

Platelet transfusion biology: from hemostatic support to inflammatory and immune signaling

by Hind Hamzeh-Cognasse, Blandine Maitre, Michele P. Lambert and Fabrice Cognasse

Received: July 6, 2026.

Accepted: October 21, 2026.

Citation: Hind Hamzeh-Cognasse, Blandine Maitre, Michele P. Lambert and Fabrice Cognasse. Platelet transfusion biology: from hemostatic support to inflammatory and immune signaling. *Haematologica*. 2026 Oct 29. doi: 10.3324/haematol.2026.301566 [Epub ahead of print]

Publisher's Disclaimer.

E-publishing ahead of print is increasingly important for the rapid dissemination of science.

Haematologica is, therefore, E-publishing PDF files of an early version of manuscripts that have completed a regular peer review and have been accepted for publication.

E-publishing of this PDF file has been approved by the authors.

After having E-published Ahead of Print, manuscripts will then undergo technical and English editing, typesetting, proof correction and be presented for the authors' final approval, the final version of the manuscript will then appear in a regular issue of the journal.

All legal disclaimers that apply to the journal also pertain to this production process.

Platelet transfusion biology: from hemostatic support to inflammatory and immune signaling

Hind Hamzeh-Cognasse^{1,#}, Blandine Maître², Michele P Lambert³, Fabrice Cognasse^{1,4,*,#}

¹ INSERM, U 1059 SAINBIOSE, Université Jean Monnet, Saint-Etienne, France.

² Université de Strasbourg, INSERM, Etablissement Français du Sang (EFS) Grand Est, BPPS UMR_S1255, Fédération de Médecine Translationnelle de Strasbourg (FMTS), Strasbourg, France.

³ Division of Hematology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA.

⁴ Etablissement Français du Sang Auvergne-Rhône-Alpes, Saint-Étienne, France.

: equal contributions

Correspondence to : * Dr Fabrice Cognasse, PhD, Etablissement Français du Sang Auvergne-Rhône-Alpes and INSERM 1059, Université de Saint-Etienne, Etablissement Français du Sang Auvergne-Rhône-Alpes-Auvergne, 25 Boulevard Pasteur, 42100 Saint-Etienne. Telephone: +33 (0) 683975883; Fax: +33 (0) 477421486; Email: fabrice.cognasse@efs.sante.fr

Authors' Contribution

FC and HHC contributed equally to the conceptualization. FC, BL, MPL and HHC contributed to the literature review, drafting, and critical revision of the manuscript. Artificial intelligence assistance (ChatGPT, OpenAI) was used solely for language editing, including grammar and spelling correction, sentence structure improvement, and optimization of figure presentation. The scientific content, data interpretation, and conclusions were developed entirely independently by the authors, who retained full control over the intellectual content of the manuscript and assume full responsibility for it.

Disclosures

No conflicts of interest to disclose.

Acknowledgements. We thank the medical and scientific staff of the Établissement Français du Sang for their continued support of our transfusion research activities. We are also deeply grateful to all blood donors whose generosity and commitment make transfusion research possible and contribute substantially to the advancement of our work. This work was supported by grants from the Établissement Français du Sang, the Association “Les Amis de Rémi” (Savigneux, France), and the French Agence Nationale de la Recherche (ANR, National Research Agency) under grant numbers ANR-22-CE17-0063 (HEASY_PLAT) and ANR-23-ASTR-0012-01 (PEDESTAL).

Abstract

Platelet transfusion remains indispensable for the prevention and treatment of bleeding in hematology, oncology, transplantation, critical care, surgery and trauma. Yet the biological impact of a platelet concentrate extends well beyond numerical correction of thrombocytopenia. Platelets are anucleate but metabolically active immune cells that express pattern-recognition receptors, release cytokines, chemokines, lipid mediators, extracellular vesicles, mitochondria-derived material and damage-associated molecular patterns; and interact with leukocytes, endothelial cells and complement. During collection, processing and storage, platelet concentrates acquire a distinct product-specific phenotype shaped by donor biology, residual plasma, additive solutions, leukoreduction, pathogen reduction, temperature and storage time. These variables affect not only post-transfusion recovery and hemostatic function, but also inflammatory signaling and immune related complications. The recipient is equally important: sepsis, chemotherapy, malignancy, neonatal immune development, endothelial activation and prior alloimmunization can determine whether transfused platelets restore hemostasis, amplify inflammation, or trigger refractoriness. This review explores platelet transfusion through the lens of a biological triad formed by the donor, the platelet product, and the recipient. We focus on how platelet immune receptors, storage-induced inflammatory remodeling, soluble biological response modifiers, extracellular vesicles and complement shape the interactions of transfused platelets with recipient leukocytes and endothelium. Alloimmunization and refractoriness are considered more briefly as recipient-dependent modifiers of platelet recovery and transfusion efficacy. The central challenge is no longer to define a single optimal platelet product, but to engineer and select the right platelet product for the right patient, at the right moment.

Introduction: platelet transfusion at the crossroads of hemostasis and immunity

Platelet transfusion has traditionally been framed as a replacement therapy: when the platelet count is too low, or platelet function is insufficient, donor platelets are administered to prevent or control bleeding. This remains clinically correct. Prophylactic transfusion thresholds in hypoproliferative thrombocytopenia, higher targets before procedures, and therapeutic transfusion during active bleeding all reflect a long history of practice supported by randomized trials and guidelines (1-6). In hematology, platelet transfusion has made intensive chemotherapy and hematopoietic stem cell transplantation safer; in trauma, surgery and intensive care, it remains a central component of hemorrhage management. Yet this pragmatic view captures only part of the biology. A platelet concentrate is not simply a bag of hemostatic fragments. It is a living, metabolically active, donor-derived cellular product, infused into a recipient whose vasculature and immune system are almost never at baseline.

Over the past two decades, platelets have been repositioned at the interface between hemostasis, innate immunity and inflammation. They express receptors able to detect microbial and endogenous danger signals; they release hundreds of stored and newly synthesized mediators; and they engage neutrophils, monocytes, dendritic cells, lymphocytes and endothelial cells through both contact-dependent and soluble pathways (7-13). The principal pathways linking the platelet product to recipient inflammatory and vascular responses are summarized in **Figure 1**.

This biology is directly relevant to transfusion medicine. Each platelet transfusion delivers not only hemostatic cells but also an immune-active cellular and acellular cargo comprising soluble biological response modifiers, extracellular vesicles, residual plasma proteins and platelets whose phenotype has been modified by preparation and storage. These components may interact with recipient leukocytes, complement and endothelium, producing beneficial, neutral or potentially harmful effects according to the clinical indication and the recipient context (9, 10, 13).

The purpose of this review is therefore to shift the paradigm of platelet transfusion from a count-based, quantitative approach to a biologically driven, qualitative model. We propose that platelet transfusion should be understood through three interacting layers: the donor, who determines the initial platelet and plasma signature; the product, whose immune and hemostatic phenotype is shaped by preparation and storage; and the recipient, whose inflammatory state determines response. This framework does not replace classical transfusion criteria, but it explains why the same platelet component can have different effects in different patients. It also provides a rationale for developing diversified platelet inventories, in which room-temperature, pathogen-reduced, cold-stored, washed, additive-solution or otherwise modified components are selected according to clinical purpose rather than tradition. The interactions among donor biology, product manufacturing and recipient susceptibility are represented in **Figure 2**.

Platelets as transfusion products: from count correction to biological function

The most common practical objective of platelet transfusion is to increase the platelet count sufficiently to reduce bleeding risk. In stable adults with therapy-induced hypoproliferative thrombocytopenia, prophylactic transfusion at a threshold of approximately $10 \times 10^9/L$ remains a widely accepted standard, although patient-specific factors such as fever, infection, coagulopathy, systemic inflammation, invasive procedures and active bleeding modify practice (2-4). Trials comparing prophylactic with no-prophylaxis strategies in haematological malignancies have confirmed that omitting prophylaxis reduces platelet exposure but increases bleeding in relevant subgroups. This supports the continued use of prophylaxis in many high-risk haematology settings (1, 5, 6). These data remain essential, but they are built largely around numerical thresholds and bleeding endpoints. They provide less information about the biological quality of the infused platelets, the inflammatory content of the product, or the immune condition of the recipient.

Post-transfusion efficacy is often assessed using the corrected count increment (CCI) or related measures, which normalize the platelet count rise for body size and platelet dose. These indices are indispensable for diagnosing refractoriness and for comparing product performance, but they cannot capture all dimensions of platelet function. Platelet concentrates differ in their ability to circulate, adhere, aggregate, support thrombin generation, interact with leukocytes, release mediators, or modulate endothelium, which may be mutually exclusive. These dimensions may diverge. The optimal characteristics of a platelet product depend on the clinical objective. Products with enhanced immediate hemostatic function may display reduced post-transfusion recovery and survival, whereas products that achieve higher and more sustained platelet count increments may be less effective for the rapid control of active bleeding. This trade-off is increasingly relevant for cold-stored platelets, pathogen-reduced components, and platelet additive solutions, which differentially affect platelet function, persistence, and safety (14-16).

