

CLINICAL INDICATIONS FOR APHERESIS AND WHOLE BLOOD POOLED PLATELETS

A National Statement

November 2015



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1	November 2013	First Draft	Platelet consensus group
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SUMMARY

Once a decision has been made to prescribe a platelet transfusion, this document provides information regarding the selection of either apheresis platelets or whole blood pooled platelets. Absolute and relative indications for particular platelet types have been determined by literature search and expert consensus.

Definitions

An **absolute indication** is one where evidence is available that either confirms or is indicative of additional clinical benefit with the prescription of a particular type of platelet component. Absolute indications will influence the supply plan for the particular type of platelet component.

A **relative indication** is one where there is a theoretical clinical benefit or other benefit for the prescription of a particular type of platelet component, however available evidence is currently lacking. A relative indication will influence the prioritisation of the particular type of platelet component, when available.

Statements

Consensus Statement 1

Once it has been determined that a platelet transfusion is required for a particular patient, the absolute indications for apheresis platelets are:

- Patients who require HLA compatible and/or HPA matched platelets ¹, such as:
 - a. Patients with platelet refractoriness due to the presence of HLA and/or HPA antibodies
 - b. Patients with neonatal alloimmune thrombocytopenia (NAIT)
- Patients who require IgA deficient platelets ² i.e. IgA deficient patients with anti-IgA and a history of an anaphylactic transfusion reaction.

Consensus Statement 2

Once it has been determined that a platelet transfusion is required for a particular patient, the relative indications for apheresis platelets in preference to whole blood pooled platelets are:

- Neonates and small children whose platelet dose requirement can be met by a split apheresis component, thereby avoiding wastage of the unused part of the whole blood pooled platelet component ³

¹ Patients with platelet refractoriness or NAIT should not have their platelet transfusion unnecessarily withheld or delayed while seeking HLA compatible or HPA matched apheresis platelets as they may benefit from random pooled whole blood derived or random apheresis platelets

² For patients with IgA deficiency and a history of anaphylactic reaction to IgA containing products, efforts should be made to source apheresis platelets from an IgA deficient donor as a priority because the panel of IgA deficient donors is very limited - it is not feasible to manufacture IgA deficient whole blood pooled platelets as this requires the pooling of 4 ABO-identical donations

³ The Australian Red Cross Blood Service (Blood Service) is unable to produce a leucodepleted platelet component from a single whole blood donation. For this reason, options for paediatric transfusion support are split apheresis platelets (one apheresis component can support repeated transfusions over a few days) or part of a pooled platelet component. In this scenario, the unused part of the pooled platelet component would be discarded

Consensus Statement 3

Once it has been determined that a platelet transfusion is required for a particular patient, there are no absolute indications for whole blood pooled platelets in preference to apheresis platelets.

Consensus Statement 4

Once it has been determined that a platelet transfusion is required for a particular patient, the relative indications for whole blood pooled platelets in preference to apheresis platelets are:

- Non-ABO-identical transfusions, especially for children, as the pooling process and lower plasma content reduces the risk of haemolysis associated with any potentially present high titre anti-A and/or anti-B ⁴

⁴ Apheresis platelets are not suspended in platelet additive solution (PAS) and for this reason have a higher residual plasma content compared with whole blood pooled platelets which are suspended in PAS. The transfusion of non-ABO-identical transfusions is only considered appropriate in circumstances when ABO compatible or tested low titre component is not available.

Background

In 1999, the Australian Red Cross Blood Service (Blood Service) identified its plan to supply 90% of its platelets as apheresis, as part of its original strategy for the implementation of universal leucodepletion of fresh components. At that time, platelets were mostly manufactured by the platelet rich plasma (PRP) method which gave a component of lower yield and quality and did not lend itself easily to leucodepletion.

By 2004, approximately 25% of platelets supplied nationally were provided as apheresis platelets increasing to 37% in 2008/09 with wide variation amongst the jurisdictions. Apheresis platelets made up 88% of platelets manufactured in WA but only 18% in NSW.

Since the late 1990s, there have been considerable advances in platelet collection, processing and testing which have had a significant impact on platelet quality and safety.

These advances include:

- National implementation of buffy coat processing (completed 2007)
- Implementation of nucleic acid testing (NAT) for hepatitis C, HIV (2000) and hepatitis B (2010)
- Leucodepletion of all platelet components (2007)
- 100% bacterial contamination screening (BCS) (2008)

As such, the quality and safety considerations prompting the original 90% target had been mitigated to some extent by 2009. As a result, after review of the available evidence at the time and consultation with external clinicians, including the National Blood Transfusion Committee, the Blood Service recommended that 60% of platelets be produced by apheresis. This recommendation was made on the basis that haematology and oncology patients, who currently receive 50 – 60% of platelets issued, as well as paediatric patients were likely to derive the greatest benefit from apheresis platelets as a consequence of the lower donor exposure.

