What's in Your Transfusion? A Bedside Guide to Blood Products and Their Preparation

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> "It admits of no doubt. We must have Blood, you know."
>
> Charles Dickens, *David Copperfield*

A general understanding of blood products and their modifications will help any physician make good decisions about transfusion. The separation of blood into products makes the fullest use of every donation: it maximizes the lifespan of each component, allows us to treat specific hematologic deficits, and offers the benefit of one donation to many patients. Every product is also modified in some way to prevent clotting, extend shelf life, improve efficacy, or reduce the risk of adverse events. Every one of these steps has been developed with patient benefit in mind, but they still have consequences that anesthesiologists have to be aware of. In some cases, these consequences have provoked complex responses: the development of Massive Transfusion Protocols and balanced "1:1:1" transfusions was essentially a scientific, clinical, and administrative effort to undo the inadvertent harms of separating whole blood into red cells, plasma, and platelets. With a limited blood supply and competing clinical requirements, understanding what you are actually transfusing is essential.

In this narrative review, I will discuss the five basic blood products and five common modifications. Each product or modification is presented within a short clinical vignette; details are supplied in the figures and tables. I have also included a brief section on important transfusion reactions and their management. Finally, there is a list of additional resources for the interested reader.

Blood Products

Our blood supply in the United States comes from around 8 million donors who give between 1 and 20 times each year.[1] Although approximately 14 million products are collected every year, there are less than 2 weeks' supply of red cells and plasma in the U.S. inventory, and sometimes less than a day's supply of platelets.[2] Forty percent of the U.S. blood supply is collected by the American Red Cross (Washington, D.C.), with most of the rest collected by other independent institutions like Blood Bank of Hawaii (Honolulu, Hawaii) or OneBlood (St. Petersburg, Florida).[1,2] These blood centers are responsible for screening donors, collecting blood, separating them as necessary, labeling blood so it can be shipped in interstate commerce if the center is so licensed, and maintaining records (fig. 1).[3–7] Hospitals and clinics pay blood collectors for their products to cover the costs of materials, testing, and labor, with the specific price dependent on the unit and local contracts. There are also many for-profit blood centers that collect plasma and cells for the commercial preparations of albumin, immunoglobins, biologic therapies, and other reagents. Donors to commercial centers are usually paid to donate, but almost all blood collected for clinical transfusion in the United States comes from unpaid volunteers.[9]

Low-titer Group O Whole Blood

A 23-yr-old woman is hurt in a car crash. At the scene she has bilateral thigh deformities, tachycardia, hypotension, and altered consciousness. In the helicopter ride to the trauma center, she receives two units of Rh-positive low-titer group O whole blood. She does not ultimately require massive transfusion. After admission, records reveal that her blood type is A-negative, and the trauma team is concerned about her risk of blood type incompatibility and other transfusion reactions.

Low-titer group O whole blood contains all the components of donor blood in a mildly dilute form (fig. 2, table 1).[1,6,10–24] Whole blood has many benefits in bleeding compared to crystalloid or component-based resuscitation, including the convenience of fewer bags, less volume per dose, and the ease of a resuscitation automatically balanced between erythrocytes, clotting factors, and platelets. The hemostatic advantages of whole blood also appear to be preserved even after several days of postcollection quarantine and up to 3 weeks of storage.[25] Many of these features make whole blood ideal for prehospital settings and air or ground ambulance transport where space and simplicity are at a premium.[26] Since prehospital patients cannot have pretransfusion testing, the whole blood must be as universally compatible as possible. All whole blood comes from group O donors, and in order to avoid incompatibility between donor plasma and patient

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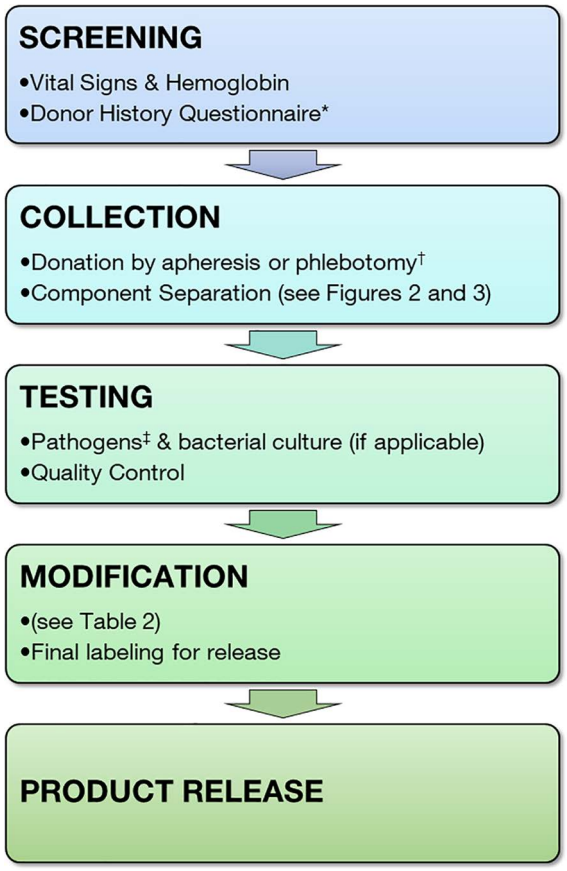

