

STORAGE LESIONS IN STORED BLOOD AND THEIR CLINICAL IMPLICATIONS

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Abstract

Background: Blood component storage makes modern transfusion medicine possible by separating donation from clinical need, yet storage is not biologically neutral. Red cells, platelets and plasma undergo progressive biochemical, structural and functional alterations collectively termed storage lesions. These changes are measurable in the laboratory, but their importance after transfusion varies with the component, manufacturing process, storage conditions, dose, rate of administration and recipient vulnerability. **Objectives:** This review examines the mechanisms, clinical implications and prevention of storage lesions across major blood components. **Methods:** Relevant experimental studies, clinical trials, systematic reviews and professional guidelines addressing blood-component storage were critically reviewed. Evidence relating to red-cell metabolism and membrane integrity, platelet activation and survival, plasma coagulation-factor stability, transfusion outcomes and mitigation strategies was synthesized narratively. **Results:** Red-cell storage is characterized by depletion of adenosine triphosphate and 2,3-diphosphoglycerate, falling pH, potassium leakage, oxidative injury, loss of membrane integrity, vesiculation, reduced deformability and accumulation of cell-free haemoglobin, bioactive lipids and inflammatory mediators. Platelets stored at room temperature develop activation, receptor shedding, metabolic exhaustion, mitochondrial dysfunction and impaired post-transfusion survival, whereas refrigeration preserves aspects of immediate haemostatic function but accelerates clearance. Frozen and thawed plasma shows variable loss of labile coagulation factors and changes related to thawing and post-thaw storage. **Conclusion:** Although these lesions are biologically plausible causes of impaired oxygen delivery, inflammation, thrombosis, hyperkalaemia or reduced haemostatic efficacy, large randomized trials have not demonstrated a general mortality advantage for routinely transfusing the freshest available red cells. Clinical concern is therefore greatest in selected settings, including neonates, massive or rapid transfusion, extracorporeal circuits, severe trauma, chronic transfusion dependence and recipients of irradiated units. Effective mitigation includes appropriate component

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selection, validated processing, temperature control, leucoreduction, additive solutions, washing or potassium reduction when indicated, rational inventory rotation and patient blood management. Storage age alone is an incomplete measure of quality; future practice should integrate donor biology, component manufacturing, molecular quality markers and recipient risk.

Keywords: Blood storage, red-cell storage lesion, platelet storage lesion, transfusion, extracellular vesicles, hyperkalaemia, oxygen delivery, haemovigilance.

Introduction

The capacity to collect, process and store donated blood is one of the foundations of contemporary medicine. It enables planned surgery, emergency resuscitation, obstetric care, cancer treatment, transplantation and long-term support for patients with inherited or acquired hematological disorders. Refrigeration slows cellular metabolism and microbial proliferation in red-cell components, while agitation at room temperature supports platelet viability and freezing preserves plasma proteins for extended periods. These procedures extend availability, but they also remove cells and proteins from the regulatory environment of the circulation. Once enclosed in a plastic bag, a blood component is exposed to hypothermia or freezing, anticoagulants, preservatives, plasticizers, altered gas exchange, prolonged contact with cellular debris and progressive accumulation of metabolic products. The resulting changes are collectively described as storage lesions.^{1,2,5}

The term storage lesion should not be understood as a single defect. It refers to a time-dependent network of biochemical, biomechanical, morphological and immunological changes that differ across red cells, platelets and plasma. Even within one component class, the lesion is influenced by donor characteristics, collection method, processing time, leucoreduction, additive solution, irradiation, pathogen-reduction technology, bag material and storage temperature. Consequently, two red-cell units of the same chronological age may not have the same metabolic reserve, degree of haemolysis or post-transfusion recovery. Chronological age is therefore a convenient inventory variable, but an imperfect biological measure of quality.^{2,3,6}

Interest in storage lesions increased when observational studies associated longer red-cell storage with infection, organ dysfunction and mortality. Laboratory research offered plausible mechanisms, including impaired deformability, nitric-oxide scavenging, iron release and inflammatory extracellular vesicles. However, observational comparisons were vulnerable to confounding because severely ill or heavily transfused patients often receive more units and therefore have a greater chance of exposure to older blood. Subsequent randomized trials comparing fresher red cells with standard-issue blood did not show a consistent survival advantage for the fresher strategy in broad adult, paediatric or neonatal populations. The modern interpretation is therefore balanced: storage lesions are real and biologically important, but their clinical expression depends on context and cannot be inferred from storage duration alone.^{4,7,8,9}

This narrative review describes how storage lesions arise, the major alterations in red cells, platelets and plasma, the pathways through which they may affect recipients, the clinical evidence concerning outcomes, and practical strategies for prevention and mitigation. Particular attention is given to settings in which a modest change in component composition may become clinically important, such as neonatal exchange transfusion, massive haemorrhage, rapid transfusion, cardiac surgery and chronic transfusion. The review also highlights unresolved questions and the movement toward quality assessment based on biological performance rather than a simple fresh-versus-old distinction.

