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REVIEW ARTICLE

Blood Component Therapy

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Given the frequency of inpatient transfusion and the possibility that delayed reactions may be noted during outpatient follow up, an update in blood component therapy is worthwhile. Noninfectious complications are far more frequent than infectious complications and require heightened clinician awareness to ensure recognition and provision of appropriate supportive care. Transfusion Associated Circulatory Overload, a preventable consequence of transfusion, is particularly common and may be preemptively managed in selected patients. Risks associated with transfusion therapy can be reduced through application of patient blood management strategies. In this context, a working understanding of the modern literature surrounding the primary blood components is valuable. Evidence-based transfusion guidelines for RBCs, platelets, plasma and cryoprecipitate optimize patient care and improve patient outcome. This review focuses on utilization of blood components and selected alternatives as well as pretransfusion testing.

INTRODUCTION

Transfusions are a frequent occurrence among hospitalized patients. Roubinian and colleagues, in a retrospective cohort study of hospitalized, non-obstetric adult patients, found that among 444,969 hospitalizations involving 275,874 patients, RBC transfusions occurred in 32,493 (11.8%) patients and during 61,988 (13.9%) of hospitalizations[1]. Compared to the non-transfused group, those receiving transfusions had lower admission hemoglobin values (9.9 g/dLvs 12.9 g/dL) and were more commonly admitted for gastrointestinal bleeding and orthopedic surgery.

New developments in the literature and establishment of the patient blood management movement have consistently driven transfusion thresholds for stable patients to lower and more restrictive levels. Anemic patients may benefit from perioperative anemia management to reduce the risk of intraoperative transfusion. Alternatives to transfusion, particularly as plasma alternatives, are gaining attention. Transfusion laboratory tests may be confusing to choose from, and will be addressed in this review. Complications of transfusion may be delayed and detected only during an outpatient hospital follow-up visit. This article will review recent developments in the literature, touch upon utilization of the transfusion services laboratory, and discuss utilization of blood components and selected alternatives.

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DONOR SCREENING

Transmission of blood-borne pathogens is prevented through application of a multi-layered process of donor screening. Unless labeled otherwise[2] blood components are collected from non-remunerated, volunteer donors. At the time of donation, prospective donors are asked to read an established set of donor education materials[3] that review the signs and symptoms of HIV, risk factors for acquiring blood-borne pathogens, definitions of what constitutes sexual contact, and medications and vaccines that constitute deferral criteria. This material educates donors as to risk factors they will be questioned about on the required, 48-item Donor History Questionnaire (DHQ)[4]. This questionnaire screens for high-risk behaviors and other factors that heighten risk, collects donor demographic and contact information, and provides an informed consent area that must be read and signed. Donors qualifying by DHQ, vital signs, minimal weight (50 kg) and hemoglobin (12.5 g/dL) requirements then proceed to donation.

Phlebotomists visually inspect the arms for evidence of track marks or lesions suspicious for Kaposi's Sarcoma and the skin is meticulously prepared prior to phlebotomy using either Povidone-Iodine or Chlorhexidine solutions.

Additional prevention is obtained through the use of modern collection kits incorporating a diversion pouch that prevents the first few mL of blood collected from entering the primary collection bag. This reduces the risk of bacterial contamination resulting from entrainment of residual skin bacteria. Specimens for testing are drawn from this diversion pouch and sent for routine testing ***(Table 1)***. Platelets, owing to the requirement for room-temperature storage, are additionally

tested for evidence of bacterial contamination.

COMPLICATIONS OF TRANSFUSION THERAPY

Risks associated with selected infectious and noninfectious complications of transfusion are enumerated in Table 2 [5-20]. Note

Table 1: Current Testing performed with each donation (AABB Standard 5.8). For selected donations, anti-CMV and Red Cell phenotype testing may also be performed.

Determination of ABO Group
Determination of Rh Type
Detection of Unexpected Antibodies to Red Cell Antigens
Testing for Infectious Disease Markers
• HBV DNA
• Hepatitis B Surface Antigen
• Anti-HBc (Hepatitis B core antigen)
• Anti-HCV
• HCV RNA
• Anti-HIV 1/2
• HIV 1 RNA
• Anti-HTLV I/II
• WNV (West Nile Virus) RNA
• Syphilis
• Antibodies to TrypanosomaCruzi*
• Antibodies to CMV (Cytomegalovirus)**

* Tested at least once. ** Tested but results do not exclude donation.

that in most instances, complications are more immediately problematic for non-infectious as opposed to infectious reactions. The exception is bacterial sepsis; a complication far more common than viral transmission.

TRANSFUSION ASSOCIATED CIRCULATORY OVERLOAD

The most common serious reaction is Transfusion Associated Circulatory Overload (TACO), an event that in one retrospective review[6] led to ICU transfer, major complications, or death in 18%, 8%, and 2% of patients, respectively. Risk factors include congestive heart failure, renal dysfunction, and age >70 years. The assessment of net volume status, including volume of preceding intravenous fluid administration (including suspension media for intravenous medications), clinical risk factors for volume overload, and post-transfusion B-type Natriuretic Peptides (Pro-NT-BNP or BNP)[21,22] are helpful in diagnosing TACO.

TRANSFUSION RELATED ACUTE LUNG INJURY

As opposed to TACO, which results from cardiogenic pulmonary edema, Transfusion Related Acute Lung Injury (TRALI) reflects a non-cardiogenic pulmonary edema state with a clinical picture similar to Acute Respiratory Distress Syndrome (ARDS). Suspected TRALI may be diagnosed using the following criteria[23]:

- Dyspnea:onset within 6 hours after transfusion,
- Hypoxia: PaO2/FiO2 ratio of < 300 mmHg,
- Infiltrates (new, bilateral):noted on the post-transfusion chest film,
- Noncardiogenic: pulmonary capillary wedge pressure < 18 mmHg or central venous pressure ≤15 mmHg)
- Competing causes – ruled out: no other risk factors present for acute lung injury

The most severe cases of TRALI are associated with activation of recipient leukocytes by preformed antibodies contained within donor products. The implicated antibodies, typically the result of sensitization during pregnancy or prior transfusion, are primarily directed against Human Leukocyte Antigens (HLA). If, by chance the recipient expresses the cognate antigen, then TRALI may result.

The prevalence of detectable HLA antibodies among women enrolled in the Leukocyte Antibody Prevalence Study (LAPS) [24] correlated with the number of full-term pregnancies: among those with zero, one, two, three, or ≥4 pregnancies expression of HLA antibodies was found in 1.7% (same as previously transfused and non-transfused males), 11.2%, 22.3%, 27.5%, and 32.2%, respectively. Donor deferral policies based upon deferral of female (particularly multiparous) donors have resulted in significant reductions in the incidence of TRALI ***(Table 2)***[13,14].

