

Can serological testing be reduced in favour of matched phenotyped red blood cells in patients with warm autoantibodies?

Callum Smallman

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Abstract

When a warm autoantibody (WAA) is found in the laboratory it is technically complex to find compatible units. The use of adsorption techniques to remove the autoantibody interference in pre-transfusion testing is labour intensive, time consuming and not guaranteed to work on all occasions. This can lead to delays in the provision of red blood cells (RBCs) to patients requiring lifesaving transfusions.

The aim of this project is to determine if decreasing adsorption frequency and the transfusion of phenotype matched RBCs in patients with WAA and warm autoimmune haemolytic anaemia (WAIHA) improves the time that RBCs become available, without increasing alloimmunisation rates or transfusion adverse events. Patient with WAA had their records from 2020 to 2021 from 17 public South Australian blood banks reviewed, with 132 patients having a total of 441 samples. Following introduction of the new protocol, 163 alloadsorptions were no longer performed saving 412 hours, and serological indirect agglutination test (IAT) crossmatching was not necessary for 150 donor units saving 41.5 hours. In total 454 hours of pretransfusion testing was saved improving the time RBCs were made available to patients. Alloimmunisation was detected in two patients however this is not believed to be attributed to the protocol, and no adverse events were observed.

Keywords: ***autoantibody, adsorption, phenotyped red blood cells, autoimmune haemolytic anaemia***

Introduction

Autoimmune haemolytic anaemia (AIHA) is an acquired heterogeneous group of diseases. AIHA is characterised by haemolysis of RBCs caused by autoantibodies with or without complement involvement which together activate macrophages, T-lymphocytes, and cytokines. The serological types of AIHA include warm autoimmune haemolytic anaemia (WAIHA), cold agglutinin disease (CAD), mixed type AIHA (mixed AIHA) and paroxysmal cold haemoglobinuria (PCH). AIHA can be classified as either primary or secondary. Primary is when the underlying cause is not identified and this accounts for approximately 50% of AIHA. Drug-induced immune haemolytic anaemia (DIIHA) is a secondary form of AIHA. DIIHA is associated with the presence of drug related antibody (+/- complement activation) leading to either intra- or extravascular haemolysis following drug administration (Michalak *et al* 2020).

All components of the immune system are involved in the pathogenesis of AIHA. The development of AIHA is associated with deregulation of central and peripheral self-tolerance along with the formation of autoreactive T-and B-cells (Michalak *et al* 2020). The AIHA clinical picture and pathological mechanism differ depending on the type with the direct antiglobulin test (DAT) enabling the clinical classification of the disease along with the isotype and thermal characteristics of the autoantibody. WAIHA shows a positive DAT for anti-IgG and or C3d, while the cold forms of AIHA (CAD and PCH) show a positive DAT for C3d. PCH, usually identified in children, is caused by the Donath-Landsteiner autoantibody (Lomas-Francis and Westhoff 2022; Barcellini and Fattizzo 2020). Mixed forms of AIHA show both characteristics of WAIHA and CAD, with DAT positive for IgG and complement (Barcellini and Fattizzo 2020). DAT testing by itself is not diagnostic of haemolytic anaemia as a negative DAT is seen in 5%-10% of patients with haemolytic anaemia (Johnson and Puca 2022).

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***Table 1**. Participant demographics from recruited participants.*

Type of AIHA	Antibody class	Antibody specificity	DAT results	Elution results
WAIHA	IgG (rarely IgA or IgM)	Broadly reactive	IgG and/or C3d	Positive – reactivity with all panel RBCs
CAD	IgM	I/i	C3d	Not performed
PCH	Biphasic IgG	Usually anti-P	C3d	Not performed
Mixed Type	IgG + IgM	Usually lack specificity of warm IgG, cold antibody I/i or lack specificity	IgG + C3d	Positive – reactivity with all panel RBCs
DIIHA	IgG	Broadly reactive in presence of drug	IgG and/or C3d	Non - reactive

Introduction

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To confirm the positive DAT is due to the autoantibody present, an elution procedure should be performed. The acid glycine elution procedure removes cell bound IgG (auto) antibody from the patient cells by the addition of a dilute acid solution leading to the dissociation of the antigen antibody bonds on the RBC membrane. This procedure results in a normal pH supernatant referred to as an eluate, that is tested against an antibody identification panel to differentiate the WAIHA from a drug-induced immune haemolytic anaemia and alloantibody. WAIHA and mixed forms of AIHA with WAA demonstrates widespread reactivity of the cell identification panel due to the removed IgG autoantibody, whereas DIIHA produces a non-reactive eluate (Table 1) (Johnson and Puca 2022).

WAIHA can present with a small amount of haemolysis and may go unnoticed, but a significant degree of haemolysis can lead to severe tissue hypoxia, yellowing of skin and mild to moderate splenomegaly (Michalak *et al* 2020). WAAs found in WAIHA are of the IgG class and/or complement binding and are reactive at 37^{o}C. WAA can be classified as clinically significant when involved in AIHA, or as clinically insignificant when not involved in harming the patient (Delaney *et al* 2020). Pathological WAAs found in WAIHA attach themselves to and lead to the extravascular haemolysis of the patient's own RBCs at approximately 37^{o}C mainly in the spleen (Michalak *et al* 2020). In extravascular haemolysis RBCs are phagocytosed by the monocyte-macrophage system of the reticuloendothelial system (Rapido 2017). The phagocytes present express receptors for the Fc region of the IgG molecule and any remaining RBCs will develop

into spherocytes due to incomplete phagocytosis (Raos *et al* 2022). IgG class WAAs are also capable of activating complement, leading to C3 complement components binding to the RBC membrane resulting in further extravascular haemolysis by Kupffer cells within the liver. Extensive activation of the complement system can lead to the formation of the membrane attack complex (MAC) on the RBC surface resulting in intravascular haemolysis (Michalak *et al* 2020) and release of free haemoglobin and the contents of RBCs into the bloodstream (Rapido 2017).

Studies by Delaney and colleagues in 2020 showed that 63% of patients with WAA will require RBC transfusions (Delaney *et al* 2020). This is most likely due to the patient's underlying illness or other associated reasons, rather than immune mediated haemolysis secondary to the WAA (Delaney *et al* 2020). Pretransfusion testing for patients with WAIHA is complex and has difficulties associated with the interpretation of results and may require specialist testing performed at a reference laboratory (Australian and New Zealand Society of Blood Transfusion, 2020). The complexity surrounding patients with WAA is the detection of masked underlying alloantibodies and the selection of appropriate RBCs for transfusion (Delaney *et al* 2020). Initial testing of patients typically includes an indirect antiglobulin test (IAT) to identify any clinically significant alloantibodies that may be present. Plasma that contains WAA will generally only provide inconclusive, pan-agglutination with all cells when tested by IAT (Drouillard 2008). This serological activity may mask the presence of clinically significant alloantibodies making them difficult to detect. The reality of this is unsettling as studies have reported the presence of concurrent alloantibodies in 10-53% of patients with WAA (Delaney *et al* 2020).

Allo- and auto-adsorptions are a labor-intensive serological procedure used to identify alloantibodies in patients with WAA by removing the autoantibody. This technique is time consuming and not guaranteed to work on all occasions, often delaying the availability of RBCs for transfusion (Garratty and Petz 2002). Failure to accurately detect and identify a patient's underlying alloantibody may lead to a haemolytic transfusion reaction (HTR) which can then be incorrectly attributed to the autoantibody (Delaney *et al* 2020; Raos *et al* 2022).

The incidence of AIHA in adults is 1 to 3 cases per 100 000 per year; a number that is much less than the number of reported WAA being up to 17% of antibody investigations (Ziman *et al* 2017). If AIHA is clinically suspected, the detection of WAA in the patient's plasma helps to further support the diagnosis (Ziman *et al* 2017).

Patients who develop WAA have alloimmunisation rates reported between 12-40%. These rates of alloimmunisation are comparable to other frequently transfused patient populations such as those with sickle cell disease (SCD) and thalassemia (Ziman *et al* 2017). A routine standardised approach to pretransfusion testing for patients with WAA has not been established and this has led to variability in testing protocols and RBC selection practices internationally (Ziman *et al* 2017).

This paper discusses a standardised approach to pretransfusion testing for patients with WAA and a protocol for the selection of RBCs for transfusion. When WAAs are encountered there must be collaboration between both the clinical and scientific communities to allow timely and correct therapeutic management of the patient.

Materials and Methods

Ethics Approval

The project was approved by the chair of CALIN HREC for publication.

Routine pretransfusion testing

Routinely, an ABO and RhD group and IAT antibody screen is performed on all pretransfusion requests. Positive antibody screens are investigated to identify antibody specificity by testing the patient's plasma by IAT against an 11-cell group O antibody identification panel including the patient's own red cells as an auto control. If there is no history of clinically significant antibodies and the current antibody screen is negative, RBCs may be released via electronic release without the need for a serological crossmatch (Figure 1) (Australian and New Zealand Society of Blood Transfusion 2020).

For patients with a positive antibody screen, 11-cell antibody panels are performed by various techniques to identify the antibody and the patients RBCs phenotyped for the corresponding antigen. Antigen negative donor RBCs are crossmatched by IAT prior to transfusion (Figure 1).

Pretransfusion testing in patients who have developed WAA includes blood group, antibody screen, antibody identification, DAT, elution, phenotyping and/or genotyping, adsorption procedures and serological crossmatch by IAT (Johnson and Puca 2022).

If the DAT is positive with anti-IgG, follow-up elution studies are performed to confirm the WAA or alloantibody. Patient's RBCs are phenotyped for the following antigens C, E, c, e, K, Jk^a, Jk^b, Fy^a, Fy^b, S, s using commercial anti-sera by the CAT or tube technique following manufacturer's

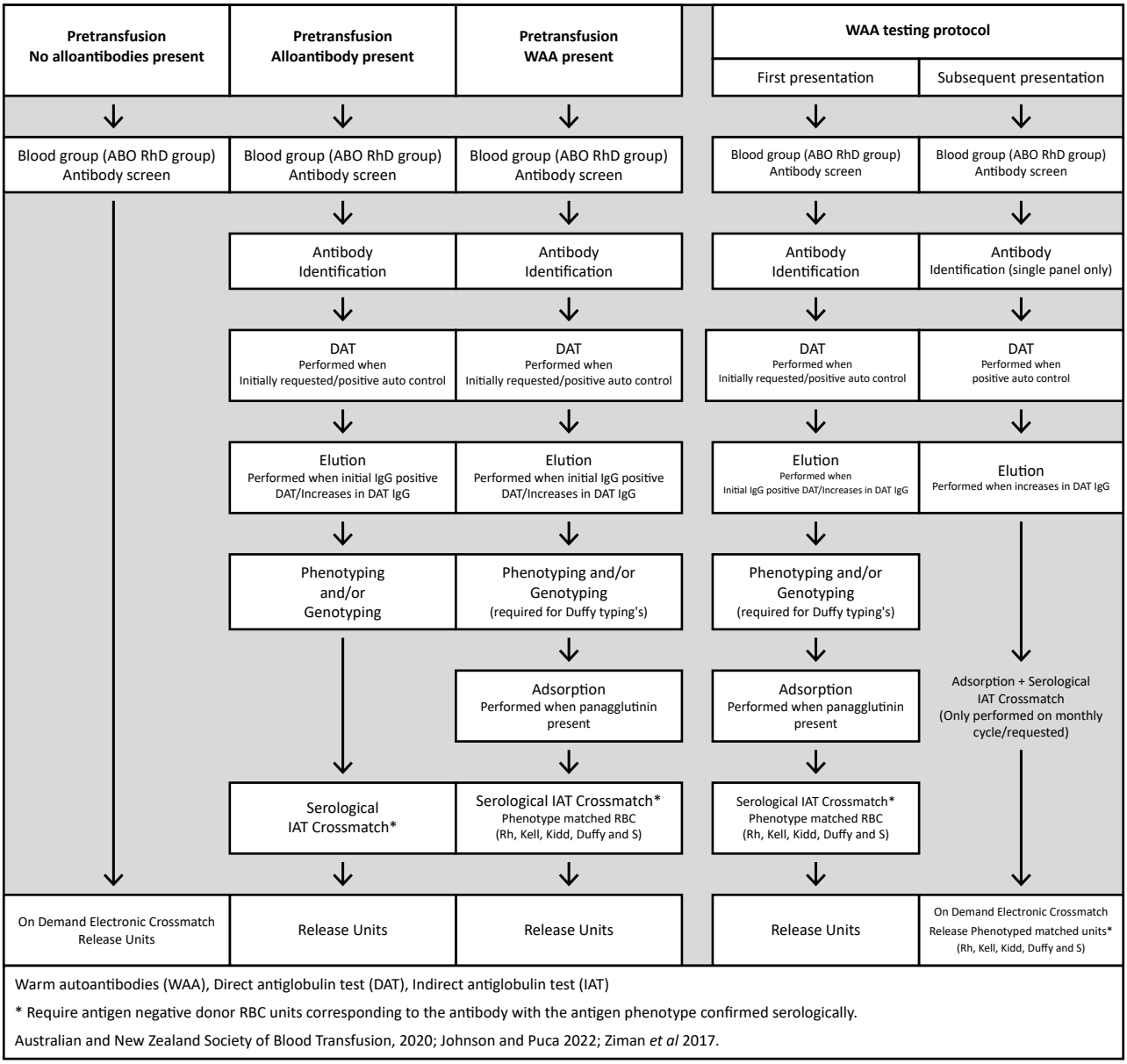

***Figure 1**. Pretransfusion testing comparison.*

instructions. Genotyping is recommended if phenotyping is not possible (Johnson and Puca 2022).

In the presence of a pan reactive WAA, allo- or auto-adsorption of the patient plasma is undertaken to remove autoantibody reactivity to determine the presence of coexisting masked alloantibodies (Australian and New Zealand Society of Blood Transfusion 2020). Briefly, the patient's plasma is added to auto- or allo-RBCs and incubated at 37^{o}C. The chosen RBCs are treated with chemicals such as ZZAP (dithiothreitol (DTT)/2-mercaptoethanol + ficin/papain) or enzyme treating (ficin/papin) to free up antigen sites increasing autoantibody binding. The adsorbed plasma is separated and is tested by IAT against an 11-cell antibody panel for presence of alloantibodies (Johnson and Puca 2022).

Prophylactic transfusion of phenotyped matched red cells should be considered. If an IAT crossmatch is performed, the absorbed plasma should be used if available and if a clinically significant alloantibody is present antigen negative red cells must be crossmatched. (Australian and New Zealand Society of Blood Transfusion 2020).

Revised pretransfusion testing in patients with WAA

In WAA patients, preferentially issuing ABO compatible phenotyped RBCs without the need for adsorptions and/or serological IAT crossmatches pretransfusion testing is recommended (Figure 1).

The following is a standardised approach to abbreviated

pretransfusion testing for patients with WAA. Patients who present with a WAA (pan-agglutination present in plasma and eluate, an anti-IgG positive DAT, and removal of pan-agglutination by adsorption studies) are subject to this protocol.

First presentation

Patients receive typical pretransfusion testing as previously described including an extended phenotype for C, E, c, e, K, Jk^a, Jk^b, S, s antigens by serological means before the initial transfusions take place. Because Fy^a and Fy^b phenotyping cannot be performed on DAT positive RBCs, genotyping must be used to confirm the presence or lack of Fy^a and Fy^b antigens. Fy^a antigen negative RBCs are provided until genotyping has been completed.

Full phenotype matched RBCs (Rh, Kell, Kidd, Duffy, and S) should be provided and serologically crossmatched against the patient's neat plasma and allo-adsorbed plasma by IAT. If full phenotype matched RBCs cannot be provided, then Rh and K phenotype matched RBCs must be provided as a minimum, followed by Kidd, Duffy and Ss phenotypes if available. Serological confirmation of the donor RBC phenotype is not required; reliance on the RBC manufacturer's reported phenotypes in relation to the donor RBCs is acceptable. Patients with underlying alloantibodies require antigen negative donor RBC units corresponding to the antibody with the antigen phenotype confirmed serologically. In emergency situations, where an RBC transfusion is required before the pretransfusion testing can be completed, phenotype matched RBCs can be provided, however the phenotype of the donor unit must be confirmed serologically when time permits.