The method of manufacture also matters. Apheresis platelets and pooled whole-blood-derived platelets differ in donor exposure, residual plasma volume, leukocyte burden, and activation state. Leukoreduction reduces HLA alloimmunization and febrile reactions but cannot eliminate platelet-derived mediators (17). Platelet additive solutions decrease plasma exposure and may attenuate some allergic or complement-mediated effects, but their impact depends on formulation and residual plasma (18, 19). Pathogen-reduction technologies improve infectious safety, yet their effects on platelet metabolism, membrane integrity, mitochondrial function, mediator release and post-transfusion recovery vary by platform. Similarly, storage temperature is no longer a neutral technical detail. Room-temperature storage supports circulation but favors bacterial growth and progressive storage lesions; cold storage reduces bacterial risk and promotes a more procoagulant phenotype, but accelerates clearance (16, 18, 20-23). These observations have challenged the prior assumptions that all platelet transfusions share the same goal. Instead, current state of the art in platelet transfusion medicine must ask which platelet product biology is best

suited to a defined clinical situation. Importantly, these product characteristics do not all operate at the same stage of the transfusion chain. Preparation method, leukoreduction, residual plasma, additive solution and pathogen reduction are determined during manufacturing, whereas storage temperature and duration are logistical variables that remain available at component issue and transfusion.

Platelets as immune cells: receptors, granules, extracellular vesicles and inflammatory signaling

Platelets are uniquely positioned to translate vascular injury into immune signaling. Their surface contains classical hemostatic receptors, including GPIb-IX-V, GPVI and integrins, but also multiple immune receptors. Among these, Toll-like receptors (TLRs) have received particular attention. Human platelets express transcripts for several TLRs and show functional responses through TLR2, TLR4, TLR7 and TLR9 in particular (15, 24-26). TLR4 recognizes lipopolysaccharide and endogenous danger-associated molecular patterns, including high-mobility group box 1 (HMGB1), whereas TLR9 recognizes unmethylated CpG-rich DNA motifs present in microbial DNA and mitochondrial DNA (15, 24-27). These receptors not only identify platelets as immune sentinels but also provide the mechanisms through which infection, tissue damage, and storage-derived danger signals can modulate platelet behavior. TLR stimulation can promote platelet activation, alpha-granule secretion, soluble CD40 ligand release, platelet-leukocyte aggregate formation and neutrophil extracellular trap generation, with effects that vary according to agonist, priming state and experimental conditions (24-27).

The platelet secretome is central to this immune function. Alpha-granules contain chemokines and cytokine-like mediators such as platelet factor 4/CXCL4, CCL5/RANTES, CXCL7, transforming growth factor-beta, vascular growth factors, P-selectin and CD40 ligand. Dense granules release ADP, ATP, serotonin, polyphosphates and calcium. Activated platelets also generate lipid mediators and expose phosphatidylserine, amplifying coagulation and inflammatory signaling (8, 10, 11). The principal platelet-derived soluble and vesicular mediators considered relevant to transfusion are summarized in **Table 1**. The CD40L/CD40 axis is particularly relevant in transfusion. CD40L is stored in platelets and released as both membrane-associated and soluble forms during activation and storage. Soluble CD40L can activate endothelial cells, B cells, monocytes and neutrophils, and has been repeatedly implicated in febrile non-hemolytic reactions, inflammatory transfusion reactions and two-hit models of lung injury (14, 28-30).

Platelets also communicate through extracellular vesicles (7, 31-34). Platelet-derived extracellular vesicles are generated during physiological activation and during storage, and can carry phosphatidylserine, tissue factor-associated procoagulant activity, HLA molecules, cytokines, microRNAs, mitochondrial proteins and even mitochondria-associated damage signals (7, 31-34). They are smaller and more diffusible than intact platelets, and may cross biological barriers more easily. This makes them plausible mediators of systemic effects after

transfusion, especially in recipients with endothelial dysfunction. MicroRNA transfer from platelet vesicles to endothelial or immune cells provides an additional layer of regulation, although its quantitative importance in transfusion recipients remains incompletely defined (31-34). Importantly, extracellular vesicles are not uniformly harmful. Depending on cargo, context and recipient state, they may promote hemostasis, inflammation, immune regulation or tissue repair (7). The field now needs assays able to distinguish vesicle subsets and functions rather than simply counting total vesicle numbers.

Complement provides another bridge between platelet products and inflammation. Platelets store complement components, bind complement regulators and can both activate and respond to complement fragments. During storage, complement activation products accumulate in platelet concentrates, particularly in plasma-rich conditions, while platelet additive solutions may reduce but not abolish this accumulation (19). Anaphylatoxins such as C3a and C5a can stimulate immune cells, increase vascular permeability and amplify inflammatory cascades, although their short half-life complicates measurement and interpretation. Complement also intersects with HLA antibody-mediated platelet clearance and with inflammatory transfusion reactions. Thus, complement should not be treated as a separate system; it is part of the same platelet-centered inflammatory network.

Storage lesion as an inflammatory amplifier

The platelet storage lesion has often been described as a gradual decline in product quality: pH falls, lactate accumulates, swirling decreases, discoid morphology is lost, platelet activation markers rise, aggregation responses deteriorate and platelet recovery after transfusion declines. This view remains useful, but it is incomplete. Storage is not simply passive aging. It is an *ex vivo* biological process in which platelets experience non-physiological temperature, agitation, gas exchange, plastic surfaces, residual leukocyte and plasma effects, metabolic stress, oxidative injury, mitochondrial perturbation and repeated mechanical stimulation. The result is not only a progressive alteration in platelet functional characteristics, but also a transformation of the inflammatory profile of the product (11, 14, 35).

Several changes are particularly relevant to transfusion reactions. Stored platelets progressively expose P-selectin and phosphatidylserine, shed extracellular vesicles, release alpha-granule contents and activate apoptotic or apoptosis-like pathways. Soluble mediators such as CD40L, PF4, soluble P-selectin, growth factors and bioactive lipids accumulate in the supernatant (11, 29, 30, 36). Experiments in animal models have shown that aged platelet supernatants can induce lung inflammation and coagulopathy, especially when the recipient has been primed by a first inflammatory hit such as lipopolysaccharide exposure (37-39). This is biologically relevant: stored platelet products contain mediators that prime neutrophils, activate endothelium and contribute to platelet-leukocyte

interactions. The clinical expression may be fever, chills, allergic-type symptoms, dyspnea or, in susceptible settings, a contribution to transfusion-related acute lung injury.

Damage-associated molecules add a further dimension. HMGB1 and mitochondrial DNA are released or accumulate during platelet storage and have been associated with transfusion adverse reactions in observational studies (32, 36, 40). Their relevance lies in their receptor biology. HMGB1 can signal through TLR4, TLR2 and RAGE, whereas mitochondrial DNA can activate TLR9 and inflammasome-related pathways. Platelets are therefore not only sources of these mediators; they may also sense them. This creates the possibility of an autocrine or paracrine amplification loop within the platelet concentrate: storage stress promotes release of HMGB1, mitochondrial material and vesicles; these signals activate platelet immune receptors; further activation increases mediator release and vesiculation. The strength of this model is that it connects storage lesion, innate immune activation, and transfusion reactions within the framework of sterile inflammation, highlighting how endogenous danger signals generated during storage may modulate recipient responses even in the absence of bacterial contamination or overt hemolysis.

However, storage lesions should not be reduced to a simple harmful scale in which “older” always means “worse.” Some storage-induced phenotypes may be useful in specific indications. Cold-stored platelets illustrate this point. Refrigeration promotes platelet activation, cytoskeletal remodeling, desialylation and faster clearance, but may preserve or enhance immediate hemostatic properties and thrombin generation (16, 18, 20, 22, 23). The same biological shift that is undesirable for prophylaxis in marrow failure may be advantageous in active bleeding, when duration of platelet circulation is less important but immediate effects on thrombin generation and hemostatic potential are more important. Pathogen reduction offers another example. It can impose platform-specific metabolic and functional stress while reducing infectious risk. Its effects cannot, however, be considered independently of storage temperature. Refrigeration and pathogen reduction modify partly overlapping biological processes, including platelet metabolism, membrane organization, activation, phosphatidylserine exposure and hemostatic function. The phenotype of a pathogen-reduced platelet stored at room temperature may therefore differ from that of the same product stored under refrigeration. The net effect depends on the pathogen-reduction platform, residual plasma, additive solution and storage duration and should not be extrapolated from either intervention studied in isolation. The next generation of platelet quality assessment must therefore move beyond generic storage time and incorporate intended use. The major manufacturing and storage variables that may shape platelet immune and hemostatic phenotypes are summarized in **Table 2**.

