Providers should exercise clinical judgment when deciding on transfusion. Values listed are guidelines and some patients may require transfusion and higher or lower values.
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### CRYOPRECIPITATE

<table>
<thead>
<tr>
<th>Blood Product Indications</th>
<th>Fibrinogen (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal TEG in bleeding pt</td>
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</tr>
<tr>
<td>Factor deficiency w/o factor concentrate</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Special Preparation Indications</th>
<th>Fibrinogen (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding</td>
<td>&lt; 150</td>
</tr>
<tr>
<td>ECMO</td>
<td>&lt; 150</td>
</tr>
<tr>
<td>Preoperative</td>
<td>&lt; 150</td>
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</table>
Providers should exercise clinical judgment when deciding on transfusion. Values listed are guidelines and some patients may require transfusion and higher or lower values.
Neonates PRBC Transfusion

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GRADE</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent pulmonary hypertension of the newborn, Extracorporeal membrane oxygenation: RBC transfusion when Hgb between 12 – 13 g/dL</td>
<td>Weak</td>
<td>Moderate*</td>
</tr>
<tr>
<td>On positive pressure and O₂: RBC transfusion when Hgb &lt; 10 - 12 g/dL</td>
<td>Weak</td>
<td>Moderate*</td>
</tr>
<tr>
<td>On positive pressure or O₂: RBC transfusion when Hgb &lt; 8 - 10 g/dL</td>
<td>Weak</td>
<td>Moderate*</td>
</tr>
<tr>
<td>On room air: RBC transfusion when Hgb &lt; 7 - 8 g/dL</td>
<td>Weak</td>
<td>Moderate*</td>
</tr>
<tr>
<td>Shock due to acute blood loss</td>
<td>Weak</td>
<td>Moderate*</td>
</tr>
<tr>
<td>Refractory Septic Shock Hgb &lt;12</td>
<td>Strong</td>
<td>Low</td>
</tr>
</tbody>
</table>

*Moderate Evidence to premature infants and Weak Evidence for term infants.

Anemia is very common in neonates. This is an especially true in premature infants due to a combination of impaired erythropoiesis and iatrogenic blood loss from frequent blood draws. Critically ill neonates are at additional risk due to myelosuppresion, and losses due to procedures and surgery.

The mainstay of treatment for neonatal anemia is PRBC transfusions. Although early studies suggested erythropoietin was a useful treatment for anemia, later studies and metaanalysis have been less promising showing only small non-clinically significant reductions in transfusions requirements. 1,2

Despite the high incidence of transfusions in hospitalized neonates, thresholds for RBC transfusion are not well-delineated 3, 4. In addition, available guidelines vary greatly in several important clinical parameters such as age, need for respiratory support and the postnatal age making comparisons difficult. 5,6,7

Most of the current data is limited to ELBW infants.4, 8 Despite evidence that ELBW infants (< 1000 grams) do well with restrictive transfusion threshold with no increase in adverse short-term outcomes such as death or major morbidity 9 there are still concerns regarding long-term neurocognitive outcomes. 4 Further guidance should be forthcoming from two large RTCs on long term outcomes of restrictive transfusion practices the Transfusion of Prematures (TOP) and Europe Effects of Transfusion Thresholds on Neurocognitive Outcome of Extremely Low Birth Weight Infants (ETTNOS) trials 9,10

Currently most major guidelines for premature low birth weight neonates are stratified based on the infant’s age and respiratory support. 4,5,6,7 In order to incorporate this subset of neonates we are recommending a range of recommended hemoglobin for each clinical scenario and where the most at risk infants (VLBW) would be considered for transfusion at a higher hemoglobin level than near term/term infants. These values have been adapted from the guidelines developed by Intermountain Health Care a leader in transfusion practice for neonates. 11 These thresholds are similar to those supported in the Cochrane review on transfusion for older ELBW infants with the exception of a slightly higher threshold proposed here for older infants on oxygen and ventilator support similar to the British and Canadian guidelines for this cohort of patients. 4,6,7