Subsequent presentation

Patients who have a known history of a WAA and a known complete phenotype should receive abbreviated pretransfusion testing including ABO Rh(D) blood group, antibody screen, basic investigation consisting of a single IAT panel performed using neat plasma, and a DAT with elution if required.

If serological findings are consistent with previous WAA activity, full phenotype matched donor RBCs based on the manufacturer's reported phenotype can be provided for transfusion without any serological crossmatching. Patients with a history of clinically significant alloantibodies require the donor RBCs to be antigen negative to the corresponding antigen. In these circumstances, the antigen phenotype must be confirmed serologically, however no serological IAT crossmatching is required.

Subsequent adsorptions are required to be performed monthly during pretransfusion testing to rule out the possibility of new alloantibody formation. Each time subsequent adsorptions are performed, serological IAT crossmatching of the donor RBC should be performed using both neat and adsorbed plasma as in initial presentations.

This protocol should be followed while the patient's sample is demonstrating WAA serological activity regardless of whether the patient has been provided full phenotype matched donor RBCs. If the patient is suspected to have had an adverse transfusion event involving a donor RBCs within the 4week period between adsorptions, a full investigation including adsorption studies should be performed on pre and post samples regardless of reaction classification, to rule out the possibility of a haemolytic transfusion reaction caused by incompatibility or the formation of an alloantibody.

***Table 2**. Summary of total WAA testing for 2020-2021.*

Year	No. WAA samples with alloantibodies / Total WAA samples	No. of patients	No. of adsorptions performed /omitted	Total time saved omitting testing (h)
2020	66/190 (34.7%)	63	55/48	113.9*
2021	88/251 (35%)	69	90/115	339.99*
Total	**154/441 (34.9%)**	**132**	**145/163****	**453.89***

*Tests omitted include adsorption studies and serological IAT crossmatching.
** A total of 163 adsorption were not performed in 132 patients, 1.2 adsorptions per patient.

All serological tests referred to in Figure 1 were performed in accordance with the Australian and New Zealand Society of Blood Transfusion Guidelines for Transfusion and Immunohaematology Laboratory Practice (Australian and New Zealand Society of Blood Transfusion 2020) and the product inserts from the relevant manufacturer's reagents. Column agglutination Testing (CAT) using BioVue cassettes, QuidelOrtho (Mulgrave Victoria, Australia) and the BioRad ID-Card system (South Granville NSW, Australia). Immulab reagent red cells were utilised in routine CAT testing (Immulab Pty Ltd South Melbourne Victoria, Australia).

Monoclonal typing reagents for Rh (C, E, c, e) and K were obtained from QuidelOrtho (Mulgrave Victoria, Australia). Monoclonal typing reagents for Jka, Jkb, S, and s were obtained from Immulab Pty Ltd (South Melbourne Victoria, Australia).

Acid elution techniques were completed using the Bio-Rad DiaCidel kit (DiaMed GmbH, South Granville NSW, Australia) following manufacturer's instructions.

Alloadsorption studies were performed at 37°C using pre-prepared ficin treated glutaraldehyde fixed (Reid 1982). Phenotyped matched alloadsorption cells were incubate with patient plasma for 30 minutes each adsorption.

***Table 3**. Typical pretransfusion approximate testing times (per procedure).*

Test	Average time taken (m)
Blood group & Antibody screen	25
Antibody investigation*	30
Adsorption procedure**	
Single	75
Double	120
Triple	165
Quad	210
IAT crossmatch*	25

*Based on single 11 cell panel or single unit. Additional testing or units will increase total time.
**Adsorption time is dependent on number of absorptions performed to remove the WAA. Each additional adsorption increases the total time by 45m.

***Table 4**. Typical pretransfusion approximate testing times (per scenario).*

Scenario	Average time taken (m)
No alloantibodies present	25
Alloantibodies present	80
Typical WAA	160*
WAA testing protocol	
First presentation	160*
Subsequent presentation	55

*Single adsorption procedure time used in scenario.

Results

Within the two-year period (2020-2021) 132 patients were identified with WAAs. A total of 441 pretransfusion samples were collected from these patients (Table 2). Of the 441 samples collected, 154 contained alloantibodies as well as a WAA. With the introduction of the WAA protocol for patients demonstrating WAA activity, 453.89 hours of serological testing was saved over the course of 2 years. These patients were subjected to an abbreviated testing procedure for subsequent presentations which resulted in significant time saving during pretransfusion testing and allowed donor units to be more readily available for transfusion. Time was saved by omitting adsorption procedures and serological IAT crossmatching by using donor RBCs that where phenotyped matched to the patient. A total of 163 adsorptions and 150 serological IAT crossmatches were no longer performed during the study period (Table 2).

Tables 3 and 4 provide details of time taken during the various stages of pretransfusion testing. Of the total 132 patients, only 21 patients did not need serological IAT crossmatching and received prophylactic antigen matched (PAM) electronic crossmatched RBC transfusions during their transfusion episodes (Table 5). The pretransfusion testing performed on these 21 patients allowed for adsorption studies and serological IAT crossmatching as per the above protocol to be not performed resulting in 367.16 h saved from a total 453.89 h of testing time. These 21 patients had a total of 188 pretransfusion samples collected with the performance of 125 adsorptions and serological crossmatching for 150 units avoided. All 21 patients had complete phenotype determined as part of their initial investigation, excluding Duffy (Fy^a, Fy^b) phenotypes which were later confirmed by genotyping.

A total of 280 PAM RBC units using the introduced protocol were transfused to these 21 patients over the two-year period. This was a combination of serological IAT and electronic crossmatched RBC units depending on the patient's pretransfusion testing. Of the 280 RBC units transfused 130 RBC units were serologically

***Table 5**. Summary of patients who had adsorptions and serological IAT crossmatching omitted 2020-2021.*

Year	No. of patients	Total WAA samples	No. of adsorptions performed /omitted	Total time saved omitting adsorptions (h)	No. of PAM units serological IAT XM/electronic /XM	Total time saved omitting IAT XM (h)	No. of adverse events	No. of alloantibodies developed
2020	9	46	15/24	51.75	69/43	8.91	-	1 (anti-f)
2021	12	142	34/101	273.9	61/107	32.58	-	1 (anti-E)
Total	**21**	**188**	**49/125**	**325.66****	**130/150***	**41.5**	**0**	**2**

Warm autoantibodies (WAA), crossmatch (XM), Indirect antiglobulin test (IAT) Prophylactic antigen matched (PAM)

*A total of 280 PAM units were transfused.
** A total of 125 adsorptions were omitted in 21 patients, 5.95 adsorptions per patient.

crossmatched and 150 RBCs were electronically released.

The abbreviated testing allowed the 21 patients to receive 150 PAM RBC units, 123 that were full phenotyped matched electronically crossmatched (mean, 5.8 units/patient; median, 3 units/patient) and 27 units that were only at a minimum RH/K electronically crossmatched to 7 of the 21 patients (mean, 1.2 units/patient; median, 0 units/patient) (Table 6).

Five of these patients (P4, P6, P16, P19, P20) had existing alloantibodies (Table 7), three patients (P5, P11, P16) had autoantibodies showing specificity of alloantibodies and one patient (P1) had an antibody directed against a reagent additive. During the study period, 2 patients developed clinically significant alloantibodies within the RH system (anti-E and anti-f) (Table 5). There were no adverse transfusion events reported in any of the 21 patients.

Discussion

The presence of an antibody that is reactive across all the antibody identification panels and including the patient's own red cells is generally a WAA (Johnson and Puca 2022). The focus of pretransfusion testing for patients with WAA and WAIHA is the provision of the most suitable blood and detection of clinically significant alloantibodies masked by the autoantibodies present. Detection of masked alloantibodies is commonly achieved by testing adsorbed patient's plasma against various antibody investigation panels by IAT (Shirey *et al* 2002). Numerous protocols have been developed detailing adsorption procedures however these protocols are time consuming, technically involved and often only performed by specialised reference laboratories (Johnson and Puca 2022; Shirey *et al* 2002; Garratty and Petz 2002).

Adsorption procedures are typically performed as either auto-adsorptions (autologous), a process which uses the patient's own red cells, or alloadsorption (allogeneic), a process which uses phenotyped donor red cells (Australian and New Zealand Society of Blood Transfusion 2020). It has been reported that most blood banks will have more than one procedure available for the detection of underlying alloantibodies, with 75% utilising auto-adsorptions and 42% using varying forms of allo-adsorption (Ziman *et al* 2017). Auto-adsorptions are the preferred method of adsorption due to minimising the risk of adsorbing alloantibodies against a high prevalence or variant antigen (Johnson and Puca 2022). Auto-adsorptions can only be used however when the patient has not been transfused within 3 months of the adsorption being performed and if there is adequate volume of patient RBCs available as many patients have significant anaemia (Ziman *et al* 2017). When auto-adsorptions are technically impractical, allo-adsorptions are reported to be used in 76% of laboratories (Ziman *et al* 2017). Allo-adsorptions are seen as one of the most complicated immunohaematology testing methods performed by the blood bank (Johnson and Puca 2022).

Allo-adsorptions are labour intensive, often taking several hours to complete (Table 3) and require the blood bank to have an adequate inventory of appropriately phenotyped donor blood to perform the procedure. Careful selection of phenotyped matched donor cells for allo-adsorption is required to minimise the risk of the donor RBCs absorbing any clinically significant alloantibodies present to corresponding antigens on the donor RBCs. Ideally allo-adsorptions leave only alloantibodies in the patient's plasma sample, however on numerous occasions even after multiple allo- or auto-adsorptions, they are ineffective due to the very high levels of autoantibody present in the patient's blood.

***Table 6**. Individual patients who had adsorptions and serological IAT crossmatching omitted 2020-2021.*

Patient No.	No. of samples collected	No. of absorptions performed/ omitted	Total No. of full PAM serologically XM RBC transfusions	Total No. of full PAM electronically XM RBC transfusions	Total No. of electronically XM Rh/K partial PAM RBC transfusions*	No. of adverse events	No. of alloantibodies developed
1	2	2/0	1	2**	6**	-	-
2	3	2/1	2	2	0	-	-
3	8	1/7	2	10	0	-	-
4	10	4/5	23***	11	0	-	1 (anti-f)
5	7	1/4	9	4	0	-	-
6	6	1/3	8	2	0	-	-
7	2	1/1	3	1	0	-	-
8	4	1/1	16	2	0	-	-
9	4	2/2	5	3	0	-	-
10	3	1/2	2	0	3	-	-
11	3	1/2	13	14	0	-	-
12	16	8/7	20	3	3	-	-
13	15	3/12	3	5	2	-	-
14	11	4/7	2	3	0	-	-
15	13	1/12	2	0	6	-	-
16	27	4/21	4	26	2	-	-
17	7	2/4	0	4	0	-	-
18	20	2/18	2	14	0	-	-
19	6	1/4	5	9	0	-	-
20	18	5/12	4***	8	0	-	1 (anti-E)
21	3	2/0	4	0	5****	-	-
Total	**188**	**49/125**	**130**	**123**	**27**	**0**	**2**

Warm autoantibodies (WAA), crossmatch (XM), Indirect antiglobulin test (IAT) Prophylactic antigen matched (PAM), Red blood cells (RBC)

* Rh and K matched must be provided at a minimum, followed by the Jk, Fy and Ss typing's.
** Combination of full/partial PAM RBC units released during emergency transfusion prior to adsorption studies being performed.
*** All units transfused before the alloantibody developed were full phenotyped matched to the patients.
**** Units released at alternative site to testing, units released before Duffy genotyping was completed.

It is then impractical to perform further adsorption on the sample as this increases the risk of missing weakly reactive alloantibodies (Johnson and Puca 2022).

Occasionally allo-adsorptions will remove an antibody to high frequency antigens (Johnson and Puca 2022). As the frequency of clinically significant antibodies to high frequency antigens is extremely low, this is accepted as a minimal risk.

The use of PAM donor RBCs for transfusion allows the frequency of adsorptions to be decreased or eliminated, thus decreasing the time in which donor units could be made available. There is no added safety or benefit

***Table 7**. Summary of patients with concurrent alloantibodies who had adsorptions and serological IAT crossmatching omitted 2020-2021.*

Patient No.	Age	Sex	Antibody	Adsorption/days during protocol antibody was identified	Involved in adverse transfusion events	No. of units transfused before alloantibody development **	Transfused before WAA development *****
1	59	F	Additive	Initial	No	-	No
4	64	M	Anti-f	3rd/113	No	4***	Yes
5	70	F	Auto-D	Initial	No	-	Yes
6	78	M	Anti-C	Historical	No	-	Yes
11	86	M	Auto-e	Initial	No	-	No
16	24	M	Anti-Cw, E Auto-C, D	Historical*/Initial	No	-	Yes
19	78	F	Anti-C	Initial	No	-	No
20	60	M	Anti-E	2nd/30	No	7****	Unconfirmed

Warm autoantibodies (WAA), Red blood cells (RBC)

* Patient 16 displayed all allo and autoantibodies stated before the WAA showed PAN agglutination activity and the protocol was commenced.
** Protocol transfusion include only.
*** Units were full phenotype matched to patient, crossmatched by IAT.
**** Units were full phenotype matched to patient. 2 units crossmatched by IAT, 5 unit electronically crossmatched.
***** Can only be determined for transfusion services included in study.

in performing allo-adsorptions when full phenotyped matched donor RBCs are used. The adsorption procedure is designed to detect antibodies to the same antigens (Rh, Kell, Kidd, Duffy and S) which are included in a routine extended phenotyping and used for full phenotype matching (Shirey *et al* 2002).

Studies from The Johns Hopkins Hospital in Baltimore Maryland (Shirey *et al* 2002) found that the use of the PAM units avoided 4.25 adsorptions per patient which is comparable to the 5.95 adsorptions avoided in the 21 patients (Table 5) in our study. Over our two-year study period, patients who had developed WAA and who were eligible to receive electronically crossmatched PAM units avoided 1.2 adsorptions per patient (Table 2).

While initial adsorption procedures are still required, subsequent pretransfusion requests will benefit from the proposed protocol making RBCs more readily available. Routine allo-adsorption turnaround times have decreased through procedural changes, as detailed below, making it faster to determine the presence of underlying alloantibodies in patients with WAA and WAIHA. Nevertheless, the adsorption procedure is still technical complex and may fail.

The introduction of 'ready to use' phenotyped donor RBCs for allo-adsorptions has made the procedure more efficient but requires the blood bank to carry an inventory of adequately phenotyped blood donors to perform the procedure in a time efficient manner (Johnson and Puca 2022). The donor RBCs may also be pretreated with enzymes or ZZAP to improve their effectiveness of adsorption, reducing the overall incubation time from 60 minutes down to 30 minutes (Shirey *et al* 2002).

The turnaround times of adsorption studies are still dependent on the strength of the WAA (Johnson and Puca 2022). Adsorption procedures are not routine tests and are not performed in every hospital-based transfusion service. In most cases, the sample must be sent to a reference laboratory to have testing completed (Australian and New Zealand Society of Blood Transfusion 2020) and this increases the wait time for transfusion and increases costs (Delaney *et al* 2020).

The use of PAM for patients with WAA and WAIHA is critical. It has been proposed in previous protocols that donor RBCs should be partially matched for Rh, Kell and Kidd system antigens only to offer protection against alloimmunisation and delayed haemolytic transfusion reactions (DHTR) due to the more immunogenic nature

of these antigens. Pretransfusion adsorption is however not precluded in these protocols (Shirey *et al* 2002). The Duffy (Fy^a, Fy^b) and S, s antigens have been included in this protocol to ensure safety of RBC transfusion without requiring more extensive pretransfusion testing because of the risk these blood group systems pose to alloimmunisation and DHTRs (Shirey *et al* 2002; Garratty *et al* 2002).