2.0 Concept and Determinants of the Blood Storage Lesion

A storage lesion begins when blood is collected and continues through processing, transport and storage. Anticoagulant-preservative solutions prevent clotting and provide substrates that support cell survival, but they cannot recreate the circulation. Red cells stored at 1-6 degrees Celsius rely almost entirely on anaerobic glycolysis. Platelets stored at 20-24 degrees Celsius remain metabolically active and require continuous gas exchange and agitation. Plasma proteins are comparatively stable when frozen, although repeated temperature changes and prolonged post-thaw storage can affect labile factors. Thus, the storage environment trades full physiological function for a controlled slowing of deterioration, with the acceptable endpoint defined by regulatory measures such as haemolysis, sterility, factor activity or post-transfusion recovery.^{1,5,11}

Donor biology is a major source of variability. Age, sex, genetic traits, ethnicity, diet, exercise, smoking, medication use and the interval between donations can influence antioxidant capacity, membrane lipid composition, glycolytic activity and susceptibility to haemolysis. Large donor studies have demonstrated reproducible differences in red-cell storage behaviour, suggesting that some donors consistently produce units with greater or lesser storage stability. This variability complicates attempts to define an exact day on which a unit becomes biologically old. It also supports the emerging concept that storage quality is an interaction among donor, processing method and recipient rather than a property determined solely by time.^{3,6,12}

Manufacturing procedures further shape the lesion. Whole-blood-derived and apheresis components experience different mechanical forces and residual plasma exposure. Pre-storage leucoreduction removes most white cells and reduces the accumulation of cytokines, proteases and leucocyte-derived debris, but it does not prevent intrinsic red-cell or platelet ageing. Irradiation prevents transfusion-associated graft-versus-host disease by damaging donor lymphocyte DNA, yet it also accelerates red-cell membrane injury and potassium leakage. Pathogen-reduction systems improve infectious safety but may alter platelet metabolism and recovery. The composition of additive solutions, oxygen permeability of the bag and time before component separation likewise influence the biochemical trajectory during storage.^{2,10,13}

Storage lesions are also component-dose and recipient-dose phenomena. A biochemical change that is trivial in one slowly transfused unit may become important when many units are given rapidly, when the supernatant is delivered directly into a central circulation, or when renal and cardiac compensatory mechanisms are limited. The same principle applies to platelet products: a moderate reduction in corrected count increment may be acceptable in an actively bleeding patient if immediate haemostatic function is preserved, but less desirable in a stable thrombocytopenic patient requiring sustained platelet survival. Clinical interpretation must therefore connect the laboratory lesion with transfusion volume, rate, indication and patient physiology.^{4,10,14}

3.0 Red Blood Cell Storage Lesion

3.1 Metabolic changes. Refrigeration reduces but does not stop red-cell metabolism

Glucose is consumed through glycolysis, lactate and hydrogen ions accumulate, and the pH of the storage medium gradually falls. As the intracellular environment becomes more acidic, glycolytic enzyme activity declines and adenosine triphosphate production diminishes. ATP is essential for membrane phospholipid organization, cytoskeletal interactions, ion pumps and cell shape. Its depletion therefore connects metabolic exhaustion with membrane instability, potassium leakage, vesiculation and impaired deformability. Additive solutions extend shelf life by supplying nutrients and increasing available volume, but the metabolic decline is delayed rather than abolished.^{1,2,5}

A prominent metabolic feature is depletion of 2,3-diphosphoglycerate, often called 2,3-DPG or 2,3-BPG. This erythrocyte metabolite binds deoxygenated haemoglobin and reduces its affinity for oxygen. When 2,3-DPG falls, the oxygen dissociation curve shifts to the left, meaning stored cells hold oxygen more tightly at a given partial pressure. Theoretical concern is that recently transfused

stored cells may unload oxygen less effectively in hypoxic tissues. Nevertheless, 2,3-DPG is regenerated after transfusion, generally over hours to days, and tissue oxygen delivery is governed by cardiac output, haemoglobin concentration, microvascular flow and local extraction as well as haemoglobin affinity. A laboratory shift in affinity therefore does not automatically translate into clinically important tissue hypoxia.^{1,5,15}

Purine metabolism also deteriorates. ATP degradation generates adenosine, inosine and hypoxanthine, while antioxidant substrates are consumed. Hypoxanthine may contribute to oxidant production after transfusion when it encounters oxygen and xanthine oxidase. Metabolomic investigations have shown coordinated changes in glycolysis, the pentose phosphate pathway, glutathione homeostasis, lipid metabolism and purine catabolism. These findings demonstrate that the lesion is not merely a fall in ATP; it is a broad rewiring of metabolism under cold, acidic and progressively oxidizing conditions. They also reveal marked donor-dependent trajectories that may help explain why chronological storage age correlates imperfectly with functional quality.^{3,6,16}

