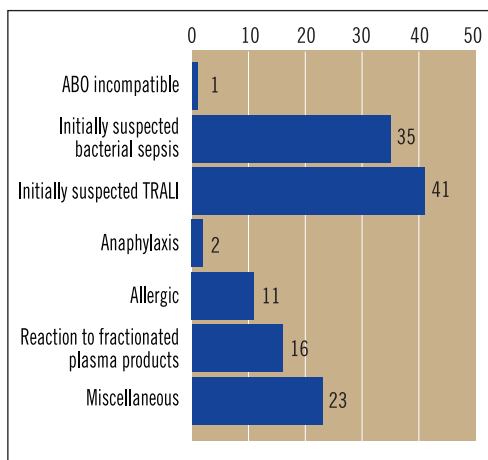


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Transfusion Reaction Reporting to ARCBS

The Transfusion Medicine Services (TMS) team coordinates transfusion reaction reporting, and clinical support at the Australian Red Cross Blood Service (ARCBS). Timely reporting of these events to ARCBS is important, particularly where there may be requirements for on-going transfusion support, specialised patient or product testing, recall of other related blood components, and/or donor management implications.

TMS recently reviewed transfusion reactions reported to ARCBS during calendar year 2006 and presented a summary at the HAA meeting on the Gold Coast. A total of 129 reactions were reported nationally. The figure below demonstrates the type and number of reactions reported across Australia.



Thirty five (35) cases were initially suspected to be transfusion-related bacterial sepsis. Five (5) were confirmed, with positive cultures in blood component and patient samples, and the organism confirmed to be identical by molecular methods. Confirmation could not be obtained in the remainder of the cases, in some cases due to component handling issues during packaging for return to the laboratory, transportation or sampling resulting in environmental contamination. Leakage from the bag was a common problem. Incomplete testing performed for either the patient or the associated component also prevented confirmation of some cases.

Suspected bacterial sepsis	National data (n=35)	
Definite	5	
Organisms isolated	Bacillus cereus	Platelets
	Enterobacter cloacae	Red cells
	Klebsiella pneumoniae	Platelets
	Ralstonia picketti	Red cells
	Salmonella serogroup B	Platelets
Re-classified as febrile non-haemolytic transfusion reaction (FNHTR)*	30	

Of 41 investigations for suspected transfusion-related acute lung injury (TRALI), 12 were classified as "definite" and 4 "possible". Donor and post-transfusion patient samples for human leucocyte antigen (HLA) and granulocyte antibody testing should be obtained if TRALI is suspected. Testing of patient pre-transfusion samples may also assist, particularly if passive acquisition of donor antibody is suspected. Of the 165 donors tested, 54 donors were found to have granulocyte or HLA antibodies (Class I and/or II). Seven (7) donors were considered as "implicated" and 16 as "associated" based on crossmatch results and antigen-antibody specificity. A proportion of donors will have such antibodies due to previous pregnancy or transfusion, and in many cases these cause no known clinical consequences.

Difficulty in classification of some TRALI reports was related to incomplete clinical information and lack of antibody specificity, as well as inability to perform crossmatch in certain cases, mostly due to logistical aspects. Many of these were classified as indeterminate. When TRALI is suspected, good clinical history, physical examination, timely investigation and follow up of potential differential diagnoses is warranted, including consideration of B-type natriuretic peptide (BNP) measurement to exclude transfusion-associated circulatory overload (TACO).

Only one case of ABO incompatible blood transfusion was reported to ARCBS. This

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is likely to represent an underestimate of these cases as they are usually reported as sentinel events through local health department channels. Other reaction types are also underrepresented, as these are not usually reported to ARCBS unless they require specialist advice, reference testing or component support.

Miscellaneous cases consisted of delayed haemolytic transfusion reactions, febrile non-haemolytic reactions, bradycardia, and transient neutropenia. Some cases could not be classified, some had alternative diagnoses made (for example, related to underlying disease) and there were a number of initially suspected but ultimately unconfirmed cases (post-transfusion purpura and transfusion-associated graft versus host disease). Reactions to fractionated plasma products included headache, urticaria, antibody-mediated haemolysis and pruritus.