In order to plan for future demand trends for platelets and determine the most appropriate split between apheresis and whole blood pooled platelets, the National Blood Authority (NBA) requested:

- A review of the clinical indications for each type of platelet component based on current evidence and expert opinion taking into account relevant Patient Blood Management (PBM) guidelines
- Based on the indications for use of each platelet component type, a recommendation of a national target of the split between apheresis and whole blood derived platelets to meet clinical demand

The Blood Service developed a set of draft consensus statements through literature search using Medline and the Cochrane database. These draft statements, and supportive documentation, were discussed and consensus derived by an invited expert clinician panel. Initially, a paper-based consensus process was conducted. If consensus could not be reached, it was a requirement that an in-person formal consensus meeting or teleconference alternative be conducted to finalise the consensus statements. Of note, cost effectiveness analysis was out of scope for the development of the clinical indications for the use of apheresis and whole blood platelets.

Product comparison

Platelets are collected and manufactured by two distinct methods: (1)

1. Whole blood pooled platelets
2. Apheresis platelets

Platelet concentrates derived from whole blood collections can be obtained via the buffy coat (BC) or platelet rich plasma (PRP) manufacturing process. Since Australia only produces whole blood derived platelets by the BC method, only this method of manufacture has been referred to for whole blood pooled platelets in this statement. The literature review was primarily confined to platelets manufactured by the BC method or apheresis.

Whole blood pooled platelets are obtained by pooling buffy coats from four separate ABO-identical whole blood donations using a platelet additive solution (PAS). The pool is centrifuged, filtered (to remove white cells) and rested (to prevent platelet clumps) to produce a leucodepleted pooled platelet unit.

Apheresis platelets are collected from a single donor by using an apheresis machine with an integrated leucoreduction system (removing $\geq 99\%$ white cells). The machine draws blood from the donor, isolates the platelets and some plasma by centrifugation and returns the remaining blood back to the donor. Often, it is possible to collect sufficient platelets from one plateletpheresis procedure to allow the collection to be split into two adult doses of platelets. Apheresis platelets are not suspended in PAS and for this reason have a higher residual plasma content compared with whole blood pooled platelets.

Apheresis platelets are significantly more costly than whole blood pooled platelets. Product prices are listed on the National Blood Authority website at www.blood.gov.au/national-product-list.

Table 1 Typical unit content of apheresis and whole blood pooled platelets based on units tested Oct 2010 – Sept 2011 (2)

	Apheresis Platelets	Whole Blood Pooled Platelets
Platelet additive solution	N/A NOTE: Validation of apheresis platelets in additive solution is expected to commence late 2013/early 2014.	Make up approximately 70% of total component volume Less plasma currently
Anticoagulant	ACD-A	CPD/CPDA
Volume (mean ± 1 SD)	183 ± 16mL	303 ± 12mL NOTE: The Blood Service implemented a new blood component expessor system, used in the processing of whole blood donations, in early 2013 which resulted in an increase in the average volume of pooled platelets to approximately 350mL per pool. However, further optimisation of the process has recently been implemented which is expected to reduce the average volume to approximately 325mL.
Platelet count (mean ± 1SD)	301 ± 41 x10 ⁹ /pack	300 ± 44x10 ⁹ /pool
pH at expiry (mean ± 1SD)	7.1 ± 0.2	7.1 ± 0.1
Leucocyte count (mean ± 1SD)	0.21 ± 0.12 x10 ⁶ /pack	0.30 ± 0.02x10 ⁶ /pool
Shelf-life	5 days at 20-24 ⁰ C with gentle agitation	5 days at 20-24 ⁰ C with gentle agitation
Modifications available	CMV seronegative, irradiated, HLA-compatible, HPA-matched, IgA deficient, low anti-A,B	CMV seronegative, irradiated

Table 2 Clinical considerations for transfusion of apheresis and whole blood pooled platelets