Fig. 1. A simple blood donor screening and collection workflow. The principal way that we ensure a safe blood supply is by selecting healthy donors and deferring those who engage in high-risk behaviors. *The Donor History Questionnaire is used by essentially all blood centers in North America.[3] Questions cover all aspects of health, emphasizing exposures that increase infection risk.[4,5] †In phlebotomy, 450 to 500 ml of whole blood is drained by gravity.[6] About 85% of red blood cells in the United States are collected by phlebotomy.[7] In apheresis, blood is drawn into a bedside centrifuge and separated by density, and then any unused fraction, *e.g.*, plasma, is returned. ‡The Food and Drug Administration requires that all donations be tested for hepatitis B and C, human immunodeficiency virus 1 and 2, human T-cell leukemia viruses 1 and 2, syphilis, West Nile virus, Chagas disease, and—in endemic donor regions—babesiosis.[8]

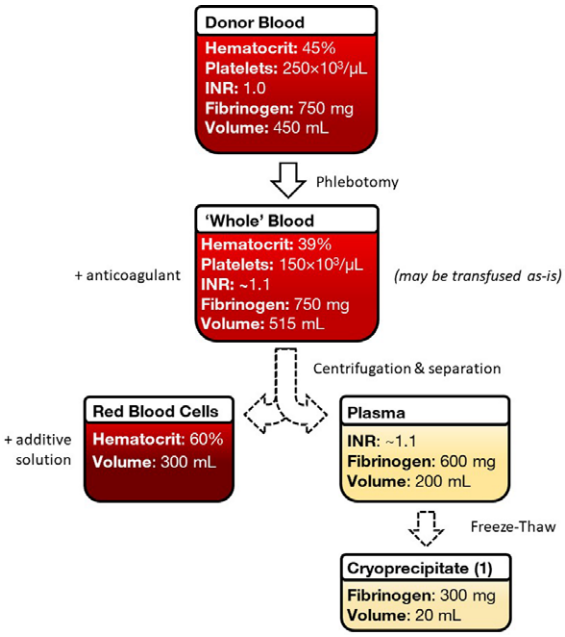

Fig. 2. Separation of whole blood into components. Donor blood is collected in anticoagulant and may be transfused as whole blood. If it is to be separated into components, then it is centrifuged. The plasma fraction containing most of the anticoagulant is expressed off the top, and the concentrated red blood cells are then mixed with an additive solution to improve shelf life. Some platelets may also be collected from the plasma or buffy coat (not shown). After freezing, plasma may be cold-thawed at 4°C to bring some proteins out of solution, or "cryoprecipitated." One unit of cryoprecipitate derived from one unit of plasma is typically pooled into bags of five units for adult dosing, with 1.25 g fibrinogen and a volume of 100 ml. All values are approximate.

red cells ("minor" ABO incompatibility), we select donors with naturally low titers of anti-A and anti-B antibodies, hence "low-titer."

Ideally, all prehospital whole blood would also be Rh-negative (D-negative), in order to avoid provoking anti-D antibodies in patients of child-bearing potential and risking future hemolytic disease of the fetus or newborn. However, only 15% of U.S. donors are Rh-negative, so many centers have cautiously implemented prehospital whole blood programs with only Rh-positive blood or mixed Rh inventories. Data to date have not shown significant harm with this approach, and protocols using postexposure Rh immune globulin can further mitigate risks.[27]

Although we do not yet have high-level evidence on the relative efficacy of whole blood *versus* components in any setting, early data and anecdotal experience in civilian and military settings are positive.[28–30] Two actively recruiting randomized trials will compare low-titer group O whole blood with component-based resuscitation in trauma over the next few years.[31,32]

The trauma team consults transfusion medicine and obstetrics, who arrange a discussion with the patient about her desire for future fertility. The patient affirms that she plans to have children, and an appropriate dose of Rh immune globulin is given.