ALLERGIC TRANSFUSION REACTIONS

A less common cause of dyspnea during transfusion is allergic reaction, although most are limited to cutaneous symptoms. In one study[25], cutaneous manifestations of pruritis and urticaria occurred in 86% and 84%, respectively, of 143 allergic reactions to platelets whereas dyspnea occurred in only 10.5%, wheezing in 3.6%, and nausea/vomiting in 2.1% to 4.2%. The authors found that recipient atopy – particularly hay fever – was a risk factor for allergic transfusion reaction to platelets. In addition, the rate of allergic transfusion reaction rates decrease with subsequent transfusions, suggesting the occurrence of desensitization. This phenomenon was also noted in a recent review[26] of severe urticarial reactions occurring in the Trial to Reduce Alloimmunization to Platelets[8].

PLATELET REFRACTORINESS

Alloimmunization to HLA (and other platelet-surface) antigens, can in some cases result in immunologic platelet

refractoriness. Platelet refractoriness, defined as a Corrected Count Increment (CCI– see Equation 1) of < 5x 103/mcL [8,9] following two sequential, ABO compatible platelet transfusions, represents a complex management issue. With modern, leukoreduced platelet products, this outcome may occur in 4% to 14% of subjects[8].

In the Trial to Reduce Alloimmunization to Platelets [8], patients with newly diagnosed Acute Myelogenous Leukemia were randomized to control, unmanipulated platelet concentrates or any of several leukocyte reduced (either by filtration or UV-B irradiation) products. At the end of the eight week study period 13% of control subjects developed both HLA alloimmunization and platelet refractoriness, whereas this combined outcome occurred in only 3-5% of the experimental arm subjects. Transfusion-related immunization to HLA occurred more commonly than did clinical refractoriness – 45% of control subjects and 17% to 21% of experimental arm subjects developed detectable antibodies. The take-away message is that laboratory evaluation for immunologic refractoriness (ie, testing for HLA or other antibodies with provision of HLA-matched/compatible platelet products) should follow, rather than precede, demonstration of clinical refractoriness. Once diagnosed, platelet refractoriness due to HLA alloimmunization may respond to transfusion from donors HLA compatible either with the recipient or their antibodies – a process known as 'HLA matching'.

Other instances where platelet refractoriness may be noted include coagulopathy of liver failure and Immune Thrombocytopenia (ITP). In the cirrhotic patient, an expanded blood volume and increased pooling in the enlarged spleen lead to reduced post-transfusion increments whereas enhanced immunologic removal effects on megakaryocytes via platelet glycoprotein-directed autoantibodies are a major etiology in ITP. In these instances, refractoriness is typically unresponsive to HLA matching.

FEBRILE NONHEMOLYTIC TRANSFUSION REACTIONS

Febrile, Non-Hemolytic Transfusion Reactions (FNHTR) occur among 0.5% to 6.8% of transfusions and may arise within 6 hours of transfusion. These reactions may consist of temperature rise (≥ 1°C) or other signs of a systemic inflammatory reaction syndrome (SIRS) such as tachycardia, blood pressure changes, tachypnea, chills, or rigors. Fever is not an absolute requirement to diagnose FNHTR provided other causes for the symptoms are ruled out and a clear temporal relationship between onset and transfusion exists. This complication is felt to be mediated, in large part, through infusion of biologic response mediators and other cellular antigens that accumulate during product storage[27]. Evaluation of these transfusion reactions also entails a careful search for competing clinical factors, including hemolytic and septic transfusion reactions or fever and chills due to underlying illness (i.e., sepsis).

Prestorage leukoreduction reduces the number of residual leukocytes contained in a transfusion product, thereby reducing the risk of FNHTR while also reducing the risk of CMV infection[28] and HLA alloimmunization[8]. In-line filters effect for 3-4 log reduction of leukocytes – equivalent to removal of more than 99.9% of leukocytes[29] - from the original unit. Alternatively, leukoreduction may be accomplished by virtue of an exclusion effect related to the high degree of specificity for platelets allowed with modern plateletpheresis instruments – referred to as 'in-process' leukoreduction. To qualify as leukoreduced, RBCs and apheresis platelets must contain fewer than 5 x 106 WBC/unit[30] (plasma and Cryoprecipitated Antihemophilic Factor (CRYO) are considered 'acellular' products and therefore not subject to minimum WBC criteria). Data demonstrating reduced FNHTR rates[10,31] as well as reduction in transmission of leukotropic viruses and HLA alloimmunization has resulted in a change to predominantly leukoreduced inventories at many blood centers.

TRANSFUSION ASSOCIATED GRAFT VERSUS HOST DISEASE

An uncommon but fatal leukocyte-associated complication is Transfusion Associated Graft Versus Host Disease (TA-GVHD), a circumstance that may occur when recipient leukocytes fail to eliminate viable donor leukocytes. During a TA-GVHD event, viable donor leukocytes recognize recipient tissue as foreign, become activated, and launch an immunologic attack against recipient tissues. The skin, marrow, and gastrointestinal tract are particularly at risk and patients may develop rash, pancytopenia, diarrhea and liver dysfunction. Other organs may also be affected.

Circumstances predisposing to TA-GVHD include unidirectional homozygosity for Human Leukocyte Antigens (HLA) – arising when the donor is either a 1st degree relative to the recipient (ie, 'directed donation') or when HLA-matched products are selected for a refractory recipient – and scenarios associated with severe degrees of recipient immunoincompetence or immunosuppression[32]. The only widely available means of prevention involves irradiation of cellular (i.e., red blood cells, platelets, granulocytes) blood components; leukoreduction alone does not prevent this complication. Indications for irradiation are listed in ***Table 3***.

HEMOLYTIC TRANSFUSION REACTIONS

Hemolytic reactions may be characterized as acute or delayed. Acute hemolytic reactions occur due to interaction between

pre-formed antibodies in the recipient or transfusion product with red cells bearing the target antigen. Most acute hemolytic transfusion reactions are due to ABO incompatibility and typically result from medical error leading to transfusion of an ABO-incompatible component.

Acute hemolytic transfusion reactions are not universally symptomatic, but associated intravascular hemolysis, resulting from rampant complement activation from binding of ABO-directed IgM and IgG against recipient (or donor) red cells, may lead to dramatic clinical deterioration. Signs and symptoms may include hypotension, shock, disseminated intravascular coagulation, hemoglobinuria (as opposed to hematuria), and a rise in hemolytic markers (such as lactate dehydrogenase, total and unconjugated bilirubin) with concomitant decline (or lack of expected hemoglobin increment) in hemoglobin. Haptoglobin may become reduced to undetectable levels.