The recipient matters: inflammatory status, age, disease context, and immune history

Transfusion biology cannot be understood by examining the transfused product alone. Platelet recipients may have varying degrees of inflammation, infection, bleeding, immunosuppression, endothelial injury, alloimmunization or developmental immaturity. This matters because many transfusion complications follow a threshold-and-hit logic. A mediator concentration that is harmless in a stable recipient may be clinically relevant in a patient whose neutrophils or endothelium are already primed. The two-hit model of transfusion-related acute lung injury remains a useful paradigm: recipient inflammation induces pulmonary endothelial activation and neutrophil sequestration; transfused biological response modifiers then provide additional priming or activation signals (37-39). Although not every platelet reaction fits this model, it captures a broader principle: transfusion outcome depends on the interaction between the specific state of the transfused product and host susceptibility.

Haematology patients provide a particularly complex setting. Acute leukemia, chemotherapy, infection, mucosal injury, broad-spectrum antibiotics and stem cell transplantation reshape innate and adaptive immunity. In this context, platelet transfusions are frequent, repeated and often administered during inflammatory instability. Chemotherapy-induced lymphopenia was once expected to reduce alloimmunization, but translational work suggests that homeostatic immune recovery, BAFF elevation and altered T-cell help may instead enhance alloantibody formation in certain settings (9, 41). Clinical studies in acute myeloid leukemia indicate that alloimmunized patients may have more activated CD4⁺ T-cell profiles, with increased follicular helper signatures and CD40/TLR ligand expression, whereas non-alloimmunized patients show more regulatory features (42). This supports the view that the recipient immune state is not background noise; it is a determinant of platelet transfusion immunogenicity.

Neonates represent an even clearer example of recipient specificity. Adult donor platelets are transfused into a developmental hemostatic and immune system that is not simply a smaller version of the adult system. Compared with adult platelets, neonatal platelets are relatively hyporeactive to several G-protein-coupled and immunoreceptor agonists and show reduced agonist-induced degranulation, P-selectin exposure, integrin activation and aggregation. This cellular hyporeactivity is partly compensated by developmentally specific properties of neonatal blood, including increased von Willebrand factor activity and larger von Willebrand factor multimers, which can support platelet adhesion under flow (43-46). At the same time, neonatal innate immunity, endothelial responses and inflammatory regulation are developmentally distinct (44, 45, 47). The PlaNeT-2 trial challenged long-standing assumptions by showing that a liberal prophylactic platelet threshold in preterm neonates increased death or major bleeding compared with a more restrictive strategy (48). Mechanistic explanations remain under investigation, but preclinical and clinical studies suggest that the transfusion of platelets from adult donors may alter neonatal inflammatory mediators, immune cell migration and systemic responses (44, 45, 49, 50). Recent pediatric

hemovigilance data also reinforce the need for age-specific transfusion science. Platelet products appear to have the highest transfusion reaction rates among pediatric blood components, with allergic and febrile non-hemolytic reactions predominating (51). These observations should not be dismissed as reporting artifacts. They suggest that platelet-rich products derived from adult donors have a particular inflammatory potential, and that pediatric recipients may react to that potential differently than adult recipients. Future clinical trials should therefore avoid treating all platelet recipients as interchangeable. Recipient age, disease, inflammatory biomarkers, endothelial activation, microbiome status, prior transfusion history and alloimmune background should be incorporated into risk models and product selection algorithms. The principal recipient contexts, biological concerns and potential product strategies discussed in this Review are summarized in **Table 3**.

Alloimmune history and refractoriness as modifiers of platelet transfusion response

Platelet transfusion refractoriness is an important modifier of transfusion efficacy, although most cases are non-immune and are associated with bleeding, fever, infection, sepsis, disseminated intravascular coagulation, splenic sequestration, graft-versus-host disease, drugs or poor product quality (52). When immune mechanisms are involved, anti-HLA class I antibodies predominate, whereas antibodies against human platelet antigens, ABO incompatibility and drug-dependent antibodies are less frequent. Leukoreduction reduces HLA alloimmunization and alloimmune refractoriness but does not eliminate exposure to HLA class I molecules expressed by the platelets themselves (17).

Single-donor apheresis platelet components expose the recipient to one donor per transfusion, whereas a therapeutic dose of pooled whole-blood-derived platelets typically represents exposure to four or five donors. This difference provides a theoretical rationale for reducing donor exposure. However, available comparative evidence has not demonstrated consistently that apheresis platelets reduce alloimmunization or immune refractoriness compared with contemporary leukoreduced pooled products. A systematic review concluded that the available evidence was insufficient to establish a difference in alloimmunization between the two product types (53-56). The clearest advantages of apheresis components in alloimmunized patients therefore relate to donor traceability and the ability to provide HLA- or HPA-selected products rather than to a proven intrinsic reduction in alloimmunization risk.

In the context of this Review, alloimmunization should therefore be regarded primarily as a recipient-state variable that affects platelet recovery, clearance and product selection rather than as the principal immune effect of transfused platelets. Crossmatch-compatible, HLA-matched, antibody-specificity-predicted or eplet-compatible platelets remain important for established immune refractoriness (52, 57-60). Future predictive approaches should integrate antibody specificity and strength with donor antigen expression, infection, inflammation, chemotherapy phase, immune reconstitution and transplantation status.

Transfusion reactions and candidate biomarkers: from hemovigilance to mechanistic prediction

Platelet components are overrepresented in several reaction categories compared with red blood cells, partly because they contain plasma, are stored at room temperature, undergo progressive activation and carry high concentrations of inflammatory mediators (11, 28, 29, 51). Febrile non-hemolytic reactions interrupt transfusion support, trigger investigations and may mask infection. Allergic reactions can occur and may recur in susceptible patients, potentially requiring product modification. Respiratory reactions, including transfusion-associated circulatory overload and transfusion-related acute lung injury, are less frequent but potentially severe.

The search for biomarkers predictive of post-transfusion complications has proved productive, but has not yet yielded definitive results. Soluble CD40L remains one of the strongest candidates. It accumulates during platelet storage, primes neutrophils, activates endothelial and immune cells, and has been associated with adverse reactions in threshold-and-hit models (28-30). HMGB1 and mitochondrial DNA extend this concept to damage-associated molecular patterns, linking platelet storage to innate immune receptors and sterile inflammation (32, 36, 40). Soluble P-selectin and CD62P expression reflect platelet activation and leukocyte-binding potential. Extracellular vesicle subsets, particularly those bearing mitochondria or phosphatidylserine, may provide functional readouts of inflammatory and procoagulant capacity. Complement split products may indicate plasma-driven activation and recipient susceptibility. However, no single mediator is likely to predict all post-platelet transfusion reactions. Future predictive strategies will likely require a multimarker approach, combining complementary biological signals rather than relying on a single biomarker. An effective biomarker panel should provide high sensitivity and specificity, with strong positive and negative predictive values, while offering a clinically relevant predictive window to enable early intervention. In addition, these biomarkers should be measurable using robust, rapid, and cost-effective assays compatible with routine transfusion practice.

A practical predictive framework should distinguish variables according to where and when they can be controlled or measured. The first group comprises manufacturing variables, including preparation method, leukoreduction, residual plasma or platelet additive solution, washing and pathogen reduction. These variables are determined primarily within blood establishments and must remain sufficiently standardized to preserve safety, scalability, inventory management and economic feasibility.

The second group comprises storage and logistical variables, particularly storage temperature, storage duration and time from collection to transfusion. These data are already available at component issue and can therefore be incorporated into clinical studies and future decision-support systems without requiring additional laboratory testing. Storage duration may be particularly informative because it integrates the cumulative biological effects of ex vivo

storage, although its clinical relevance is likely to depend on the preparation method, storage condition and transfusion indication.

The third group comprises late-accumulating soluble or vesicular biomarkers, including sCD40L, HMGB1, mitochondrial DNA, extracellular-vesicle subsets and complement activation products. Routine measurement of these biomarkers before every transfusion is currently unlikely to be technically or economically feasible. Their concentrations may be relatively low immediately after manufacture and become more informative later, when the components have reached hospital transfusion services. For this reason, mediator profiling should initially be incorporated into prospective studies using samples collected at component issue or immediately before transfusion. These final-product measurements should then be linked to recipient characteristics and standardized clinical outcomes. Near-term risk stratification should rely primarily on manufacturing and storage variables already captured in blood-establishment and hospital information systems, while biomarker panels remain research tools requiring clinical validation.

Beyond clinical and biological characteristics, recipient genetic factors may also contribute to variability in transfusion responses. HLA haplotypes and other immune-related genetic variants could influence the threshold of immune activation and susceptibility to transfusion-related complications. Although their predictive value remains to be established, these factors represent a potential additional layer for future multimodal risk assessment. Importantly, biomarkers should be validated against clinically standardized outcomes and not merely against laboratory activation markers. A high mediator level may be biologically interesting but clinically irrelevant unless it improves prediction, prevention or product selection.

Toward personalized platelet transfusion: matching product biology to clinical need

An illustrative framework linking dominant clinical needs to purpose-built platelet profiles is presented in **Figure 3**. The future of platelet transfusion will likely involve a diversified inventory rather than a universal product. Conventional room-temperature platelets remain appropriate for many hypoproliferative patients because post-transfusion recovery and survival are critical. Pathogen-reduced platelets may be preferred when infectious safety, inventory simplicity or regulatory strategy is prioritized, provided the expected platelet increment and bleeding context are considered. Washed or plasma-reduced platelets may help selected patients with recurrent allergic reactions. HLA-selected products remain essential for alloimmune refractoriness. Cold-stored platelets may serve a different purpose: immediate hemostatic support in active bleeding, trauma, surgery or massive transfusion, where rapid clot formation and thrombin generation may matter more than long-term circulation (16, 18, 20, 22, 23).

