

# **Transfusion Therapy: Clinical Principles and Practice, 4th Edition**

## **Chapter 1. Blood Components: Preparation and Modification**

The collection, processing, and provision of blood and blood components to patients is a discipline in medicine facing three very different directions. The first is the motivation and management of volunteer donors who are the source of components that will be used to treat patients. Second is the highly regulated collection of the source blood components, testing of the donors, and manufacture of products. These processes are licensed by the overseeing regulatory authority [the Food and Drug Administration (FDA) in the United States, for example] and standardized by appropriate professional oversight associations, such as AABB.

The third aspect of blood component provision is interaction with the medical teams providing treatment to patients, in order to provide for the routine and special needs of patients served in their particular medical community. The components produced may be specially designed for the needs incurred when treating high-level trauma patients. A different array of components is required for patients undergoing intensive chemotherapy, cellular therapy, or other cancer treatment-related interventions. Component modifications produce some commonly prepared special products that receive their final product changes just before transfusion, to meet special patient needs.

Component production is continually examined to improve safety of the products. Improvements in donor screening and testing are continually being offset by the emergence of new infectious diseases. Significant advances have been made over the last 40 years in decreasing the infectious disease risks in plasma-based products through pathogen inactivation interventions. Despite donor testing and care in collection, the risk of bacterial contamination remains in platelet production, for example, because the method of collection cannot exclude all bacteria from the original product, and the required storage conditions for platelets allow for growth of included bacteria. New and improved methods for preparing platelets promise additional decrease for this risk.

Cooperation between blood collection and processing agencies and experts in patient care fields will facilitate specialized treatments of the future just as they have supported treatments in the past.

## **Chapter 2. Red Cell Transfusion Therapy in Anemia**

Anemia, whether acute or chronic, presents significant global health issues. It has a multitude of causes for which RBC transfusion, traditionally, has played a significant role. Although Red Blood Cell (RBC) transfusions provide life- or limb-saving therapy in specific clinical situations and patient populations, clinicians must address alternative options based on the etiology of anemia, transfusion risks, and subsequent outcomes.

Transfusion remains one of the most common and overutilized procedures performed in health care today. In high-income countries, transfusion occurs most commonly among patients undergoing cardiovascular surgery, massive trauma, transplant surgery, and hematologic or solid-malignancy treatment. On the basis of current randomized controlled trials and multiple observational and prospective studies, the preponderance of data support restricting RBC transfusion when the hemoglobin concentration is  $>7.0$  g/dL. Currently, maximizing transfusion effectiveness focuses on prescribing RBC transfusion at a nadir of 7.0 g/dL hemoglobin concentration in most clinical settings. A 7.5 g/dL threshold for transfusion appears to be safe and effective for those undergoing cardiovascular surgery. In patients with acute coronary syndromes and acute myocardial infarction, transfusion at a threshold of 8.0 g/dL appears prudent.

Acknowledging hemoglobin *thresholds* as opposed to *triggers* distinguishes a *trigger* as an automatic or reflex order, whereas a *threshold* indicates a hemoglobin level at which patients are safely maintained and unnecessary transfusions avoided. This implies that hemoglobin levels alone are not a sole criterion for transfusion. All clinically relevant symptoms and signs must be considered for each patient. Outside of massive hemorrhage, embedding single-unit strategies to limit RBC exposure reflects current transfusion practice.

Concerns expressed recently suggest that changes related to RBC storage adversely affect transfusion efficacy. Although laboratory studies indict “storage lesion” issues, recent RCTs find no correlation between the storage interval and clinical outcomes. Continued research into RBC storage and processing, as well as recipient and donor proteomics and metabolomics, is ongoing, but the results require evaluation before practices could be changed.

Carefully conducted, well-designed clinical trials furnish clinicians with important information about transfusion therapy. Ongoing studies involving oxygen physiology, therapeutics, storage-related changes, pretransfusion and molecular testing, as well as interventions to reduce transfusion risks provide new opportunities for defining future transfusion practices.

### **Chapter 3. Platelet Transfusion Therapy**

Recommendations exist for appropriate platelet dosing in the setting of amegakaryocytic thrombocytopenic bleeding. For central nervous system, retinal, or life-threatening bleeding, higher posttransfusion target platelet counts (eg, 75,000 to 100,000/ $\mu$ L) are typically used. Newer guidelines will also help guide thresholds for platelet transfusion and provide recommendations in which transfusion is likely to improve hemostasis and benefit the patient.