In one study[15] the frequency of ABO incompatible mistransfusion events was 1:38,000 transfusions, but nearly half (47%) of recipients experienced no untoward clinical or laboratory consequences. Fifty percent experienced either clinical (43%) or laboratory-only (7%) findings leading to an estimated frequency of symptomatic acute hemolytic transfusion reaction in the range of 1:76,000. As there were only 5 deaths, the risk of fatal hemolytic transfusion reaction was 1:1,800,000. These estimates are in agreement with those reported by the United Kingdom's Serious Hazards of Transfusion (SHOT) hemovigilance program that estimates a risk of ABO incompatible transfusion at 1:100,000 units and risk of fatality due to 'incorrect blood component transfused' at 1:1,500,000 units[33].

Safeguards to prevent Acute Hemolytic Transfusion Reactions include regular staff training, positive patient identification systems, labeling of specimens at the bedside, rejection by the blood bank of mislabeled specimens, and two-person verification of component and recipient prior to transfusion. Positive patient identification systems utilize handheld barcode readers or Radio Frequency Identification (RFID) chips embedded in the patient's hospital wristband and blood containers[34,35] as well as point-of-care label printing to significantly reduce the risk of wrong-blood-in tube.

Wrong-blood-in-tube (WBIT) errors are estimated to occur at a rate of 1:1111 to 1:3333 specimens among patients[36,37]and 1:50,000 among volunteer blood donors[38]. WBIT errors can initiate a chain of events leading to mistransfusion. Blood banks frequently have 'second specimen' policies in place that mandate confirmatory testing of a second specimen in new patients prior to issuing type-specific (ie, non-Group O) red cells. Requests from the blood bank for a second specimen should therefore be respected as they represent normal operation of a quality system aimed at enhancing patient safety.

Delayed hemolytic reactions occur when recipients develop antibodies against non-ABO antigens expressed on transfused red cells. Delayed hemolysis ensues when the immune system is either challenged (primary sensitization) or rechallenged (leading to an anamnestic antibody response) with foreign antigens (most commonly those within the Rh,Kell, Duffy,and Kidd[39,40] red cell antigen systems).

In delayed hemolytic reactions, hemolysis is most often extravascular with clearance of sensitized red cells in the spleen and reticuloendothelial system. Patients may experience fatigue, malaise, and mild elevations in bilirubin. In a nonbleeding patient, the hemoglobin will typically decline toward pretransfusion levels, the absolute nadir being related to the rate of clearance, endogenous erythropoietic response, and number of antigen-positive units the patient received.

Hemolytic reactions become apparent on post-transfusion testing. In addition to other clinical supportive evidence, the Direct Antiglobulin Test (DAT) turns positive, and a causative antibody can usually be eluted from the surface of DAT-positive red cells. Segments (lengths of tubing containing donor red cells from the original unit) may still be retained by blood bank for testing purposes. Donor cells from these segments can be typed for the implicated antigen to determine the number of antigen positive units transfused to the patient. Future transfusions should be antigen-negative for any historical or currently active alloantibodies and crossmatch compatible (at anti-human globulin phase) with the patient's serum.

SEPTIC TRANSFUSION REACTIONS

Septic transfusion reactions occur most commonly with platelets ***(Table 2)*** owing to the necessity for room temperature storage, a requirement for preservation of platelet function. Septic transfusion reactions to red cells are estimated at 1:250,000 transfusions respectively[12]. Standard treatment of septic reactions – including administration of broad spectrum antibiotics, and fluid and vasopressor resuscitation as indicated should ensue. Immediate cessation of the transfusion is required with delivery of the residual unit to the blood bank for gram stain, culture, and testing of the post-transfusion specimen via DAT (since acute hemolytic transfusion reaction would be within the differential). Blood cultures in the patient should be drawn from a peripheral site and from the catheter used to infuse the implicated blood component. If fevers previously occurred in relation to utilization of the implicated catheter then catheter colonization or infection should be suspected.

Table 2: Current transfusion risks for blood products collected and manufactured in the United States (except HTLV I/II, UK estimate used).

Complication	Estimated Risk	Notes
Transfusion Associated Circulatory Overload (TACO)	1:12.5 [5-7] to 1:68 [5]	Rate [5] determined via a 1 month prospective observation period when recipients were evaluated within 24 hours of (non-ED, non-OR) receipt of plasma transfusion using a set of clinical, laboratory, and radiologic variables associated with volume overload. Historic rate (clinician reported) of TACO was 1:1566 suggesting under-recognition. After TACO, 18% of patients required ICU transfer, 8% suffered a major complication, 2% died [6].
Fever*	1:15 [7]	Among participants within the Platelet Dosing Study [8], a multicenter, randomized controlled trial that examined the effects of prophylactic platelet transfusion among bleeding outcomes among hematology-oncology patients with hypo-proliferative thrombocytopenia. Estimates among other populations and for different blood product types may differ (ie, fever likely higher for RBC than platelets). As opposed to reference [8] that used prospective evaluation for reactions (and, hence, greater reliability of detection), reference [10] relied upon clinician recognition and reporting (hence under-recognition/under-reporting a factor); the higher estimate was derived during pre-universal leukoreduction; the lower estimate during post-universal leukoreduction. Alloimmunization to HLA antigens with subsequent platelet refractoriness (defined as a CCI of < 5000 after two sequential transfusions of ABO compatible platelets) during the 8 week Trial to Reduce Alloimmunization to Platelets [8] was 5% in the filtered, apheresis platelet group – a product that best approximates modern platelet inventory.
HLA Alloimmunization with Refractoriness*	1:20 [8]	
Allergic/Hyper-sensitivity*	1:52 [7]	
Sinus Tachycardia*	1:55 [7]	
Rigors or Chills*	1:90 [7]	
Febrile Nonhemolytic Transfusion Reactions	1:222[a] to 1:909[b] [10] 1:303[c] to 1:526[c] [10]	
Septic Transfusion Reactions*	1:41,173 to 1:193,305 [11]	For 2004-2006; apheresis platelet collections – lower estimate of septic transfusion reactions is for collections utilizing single-needle collections. Most septic reactions (16/20 due to *Staphylococcus sp* and occurred on Day 5 (13/20) after collection). Septic transfusion reactions occurring with RBC transfusion is much less frequent, about 1:250,000 units [12].
Transfusion Related Acute Lung Injury† (TRALI)	1:38,022 to 1:238,095 [13]† 1:434,782 [14][ε]	†For 2008-2011; higher risk estimate is specific for AB plasma; lower risk estimate is for non-AB plasma. Study evaluates reduced risk of non-AB plasma for TRALI following conversion to predominantly male-only plasma donor population. Owing to its rarity among donors and demand as universal donor plasma for trauma resuscitation, restriction of AB plasma donors to male-only restriction was not feasible. ε For 2008; RBC risk estimate not statistically different from Platelet estimate (1:500,000) [13].
Acute Hemolytic Transfusion Reactions	Symptomatic, 1:76,000; Fatal, 1:1,800,000[16]	Analysis of transfusion errors reported by over 250 transfusion services to the New York State Department of Health between 1990 through 1998 comprising approximately 9,000,000 transfusions.
Septic Transfusion Reactions[c]	1:250,000 [15]	Estimated based upon multiple sources.
HBV	1:282,000 to 1:357,000 [16]	For 2006-2008; window period 44 days; Current estimate is reflective of a reduction from 1997 to 1999 risk of 1:86,000 to 1:110,000
Fatal Septic Transfusion Reaction*	1:498,711 [11]	For 2004-2006; American Red Cross data.
Variant Creutzfeldt-Jakob Disease	1:480,000 to 1:134,000,000 [17]	Risk model provided both high (1:480,000) and low (1:134,000,000) per RBC transfusion risk estimates based upon UK prevalence estimates.
HCV	1:1,149,000 [18]	For 2007-2008; HIV window period 9.1 days; HCV window period 7.4 days.
HIV	1:1,467,000 [18]	
HTLV I/II	1:9,090,909 [19]	For 2002-2006 among UK blood donors; window period 46 days. Tested using similar EIA platforms used in the United States. In a US study [20]; the confirmed-positive rate for HTLV I/II in repeat donors was found to be 1:737,000 donations, or 1 donor requiring lookback investigation per 921,000 tested allogeneic (both first-time and repeat) donations.