Stored Red Blood Cells

A 30-week-old, 1,050-g neonate with multiple congenital abnormalities is scheduled for repair of anorectal malformations. Her preoperative hemoglobin is 6.8 g/dl, and 10 ml/kg red blood cells is transfused before surgery. The transfusion is uneventful, but the

Table 1. The Five Common Blood Component Products Available for Clinical Transfusion

Product	Contents and Laboratory Values	Volume	Preservative	Shelf Life	Typical Purchase Price[1]
Low-titer group O whole blood	Hematocrit: 39% Platelets: 150×10^3/μl* INR ~1.1 Fibrinogen: 240 mg/dl <256 anti-A and anti-B Ab titers[10,11]	515 ml	Buffered citrate	21–35 d at 1–6°C[12] (7–14 d for best platelet function)[13]	$500
Red blood cells	Hematocrit: 50–65%[14] Trace plasma	250–300 ml	Buffered citrate, additive solution	42 d at 1–6°C (in additive solution)[6]	$200–$220
Plasma†	Plasma: INR: ~1.1[15]	200–400 ml	Buffered citrate	1 yr frozen (up to 7 in some circumstances)[6] Up to 5 d after thawing[16]	$45–$60
Platelets	Hematocrit: not applicable (trace red blood cells)‡ Platelets: $3–4 \times 10^{11}$ total INR: 1.1 (in plasma) or 2.1 (in additive solution) Fibrinogen: 500 mg (in plasma) 150 mg (in additive solution)	250 ml	Buffered citrate, ± additive solution[17,18,19]	Up to 5 d (7 with some testing methods)	$500 ($625 for pathogen-reduced)
Cryoprecipitate	Fibrinogen: 300 mg (1.5 g per five-unit pool)[20] Other concentrated factors: factor VIII, factor XIII, vWF, fibronectin. Trace immunoglobulins, antithrombin	20 ml (100 ml per five-unit pool)	Buffered citrate	1 yr frozen, 6 h after thawing	$250–$300 per five-unit pool

*If nonleukoreduced, or if a platelet-sparing leukoreduction filter is used. †Although "fresh frozen plasma" is a common term for plasma, only approximately 25% of plasma units in the United States are frozen within 8 h of collection and truly "fresh frozen." Most hospitals use 8-h fresh frozen plasma and plasma frozen within 24 h ("FP24") interchangeably.[1] ‡Not applicable. However, because of the trace red blood cells in any platelet unit,[6,21] Rh type is matched when feasible. If an Rh-negative patient of childbearing potential receives an Rh-positive unit, it may be appropriate to give anti-Rh antibody (*e.g.*, RhoGAM, Kedrion Biopharma, USA) to prevent Rh alloimmunization.[22–24]

INR, international normalized ratio; vWF, von Willebrand factor.

posttransfusion hemoglobin is 8.3 g/dl. The neonatology fellow is concerned that the hemoglobin did not rise further, and suggests a hemolysis workup.

Stored red blood cells contain red cells (erythrocytes), citrate anticoagulant, additive solution, some white blood cells, and trace plasma. A unit of red cells in additive solution has a hematocrit of around 60%, although this may vary from 50 to 70%. Although now less common, red cells stored without additive solution may have a hematocrit greater than 80%. One unit in additive solution will raise the hemoglobin in a 70-kg adult by around 1 g/dl, although there is substantial variation.[33] In a small neonate, these variations are exaggerated, and the absolute rise may be as little as 1.0 g/dl or as much as and 3.0 g/dl after a 10- to 15-ml/kg dose.[14]

The hemoglobin level is currently the most common and widely explored guide to red cell transfusion. In the 24 yr since the publication of the Transfusion Requirements in Critical Care trial,[34] greater than 36,000 mostly adult, usually hemodynamically stable patients have been enrolled in experiments to identify the ideal trigger for a erythrocyte transfusion,[35] with the conclusion that a "restrictive" trigger somewhere between 7 and 8 g/dl is appropriate for most patients in most circumstances.[36] The lack of sharply marked benefit or harm for transfusions between 7 and 10 g/dl, however, suggests that better and more physiologic measures to guide red cell transfusion are desperately needed. It should be noted that the safety and clinical equivalence of "older" units near the end of their shelf life have also been firmly established in large, randomized trials in adults and children.[37]

The neonatology attending consults with transfusion medicine. A residual segment of the unit is tested and found to have a hematocrit of 49%, accounting for the lower-than-expected rise in patient hemoglobin. The child has a successful and uncomplicated surgery.

Plasma

A 55-yr-old woman with end-stage liver disease awaiting transplant is transferred to the intensive care unit for suspected sepsis in the setting of spontaneous bacterial peritonitis and an upper gastrointestinal bleed. Her international normalized ratio (INR) is 2.9. The critical care resident orders two units of plasma to be transfused before placing a central line.