There are no standardised recommendations for the selection of RBC units for patients with WAA and WAIHA who have been investigated by their transfusion service. There is variation between institutions with some providing a higher level of antigen matched units then others (Delaney *et al* 2020). The extent of the antigen matching provided to the patient is determined by the treating transfusion service, but not all transfusions will reflect their service's local policies given the feasibility and sometimes difficulty in finding full antigen matched cells and the urgency for transfusion (Delaney *et al* 2020).

The decision to transfuse a patient should be based on relevant patient blood management guidelines of the treating institution (Johnson and Puca 2022). An effort should be made to provide transfusion support with full PAM blood to patients with WAA and WAIHA. In cases where phenotype matching for all antigens is not possible, the transfusion service must assess their donor inventory and the urgency of the clinical situation (Shirey *et al* 2002). As outlined in the protocol above, if fully antigen-matched units are not readily available, the 'best matched' is selected. This process was performed for a total of 27 donor units (Table 6) for seven different patients who underwent adsorptions at their next adsorption due date (monthly) as per the protocol to exclude the formation of new alloantibodies to antigens that could not be matched. No alloantibodies were formed in these patients.

The technique selected for crossmatching donor units for patients with WAA and WAIHA should be based on local policies, however due to the nature of these autoantibodies the donor unit will appear as serologically incompatible by IAT. Crossmatching to find the "least incompatible" should be discouraged as there is no clinical benefit to the patient (Johnson and Puca 2022; Garratty *et al* 2002). Discussions with the treatment team should detail the extent of compatibility testing performed and that the survival rate of the transfused RBCs are like the patient's own circulating RBCs (Johnson and Puca 2022).

The desired outcome of the above protocol is to improve safety by avoiding alloimmunisation and haemolytic transfusion reactions. Additional benefits include a considerable time and financial saving due to the added ability to avoid serological testing such as adsorptions and serological IAT crossmatching. By omitting these serological protocols in favor of using PAM units, there is an increase in the rate at which RBCs are made available to patients which is complemented by the practice of blood banks and blood suppliers by increasing the percentage of antigen typed units available in their blood banks (Delaney *et al* 2020). This decision to implement such a protocol should be made in consultation between a transfusion medicine specialist and the laboratory director (Australian and New Zealand Society of Blood Transfusion 2020).

The confirmation of a patient's complete phenotype is recommended prior to transfusion in chronically transfused patients with SCD and thalassemia. It has also been suggested for transfusion management of AIHA patients to prevent alloimmunisation (Raos *et al* 2022). The benefits of complete phenotyping for patients with WAIHA include the possible alloantibodies the patient can produce can be determined allowing antibody investigation to be selective, the number of donors used for alloadsorptions can be limited (one in most cases), and the interpretation of alloadsorption studies is simplified as the auto and alloantibody specificities can be distinguished from each other (Shirey *et al* 2002).

When a patient presents with a WAA it may not be possible to obtain a complete phenotype due to the positive DAT. The use of anti-human globulin (AHG) reactive antisera may not be suitable when patients present with a positive DAT forcing the laboratory to use monoclonal antisera. While the use of monoclonal antisera has become standard practice for many of the common blood group antigens, there are several which still rely on polyclonal technology, particularly Duffy (Raos *et al* 2022). The use of EDTA-glycine hydrochloric acid or chloroquine treatment methods have been utilised to remove the bound IgG from the RBCs making it possible to use AHG-reactive antisera, however these treatments are not always successful and can be manually intensive (Raos *et al* 2022; Johnson and Puca 2022). Recent RBC transfusions may also preclude accurate phenotyping (Shirey *et al* 2002).

Molecular technology is becoming widely used in all areas of blood banking due to the technology's ability to overcome many of the limitations seen in serological testing. Genotyping is unaffected when the patients RBC are coated with antibody or recent transfusions (Johnson and Puca 2022) and it is seen as the gold standard for complex problems at reference laboratories (Raos *et al* 2022). Genotyping of patient and donor units is recognised to be beneficial and cost effective, however

it is only with more widespread use that these assays will achieve a higher throughput rate leading to decreased turnaround time and lower costs (Raos *et al* 2022). The exercise of genotyping only needs to be performed once for it to be included in the patient's transfusion record (Westhoff 2019). The integration of molecular testing to the transfusion service has the potential to reduce the labor-intensive phenotyping tests and provide a better matched RBC unit (Singhal *et al* 2017). Next generation sequencing will allow for a greater level of accuracy in blood group predictions in both the donor and patient populations and it may detect variants that are not currently predefined by the assay currently used (Raos *et al* 2022).

The use of PAM unit for patients with WAA is not only to reduce the frequency which adsorption and serological IAT crossmatching are performed, but also to increase the safety by reducing alloimmunisation rates (Delaney *et al* 2020). The most frequent alloantibodies identified are those within the Rh system (50% of patients) and Kell in 20% of patients (Ziman *et al* 2017). There is no method currently available to identify which patients are at risk of alloimmunisation and who would benefit from receiving PAM blood (Kacker *et al* 2014).

Reports have demonstrated that the incidence of new alloimmunisations in patients who have already developed WAA is up to 15.1% (Delaney *et al* 2020), suggesting that there is a higher risk of alloimmunisation in the WAA population than in the general patient population, being 4.4%-10.5% (Delaney *et al* 2020). Suggested factors attributed to alloimmunisation include the patient's inflammatory state and number of transfusions received, however these factors may not be enough to cause alloimmunisation without an identified genetic predisposition towards alloimmunisation (Delaney *et al* 2020).

When the PAM protocol is used by a laboratory, it does not protect patients from receiving non-antigen matched cells at different institutions or if the WAA fall below detection level. There is also a possibility that the patient may have received non-antigen matched RBCs prior to developing the WAA or initial presentation at the facility (Delaney *et al* 2020). Shirey and colleagues (2002) showed that with the use of a PAM protocol there were no new alloimmunisations, however the use of this protocol at various institutions internationally as reported by Delaney and colleagues in 2020, found that it provided no protective effect from new alloimmunisation. The latter results have been attributed to varying degrees of matching, RBC availability, urgency of transfusion, presence/absence of the WAA at the time of transfusion and patients receiving care at another institution which did not provide PAM RBC units (Shirey *et al* 2002; Delaney *et al* 2020).

During our two-year study period using the protocol, alloimmunisation was detected in two male patients (Table 6 & 7) who developed clinically significant antibodies directed against the Rh system. Both these patients had adsorptions and serological IAT crossmatching omitted.

The anti-f alloantibody was detected in patient 4 (P4) after routine adsorption studies were performed for the third time 113 days into the protocol, and at this point of the treatment P4 had been transfused 4 RBC units (Table 7). These units were full phenotype matched (patient phenotype: R1R1 K-) and crossmatched by IAT-P4 was yet to have serological IAT crossmatching omitted. Elution studies performed showed autoantibody activity. The alloimmunisation is believed to be attributed to past transfusions received from a different institution prior to the development of WAA and subsequent inclusion into the protocol. It is also possible that the anti-f was initially present but was below detectable level for routine pretransfusion testing.

The anti-E alloantibody was detected in patient 20 (P20) after adsorption studies were performed for the second time, 30 days after P20 entered the protocol (Table 7). During this time, 7 RBC units were transfused with 2 of these units serologically IAT crossmatched and 5 were electronically crossmatched. All the units transfused were full phenotype matched. Prior to the development of the WAA and subsequent involvement in the protocol, P20 was transfused a single random donor RBC unit, with routine pretransfusion testing showing a negative antibody screen. The unit was confirmed to be E antigen positive.

Alloimmunisation has implications on laboratory testing and clinical consequences for patients including DHTR and increased workloads for future pretransfusion testing, increased challenges in finding appropriate RBC units, and delays in provision of RBCs for patients (Singhal *et al* 2017).

There were no documented adverse events in patients who received PAM units with no preceding absorptions or serological IAT crossmatching. A similar finding was also reported by Shirey and colleagues in 2002 (Shirey *et al* 2002). The risk of a transfusion reaction in patients with WAA appears to be no higher than in other patient populations requiring transfusion (Johnson and Puca 2022). Studies have shown that commonly seen adverse events in patients with WAIHA are febrile non-haemolytic and allergic reactions with no reports of serological incompatibility.

Most patients with WAIHA will tolerate a serologically incompatible RBC transfusion without an increase in their underlying haemolysis (Chen *et al* 2020).

The time and cost of providing PAM units to patients with WAA to increase safety and decrease frequency of serological testing has not been determined and could vary considerably depending on the transfusion service, agreements with blood suppliers/manufacturers, frequency of donor phenotypes, and the availability of units in inventory (Shirey *et al* 2002). Reports in patients with SCD have shown that patient antigen phenotyping and limited PAM are extremely costly however a single alloimmunisation event can be more costly, highlighting the need for a screening test to determine alloimmunisation risk (Kacker *et al* 2014).

The described protocol has shown significant time saving in serological testing allowing patients suffering from WAA and WAIHA to receive transfusions sooner. The protocol has presently not yet reached its full potential in terms of time saving. Currently, adsorption and serological IAT crossmatching are performed on a monthly basis in subsequent presentations. Future time saving could be experienced by increasing the time frame they are avoided. Alternatively, these steps could be removed from subsequent pretransfusion testing when serological findings are consistent with previous WAA activity. Adsorptions which are currently performed on pre and post samples to investigate all adverse transfusion events that involve donor RBCs could be abbreviated to be performed only in suspected cases of haemolytic transfusion reactions (acute or delayed). For the protocol to reach its full potential, future studies, risk assessments and further consultation between a transfusion medicine specialist and the laboratory director should be performed.

Conclusion

Patients that present with WAA and WAIHA can often pose a challenge to the transfusion service, complicating pretransfusion testing and delaying the provision of RBCs for transfusion. Routine testing for these patients is tedious and labor intensive.

It is recommended that the patient's complete phenotype be determined during their initial pretransfusion testing either by molecular techniques or in combination with serological phenotyping to allow the use of PAM donor units.

By applying the PAM protocol outlined in this study, patient benefits include a decrease in alloimmunisation rates and the risk of DHTR. By employing the PAM protocol, costly, lengthy, and time consuming pretransfusion adsorption studies would be limited, rarely needing to be performed while the WAA is active and ensuring readily available compatible red cells for transfusion.

This protocol has had the greatest impact in tertiary care and general hospital inpatients providing an effective means to provide efficient and safe transfusions.

Further larger studies are required to confirm that the PAM algorithm is efficient and cost effective and importantly, safe.

Acknowledgements

I wish to acknowledge the support and guidance of Professor David Roxby.

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Evaluation of the MBT STAR®Carna IVD assay to detect carbapenemase producing *Enterobacterales* in Australia

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Abstract

Clinical microbiology laboratories require rapid, effective and accurate tests to detect carbapenemase producing *Enterobacteriaeceae* (CPE). In this study the MBT STAR® Carba IVD assay (MBT) (Bruker Daltonik GmbH, Bremen, Germany) was evaluated for the detection of CPEs using 173 *Enterobacteriaceae* isolates (139 CPE positive and 34 CPE negative isolates). Positive isolates were confirmed using the AusDiagnostics Multiplex CRE 16 well PCR assay. The MBT assay had a sensitivity of 98.5% and specificity of 89%. The positive and negative predictive values were 97% and 94% respectively. Sixteen isolates (9%) required repeat testing due to borderline results. The MBT assay is fit for purpose. The need for repeat testing of isolates with borderline results will however impact on turnaround times, laboratory workflow and financial costs. These factors should be considered prior to test implementation.

Keywords: ***carbapenemase producing Enterobacterales, MBT STAR® Carba assay***

Introduction

Australia has relatively low rates of CPE infections. Imipenemase (IMP) (59.9%), New-Delhi metallo-β-lactamase (NDM) (24.3%) and Oxacillinase (OXA)-like 48 (9.8%) carbapenemases constitute 94% of isolates (CarAlert 2020). This contrasts with a much lower prevalence of Class B carbapenemases in the Americas and Europe (Cheng and Kwong, 2017).

Phenotypic CPE detection methods such as the carbapenemase inactivation method (CIM), are limited by increased turnaround times (Złoch *et al* 2021). The MBT assay evaluated in this study is a rapid phenotypic method utilizing a carbapenem antibiotic, whose β-lactam ring will be hydrolysed by active carbapenemase containing bacteria (Ota *et al* 2021). This causes a mass shift detected by Matrix-Assisted Laser Desorption Ionization Time-of-Flight Mass Spectrometry (Oviaño *et al* 2020).

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Materials and methods

A total of 173 isolates with raised MIC to meropenem (=> 0.25 µg/ml) (VITEK®2 (bioMérieux) Antimicrobial Susceptibility Testing system), were screened using the CIM. Of these, 139 CIM positive CPE isolates were known positives collected between 2008 – 2021. Positive isolates were confirmed using an assay that detects bacterial carbapenemase genes (AusDiagnostics Multiplex CRE 16 well PCR) (Meunier *et al* 2018). Table 1 outlines the type of organisms and the CPE genes detected. The remaining 34 CIM negative isolates were collected prospectively (February - August 2021) and are outlined in Table 2.

Isolates were subcultured twice (Columbia horse blood agar - bioMérieux) and tested with the MBT, following manufacturer's instructions. Statistical analysis was performed using the http://vassarstats.net/ website to calculate sensitivity, specificity and positive and negative predictive values at the 95% confidence interval.

Results

The positive predictive value (PPV), negative predictive value (NPV), sensitivity and specificity were 97%, 94%, 98.5% and 88.9% respectively, fulfilling the manufacturer's requirements in the Australian context.