* Apheresis Platelets. [a] Platelet Concentrates. [c] Red Blood Cells. †Plasma.

The implication of the catheter in suspected septic reactions was recently studied by Ricci and colleagues[41] who evaluated 999 transfusion reactions among 489,000 transfusion (a rate of 2:1000 transfusions) events over a 5 year study period). Of the reactions, 738 occurred in association with transfusion via an indwelling central venous catheter (CVC), 217 via peripheral access, 44 via unspecified access. Although 10% of these reactions were associated with a positive blood culture, none of the organisms cultured were concordant with organisms cultured from residual blood components. The authors concluded that investigation of febrile reactions occurring during transfusion should take into account the route of administration and the possibility of catheter-related infection.

PATIENT BLOOD MANAGEMENT

Patient Blood Management (PBM) describes a transfusion culture aimed at identification and reduction of unnecessary transfusions through patient-centered modalities that include preoperative anemia diagnosis and management, adherence to restrictive transfusion thresholds, application of intraoperative techniques (such as minimally invasive surgery and intraoperative cell-salvage), and use of transfusion alternatives where possible[42]. Within the PBM paradigm, clinicians are encouraged to move away from specific hemoglobin triggers and arbitrary (ie, 2 unit) transfusion orders and instead take into account patient symptoms and comorbidities and a strategy aimed at transfusing the least number of units to accomplish resolution of those symptoms.

RED BLOOD CELLS (RBCS) – PATIENT BLOOD MANAGEMENT CONSIDERATIONS

A key function of RBCs is to carry oxygen. Equipoise between too few RBC transfusions versus over-transfusion should be considered. Carson, et al, studied postoperative outcomes in 300 patients who refused red cell transfusion for religious reasons. A progressive increase in mortality was observed as their hemoglobin progressively fell below 7.0 g/dL. No deaths occurred in patients with postoperative hemoglobin levels between 7.1 and 8.0 g/dL[43]. Randomized controlled trials[45-48] ***(Table 4)*** and a recent evidence-based guideline statement[48] support both the application of clinical criteria ***(Table 5)*** and restrictive hemoglobin thresholds (ie, 7 to 8 g/dL in non-ACS patients) to transfusion decision-making.

Table 3: Clinical Indications for Irradiated Components

Intrauterine transfusions
Pre-mature, low birthweight infants
Newborns born with severe hemolytic disease of the fetus and newborn (HDFN)
Inherited immunodeficiency disorders
Hematologic malignances or sold tumors
Candidates and recipients of peripheral blood stem cell and marrow transplant
Components that are HLA matched or directed donation units from family members or relatives
Patients undergoing immunosuppressive chemotherapeuticagents that alter lymphocyte function

The higher the transfusion burden, the higher the risk of infection. In a meta-analysis of randomized, controlled trials evaluating restrictive (≤8 g/dL) compared to liberal (≥ 9 g/dL) hemoglobin transfusion thresholds, Rohde, et al[49] found the pooled risk of all serious infections to be higher in liberal transfusion groups 16.9% [95% CI, 8.9% to 25.4%] compared

Table 4: Recent Studies Comparing Restrictive to Liberal Transfusion Thresholds in Various Patient Populations

Study	Patient Population	Arms	Primary Outcome
TRICC Hebert, et al, NEJM 1999 [44]	838 Critical Care patients [RCT]	7 g/dL (n=418) vs 9 g/dL (n=420)	30 Day ACM: (18.7% vs 23.3%, p = 0.11)
TRACS Hajjar, et al, JAMA 2010 [45]	502 Cardiac Surgery with Cardiopulmonary Bypass [RCT, noninferiority study]	8 g/dL (n=249) vs 10 g/dL (n=253)	NI margin for 30 day ACM predefined at -8%: Observed between group difference 1% [95% CI, -6% to 4%], p = 0.85.
FOCUS Carson, et al, NEJM 2011 [46]	2016 Patients with CAD/Risk of CAD after Hip Fracture Surgery	< 8 g/dL (n=1009) vs 10 g/dL (n=1007)	Death or inability to walk across room unassisted at 60 days: Abs Risk Difference 0.5 percentage points [95% CI, -3.7 to 4.7]
Acute UGI Bleed Villanueva, et al, NEJM 2013 [47]	921 Patients with severe Upper GI bleeding	< 7 g/dL (n=461) vs < 9 g/dL (n=460)	45 Day ACM: 91% restrictive vs 95% liberal; HR for death with Restrictive Strategy 0.55 [95% CI: 0.33 to 0.92], p = 0.02.

Table 5: Clinical Criteria for Red Cell Transfusion (Adapted from Carson, et al[46]).

Clinical Criteria*
Chest Pain deemed Cardiac in Origin
Congestive Heart Failure
Unexplained Tachycardia or Hypotension Unresponsive to fluid Replacement

** In patients with dementia, FOCUS investigators useda hemoglobin trigger of < 8 g/dL.*

to restrictive groups 11.8% [95% CI, 7.0% to 16.7%] with a risk ratio of 0.82 [95% CI, 0.72 to 0.95] supporting a reduced serious infection risk when restrictive transfusion thresholds are in place.