Providers should exercise clinical judgment when deciding on transfusion. Values listed are guidelines and some patients may require transfusion and higher or lower values.
Providers should exercise clinical judgment when deciding on transfusion. Values listed are guidelines and some patients may require transfusion and higher or lower values.
Pediatric patients with congenital heart disease often require transfusion. To date, there is minimal evidence and a lack of agreement addressing the optimal hemoglobin concentration indicated for receiving RBC transfusion. The goal of RBC transfusion aims to increase oxygen carrying capacity while concurrently being conscious of risks and possible adverse outcomes associated with transfusion. Congenital cardiac disease patients are classified into two categories: cyanotic vs. acyanotic, and, within each category, symptomatic vs. asymptomatic; consequently, each classification warrants its own transfusion threshold. The most recent contribution to this subject is a prospective randomized controlled study by Cholette et al. published in 2016 comparing conservative versus liberal hemoglobin threshold in infants with congenital heart disease. In 105 patients with biventricular repairs, a liberal Hgb threshold of 7 g/dL was compared with a conservative threshold of 9.5 g/dL. Based on the results in terms of clinical outcomes, there was no statistical difference found in either arm. Similarly, in the subgroup analysis of pediatric patients with acyanotic asymptomatic disease in the TRIPICU study, a restrictive threshold of 7 g/dL was not associated with any significant difference in adverse outcomes compared to the liberal threshold of 9 g/dL. Gast-Bakker et al. also found that a restrictive threshold of 8g/dL vs. a liberal 10 g/dL in surgical patients (Risk Adjustment for Congenital Heart Surgery Score /RACHS ≤ 3) with acyanotic heart disease lead to shorter hospital stays with equivalent medical outcomes. In patients with congestive heart failure due to a large left to right shunt a higher hemoglobin level is sometimes suggested however, given its association with decreased pulmonary blood flow and reduction in pulmonary over circulation.

Currently there is little data available for patients with cyanotic congenital heart disease especially those with single ventricle physiology. In the most recent study by Cholette, 57 cyanotic patients undergoing surgical repair (with the inclusion of 12 patients undergoing stage 1 and 14 patients undergoing stage 2 palliation) with a liberal threshold of 9 g/dL along with a clinical indication such as tachycardia or hypotension vs. a conservative threshold of 12 g/dL. There was no statistical significance in terms of clinical outcomes in either arm. Unfortunately, the low power to detect a difference is a shortcoming of this study. Therefore, as the authors stated, whether this subgroup of patients may, or may not, tolerate conservative transfusion strategies remains to be determined. In an earlier study of patients with single ventricle physiology undergoing cavopulmonary palliation (33 stage 2 and 27 stage 3 patients), Cholette et al. found no significant difference in primary clinical outcome measure (peak arterial lactate) between the restrictive group receiving RBC transfusion at threshold of 9 g/dL vs. 13 g/dL in the liberal group. As stated in the Cochrane review on this topic, there is little high quality data to provide guidelines in this patient population and therefore practice is strongly influenced by each center’s experience.

Pending further studies, we feel there is currently insufficient evidence to clearly define transfusion thresholds for all sub groups of patients with congenital heart disease.