Table 1. *Summary of positive isolates used in the study and their known genotypes.*

	Carbapenemase										
Enterobacterales	**IMI**	**IMP**	**IMP & OXA-1**	**KPC**	**NDM**	**NDM & OXA-1**	**NDM & OXA-48**	**NDM, OXA-4 & OXA-1**	**OXA-48**	**VIM**	**Total**
Citrobacter braakii		1	-	-	-	-	-	-	-	-	1
Citrobacter farmeri		3	-	-	-	-	-	-	-	-	3
Citrobacter freundii		7	-	-	-	-	-	-	-	-	7
Citrobacter koseri		-	-	-	-	-	-	-	1	-	1
Enterobacter asburiae		1	-	-	-	-	-	-	-	-	1
Enterobacter cloacae	1	43	1	-	-	-	-	-	1	1	47
Escherichia coli		4	-	-	9	3	3	-	5	-	24
Klebsiella aerogenes		1	-	-	-	-	-	-	-	-	1
Klebsiella oxytoca		5	-	-	-	-	-	-	-	-	5
Klebsiella pneumoniae		32	-	2	3	1	1	1	5	-	45
Morganella morganii		1	-	-	-	-	-	-	-	-	1
Proteus mirabilis		1	-	-	-	-	-	-	-	-	1
Serratia marcescens		1	-	-	-	-	-	-	1	-	2
Grand Total	**1**	**100**	**1**	**2**	**12**	**4**	**4**	**1**	**13**	**1**	**139**

Table 2. *Summary of positive isolates used in the study and their known genotypes.*

Enterobacterales	**Amikacin Resistant**	**AmpC & ESBL**	**ESBL**	**Gentamicin Resistant**	**Negative**	**Grand Total**
Citrobacter koseri	-	-	-	-	1	1
Delftia acidovorans	-	-	-	1	-	1
Enterobacter cloacae	-	-	-	-	4	4
Escherichia coli	-	1	7	3	4	15
Klebsiella pneumoniae	-	-	4	-	2	6
Morganella morganii	-	-	-	-	1	1
Proteus mirabilis	1	-	1	-	2	4
Serratia macescens	-	-	-	-	1	1
Serratia ureilytica	-	-	-	-	1	1
Grand Total	**1**	**1**	**12**	**4**	**16**	**34**

Table 3. *Borderline results for the MBT STAR® Carba IVD Assay.*

Isolate Number	Enterobacterales	Carbapenemase	Meropenem Etest MIC	Carba STAR Assay	Repeat Testing Carba STAR Assay	Carba STAR Assay testing with 60 minute incubation
1	*Klebsiella pneumoniae*	OXA-48 Like	>32	Borderline	Positive	-
2	*Enterobacter cloacae*	IMP	2	Borderline	Positive	-
3	*Klebsiella pneumoniae*	IMP	0.5	Borderline	Positive	-
4	*Klebsiella pneumoniae*	NDM, OXA-48	>32	Borderline	Positive	-
5	*Enterobacter cloacae*	IMP	>32	Borderline	Positive	-
6	*Klebsiella pneumoniae*	IMP	1	Borderline	Positive	-
7	*Klebsiella pneumoniae*	OXA-48 Like	>32	Borderline	Positive	-
8	*Klebsiella pneumoniae*	IMP	2	Borderline	Positive	-
9	*Klebsiella oxytoca*	IMP	0.5	Borderline	Borderline	Positive
10	*Klebsiella pneumoniae*	IMP	1	Borderline	Positive	-
11	*Klebsiella pneumoniae*	IMP	32	Borderline	Negative	Positive
12	*Klebsiella pneumoniae*	IMP	0.5	Borderline	Positive	-
13	*Escherichia coli*	IMP	0.5	Borderline	Positive	-
14	*Escherichia coli*	Negative	0.5	Borderline	Negative	-
15	*Escherichia coli*	Negative	0.5	Borderline	Negative	-
16	*Escherichia coli*	Negative	1	Borderline	Negative	-

Table 4. *False positive and negative results for the MBT STAR® Carba IVD Assay.*

Organism Name	Carbapenemase	Ambler Classification	Meropenem Etest MIC	Carba STAR Assay Result 1 (30 minute)	Carba STAR Assay Repeat Result 2 (30 minute)	Carba STAR Assay Repeat 3rd attempt (60 minute)
Escherichia coli	IMP	B	>32	Negative	Borderline	Positive
Escherichia coli	IMP	B	0.25	Negative	Positive	-
Klebsiella pneumoniae	IMP	B	0.25	Negative	Positive	-
Klebsiella pneumoniae	IMP	B	>32	Negative	Negative	Positive
Enterobacter cloacae	Negative	-	0.5	Positive	Negative	-
Serratia ureilytica	Negative	-	0.5	Positive	Negative	-

Sixteen (9%) borderline results were re-tested (Table 3). Potential causes of the borderline results could be due to low organism concentration secondary to the recommended "1 µL loop-full" sampling of organism from the agar plate (Złoch *et al* 2021) or the substitution of Columbia horse blood agar (bioMérieux), for the recommended medium (Becton Dickinson) which is not available in Australia.

Repeat testing resolved six discordant results (four false negative, two false positive) (Table 4). Four of the false negatives were positive on retesting with two requiring a longer 60-minute incubation. False negatives may be related to low zinc in the agar affecting metallo-β-lactamase enzyme activity and reduced carbapenem hydrolysis (Tan *et al* 2021). To the authors' knowledge, this is the first report of false positive MBT results for *Enterobacter cloacae* and *Serratia ureilytica*. Both were CPE negative upon re-testing. False positives may have resulted from operator error.

Discussion

Limitations of the assay include labour intensity as testing 3 to 4 isolates took 90 to 100 minutes, and the cost as MBT is six times more expensive than other phenotypic assays, based on June 2021 costings (Anantharajah *et al* 2019). Although the MBT is cheaper than the AusDiagnostics MT CRE EU assay, this assay has the added advantage of providing gene detection results, essential for surveillance/mandatory reporting to the National Alert System for Critical Antimicrobial Resistances (Australian Commission on Safety and Quality in Health Care, 2021).

The potential for false negatives through use of the CIM, without PCR confirmation was a limitation of this study. In addition, this single centre evaluation limited the CPE epidemiology to locally prevalent phenotypes. A nationwide study would facilitate testing of less common carbapenemases and assist in determining the rates of discordant results. Studies on turnaround times to notification of CPEs are also required.

The MBT assay is fit for CPE detection within the Australian setting. Repeat testing of borderline results, increased turnaround time, and cost are factors warranting careful consideration for the introduction of this assay.

Disclaimer

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sector.

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Babesia infection in a returned traveller

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Abstract

This case study describes a Babesia sp infection in a 60-year-old woman who had travelled to North America and Canada. On her return she presented with fevers, headaches and myalgia. Tests were performed for respiratory viruses and influenza. A full blood count (FBC) and electrolytes and liver function tests (ELFTs) were also requested. Abnormalities were detected in the ELFT results and the FBC gave an abnormal lymphocyte flag and high monocyte count. On examination of the blood film, intra- and extracellular parasites were seen and these were then diagnosed as Babesia sp. She was also found to have either an active or past Lyme disease (borreliosis) infection. She was hospitalised and treated but went into respiratory distress. After further treatment, she was cleared of the infection and discharged.

Introduction

Babesia is a protozoan parasite that causes infection in humans and animals which was first discovered in cattle in 1888. It was recognised in 1893 by Smith and Kilbourne as the cause of Texas cattle fever. *Babesia microti* is the main cause of human infection and is endemic in the north-eastern and upper midwestern United States. The primary reservoir for *B. microti* is the white-footed mouse, but the parasite also has been found in shrews, chipmunks, voles, and rats. It is transmitted by the Ixodes tick vector or via blood transfusion (Figure 1). Most human infections are mild or asymptomatic, but infection is life threatening in the immunosuppressed or splenectomised patient. Co-infection with *Borrelia burgdorferi* (Lyme disease) is common and is also known to worsen disease progression (Vannier and Krause 2012; Vannier *et al* 2015).

Fever is the main symptom of babesiosis and is often accompanied by a series of non-specific symptoms, explaining why diagnosis may be delayed or missed. The diagnosis is confirmed by identification of babesia organisms on blood smears or detection of babesia DNA by PCR. Most patients have complete recovery following a standard seven to 10 day course of antimicrobial therapy (Vannier *et al* 2015).

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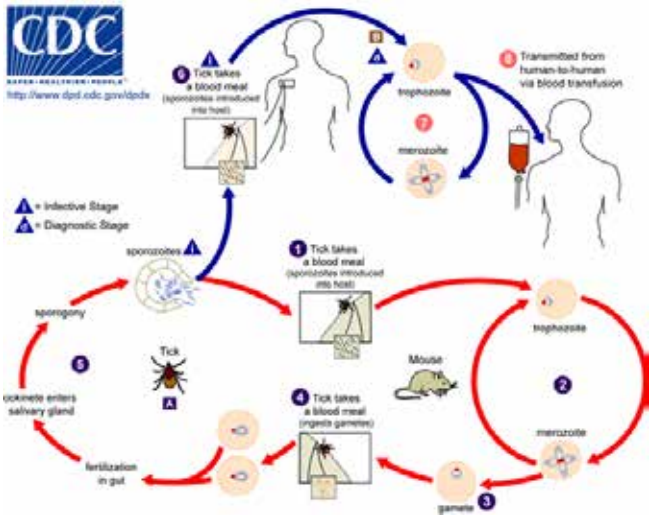

***Figure 1**. Life cycle of Babesia sp.*
https://www.cdc.gov/dpdx/babesiosis/index.html

Case report

A 60-year-old female travelled to Los Angeles, Boston, New York and Toronto.

Symptoms started with fever, chills and profuse night sweats when overseas. Fifteen days later after arriving home, she presented to her GP with a fever of 38.9°C, headaches, myalgia, rash, sore throat and three days of diarrhoea. There was no recollection of any tick bite and she had blood tests for respiratory viruses, influenza serology, FBC and ELFTs.

***Table 1**. ELFT results at presentation.*

	Result	Units	Reference Interval
Sodium	**134 L**	mmol/L	135-145
Potassium	4.0	mmol/L	3.5-5.5
Chloride	101	mmol/L	95-110
Bicarbonate	24	mmol/L	20-32
Anion Gap	9	mmol/L	<16
Ca (corr)	2.27	mmol/L	2.10-2.60
Phosphate	**0.77 L**	mmol/L	0.8-1.50
Urea	3.5	mmol/L	3.0-8.0
Urate	0.285	mmol/L	0.150-0.400
Creatinine	57	umol/L	45-85
eGFR	>90		>59
Gluc R	6.0	mmol/L	3.6-6.0
Protein	66	g/L	63-80
Albumin	**29 L**	g/L	32-44
Globulin	37	g/L	22-43
T Bilirubin	**25 H**	umol/L	<16
ALP	**177 H**	U/L	30-115
AST	**53 H**	U/L	10-35
ALT	**84 H**	U/L	5-30
GGT	**101 H**	U/L	5-35
LDH	**366 H**	U/L	120-250
Cholesterol	**3.3 L**	mmol/L	3.9-5.5

***Table 2**. FBC results at presentation.*

	Result	Units	Reference Interval
Hb	**112 L**	g/L	115-165
Hct	**0.34 L**		0.35-0.47
RCC	4.0	10^{12}/L	3.9-5.6
MCV	85	fL	80-100
WCC	7.8	10^9/L	3.5-10.0
Neutrophils	5.23	10^9/L	1.5-6.5
Lymphocytes	1.52	10^9/L	0.8-4.0
Monocytes	**0.97 H**	10^9/L	0-0.9
Eosinophils	0.01	10^9/L	0-0.6
Basophils	0.03	10^9/L	0-0.15
Platelets	158	10^9/L	150-400

Results

There were no respiratory viruses detected (influenza A or B, RSV, rhinovirus, parainfluenza) and low levels of influenza antibody consistent with a past infection or vaccination.

Her ELFT results are shown in Table 1 and FBC results in Table 2.

There was an "atypical/reactive lymphocyte' flag generated by the analyser and along with the raised monocyte count prompted a blood film being made and reviewed.

The Cellavision® image capture for the white cells are shown in Figure 3 and Figure 4 shows the red cell and platelet images.

