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Platelet Products in Clinical Practice: Manufacturing, Dose, and Safety Considerations

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KEY POINTS

- Platelet components used for transfusion are produced through distinct manufacturing pathways that influence dose, storage conditions, residual red cell content, and safety mitigation strategies.
- Clinicians treating thrombocytopenic patients often consider both apheresis platelets and whole blood–derived platelet (WBDP) pools, which are clinically comparable but differ in production methods and certain product characteristics. Safety profiles depend on processing and mitigation strategies.
- Understanding these differences helps guide product selection for specific clinical scenarios including HLA matching, RhD-negative recipients, or pathogen-reduced products.

Whole Blood Platelet Production

Manual whole blood-derived platelets (WBDP) in the United States are manufactured using the platelet-rich plasma (PRP) method, involving a two-step differential centrifugation process within a closed system.

First, whole blood is centrifuged at a slow speed to sediment red and white blood cells while concentrating platelets in the supernatant plasma, creating PRP. The PRP is then centrifuged at a higher speed to sediment platelets. Plasma is expressed, and the sedimented platelets are resuspended in 40-70 mL of plasma.

The entire process occurs within a closed, disposable plastic bag system, reducing the risk of bacterial contamination. Pre-storage leukoreduction is now standard practice, and pooling and filtration can be performed either pre- or post-storage using U.S. Food and Drug Administration (FDA) -approved systems. In the United States, WBDP products have a 5-day shelf life from the time of collection. This can be extended to 6 or 7 days when FDA-approved or cleared bacterial detection risk control strategies are implemented.

In addition to the manual method, an automated single integrated closed system workflow is available that combines 4-6 WBDP to create a leukoreduced pooled platelet product[1]. Software is used to achieve the desired platelet count defined by the supplier manufacturer.

Apheresis Platelets Production

Apheresis platelets are collected using an automated instrument utilizing a sterile collection kit. Current apheresis platforms isolate platelets suspended in plasma via a sterile centrifuge-based apparatus. Integrated software supports leukoreduction and platelet concentration during collection.

Typically, one to three platelet units may be collected from a single donor based on the donor's size and platelet count. Apheresis platelets are the preferred source when HLA-matched or crossmatched products are required and are currently the only platelet product used for cold stored platelet manufacturing and pathogen reduction in the U.S.[2,3]

Platelet Additive Solutions (PAS)

Platelets are initially collected in plasma, but this can be replaced by PAS during manufacturing. This process is analogous to the use of additive solutions for red blood cells. PAS also reduces the risk of allergic and minor incompatibility hemolytic reactions by reducing plasma allergens and isohemagglutinins.[4] In the U.S., the solution most used is PAS C which contains citrate, phosphate, and acetate.

Platelet Dose and Therapeutic Equivalence

According to FDA regulations, WBDP should contain at least 5.5×10^{10} platelets per unit.[5] In practice, 4-6 individual WDBP units are pooled to achieve a dose of $2.5\text{-}4 \times 10^{11}$ platelets. Apheresis platelet products should routinely contain at least 3.0×10^{11} platelets, although a standard dose is not mandated. Low-yield apheresis units ($<3.0 \times 10^{11}$) may still be transfused if labeled with actual content[3]. In practice, low yield platelets typically contain $2.0\text{-}2.9 \times 10^{11}$ platelets. Individual suppliers set criteria for the average percent of platelet units that may be distributed as low dose pools.

The Platelet Dose (PLADO) Trial, one of the largest and most influential trials on platelet transfusion dosing, demonstrated that platelet dose had no effect on the

incidence of clinically significant bleeding with prophylactic transfusion[6]. The percentage of patients experiencing WHO grade 2 or higher bleeding was 71%, 69%, and 70% in the low-, medium-, and high-dose groups, respectively. This was not statistically significant, although median intertransfusion intervals were significantly different at 1.1, 1.9, and 2.9 days, respectively. High-dose platelets were associated with increased transfusion-related adverse events (TRAEs)[7]. Furthermore, the PLADO Trial also demonstrated that the platelet source (WBD vs apheresis) did not significantly affect bleeding outcomes or TRAE risk when leukoreduced products were used. Although apheresis platelets produced modestly higher posttransfusion increments, this did not translate into measurable clinical benefit for bleeding prevention. Similar data is not available for dose recommendations in actively bleeding patients.

Based on a systematic review of available RCTs and observational studies, the Association for the Advancement of Blood & Biotherapies (AABB) has published recommendations for platelet transfusion thresholds for predefined clinical populations such as thrombocytopenic patients requiring lumbar puncture[8].

Apheresis platelets in plasma typically will lead to a higher increment in platelet count compared to an apheresis platelets in PAS or an apheresis platelet in plasma that has undergone pathogen reduction technology (PRT).[9,10] Thus while restrictive platelet transfusion strategies are often appropriate, it is important to recognize that PAS and PRT products often lead to lower platelet increments.