3.2 Oxidative injury. Red cells continuously encounter oxygen and contain abundant haemoglobin and iron, making them intrinsically vulnerable to oxidation. In vivo, antioxidant enzymes and metabolic pathways are supported by plasma and organs that remove damaged cells. During storage, reducing equivalents decline and reactive oxygen species modify haemoglobin, band 3 and cytoskeletal proteins. Haemoglobin oxidation produces methaemoglobin and denatured haemichromes that associate with the membrane. Oxidized band 3 clusters can promote binding of naturally occurring antibodies and signal senescent-cell clearance after transfusion. Lipid peroxidation reduces membrane flexibility, while oxidation of spectrin, ankyrin and other proteins weakens the membrane skeleton.^{2,3,17}

Oxidative and metabolic injuries amplify one another. Reduced glutathione and nicotinamide adenine dinucleotide phosphate are needed to neutralize oxidants, but their regeneration depends on active metabolism. As metabolism slows, oxidant defence weakens; as proteins and membranes oxidize, transport and enzyme function deteriorate further. Storage under reduced oxygen tension and newer antioxidant or metabolic additives are therefore being studied as strategies that address an upstream driver rather than a single downstream marker. The challenge is to improve quality without adding toxicity, excessive cost or manufacturing complexity and without compromising bacterial safety or component availability.^{3,16,17}

3.3 Membrane and morphological changes. Fresh erythrocytes are deformable biconcave discs that traverse capillaries narrower than their resting diameter. During storage, discocytes progressively develop echinocytic projections and may become spherocytocytes or dense spherocytes. These changes reflect ATP depletion, altered cation balance, membrane loss and cytoskeletal injury. Some early shape changes reverse after transfusion when cells regain metabolic substrates, whereas cells that have lost substantial membrane surface through vesiculation cannot fully recover. Reduced surface-area-to-volume ratio and increased rigidity may impair splenic passage and shorten post-transfusion survival.^{1,2,18}

Membrane vesiculation releases small extracellular vesicles containing phospholipids, oxidized proteins, haemoglobin and other red-cell constituents. Vesiculation may be partly protective because it removes damaged membrane domains, but it also leaves the parent cell smaller and less deformable. Red-cell-derived vesicles can expose phosphatidylserine, provide procoagulant surfaces, scavenge nitric oxide and interact with endothelium, platelets and immune cells. Their biological activity varies with size, composition and method of measurement, and laboratory isolation is not standardized. Consequently, extracellular vesicles are compelling mediators of potential clinical effects, but their precise dose-response relationships in transfusion recipients remain incompletely defined.^{3,19,20}

3.4 Ionic changes and potassium leakage. The red-cell membrane normally maintains a high intracellular potassium concentration through the sodium-potassium ATPase. Refrigeration suppresses the pump, while ATP depletion and membrane injury permit potassium to diffuse into the extracellular storage solution. Supernatant potassium therefore rises with storage time and increases more rapidly after irradiation. For most stable adults receiving blood at ordinary rates, the potassium load is diluted and excreted without consequence. Risk becomes clinically relevant during rapid large-volume transfusion, particularly in neonates and small children, patients with renal failure, severe acidosis or shock, and procedures delivering blood close to the heart, including cardiopulmonary bypass and extracorporeal membrane oxygenation.^{10,13,21}

Sodium moves into cells as potassium exits, while failure of calcium pumps and other ion-regulatory systems contributes to altered hydration and membrane organization. Osmotic fragility may increase, and a subpopulation of cells becomes susceptible to haemolysis. Extracellular free haemoglobin rises as cells rupture or haemoglobin is released in vesicles. Although allowable haemolysis at expiry is regulated and usually remains low, even modest amounts of cell-free haemoglobin have biological activity: they bind nitric oxide, promote vasoconstriction and may participate in oxidative and renal injury. The clinical importance depends on concentration, clearance by haptoglobin and haemopexin, recipient endothelial health and the magnitude of transfusion.^{2,3,22}

3.5 Nitric oxide biology and microcirculation. Nitric oxide supports vascular relaxation and regulates platelet and endothelial activity. Stored red cells may disturb this system through rapid scavenging by cell-free haemoglobin and haemoglobin-containing vesicles. Changes in red-cell deformability can also affect capillary transit and the release or carriage of vasoactive signals. These mechanisms offer a plausible link between the storage lesion and impaired microvascular perfusion even when systemic haemoglobin concentration rises. However, measurements of microcirculatory flow, oxygen extraction and clinical outcomes have not consistently shown that older standard-issue cells cause meaningful harm. The gap between mechanistic plausibility and trial results is central to the storage-lesion debate.^{3,19,22}

3.6 Inflammatory and immune modulatory changes. Residual leucocytes can release cytokines during storage, which is one reason pre-storage leucoreduction has become common in many blood systems. Even leucoreduced red-cell units accumulate bioactive lipids, soluble proteins, extracellular vesicles, free haemoglobin, iron-containing compounds and damage-associated molecular patterns. These substances may activate endothelium, prime neutrophils or influence monocyte and macrophage responses. In susceptible recipients, they have been proposed as contributors to febrile reactions, transfusion-related acute lung injury, infection or organ dysfunction. Yet many such outcomes are multifactorial, and transfusion itself, underlying illness and the number of units administered are difficult to disentangle.^{2,4,20}