Of interest, the use of Intravenous Iron formulations to reduce reliance upon red cell transfusions found that while transfusions could indeed be reduced – risk ratio 0.74 [95% CI, 0.62 to 0.88]) – this reduction came at the cost of slightly higher infection risk – relative risk of 1.33 [95% CI, 1.10 to 1.64][50]. The authors note, however, that their findings could also represent a false positive finding since infection was not a predefined endpoint of the studies encompassed by their review leading to introduction of bias due to missing data. A common thread linking infectious risk of red cells and intravenous iron may be infusion of free iron, an essential nutrient for microbes. Patients enrolled in the trials summarized in ***Table 4*** resemble patients encountered in clinical practice. Of note, there was no major difference in mortality or serious cardiovascular outcomes between the two arms of these studies. Subjects enrolled in the Transfusion Trigger Trial for Function Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS) study[46] were ≥ 50 with Coronary Artery Disease (CAD) or CAD risk factors (the mean age was 81.5 ± 9.0). Those enrolled in the Transfusion Requirements in Critical Care (TRICC) trial[44] were critically ill adults with a mean age of 57.1 ± 18.1 years. The Transfusion Requirements after Cardiac Surgery (TRACS) study[45] enrolled patients undergoing elective Coronary Artery Bypass Graft or Valvular surgery employing cardiopulmonary bypass; subjects had a mean age of 58.6 ±12.5 and more than 30% had prior histories of diabetes mellitus, unstable angina, and myocardial infarction.

Patients in the restrictive arms were far less likely to receive any blood and, when transfused, received far fewer total red blood cell units than did subjects randomized to liberal strategies. In the FOCUS study[46] for example, nearly 60% of subjects in the restrictive arm (compared to only 3.3% in the liberal arm) were able to completely avoid receipt of red cells following randomization. The total number of units transfused to subjects in the restrictive arm was 652 units, compared to 1866 units to subjects in the liberal arm.

In the Transfusion Strategies for Acute Upper Gastrointestinal Bleeding trial[47], only 49% of patients randomized to the restrictive arms received red cells compared to 86% of subjects in the liberal arm. The mean number of units transfused per patient was also lower in the restrictive arm (1.5±2.3 compared to 2.9±2.2 in the liberal arm). Of particular interest was the finding that patients with cirrhosis were at greater risk of further bleeding when randomized to the liberal strategy arm (22% compared to 12% in the restrictive arm). There were also small, but statistically significant increases in cardiac complications (acute coronary syndrome and pulmonary edema) and transfusion reactions among patients in the liberal arm (16% vs 11% for cardiac complications and 9% vs 3% for transfusion reactions).

The transfusion decision tool utilized in the FOCUS study[46] is presented in ***Table 5***. This allowed investigators to temper their decision making by including clinical features alongside prevailing hemoglobin levels. It also explains the increase in these clinical findings among patients randomized to the restrictive arm, since these very features were incorporated into the decision to transfuse.

In the setting of perioperative anemia, a recent systematic review[51] concluded that patients with preoperative iron deficiency anemia demonstrate earlier and more robust responses to intravenous iron compared to oral iron. Additionally, a short preoperative regimen of erythropoietin (EPO) or EPO plus IV Iron appears to significantly reduce red cell transfusion rates in selected patients.

Red cell substitutes (none are currently FDA approved) are not as safe as standard red cell products or asanguinous resuscitation fluids. A meta-analysis of sixteen trials involving five different hemoglobin based blood substitutes in 3711 patients concluded that excess occurrences of death and myocardial infarction occurred with the use of these products compared to control groups (Relative Risk: 1.30, 95% CI:1.05, 1.61; and 2.71, 95% CI:1.67, 4.40, respectively)[52].

PLATELETS

Platelets are critical in primary hemostasis; severe degrees of impairment or thrombocytopenia are associated with 'platelet-type' bleeding characterized by petechiae, ecchymoses, epistaxis, and other mucocutaneous (i.e., gingival bleeding, menorrhagia) bleeding. Wet purpura is an ominous sign that may portend subsequent, more severe hemorrhagic sequelae.

Platelets are available as either Platelet Concentrates or Apheresis Platelets. Providers may confirm with their Transfusion Medicine Service/Blood Bank the products locally available. To achieve a typical adult platelet dose, 4 to 6 platelet concentrates are pooled at time of issue (i.e., a 'six-pack' of platelets) into a single bag. Alternatively, a single Platelets Pheresis unit constitutes an adult platelet dose.

In the Optimal Platelet Dose Strategy for Management of Thrombocytopenia (PLADO) study[9], patients with hematologic or oncologic malignancies and hypoproliferative thrombocytopenia were randomized to three different (prophylactic) platelet-dosing strategies when the morning platelet count was ≤ 10 K/mcL. The primary outcome of World Health Organization (WHO) Grade 2 or greater bleeding was reached in approximately 70% of all groups regardless of platelet transfusion dose (1/2, 1, or 2 apheresis units per episode in nonbleeding patients). The median (IQR) post-transfusion (measured within 4 hours) platelet increment following 1 apheresis platelet unit transfusion among subjects with a median Body Surface Area of 1.9 m2 was $19^{11\text{-}30}$ K/mcL.

For patients undergoing treatment for Acute Myelogenous Leukemia or Autologous Hematopoietic Stem Cell Transplantation (HSCT)[53], prophylactic platelet transfusion (ie, when the platelet count was < 10K/mcL) was compared to therapeutic platelet transfusion (platelet transfusion only when a thrombocytopenic patient is bleeding). The therapeutic arm in the study received a third fewer platelet transfusions however, a difference in bleeding risk emerged based upon diagnosis. Increased risk of (mostly central nervous system) bleeds was observed among AML patients randomized to the therapeutic arm, while those undergoing autologous HSCT had no difference in risk of major hemorrhage between strategies.

In a subsequent randomized study by Stanworth and colleagues [54], 600 patients 16 or older receiving chemotherapy or undergoing stem cell transplantation were randomized to therapeutic or prophylactic platelet transfusion strategies. The primary outcome of this noninferiority study (WHO Grade 2 bleeding or higher up to 30 days after randomization) occurred more frequently in the therapeutic (50%) than in the prophylactic group (43%; adjusted difference in proportions, 8.4 percentage points, 95% CI: 1.7 to 15.2; p=0.06 for noninferiority – therefore, the study did not establish noninferiority for the therapeutic strategy). Patients in the therapeutic group developed their first bleed sooner than-, had a higher proportion of higher severity bleeds than, and had a higher number of days with bleeding- than did the prophylactic group.

These studies continue to support the practice of prophylactic platelet transfusions in severely thrombocytopenic, non-bleeding patients receiving chemotherapy and stem cell transplantation when platelet counts fall to below 10 K/mcL or less[55]. In other circumstances, platelets are typically transfused prior at counts < 50 K/mcL prior to non-neuraxial surgery or diagnostic lumbar puncture and at platelet counts < 100 K/mcL prior to central nervous system or intraocular bleeding[56].

PLASMA

Plasma is a source of all coagulation factors and may be used in the setting of bleeding when either multiple coagulation factors are reduced (such as dilutional coagulopathy or warfarin anticoagulation) or for bleeding disorders where the deficient factor lacks an approved or readily available specific factor concentrate ***(Table 6)***. The use of plasma in a bleeding patient with coagulation test derangements (ie, INR elevation) is justifiable, whereas prophylactic transfusion prior to procedures in a non-bleeding patient is controversial. Two authoritative meta-analyses[57,58] encompassing 80 randomized, controlled trials of plasma transfusions across multiple patient populations and clinical applications conclude"no consistent evidence of significant benefit for prophylactic and therapeutic [plasma] use across the range of indications evaluated".