Bacterial Contamination affecting Platelet Products

Bacterial mitigation strategies used to reduce risks associated with platelet products include bacterial detection methods, PRT, and cold storage manufacturing. Primary bacterial culture testing has been standard practice in the US since 2004. Large volume delayed sampling (LVDS) improves detection rates, with interdiction of contaminated apheresis platelets exceeding 70%.[11] A meta-analysis of studies performed after implementation of a primary culture method (2005-2018 publications) reported the overall mean contamination rate as 0.40 per 1000 components for WBDP using PRP method and 0.22 per 1000 components for apheresis platelets.[12] The rate of contamination of WBDP decreased with time, possibly due to implementation of chlorhexidine cleansing of the phlebotomy site[13] The most commonly detected organisms are coagulase-negative *Staphylococcus* species (accounting for 48% of isolates), followed by *Micrococcus luteus*, *Bacillus species*, and less frequently, potential pathogens including *Staphylococcus aureus*, *Serratia marcescens*, *Klebsiella pneumoniae*, and *Cutibacterium acnes*.[14,15]

In the U.S., PRT is currently only approved for apheresis platelet products. Ultraviolet light with a photosensitizer crosslinks nucleic acids and inactivates certain bacteria, viruses, parasites, and residual leukocytes, and, therefore, eliminates the need for bacterial detection.[10] Cold stored platelets do not require a bacterial detection step.[2]

Residual Red Cell Content and RhD Sensitization

Residual red cell content is relatively low in platelet products but varies with manufacturing method. WBDP pools generally contain more residual red cells than apheresis platelets, although automated pooling reduces this difference.[16] ASCO data suggests that average residual RBC content is approximately 0.036 mL for WBDP products and 0.00043 mL for apheresis products.[17]

The risk of RhD alloimmunization from platelet transfusion is low but not negligible. The 2015 ADAPT study indicated a 1.4% alloimmunization rate when RhD negative patients receive RhD positive platelets.[18] A 2024 metanalysis indicated that alloimmunization risk varies by recipient and product characteristics. Females had a 2x higher rate of anti-D immunization and recipients of WBD pools had a 5x higher rate.[19] Sensitization can be prevented with administration of Rh immune globulin when clinically indicated.

TRALI Risk by Platelet Type

Contemporary hemovigilance data demonstrate lower TRALI rates with PAS and PRT platelet products. Estimated rates are approximately 13.5 cases per million units for pooled WBDP, 4.4 per million units for plasma-suspended apheresis platelets, 0.8 per million units for PAS apheresis platelets, and 0.5 per million units for pathogen-reduced PAS apheresis platelets. These findings reflect the impact of donor selection, plasma reduction, and PRT.[20] Some blood centers now use the same donor selection criteria for WBDP as those used for high-plasma containing components; this practice would be expected to create equivalent risk for WBDP as plasma-suspended apheresis.

HLA Alloimmunization and Platelet Refractoriness

Class I HLA alloimmunization remains the primary cause of platelet transfusion refractoriness. The landmark Trial to Reduce Alloimmunization to Platelets (TRAP) demonstrated that pre-storage leukoreduction significantly reduces HLA alloimmunization and established leukoreduction as the cornerstone of HLA alloimmunization prevention.[21] The study findings showed no difference in alloimmunization between leukoreduced apheresis platelets and leukoreduced WBDP. Subsequent studies conducted have not demonstrated an increased risk of HLA alloimmunization or platelet refractoriness associated with PRT.[21]

TA-GVHD Prevention

Pathogen reduction inactivates donor T lymphocytes and is considered sufficient to prevent TA-GVHD in platelet products. As a result, irradiation is generally not required for PRT platelets.[22] For non-PRT platelets, the product should be irradiated before transfusing to at-risk patients. ■

Feature	Apheresis Platelets	Whole Blood-Derived Platelets	Cold-Stored Platelets
Manufacturing Method	Collected via apheresis instrument with sterile centrifuge-based apparatus; continuous or intermittent flow; up to 4 units from 1 donor	Two-step centrifugation: soft-spin separates RBCs, hard-spin sediments platelets; One-step centrifugation for automated method; individual units are resuspended in 40-70 mL plasma; pooled from 4-6 donors are FDA approved	Apheresis-derived only per FDA guidance; stored at 1-6°C rather than room temperature
FDA Minimum Platelet Count per Unit	≥3.0×10^{11} platelets	≥5.5×10^{10} platelets	≥3.0×10^{11} platelets
Standard Expiration	5 days; extendable to 7 days with bacterial detection (PRT – 5 days only)	5 days; extendable to 7 days with bacterial detection	Extended storage up to 14 days at 1-6°C
Bacterial Contamination Rate	Lower: 0.22 per 1000	Higher: 0.40 per 1000	Lowest due to refrigerated storage
Bacterial Mitigation Strategies	Primary culture, LVDS, secondary culture, rapid testing, OR PRT	Primary culture, LVDS, secondary culture, rapid testing;	No bacterial detection required; cold storage inhibits bacterial proliferation
Pathogen Reduction Eligibility	Yes – only apheresis platelets eligible for PRT in U.S.	No – PRT not available for WBDP in U.S.	PRT may be used to provide additional safety benefits

Feature	Apheresis Platelets	Whole Blood-Derived Platelets	Cold-Stored Platelets
RBC Content	Minimal (mean ~0.00043 mL/unit)	Higher than apheresis; automated processing has fewer RBCs than manual methods	Same as apheresis source product
RhD Alloimmunization Risk	Lower due to minimal RBC content	Higher: 1.4% alloimmunization rate in RhD-negative recipients (ADAPT study); females 2× higher risk; WBDP recipients 5× higher risk vs apheresis	Same as apheresis source product
TRALI Risk (per million units)	Plasma-suspended: 4.4; PAS: 0.8; PRT-PAS: 0.5	Pooled WBDP: 13.5 (some facilities screen donors to reduce risk)	Data limited; expected like apheresis source
HLA Alloimmunization Risk	No significant difference when leukoreduced (TRAP trial); PRT does not increase risk	No significant difference when leukoreduced (TRAP trial, PLADO trial)	Expected to be like leukoreduced apheresis
TA-GVHD Prevention	PRT eliminates need for irradiation; non-PRT requires irradiation for at-risk patients	Requires irradiation for at-risk patients; PRT not available	Requires irradiation for at-risk patients
Special Indications	Required for HLA-matched product	Clinically equivalent for prophylactic use (PLADO)	For the treatment of active bleeding when conventional platelets are not available, or their use is not practical per FDA guidance. Not for prophylactic use.

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