ARCBS data collection helps to establish patterns which can pave the way to new interventions that can increase blood safety. These reports have helped to identify areas for further patient, donor and product safety developments, such as enhanced donor skin cleansing, implementation of a component bag diversion pouch at the time of collection and recent agreement by Australian Governments to fund the introduction of routine bacterial screening of platelets. In July 2007, ARCBS commenced male predominant clinical plasma as a risk reduction strategy to reduce the incidence of TRALI, in line with international practice. ARCBS also uses national Australian transfusion reaction data for benchmarking with international partners.

A national haemovigilance system is currently in development under the auspices of a national Haemovigilance Working Group, established by the National Blood Authority (NBA). The Group has to date agreed on some initial aims and is working to define a common data set.



Unexpected Consequences of Passive Antibody Transfer in Patients Receiving Intravenous Immunoglobulin (IVIG)

Passive antibody transfer with IVIG has great therapeutic value for immune replacement in patients with immunodeficiencies, and for immune modulation in many conditions. However, as the following cases illustrate, antibody transfer can also have unintended consequences, some of which could potentially be harmful.

Case 1: A diagnostic dilemma following passive acquisition of antibodies to human T-cell lymphotropic virus type I/II.^{1,2}

In a recent letter to the *Medical Journal of Australia*, Kennedy et al described two patients who were receiving prophylactic IVIG weekly following allogeneic stem cell transplantation.

Each patient had undergone serological testing for antibodies to human T-cell lymphotropic virus type I/II (HTLV I/II) prior to transplantation and had been negative, as had their transplant donors. However, at day 100 following transplantation, both patients tested positive for anti-HTLV I/II.

It was initially unclear whether this represented true primary infection with HTLV I/II. However, further investigation revealed each patient had received IVIG from the same manufacturer and batch, and that the batch in question contained titres of anti-HTLV I/II, which had been passively transferred.

Both patients were once again negative for anti-HTLV I/II with further testing at 12 months, consistent with the eventual clearance of the passively transferred antibody.

Case 2: Immune haemolysis following passive acquisition of blood group antibodies.

A 57 year-old woman had been receiving monthly infusions of IVIG for treatment of chronic inflammatory demyelinating polyneuropathy.

Ten days following an infusion of 0.5mg/kg of IVIG, she presented with increasing fatigue and was noted to be clinically jaundiced.

Investigation revealed a fall in haemoglobin from 112g/L to 81g/L, with an associated hyperbilirubinaemia (78mg/L, normal range 3–8), elevated lactate dehydrogenase (558U/L, normal range 50–350), undetectable haptoglobin, and a positive direct antiglobulin test: all findings consistent with an immune haemolytic anaemia. Further investigation demonstrated that the patient was of blood type A with the presence of an acquired anti-A, which had not been present on previous screening. She had received no other blood products in the intervening period. The haemolysis resolved over seven days without specific therapy, and the anti-A was no longer detectable by day 10.

Practice Points

IVIG is a blood product, with each batch made from a pool of plasma collected from several thousand donors.

The antibody composition of each batch reflects that of its constituent donor pool.

With each infusion of IVIG, a multitude of different antibodies are passively transferred to the patient, which forms the basis of its mechanism of action.

However, individual batches of IVIG may also contain varying titres of clinically significant antibodies, some of which may be present in sufficient quantities to produce clinical consequences.

In some cases, certain passively acquired antibodies may distort the results of serological testing, or induce an immune response in the recipient. A range of reactions similar to those seen here has been described³, including (rarely) haemolytic disease of the newborn following maternal treatment with IVIG⁴, and, more frequently, acquisition of antibodies to cytomegalovirus (CMV) mimicking primary CMV infection and seroconversion⁵.

Plasma-derived products used in Australia (both domestic and overseas) are prepared to extremely high standards and are tested to ensure batches meet the same stringent regulatory requirements, including levels of undesirable antibodies (e.g. those to ABO blood group antigens).

Careful donor selection and screening, including exclusion of donors who have been implicated in cases of transfusion-related acute lung injury, also assists in reducing the incidence of adverse clinical consequences related to passive antibody transfer.



However, variation between products and batches of IVIG does occur, and these may have clinical consequences. The antibody profile of these products may also differ, reflecting the:

- Geographic locations, infectious exposures and immunity of their respective donor populations;
- Testing performed;
- Starting plasma source (“recovered” from whole blood donation, or collected by apheresis); and
- Manufacturing methods.