Providers should exercise clinical judgment when deciding on transfusion. Values listed are guidelines and some patients may require transfusion and higher or lower values.
In patients suffering from severe traumatic brain injury (TBI), anemia can worsen neurological outcomes, cerebral ischemia, and overall survival rate. Nevertheless, the hemoglobin threshold for transfusion in patients with TBI is under debate due to consideration of complications associated with transfusion. The current guidelines produced by the British Journal of Haematology made a grade 2D recommendation a hemoglobin threshold range between 7-9 g/dL. Based on a randomized clinical trial conducted by Robertson et al. on adult patients with severe TBI, those whom were assigned in the liberal transfusion threshold (10 g/dL) did not result in improved neurological outcomes compared to the restrictive threshold group (7 g/dL). In fact, there was a higher adverse event risk associated with the liberal threshold group involving thromboembolic events and severe progressive hemorrhagic events. This finding was reiterated in retrospective review study on 1607 pediatric patients with TBI by Acker et al. In comparison to similar patients who did not receive transfusion, those who did had a higher risk of adverse outcomes including death. These risks equalize around among the two groups at the transfusion threshold of 8 g/dL. Similar findings are also noted in a study done by Al-Dorzi et al. The desired benefit of brain tissue oxygenation has not been established with transfusion. Studies by Figaji et al. and Zygun et al. have shown transient increase in brain tissue oxygen that came back to baseline within 24 hours without appreciable effect on cerebral metabolism. A systematic review on RBC transfusion by Boutin et al. demonstrates statistically similar mortality rate in patients who were transfused and those who weren’t. As the exact threshold for transfusion for TBI still need to be elucidated, based on the above studies and recommendations in consultation with local surgeons, we recommend to restricting transfusion in patients with acute TBI (< 1 week) to Hgb < 9 g/dL. This may be liberalized to Hgb < 7-8 mg/dL depending on symptoms in patients with subacute injuries.

Providers should exercise clinical judgment when deciding on transfusion. Values listed are guidelines and some patients may require transfusion and higher or lower values.
Sepsis contributes abundantly to the morbidity burden in the pediatric ICU. We are quick to rely on RBC transfusion due to especially in these patients due to sepsis’ potential effects on hemodynamics and oxygen delivery. With current studies and new findings, a liberal approach on transfusion might be unnecessary. It is prudent to establish an optimal transfusion threshold as both anemia and RBC transfusions have undesirable adverse side effects to critically ill children. Randomized studies on both adult (998) and pediatric (228 and 137) patients with sepsis/septic shock have shown similar rate of adverse outcomes in patients receiving RBC transfusion at a threshold of 9-9.5 g/dL vs. those receiving transfusion at a threshold of 7 g/dL.26,27,28 Albeit, the recommendation is not applicable to certain pediatric populations including premature infants, patients with severe hypoxemia, hemodynamic instability, active blood loss, or cyanotic disease.27 This recommendation is further supported by the “Surviving Sepsis Campaign 2012” where, based on a consensus committee of 68 international experts, a grade 1B recommendation was agreed on hemoglobin targets in pediatric patients with severe sepsis. The committee suggests a liberal threshold of 10 g/dL in patients with superior vena cava saturation (SvcO₂) < 70%. A threshold of 7 g/dL is reasonable when patients have been stabilized from shock & hypoxemia.29

Anemia in Patients Receiving Radiation Therapy PRBC Transfusion

The microenvironment of solid tumors is hypoxic compared with normal tissue, and this hypoxia is associated with decreased radiosensitivity. It has been postulated that hypoxia may function as a mutagen by elevating superoxide and other oxygen radical level that eventually result in chromosomal breaks and/or rearrangements. Hypoxia coupled with acidity further results in impairment of cellular repair capabilities. The ability of radiation therapy to eradicate malignant cells critically depends upon the intratumor content of molecular oxygen, a potent radiosensitizer involved in mediating DNA damage.30

Harrison reviewed several studies that evaluated head and neck or cervical cancer outcomes by pre-radiation hemoglobin levels. He found in nearly all studies that a low pretreatment hemoglobin level, even within the range of 12-14 g/dL, was a significant prognostic indicator of disease control and survival, irrespective of disease specific characteristics such as tumor stage or lymph node involvement.30,31 Hu reviewed studies focusing specifically on head and neck oncologic patients. He referenced papers by Blitzer et al and Dubray et al that suggest an association between hemoglobin and years of local-regional control. A study by von Acht even showed that a drop in hemoglobin during treatment by more than 1mmol/L resulted in significantly lower disease free survival rate32-35 Thus, transfusions are useful in patients with particularly low hemoglobin levels (<10 g/dl) who are undergoing radiation therapy.30-32