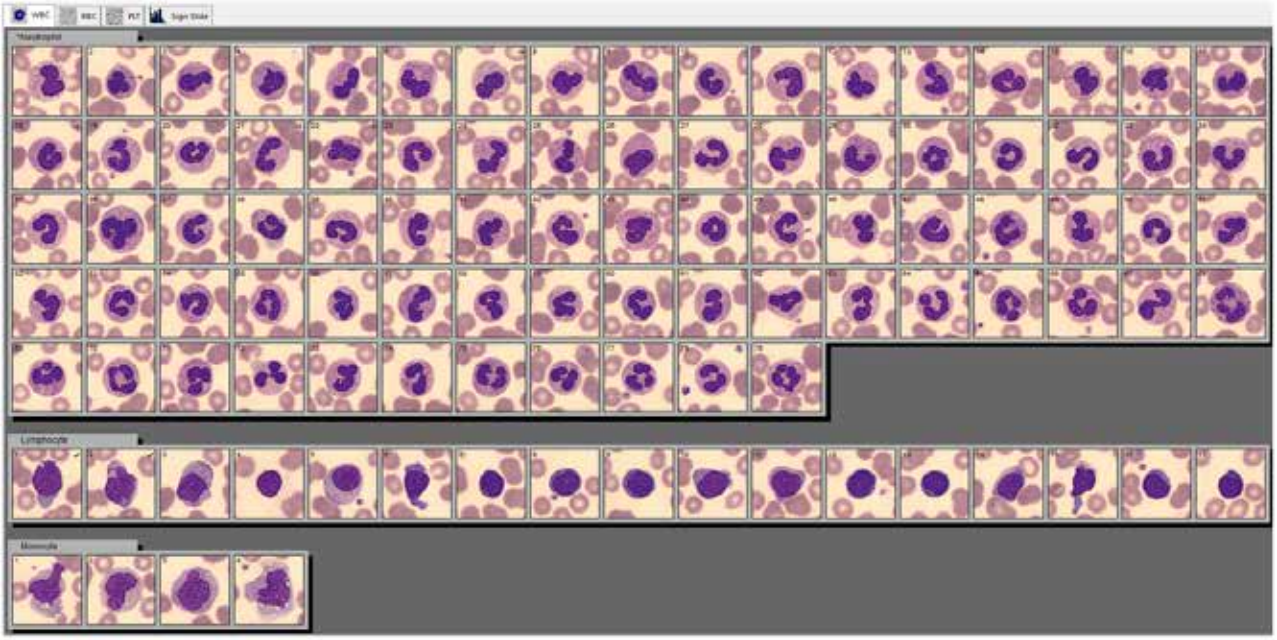

***Figure 3**. Cellavision® white blood cell images.*

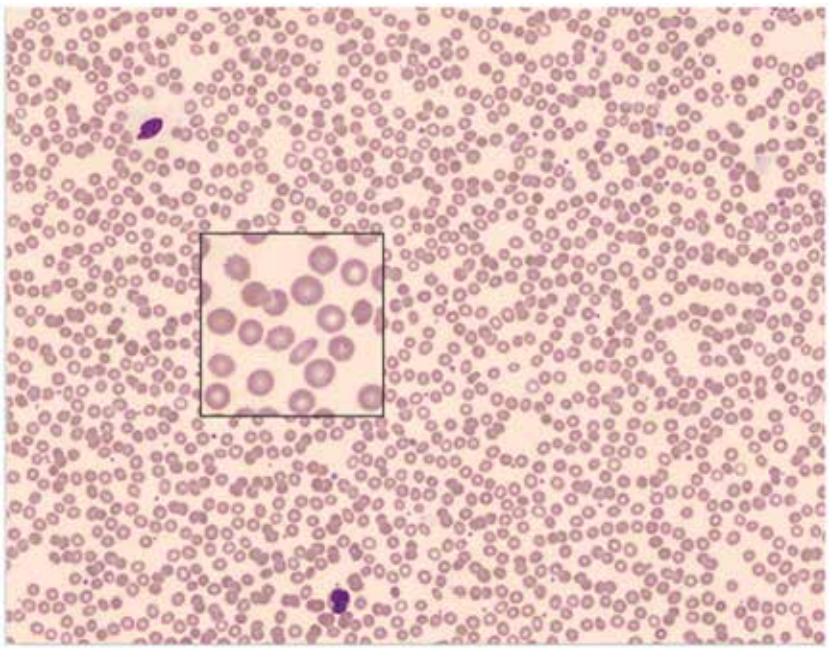

***Figure 4**. Cellavision® red cell and platelet images.*

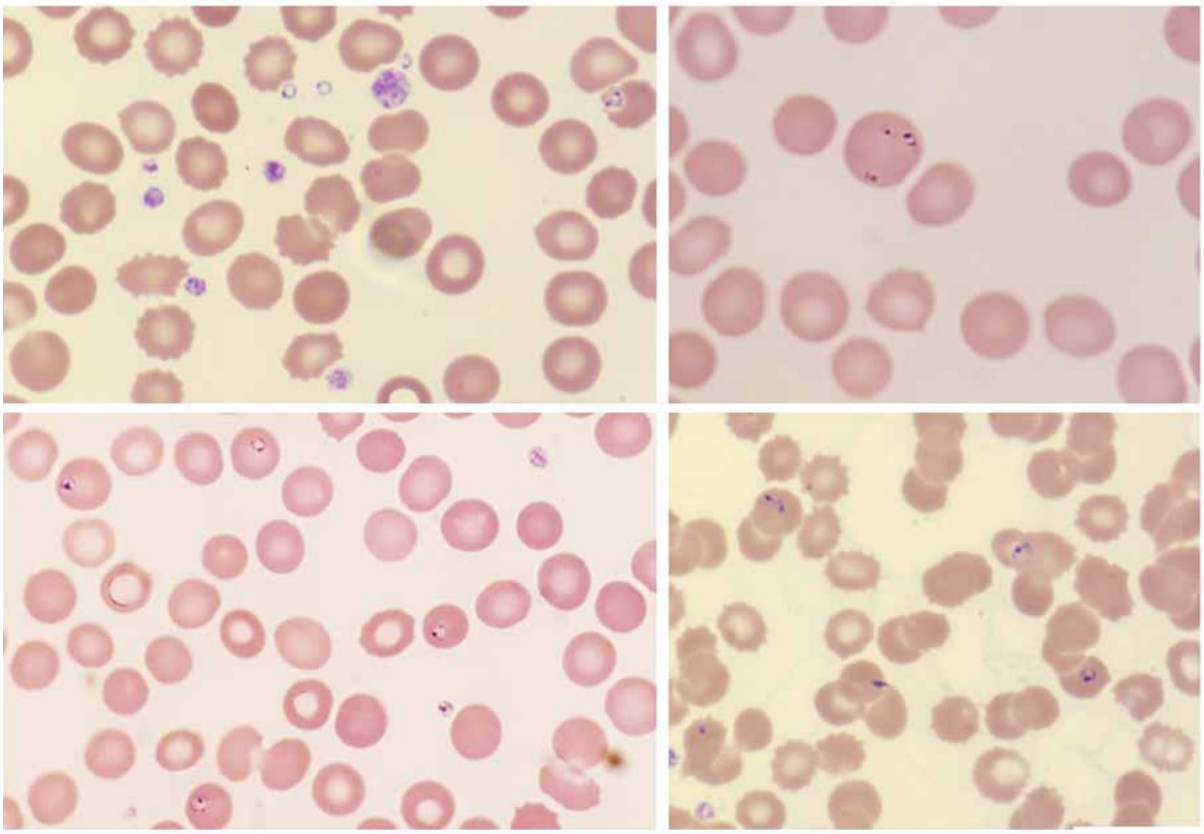

***Figure 5**. Intra- and extracellular parasites found in the blood film. Modified Wright stain (100x).*

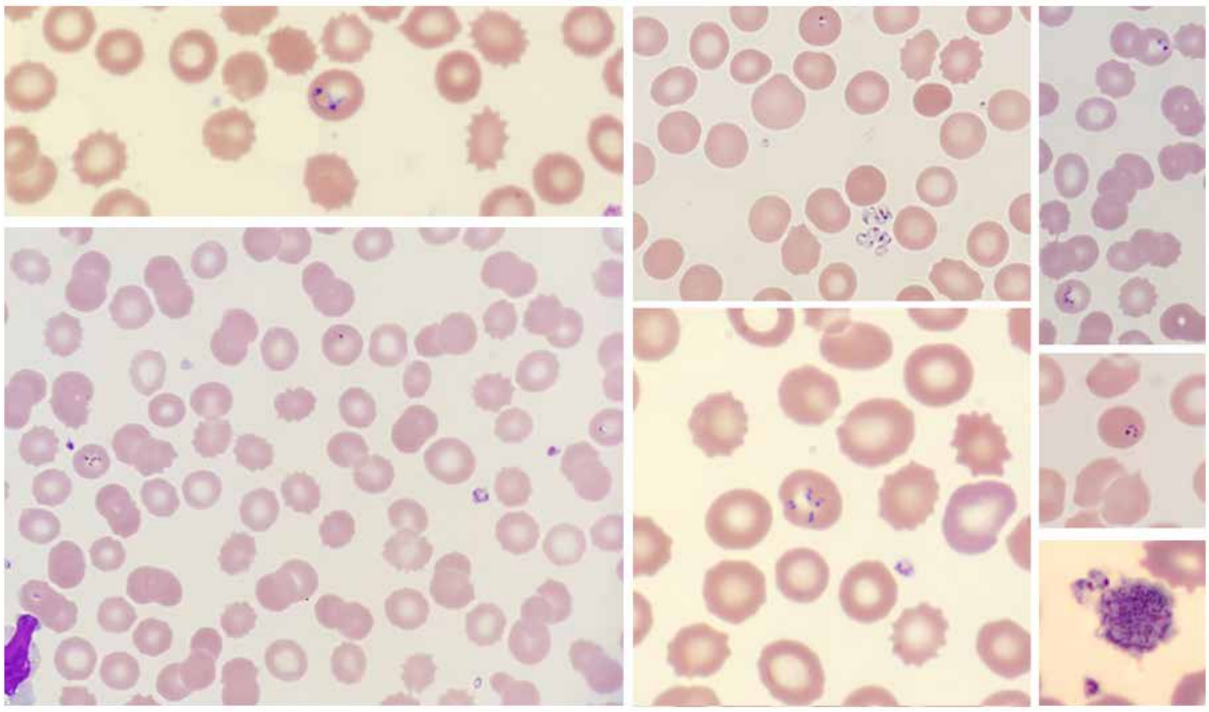

***Figure 6**. Intra- and extracellular parasites found in the blood film. Modified Wright stain (40x – 100x).*

More parasites were then found on the Romanowsky stained film (Figs 5 and 6). Thick and thin films were then prepared and images from these are shown in Figures 7 and 8. A malaria ICT and Illumigene® DNA test was performed and these were both negative.

A parasite density count was performed and showed a parasitaemia of 1.62% or 65,000 parasites/ul blood. There were tetrads of merozoites in Maltese Cross formation also present. A diagnosis of Babesia sp was then made.

As Lyme disease is a common co-infection of babesiosis, this test was also done and showed positive Lyme IgG and IgG immunoblot results that suggested either active or past Lyme borreliosis.

Treatment

The patient was immediately sent to the emergency department as this can be a life-threatening infection. The treatment for babesiosis is a combination of I.V. lincomycin and quinine, with oral clindamycin and treatment for the Lyme disease is a 10-day course of doxycycline.

Parasite density counts started dropping after treatment began – this is shown in Figure 9.

Over the first four days in hospital the patient appeared to improve but early on day five she went into respiratory distress and was sent to the ICU.

More therapy was given in response to worsening symptoms but the introduction of more drugs led to liver

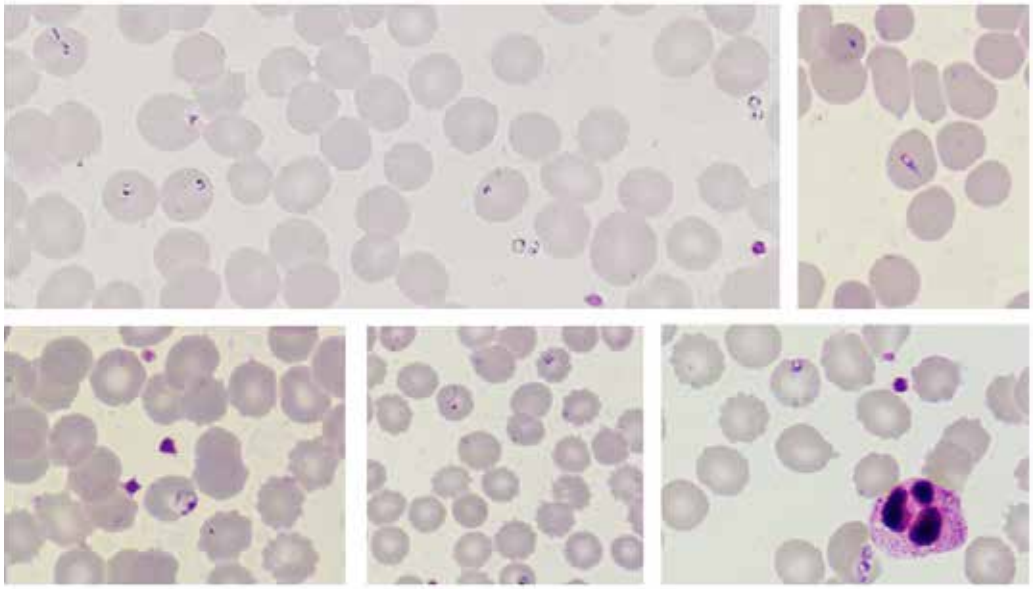

***Figure 7**. Thin film Giemsa stain at pH 7.2. Magnification 100x.*

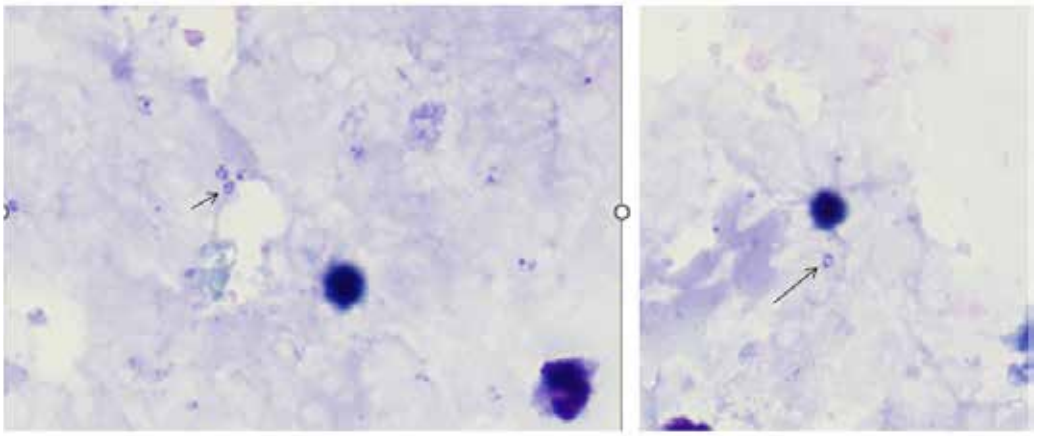

***Figure 8**. Thick film Giemsa stain at pH 7.2. Magnification 100x. Arrow indicate parasites.*

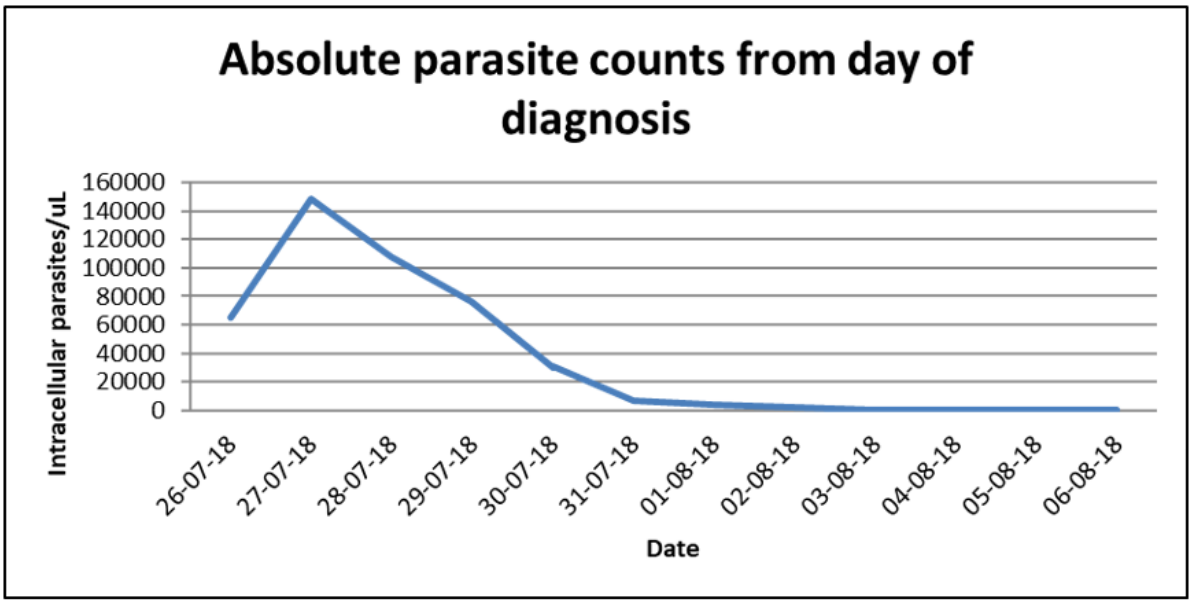

***Figure 9**. Parasite counts from day one of hospital admission.*

inflammation due to the by-products of haemolysis. The AST, ALT and GGT all increased by up to four times the reference range, peaking at day 16 after admission.

She then started to stabilise and on day 18 was released from hospital.

Her liver enzymes had returned to near normal by day 31 from diagnosis and no babesia was detected.

Discussion

B. microti and *B. divergens* are the two strains of babesia responsible for human infection. *B. microti* is the eitiologic agent for babesiosis in the U.S. and *B. divergens* is the cause of babesiosis in Europe. Endemic regions in the U.S. include California, Washington, New York, New Jersey, Conneticut, Maryland, Virginia, Minnesota, Missouri, Wisconsin and Georgia (CDC Babesiosis).

Like malaria, sporozoites infect the host's red blood cells and these infected red cells contain pleomorphic ring forms similar to the early trophozoites of *P. falciparum*. Trophozoites range in size from 1.0 to 5.0 µm and the host red cells do not enlarge, change colour or contain stippling. After parasites divide, they form multiple ring forms and the occasional characteristic. Maltese cross formation (tetrad). Extracellular trophozoites and merozoites can also occur.

The incidence of infection in the United States range between seven and 1,250 per 100,000 population in endemic areas. There has only been one case on record in Australia that is thought to be locally acquired and that was in 2012 (Senanayake *et al* 2012).

This case involved a 56-year-old man with no recent travel history. He received a blood transfusion after motorbike accident but after a long hospital stay of many months and deteriorating health, babesia was discovered on blood film. Even with treatment, he suffered multi-organ failure and a fatal asystolic arrest. The blood transfusion was cleared of the source of the parasite and it is still unknown how he acquired the infection.

The usual fatality rate is 6-9% in hospitalised patients but up to 20% in immunosuppressed or transfusion-transmitted patients (CDC 2023).

There are currently no screening tests performed to detect babesia in donor blood and the Red Cross Blood Service use a risk management framework to monitor infectious disease developments in Australia and other countries. Other tick-borne infections such as ehrlichiosis, anaplasmosis, babesiosis and Lyme disease are included in this.

Conclusion

This case study illustrates a rarely seen 'imported' infection. The patient was symptomatic and presented with some of the classic signs of babesiosis. Prompt diagnosis led to treatment being commenced and even though her condition worsened, she was cleared of the parasite and was able to be discharged from hospital in less than three weeks.

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The case for a Clinical Scientist (Transfusion Medicine)

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Abstract

Transfusion Medicine (TM) is a rapidly evolving field of medicine that plays a vital role in the supportive care of patients in both treatment and prevention of disease. TM has been subjected to a recent increase in complex regulatory requirements and expectations in blood and blood product management. Modern TM transcends the traditional role of a transfusion laboratory and the medical scientist. Contemporary pathology and technological advancements are creating a multidisciplinary work environment challenging the conventional roles of medical scientists. In the highly specialised area of immunohaematology this has created a void of skills, knowledge and expertise.

Collectively, these changes have shown a new role is needed and that is of a Clinical Scientist-TM. This role is for an expert and specialist within the field of transfusion science. A role that contributes to the overall care of a patient through transfusion clinical oversight and management as part of the multidisciplinary transfusion team.

Keywords: ***transfusion medicine, clinical scientist, immunohaematology***

Introduction

Transfusion Medicine (TM) is a field of medicine that plays a vital role in the supportive care of patients in both treatment and prevention of disease, with transfusion therapy an essential part of haematology practice. Traditionally, TM can be classified into three discrete areas: blood collection (donor centre), pre transfusion testing-immunohaemology (transfusion laboratory pathology) and blood administration (health services). Modern TM however covers additional regulatory aspects of transfusion including haemovigilance and patient blood management (PBM). Rapidly evolving over the last few decades and occupying key components of modern medicine, the future of TM is in cellular therapies, genomics and personalised medicine (Seifried *et al* 2011).

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Transfusion Medicine is seen as a relatively new specialty and considered a medical discipline in some countries.

Haematologists are pathologists specialising in the diagnosis and management of patients with blood and bone marrow diseases. Their time is shared between performing diagnostic work within a laboratory and providing clinical care to patients. In the Australian training framework for haematologists, TM is offered as a sub-specialty within a 5-year program (Royal College of Pathologists of Australia 2023). The rapid expansion in the fields of haematology and TM are placing increased demands on the role of the haematologist and combined with rising expectations of transfusion medicine in an emerging complex regulatory environment, has led to the necessity of new clinical roles in the discipline (Miller *et al* 2015).