Table 6: Selected Factor Concentrates and Recombinant Factors. This list is not exhaustive and other formulations exist for FIX, FVIII, and VWF/FVIII concentrates.

Blood Product	Coagulation Factor	Concentrate/ Recombinant Form	Manufacturer	FDA Labeled Indications	Typical Dosing
Plasma (Contains all endogenous coagulation factors)	FVII	rVIIa NovoSeven [76]	NovoSeven – Novo-Nordisk, Denmark	Bleeding or peri-operative management in patients with hemophilia A or B with inhibitors, acquired hemophilia, congential Factor VII deficiency, Glanzmann'sthrombasthenia with refractoriness to platelet transfusion	15 -30 mcg/kg for congenital factor VII deficiency 70 -90 mc/kg for all other indications listed.
	FII,FVII,FIX,FX	Prothrombin Complex Concentrate (Human), KCENTRA [67]	CSL Behring, Germany	Urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist therapy with major bleeding, the need for urgent surgery or invasive procedure.	25 – 50 units factor IX/body weightdepending upon INR values. Maximum dose not to exceed 2500 – 5000.
	FII,FIX,FX (reduced VII)	Factor IX Complex Profilnine [77]	GrifolsBiologicals, USA	Prevention and control of bleeding in patients with Factor IX deficiency due to hemophilila B	Body weight (kg) x 1.0IU/kg x desired increase in Factor IX= Number of Factor IX IU required
	FIX	Coagulation Factor IX (Recombinant) BeneFIX [78]	Wyeth Biopharma, USA	Prevention and control of bleeding in patients with Factor IX deficiency due to hemophilila B	Body weight (kg) x 1.0IU/kg x desired increase in Factor IX (IU/dL) = Number of Factor IX IU required
	Antithrombin III	ATryn (Recombinant ATIII) [79]	GTC Biotherapeutics	Prevention of peri-operative and peri-partum thromboembolic events in hereditary antithrombin deficient patients	Bolus (IU): Body weight (kg) x [(100-baseline ATIII)/x]; Maint (IU/hr): Body weight (kg) x [(100-baseline ATIII)/y]
		Thrombate III (pooled plasma derived) [80]	Grifols Therapeutics	Treatment of patients with hereditary antithrombin III deficiency in connection with surgical or obstetrical procedures or when they suffer from thromboembolism	Dose (IU): Body weight (kg) x [(Desired ATIII% – Baseline ATIII%)/(1.4%/IU)] (z)
Cryoprecipitate (enriched for Fibrinogen VWF, FVIII, FXIII)	FI (Fibrinogen)	Fibrinogen Concentrate (Human) RiaSTAP [81]	CSL Behring, Germany	Treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenemiaand hypofibrinogenemia	Single use vial containing 900 mg to 1300 mg lyophilized fibrinogen concentrate. Target level (mg/dL– measured level (mg/dL) / 1.7 mg/dL per mg/kg body weight
	FXIII	Factor XIII Concentrate (Human) Corifact [82]	CSL Behring, Germany	Prophylactic and peri-opertive management of patients with congenital Factor XIII	40 IU per kg body weight;rate not to exceed 4mL per min. Adjust dose ±5 IU to maintain trough level of Factor XIII activity
	vWF/FVIII	vWF Concentrate/ Coagulation Factor VIII Complex (Human) Wilate [83]	Octapharma, Austria	Treatment of spontaneous and trauma-induced bleeding episodes in patient with severe vWD as well as moderate vWD with ineffective or contraindicated desmopressin	Minor hemorrhage: 20 -40 IU/kg (loading dose) 20-30 IU/kg q12-24 hr (maintenance dose) Major hemorrhage: 40 -60 IU/kg (loading dose) 20 -240 IU/kg q 12 -14 hrs (maintenance dose)
	FVIII	Antihemophilic Factor (Recombinant) Advate [84]	Baxter Healthcare, USA	Control and prevention of bleeding episodes and perioperative management in patients with hemophilia A Routine prohylaxis to reduce bleeding episodes in patients with hemophilia A	Total dose (IU)/kg x 2 IU/dL Or Body weight (kg) x desired factor VIII Rise (IU/dL) x 0.5 IU/lg per IU/dL

Surgical Setting: x=2.3, y=10.2; Pregnancy: x=1.3; y=5.4; adjust ATryn infusion rates as described in package insert or according to institutional protocols. z: monitor ATIII activity levels at least every 12 hours and prior to next dose to maintain ATIII levels at >80% or according to institutional protocols. ATIII enhances heparin effect, so heparin dosing should be adjusted accordingly.

The trigger for plasma transfusion is often a prolonged Prothrombin Time (PT) or International Normalized Ratio (INR). Segal, et al[59] reviewed the literature to determine whether prolongations of the PT or INR predict excessive bleeding during invasive procedures. Among the 14 of 25 reviewed studies that included a comparison group, no significant risk difference could be demonstrated for the outcome of bleeding between those with normal versus abnormal preprocedural coagulation test results. The firmness of this conclusion was tempered by the wide confidence intervals about the event rates and risk differences as well as limitations of the studies themselves. Not all studies reported the degree of coagulation test prolongation, either.

Abdel-Wahab and colleagues[60] reviewed INR responses following plasma infusion in patients with mild coagulopathy (INR 1 to 1.85) and a wide range of medical and surgical conditions. No dose-response effect could be demonstrated, and the delta INR following plasma transfusion was negligible. Likewise, Holland and colleagues[61] confirmed the findings of Abdel-Wahab and further concluded that in patients with high normal to mildly elevated INRs (1.3 to 1.6), supportive care and treatment of the underlying condition alone were sufficient for natural correction of prolonged coagulation tests.

Also, recall that Heparin effect – suggested by isolated prolongation of the activated Partial Thromboplastin Time (PTT) in a patient receiving heparin – is reversed by protamine sulfate, not plasma. The effects of Low Molecular Weight Heparin and Fondaparinux are not reflected by routine tests of coagulation. With these latter two agents, routine coagulation test results (ie, PT/INR and PTT) are usually normal even in the face of therapeutic anticoagulation. An isolated prolongation of the PTT could also reflect presence of a Lupus Anticoagulant – which typically portends thrombotic, rather than hemorrhagic risk.

Coagulation test results therefore, should be interpreted in the proper context. Mild, stable elevations in test parameters in nonbleeding patients with no history of major bleeding would not be as impactful as the same parameters in a patient with ongoing stigmata of coagulopathy.