Stored plasma contains all the acellular chemical and protein ingredients of blood, including albumin, coagulation factors, and immunoglobulins. Dilution with anticoagulant lowers the coagulation factor activity in stored plasma

to around 80%, or roughly an INR of 1.1.[15] Although this seems normal, we know that plasma transfusion only modestly lowers INRs in the 1.5 to 3.0 range,[38] that the effect weakens with each additional transfusion,[39] and that prophylactic plasma before invasive procedures may not reduce bleeding complications.[40] In the complex coagulopathy and physiology of liver disease, attempting to correct abnormal results with large volumes of plasma may in fact worsen bleeding.[41,42] With the widespread availability of prothrombin complex concentrates for warfarin reversal and recombinant antithrombin for heparin resistance, there are now few indications for plasma transfusion outside of major hemorrhage, disseminated intravascular coagulation with bleeding, or apheresis exchange.[43]

After reviewing the orders, the transfusion medicine physician on call recommends proceeding without transfusion, or ordering additional coagulation testing. A rapid thromboelastogram is performed, which has a normal reaction time, clotting time, alpha angle, and a mildly elevated maximum amplitude. The resident defers transfusion, and the line is placed with minimal bleeding.

Platelets

During separation from cardiopulmonary bypass after a combined aortic valve replacement and single-vessel coronary artery bypass graft in a 59-yr-old man, the surgeon reports severe bleeding in the mediastinum and urges the transfusion of several units of platelets. Viscoelastic testing with heparinase sent before separation from bypass did not detect any coagulation deficits.

Units of platelets contain platelets (thrombocytes), plasma, storage solution, and trace amounts of red and white blood cells. Almost all platelets in the United States are now collected in concentrated units by apheresis from a single donor, although a few are still collected from whole blood of multiple donors and pooled (fig. 3).[6] Prophylactic platelet transfusion triggers for stable medical patients have been established in adults and children, and most adults do not require transfusion until the platelet count is less than $10 \times 10^3/\mu l$.[44,45] Periprocedural or surgical platelet transfusion, by contrast, suffers from a lack of high-quality trials or studies.[46] Many guidelines recommend platelet count thresholds for specific surgeries or procedures, and these are dubiously interpreted as goals for transfusion or indications for prophylaxis.[47,48] Part of the problem with interpreting suggested platelet counts as transfusion goals is that stored platelets do not function as well as native platelets, especially right after transfusion. A patient with a platelet count of $50 \times 10^3/\mu l$ who is transfused up to $80 \times 10^3/\mu l$ is therefore not necessarily equivalent to a patient who already has a count of $80 \times 10^3/\mu l$.[49,50]

Platelets stored "cold" at refrigerator temperatures are receiving renewed interest. Cold-stored platelets appear to have immediate hemostatic benefits and a reduced risk of infection compared to standard room-temperature

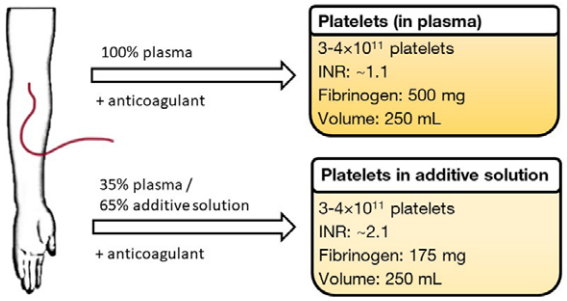

Fig. 3. Collection and modification of apheresis platelets. Initially, platelets are collected in a solution of citrate-anticoagulated donor plasma or a mixture of 35% plasma and 65% platelet additive solution. Leukocytes are separated from platelets as part of the apheresis process.

platelets, although at the expense of shortened posttransfusion survival.[51,52] There are also a number of studies assessing freeze-dried or frozen platelet preparations, as well as novel biotherapies using platelet-like synthetic particles. Randomized trials are in process to assess their efficacy and safety in several settings.[53]

After reviewing the coagulation tests, the anesthesiologist informs the surgeon that there is no apparent indication for transfusion. After a brief period of packing with laparotomy sponges, the surgeon identifies a small posterior mediastinal injury and repairs it. No platelet transfusions are given, and separation is completed uneventfully.

Cryoprecipitate

A 23-yr-old woman with no significant past medical history is in the third stage of labor. Her estimated blood loss so far is 1,300 ml, and the obstetrician reports continued bleeding. A fibrinogen drawn immediately after delivery is 177 mg/dl.

Cryoprecipitated antihemophilic factor, commonly known as "cryo," is a plasma derivative containing concentrated fibrinogen, factor VIII, factor XIII, von Willebrand factor, and fibronectin (table 1).[20] One unit of plasma will make one unit of cryoprecipitate (fig. 2), which is often combined into a five-unit pool for easy dosing in adults. Transfusing two five-unit pools will increase the fibrinogen level by 80 to 100 mg/dl in a stable adult patient. Since cryoprecipitate is pooled from multiple sources, there is higher risk for bacterial growth, and depending on how it was prepared, it must be transfused within 4 to 6 h of thawing. Use of cryoprecipitate is steadily increasing across the United States.[54,55] Possible explanations include the widespread adoption of viscoelastic testing platforms—which tend to emphasize fibrinogen deficiencies[56–58]—and a generally increased awareness of the dangers of coagulopathy. Over the last 10 yr, most major perioperative societies in the United States and Europe

have increased their recommended fibrinogen targets in a variety of bleeding scenarios.[59–63] The evidence behind these recommendations is not strong, but there are some data that fibrinogen replacement is a beneficial alternative to platelet transfusion in postcardiopulmonary bypass bleeding,[64,65] and there are a few studies backed by expert consensus supporting cryoprecipitate in postpartum hemorrhage.[66,67]