Providers should exercise clinical judgment when deciding on transfusion. Values listed are guidelines and some patients may require transfusion and higher or lower values.
In patients with sickle cell disease (SCD), transfusion of red blood cells (RBC) may prevent complications and improve outcomes. Overall, however, there is limited evidence from large studies or randomized controlled trials to provide clear standards for clinical practice in pediatrics.

The goals of RBC transfusion in SCD patients are not only to increase oxygen delivery to tissues by increasing hemoglobin level but also to decrease blood viscosity by decreasing the proportion of circulating RBCs with hemoglobin S. RBC transfusion may be accomplished by simple transfusion or exchange transfusion. Simple transfusion provides normal donor RBCs and primarily increases oxygen-carrying capacity while exchange transfusion removes sickled cells and replaces them with donor RBCs. Exchange transfusion is associated with a decreased risk of creating a hyperviscous state in the blood but carries a higher risk of transfusion-associated complications such as transfusion reaction, infection, alloimmunization and central line-related issues.36,39

**ACUTE CHEST SYNDROME**

Acute chest syndrome (ACS) is a common complication of SCD defined as an acute illness with fever, respiratory symptoms, and a new pulmonary infiltrate on chest radiograph. While the specific cause of ACS is not always identifiable, it is likely that intrapulmonary sickling contributes to the disease process. ACS can progress to multisystem organ failure, which involves other organs including the brain, liver, and kidneys. Early RBC transfusion for hemoglobin less than 10 g/dL is recommended in the treatment of ACS, in addition to aggressive hydration, broad-spectrum antibiotics, respiratory support, and pain management. The evidence report from the National Institutes of Health (NIH) supports simple RBC transfusion of 10 mL/kg for any patient with ACS and a hemoglobin that is more than 1 g/dL below their baseline.44 The goal of transfusion should not exceed 10-11 g/dL.3,7 A critical review of the literature by Josephson et al. noted that simple transfusion could improve symptoms if given within the first 24 hours of diagnosis. For patients who are in more critical condition or have rapidly declining clinical status, exchange transfusion is indicated.36 The NIH suggests exchange transfusion for multi-lobar presentation, pleural effusions, rapid disease progression, and/or severe hypoxemia.44 Exchange transfusion would also be indicated in a patient with ACS who has already received a simple transfusion but has clinical signs of disease progression.

**SURGERY**

For patients with SCD who are undergoing elective surgery, there is increased risk of perioperative complications, morbidity, and mortality. General anesthesia alone can be problematic as it raises the risk of intrapulmonary sickling. This risk is then coupled with the possible complications related to either the surgery (infection, bleeding) or underlying SCD (acute pain crisis, ACS, stroke). For most cases involving general anesthesia, it is recommended to prophylactically transfuse for hemoglobin less than 10 g/dL, with goal of hemoglobin level of 10 g/dL, in order to reduce or prevent perioperative and postoperative complications in patients with SCD.43

Transfusion can be done immediately preoperatively or up to 14 days beforehand.43

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Platelet Transfusions

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation</strong></td>
<td><strong>Strength</strong></td>
</tr>
<tr>
<td>Non-bleeding Neonate: &lt; 20,000/mm³</td>
<td>Weak</td>
</tr>
<tr>
<td>Non-bleeding patient: 10,000-20,000/mm³</td>
<td>Weak</td>
</tr>
<tr>
<td>Unstable neonate: &lt; 50,000/mm³</td>
<td>Weak</td>
</tr>
<tr>
<td>Invasive procedure (not Neurosurgery): &lt; 50,000/mm³</td>
<td>Weak</td>
</tr>
<tr>
<td>Epidural Anesthesia: &lt; 80,000/mm³</td>
<td>Weak</td>
</tr>
<tr>
<td>Neurosurgery or Major bleed: &lt; 100,000/mm³</td>
<td>Weak</td>
</tr>
<tr>
<td>ECMO: &lt; 100,000/mm³</td>
<td>Weak</td>
</tr>
<tr>
<td>Bleeding patient: &lt; 50,000</td>
<td>Weak</td>
</tr>
<tr>
<td>Bleeding in a patient with platelet dysfunction: N/A</td>
<td>Strong</td>
</tr>
</tbody>
</table>