The recommended doses should be adjusted for the patient’s size with the use of current platelet content data for both whole-blood-derived platelets and apheresis platelets. Standard doses are convenient *starting* points for platelet transfusion in most patients if they increase the platelet count enough to produce the desired clinical outcome. Adjustments to dose and frequency of transfusion are often required because of coexisting clinical factors. More data are needed in diverse clinical settings to determine the appropriate threshold, dose, and frequency of platelet transfusion. Until these studies are completed and more RCTs are performed, extrapolation from the few existing reports will have to suffice.

### **Chapter 4. Plasma Therapy: Available Components, Indications, Dosing, and Special Circumstances**

Plasma transfusion is an important, often life-saving therapy for bleeding patients or those undergoing major invasive procedures. Simple-appearing on the surface, plasma therapy is nonetheless highly complex. Dosing of plasma should be strictly driven by laboratory and clinical criteria and should follow weight-based algorithms to ensure efficacy. Complexity in plasma therapy resides not only in dosing approaches, but also in the various forms of plasma products now routinely available for care.

In order to be the best possible consultants for our clinician colleagues, and to maximize patient safety, transfusion medicine specialists must remain vigilant regarding the following:

- Availability of new plasma formulations.
- Evolution of pathogen inactivation technologies.
- Possible adverse events associated with plasma infusion.
- Emergence of human-derived or recombinant coagulation factors, which may offer superior alternatives to allogeneic plasma therapy.

In addition, while there is increasing evidence accumulating from retrospective studies helping us to understand when plasma therapy may be appropriate in various disorders, a future goal of the transfusion community should be the performance of rigorous, prospective clinical trials to more sharply define the role plasma should play in clinical settings.

### **Chapter 5. Cryoprecipitate: Indications and Dosing**

Cryoprecipitate contains more concentrated fibrinogen, Factor VIII, vWF, Factor XIII, and fibronectin than plasma products. Most of these proteins are also available as plasma-derived or recombinant concentrates. When the individual component is not available, one to two pools from five donors each are frequently administered, most often to replete fibrinogen. It may be used in trauma, obstetric hemorrhage, uremic bleeding, cardiothoracic surgery, or individual-factor replacement therapy. Because cryoprecipitate is a blood component, the risks of receiving it mirror those in platelet or plasma transfusions. More recent trends include the use of viscoelastometry to provide a more targeted approach to improving clotting.

### **Chapter 6. Granulocyte Transfusion**

Granulocyte transfusion has been used to treat life-threatening bacterial and fungal infections that are refractory to standard antimicrobial therapy. Recovery of adequate neutrophils is the strongest predictor of progression of and recovery from invasive infections. Obtaining and transfusing sufficient granulocytes are key to conferring any benefit to patients. Optimal granulocyte mobilization can be achieved in normal donors when a combination of granulocyte colony-stimulating factor and dexamethasone are used. Studies have shown mixed results regarding the efficacy of granulocyte transfusions. Early initiation of granulocyte transfusion therapy may increase the response rates in children. Patient weight and the number of transfused cells per kilogram of body weight have been found to be major determinants of survival in pediatric patients. There is paucity of evidence to determine the effect of granulocyte transfusions to all-cause mortality. More prospective, large, randomized, controlled studies are needed to determine the efficacy of high-dose granulocyte transfusion therapy. An international registry may be useful in gathering sufficient data to provide definitive answers.

### **Chapter 7. Blood Derivatives and Growth Factors**

Both plasma-derived therapies and recombinant growth factors are vitally important to the patients who receive them. Yet, it should be noted that most of the therapies discussed in this chapter are quite expensive. The global market for plasma-derived therapies has been growing at a rate of ~10% per year. However, the United States and Europe, which account for a small percentage of the global population, consume 75% of the total plasma-derived therapies produced.

Approximately 70% of the plasma fractionated globally is collected in the United States, likely due to the risk of variant Creutzfeldt-Jakob disease and other infectious diseases in various countries. An estimated 35 million liters of plasma are fractionated worldwide each year; however, only about 35% is recovered plasma. Production costs of plasma-derived therapies are much higher than traditional pharmaceuticals and are estimated to be about 65% of the product price. This is mainly due to the high cost of the raw material including remuneration of donors for source plasma. As more plasma-derived proteins are fractionated, the consequent cost of each individual one may decrease.

There are inherent risks in plasma-derived therapies, namely allergic reactions/anaphylaxis and infectious disease transmission. Despite the manufacturing procedures used, there are still risks of prion

disease as well as new viruses. The benefits and risks of these products should be evaluated for each patient. Overall, these therapies have become much safer over the past 20 years with few reports of infectious disease transmission.