Iron handling provides another potential pathway. A fraction of stored erythrocytes, particularly the most damaged subpopulation, may be cleared soon after transfusion by splenic and hepatic macrophages. Rapid erythrophagocytosis delivers a concentrated iron load to the mononuclear phagocyte system and can transiently increase non-transferrin-bound iron when transferrin capacity is exceeded. Experimental studies suggest that this may promote inflammation or microbial growth under certain conditions. The effect is likely most relevant after multiple units or in recipients with infection, chronic inflammation or altered iron metabolism, but routine clinical evidence remains insufficient to justify withholding normally licensed older units on this basis alone.^{3,23}

4.0 Platelet Storage Lesion

Platelets present a different preservation problem because they are metabolically active fragments designed to sense vascular injury and respond rapidly. Conventional platelet concentrates are stored at 20-24 degrees Celsius with continuous gentle agitation to maintain gas exchange. This

temperature preserves circulation time better than refrigeration, but it permits bacterial proliferation and limits shelf life. During storage, platelets consume glucose, produce lactate, alter the pH of the medium and undergo progressive activation. The term platelet storage lesion encompasses metabolic exhaustion, mitochondrial dysfunction, cytoskeletal reorganization, receptor changes, granule release, loss of discoid shape and reduced responsiveness to selected agonists.^{11,24,25}

Stored platelets gradually change from smooth discs to spheres with pseudopodia. Activation markers such as P-selectin increase, alpha and dense granules are released, and soluble mediators accumulate in the supernatant. Glycoprotein receptors involved in adhesion and aggregation may be cleaved or internalized. Mitochondrial membrane potential and the capacity to generate ATP decline, while apoptosis-like signalling, phosphatidylserine exposure and microparticle formation increase. These changes can reduce in vivo recovery and survival after transfusion. Laboratory aggregation responses may also fall, although some hyporesponsiveness reflects reversible desensitization and does not necessarily predict failure to arrest bleeding.^{24,25,26}

The clinical purpose of a platelet transfusion determines which quality feature matters most. For prophylaxis in a stable patient with marrow failure, good post-transfusion recovery and sustained circulation are desirable because they maintain the platelet count between transfusions. For active haemorrhage, immediate adhesion, aggregation and clot support may be more important than long survival. This distinction helps explain interest in cold-stored platelets. Refrigeration at approximately 1-6 degrees Celsius enhances or preserves several immediate haemostatic responses and reduces bacterial growth, but cold-induced glycoprotein changes promote hepatic clearance and shorten circulation time. Cold storage may therefore produce a stronger short-lived haemostatic product while making it less suitable for routine prophylaxis.^{25,27,28}

Clinical studies generally find that fresher room-temperature platelets produce higher corrected count increments than older platelets. However, systematic review evidence has not established a consistent effect of platelet age within licensed storage periods on major bleeding, sepsis or mortality. Count increment is an important surrogate, but it does not capture endothelial support, clot strength or the complex interaction between transfused platelets and the recipient's coagulation system. Recent trauma studies of cold-stored platelets have focused on safety and feasibility and have not shown a clear excess of thrombotic complications, but larger outcome trials and clearer indication-specific standards remain necessary.^{14,24,28}

Bacterial contamination is uniquely important for room-temperature platelets. Skin flora or small numbers of organisms entering during collection can proliferate despite donor screening and aseptic processing. Storage duration therefore affects not only cellular quality but infectious risk. Diversion pouches, improved skin disinfection, bacterial culture, rapid testing and pathogen reduction are used to mitigate this hazard. These interventions may permit longer inventory availability, but they can also influence platelet yield, activation, recovery or cost. The optimal system balances haemostatic performance, bacterial safety, wastage and reliable access during emergencies.^{11,25}

Platelet additive solutions replace part of the donor plasma and can improve standardization, reduce plasma-associated reactions and support metabolism. Their composition affects buffering, acetate utilization and platelet activation. Pathogen-reduction technologies damage nucleic acids to prevent replication of infectious agents and contaminating leucocytes; because platelets lack nuclei but retain mitochondria and complex signalling systems, treatment can still alter function and post-transfusion increments. These effects should be interpreted as part of a manufacturing-specific lesion rather than attributed to storage time alone.^{11,24,26}

5.0 Plasma Storage Lesions

Plasma is stored to preserve coagulation factors and other proteins rather than living cells. Fresh frozen plasma or plasma frozen within a specified processing interval can be kept for prolonged periods at subzero temperatures, with exact shelf life determined by local regulation and storage

temperature. Freezing largely arrests enzymatic activity, but the rate of freezing, depth and stability of temperature, thawing method and duration of post-thaw storage influence quality. Factors V and VIII are relatively labile, while fibrinogen and many vitamin K-dependent factors are more stable. Thawed plasma held under validated refrigerated conditions therefore shows a gradual and unequal decline in factor activities rather than a uniform loss of coagulation capacity.^{29,30}