Neonate without bleeding

Thrombocytopenia is one of the most common hematologic findings occurring in 30% of all patients and >75% of very low birth weight (VLBW) infants. Platelet transfusions are not benign and include risks of infection transmission, alloimmunization, febrile reactions, hemolytic reactions, allergic reactions, transfusion-related lung injury, and transfusion-related intestinal injury. Currently, thrombocytopenic hemorrhage accounts for only 2% of the NICU platelet transfusions, whereas prophylactic administration accounts for 98%.45 While thrombocytopenia is a risk factor for bleeding in neonates, several prospective and retrospective studies have shown there is a poor correlation between severity of thrombocytopenia and clinically significant bleeding.46 In addition; multiple studies suggest that thrombocytopenia is well tolerated. In a trial of 152 very low birth weight infants randomized to be transfused at either <150,000 cells/mm³ or <50,000/mm³, there was found to be no difference in frequency or severity of IVH.45 A separate study by Stanworth et al showed moderate thrombocytopenia (50,000 - 150,000/mm³) was not detrimental to short-term neonatal outcome, specifically risk of progression to intraventricular hemorrhage (IVH).47 Based on retrospective and case control studies, the Australian Pediatric and Neonatal Blood Management Guidelines concludes that platelet transfusions, though often used in severely thrombocytopenic preterm infants to prevent or treat IVH or other active bleeding, have no clear evidence of benefit or harm.48 Currently a large multicenter randomized control trial, The PlaNet-2 study, is underway to assess outcomes in liberal versus restrictive prophylactic platelet transfusion strategies (50,000/mm³ versus 25,000/mm³) in premature infants. This study will hopefully provide more guidance regarding appropriate thresholds.51 Until then the NICU at DCMC has elected to use a conservative threshold of 50,000/mm³ to 100,000 /mm³ for ELBW infants

Currently suggested transfusion threshold for stable patients range from 20,000-50,000/mm³ in the Australian guidelines, 20,000-30,000/mm³, based on guidelines published by Norfolk in the UK49, and less than 30,000/mm³, based on an article in Critical Care Medicine.50 Higher thresholds of 30,000 – 50,000/mm³ are recommended by various authors for clinically unstable neonates including those with neonatal alloimmune thrombocytopenia.46,48,52

For neonates undergoing invasive procedures, neurosurgical interventions, or those with major bleeding, please refer to general pediatric guidelines below. Prophylactic platelets may also be indicated in the presence of platelet dysfunction, depending on the severity of the dysfunction but regardless of the platelet count.

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Non-bleeding patient

Prophylactic platelet transfusion is often used in neonates and pediatric patients with critical illness; however, there is limited evidence in this patient population and much evidence is applied from studies with adult patients. The American Association of Blood Banks (AABB) recommends that platelets should be transfused prophylactically to reduce the risk for spontaneous bleeding in patients with a platelet count of 10,000/mm³ or less. This recommendation is based on three randomized controlled trials (n=1047) that compared bleeding outcomes in patients with radiation and/or chemotherapy induced hypoproliferative thrombocytopenia assigned to receive or not receive prophylactic platelet transfusions. Prophylactic platelet transfusions were found to significantly reduce the risk for spontaneous World Health Organization (WHO) Grade 2 (mild clinically significant blood loss) or greater bleeding (OR 0.53, 95% CI 0.32 to 0.87). Four other randomized control trials (n = 658) assigned patients to prophylactic platelet transfusion at platelet count less than 10,000/mm³, 20,000/mm³, or 30,000/mm³. A greater platelet count threshold was not associated with a significantly lower incidence of WHO Grade 2 or greater bleeding (OR, 0.74 [CI, 0.41 to 1.35]) or bleeding-related mortality (OR, 0.37 [CI, 0.02 to 9.22]).