Recently, human-derived fibrinogen concentrates and commercially manufactured pathogen-reduced cryoprecipitate have emerged as alternatives to traditional cryoprecipitate transfusion. Fibrinogen concentrates can be stored dry and reconstituted at the bedside,[68] and pathogen-reduced cryoprecipitate can be kept thawed for up to 5 days.[69] These features may make them attractive for situations where rapid delivery of traditional cryoprecipitate is not possible.

The hospital Maternal Hemorrhage Protocol is activated. The patient receives 10 units of cryoprecipitate, after which her fibrinogen is 201 mg/dl. She receives another 10 units of cryoprecipitate. Hemostasis is achieved shortly afterward, and her final fibrinogen is 244 mg/dl. Subsequent recovery is uncomplicated.

Modifications to Stored Blood

Blood products may be modified during or after manufacture to reduce the risk of specific complications. As many as 1 in 50 transfusions causes some reaction, and severe or life-threatening complications occur in roughly 1 in 10,000 transfusions.[1,36] Not every reaction can be avoided, but many risks can be greatly reduced by modification.

Additive Solutions

An 81-yr-old woman arrives in the postanesthesia care unit after craniotomy for resection of a glioblastoma. Her first postoperative platelet count is $79 \times 10^3/\mu l$, and the neurosurgery resident orders one unit of apheresis platelets. Fifteen minutes after starting the transfusion, the recovery nurse reports that the patient has an erythematous rash on her chest with a raised, central wheal. She is otherwise stable.

Additive solutions are buffered salt and sugar mixtures that can be blended into a stored product to improve the function or lifespan of stored cells. All available red cell additive solutions extend their lifespan out to 6 weeks (table 1), and newer additive solutions not yet in wide use have demonstrated improved posttransfusion recovery rates and even longer shelf-lives.[70] Modern platelet additive solutions, by contrast, do not much alter platelet function or lifespan.[71,72] However, platelet additive solutions replace 50 to 80% of the plasma content from the platelet unit, which allows more plasma to be reserved for plasma transfusions, reduces rates of allergic reactions, and may reduce the risk of hemolysis from minor plasma incompatibility.[72,73]

After examining the patient, the anesthesiology resident diagnoses an allergic transfusion reaction. The patient receives 25 mg diphenhydramine, the rash begins to resolve, and the transfusion is restarted without further incident. When discussing the case, the transfusion medicine physician on call notes that the hospital is phasing out their supply of platelets in plasma in favor of platelets in additive solution.

Leukoreduction

A 71-yr-old, 81-kg man with a history of atrial fibrillation undergoes repair of a traumatic hip fracture. In the postanesthesia care unit, his hemoglobin is 6.2 g/dl, and he receives one unit of red blood cells. Fifteen minutes into the transfusion, he complains of chills, and his temperature is 38.2°C.

White blood cells release cytokines and other inflammatory mediators into the liquid portion of the unit during storage. These factors can cause a number of adverse events, of which fevers are the most common. After removing the white blood cells through filtration or centrifugation—"leukoreduction" of the blood—fever and other complications are less frequent (table 2).[1,74–82] More than 97% of blood products in the United States are leukoreduced by the collecting blood center before storage,[79,81,83] and this practice is universal in Canada, the United Kingdom, Australia, and New Zealand.[76,83] Some commercial leukoreduction filters will also remove platelets, and for this reason, not all whole blood units for transfusion are leukoreduced.[81] Since febrile, nonhemolytic transfusion reactions are caused by donor rather than recipient factors, there is no benefit in routine transfusion premedication with an antipyretic.[84]

The transfusion is stopped immediately, and a reaction workup is started. Clerical checks reveal no errors, there is no evidence of hemolysis in a posttransfusion specimen, and a direct antiglobulin test is negative. The transfusion medicine service makes a diagnosis of a febrile, nonhemolytic transfusion reaction, and the remainder of the unit is discarded. A second transfusion is completed without incident.

Irradiation

An 8-yr-old girl is scheduled for resection of a tibial osteosarcoma. During the surgery, the anesthesiologist orders a unit of red blood cells to correct a hemoglobin of 6.8 g/dl. Shortly afterward, the blood bank calls to ask if the anesthesiologist wants the blood to be irradiated.