Medical scientists specialise in performing medical laboratory tests on blood, other body fluids and tissues. They assist clinicians in the diagnosis, treatment and prevention of disease (Australian Institute of Medical and Clinical Scientists - About Medical Science). In the Australian context there is diversity across tertiary institutions in how transfusion science is offered. Either it is part of a haematology major on its own, both

components of an undergraduate degree in Medical Laboratory Science. The role of a medical scientist in a pathology transfusion laboratory is primarily to oversee and perform immunohaematology testing - the serological study of antigens and antibodies. Additional responsibilities include management and preparation of blood and blood products. Historically in this field, serological testing has been labour intensive and manually orientated, demanding a high level of technical skills and formal qualifications.

Pathology organisational structure and laboratory medicine are changing. Driven primarily by economics and advancements in automation, contemporary pathology is realising the centralisation and consolidation of testing into large core laboratories (Ferraro *et al* 2016). This is challenging the traditional role of the medical laboratory scientist in support of the multidisciplinary scientist role, contributing to a "deskilling" of the workforce (Badrick and St John 2012). Emerging technologies are placing additional strain on the skill set of the contemporary workforce in a transfusion laboratory. An example is that the scope of immunohaematology has significantly expanded over the last few decades to include more specialised areas of testing, including the study of granulocyte and platelet antigens and antibodies, transplantation immunology and genomics.

The creation of new clinical roles, modern-day skill set challenges and the necessity to ensure continuance of a skilled workforce, gives rise to a case for a Clinical Scientist Transfusion Medicine (CS-TM) in contemporary pathology. A role that in addition to being an expert and specialist within the field of transfusion science, displays the experience and knowledge required to provide day-to-day clinical supervision and oversight of a transfusion laboratory. A role that is equipped to respond to regulatory requirements within the sector, and a role that is adding value to the profession offering a career pathway. Most importantly, a role that contributes to the overall care of a patient through high level clinical transfusion oversight and management as part of the multidisciplinary transfusion team.

Background

Pathology

Pathology has evolved over the centuries, alongside medicine, technological and scientific advancements (Robinson 2021). Historically, it consisted of two main divisions: anatomical pathology (study of body parts) and clinical pathology (study of body fluids) (Burke 2000). Clinical pathology was traditionally service-oriented and used by physicians (pathologists) when performing autopsies and analysing body fluids to solve clinical problems (Burke 2000). In the 18th century, aided by the microscope, there was a shift in the concept of disease from organ-based to cell-based. This was the beginning of modern clinical pathology (Robinson 2021). Laboratory medicine on the other hand, has its origins in the academic setting and traditionally emphasised science, research and teaching. Laboratory physicians would apply results of laboratory tests to diagnose clinical problems (Burke 2000).

Discovery in the early 1900s, including the development of chemical analysis of body fluids and discovery of the ABO blood group systems, results in an increase in requests by clinical physicians for laboratory testing. This created demand for full-time hospital laboratory physicians and clinical pathologists were the obvious choice (Burke 2000). Distinctions between clinical pathology and laboratory medicine were becoming blurred, precipitated by the establishment of the disciplines within academic departments of laboratory medicine and eventually these departments became integrated with pathology (Burke 2000). Today, clinical pathology and laboratory medicine are terms used interchangeably, and often collectively referred to as pathology.

Medical scientist

The rapid pace of research and technology in the first half of the 20th century resulted in necessity for the laboratory pathologist to have a full-time assistant, a laboratorian. This role performed analytical work and developed methods (Streitberg *et al* 2008). As laboratory medicine evolved, so did the skills and academic requirements of the laboratorian combined with the need for professional recognition.

Predicated on and eponymous, the Pathological and Bacteriological Laboratory Assistants Association UK (PBLAA) was the first professional body established in Australia in 1913, later branching into the Society of Laboratory Technicians of Australasia in 1932 (Hicks 2019). Today, the current peak professional body representing medical scientists in all disciplines of pathology, and the only one to offer Transfusion Science as a postgraduate qualification, is the Australian Institute of Medical and Clinical Scientists (AIMS).

Australian qualification requirements of laboratorians were initially modelled off the UK training pathway. A laboratory assistant of the 1950s held a Federal Diploma obtained from Colleges of Advanced Education, based on a countrywide minimum education standard. This was later updated to a "Professional Diploma" in 1966 and students graduated as medical technicians (Hicks 2019). In the early 1980s, the training of medical technicians changed to meet the level of complexity of testing available,

resulting in tertiary institutions offering a range of courses including specialisation. This ultimately reflected in a professional name change from medical technician to medical technologist (Streitberg *et al* 2008). More recent changes to the profession came in 1988, when after a national review of higher education, the Colleges of Advanced Education were granted university status. The industry now offered a bachelor undergraduate degree with the graduates called medical scientists (Streitberg et al 2008; Hicks 2019). Since the late 1980s, the core specialisties biochemistry, haematology, microbiology and anatomical pathology have expanded significantly, reflecting technological developments and demands of modern-day health services. New disciplines and areas of learning including biotechnology, molecular genetics and transfusion science are examples of these (Streitberg *et al* 2008).

Contemporary pathology

Contemporary medical scientists are among a range of laboratorians (laboratory assistants and technicians) that comprise the workforce in the field of laboratory medicine in pathology. They are employed in public hospitals, private medical pathology laboratories, research or academia. As predicted by Streitberg *et al* (2008), the medical scientist role in a pathology laboratory is changing in response to evolution of the field alongside scientific and medical discoveries. One such driver of change is automation of routine tests. Many complex laboratory tasks are now routine, making the high-level skills of a medical scientist redundant or rarely required. This has resulted in the duties of a medical scientist often not reflective of their level of training and contributing to blurring of role boundaries between medical scientists and other laboratorians (Badrick *et al* 2012). Additionally, scientists are expressing a decrease in overall job satisfaction, in part due to lack of technical challenges (Badrick *et al* 2012). Technological advancements are further driving pathology organisational consolidation, resulting in medical scientists increasingly working in multidisciplinary roles in core laboratories and compounds the issues of skills and knowledge retention across the industry.

A solution suggested by Badrick *et al* (2012) to address the skill set deficiency, is to redefine the qualification requirements and curriculum contents for a medical laboratory scientist. This would be realised through an undergraduate degree, limited in specialisation but offering strong foundations in the biological sciences to ensure workforce-ready graduates. Then at the postgraduate level, the relevant laboratory medicine subjects would be offered in more detail, graduating experts in the field (Badrick *et al* 2012). Both qualifications potentially offer greater job satisfaction and distinct career pathways.

Retention of well-trained professionals in the field of laboratory medicine is required to maintain quality standards in pathology. Statistical modelling has predicted a future shortfall in the profession (Badrick *et al* 2012) including clinical (senior) medical scientists (O'Connor *et al* 2018). Factors impacting on recruitment and retention include a workforce approaching retirement age, low salaries in comparison to other healthcare sectors, decreased job satisfaction and lack of career pathway in part contributed by lack of professional registration (Badrick *et al* 2012). Unlike comparable developed western countries, Australian medical scientists are not required to be registered. The rationale is that medical scientists are considered to not directly influence patient outcomes and are sufficiently controlled through a registered pathologist and the National Australian Testing Authority (NATA) accreditation (Hicks 2019). This is despite the estimation that at least 70% of all medical decisions are based on medical laboratory results from tests performed by medical scientists and other laboratorians (Royal College of Pathologists of Australasia 2018) demonstrating how integral pathology is to healthcare and the necessity of quality clinical oversight.

Clinical Scientist-TM

From a transfusion laboratory perspective, contemporary pathology organisational structure combined with automation advancements are creating a void of skills, knowledge and expertise in the highly technical and specialised area of immunohaematology. In the evolving area of transfusion medicine, there is a need to preserve scientific experience, expertise, in addition to responding to the complex contemporary regulatory equipment and highly specialised roles can achieve this. One such role is a clinical scientist transfusion medicine.

In the Australian context, postgraduate studies for medical scientists in transfusion science is only available via a Fellowship of AIMS-Transfusion Science. Postgraduate studies are demanding and require a highly motivated, self-directed individual. On successful completion of a Fellowship of AIMS-Transfusion Science and in conjunction with workplace experience, the new clinical scientist-transfusion science will hold a unique position in the laboratory. In this position, they will be a subject matter expert for the transfusion laboratory, demonstrating an in-depth knowledge of methodologies and instrumentation (Royal College of Pathologists of Australasia 2019), while providing day-to-day transfusion laboratory operational oversight. They will also play a key role in laboratory quality management and laboratory regulatory requirements including blood and blood product management.

In this article, I use the term clinical scientist-transfusion medicine (CS-TM) for someone fulfilling this role. A justified subtle name change in response to the expanded role in context of the contemporary transfusion laboratory and modern transfusion medicine expectations within the sector.

Some key technical considerations and regulatory requirements that contribute to the necessity of this role are explored below.

Technical Considerations

Automation

Since the discovery of the ABO system, tube technology has been the backbone of immunohaematological methods; simple, rapid and inexpensive. This technique is labour intensive, lacking in standardisation, objectivity and sensitivity, but most importantly, unable to be automated.

Predicated on the first large scale blood grouping machines used in donor centres during the 1960s, automation for red blood cell (RBC) serology in the routine pathology laboratory was slow to arrive. Early available platforms included microtiter plates, solid phase red cell adherence assay and the erythrocyte-magnetised technique. These all had different strengths and weaknesses and all professed automation (Garratty 2010). It was however, column agglutination technology (CAT), introduced by Lapierre *et al* in 1990, that caused a "mini revolution in RBC serology" within the sector (Garratty 2010). CAT is the predominant technology in use today.

Computer technology advancements were a key driver for automation development. Towards the end of the 1970s, analytical analysers becoming embedded with computers, offering pathology greater efficiencies and improvements in a workflow and creating the vision towards a future of high-volume automated testing (Streitberg *et al* 2008). Concurrently, laboratories introduced computers as laboratory information systems (LIMS). Analysers could now be interfaced, facilitating download of results and automatic generation of reports (Streitberg *et al* 2008).

Contemporary RBC serology system solutions offer a range of immunohaematology analysers from small compact semi-automated to the large complete automated platforms across the available technologies. Testing is under computer control using bar-code identification of reagents and samples requiring minimal volumes of both (Roxby 2011). Analysers are intuitive to operate and offer a range of test profiles. Methods are sensitive, accurate and reproducible demanding minimal operator intervention and execute tests in the most time efficient manner. Systems can be either uni-or bi-directionally interfaced, removing the need for manual result entry (Roxby 2011). Additional features include software for centralization of data management, interpretive result decision-making algorithms and remote result management and support services. Routine operation of analysers within a transfusion laboratory have become task-oriented, requiring a simpler skill level.

Automation, however, is not available or appropriate for all test methods, techniques and samples. For example, adsorptions, elution and haemagglutination inhibition assays (Hamilton 2016) and patients displaying complex serological pictures-cold haemagglutinin disease, all require traditional manual techniques. Immunohaematology results are based on interpretation of end points and deciphering of complex patterns. This is a skill that is being replaced by software with interpretive result decision-making and one that is being lost.

Although automation requires simpler skill level, an expert individual is still required to provide high level day-to-day operational supervision of the platform in use and be able to demonstrate specialised technical skills for manual testing when required. Additionally, the laboratory requires an individual who has the appropriate skill set for the overall management and oversight of procurement, installation, validation, and interfacing of immunohaematology system solutions ensuring compliance with regulatory requirements (Australian Commission on Safety and Quality in Health Care 2022. Requirements for transfusion laboratory practice; Andriesson 2022). A CS -TM is such an individual.

Reagents

Reagents are pivotal in blood group serology and are used in the detection of antigen and antibodies. There have been numerous immunohaematology reagents (IHRs) over the last century with the good ones still in use e.g., low-ionic-strength-solution (LISS), anti-human globulin (AHG) and monoclonal antibodies (MoAbs) (Marks 2014). Some however are confined to history and removed from the routine testing repertoire due to expense, inability to obtain raw material and stringent manufacturing regulations or replacement e.g. Lectin panels (Gorakshakar and Kanjaksha 2016). Lectins, proteins of non-immune origin identified for their haemagglutination properties, have historically been available in commercial kits as well as single use for the classification of poly-agglutination states. Currently in Australia, only the single use *Dolichous biflorus* and *Ulex europaeus* reagents are available. Some have been added more recently in response to emerging technologies such

as recombinant blood group proteins (rBGPs) and DNA Arrays (Hamilton 2016; Seltsam *et al* 2016).

Routine IHRs can be broadly divided into categories based on their characteristics. These include: potentiators (e.g. albumin, low ionic-strength saline), enzymes (e.g. papain, bromelain, trypsin), antiglobulin sera (monoclonal and polyclonal), red cell panels (unmodified or modified) and reagents from non-immune origins (e.g. lectins) (Armstrong 2020). There is no single perfect IHR to use in all testing scenarios. Choice of reagent requires an in-depth knowledge of performance characteristics, identity and nature of the antigen or antibody to be detected combined with the testing technique, method, and platform all in relation to the reagent itself.

In a routine transfusion laboratory, contemporary reagents are selected from a catalogue and ready to use. To ensure that IHRs display the essential required characteristics, the industry is highly regulated, and manufactures are mandated to comply with Good Manufacturing Practice (GMP). In Australia, the Therapeutic Goods Administration (TGA) conformity assessment requirements must also be met (Therapeutic Goods Administration. Good manufacturing practice an overview).

Quality pathology laboratory results are reliant on quality reagents. Foundational knowledge of IHRs and their application is being challenged, driven by automation, manufactured ready to use reagents and the multidisciplinary scientist role. Laboratories require an experienced, qualified individual for verification and validation of reagents ensuring they are fit for purpose and with an in-depth understanding of IHRs and their applications. A CS-TM has the qualifications and experience to provide the necessary quality oversight of reagent choice and application.

The crossmatch

The first serological crossmatch was performed in 1908, between donor (wife) and recipient (husband) based on Landsteiner's discovery and subsequent classification of human red blood cells into four key groups, A, B, AB and O. It was now possible to check for clumping (agglutination) and haemolysis when mixing the blood of a donor with that of a recipient, preventing ABO incompatibilities (Marks 2014). Slow in uptake but routinely performed by the 1940s, the serological crossmatch impacted profoundly on all aspects of clinical medicine. It was now possible to undertake more complicated surgery and treat haemorrhaging obstetric and trauma patients without fear of an immediate haemolytic transfusion reaction (Sandler and Abedalthagafi 2009). Additional improvements in transfusion safety were realised in 1945 by Coombs *et al*, with the detection of "incomplete" antibodies. This method utilised rabbit AHG and became a routine method applied in both crossmatching and antibody screening. The Indirect Coombs Test, as it is known today, remains the most effective of all laboratory methods for detection of clinically significant allo-red cell antibodies aiding in serologic compatibility of RBC for transfusions (Sandler and Abedalthagafi 2009; Marks 2014).

Crossmatching historically has been manual and laborious requiring high levels of technical skill. All available techniques to detect serological incompatibilities were used including testing and reading results at room temperature (RT) and 37°C, followed by the indirect antiglobulin test (IAT). Enhancement of reactions were realised through the modifications of the red cells to increase their sensitivity by use of additional reagents and enzymes such as trypsin, papain, ficin, bromelain and auto controls were routinely included (Roxby 2011). Over time acceptance and use of a commercial red cell panels with improved sensitivity for the antibody screen changed the approach to only detecting antibodies of clinical significance. In the 1980s this paved the way to abbreviate the serological crossmatch to the type and screen approach combined with a saline immediate spin (Sandler and Abedalthagafi 2009). Further abbreviation was realised in the 1990s with the electronic crossmatch (eXM) becoming a surrogate for the saline immediate spin crossmatch, saving additional time, reagents, and labour. The eXM is driven by algorithms and logic rule tables embedded in the Laboratory Information Management System (LIMS) (Garratty 2010).