## **Chapter 8. Platelet-Rich Plasma**

The theory behind platelet-rich plasma (PRP) is appealing. Platelets play a central role in healing, not only as central mediators of hemostasis and thrombosis, but also as important regulators of immune and inflammatory processes. By isolating a platelet-enriched fraction and delivering it directly into the injured area, it seems intuitive that PRP would promote healing. Why then have there been such mixed results in the many randomized controlled trials conducted to date? It may be that it is not yet understood how to fully harness the healing powers of PRP. The constituents within PRP that are necessary for healing, appropriate delivery, and dosage are not comprehended. However, researchers in the PRP field are trying to answer these questions. As more rigorous basic science testing is integrated into the PRP clinical arena, answers may develop. These answers may make PRP a more powerful adjuvant for healing or prove that PRP is little more than a placebo.

## **Chapter 9. The Transfusion Reactions and Adverse Events of Transfusion**

Although transfusions are extremely common, they are also mostly safe. Although a reaction or adverse event could happen in up to 1% of the transfusions, the most common are febrile nonhemolytic transfusion reactions and mild allergic reactions, which are not life-threatening. Conversely, similar signs and symptoms such as fever and changes in other vital signs could point to a serious condition such as a septic reaction from a contaminated platelet unit or transfusion-related acute lung injury from any blood product. Close and consistent patient monitoring and early recognition of a reaction are essential to avoid significant morbidity and mortality. In this chapter, we have reviewed the types of reaction and how they are manifested, as well as their pathophysiology and how to treat and prevent them. We also emphasize the importance of monitoring the patient in the days and weeks following a transfusion, for the occurrence of a delayed hemolytic transfusion reaction (DHTR) may be missed without a strong clinical suspicion. A particularly vulnerable patient population, in whom DHTRs are not rare, are patients with sickle cell anemia because the symptoms of a DHTR may mimic a pain crisis. Furthermore, such patients may have been sensitized to red cell antigens but have undetectable levels of alloantibodies in the pretransfusion testing. If their history of alloimmunization is unknown in the facility where they are to be transfused, they are at risk of developing a DHTR. This situation continues to challenge us as we strive to find a solution to ensure that alloimmunization records are shared among institutions.

## **Chapter 10. Transfusion Therapy in Autoimmune Hemolytic Anemia**

Autoimmune hemolytic anemia is characterized by the properties of the pathogenic red cell autoantibodies and the presumptive etiology. The direct antiglobulin test to detect bound IgG and/or complement on the surface of the patient's red cells and other immunohematologic tests distinguish among warm autoimmune hemolytic anemia, cold agglutinin syndrome, paroxysmal cold hemoglobinuria, and drug-induced immune hemolytic anemia. The presence of autoantibodies may interfere in routine pretransfusion typing and compatibility tests, necessitating special studies to select appropriate blood for transfusion. If AIHA is suspected, the clinical history should be communicated to the transfusion service to coordinate the approach to patients with a complex serologic picture so that appropriate testing can be performed to minimize the risk of transfusion. Although transfused RBCs may not have normal survival in patients with red cell autoantibodies, most patients with AIHA tolerate

transfusion and derive at least a temporary benefit. A necessary transfusion should never be withheld on the basis of universally incompatible crossmatch results due to the presence of a panreactive autoantibody. The decision to transfuse should consider the severity of anemia, the risk of withholding transfusion, and the potential benefit of alternative therapy.

### **Chapter 11. Pregnancy and Postpartum Transfusion Considerations**

There is a sparsity of evidence-based data regarding the proper management of peripartum hemorrhage. Regardless, although the risk factors for peripartum hemorrhage are not well-understood, it is known that certain medical conditions predispose a patient to the potential for significant hemorrhage, and the health-care team must be aware and prepared. As the industry moves forward, health-care teams must harness the power of the data accumulated in the electronic medical records and use it to better characterize the fate of expecting mothers. The industry must strive to be more proactive in providing the proper care to hemorrhaging women, a worldwide too-common cause of maternal morbidity and mortality.

### **Chapter 12. Intrauterine, Neonatal, and Pediatric Transfusion Therapy**

Advances in the care of critically ill fetuses, newborns, and older children have necessitated dramatic changes in the transfusion service's response to the needs of pediatric patients. The interplay of these advances and better understanding of the physiology and pathology of the affected fetus, the premature infant, or the child with special needs undergoing surgery have resulted in a need to provide special selection, packaging, and administration of blood components for these patients. There is tremendous diversity among clinicians in pediatric transfusion practice. Further education and/or research is needed to promote better pediatric transfusion practice.