Even after leukoreduction, there are a large number of remaining white blood cells in any unit of whole blood, red cells, and platelets. In a severely immunocompromised patient, these white blood cells may become established and cause a severe multiorgan syndrome called transfusion-associated graft-*versus*-host disease, which is fatal in greater than 90% of cases.[85] Fortunately, transfusion-associated graft-*versus*-host disease is both rare and preventable with irradiation. The selected unit is exposed to a modest dose from a radioisotope or x-ray emitter, and the damage this causes to the white cell DNA stops further replication (table 2). Because transfusion-associated graft-*versus*-host disease is so

Table 2. Common Blood Component Product Modifications

Modification	Effects	Products	Indication	Notes
Additive solutions	Buffers pH and provides electrolytes and energy substrates	Red blood cells* Platelets	Extend shelf life Improve cell recovery Preserve plasma for other indications Reduce transfusion reactions	Addition of additive solution to platelets reduces fibrinogen content to 200 mg and increases INR to ~3.0
Leukoreduction	Removes most white blood cells[69]	Red blood cells Whole blood† Platelets	Reduces: Febrile reactions[68] Human leukocyte antigen alloimmunization[64] Cytomegalovirus infection[67,70]	97% of all U.S. red blood cells and platelets are leukoreduced at the collecting blood center[1]
Irradiation	Nucleotide damage prevents leukocyte replication	Red blood cells Whole blood Platelets	Reduces risk of transfusion-associated graft-*vs.*-host disease in immunocompromised, immunodeficient, or patients receiving blood from matched or related donors	After an erythrocyte unit is irradiated, its total shelf life is reduced from 42 to 28 d
Pathogen reduction	Prevents nucleotide transcription and replication with using a covalently bonded adduct	Platelets Plasma Cryoprecipitate	Reduces risk of bacterial and viral infection‡ Eliminates need for irradiation	Posttransfusion platelet count boost is reduced from ~30×10^3/μl to ~20×10^3/μl Adds ~$125 to the cost of the unit
Washing	Removes residual plasma and storage solution	Red blood cells Platelets	Reduces: Allergic or anaphylactic reactions[72] Removes excess glycerol or potassium from frozen or old units	Breaks sterile seal of unit, so red cells must be used within 24 h, and platelets within 4 h[65]

*Standard buffered citrate solution contains citrate, phosphate, and dextrose. There are four erythrocyte additive solutions in the United States: AS-1, AS-3, AS-5, and AS-7, which all contain additional dextrose and adenine. AS-3 includes additional phosphate and citrate. The others all include 500 to 1,000 mg mannitol. †Some whole blood units for transfusion are not leukoreduced, because platelet-sparing filters are not available with all storage solutions.[71] ‡Certain pathogens including hepatitis A, hepatitis E, human parvovirus B19, poliovirus, and *Bacillus cereus* spores are not inactivated.

INR, international normalized ratio.

rare and the exact risk factors are not well-defined, different institutions will have different triggers for irradiation.[85] Commonly shared indications include stem cell transplants, congenital immunodeficiencies, intrauterine transfusions, lymphoid malignancies, and children less than 4 to 12 months of age. Irradiation shortens the acceptable shelf life of the red cell unit to either 28 days or the original expiration date, whichever is sooner. Irradiation may also increase the potassium content of the unit, which has rarely been implicated in cases of transfusion-associated hyperkalemic arrest, usually in small children administered blood rapidly through a central line during a surgery.[86]

The anesthesiologist submits a corrected order asking for irradiated blood, and the transfusion and surgery are completed without complications. After the case, a working group is convened between the operating room, surgery, anesthesiology, and the blood bank to create a standard procedure for ordering irradiated blood.

Pathogen Reduction

A 64-yr-old man is in intensive care after open repair of a thoracoabdominal aortic aneurysm. Three units of platelets were transfused intraoperatively. On postoperative day 1, the blood bank is notified by the donor center that a pretransfusion surveillance culture from one of the platelet units has growth in both aerobic and anaerobic bottles. Patient blood cultures are all negative.

Thorough skin preparation before blood donation reduces, but cannot completely eliminate, the burden of bacteria. Some bacteria are always inoculated into the donated blood, although most colonies do not survive at refrigerator temperatures. Platelet units have the highest risk of bacterial transmission because they are stored at room temperature, with a contamination rate of approximately 1 in 1,000 units.[87,88] Traditional pretransfusion bacterial surveillance methods were insufficient to detect most of these contaminations.[89] It should be noted, however, that reactions requiring fluids, antibiotics, or vasopressor administration occur after fewer than 1:10,000 transfusions,[90–92] with an estimated 10 attributable deaths per year in the United States.[92] *Staphylococcus, Streptococcus*, and Gram-negative bacteria are usually implicated in septic reactions, but the majority of positive cultures are caused by generally nonvirulent bacteria such as *Cutibacterium*.