Corrected Count Increment (CCI) 1 hour and 18-24 hours	No significant difference between apheresis and BC pooled platelets (3, 4).
Prevention of haemorrhage	No significant difference, but both studies compared apheresis with pooled platelets-PRP method (5, 6).
In-vitro haemostatic potential	Similar overall. Circulating recovery (5 days) is similar; hypotonic shock recovery slightly favours apheresis; ADP-, collagen- and epinephrine-induced aggregation is similar; pH is similar; activation marker CD62P is similar. (3, 5, 7, 8).
Alloimmunisation and platelet refractoriness	No significant difference if components are all leucodepleted (9).
Acute non-haemolytic transfusion reactions	No significant difference (3, 9-12).
Confirmed positive bacterial contamination screening rates	Both low. Blood Service data: Apheresis 0.04% vs Pooled 0.12% (Apr 2008 – Apr 2013) International data: Apheresis 0.09% vs Pooled 0.06% (13) http://www.transfusion.com.au/adverse_events/risks/transfusion-transmissible-infection-surveillance-australia
Other transfusion transmissible infections	Both low, but no comparable studies available.
TRALI	No comparable studies available of apheresis platelets and BC pooled platelets in platelet additive solution. No difference between TRALI risk in two studies that compared pooled PRP platelets and apheresis platelets (14, 15) and one study that compared BC pooled platelets in plasma and apheresis platelets (16).

Points to consider

PLATELET CONTENT AND QUALITY

- Similar platelet content in apheresis platelets and pooled platelets
i.e. $301 \pm 41 \times 10^9$ /pack vs $300 \pm 44 \times 10^9$ /pool (2).
- Similar number of residual white cells are found
i.e. $0.21 \pm 0.12 \times 10^6$ /apheresis unit vs $0.30 \pm 0.02 \times 10^6$ /pooled platelet unit.
- A review of *in vitro* and *in vivo* studies by Schrezenmeier comparing platelet survival, activation and clot formation did not demonstrate that one method of preparation is consistently superior to the other; however noted that, due to inter-donor variability, pooled platelets may lead to a reduction in component variation (7).

EFFICACY

- Corrected count increment (CCI) is often used as a surrogate marker of platelet efficacy.
- 1 hour and 18-24 hour CCI are no different between apheresis platelets and pooled platelets produced by the BC method (3).
- In AML patients undergoing myeloablative transplant, both types of platelets (pooled PRP and apheresis) were just as effective in preventing haemorrhage (5) using time to red cell transfusion as a surrogate. There is also no difference in Grade ≥ 2 bleeding in haematology/oncology patients transfused with apheresis or pooled platelets (6).

ACUTE NON-HAEMOLYTIC TRANSFUSION REACTIONS

The most common adverse reaction to platelets is febrile non haemolytic transfusion reaction (FNHTR) and the rate does not differ between apheresis platelets and whole blood pooled platelets as long as they are leucodepleted (9-11). Further trials have also indicated that the incidence of severe platelet reactions including bronchospasm and extensive urticaria does not differ (9).

Currently, there is no convincing data to suggest that the rate of transfusion-related acute lung injury (TRALI) is different between apheresis and whole blood pooled platelets, despite pooled platelets containing the least plasma (14-16). TRALI has still been reported even with transfusions of small volumes of plasma (18). Blood Service data shows that platelets implicated in TRALI investigations are normally transfused with other blood components. In these situations, it can be difficult to distinguish which components are implicated.

TRANSFUSION TRANSMISSIBLE INFECTIONS (TTI)

One of the strongest rationales for advocating the use of apheresis platelets is that the risk for TTI is higher with increased donor exposure. However, with ongoing improvements in donor screening, collection, manufacture and testing some of these risks have been mitigated.

Bacterial infection

Since April 2008, all platelet units supplied by the Blood Service have undergone pre-release bacterial contamination screening. Several international studies including a large prospective study comparing contamination rates in more than 15,000 apheresis platelets and 37,000 whole blood pooled platelets found equal rates of confirmed positives in both platelet types (13). Blood Service data, from commencement of bacterial contamination screening (BCS) until April 2013, indicates that the confirmed positive rate for apheresis

platelets was 0.04% vs 0.12% for whole blood pooled platelets. Almost 80% of bacteria identified were *Propionibacterium* species which is a common skin commensal and is considered nonpathogenic to non-immunocompromised patients. The remaining 20% of bacterial contaminants mainly consisted of other skin flora like Coagulase negative staphylococcus and *Staphylococcus epidermidis*. Approximately half of the platelets found to be BCS positive (either initial machine positive or confirmed positive) had already been transfused at the time of the initial machine positive flag and, in all cases, no evidence of transfusion-associated sepsis was reported. Therefore, although the rate of confirmed positive bacterial contamination is higher for whole blood pooled platelets, this may not translate into higher infection rates. Since the implementation of routine bacterial contamination screening of platelets, the Blood Service has only received three reports of confirmed transfusion-transmitted bacterial infection; two cases associated with red cell transfusions and one case associated with a whole blood pooled platelet transfusion.