Over the last 100 years, we have witnessed the rise and fall of the serological crossmatch, now predominantly replaced by the eXM, a fully automated electronic approach, which substantially removes the operator's agency in critical thinking associated with the task. Not all patients however are suited to or eligible for an eXM. These patients require traditional serological testing techniques to determine compatibility and for some the technique is the traditional manual technique. This is a skill set disappearing from the contemporary workforce of the multidisciplinary medical scientist in a transfusion laboratory.

Emerging Technologies

Artificial Intelligence

Computer technology advancements are already demonstrating the potential application of Artificial Intelligence (AI) in transfusion medicine. An example of this is clinical decision-making when predicting the need for products, with pre-operative evaluation of

the peri-operative requirements (Feng 2021). Other potential future applications include partnering with bioinformatics in the field of genomics to aid in precision and personalised medicine, creation of algorithms to predict blood groups and the analyses of large data sets to identify new biomarkers (Lane 2021).

Genomics

Genomics is having a profound impact in all areas of medicine, including transfusion medicine, since the molecular nature of red cell and human platelet antigens (HPAs) have been defined. Its applications have become an invaluable tool as an alternative and adjunct in addressing the limitations of immunohaematology tests. Examples include the inference of phenotype in absence of serology, resolution of complex serological scenarios where the antibody-based methods cannot be applied, lack of commercial phenotyping reagents, evaluation of the risk of haemolytic disease of the foetus and newborn (HDFN) and foetal-neonatal alloimmune thrombocytopenia (FNAIT) identifying candidates for Rh-Immune globulin and guide transfusion support for bone marrow transplant recipients (Westoff 2019). In transfusion medicine, genotyping of blood donors for all genetically understood antigens has begun to change practice. The genomic approach in antigen matching is justified as it leads to improved transfusion therapy for some recipients in certain scenarios e.g prophylactic antigen matching approach in sickle cell disease (SCD), patients on monoclonal antibody therapy (anti-CD38) and the pan-agglutinating picture (Westoff 2019).

Availability and application of genotyping is still evolving with routine high throughput genotyping confined to large hospitals and blood donor centres due to a lack of equipment and a dedicated environment in most pathology transfusion service providers (Westoff 2019). The present approach is utilisation of genotyping alongside conventional ABO typing and antibody screening - not in isolation.

Current PCR-based genotyping assays have limitations including inability to fully characterize all genetically understood antigens. These limitations can be overcome by the emerging technology, next generation sequencing (NGS) (Lane 2021). As the cost of NGS continues to drop and bioinformatic technology advances, we will come to see patient genome sequencing as part of clinical care, supporting precision-based medicine (Orzinska *et al* 2019). In transfusion medicine, a patient may even come to have an "extended blood group profile as part of their medical record to be used to inform selection of the optimal transfusion therapy" (Westoff 2019).

The use and application of genotyping for platelet and red cell antigens, combined with other emerging technologies is changing transfusion medicine and transfusion laboratory practice. In the contemporary context, this demands that an individual in the laboratory is versed in the complexities of genomics combined with an understanding of result interpretation in the appropriate clinical context. In a future context, transfusion genomics as an emerging discipline, will further challenge us with a new type of data, requiring specialized information technology resources and a workforce with computational expertise (Orzinska *et al* 2019). A CS-TM is well placed to bridge the current gap in knowledge and application of genotyping in transfusion medicine, while looking towards the future to ensure upskilling.

Modern TM

Transfusion medicine transcends the traditional role of the pathology laboratory. It is unique in that it combines both clinical and laboratory aspects, bringing together medical and scientific skills. Transfusion medicine, as a discipline, continues to expand. Over the last two decades, it has been increasingly subjected to a complex regulatory environment with requirements on quality and expectations of management of a finite resource. Combined these aspects have led to the necessity of new clinical roles in the discipline (Miller *et al* 2015).

From a laboratory perspective, these contemporary demands make a haematologist and a CS-TM compatible roles, affording the haematologist more time for patient care while the CS-TM assumes laboratory management, quality oversight and regulatory responsibilities (Royal College of Pathologists of Australasia 2019). Factors contributing to the necessity of a CS-TM in pathology include clinical governance regulatory requirements, blood inventory management, patient blood management, pathology regulatory and supervisory requirements. These aspects in detailed below.

The haematologist

Haematology is a rapidly developing discipline. Drivers for supply and demand of haematology services include the ageing population, cancer incidence and prevalence, the ever-increasing range of therapeutic options combined with better survival rates and the development and application of genomics (Royal College of Pathologists of Australasia 2018). Haematologists, in addition to dividing their time between clinics, hospitals and the laboratory, act as clinical consultants to their medical colleagues on the diagnosis and management of their patient's disease when it impacts on the haematopoietic/haemostatic systems. This is due to the highly specific knowledge

and skills necessary for haematology and transfusion medicine, which are not or insufficiently covered by other medical disciplines (Royal College of Pathologists of Australasia 2018).

The Australian training framework for a haematologist is available via one of two pathways with both pathways affording TM a small percentage of the total curriculum (Royal College of Pathologists of Australasia 2023). It was suggested in a 2018 Australian Haematology workforce review that only approximately 10% of pathologist trainees specialise solely in laboratory haematology (O'Connor *et al* 2018; Royal College of Pathologists of Australasia 2018). The remainder 90% choose the dual training pathway, with the majority choosing physician as their second specialty (Royal College of Pathologists of Australasia 2018). This demonstrates the strong clinical role of the haematologist and questions their capacity to provide adequate laboratory supervision in their pathologist role (NPAAC 2021). Workforce modelling for haematologists into 2030 has predicted a shortfall (Royal College of Pathologists of Australasia 2018) placing further future constraints on the haematologist laboratory supervision availability.

A haematologist in laboratory medicine does not practice in isolation. Their role requires other non-medically qualified technical and scientific staff to manage the daily laboratory operations and perform the testing (Royal College of Pathologists of Australasia 2019). Collectively, the roles are complimentary and fundamental to the provision of high-quality pathology care and transfusion service. A CS-TM is one such complementary role. This role can provide clinical oversight (where in scope), act as liaison between distinct clinical groups, supervise day-to-day laboratory testing, review, and report results, ensure compliance with national regulatory standards. In the laboratory context, a CS-TM supports a haematologist in their clinical laboratory responsibilities.

Clinical governance

Clinical governance has become a driver of healthcare reform in the 21st century. It ensures that health service organisations and their systems deliver a safe and high-quality health care, while continously looking to improve their services. Clinical governance is the responsibility of all healthcare organisations and involves all stakeholders including the governing body, executive, clinician, consumer and patient (Australian Commission on Safety and Quality in Health Care. National Model Clinical Governance Framework).

Clinical governance is actualised through guidelines and standards. In Australia, issues in healthcare safety were recognised towards the end of the 20th century. Healthcare safety became a public and political issue after the publication of adverse events in hospitals. In response, a national safety council was established to be responsible for quality issues in healthcare, today referred to as The Australian Commission on Safety and Quality in HealthCare (ACSQH) (Balding 2008).

In 2011, the ACSQH released The Australian National Safety and Quality Health Service (NSQHS) Standards, to provide a nationally consistent statement of the level of care consumers can expect. Standard 7 is specific to blood management, covering all elements in the blood management and clinical transfusion process including clinical governance, availability and safety of blood and blood products and the principles of patient blood management (PBM). Despite being specific to health service providers, Standard 7 is relevant to pathology laboratories (Australian Commission on Safety and Quality in Health Care. Safety and Quality. Blood Management Standard).

The National Pathology Accreditation Advisory Council (NPAAC) is the main regulatory body for pathology. Established in 1979, NPAAC makes recommendations on matters relating to the accreditation of pathology laboratories, mandatory since 1986 (Australian Commission on Safety and Quality in Health Care 2022. Requirements for transfusion laboratory practice). Clinical governance is fundamental to the transfusion process. Mandated through NPAAC standards a transfusion laboratory must be part of a quality system, one that actively manages patient and transfusion safety, appropriate prescribing and clinical use of blood and blood products (NPAAC 2021, S 1.1). Laboratories must also demonstrate oversight of transfusion related activities and PBM (Australian Commission on Safety and Quality in Health Care 2022. Requirements for transfusion laboratory practice). Requirements of contemporary standards has created demand for new roles within the sector. An example of this are the roles of Transfusion Nurse/Co-ordinator (within a health service) and a Medical Scientist with transfusion speciality experience and expertise (in pathology), a role suited to a CS-TM.

The NPAAC laboratory standard, "The Requirements for Supervision in the Clinical Governance of Medical Pathology Laboratories" (6th ed 2021), defines the roles and responsibilities required for laboratory supervision. One of these roles is a CS working within their scope of practice (NPAAC 2021). The standard acknowledges that good governance requires appropriate supervision of clinical services. This is echoed by The Royal College of Pathologists Association (RCPA) who state, "laboratories operating at the highest level of clinical and scientific governance should have both a pathologist and clinical

scientist with scope of practice in their disciplines" (Royal College of Pathologists of Australasia 2018).

Clinical governance standards currently validate the role of a clinical scientist in providing laboratory clinical oversight in scope. Ferraro *et al* (2016) argues that supporting and encouraging laboratory scientists to take up a position of shared clinical leadership will have the upstream effect of improving clinical effectiveness and promoting laboratory medicine while ensuring professional relevance and value in today's healthcare environment (Ferraro *et al* 2016).

The important role that a laboratory professional assuming clinical governance plays in pathology is demonstrated in Figure 1.

Blood management

Blood and blood products are a critical component of healthcare and have been managed in Australia by the National Blood Authority (NBA) since 2003 (National Blood Authority Overview and Role of the NBA). Good inventory management demands the sustainable and appropriate use of blood and blood products. In 2010, in response to identifying that health providers within the sector required guidance in the practice of good inventory management, a national statement was released. This statement is referred to as "The Stewardship Statement" and outlines the stewardship expectations for health providers of blood and blood products (National Blood Authority National Stewardship program). It includes acknowledgment of the invaluable role of, and collaborative relationship required between hospitals, doctors, laboratories and other health providers, ensuring the responsible, sustainable and appropriate use of blood and blood products.

Over the last two decades, the role and scope of the transfusion laboratory has expanded significantly in relation to management of blood and blood products. A laboratory must demonstrate good inventory management ensuring product availability and integrity, while facilitating equitability and minimising wastage of a precious resource. Laboratories are responsible for ordering, storage, handling, transport arrangements and issuing all blood and blood products requested by a health service. Management of blood and blood products across a network of laboratories is time consuming

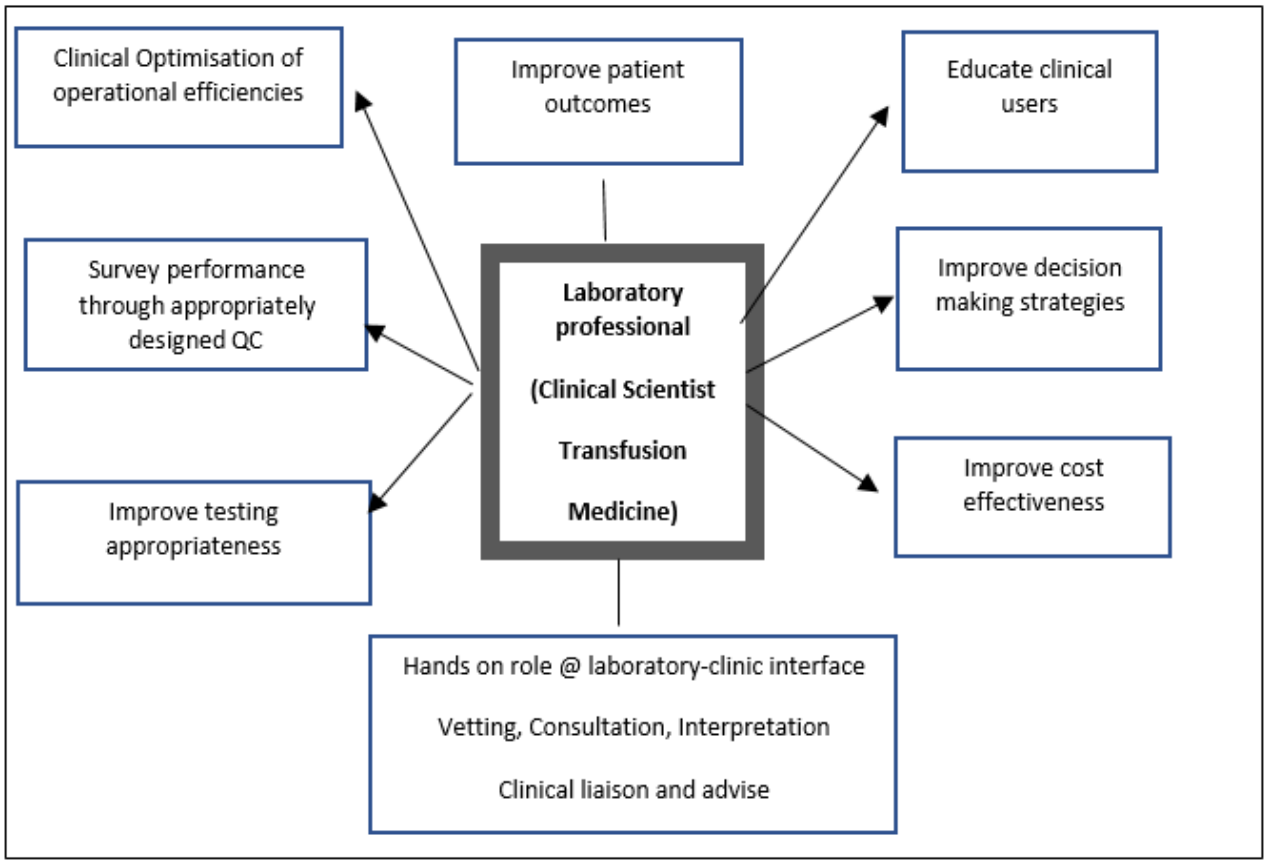

***Figure 1**. Role of laboratory medicine as a medical discipline and profession. Adapted from Ferraro* et al *2016.*

and success requires simple procedures reflective of regulations, with an understanding of local arrangements and requirements within the sector.

The transfusion laboratory, as custodians of blood and blood products, is a primary contact for clinical queries. Responding to these queries demands a depth of knowledge in product availability, acquisition, application, and appropriateness. Contemporary expectations of good blood management require a dedicated role. (Table 1) This role is suited to a CS-TM.

Patient Blood Management

PBM is a patient-centred blood management approach now central to transfusion medicine. This practice exemplifies a paradigm shift in transfusion practice over the last 20 years, from a unilateral decision making "one-size-fits all", to an individual needs approach involving a multi-disciplinary team (Thompson *et al* 2009). In Australia, further guidelines exist to manage PBM and set best practice standards, reflecting scientific literature and clinical expertise (National Blood Authority Patient Blood Management Guidelines).

Transfusion medicine guidelines and standards are maintained by Patient Blood Management Committees (PBMCs). These committees are essential for clinical governance of transfusion services within an institution. The committee is responsible and accountable for the delivery of safe and appropriate transfusion processes, while providing oversight and ensuring adoption of guidelines and standards reflecting best evidence-based practice. Pathology, specifically the transfusion medicine discipline is integral to the PBMC, as it provides clinical and scientific expertise and oversight. The chair of the PBMC is often either a haematologist associated with the transfusion service provider or other healthcare professional involved in supporting transfusion for patients, for example an anaesthetist. The chair is supported in this role by a transfusion scientist and a transfusion or PBM nurse/co-ordinator with representations from other relevant clinical areas as appropriate. A PBMC today has a substantially expanded scope, requiring diverse expertise, compared to an HTC at the beginning of the 21st century (Patient Blood Management Committee Handbook 2014). See Table 2.

Summary

The role of CS-TM is a necessary role for any quality pathology organisation. This postgraduate qualification is available through the Australian peak professional body for medical scientists, AIMS. In this article, I have explored ideas and concepts that give credibility to a subtle name change for this post graduate qualification, a change from clinical scientist transfusion science to clinical scientist transfusion medicine.