Clinicians using IVIG, as well as laboratories performing serology testing, should maintain an awareness of the possible consequences of passive transfer of clinically significant antibodies, even in patients who have been receiving long term therapy, such that spurious results can be identified and investigated appropriately. The potential for false positive results (due to the numerous antibodies in the product) should also be communicated clearly to patients receiving IVIG products to assist in allaying patient anxiety until such time as the result can be confirmed via rigorous scientific processes.

As with all blood products, records of the individual batch numbers used should be kept to enable complete tracing and investigation of any adverse reactions. All adverse reactions should be reported to the sponsor of the product.

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Disaster Planning for your Blood Fridge

Disasters happen! Make plans for when they happen to you.

Blood fridge failure does happen, and it could happen to you. Reports of such failures and requests for stock to replace precious supplies of blood components and products that have been lost as a result are, unfortunately, not infrequent.

The most frequently identified reasons for blood fridge-related product losses include:

- Preventative maintenance problems;
- Power failures;
- Alarm problems, such as malfunctioning alarms, incorrectly set limits, failure to respond to activated alarms; and
- Delays in moving stock to appropriate alternative storage.

This is an important issue that we would encourage you to discuss at your Transfusion Committee.

All blood refrigeration MUST comply with the Australian standards AS3864 (1997). This standard covers alarms, temperatures, recorders, maintenance, calibration and other details. Meeting this requirement is the starting point for the safe keeping of blood supplies.

But what happens when your blood fridge breaks down?

Murphy’s Law will apply in that the fridge will misbehave over a long weekend, with few laboratory staff, no maintenance staff around and the most junior members of staff on duty when the crisis hits.



So what can you do?

You can – and should – prepare for such a disaster. Decide on a procedure to be followed, write it down and ensure it is read by all necessary staff members. Items to include would be:

- A record of the event, including the maximum/minimum temperature reached;
- Who found the problem;
- Who to report it to (with phone numbers);
- Who to call in – maintenance, repair persons, laboratory manager, director of nursing etc (with phone numbers); and
- A template for the responsible person to record the date, what the problem was, actions taken and the outcome including listing items lost.

What to do with the fridge contents?

Our suggestion is that, as part of your plan, you locate, in advance, the nearest available laboratory or hospital which has a fridge that complies with AS3864. Negotiate with them to take on your stock should your fridge fail. You can, of course, offer the converse, i.e. if their fridge breaks down, you look after their blood.

Make sure you have sufficient shippers and coolant blocks at the right temperature so you can pack and transport the blood to the other laboratory or hospital in the right condition.

If you are a laboratory and lose all your stock, you should notify the ARCBS in your capital city. If you are a hospital, then inform your laboratory provider of transfusion services.

Planning will not stop a disaster but it may well make life easier. More importantly, it will help preserve the blood that was placed in your care and make sure it is available in your institution when patients need it.



The Risk of Transfusion Delay or Avoidance

From Transfusion Update 2007

Professor Roslyn Yomtovian was a guest speaker at Transfusion Update 2007, ARCBS Transfusion Medicine Services' annual conference, held at the Adelaide Festival Centre over three days in May.

Professor Yomtovian is based in the Department of Pathology at Case Western Reserve University School of Medicine, Cleveland, Ohio. She presented an impressive marathon effort – three sessions in as many days.

Her presentation, "Avoidance of RBC transfusion poses the biggest risk to patients today" was part of a session on "The biggest risk to patients today" on the first day of the conference.

While many of the speakers at the conference cautioned against over-transfusion or unnecessary transfusion, Yomtovian's message was that avoiding transfusion carried its own risks, and this message is sometimes lost when the over-riding message is to avoid unnecessary transfusion.

Dr Yomtovian posed the question, "Is the problem over-transfusion itself, or a way to justify and/or rationalise a desire to reduce transfusion in an era of diminishing and more costly blood resources?"

Dr Yomtovian's belief is that the statement, "The safest transfusion is the one not given" needs to be replaced with

"The safest transfusion is the one given to the correct patient, at the correct time and of the correct type and amount."