Repeated freeze-thaw cycles can denature proteins, activate complement and coagulation pathways, and generate precipitates or particles. In routine blood banking, validated procedures are designed to avoid such cycles. During post-thaw storage, factor VIII activity commonly decreases more rapidly than many other factors, whereas haemostatic concentrations may remain adequate for several days in products designated as thawed plasma. The clinical suitability of a plasma unit must be judged against the indication: urgent balanced resuscitation may value immediate availability, whereas replacement for a specific severe factor deficiency may require a product known to contain adequate activity or a purified factor concentrate.^{29,30}

Plasma also carries extracellular vesicles, lipids, complement proteins, antibodies and soluble mediators whose concentrations may change with processing and storage. Residual cells can fragment, while contact activation and microparticle generation may add procoagulant activity. These changes are less visibly discussed than red-cell or platelet lesions because plasma release criteria emphasize factor content and sterility, yet they may contribute to variability among units. Donor-related antibody risk and plasma volume remain more established determinants of allergic reactions, transfusion-related acute lung injury and circulatory overload than storage age itself.^{20,29}

Cryoprecipitate is produced by controlled thawing of frozen plasma and contains concentrated fibrinogen, factor VIII, von Willebrand factor, factor XIII and fibronectin. Its quality depends on source plasma, preparation, freezing and thawing conditions and storage after pooling. Because fibrinogen replacement is often urgent and dose dependent, delays, wastage and variability can have direct clinical consequences. Where available, fibrinogen concentrate offers standardization and rapid preparation, but cost, licensing and local practice influence use. The broader lesson is that a storage lesion must be interpreted in relation to the therapeutic target of each component rather than treated as one universal process.^{29,31}

6.0 Clinical Implications of Red-Cell Storage

6.1 Oxygen delivery and transfusion efficacy. The principal purpose of red-cell transfusion is to improve oxygen-carrying capacity, but an increase in haemoglobin does not guarantee improved tissue oxygenation. Stored cells with depleted 2,3-DPG, reduced deformability and altered nitric-oxide interactions could theoretically unload oxygen less readily or traverse the microcirculation less efficiently. In most recipients, however, transfused red cells restore ATP and 2,3-DPG after re-entry into the circulation, and the cardiovascular system adjusts flow and extraction. Randomized comparisons have not demonstrated that issuing very fresh cells routinely produces superior survival or organ function compared with standard inventory practice.^{7,8,9,15}

6.2 Mortality and organ dysfunction. Early retrospective studies reported associations between older red cells and death, infection, prolonged ventilation, renal injury or multiple-organ failure, especially in cardiac surgery and critical care. These signals were important enough to justify randomized trials. The ABLE trial in critically ill adults, the INFORM trial across hospitalized patients and the TRANSFUSE trial in critically ill patients compared fresher red cells with standard-issue or older cells. Across these large studies, fresher blood did not reduce mortality. Trial populations and storage contrasts were not identical, but the overall result strongly argues against a broad policy of reserving the freshest units for all recipients.^{7,8,9}

The absence of a general mortality effect does not mean every storage-associated change is harmless or that all subgroups have been fully studied. Randomized trials often compare mean storage ages that overlap substantially and exclude extremely old or improperly stored units. Rare

adverse events, very rapid high-volume transfusion and small vulnerable populations may be underrepresented. Furthermore, mortality is a distant outcome influenced by many clinical variables. Storage lesions may affect laboratory endpoints or short-term physiology without measurably changing overall survival. Evidence should therefore prevent exaggerated claims in both directions: neither universal harm nor complete biological irrelevance is justified.^{4,7,9}

6.3 Hyperkalaemia and cardiac complications. Transfusion-associated hyperkalaemia is among the clearest clinically actionable consequences of red-cell storage. Risk increases with older or irradiated cells, rapid infusion, large transfused volume, low recipient blood volume, renal dysfunction, shock and acidosis. Neonates and infants undergoing exchange transfusion, cardiac surgery or extracorporeal support are especially vulnerable because a single unit may represent a large proportion of circulating volume. Severe hyperkalaemia can cause conduction abnormalities, ventricular arrhythmia or cardiac arrest. Prevention depends on identifying high-risk situations rather than assuming that every stored unit creates the same danger.^{10,13,21}

Practical measures may include using relatively fresh units according to local neonatal or massive-transfusion policy, irradiating as close as feasible to transfusion, washing red cells, using potassium adsorption filters where validated, reducing storage time after irradiation, controlling infusion rate and monitoring electrolytes during high-risk transfusion. Washing removes much of the extracellular potassium but takes time, may reduce red-cell recovery and shortens the post-processing expiry. Any mitigation strategy must therefore be planned with the blood bank and balanced against the danger of delaying urgently needed transfusion.^{10,13,21}

6.4 Haemolysis, nitric-oxide scavenging and renal stress. Cell-free haemoglobin and haem released from stored units can consume nitric oxide, promote oxidative injury and be filtered by the kidney. In ordinary transfusion, scavenger proteins and dilution limit exposure. During massive transfusion or in patients with pre-existing haemolysis, endothelial dysfunction or renal injury, these protective systems may be more easily overwhelmed. Dark urine, rising plasma-free haemoglobin, reduced haptoglobin or acute kidney injury after transfusion requires assessment for an acute haemolytic reaction, mechanical haemolysis and other causes; it should not be attributed automatically to normal storage lesion.^{3,22,23}