Cold-stored platelets have forced the field to reconsider what platelet quality means. The old objection was that refrigerated platelets are cleared too rapidly. This remains relevant for prophylaxis, but it does not automatically rule

them out for therapeutic use, such as in cases of haemorrhage. Recent human studies show a functional divergence: room-temperature platelets may better restore integrin-dependent aggregation after aspirin exposure, whereas cold-stored platelets may enhance thrombin generation and procoagulant activity (22). Experimental work combining cold storage with pathogen reduction further suggests that a cold hemostatic phenotype can be partly preserved, although late storage may compromise clot strength depending on platform and duration (21). These data should not be interpreted as a contest between cold and room temperature. They indicate that different storage conditions manufacture different platelet phenotypes.

Pathogen reduction, additive solutions and storage temperature should therefore be treated as design variables. Their effects are not fixed; they depend on the platform, residual plasma, donor characteristics, platelet preparation method and clinical endpoint. For example, a product with lower metabolic activity but reduced clot firmness late in storage may still be useful if transfused early for bleeding but less desirable for prolonged prophylaxis. A product with lower plasma content may reduce allergic or complement-mediated effects but alter platelet recovery or mediator dilution. The central regulatory challenge is that many current quality metrics were designed for conventional room-temperature platelets and may not capture the intended function of alternative products.

A personalized platelet transfusion strategy can be conceptualized as a donor-product-recipient triangle. The art of transfusion medicine is to align several variables rather than to optimize one in isolation. Although the clinical relevance of donor and product characteristics has sometimes been questioned, recent donor-component-recipient linked studies indicate that platelet components are not biologically interchangeable. In a large pediatric cohort, storage in platelet additive solution, pathogen reduction, storage beyond three days, male donor sex and donor age of 40 years or older were independently associated with lower post-transfusion platelet increments. Platelet additive solution, pathogen reduction, longer storage and older donor age were also associated with a greater subsequent platelet transfusion burden, although these characteristics were not associated with hospital length of stay or mortality. In a separate adult vein-to-vein cohort, donor and product characteristics, including donor body mass index, platelet concentration, pathogen reduction, platelet additive solution, component splitting and storage duration, were associated with post-transfusion platelet increments and/or subsequent red-cell requirements. These observational associations do not yet justify prescriptive product-allocation algorithms, but they challenge the assumption that donor and product characteristics are clinically irrelevant and support prospective, indication-specific validation (61, 62).

Several research priorities follow. First, paired donor-component-recipient biobanks should be embedded within hemovigilance programs, linking manufacturing data, storage conditions, mediator profiles, vesicle signatures and functional assays to standardized clinical outcomes. Second, platelet quality testing should include both hemostatic and immune-inflammatory dimensions, such as thrombin generation, viscoelastic clot formation, platelet-leukocyte

aggregate formation, extracellular-vesicle phenotyping and DAMP quantification. Third, randomized and prospective studies should be indication-specific because prophylaxis in marrow failure, active surgical or traumatic bleeding, neonatal thrombocytopenia and alloimmune refractoriness represent biologically distinct questions.

The scale of this research should not be underestimated. Each transfusion episode represents a unique combination of donor biology, manufacturing process, storage trajectory and recipient state. Robust predictive models will therefore require very large, multicenter, donor-component-recipient linked datasets, repeated transfusion episodes and sufficient representation of uncommon products and recipient phenotypes. Artificial intelligence may help integrate these high-dimensional data, but only if the variables and clinical outcomes are standardized, biologically interpretable and externally validated.

Such studies will require coordinated partnerships among blood establishments, hospital transfusion services, hematologists, intensivists, neonatologists, surgeons, immunologists, platelet biologists, hemovigilance specialists, biostatisticians, bioinformaticians and data engineers. Harmonized component identifiers, common data models and prospective sample collection at the time of transfusion will be essential to move from statistical associations to actionable product-selection strategies. Finally, the development of ex vivo-derived platelets should consider that distinct clinical situations may require different platelet phenotypes and that a single universal platelet product may not be optimal for all indications.

Conclusion

Platelet transfusion has entered a conceptual transition. It remains an essential life-saving hemostatic therapy, but it should no longer be viewed only as a numerical correction of thrombocytopenia. Transfused platelets carry receptors, granules, soluble mediators, vesicles, mitochondria-associated signals and alloantigens. During storage, they acquire a manufactured phenotype that may promote circulation, hemostasis, inflammation, clearance or immune recognition depending on processing and conditions. The recipient determines how this product phenotype is expressed clinically. The optimal platelet product is therefore not universal: each patient requires a platelet biology tailored to the clinical context, transfusion objective, and recipient state. A patient with life-threatening hemorrhage may benefit from a product biased toward immediate thrombin generation; a patient with marrow failure may need platelets that circulate longer; a preterm neonate or septic patient may be vulnerable to excessive inflammatory amplification. The next advance in transfusion medicine will therefore come from integrating platelet physiology with product engineering and recipient immunology. The goal is not one ideal platelet concentrate, but a rational inventory of purpose-built platelet products matched to the right patient at the right time.

Bibliographies

1. Crichton GL, Estcourt LJ, Wood EM, et al. A therapeutic-only versus prophylactic platelet transfusion strategy for preventing bleeding in patients with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation. *Cochrane Database Syst Rev*. 2015;2015(9):CD010981.
2. Kaufman RM, Djulbegovic B, Gernsheimer T, et al. Platelet transfusion: a clinical practice guideline from the AABB. *Ann Intern Med*. 2015;162(3):205-213.
3. Metcalf RA, Dhiman P, Stanworth SJ. Personalized platelet transfusion predictions for neonates. *JAMA*. 2025;334(14):1240-1242.
4. Metcalf RA, Nahiriak S, Guyatt G, et al. Platelet transfusion: 2025 AABB and ICTMG international clinical practice guidelines. *JAMA*. 2025;334(7):606-617.
5. Stanworth SJ, Estcourt LJ, Powter G, et al. A no-prophylaxis platelet-transfusion strategy for hematologic cancers. *N Engl J Med*. 2013;368(19):1771-1780.
6. Stanworth SJ, Walsh TS, Prescott RJ, et al. Thrombocytopenia and platelet transfusion in UK critical care: a multicenter observational study. *Transfusion*. 2013;53(5):1050-1058.
7. Burnouf T, Chou ML, Lundy DJ, Chuang E-Y, Tseng C-L, Goubran H. Expanding applications of allogeneic platelets, platelet lysates, and platelet extracellular vesicles in cell therapy, regenerative medicine, and targeted drug delivery. *J Biomed Sci*. 2023;30(1):79.
8. Cognasse F, Hally K, Fauteux-Daniel S, et al. Effects and side effects of platelet transfusion. *Hamostaseologie*. 2021;41(2):128-135.
9. Jackman RP, Thomas KA. Immune response to platelet transfusions. *Curr Opin Hematol*. 2025;32(6):357-363.
10. Mandel J, Casari M, Stepanyan M, Martyanov A, Deppermann C. Beyond hemostasis: platelet innate immune interactions and thromboinflammation. *Int J Mol Sci*. 2022;23(7):3868.
11. Morrell CN. Immunomodulatory mediators in platelet transfusion reactions. *Hematology Am Soc Hematol Educ Program*. 2011;2011:470-474.

12. Scherlinger M, Richez C, Tsokos GC, Boillard E, Blanco P. The role of platelets in immune-mediated inflammatory diseases. *Nat Rev Immunol*. 2023;23(8):495-510.
13. Semple JW, Italiano JE Jr, Freedman J. Platelets and the immune continuum. *Nat Rev Immunol*. 2011;11(4):264-274.
14. Cognasse F, Duchez AC, Audoux E, et al. Platelets as key factors in inflammation: focus on CD40L/CD40. *Front Immunol*. 2022;13:825892.
15. Hally K, Fauteux-Daniel S, Hamzeh-Cognasse H, Larsen P, Cognasse F. Revisiting platelets and toll-like receptors (TLRs): at the interface of vascular immunity and thrombosis. *Int J Mol Sci*. 2020;21(17):6150.
16. Marini I, Aurich K, Jouni R, et al. Cold storage of platelets in additive solution: the impact of residual plasma in apheresis platelet concentrates. *Haematologica*. 2019;104(1):207-214.
17. Trial to Reduce Alloimmunization to Platelets Study Group. Leukocyte reduction and ultraviolet B irradiation of platelets to prevent alloimmunization and refractoriness to platelet transfusions. *N Engl J Med*. 1997;337(26):1861-1869.
18. Capocelli KE, Dumont LJ. Novel platelet storage conditions: additive solutions, gas, and cold. *Curr Opin Hematol*. 2014;21(6):491-496.
19. de Wit YES, Vlaar R, Gouwerok E, et al. Platelet concentrates in platelet additive solutions generate less complement activation products during storage than platelets stored in plasma. *Blood Transfus*. 2023;21(2):157-167.
20. Aurich K, Wesche J, Ulbricht M, et al. Divalent magnesium restores cytoskeletal storage lesions in cold-stored platelet concentrates. *Sci Rep*. 2022;12(1):6229.
21. Jimenez-Marco T, Torres-Reverte N, Quetglas-Oliver M, Morell-Garcia D, Ballester-Servera C. Comparison between cold-stored platelets treated with riboflavin and UV light versus untreated cold-stored platelets. *Blood Transfus*. 2026;24(4):325-333.
22. Kogler VJ, Miles JA, Özpolat T, et al. Platelet dysfunction reversal with cold-stored vs room temperature-stored platelet transfusions. *Blood*. 2024;143(20):2073-2088.
23. Stranden G, Sivertsen J, Bjerkvig CK, et al. A pilot trial of platelets stored cold versus at room temperature for complex cardiothoracic surgery. *Anesthesiology*. 2020;133(6):1173-1183.
24. Andonegui G, Kerfoot SM, McNagny K, et al. Platelets express functional Toll-like receptor-4. *Blood*. 2005;106(7):2417-2423.