Prestorage pathogen reduction eliminates the need for surveillance cultures by preventing replication of viruses or bacteria in the unit (table 2). In most U.S.-licensed pathogen reduction technologies, the unit is infused with a psoralen compound that covalently binds to nucleotides after exposure to ultraviolet light. These covalent adducts prevent DNA and RNA transcription and replication. A happy side effect is the inhibition of leukocyte division, eliminating the need to irradiate if irradiation was indicated.[93] Although pathogen reduction is effective for its stated purpose, it adds around $125 to the cost of every unit,[1] reduces the average posttransfusion platelet count boost from 30,000 to 20,000 cells/mm^{-3}, and increases transfusion requirements.[94] In

Table 3. Important Transfusion Reactions in Perioperative Practice

Reaction (and Cause)	Timing/Rate	Clinical Features	Management
Acute hemolytic transfusion reaction (usually ABO incompatibility)[96]	Usually immediate (but within 24 h) 1 in 70,000–100,000 transfusions	Fever/chills and rigors Back or flank pain Dark or red urine Diffuse bleeding or oozing Mortality ~25%	Stop transfusion Bolus crystalloid and loop diuretics Close supportive care
Delayed hemolytic transfusion reaction (usually non-ABO incompatibility)[96]	5–10 d (but between 1 and 28 d) 1 in 2,000–5,000 transfusions	Often asymptomatic Possible fever, fall in hemoglobin, jaundice and hyperbilirubinemia Rarely, hypotension or acute kidney injury	Usually no treatment required Follow symptoms, hemoglobin, creatinine
Febrile, nonhemolytic transfusion reaction (usually proinflammatory cytokines accumulating during storage)[96]	Minutes to hours 1 in 200–2,000 red cells 1 in 20–200 platelets	Fever (>1°C rise from baseline) Rigors and chills	Stop transfusion Rule out hemolytic reaction Treat with antipyretic Pretreatment for future transfusions is not supported by evidence
Anaphylaxis (severe hypersensitivity to donor)[97]	Usually immediate 1 in 20,000–47,000 transfusions	Shock Bronchospasm/edema Rigors Normothermia	Epinephrine Supportive care Washed red blood cells/platelets in transfusion urgently required
Allergic (mild-to-moderate hypersensitivity to donor)[97]	Minutes to hours 1 in 100 transfusions	Rash (localized ↔ severe) Urticaria Pruritus Swelling (localized ↔ severe)	Pause transfusion Treat with antihistamines ± steroids Consider resuming transfusion if symptoms are mild and resolving Pretreatment for future transfusions is not supported by evidence
Sepsis (bacterial contamination)[98]	Minutes to hours 1 in 2,000 (bacterial transmission) 1 in 10,000 (reactions requiring support)	Fever or chills/rigors Shock Dyspnea Nausea/vomiting	Stop transfusion (if ongoing) Broad-spectrum antibiotics Supportive care
Transfusion-related acute lung injury (typically donor antibodies reacting with primed host neutrophils)[99]	Usually during the transfusion, but must occur within 6 h	Hypoxemia Normo- or hypotension Pulmonary edema by imaging No cardiac cause/alternate cause of lung injury Mortality 10–15%	Stop transfusion (if ongoing) Positive pressure ventilation (required in ~70% of cases) No role for steroids
Transfusion-associated circulatory overload (acute volume overload)[100]	Usually during the transfusion 1 in 100 (all transfusions) 1 in 600 (single-unit transfusions)	Hypoxia Pulmonary edema Hypertension Tachycardia	Stop transfusion Upright position Provide oxygen Positive pressure ventilation as needed Loop diuretics If transfusion still needed, use slow rates

2020, the Food and Drug Administration (Silver Spring, Maryland) released new guidance for blood centers requiring either more sensitive bacterial testing for platelet units, or adoption of pathogen reduction.[95] Many blood collection agencies, including the American Red Cross, are transitioning to pathogen reduction for all platelet units.[96]

After several days of empiric therapy with broad-spectrum antibiotics, the laboratory identifies the surveillance cultures as Cutibacterium acnes. *On the recommendation of the infectious disease department, further broad-spectrum therapy is discontinued. The patient never displays signs of sepsis.*

Washing

A 34-yr-old woman with no history of transfusion suffers a hepatic artery injury during a cholecystectomy. Immediately upon transfusion of one unit of red blood cells, she develops severe hypotension and tachycardia, and increased peak ventilatory pressures. The anesthesiologist stops the transfusion immediately and administers epinephrine. On postoperative day 1, her hemoglobin is 4.4 g/dl. The surgeon is concerned that the patient cannot be safely transfused again.