Two other recent randomized controlled trials of Hematology/Oncology patients compared prophylactic platelet transfusion with a therapeutic policy based on a daily assessment of bleeding, transfusing only to those with bleeding greater than WHO Grade 1 (petechial bleeding). Both studies found that groups without prophylaxis led to higher rates of WHO Grade 2-4 bleeding. Other guidelines recommend that prophylactic transfusions should be given to patients receiving intense chemotherapy at a threshold 10,000/mm³ and increasing threshold to 20,000/mm³ in patients who are febrile and/or receiving antibiotic therapy for suspected bacterial or fungal infection.

Invasive procedure (not Neurosurgery)

As there is a lack of reliable evidence regarding platelet transfusions in pediatric patients undergoing surgery, much evidence is pulled from adult patients. These guidelines for platelet transfusions in thrombocytopenic surgical patients and patients undergoing invasive procedures are largely based on expert opinion and clinical experience. Thus, the Australian guidelines use 50,000/mm³ as the threshold for patients undergoing invasive surgeries, lumbar punctures, central-line insertions, biopsies, or spinal anesthesia. The threshold for epidural anesthesia is 80,000/mm³. In addition, an article in the Journal of Vascular Interventional Radiology reported 80% expert consensus to have a platelet threshold of 50,000/mm³ in both low risk procedures and procedure with significant bleeding risk. The AABB suggests prophylactic transfusion for platelet counts less than 20,000/mm³ and less than 50,000/mm³ for central venous catheter (CVC) placement and lumbar puncture, respectively. Eight observational studies of CVC placement in the setting of thrombocytopenia were identified (n = 1311). In a multivariate analysis, only patients with pre-procedure platelet count less than 20,000/mm³ were at increased risk for bleeding. Data from seven observational studies of children or adults who were thrombocytopenic and had diagnostic or therapeutic lumbar puncture were evaluated. The largest was a single-center observational study of 5223 lumbar punctures in 956 pediatric patients with acute lymphoblastic leukemia. A total of 199 LPs were performed with platelet counts of 20,000/mm³, and 742 LPs were performed with platelet counts between than 21,000/mm³ and 50,000/mm³. No bleeding complications were seen, regardless of platelet count. Finally, the Australian Patient Blood Management Guidelines cited three fair-quality studies that investigated the effect of platelet transfusion on patient outcomes in perioperative cardiac patients. Two of the three studies demonstrated no association between administration of platelets and hospital mortality.

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Norfolk and colleagues as well as Parker report a consensus for platelet transfusion thresholds in Neurosurgery or posterior eye procedures to be 100,000/mm$^3$.\textsuperscript{49,50}

**ECMO**

Blood product transfusion protocols for ECMO patients are not currently evidence-based, but rather based on individual center experience and consensus guidelines. Frequent platelet transfusions of 10 ml/kg, are given to maintain a platelet count greater than 100,000/mm$^3$ particularly in neonates.\textsuperscript{50,56} The threshold for platelet transfusion may be reduced in older patients with an inherent lower risk of intracranial hemorrhage and who are stable on ECMO. In addition, there may also be significant platelet dysfunction despite regular platelet transfusions; platelet function tests can be performed to measure the platelet activity and aggregation. For example, thromboelastography (TEG) platelet mapping can be used to evaluate the degree of platelet inhibition using arachidonic acid and adenosine diphosphatase.\textsuperscript{56}