### **Chapter 13. Transfusion Therapy in Hematopoietic Stem Cell Transplantation**

Hematopoietic stem cell transplantation (HSCT) patients frequently require transfusion support and must receive special consideration with regard to the transfusion of blood components, particularly in the setting of major, minor, and bidirectional ABO-incompatible HSCTs. Each category of ABO-incompatible HSCT includes risk of adverse events (eg, pure red cell aplasia, delayed engraftment). It is important to understand potential complications associated with ABO-incompatible HSCTs as they oftentimes lead to an increased transfusion requirement. In general, the availability of evidence regarding transfusion practice and transfusion thresholds in the HSCT population is limited, especially in pediatric patients. Existing guidelines are typically extrapolated for these populations in routine practice. However, blood transfusion can be safely performed based on the phase of the HSCT process for a given HSCT patient.

### **Chapter 14. Transfusion Practice in Solid Organ Transplantation**

In the 30-plus years since the Organ Procurement and Transplantation Network was founded, organ transplantation practices and recipient survival have made remarkable gains. From donor testing to recipient immunosuppressive and immunomodulatory strategies, the technology in existence now largely surpasses anything that was available in the 1980s. However, one of the most important and consistent safety measures in organ transplantation that has not changed is confirmation of ABO group to prevent unintended incompatible transplants. Interestingly, the practice of ABO-incompatible organ transplantation is now commonplace. This is due to the continuing shortage of available organs

combined with advances in drug therapy. In addition, various desensitization techniques are being used to increase graft survival and prevent acute intravascular hemolysis, making incompatible transplants a daily event at many places.

Transplant planning must include conservative transfusion strategies to avoid HLA allosensitization, protocols for transfusion management of ABO-incompatible transplants, and protocols for massive transfusion events. Preoperative anemia management strategies and perioperative autologous blood transfusions may help reduce the number of transfusions needed intraoperatively and in the postoperative period. As with any blood component therapy, prevention of infectious disease transmission is of the utmost importance. The widespread use of leukocyte reduction has largely mitigated the risk of cytomegalovirus transmission. However, prevention of other infections relies largely on accurate and timely screening of donors. To this end, organ-transmitted blood-borne infections still remain a significant risk in this population, particularly recipients of organs from deceased donors.

### **Chapter 15. Transfusion Support and Hemostatic Monitoring in Patients Connected to Extracorporeal Devices**

Patients requiring extracorporeal life support (ECLS) are critically ill and have a high mortality rate. Although current devices are safer than when ECLS originally debuted in the 1950s, there remain many complications related to its usage. Bleeding and thromboembolic complications due to systemic anticoagulation from ECLS devices represent major adverse events. Heparin is the most frequently prescribed anticoagulant but other anticoagulants have also been used. There are a few guidelines on how to monitor anticoagulation in these patients but they are not patient- or age-specific and there has not been any study investigating the use of anticoagulation in ECLS. Therefore, this represents an area for future research. Furthermore, many patients require transfusions. Similar to the anticoagulation issue, active research is much needed to define a specific threshold for transfusions in order to avoid inappropriate use of blood components and to improve clinical outcomes. Other pediatric issues also need to be addressed because many on ECLS are pediatric patients with unique concerns.

### **Chapter 16. Transfusion-Related Considerations in Jehovah's Witness Patients**

Although Jehovah's Witness patients may be challenging to manage in the setting of critical anemia and surgery, they have inspired many advancements in medicine, including the development of bloodless surgery programs and minimally invasive surgery as well as patient blood management programs. Continued multidisciplinary research is necessary to develop safe and effective alternatives to transfusion for this unique group of patients.

### **Chapter 17. Principles of Hemostasis and Laboratory Testing**

Hemostasis is an intricate system with multiple pro- and anticoagulant participants. Disorders can arise from inherited, acquired, or iatrogenic defects (the latter in the case of therapeutic anticoagulation). Similarly, coagulation laboratory testing is complex. It is best to proceed through a stepwise process, starting with a clinical situation with a reasonable pretest probability of detecting a coagulation laboratory abnormality. If such a situation is present, screening tests should be performed to establish a differential diagnosis and then appropriate follow-up testing should be chosen to narrow the differential diagnosis and/or to characterize the disease. Consultation with a laboratory medicine physician who specializes in coagulation helps streamline the process, reach a diagnosis faster, and reduce testing cost.