25. Cognasse F, Nguyen KA, Damien P, et al. The inflammatory role of platelets via their TLRs and siglec receptors. *Front Immunol*. 2015;6:83.
26. Cognasse F, Lafarge S, Chavarin P, Acquart S, Garraud O. Lipopolysaccharide induces sCD40L release through human platelets TLR4, but not TLR2 and TLR9. *Intensive Care Med*. 2007;33(2):382-384.
27. Panigrahi S, Ma Y, Hong L, et al. Engagement of platelet toll-like receptor 9 by novel endogenous ligands promotes platelet hyperreactivity and thrombosis. *Circ Res*. 2013;112(1):103-112.
28. Cognasse F, Sut C, Fromont E, et al. Platelet soluble CD40-ligand level is associated with transfusion adverse reactions in a mixed threshold-and-hit model. *Blood*. 2017;130(11):1380-1383.
29. Khan SY, Kelher MR, Heal JM, et al. Soluble CD40 ligand accumulates in stored blood components, primes neutrophils through CD40, and is a potential cofactor in the development of transfusion-related acute lung injury. *Blood*. 2006;108(7):2455-2462.
30. Sahler J, Spinelli S, Phipps R, Blumberg N. CD40 ligand (CD154) involvement in platelet transfusion reactions. *Transfus Clin Biol*. 2012;19(3):98-103.
31. Laffont B, Corduan A, Plé H, et al. Activated platelets can deliver mRNA regulatory Ago2•microRNA complexes to endothelial cells via microparticles. *Blood*. 2013;122(2):253-2561.
32. Marcoux G, Magron A, Sut C, et al. Platelet-derived extracellular vesicles convey mitochondrial DAMPs in platelet concentrates and their levels are associated with adverse reactions. *Transfusion*. 2019;59(7):2403-2414.
33. Boilard E, Duchez AC, Brisson A. The diversity of platelet microparticles. *Curr Opin Hematol*. 2015;22(5):437-444.
34. Boudreau LH, Duchez AC, Cloutier N, et al. Platelets release mitochondria serving as substrate for bactericidal group IIA-secreted phospholipase A2 to promote inflammation. *Blood*. 2014;124(14):2173-2183.
35. Liu C, Su Y, Guo W, Ma X, Qiao R. The platelet storage lesion, what are we working for? *J Clin Lab Anal*. 2024;38(1-2):e24994.
36. Cognasse F, Sut C, Hamzeh-Cognasse H, Garraud O. Platelet-derived HMGB1: critical mediator of SARs related to transfusion. *Ann Transl Med*. 2020;8(4):140.
37. Silliman CC, Bjornsen AJ, Wyman TH, et al. Plasma and lipids from stored platelets cause acute lung injury in an animal model. *Transfusion*. 2003;43(5):633-640.

38. Silliman CC, Boshkov LK, Mehdizadehkashi Z, et al. Transfusion-related acute lung injury: epidemiology and a prospective analysis of etiologic factors. *Blood*. 2003;101(2):454-462.
39. Vlaar AP, Hofstra JJ, Kulik W, et al. Supernatant of stored platelets causes lung inflammation and coagulopathy in a novel in vivo transfusion model. *Blood*. 2010;116(8):1360-1368.
40. Cognasse F, Hamzeh Cognasse H, Eyraud MA, et al. Assessment of the soluble proteins HMGB1, CD40L and CD62P during various platelet preparation processes and the storage of platelet concentrates: the BEST collaborative study. *Transfusion*. 2023;63(1):217-228.
41. Jackman RP, Darst O, Gaillard B, et al. Enhanced alloresponse to platelet transfusion due to immune dysregulation following ablative chemotherapy in mice. *Front Immunol*. 2023;14:1281123.
42. Khelfa M, Leclerc M, Kerbrat S, et al. Divergent CD4(+) T-cell profiles are associated with anti-HLA alloimmunization status in platelet-transfused AML patients. *Front Immunol*. 2023;14:1165973.
43. Baker-Groberg SM, Lattimore S, Recht M, McCarty OJ, Haley KM. Assessment of neonatal platelet adhesion, activation, and aggregation. *J Thromb Haemost*. 2016;14(4):815-827.
44. Davenport P, Sola-Visner M. Immunologic effects of red blood cell and platelet transfusions in neonates. *Curr Opin Hematol*. 2022;29(6):297-305.
45. Davenport P, Sola-Visner M. Platelets in the neonate: not just a small adult. *Res Pract Thromb Haemost*. 2022;6(3):e12719.
46. Shenkman B, Linder N, Savion N, et al. Increased neonatal platelet deposition on subendothelium under flow conditions: the role of plasma von Willebrand factor. *Pediatr Res*. 1999;45(2):270-275.
47. Ferrer-Marin F, Chavda C, Lampa M, et al. Effects of in vitro adult platelet transfusions on neonatal hemostasis. *J Thromb Haemost*. 2011;9(5):1020-1028.
48. Curley A, Stanworth SJ, Willoughby K, et al. Randomized trial of platelet-transfusion thresholds in neonates. *N Engl J Med*. 2019;380(3):242-251.
49. Moore CM, Lorusso A, Morgan L, et al. Safety and feasibility of platelet transfusion through long catheters in the neonatal intensive care unit: an in vitro study. *Arch Dis Child Fetal Neonatal Ed*. 2023;109(1):70-73.
50. Moore CM, O'Reilly D, McCallion N, Curley AE. Changes in inflammatory proteins following platelet transfusion in a neonatal population. *Pediatr Res*. 2023;94(6):1973-1977.

51. Stone EF, Chacreton D, Jimenez A, et al. Epidemiology of pediatric transfusion reactions. *JAMA Netw Open*. 2026;9(4):e269274.
52. Cohn CS. Platelet transfusion refractoriness: how do I diagnose and manage? *Hematology Am Soc Hematol Educ Program*. 2020;2020(1):527-532.
53. Gammon RR, Devine D, Katz LM, et al. Buffy coat platelets coming to America: are we ready? *Transfusion*. 2021;61(2):627-633.
54. Garraud O, Cognasse F, Tissot JD, et al. Improving platelet transfusion safety: biomedical and technical considerations. *Blood Transfus*. 2016;14(2):109-122.
55. Prudent M. What about platelet function in platelet concentrates? *Hamostaseologie*. 2020;40(4):500-508.
56. van der Meer PF. Platelet concentrates, from whole blood or collected by apheresis? *Transfus Apher Sci*. 2013;48(2):129-131.
57. Petz LD, Garratty G, Calhoun L, et al. Selecting donors of platelets for refractory patients on the basis of HLA antibody specificity. *Transfusion*. 2000;40(12):1446-1456.
58. Duquesnoy RJ. Structural epitope matching for HLA-alloimmunized thrombocytopenic patients: a new strategy to provide more effective platelet transfusion support? *Transfusion*. 2008;48(2):221-227.
59. Nambiar A, Duquesnoy RJ, Adams S, et al. HLAMatchmaker-driven analysis of responses to HLA-typed platelet transfusions in alloimmunized thrombocytopenic patients. *Blood*. 2006;107(4):1680-1687.
60. Seike K, Fujii N, Asano N, et al. Efficacy of HLA virtual cross-matched platelet transfusions for platelet transfusion refractoriness in hematopoietic stem cell transplantation. *Transfusion*. 2020;60(3):473-478.
61. Goel R, Karam O, Warden DE, et al. Platelet transfusion practices and outcomes in neonates and children. *JAMA Netw Open*. 2026;9(1):e2554531.
62. Roubinian NH, Plimier C, Thomas KA, et al. Associations of blood donor and product characteristics with platelet transfusion outcomes. *Blood Adv*. 2026;10(8):2582-2591.
63. Blumberg N, Spinelli SL, Francis CW, Taubman MB, Phipps RP. The platelet as an immune cell-CD40 ligand and transfusion immunomodulation. *Immunol Res*. 2009;45(2-3):251-260.