6.5 Inflammation, infection and lung injury. Stored supernatant contains substances capable of priming neutrophils and activating endothelium in experimental systems. A two-hit model has been proposed in which recipient inflammation provides the first hit and transfused mediators provide a second stimulus for tissue injury. This framework is biologically plausible for transfusion-related acute lung injury and other inflammatory complications, but modern haemovigilance identifies donor anti-leucocyte antibodies and recipient clinical factors as major determinants. Leucoreduction and donor-selection policies have altered risk. Current evidence does not support choosing universally fresh red cells as a substitute for established reaction-prevention measures.^{2,4,20}

6.6 Thrombosis and coagulation. Phosphatidylserine-exposing red-cell vesicles can support assembly of coagulation enzyme complexes, while cell-free haemoglobin may impair nitric-oxide-mediated inhibition of platelet activation. These mechanisms suggest a potential prothrombotic effect. Conversely, severe illness, surgery, cancer, immobility and central venous access already create strong thrombotic risks, making small transfusion-specific effects difficult to isolate. Clinical studies have not established storage age as an independent indication for anticoagulation or for fresh-only transfusion. The appropriate response remains standard thrombosis assessment and avoidance of unnecessary transfusion.^{3,19,20}

7.0 High-Risk Clinical Settings

Neonates deserve special consideration because of their small circulating volume, immature renal handling and frequent exposure to rapid transfusion through central access or extracorporeal circuits. Potassium, citrate, acid load and other supernatant constituents can represent a

proportionally large dose. In exchange transfusion, massive neonatal haemorrhage, extracorporeal membrane oxygenation and cardiac surgery, component specifications may include limits on age, irradiation timing, haemoglobin S status, leucoreduction, cytomegalovirus risk and compatibility. These policies are designed around the whole risk profile, not storage lesion alone, and should follow validated local and national guidance.^{10,13,21}

Massive haemorrhage is another setting in which small unit-level differences may accumulate. Patients can receive red cells, plasma and platelets faster than metabolic products are cleared. Hyperkalaemia, hypocalcaemia from citrate, hypothermia, acidosis and dilutional coagulopathy may occur simultaneously. The immediate priorities are haemorrhage control, balanced component delivery, warming, electrolyte monitoring and correction of physiological derangements. Seeking exceptionally fresh units should not interrupt a functioning massive-transfusion protocol, although inventory planning can make appropriate components available for defined high-risk groups.^{10,31,32}

Chronically transfused patients, including those with thalassaemia, sickle cell disease or marrow failure, face a different problem. A red-cell unit with better post-transfusion survival may lengthen the interval between transfusions and reduce cumulative donor exposure. Younger red cells are sometimes selected for chronic programmes, but alloantigen matching, iron burden, haemolytic reaction prevention and continuity of supply may be equally or more important. The benefit of fresh allocation must be weighed against inventory pressure and fairness to other patients. Biological quality markers might eventually allow selection of units with predicted long survival without relying solely on collection date.^{3,12,33}

Cardiac surgery and extracorporeal support combine rapid transfusion, hypothermia, mechanical shear, inflammation and direct delivery of blood into circuits. These factors can magnify potassium load, haemolysis and endothelial stress. Nonetheless, randomized evidence in cardiac and critically ill populations does not demonstrate a consistent clinical benefit from routinely fresher red cells. Targeted safeguards, including circuit design, electrolyte monitoring, avoidance of unnecessary transfusion and adherence to irradiation-expiry rules, are more evidence-aligned than a blanket fresh-blood policy.^{7,9,10}

Sepsis, trauma and severe endothelial dysfunction remain biologically plausible contexts in which extracellular iron, vesicles or cell-free haemoglobin could exert greater effects. Yet these patients also have profound endogenous inflammation, altered microcirculation and organ injury. This makes causal attribution particularly difficult and emphasizes the need for trials enriched for mechanistically defined risk rather than broad diagnostic labels. Until such evidence is available, clinicians should use restrictive, indication-based transfusion and monitor the patient's response instead of assuming that storage age predicts benefit or harm.^{4,23,32}

8.0 Prevention and Mitigation

The first mitigation strategy is to avoid transfusion that is unlikely to benefit the patient. Patient blood management combines detection and treatment of anaemia, minimization of blood loss, optimization of haemostasis and evidence-based transfusion thresholds. Fewer unnecessary units mean less exposure not only to storage lesions but also to alloimmunization, circulatory overload, infection and clerical error. Restrictive red-cell thresholds are safe for many haemodynamically stable patients, although symptoms, active bleeding, cardiovascular disease and individual goals must guide decisions.^{32,34}