Certainly if a patient demonstrates signs of active bleeding on physical examination – new spontaneous ecchymoses or petechiae, large hematomas at procedural or intramuscular injection sites, oozing or bleeding from catheterization or intravenous access sites, labile or actively decompensating coagulation status (progressive prolongations of routine tests

of coagulation or significant changes from previous baseline – particularly if accompanied by a declining hemoglobin level), has acute organ failure, is receiving ongoing anticoagulation, or particularly if there has been a previous history of major bleeding – then abnormal coagulation and platelet count values would better justify preemptive or prophylactic transfusions prior to surgery. Appropriate reversal agents (rather than plasma), or an appropriate anticoagulant-free window, should be considered in the setting of anticoagulant therapy depending upon the clinical situation.

Thrombotic Thrombocytopenic Purpura (TTP) is caused by emergence of an autoantibody directed against ADAMTS-13 (A Disintegrin and Metalloprotease with Thrombospondin-type 1 repeats -13), an endothelial cell luminal-side protease that cleaves emerging strands of vWF at the A-2 Domain. The autoantibody depletes ADAMTS-13 leading to accumulation of attached ultra-large molecular weight multimers of vWF which promote microvascular thrombosis through platelet activation[62].

Plasma exchange is the primary treatment for TTP and both reduces the titer of autoantibodies directed against ADAMTS-13 and replaces deficient ADAMTS-13 with donor derived ADAMTS-13 through the use of donor plasma as the replacement medium.

Plasma, as opposed to albumin, saline or cryoprecipitate-poor plasma, is the replacement medium of choice during plasma exchange treatment of TTP and any delay in initiation of therapeutic plasma exchange should be addressed with infusion of plasma and initiation of steroids[63]. A randomized controlled trial comparing standard plasma against cryoprecipitate poor plasma (ie, the supernatant plasma from CRYO production – see below) plasma[64] demonstrated no difference in response rates by day +6 or +13 of treatment.

The rationale for cryoprecipitate poor plasma revolves around its reduced concentration of larger multimers of von Willebrand Factor. However, this reduction in vWF that occurs during cryoprecipitation is also accompanied by a reduction in ADAMTS-13 rendering cryoprecipitate poor plasma a less effective ADAMTS-13 replacement medium[65]. Standard, Fresh Frozen Plasma (FFP), therefore, remains the authors' replacement medium of choice for therapeutic plasma exchange in the setting of TTP.

Figure 1: **Calculation of the Corrected Count Increment (CCI)**

$$CCI = \frac{\text{(1-hour Post-Count – Pre-Count) x BSA}}{\text{Platelet Dose (x } 10^{11}\text{)}}$$

Pre- and Post-counts are expressed as K/mcL, BSA is m^2; the average number of platelets (i.e., platelet dose) in a single apheresis platelet unit = 4×10^{11}.

Sample Calculation: A patient with hypoproliferative thrombocytopenia and BSA 1.4 m^2 presented with epistaxis and a platelet count of 8 K/mcL. After receiving a single apheresis unit of platelets, the epistaxis resolved and a post-transfusion platelet count measured within 1 hour transfusion was 32 K/mcL.

CCI = [(32,000 – 8,000) x 1.4] / 4 = 8400/mcL representing an adequate (>5000/mcL) increment.

In the treatment of dilutional coagulopathy or warfarin reversal in a bleeding patient, it is reasonable to include plasma as a therapeutic option. Varying doses are reported in the literature, but a dose of 15 to 20 mL/kg is reasonable. For whole-blood derived plasma units, the volume per unit is typically in the range of 270 to 300 mL. However, plasma alone incompletely reverses the INR and has a limited duration of effect (no more than 8 hours) upon the degree of resultant correction achieved among warfarin-treated patients[66]. Given the prolonged duration of effect of warfarin, rebound elevations in the INR may occur if concomitant Vitamin K is omitted.

For the treatment of bleeding in a warfarin treated patient, a four-factor Prothrombin Complex Concentrate (KCENTRA, CSL Behring, Marburg Germany) was recently approved by the Food and Drug Administration (FDA). It is dosed according to the degree of INR elevation and administered as 25, 35, and 50 Factor IX units/kg body weight when the INR is 2 to <4, 4 to 6, and >6, respectively. Dosing should not exceed 2500, 3500, or 5000 Factor IX units, respectively[67].

In a randomized, plasma-controlled noninferiority trial of KCENTRA[68] (also known as Beriplex in other countries), warfarin-treated adults with acute bleeding events were randomized to plasma or KCENTRA with co-primary endpoints of hemostatic efficacy and rapid INR reduction (to ≤ 1.3 at 0.5 hours after end of infusion. Notably, subjects with history of thrombosis or Antiphospholipid Antibody Syndrome were excluded. KCENTRA dosing was carried out as described above, and plasma was dosed at 10, 12, and 15 mL/kg, respectively based upon the above-stated INR categories.

Effective hemostasis was achieved in 72.4% of KCENTRA treated and 65.4% of plasma treated subjects. Rapid INR correction was achieved 62% of KCENTRA patients compared to 9.6% of plasma treated patients. Thromboembolic complications and deaths were evenly distributed between groups.

A recent systematic review[69] concluded that: 1) prospective studies in cardiac surgery support a reduction in allogeneic red cell transfusion and reduction in chest tube drainage with the use of Prothrombin Complex Concentrates (PCCs) in the setting of warfarin reversal and, 2) that although PCCs

more rapidly correct the INR in warfarin treated patients than does plasma, functional outcomes in intracranial hemorrhage remain poor regardless of reversal strategy.

PCCs allow administration of significant amounts of clotting factors in a small volume whereas adequate plasma doses may exceed 1.2 to 1.4 liters and require additional delay for ABO typing, thawing, and labeling. Therefore, PCCs remain a reasonable alternative to plasma for warfarin reversal particularly when volume overload is a significant concern and the bleeding is critical.

CRYOPRECIPITATED ANTIHEMOPHILIC FACTOR (CRYO)

CRYO is the cold-insoluble portion of plasma that is enriched for Fibrinogen, von Willebrand Factor, and Factors VIII and XIII[70]. Many of the primary constituents of CRYO have gradually been recapitulated in either Factor Concentrate or Recombinant Single Factor form ***(Table 6)***. Currently, the major remaining indication for CRYO is acquired hypofibrinogenemia. A recently approved Fibrinogen Concentrate (RiaStap, CSL Behring, Marburg, Germany) is now available, however, the FDA-approved indications for RiaStap are limited to bleeding in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia (but not dysfibrinogenemia)[71].

Indications for CRYO include the development of dilutional coagulopathy during massive transfusion in bleeding patients or prophylactically in severely hypofibrinogenemic patients prior to major invasive procedures. In such patients, transfusion of CRYO can be considered when the fibrinogen level is below or declining toward 100 mg/dL[72]. During massive transfusion or active bleeding, it is reasonable to maintain fibrinogen levels in the 150 mg/dL range[73]. A single unit of CRYO contains approximately 250 mg/dL of fibrinogen; and dosing can either be estimated as 1 unit per 5 kg/body weight (each unit estimated to raise the fibrinogen by 5 to 10 mg/dL) or through calculation ***(See Figure 2)***.