64. Aloui C, Prigent A, Sut C, et al. The signaling role of CD40 ligand in platelet biology and in platelet component transfusion. *Int J Mol Sci.* 2014;15(12):22342-22364.
65. Hamzeh-Cognasse H, Laradi S, Osselaer JC, Cognasse F, Garraud O. Amotosalen-HCl-UVA pathogen reduction does not alter poststorage metabolism of soluble CD40 ligand, Ox40 ligand and interleukin-27, the cytokines that generally associate with serious adverse events. *Vox Sang.* 2015;108(2):205-207.
66. Laflamme G, Hamzeh-Cognasse H, Cognasse F, Loubaki L. Pilot study on cannabis-induced alterations in platelet function: implications for transfusion medicine. *Platelets.* 2026;37(1):2644368.
67. Sut C, Tariket S, Aubron C, et al. The non-hemostatic aspects of transfused platelets. *Front Med (Lausanne).* 2018;5:42.
68. Tariket S, Sut C, Arthaud CA, et al. Modeling the effect of platelet concentrate supernatants on endothelial cells: focus on endocan/ESM-1. *Transfusion.* 2018;58(2):439-445.
69. Addas-Carvalho M, Origa AF, Saad ST. Interleukin 1 beta and tumor necrosis factor levels in stored platelet concentrates and the association with gene polymorphisms. *Transfusion.* 2004;44(7):996-1003.
70. Heestermans M, Arthaud CA, Prier A, et al. Association of high mobility group box 1 (HMGB1) levels with donor's age, sex and ABO blood group in single-donor apheresis platelet concentrates. *Vox Sang.* 2025;120(7):659-663.
71. Schleuning M, Böck M, Mempel W. Complement activation during storage of single-donor platelet concentrates. *Vox Sang.* 1994;67(2):144-148.
72. de Wit YES, Hamzeh-Cognasse H, Cognasse F, Ten Brinke A, Zeerleder SS. DAMPS and complement activation in platelet concentrates that induce adverse reactions in patients. *Transfusion.* 2022;62(9):1721-1726.
73. Cardigan R, Sutherland J, Wadhwa M, Dilger P, Thorpe R. The influence of platelet additive solutions on cytokine levels and complement activation in platelet concentrates during storage. *Vox Sang.* 2003;84(1):28-35.
74. Duchez AC, Fauteux-Daniel S, Ebermeyer T, et al. Lipidomic analysis of differently prepared platelet concentrates in additive solution during storage. *Blood Transfus.* 2023;21(5):409-421.
75. Duchez AC, Fauteux-Daniel S, Sut C, et al. Bioactive lipids as biomarkers of adverse reactions associated with apheresis platelet concentrate transfusion. *Front Immunol.* 2023;14:1031968.
76. Pavenski K, Freedman J, Semple JW. HLA alloimmunization against platelet transfusions: pathophysiology, significance, prevention and management. *Tissue Antigens.* 2012;79(4):237-245.

77. Refaai MA, Blumberg N. Transfusion immunomodulation from a clinical perspective: an update. *Expert Rev Hematol.* 2013;6(6):653-663.
78. Aloui C, Barlier C, Claverol S, et al. Differential protein expression of blood platelet components associated with adverse transfusion reactions. *J Proteomics.* 2019;194:25-36.
79. Garraud O, Hamzeh-Cognasse H, Chalayer E, et al. Platelet transfusion in adults: An update. *Transfus Clin Biol.* 2023;30(1):147-165.
80. Apelsest TO, Hervig TA, Wentzel-Larsen T, Bruserud O. Cytokine accumulation in photochemically treated and gamma-irradiated platelet concentrates during storage. *Transfusion.* 2006;46(5):800-810.
81. Prudent M, Crettaz D, Delobel J, Tissot JD, Lion N. Proteomic analysis of Intercept-treated platelets. *J Proteomics.* 2012;76 Spec No.:316-328.
82. Tauszig ME, Picker SM, Gathof BS. Platelet derived cytokine accumulation in platelet concentrates treated for pathogen reduction. *Transfus Apher Sci.* 2012;46(1):33-37.
83. Rebullà P, Prati D. Pathogen reduction for platelets-a review of recent implementation strategies. *Pathogens.* 2022;11(2):142.
84. Gulliksson H, AuBuchon JP, Cardigan R, et al. Storage of platelets in additive solutions: a multicentre study of the in vitro effects of potassium and magnesium. *Vox Sang.* 2003;85(3):199-205.
85. Picker SM, Speer R, Gathof BS. Evaluation of processing characteristics of photochemically treated pooled platelets: target requirements for the INTERCEPT Blood System comply with routine use after process optimization. *Transfus Med.* 2004;14(3):217-223.
86. Reddoch-Cardenas KM, Bynum JA, Meledeo MA, et al. Cold-stored platelets: a product with function optimized for hemorrhage control. *Transfus Apher Sci.* 2019;58(1):16-22.
87. van der Meer PF, Klei TR, de Korte D. Quality of platelets in stored whole blood. *Transfus Med Rev.* 2020;34(4):234-241.
88. Vamvakas EC. Relative safety of pooled whole blood-derived versus single-donor (apheresis) platelets in the United States: a systematic review of disparate risks. *Transfusion.* 2009;49(12):2743-2758.
89. Chou ML, Babamale AO, Walker TL, et al. Blood-brain crosstalk: the roles of neutrophils, platelets, and neutrophil extracellular traps in neuropathologies. *Trends Neurosci.* 2023;46(9):764-779.

90. Alhamad FA, Hussien A, Alqahtani F. Association between platelet transfusion and mortality rate among preterm neonates in the eastern province, Saudi Arabia. *Med Arch*. 2022;76(4):278-282.
91. Ferrer-Marín F, Sola-Visner M. Neonatal platelet physiology and implications for transfusion. *Platelets*. 2022;33(1):14-22.
92. Paglino JC, Pomper GJ, Fisch GS, Champion MH, Snyder EL. Reduction of febrile but not allergic reactions to RBCs and platelets after conversion to universal prestorage leukoreduction. *Transfusion*. 2004;44(1):16-24.
93. Kasperska-Zajac A, Rogala B. Platelet activation during allergic inflammation. *Inflammation*. 2007;30(5):161-166.
94. Pitman JP, Payrat JM, Park MS, et al. Longitudinal analysis of annual national hemovigilance data to assess pathogen reduced platelet transfusion trends during conversion to routine universal clinical use and 7-day storage. *Transfusion*. 2023;63(4):711-723.
95. Blandin L, Dougé A, Fayard A, et al. Platelet transfusion refractoriness and anti-HLA immunization. *Transfusion*. 2021;61(6):1700-1704.
96. Youk HJ, Hwang SH, Oh HB, Ko DH. Evaluation and management of platelet transfusion refractoriness. *Blood Res*. 2022;57(S1):6-10.
97. Couvidou A, Angénieux C, Ruch L, et al. Marginal zone B cells are responsible for the production of alloantibodies following platelet transfusion in mice. *Blood Adv*. 2023;7(8):1356-1365.
98. Couvidou A, Rojas-Jiménez G, Dupuis A, Maître B. Anti-HLA Class I alloantibodies in platelet transfusion refractoriness: From mechanisms and determinants to therapeutic prospects. *Front Immunol*. 2023;14:1125367.
99. Panch SR, Guo L, Vassallo R. Platelet transfusion refractoriness due to HLA alloimmunization: Evolving paradigms in mechanisms and management. *Blood Rev*. 2023;62:101135.
100. Boothby AB, Tanner MK, Alswied A, et al. Cumulative donor-specific antibody threshold predicts platelet transfusion response in HLA-alloimmunized patients. *Blood Adv*. 2024;8(17):4689-4699.
101. Couvidou A, Wald M, Angénieux C, et al. Anti-HLA class I IgG subclasses skew platelet activation mechanisms in transfusion refractoriness. *Haematologica*. 2026;111(2):535-545.
102. Cholette JM, Muszynski JA, Ibla JC, et al. Plasma and platelet transfusions strategies in neonates and children undergoing cardiac surgery with cardiopulmonary bypass or neonates and children supported by extracorporeal

membrane oxygenation: from the transfusion and anemia expertise initiative-control/avoidance of bleeding. *Pediatr Crit Care Med*. 2022;23(13 Suppl 1 1S):e25-e36.

103. Lieberman L, Karam O, Stanworth SJ, et al. Plasma and platelet transfusion strategies in critically ill children with malignancy, acute liver failure and/or liver transplantation, or sepsis: from the transfusion and anemia expertise initiative-control/avoidance of bleeding. *Pediatr Crit Care Med*. 2022;23(13 Suppl 1 1S):e37-e49.

104. Maier CL, Stanworth SJ, Sola-Visner M, et al. Prophylactic platelet transfusion: is there evidence of benefit, harm, or no effect? *Transfus Med Rev*. 2023;37(4):150751.