She outlined the risks in blood avoidance, under-transfusion and delayed transfusion. Failure to receive transfusion therapy in a timely manner is a frequently overlooked problem in the transfusion medicine process. A transfusion received too late is, by definition, equivalent to one not given.

Contributing factors to delay or avoidance of transfusion included fear of litigation, decisions about cost, concerns about disease transmission, the diminished availability of, and increased competition for resources.

The emergence of blood substitutes, a bias towards "less is better", the administrative complexity of the transfusion process and a tendency to generalise transfusion efficacy very broadly from narrowly based studies were also offered as reasons for under-transfusion.

Dr Yomtovian demonstrated her argument with five case studies where failure of timely transfusion resulted in the death of patients. Her presentation, including these case studies, is available at www.transfusion.com.au: <http://www.transfusion.com.au/FILES/conferences/TMU2007/roslyn%20yomtovian.pdf>.

Universal Blood Type Conversion Becomes a Reality

Maintaining a consistent and reliable supply of red cells is a daily challenge for blood services around the world. A key element of that challenge is the maintenance of appropriate quantities of all blood types.

As recently reported in mainstream media, a process has been discovered that allows A, B and AB type red blood cells to be changed to O type cells, making them universally transfusable.

This development allows for the possibility of the conversion of all red blood cells to type O, reducing transfusion risks associated with mismatched blood types and assisting with inventory level issues related to maintaining stocks of all blood types.

The process removes A and B antigens via a washing process, demonstrated in an animation at www.zymequest.com.

The New York Blood Centre conducted research in the 1980s using green coffee beans that allowed researchers to successfully convert type B to type O. This research has been furthered by a US company which has successfully created an enzyme conversion process that converts A, B and AB red cells to 'ECO' – enzyme-converted Group O cells, using two enzymes that make the removal of both A and B antigens possible. An intestinal bacterium, *Bacteroides fragilis*, removes the B antigen and *Elizabethkingia meningosepticum*, associated with infant meningitis, removes the A antigen.

Commercialisation and clinical adoption of this process is still some time away, with early clinical trials currently underway to ensure blood that has undergone this process is safe for transfusion.

Residual Risk Estimates for Transfusion-Transmitted Infections

Agent and testing standard	Window period (days)	Estimate of residual risk 'per unit' ^a
HIV (antibody + RNA)	9	Less than 1 in 10 million
HCV (antibody + RNA)	5.4	Less than 1 in 10 million
HBV (HBsAg)	38	Approximately 1 in 660,000
HTLV I & II antibody	51	Less than 1 in 10 million
CMV (antibody negative)	46	Approximately 1 in 127,000
CMV (untested /WBC filtered)	N/A	Risk of recipient infection approximately 2.5% ^b
Variant Creutzfeldt-Jakob Disease (vCJD) [No testing]		Possible. Not yet reported in Australia. See section below.
Malaria (antibody)	N/A	1 in 4.9 million to 1 in 10.2 million

^a HIV, HCV, HBV risk estimates are based on ARCBS data from 1 January 2005 to 31 December 2006. HTLV risk estimate based on data from 1 January 2004 to 31 December 2006. For other agents refer below

^b Average risk of infection in recipients of WBC-reduced components, taken from Vamvakas, E. *Transfusion Medicine Reviews* 2005. 19(3):181-199

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Malaria: Seed CR. *Residual Risk Estimates for Transfusion Transmitted Malaria (TTM)*. ARCBS DPARC: November 9/10 2005 meeting

CMV: Seed CR. *Risk Estimate – Transmission of CMV By 'Seronegative' Blood*. ARCBS DPARC: August 14/15 2007 meeting

ARCBS publishes estimates of the residual risks of transfusion-transmitted infections in every edition of Medilink as a service to clinicians to guide transfusion decision-making and informed consent processes.

There have been no reported cases of transmission by transfusion of classical Creutzfeldt-Jakob Disease (cCJD), and retrospective studies suggest that the possibility of such transmission of cCJD is remote.

To date, no Australian has been infected with vCJD. In the UK, there have been a small number of reported cases of putative transfusion transmission since 2004. In Australia, as a precaution, people who have spent a cumulative period of six months in the UK between 1 January 1980 and 31 December 1996 and/or had a transfusion in the UK between 1 January 1980 and the present time are not accepted as blood donors.