Anaphylactic transfusion reactions are a rare but life-threatening complication of transfusion. These reactions are usually idiopathic responses to an allergen in the donor plasma, although a subset of cases is attributed to anti-IgA reactions among patients with absolute IgA deficiency. Washing the residual plasma from cellular products such as red blood cells or platelets will usually render them safer for transfusion, and this can be done presumptively even in the absence of a clearly identified allergen. The washing process requires breaking the sterile seal of the unit, so even if all precautions are taken, it must be transfused

Table 4. Further Resources

Title	Authors/Editors	Notes
Practical Transfusion Medicine, 6th Edition	Michael F. Murphy David J. Roberts Mark H. Yazer Nancy M. Dunbar	An excellent, brief, and accessible textbook on all aspects of transfusion medicine.
Perioperative Transfusion Medicine, 2nd Edition	Bruce D. Spiess Richard K. Spence Aryeh Shander	A comprehensive textbook on blood supply, blood banking, oxygen physiology, and transfusion medicine written with anesthesiologists in mind.
Association for the Advancement of Blood and Biotherapeutics Technical Manual, 20th Edition	Claudia Cohn Meghan Delaney Susan T. Johnson Louis M. Katz	A highly detailed reference book aimed at transfusion medicine physicians and technicians, but containing clearly written details about blood contents, processing, and regulation.
Circular of Information	American Red Cross Association for the Advancement of Blood and Biotherapeutics America's Blood Centers Armed Services Blood Program	A pamphlet with brief but comprehensive information about blood components and component modification intended to provide detailed information for any physician or provider about blood in the U.S. supply. Available at: https://www.redcrossblood.org/content/dam/redcrossblood/forms-and-certificates/Circular%20of%20Information%202017.pdf. Accessed August 3, 2023.
BBGuy.org	Joseph Chaffin	A free, online educational resource including videos, glossary, and podcast episodes with major figures in blood banking, transfusion, anesthesiology, and emergency care.

promptly (table 2).[75] Washing is time-consuming, so it is usually only suitable for planned transfusions of a limited number of products. Patients with anaphylactic reactions who require plasma transfusion may be a challenge to care for. Case reports of anaphylactic reactions to prothrombin-complex concentrates suggest that factor concentrates are not necessarily safe substitutes for plasma.[97] Washing is also used to remove glycerol from frozen units or concentrated electrolytes such as potassium from older units.

After consultation with the transfusion medicine service, the patient is issued a unit of washed red blood cells. The transfusion is started slowly, and the patient shows no signs of reaction. Two more washed erythrocyte units are transfused without incident.

Transfusion Reactions

A 35-yr-old woman with a history of autoimmune liver disease complicated by renal failure on hemodialysis is undergoing a simultaneous liver–kidney transplant. The liver transplant was uncomplicated, but during the kidney transplantation, the surgeon states that there is significant mucosal bleeding. Coagulation testing is notable for a platelet count of $32 \times 10^3/\mu l$. Shortly after transfusing one unit of apheresis platelets, the anesthesiologist observes increased peak inspiratory pressures and frothy secretions in the endotracheal tube. The patient is hemodynamically stable.

Many product modifications are made with the intention of reducing transfusion reactions. Apart from the reactions encountered in cases above, there are many others that the anesthesiologist may encounter at the bedside. For example, transfusion-related acute lung injury is an inflammatory syndrome typically caused by donor antileukocyte antibodies interacting with primed recipient white blood cells in the lung, which leads to acute respiratory distress.[98] Since the introduction of widespread leukoreduction and screening of parous donors for antileukocyte antibodies, rates of these reactions have fallen, but they still occur in every 5,000 to 10,000 transfusions, and up to 5% are fatal.[99] This, and other important reactions that may be encountered by the anesthesiologist, such as hemolytic reactions, allergic reactions, and volume overload, are summarized in table 3.[98,100–104]

The anesthesiologist sends an arterial blood gas that returns a P_{AO_2} of 72 mmHg on a fractional inspired oxygen tension of 0.6. She makes a diagnosis of transfusion-related acute lung injury, and calls the transfusion medicine service to report the reaction. The patient's workup is otherwise normal, and the rest of the transplant proceeds without complications. In the intensive care unit, the patient's chest x-ray is notable for diffuse bilateral pulmonary infiltrates. After 2 days, she is successfully weaned from the ventilator.

Summary

Stored blood is one of our greatest medical innovations. More than 100 yr of transfusion science has resulted in a blood supply that is astonishingly safe, flexible, and predictable. However, every transfusion is still a balance of benefits and risks. Blood products now come in many forms with many possible modifications, and the physician at the bedside must be aware of what they are giving and what that will mean for their patients. For the interested reader, I have provided a brief list of articles, books, and online resources for further education (table 4). New ideas and techniques to improve the efficacy and safety of stored blood are always needed.

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Competing Interests

The author declares no competing interests.

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