Table 1. *The CS-TM role in blood management.*

Responsibilities of good blood and blood product management include:
- establish systems that manage blood and blood product transfers to prevent wastage and maintain cold chain and product integrity - manage fractionated, including intravenous and subcutaneous immunoglobulin blood product inventories - manage fresh component inventories - review patterns of inventory holdings across local network to ensure availability and minimise wastage - provide procedures and training in inventory management - provide education on product use and appropriateness - build collaborative relationships with clinical staffs - ensure best laboratory practice with procedures - ensure all equipment maintained to mandatory standards - validate transport systems across a network - prepare and upkeep local blood contingency plans

***Table 2**. Responsibilities of the PBMC.*

Patient Blood Management Committee (PBMC) responsibilities include:

- establishing local transfusion policy and procedures
- auditing against standards
- monitoring transfusion-related risks
- actively participate in Haemovigilance surveillance systems both local and national
- encourage internal and external reporting of adverse events
- monitor clinical effectiveness of transfusion, ensuring appropriate indicators
- education and training of all staffs involved in the transfusion chain
- responding to recalls and look backs
- management of the availability and safety of blood and blood products inclusive of storage, transport, and wastage reviews
- recommendation and implementation of new blood products and equipment
- contingency planning for blood shortages
- subject matter experts as a resource for clinicians and other team members involved in the transfusion process.

***Table 3**. CS-TM role and responsibilities.*

Responsibilities of a Clinical Scientist -Transfusion Medicine include:

- support and provide clinical leadership where in scope
- ensure clinical governance needs are met
- play key role in regulatory compliance and quality management for scope
- contribute to strategic planning of the transfusion laboratory and provision of transfusion service
- be accountable for the transfusion service within a healthcare provider organisation
- support and encourage collaboration and multidisciplinary teamwork
- actively support quality improvement including Haemovigilance across both laboratory and health service
- active participation in PBMCs and other sector oriented working parties, committees
- familiarity with PBM guidelines and best practice
- in depth blood product and component knowledge, acquisition, availability, appropriateness
- be a subject matter expert for laboratory pathology organisation
- responsible for day-to-day operational supervision of transfusion laboratory
- established standards of practice and the needs of the local organisation
- awareness of and operational compliance with relevant Standards for accreditation
- responsible for instrument and method selection, validation, and ongoing monitoring
- responsible for selection of reagents and consumables to ensure appropriate, quality results
- vision for application of emerging technologies and opportunities for implementation
- offer advice on testing and result interpretation
- responsible for result reporting
- play a key role in the training of laboratory staff and clinical staff
- be a patient advocate
- act as a consultant for clinicians and patients

This a new role modelled from the traditional but reflects the contemporary in the name is a role that is an expert and specialist within the field of transfusion science, that can respond to the complex clinical regulatory environment of the rapidly evolving field of transfusion medicine and that contributes to the overall care of a patient through clinical oversight and management as part of the multidisciplinary transfusion team. Responsibilities of a CS-TM in response to the demands of contemporary transfusion medicine are detailed in Table 3.

Conclusion

TM is a rapidly evolving field of medicine with increasing regulatory requirements. Modern TM transcends the traditional role of a transfusion laboratory and the medical scientist. In contemporary pathology, the conventional roles of medical scientists are being challenged by technological advancements and organisational restructure. These changes combined have created the necessity of a new role in the transfusion laboratory. This role is a CS-TM - an expert in their scientific field, an important part of the transfusion process and one that can respond to demands of contemporary TM. A role that acts as a laboratory transfusion medicine consultant for colleagues, clinicians and patients.

Acknowledgements

I would like to acknowledge the guidance and advice of my daughter, Ursula Rodrigues.

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Journal-based CPD No. 92
Page 1 of 1

Questions relating to the article *'Can serological testing be reduced in favour of matched phenotyped red blood cells in patients with warm autoantibodies?'* at page 103 of this issue.

1.	Routine testing for patients that present with warm autoantibody (WAA) and warm autoimmune haemolytic anaemia (WAIHA) is tedious and labor intensive.	True/False
2.	Autoimmune haemolytic anaemia (AIHA) is an acquired heterogeneous group of diseases characterized by haemolysis of RBCs.	True/False
3.	The serological types of AIHA include warm autoimmune haemolytic anemia (WAIHA), cold agglutinin disease (CAD), mixed type AIHA (mixed AIHA) and paroxysmal cold haemoglobinuria (PCH).	True/False
4.	The incidence of AIHA in adults is 1 to 3 cases per 10 000 per year.	True/False
5.	WAIHA shows a negative DAT for anti-IgG and or C3d.	True/False
6.	Auto-adsorptions are a serological procedure used to identify alloantibodies..	True/False
7.	The WAA protocol is time saving due to using donor RBC's phenotyped matched to the patient.	True/False
8.	There are no standardised recommendations for the selection of RBC units for patients with WAA and WAIHA who have been investigated by their transfusion service.	True/False
9.	The use of PAM donor RBCs for transfusion allows the frequency of adsorptions to be decreased or eliminated, thus increasing the time in which donor units could be made available.	True/False
10.	There were no documented adverse events in patients who received PAM units with no preceding absorptions or serological IAT crossmatching.	True/False

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Journal-based CPD No. 93
Page 1 of 1

Questions relating to the article '*Evaluation of the MBT STAR® Carba IVD assay to detect carbapenemase producing Enterobacterales in Australia*' at page 115 of this issue.

1.	Positive isolates were confirmed using the AusDiagnostics Multiplex CRE 16 well PCR assay.	True/False
2.	The MBT assay evaluated in this study is a rapid phenotypic method utilizing a carbapenem antibiotic, whose β-lactam ring will be hydrolysed by active carbapenemase containing bacteria.	True/False
3.	Isolates were subcultured once (Columbia horse blood agar).	True/False
4.	The recommended medium is Becton Dickinson.	True/False
5.	MBT is five times more expensive than other phenotypic assays, based on June 2021 costings.	True/False
6.	The MBT assay has the added advantage of providing gene detection results, essential for surveillance/mandatory reporting to the National Alert System for Critical Antimicrobial Resistances.	True/False
7.	Carbapenemase producing *Enterobacteriaeceae* (CPE) in this study included *Citrobacter farmer*, *Klebsiella oxytoca* and *Enterobacter asburiae*.	True/False
8.	173 *Enterobacteriaceae* isolates were evaluated in this study.	True/False
9.	The MBT assay had a sensitivity of 98.5% and specificity of 89%..	True/False
10.	10% of isolates required repeat testing due to borderline results.	True/False

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The title of the article should not exceed three lines (40 characters per line), including punctuation and spacing. All authors must be identified on the title page (e.g. William Smith, Susan Yeo, ..."). Where applicable, the title page should also include the name of the institution with which each author is affiliated and to which the work should be attributed. In the case of multiple authors, the name, postal address, email address, telephone and facsimile number of the author responsible for correspondence relating to the manuscript should be indicated.

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The abstract should be approximately 150 words and should make sense when read alone or in conjunction with the article. The abstract should be a concise overview that describes the important details of the article including the purpose of the study/investigation, basic procedures (study subjects/experimental animals/observational and analytic methods) and the results and principal conclusions. New and important aspects of the work and its implications may also be included. References should not be included.

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Wherever possible, observational or experimental articles should be divided into sections headed:

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Introduction

Clearly state the purpose of the article leading the reader from the known to the unknown. Summarise the rationale for the study and state the question to be answered as appropriate. Give only strictly pertinent references, and do not review the subject extensively.

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Present the materials and methods in a logical sequence. Describe the selection of the observational or experimental subjects (patients or experimental animals, including controls) clearly. Notification of ethics approval must be given where relevant. Identify the methods, apparatus and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods. Adequately describe new or substantially modified methods. Identify precisely all drugs and chemicals used, including generic name(s), dosage(s), and route(s) of administration. Do not identify patients or hospitals without consent.

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Present the results in the same sequence as given in the Materials and methods; use tables and illustrations where these will help the reader understand the work being presented. Do not repeat in the text all the data in the tables or illustrations.

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Acknowledgements

Acknowledge individuals who have made substantial contributions to the study including technical work and financial support. Authors are responsible for obtaining consent from all the individuals acknowledged by name as inclusion may be interpreted as an endorsement of the article's contents.

References

The AJMS uses a modified Harvard System (author-date system).

Throughout the body of the manuscript cite the author/s name and the publication year in parentheses as in the following examples:

(i) Research in this area (Jones 1999) …

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Examples of the correct form for references are given below:

Journal Reference:

Stein MK, Downing RW, Rickels K 1978. Self-estimates in anxious and depressed outpatients treated with pharmacotherapy. *Psychol Rep* 43: 487-492.

Personal Author(s) of a book:

Osler AG 1976. *Complement: mechanisms and functions*. Englewood Cliffs: Prentice-Hall.

Editor, Compiler, Chairman as Author:

Rhodes AJ, Van Rooyen CE, comps. 1968. *Textbook of virology: for students and practitioners of medicine and the other health sciences*. 5th ed. Baltimore: Williams and Wilkins.

Chapter in Book:

Weinstein L, Swartz MM 1974. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. *Pathologic physiology: mechanisms of disease*. Philadelphia: WB Saunders; 457-472.

Online documents:

National Center for Biotechnology Information. OMIM: online Mendelian inheritance in man. http://www.ncbi.nlm.nih.gov/omim. Accessed February 25, 2007.

Tables

Number tables consecutively with Arabic numerals and supply a brief title for each. Give each column a short or abbreviated heading. Place explanatory matter in footnotes, not in headings. Explain in footnotes all non-standard abbreviations used in each table.

For footnotes, use the following symbols in this sequence:

* † ‡ § ¶ ** ††

In preparing tables, consideration should be given to the page width of the Australian Journal of Medical Science. All tables should be prepared for publication vertically. In the text, cite each table in consecutive order, and mark in the margin of the text its approximate location.

If data from another published or unpublished source is used, written permission must be obtained and a copy must accompany the manuscript.

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Colour illustrations may be submitted on a USB stick. Images should be scanned at a minimum of 300 dpi.

When plotting points, the following symbols are preferred:

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In most instances, figures will be reduced to one column in width. All letters and numbers should be drawn to be at least 1.5 mm high after reduction, symbols at least 1.0 mm. Titles for illustrations belong in the legends for illustrations and not on the illustrations themselves.

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When symbols, arrows, numbers, or letters are used to identify parts of illustrations, identify and explain each one in the legends. The figure legend must contain a boldface (a) name ("Figure" + arabic figure number) and (b) substantive title.

Abbreviations

Use only standard abbreviations (see list of commonly used abbreviations).

Avoid abbreviations in the title. The full term for which an abbreviation stands must precede its first use in the text unless it is a standard abbreviation for a unit of measurement.

Report measurements in the units in which the measurements were made. In most countries the International System of Units (SI) is standard.

Commonly used abbreviations

Abbreviation or Symbol	Standard Units of Measurement
g	gram
g	gravity
Hz	hertz
h	hour
IU	international unit
K	kelvin
kg	kilogram
L	liter, litre
m	meter, metre
min	min
M	molar
mL	millilitre
mol	mole
N	newton
nm	nanometre
p	probability
rpm	revolutions per min
s	second
wk	week
yr	year

Additional information

The following are useful sources of information. The first two publications are used by the AJMS as standard references.

Style Manual Committee. Council of Biology Editors. *Scientific style and format: the CBE manual for authors, editors, and publishers.* 6th ed. Cambridge University Press, 1994.

Style manual for authors, editors and printers. 6th ed. John Wiley & Sons Australia Ltd, 2002.

O'Connor M, Woodford FP. *Writing scientific papers in English: an ELSE-Ciba Foundation guide for authors.* Amsterdam, Oxford, New York: Elsevier-Excerpta Medica, 1975.

Day RA. *How to write and publish a scientific paper.* Philadelphia, Institute for Scientific Information Press, 1979.

Zeiger M. *Essentials of writing biomedical research papers*. 2nd ed. New York, McGraw-Hill, 2000.

Matthews JR, Matthews RW. *Successful scientific writing: a step-by-step guide for the biological and medical sciences*. 3rd ed. Cambridge, Cambridge University Press, 2007 [Also available in eBook format.]

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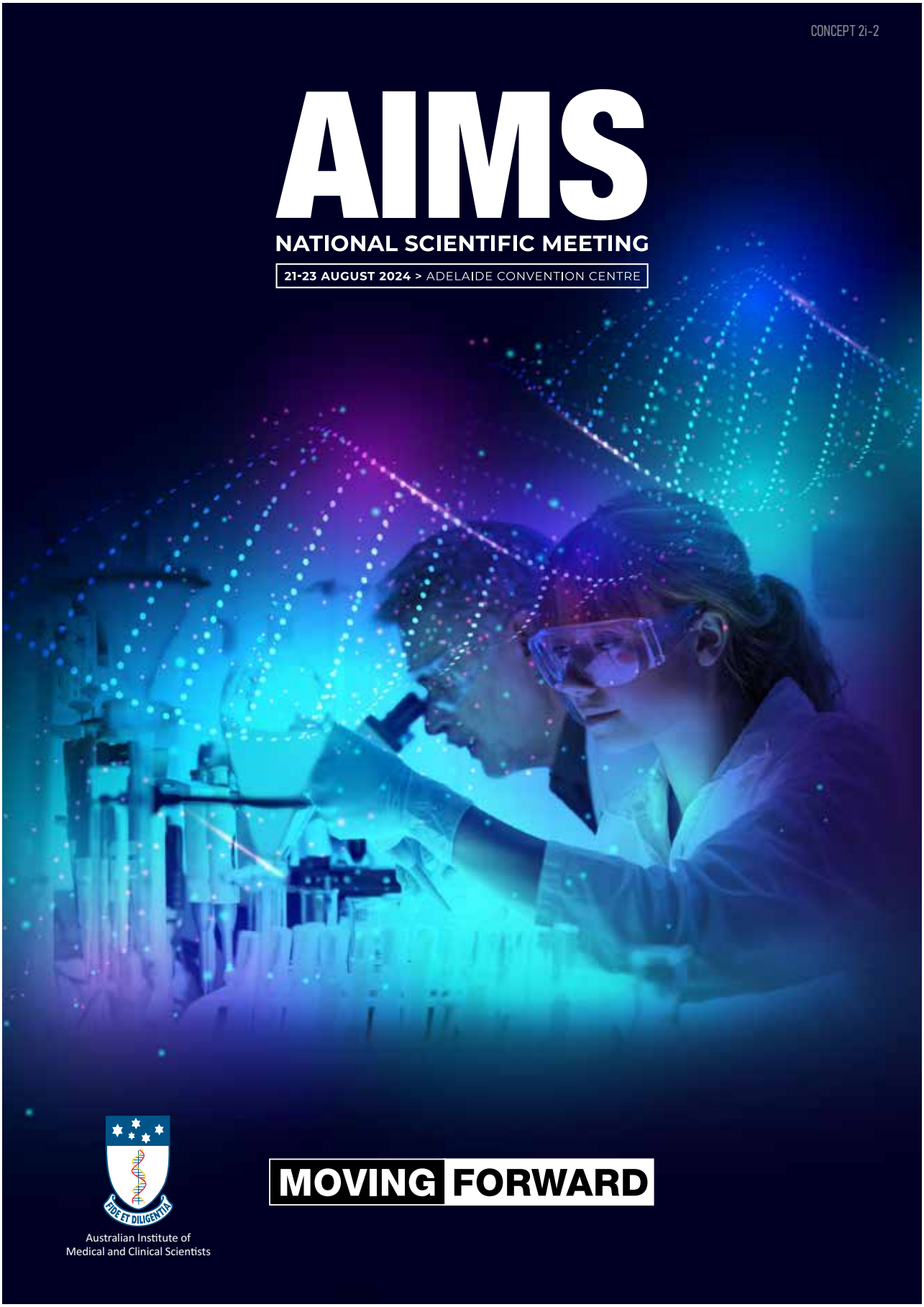
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