**Bleeding patient (excluding Neurosurgical patients/ICH)**

Parker sets the transfusion threshold for patients with bleeding at less than 40,000-50,000/mm$^3$.\textsuperscript{49} UK and Australian guidelines use 50,000/mm$^3$ as the threshold for major hemorrhage requiring massive transfusion and gastrointestinal hemorrhage.\textsuperscript{48,49}

**Bleeding in a patient with platelet dysfunction**

Patients with platelet dysfunction such as patients with chronic kidney failure, those on anti-platelet medications, or those who have undergone cardiopulmonary bypass, may bleed despite normal platelet count. Thus, transfusion should be based according to clinical response.\textsuperscript{49}

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Fresh Frozen Plasma

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Strength</td>
</tr>
<tr>
<td>Bleeding w/INR &gt; 1.5</td>
<td>Strong</td>
</tr>
<tr>
<td>CVL/General Surgery PreOp w/INR &gt; 2</td>
<td>Strong</td>
</tr>
<tr>
<td>Neurosurgery PreOp w/INR &gt; 1.5</td>
<td>Strong</td>
</tr>
<tr>
<td>Mod/ High Risk Percutaneous Biopsy w/INR &gt; 1.5</td>
<td>Strong</td>
</tr>
<tr>
<td>ECMO w/INR &gt; 2</td>
<td>Weak</td>
</tr>
<tr>
<td>Abnormal TEG result in bleeding patient</td>
<td>Indeterminate</td>
</tr>
</tbody>
</table>

Historically, Fresh Frozen Plasma (FFP) has been overused. Several factors have lead to inappropriate use. Firstly, although PT and aPTT were never designed to predict bleeding risks for invasive procedures, and mild to moderate elevations do not indicate a hemostatic defect in most patients, many physicians still believe that FFP is needed to prevent iatrogenic bleeding during procedures. Indeed current guidelines do not support its use even for high risk procedures until the INR is >1.5-2.0. In addition some clinicians still use FFP for volume replacement or as prophylaxis and peri/intraventricular hemorrhage in preterm infants despite recommendations against these practices.

Before infusion of FFP, the benefits must outweigh the risks of transfusion of a blood product, which include infection, transfusion reactions, TRALI, etc. For example, a retrospective analysis of adult ICU patients undergoing central venous cannula placement that received FFP prior to the procedure to correct INR, found these patients had a similar bleeding prevalence to those that did not receive FFP, but had a much higher rate of “acute lung injury” in 48 hours following transfusion. In another example, a prospective study of critically ill children, FFP transfusions were associated with a higher rate of organ dysfunction, nosocomial infections, and prolonged length of stay. In light of the unclear benefits of FFP and known risks, clinicians must exercise caution when considering its use. The following are guidelines for the use of FFP in various clinical settings.

### Bleeding patients with coagulation abnormalities

On the basis of many observational and randomized studies, experts do not recommend use of prophylactic FFP to correct coagulation test abnormalities in non bleeding patients. The use of FFP in bleeding patients has not been widely studied and thus recommendation rest on expert opinion. Although data quality is poor, most experts support the use of FFP in patients with active bleeding and coagulopathy with an INR> 1.5 being the most often cited threshold.

### Pre-procedural use of FFP

In critically ill infants and children the use of FFP and its effect on bleeding events and mortality remains poorly understood thus the use of FFP infusion for prophylaxis prior to procedures is controversial. According to expert opinion in guidelines produced by the NBAA, children with an INR ≤2 can undergo invasive procedures without serious bleeding. In certain situations such as in fetal and neonatal conditions, cardiac and other surgical procedures, even higher values maybe well tolerated. Guidelines produced by Patel et al for peri-procedural management of coagulation status and hemostasis risk in percutaneous image-guided interventions, state that low risk procedures can be safely performed with INR up to 2.0 whereas moderate to high risk procedures INR should be corrected to 1.5. It is important to note, that there is minimal data available upon which to make recommendations, and thus they stem largely from expert opinion.