Tables

Table 1. Platelet-derived inflammatory mediators relevant to transfusion

Mediator or structure	Main source within platelet product	Change during storage	Principal targets	Potential transfusion relevance	References
Soluble CD40L/CD154	Alpha-granules; membrane shedding from activated platelets	Accumulates in platelet concentrates, often with activation	Endothelium, neutrophils, monocytes, B cells, platelets	Febrile reactions, inflammatory reactions, TRALI cofactor, adaptive immune modulation	(28 , 30 , 40)
P-selectin/CD62P and soluble P-selectin	Alpha-granule membrane; activated platelet surface	Surface expression and soluble forms increase with activation/storage	PSGL-1 on neutrophils and monocytes	Platelet-leukocyte aggregates, endothelial inflammation, clearance	(28 , 40)
PF4/CXCL4	Alpha-granules	Released during activation and storage	Monocytes, neutrophils, endothelium, immune complexes	Leukocyte recruitment, inflammation, heparin/PF4 immune biology	(11, 14 , 40)
CCL5/RANTES	Alpha-granules	May accumulate or remain product-dependent	Monocytes, T cells, endothelium	Leukocyte recruitment, vascular inflammation	(11, 14 , 40)
IL-1beta and related inflammatory cytokines	Platelet synthesis and vesicle-associated pools	Variable; may be vesicle-associated	Endothelium, leukocytes	Fever, endothelial activation, inflammatory amplification	(30, 63-65, 66 , 67, 68 , 69)
HMGB1	Platelets and extracellular vesicle-associated release	Increases with preparation/storage in some products	TLR4, TLR2, RAGE	Sterile inflammation, neutrophil activation, candidate biomarker of reactions	(36, 40, 70)
Mitochondrial DNA	Mitochondria-bearing vesicles, damaged mitochondria	Accumulates with platelet stress/storage	TLR9, inflammasome-related pathways	DAMP-driven inflammation, adverse reaction association	(32, 34)
Platelet extracellular vesicles	Plasma membrane budding, exosome-like release, storage-induced vesiculation	Increase with activation/storage; composition varies	Platelets, monocytes, neutrophils, endothelium	Procoagulant activity, immune signaling, DAMP transport, biomarker potential	(31 , 32 , 33, 34)
Complement activation products	Residual plasma and platelet-complement interactions	Accumulate, especially in plasma-rich products	Platelets, leukocytes, endothelium	Febrile/allergic-type reactions, inflammatory amplification	(19, 71-73)
Bioactive lipids, including lysophosphatidylcholines	Platelet membranes and	Accumulate in aged products	Neutrophils, endothelium	Neutrophil priming, two-hit lung injury models	(37-39, 74, 75)

Mediator or structure	Main source within platelet product	Change during storage	Principal targets	Potential transfusion relevance	References
	stored supernatant				

Table 2. Product variables shaping platelet immune and hemostatic phenotype

Product variable	Expected biological effect	Potential advantage	Potential limitation	Clinical context where relevant	References
Apheresis vs pooled whole-blood-derived platelets	Alters donor exposure, plasma composition, activation and inventory logistics	Single-donor exposure for apheresis; scalable production for pooled products	Donor variability; different activation profiles	General platelet support, alloimmunized patients, inventory planning	(53-56)
Leukoreduction	Reduces residual leukocytes and leukocyte-derived cytokines; lowers HLA alloimmunization	Reduces febrile reactions and alloimmunization risk	Does not remove platelet-derived HLA or mediators	Hematology/oncology, stem cell transplantation	(17, 76-79)
Plasma-rich storage	Maintains plasma proteins but preserves allergenic and complement substrate burden	Familiar standard; supports platelet metabolism	Allergic reactions, complement activation, ABO/plasma issues	Conventional prophylaxis; settings without PAS	(16, 18, 19)
Platelet additive solutions	Reduce plasma volume and dilute plasma mediators	May reduce allergic reactions and some complement activation	May alter platelet metabolism or recovery depending on formulation	Recurrent allergic reactions, inventory standardization	(16, 18, 19)
Pathogen reduction	Inactivates broad range of pathogens and residual leukocytes	Infectious safety, possible reduction in irradiation need depending on policy	Platform-specific effects on recovery, metabolism, mediator release	Regions prioritizing infectious risk reduction; inventory simplification	(21, 61, 62, 70, 80-83)
Room-temperature storage	Preserves post-transfusion recovery better than cold storage	Suitable for hypoproliferative thrombocytopenia	Bacterial growth risk, short shelf life, progressive storage lesion	Haematology prophylaxis and routine support	(16, 18, 22)
Cold storage	Promotes procoagulant/hemostatic phenotype but rapid clearance	Immediate hemostatic activity, reduced bacterial growth, longer potential storage	Shorter circulation, desialylation/clearance, need indication-specific metrics	Trauma, surgery, massive bleeding, selected emergency use	(16, 20-23)
Washing/plasma reduction	Removes plasma proteins and some soluble mediators	Reduces recurrent allergic reactions	Platelet loss, shorter shelf life, logistical burden	Recurrent severe allergic reactions	(18, 84, 85)
Storage duration	Progressive metabolic, activation and inflammatory changes	Inventory flexibility when extended safely	Accumulation of soluble mediators and vesicles; functional decline	Product selection, adverse reaction risk stratification	(11, 35, 40, 61, 62)

Table 3. Recipient contexts and platelet transfusion risks

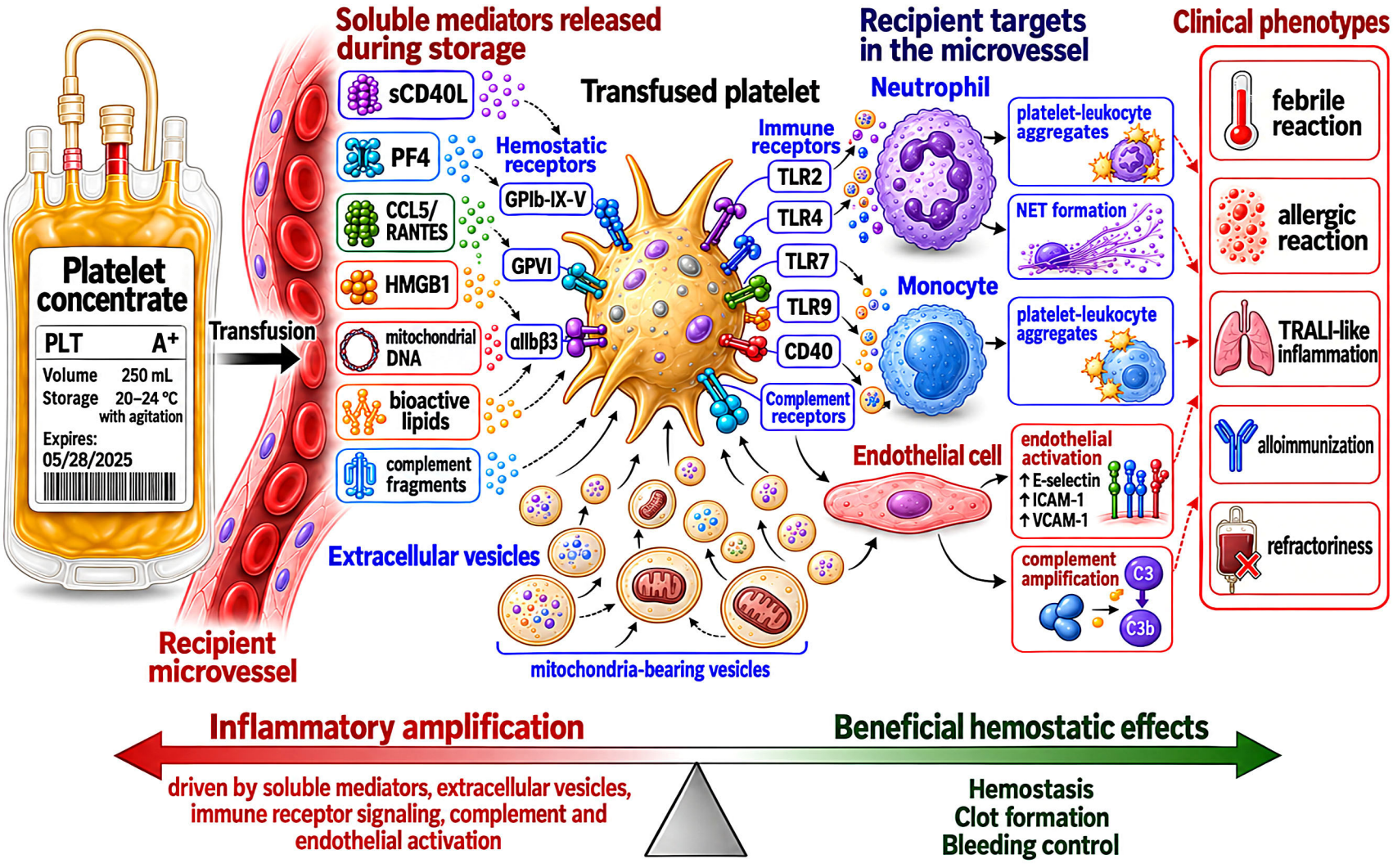
Recipient context	Dominant transfusion need	Specific biological concern	Product strategy to consider	Research priority	References
Hypoproliferative thrombocytopenia after chemotherapy	Sustained count increment and bleeding prevention	Repeated exposure, infection, mucosal inflammation	Room-temperature leukoreduced platelets; HLA-selected if refractory	Predict bleeding beyond platelet count; integrate inflammation	(1-6)
Hematopoietic stem cell transplantation	Support during aplasia and procedures	Alloimmunization, infection, endothelial injury	Leukoreduced; HLA-compatible when needed; careful donor planning	Alloimmune risk prediction during immune reconstitution	(17, 42, 52)
Active surgical or traumatic bleeding	Immediate hemostatic effect	Coagulopathy, endothelial damage, massive transfusion interaction	Consider cold-stored or hemostasis-biased products where available	Indication-specific trials using bleeding and survival endpoints	(16, 21-23, 86, 87)
Sepsis or systemic inflammation	Variable: prophylaxis or bleeding support	Primed neutrophils/endothelium; two-hit inflammatory risk	Avoid unnecessary prophylaxis; consider mediator-reduced strategies	Product-recipient inflammatory biomarker studies	(37-39, 88, 89)
Preterm neonates	Prevention/treatment of bleeding with developmental specificity	Adult-neonatal platelet mismatch; inflammation; PlaNeT-2 signal	Restrictive thresholds; minimize exposure; product tailoring under study	Mechanisms of platelet-induced neonatal inflammation	(44, 45, 61, 90, 91)
Recurrent allergic reactions	Maintain support with fewer reactions	Plasma proteins, complement, recipient atopy	PAS, plasma reduction or washed platelets	Identify reaction endotypes and preventive strategies	(18, 19, 92-94)
HLA alloimmune refractoriness	Effective count increment with compatible platelets	Anti-HLA antibodies, eplet mismatch, inflammation	Crossmatch-compatible, HLA-matched or ASP/eplet-compatible platelets	Clinical calibration of antibody strength and compatibility algorithms	(79, 95-101)
Pediatric oncology/hematology	Prevention/treatment of bleeding	Higher reported platelet reaction rates; repeated exposure	Age-appropriate hemovigilance; tailored premedication/product modification	Pediatric-specific reaction prediction and prevention	(51, 61, 91, 102-104)