Viral infection

The introduction of nucleic acid testing (NAT) for hepatitis C and HIV in 2000 and for hepatitis B in 2010 has further reduced the window period for viral detection, thereby reducing the infectious risk of contracting these viruses via a blood transfusion. The Blood Service TTI residual risk estimates, based on data from 1 January 2011 and 31 December 2012, are approximately 1 in 26 million for HIV, 1 in 26 million for hepatitis C and 1 in 538 000 for hepatitis B. No cases of transfusion transmitted hepatitis C have been reported in Australia since 1991, none for HIV since 1998 and three probable cases of hepatitis B in the 2005-2011 period (19). Although, theoretically, the risk of transmission of infectious agents would be expected to be higher in whole blood pooled platelets, no epidemiological studies or clinical trials have demonstrated this.

The introduction of 100% leucodepletion has also reduced the risk of transmission of CMV which is located primarily in the white cells. The recent SaBTO guidelines (20) from the UK state that the rates of transfusion-transmitted CMV are very low with both leucocyte depletion and serology screening and that the two techniques are probably equivalent. Hence, for all patient groups, including those undergoing haematopoietic stem cell transplant and solid organ transplant, CMV seronegative blood products can be replaced with leucodepleted blood components. However, it recommends that CMV seronegative blood products should be provided for intrauterine transfusions (IUT), pregnant women and neonates, up to 28 days post expected date of delivery, because of the potential severity of the consequences of CMV infections and the difficulty in monitoring neonates for infection. There is no published evidence to support that, with universal leucodepletion, whole blood pooled platelets have a higher risk of CMV TTI compared to apheresis platelets.

Emerging infections

There are, however, other TTIs for which the Blood Service does not currently test and, as such, there remains a theoretically higher risk of TTIs with whole blood pooled platelet transfusions due to the higher donor exposure.

ALLOIMMUNISATION AND PLATELET REFRACTORINESS

The other frequently cited indication for favouring apheresis platelets is the lower risk of alloimmunisation, and subsequent development of platelet refractoriness, because of the reduction in donor exposures. With the introduction of 100% leucodepletion, this risk is now substantially mitigated.

The Trial to Reduce Alloimmunisation to Platelet study group (TRAP) showed that the rate of formation of HLA and HPA antibodies were similar in leucocyte filtered whole blood pooled platelets and apheresis platelets and, hence, both were equally effective in preventing alloimmune platelet refractoriness; the alloimmunisation rate being 7% (4-13%) for filtered whole blood pooled platelets and 8% (4-14%) for filtered apheresis platelets (9).

More recently Heddle et al (3) conducted a systematic review in 2008 which evaluated 10 RCTs. There have also been some non-randomised studies (21, 22). Whilst these studies found an increase in refractoriness and alloimmunisation with the use of WB derived platelets compared with apheresis platelets, not all studies included prestorage leucodepleted components and there was significant variation in how platelet refractoriness was defined. Heddle noted that the included studies were not powered for equivalence and RCTs should be conducted. One hour and 18-24 hour CCI are no different between apheresis platelets and pooled platelets produced by the BC method (3).

The available evidence confirms that apheresis platelets have a lower adverse reaction rate and a higher platelet increment when compared with nonleucodepleted whole blood derived platelets. However overall, there is no evidence that apheresis platelets and whole blood pooled platelets have a clinically significant difference in their rates of alloimmunisation providing they have been leucodepleted.

For patients who are predicted to require long term platelet support, most commonly haematology and oncology patients (utilising 60% of the current total platelet supply) and patients with congenital platelet disorders, avoidance of alloimmunisation is desirable. Efficacy of leucodepletion rather than number of donor exposures is now understood to be critical to alloimmunisation prevention. Studies have not yet been performed to compare long term risk between transfusion with apheresis and whole blood pooled platelets in patient groups who receive multiple platelet transfusions.

Statements

Consensus Statement 1

Once it has been determined that a platelet transfusion is required for a particular patient, the absolute indications for apheresis platelets are:

- Patients who require HLA compatible and/or HPA matched platelets ⁵, such as:
 - a. Patients with platelet refractoriness due to the presence of HLA and/or HPA antibodies
 - b. Patients with neonatal alloimmune thrombocytopenia (NAIT)
- Patients who require IgA deficient platelets ⁶ i.e. IgA deficient patients with anti-IgA and a history of an anaphylactic transfusion reaction.

Brief Description

There is no current evidence of different rates of TTI, alloimmunisation (and hence platelet refractoriness), acute reactions or clinical efficacy in terms of prevention or treatment of bleeding between apheresis platelets and whole blood pooled platelets.