Once a diagnosis of a hemostatic disorder is made, bleeding can be treated using a variety of methods, including local control, pharmaceuticals, factor concentrates, or transfusion therapy.

## **Chapter 18. Pathophysiology and Management of Hemostatic Disorders**

Hemostasis is an intricate system with multiple pro- and anticoagulant participants. Disorders can arise from inherited, acquired, or iatrogenic defects. Congenital disorders usually originate from a single pathway abnormality that can be corrected with specific factor concentrate. If not available, alternatives such as blood products or prothrombin complex concentrates (PCCs) can be considered. In contrast, acquired disorders of hemostasis are typically multifactorial. Laboratory evaluation can assist the physician in determining rational intervention with transfusion and pharmacologic treatments. In general, newer products (eg, fibrinogen concentrate, Factor XIII concentrate, four-factor PCCs, porcine recombinant Factor VIII, emicizumab) and better laboratory testing should lead to improvements in the ability of physicians to treat patients with complex disorders of hemostasis. Often, a patient's unique constellation of laboratory abnormalities and clinical presentation calls for customized therapy and it is crucial to monitor effectiveness with clinical response and laboratory assays.

Therapeutic anticoagulation remains a delicate balance. Although older medications suffered from medication/diet interactions and narrow therapeutic ranges, they were monitored by widely available laboratory assays. In contrast, newer agents, although possessing better pharmacodynamics and requiring fewer dose adjustments, pose a challenge to laboratories due to the need to implement appropriate monitoring assays.

## **Chapter 19. Patient Blood Management**

A PBM program is an important patient safety and quality measure that can also lead to cost savings. To implement a successful program, hospitals need sufficient resources to support the people who can accomplish the methods and techniques that are discussed above. The return on investment can be 400%. Institutions also need sufficient information technology support to obtain the data required to improve practice. Education, evidence-based transfusion guidelines, and best practice advisories effectively encourage good practice and reduce unnecessary transfusions.

The specific activities performed by a PBM program can vary by institution and are defined by the executive management team of the facility. Guidance is available from various professional organizations. More information on the AABB/Joint Commission PBM certification may be found on the AABB website ([aabb.org/pbm](http://aabb.org/pbm)). With a successful PBM program, institutions can reduce risk, improve outcomes, and reduce cost, which together, increases the value of health-care delivery.

## **Chapter 20. Hemovigilance**

Hemovigilance plays a vitally important role in ensuring and enhancing patient safety. The data on adverse reactions and events (including how these events relate to blood donors and the blood components themselves) submitted to hemovigilance systems can serve to stimulate important advances in blood transfusion safety. Hemovigilance programs exemplify robust and effective hemovigilance systems providing ongoing transfusion safety benefits. The hemovigilance systems in the United States are currently less robust and are once again undergoing changes, but hope remains that effective hemovigilance at a national level can be a beneficial reality.

## **Chapter 21. Medical-Legal Issues in Transfusion Medicine**

The law permeates every aspect of transfusion medicine, blood banking, and cellular therapy. The specter of medical malpractice litigation is ever present. Fortunately, it is not necessary to keep legal concepts forever in the forefront of one's thoughts. Policies, procedures, and the use of best practices at all times enable laboratories and clinical services to keep up with legal responsibilities. Nevertheless, it is important to know how to identify legal concerns when they arise in practice, and to have a sense of how to proceed when legal concerns reveal themselves. The purpose of this chapter has been to help practitioners be more informed about the legal aspects of transfusion practice, in order to know how to guard against legal missteps in daily practice and respond effectively when legal concerns arise.

## **Chapter 22. Quality and Regulation in Transfusion Medicine**

Successful quality assessment programs create "an environment of watchful concern." They should be conducted in a professional, nonadversarial, and educational manner. Despite the difficulties caused by some disagreement about treatment options (such as when RBC transfusions are indicated in the acutely anemic patient) and the necessity of using surrogate markers due to the lack of data (such as those needed to establish oxygen deficit) by which definitive decisions can be made, the assessment of transfusion practices provides many benefits. It can improve the judgment and enhance the knowledge of physicians and other health-care professionals; provide useful information about patient management; decrease the risk of litigation; reduce costs; help to ensure compliance with accreditation and regulatory requirements; conserve the blood supply; provide an opportunity to demonstrate a high level of quality and value to the public and institutional oversight boards; and help create, document, and sustain excellence in patient care.