Pre-storage leucoreduction reduces white-cell content and limits accumulation of leucocyte-derived cytokines. It lowers febrile non-haemolytic reactions, HLA alloimmunization and cytomegalovirus transmission risk in appropriate settings, although it does not prevent the intrinsic red-cell lesion. Gentle collection and processing, prompt component separation, validated centrifugation and uninterrupted temperature control reduce avoidable damage. Continuous quality systems should

monitor haemolysis, component volume, cell yield, sterility, storage temperatures and expiry compliance rather than treating storage time as the only relevant indicator.^{2,11,35}

Modern additive solutions contain combinations of saline, adenine, glucose, mannitol, phosphate or other substrates that support ATP production, osmotic stability and membrane preservation. Rejuvenation solutions can restore ATP and 2,3-DPG in selected red-cell units before transfusion, particularly frozen or rare units, but require validated processing and removal of excess compounds. Research strategies include alkaline or phosphate-rich additives, antioxidant supplementation, anaerobic or hypoxic storage and improved bag materials. Each intervention must demonstrate not only better laboratory markers but acceptable post-transfusion recovery, safety, manufacturing feasibility and cost-effectiveness.^{1,3,16}

Washing red cells or platelets removes a large proportion of supernatant potassium, plasma proteins and accumulated soluble mediators. It is useful for specific indications, including recurrent severe allergic reactions and selected neonatal or hyperkalaemia-risk situations. It is not a routine cure for storage lesions because washing causes cell loss, adds processing time, may activate or damage cells, creates an open or functionally altered system and shortens expiry. Decisions should be indication specific and made early enough to avoid dangerous delays.^{10,13,35}

For platelet products, prevention involves close control of collection, agitation, gas exchange, pH, bacterial risk and storage duration. Room-temperature storage remains suited to prophylactic support because of better circulation, while cold-stored platelets may be advantageous when immediate haemostasis and logistical resilience are priorities. Pathogen reduction and bacterial testing improve safety but affect cost and, in some settings, post-transfusion increments. Hospitals should align inventory with their case mix: oncology services, trauma centres and remote facilities may legitimately require different platelet strategies.^{24,25,27}

Inventory management must preserve equitable access and minimize wastage. First-in-first-out or oldest-compatible-unit issue is efficient and is supported by trials showing no general benefit of fresher red cells. Exceptions should be explicit, evidence-informed and narrow, such as defined neonatal procedures or exchange transfusion. Unstructured requests for fresh blood can increase expiry, destabilize stock and paradoxically reduce availability during emergencies. Communication between clinicians and transfusion laboratories is therefore a clinical safety intervention in its own right.^{7,8,9}

Bedside practice can reduce the impact of storage-related constituents. Components should be inspected, correctly identified, warmed only with approved devices when indicated and transfused at an appropriate rate. High-risk massive or neonatal transfusion requires monitoring of potassium, ionized calcium, acid-base status and temperature. A poor clinical response should prompt assessment for ongoing bleeding, haemolysis, alloimmunization, sepsis, splenic sequestration or platelet refractoriness rather than immediate attribution to component age. Haemovigilance reporting helps distinguish recurrent manufacturing problems from patient-specific events.^{10,21,35}

9.0 Laboratory Assessment and Quality Indicators

Regulatory quality tests are necessarily practical. Red-cell haemolysis at expiry, haemoglobin content, volume and post-transfusion recovery are widely used, while platelet swirling, pH, count, sterility and recovery provide complementary information. Plasma specifications focus on factor activity, freezing intervals, storage temperature and visual integrity. These measures define an acceptable population of products but may not predict the behaviour of an individual unit in an individual recipient. A unit can meet haemolysis limits while differing substantially in deformability, vesicle burden, antioxidant reserve or susceptibility to rapid clearance.^{1,3,11}

Research assays include ektacytometry for deformability, osmotic fragility, morphology scores, ATP and 2,3-DPG, extracellular potassium, cell-free haemoglobin, phosphatidylserine exposure, microvesicle characterization and metabolomic or proteomic profiles. Platelet studies assess

aggregation, adhesion under flow, thromboelastography, mitochondrial respiration, activation markers and corrected count increment. No single assay captures the entire lesion. Moreover, technically sophisticated markers must show reproducibility, feasible turnaround and a relationship with meaningful clinical outcomes before becoming release tests.^{3,6,24}

The ideal quality marker would be measured rapidly before issue, remain stable enough for decision-making, and predict post-transfusion efficacy or toxicity better than age. Candidate approaches may combine donor history, manufacturing variables and a small biomarker panel. Machine-learning models could identify patterns associated with haemolysis or recovery, but they require diverse external validation and transparent performance. Such tools should support rather than replace clinical judgment, and allocation algorithms must avoid creating unjustified hierarchies of donors or restricting supply on the basis of poorly validated biological differences.^{6,12,16}

10.0 Current Evidence, Controversies and Research Gaps

The central controversy is the apparent mismatch between striking laboratory deterioration and largely neutral randomized red-cell trials. Several explanations coexist. Many storage changes are reversible after transfusion; physiological reserve may compensate; licensed limits exclude severely damaged products; and the difference in mean age between trial groups may be smaller than the difference studied in mechanistic experiments. It is also possible that harmful and beneficial effects vary among units and recipients and therefore average toward no effect in broad populations. This does not invalidate either laboratory science or clinical trials; it shows that they answer different questions.^{3,4,7}