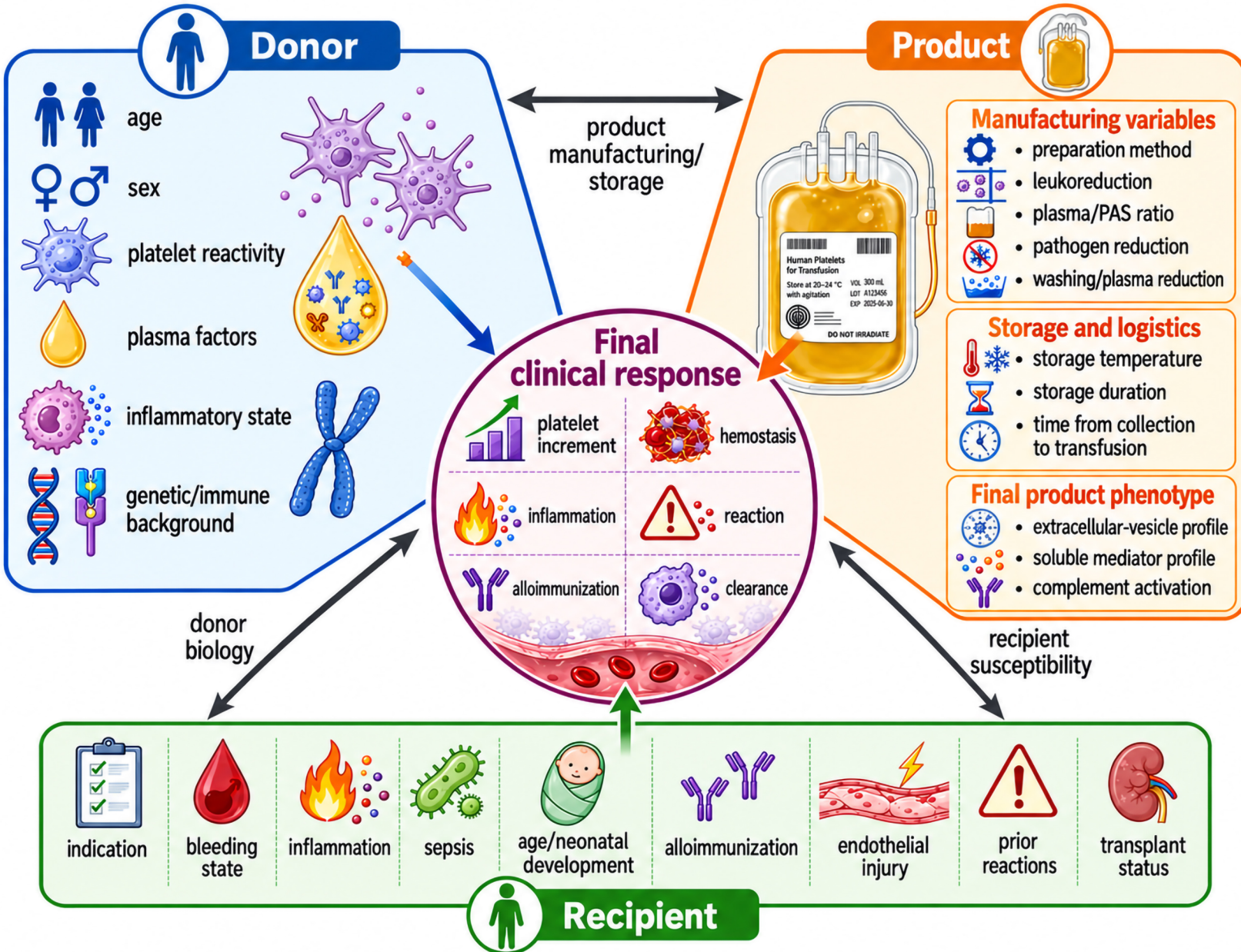
Figures

Figure 1. From platelet concentrate to inflammatory signaling. Platelet transfusion delivers both hemostatic function and inflammatory information. During storage, platelets release soluble biological response modifiers, extracellular vesicles and damage-associated molecular patterns. These signals interact with platelet immune receptors and recipient leukocytes, complement and endothelium. The clinical outcome depends on the balance between desired hemostasis and inflammatory amplification in a susceptible host.

Figure 2. The donor-product-recipient framework. Platelet transfusion outcome is determined by interactions among donor biology, manufacturing variables, the storage trajectory and recipient susceptibility. Manufacturing variables are fixed primarily within blood establishments, whereas storage information remains available at component issue. Soluble and vesicular mediator profiles represent the final biological phenotype of the product but currently remain primarily research measurements. No individual variable acts in isolation.

Figure 3. Purpose-built platelet profiles for precision transfusion. Precision platelet transfusion does not imply the use of one product for all indications or a rigid one-to-one allocation. It requires matching the dominant clinical objective—sustained recovery, rapid hemostatic activity, enhanced pathogen safety, reduced plasma exposure or antigen compatibility—to an appropriate platelet product profile. Product characteristics are modular, and preparation method, platelet additive solution, pathogen reduction, storage temperature, washing and HLA/HPA selection may coexist within the same component. The proposed matches remain indication-specific strategies requiring prospective clinical validation.





Clinical context

Desired platelet profile

Product strategy



marrow failure

sustained recovery and persistence



active bleeding

rapid hemostatic activity



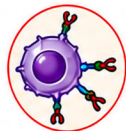
infectious-risk reduction

enhanced pathogen safety



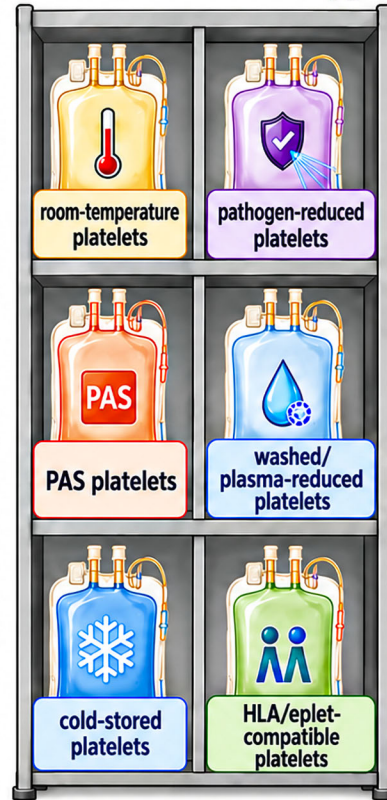
recurrent allergic reactions

reduced plasma and mediator exposure



alloimmune refractoriness

antigen compatibility



room-temperature platelets

pathogen-reduced platelets

PAS or washed/plasma-reduced platelets

HLA/HPA/eplet-compatible platelets

Product attributes may be combined within the same component.

right platelet product - right patient - right time.