Acquired hypofibrinogenemia also occurs in Disseminated Intravascular Coagulation (DIC). In this circumstance, transfusion of CRYO becomes indicated when bleeding develops in the setting of prolonged coagulation test results and hypofibrinogenemia. Because of its position in the common pathway of hemostasis, very low levels of fibrinogen can contribute to additional prolongation of PT/INR and PTT. Additional blood components, such as platelets and plasma may also be required, but definitive treatment requires correction of the underlying driver (ie, sepsis).

In the appropriate settings, patients with Factor Deficiencies, such as von Willebrand Disease, Hemophilia A, Congenital Antithrombin III Deficiency should preferentially receive the appropriate Factor Concentrate (some options recombinant) whenever available rather than Plasma or CRYO ***(Table 6)***[67, 76-84].

Figure 2: **Calculation of Cryoprecipitate Dose (Desired Delta Fibrinogen = Desired Fibrinogen (mg/dL) – Current Fibrinogen (mg/dL). A typical target fibrinogen in a bleeding patient might be 150 to 200 mg/dL.**

Total Blood Volume (TBV mL) =	70 mL/kg x Kg body weight
Total Plasma Volume (TPV mL) =	TBV x (1-Hct)
Conversion of TPV mL to TPV dL =	TPV in mL x 1 dL/100 mL
Fibrinogen deficit (mg) =	Desired Delta Fibrinogen (mg/dL) x TPV (dL)
CRYO dose (number of units) =	Fibrinogen Deficit (mg)/250 mg Fibrinogen per unit of CRYO

Following completion ofmassive transfusion in a 70 kg trauma patient, postoperative oozing from all catheter sites surgical drains persists. The PT, INR, PTT are prolonged, the Hematocrit is 70%, and a measured fibrinogen level is determined to be 40 mg/dL. The decision is made to transfusion CRYO first, then recheck all coagulation parameters.

TBV = 70 mL/kg x 70kg = 4900 mL

TPV = 4900 mL x (1-0.30) = 3430 mL; 3430 mL x 1 dL/100 mL = 34.3 dL

Fibrinogen Deficit (in mg) = (200 mg/dL– 40 mg/dL) x 34.3 dL = 5488 mg Fibrinogen

CRYO Dose (number of units) = 5488 mg Fibrinogen/250 mg Fibrinogen per unit

= 22 units*

*At many centers, a conversion to pre-pooled units of CRYO is occurring. Rather than individual unit dosing, the dose is rounded to the minimum number of pooled CRYO supplied by the vendor – in most cases, 5 Units.

For the calculation above, therefore, the patient was administered 20 Units of CRYO (issued from the blood bank as 4 bags of pre-pooled CRYO (each bag containing 5 units).

Because Fibrinogen resides in the common pathway, severe deficiencies result in prolongations of both PT and PTT. Following transfusion, the expected increment in Fibrinogen level was realized along with normalization of the PT, INR, and PTT.

PRETRANSFUSION TESTING

When red blood cell transfusion becomes a strong consideration, pretransfusion testing becomes necessary. This testing consists of an ABO Rh (Type) Antibody Screen (Screen) and Crossmatch (Cross). For patients whose final transfusion decision is unclear, a Type & Screen may be sufficient. For patients in whom transfusions are very likely, a Type & Cross (this test includes the antibody screen) is ordered. The Type & Cross requires designation of the number of units to be cross-matched for the patient. In clinical circumstances, such as rapidly exsanguinating bleeds, there may be not be sufficient time for standard pretransfusion testing. For these scenarios, Group O (or type specific, if known), uncrossmatched blood may be issued as an emergency measure.

Patients with red cell antibodies may require extended laboratory workup to further define the specificity of the antibody or antibodies present. If multiple antibodies are present, the investigation could become quite protracted. In such cases, the procurement of antigen-negative red cells may also be delayed. Fortunately, this circumstance is rare among most patient populations.

It is instructive, however, from the standpoint that if a patient is known to be alloimmunized against red cell antigens then

preoperative planning should incorporate additional time needed for laboratory investigation and procurement of antigen negative, cross-match compatible units.

Pretransfusion specimens for Type & Screen or Type & Cross(match) will be rejected if improperly labeled (bearing full name and medical record number of patient, name of phlebotomist and time and date of draw). Acceptable specimens remain active for 72 hours, after this point a new specimen must be drawn. This interval seeks to strike a balance between reduced recipient testing and ensured detection of emerging antibodies. In certain circumstances (clinician attestation to absence of pregnancy, transplant or transfusion in the patient for the past 3 months) the pretransfusion specimen may be extended to 10 to 14 days depending upon local blood bank policies.

PREMEDICATION PRIOR TO TRANSFUSION

A randomized, placebo-controlled trial of acetaminophen and diphenhydramine premedication among subjects admitted for leukemia or hemotopoietic stem cell transplant demonstrated no significant difference in the risk of overall transfusion reactions using leukoreduced products[74]. A similar lack of overall benefit was noted in a prior trial[75]. The routine use of premedication in unselected transfusion recipients does not, therefore, represent evidence-based practice. Premedication should therefore be reserved for patients with an established pattern of transfusion reactions or for those whose clinical circumstance would poorly tolerate a transfusion reaction.

CONCLUSION

Blood centers and hospital transfusion services employ a multi-layered screening process to reduce donor and recipient risk. While these deferral and testing practices effectively reduce infectious risks, noninfectious complications of blood transfusion – which are typically more common and immediately problematic – remain a concern. Transfusion Associated Circulatory Overload is especially common and potentially preventable through risk factor assessment and possibly administration of diuretic therapy in selected patients. Selected patients may benefit from receipt of irradiated blood components - irradiation being the only widely available modality known to effectively prevent TA-GVHD.

Recognition of transfusion-related risks has driven institutions to re-evaluate transfusion practices and bring them in line with evidence-based guidelines. The safety of restrictive transfusion thresholds for red blood cell and platelet transfusions in otherwise nonbleeding patients have been verified by large clinical trials. Recent studies argue against a conversion to a no-prophylaxis platelet transfusion strategy among hematology oncology patients. Prophylactic plasma transfusion has been studied in two, large meta-analyses comprising over 80 studies that call into question its therapeutic benefit. Therapeutic plasma transfusion in bleeding patients with documented coagulopathy continues to remain a reasonable modality. In patients with bleeding in the setting of warfarin anticoagulation, a recently approved four-factor prothrombin complex concentrate is now available for use as a plasma alternative. Cryoprecipitate may be administered in bleeding patients with hypofibrinogenemia. While the factors contained within CRYO are also available as factor concentrates and recombinant forms, the use of these agents is generally restricted to those with congenital bleeding disorders (in the case of Hemophilia A, B, congenital afibrinogenemia, and von Willebrand Disease) or off-label circumstances when alternatives are either unavailable or based upon institutional experience.

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