Patients who have developed HLA or HPA antibodies due to previous transfusions or pregnancy may have very poor platelet increments to random donor platelets and need platelets collected by apheresis from HLA compatible or HPA matched donors.

Neonatal alloimmune thrombocytopenia (NAIT) is a life-threatening condition where maternal HPA antibodies cross the placenta and cause immune thrombocytopenia in the foetus and newborn. Platelets that do not possess the relevant HPA antigen obtained from typed apheresis donors are indicated for treatment of this condition. However, good responses to random donor platelets by neonates affected by NAIT have also been reported (23).

IgA deficient platelets are provided for individuals with anti-IgA and a history of an anaphylactic transfusion reaction. IgA deficient platelets are only collected by apheresis.

In 2012, the supply of HLA compatible/HPA matched platelets to Australian states and territories ranged from 1% -5.1% of all platelets supplied, which overall, represents only a small proportion of platelet supply. In 2012, only 0.09% of all platelets supplied were IgA deficient.

Consensus Statement 2

Once it has been determined that a platelet transfusion is required for a particular patient, the relative indications for apheresis platelets in preference to whole blood platelet pools are:

- Neonates and small children whose platelet dose requirement can be met by a split apheresis component, thereby avoiding wastage of the unused part of the whole blood pooled platelet component ⁷

⁵ Patients with platelet refractoriness or NAIT should not have their platelet transfusion unnecessarily withheld or delayed while seeking HLA compatible or HPA matched apheresis platelets as they may benefit from random pooled whole blood derived or random apheresis platelets.

⁶ For patients with IgA deficiency and a history of anaphylactic reaction to IgA containing products, efforts should be made to source apheresis platelets from an IgA deficient donor as a priority because the panel of IgA deficient donors is very limited - it is not feasible to manufacture IgA deficient whole blood pooled platelets as this requires the pooling of 4 ABO-identical donations.

Brief Description

The Blood Service is unable to produce a leucodepleted platelet component from a single whole blood donation. For this reason, options for paediatric transfusion support are split apheresis platelets (one apheresis component can support repeated transfusions over a few days) or part of a pooled platelet component. In this scenario, the unused part of the pooled platelet component would be discarded.

CMV seronegative platelets are collected through both apheresis (51%) and whole blood pooled platelets (49%) and therefore both types of platelets could potentially be used for IUT, neonates and pregnant women. As one apheresis bag may be split into four paediatric bags for neonates and small children needing platelet support over a few days (dose of platelets is 5-10ml/kg), apheresis platelets are generally preferred in the paediatric setting, primarily to avoid component wastage.

It is also relevant to consider that the volume of plasma is greater in apheresis platelets compared with whole blood platelet pools (which are suspended in additive solution) and for this reason there is also a theoretical increased risk of TRALI, allergic type reactions and, if crossing ABO groups, haemolysis from apheresis platelets. The Blood Service will commence validation of apheresis platelets in additive solution in 2014.

Consensus Statement 3

Once it has been determined that a platelet transfusion is required for a particular patient, there are no absolute indications for whole blood pooled platelets in preference to apheresis platelets.

Consensus Statement 4

Once it has been determined that a platelet transfusion is required for a particular patient, the relative indications for whole blood pooled platelets in preference to apheresis platelets are:

- Non-ABO-identical transfusions, especially for children, as the pooling process and lower plasma content reduces the risk of haemolysis associated with any potentially present high titre anti-A and/or anti-B ⁸

Brief Description

Plasma may contain high titre anti-A and/or anti-B which may cause haemolysis if given to non-ABO-identical recipients, especially to children. A proportion of group O apheresis platelets are currently tested to identify units containing low titre anti-A and anti-B which may be used in situations where group O platelets are transfused to a non-group O patient. However, if not available, whole blood pooled platelets are preferable as the pooling process and lower plasma content reduces the risk of haemolysis associated with any potentially present high titre anti-A and/or anti-B.

⁷ The Australian Red Cross Blood Service (Blood Service) is unable to produce a leucodepleted platelet component from a single whole blood donation. For this reason, options for paediatric transfusion support are split apheresis platelets (one apheresis component can support repeated transfusions over a few days) or part of a pooled platelet component. In this scenario, the unused part of the pooled platelet component would be discarded

⁸ Apheresis platelets are not suspended in platelet additive solution (PAS) and for this reason have a higher residual plasma content compared with whole blood pooled platelets which are suspended in PAS. The transfusion of non-ABO-identical transfusions is only considered appropriate in circumstances when ABO compatible or tested low titre component is not available.

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