Future studies should move beyond a single storage-day threshold. Factorial designs could examine donor traits, processing methods, irradiation timing, oxygen tension and recipient phenotype. Outcomes should include immediate physiology, organ injury, infection, thrombosis, transfusion interval and patient-centred recovery, not mortality alone. Biobanked donor-unit samples linked to recipient outcomes would allow molecular features to be tested prospectively. Standardized methods for extracellular vesicles, deformability and haemolysis are essential so that results can be compared across centres.^{3,6,12}

Platelet research requires indication-specific endpoints. A product optimized for prophylaxis should be judged by recovery, survival, bleeding prevention and transfusion interval, while a product for trauma should be judged by haemostatic effectiveness, blood-product use, thrombotic safety and survival. Cold storage, cryopreservation and pathogen reduction should not be ranked by one laboratory assay. Pragmatic trials that reflect transport delays, remote hospitals and variable donor supply are especially important because logistical availability can itself determine clinical benefit.^{24,27,28}

In plasma, better evidence is needed on how post-thaw age and manufacturing methods affect haemostatic efficacy in active bleeding. Conventional coagulation tests measure only part of plasma function and may not reflect clot stability, endothelial interactions or the contribution of extracellular vesicles. Studies should relate factor profiles and global haemostatic assays to dose-adjusted clinical outcomes. They should also compare the value of rapidly available thawed plasma with potentially higher factor activity in freshly thawed products, because treatment delay can outweigh modest biochemical deterioration.^{29,30,31}

Resource-limited blood systems face additional priorities. Inconsistent electricity, limited temperature monitoring, transport delays, shortages of sterile consumables and inadequate bacterial testing can cause preventable deterioration that is more important than subtle differences within a validated shelf life. Investment in reliable cold chains, staff training, preventive maintenance, quality control and haemovigilance is therefore essential. Local policies should be evidence based but realistic, avoiding unnecessary fresh-only rules that increase wastage and worsen shortages. Research from African and other underrepresented settings is needed because donor characteristics,

infectious burdens, component production and clinical use differ from high-income trial environments.^{11,35}

11.0 Practical Clinical Interpretation

Storage lesions should be regarded as a spectrum of component changes, not as proof that an older licensed unit is unsafe. For most adult recipients, standard-issue red cells are appropriate, and randomized evidence does not support routine preferential allocation of the freshest units. The transfusion decision should be based on clinical need, expected benefit and alternatives. Where a defined risk exists, such as rapid neonatal transfusion or use of irradiated red cells in a patient vulnerable to potassium, the laboratory should be informed early so that suitable mitigation can be arranged.^{7,8,9,10}

Clinicians should separate three questions: whether the patient needs transfusion, which component and dose best address the deficit, and whether the recipient requires a special product modification. Conflating these questions leads to vague requests for fresh blood that may not address the actual hazard. For example, potassium risk may be better managed by washing, filtration, slower administration and monitoring; allergic risk may require washing; alloimmunization requires antigen matching; and bacterial risk in platelets requires validated testing or pathogen reduction. Storage age is only one variable in a larger transfusion prescription.^{10,11,33}

The transfusion service, in turn, should make storage-related risks visible through clear policies, staff education and accessible consultation. Policies should define component shelf lives, irradiation rules, neonatal specifications, emergency release procedures, post-thaw plasma use and platelet bacterial-risk controls. Deviations and suspected reactions should be documented and investigated. A mature safety system does not promise biologically unchanged blood; it manages predictable deterioration within validated limits and matches special processing to patients most likely to benefit.^{11,13,35}

12.0 Conclusion

Storage lesions are unavoidable consequences of preserving blood outside the body. Red cells lose metabolic energy and 2,3-DPG, accumulate potassium and lactate, undergo oxidative membrane injury, shed vesicles and become less deformable. Platelets develop activation, metabolic and mitochondrial dysfunction, receptor alterations and reduced survival, while frozen and thawed plasma experiences selective loss of labile factors and processing-related variability. These changes have credible pathways to impaired oxygen delivery, hyperkalaemia, inflammation, thrombosis, haemolysis or reduced haemostatic efficacy. Their clinical importance, however, is neither uniform nor determined by storage age alone.^{1,2,3,24,29}

Large randomized trials show that routinely issuing very fresh red cells does not improve mortality compared with standard inventory practice in broad patient groups. This evidence supports efficient stock rotation while preserving targeted exceptions for high-risk circumstances. The most defensible approach combines patient blood management, validated manufacturing, leucoreduction and temperature control, careful irradiation practice, selective washing or potassium reduction, appropriate platelet and plasma strategies, and close physiological monitoring during rapid transfusion. Future progress will come from linking donor biology and component biomarkers to recipient-specific outcomes. The goal is not merely fresher blood, but the right component, of demonstrable quality, for the right patient at the right time.^{7,8,9,12,35}

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