Providers should exercise clinical judgment when deciding on transfusion. Values listed are guidelines and some patients may require transfusion and higher or lower values.
ECMO

Blood product transfusion protocols for ECMO patients are not currently evidence-based but rather based on individual center experience and consensus guidelines. Per the Extracorporeal life support organization (ESLO) transfusion guidelines, FFP may be administered if the INR is > 1.5-2.0 and/or if there is significant bleeding. 56

Abnormal TEG result in bleeding

According to the NBAA, the use of Thromboelastography (TEG) which tests clotting development and fibrinolysis, may reduce the volume of FFP transfused. 61 A recent meta-analysis of discovered that using a TEG-based transfusion algorithm avoided the overuse of FFP compared with a protocol that was not TEG-based.58 However, based on the lack of specific guidance from national and international guidelines we defer to individual practitioners to determine whether FFP is appropriate.

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The recommended threshold for cryoprecipitate infusion before an invasive procedure is a fibrinogen level less than 150 mg/dL. The American Association of Blood Banks Transfusion Guidelines agree with the use of cryoprecipitate for hypofibrinogenemia while undergoing invasive procedure and state that it can also be used in pre-operative patients with factor XIII deficiency in the event that factor XIII concentrate is not available. Cryoprecipitate should also be considered in actively bleeding patients before or during invasive procedures, regardless of fibrinogen level. The effects of cryoprecipitate on mortality and bleeding events in this population are not known and not well studied, but the overall goal remains to decrease risk of bleeding before or during the procedure.

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Irradiated Blood Products

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected or confirmed congenital T cell defect</td>
<td>Strong</td>
</tr>
<tr>
<td>Transfusion of HLA matched blood products</td>
<td>Strong</td>
</tr>
<tr>
<td>Transfusion from 1st degree relatives</td>
<td>Strong</td>
</tr>
<tr>
<td>Patients on chronic immunosuppressive therapy</td>
<td>Strong</td>
</tr>
<tr>
<td>Infants up to 3 months corrected age</td>
<td>Weak</td>
</tr>
<tr>
<td>Patients with known OR suspected malignancy</td>
<td>Strong</td>
</tr>
<tr>
<td>Transplant recipients (stem cell or solid organ)</td>
<td>Strong</td>
</tr>
<tr>
<td>Neonates up to 6 months of age who have received intrauterine transfusion</td>
<td>Strong</td>
</tr>
</tbody>
</table>

Transfusion-associated graft-versus-host disease (TAGVHD) is a rare and usually fatal complication of transfusion of cellular blood products. It is caused by failure to destroy donor T lymphocytes, which then proliferate and cause an immune response. TAGVHD occurs mainly in immunocompromised recipients, but can also occur in immunocompetent people who have received blood products from a related or human leucocyte antigen (HLA)-matched donor. TAGVHD can be prevented by using gamma radiation to irradiate cellular blood components that inactivate lymphocytes that could cause TAGVHD. Irradiation is performed by gamma or X-rays within 14 days of donation, and it then has a shelf life of 14 days.

There are three major guidelines that have been published in Great Britain, Australia, and Canada that discuss which pediatric patient population should receive irradiated packed RBCs and platelets.

According to Blood Management Guidelines in Australia, platelets and red cells should be irradiated for patients with severe acquired T-cell dysfunction related to either disease or drug therapy, or patients with HLA-matched cellular blood products.

Irradiated blood products should also be considered for neonatal exchange transfusion, provided irradiation does not unduly delay transfusion, premature infants especially those with extreme prematurity (< 28 weeks) or very low birth weight and certain patients undergoing chemotherapy depending on degree of immunosuppression.

Similarly, according to the Handbook on Transfusion Medicine from the United Kingdom, indications for transfusions with irradiated blood are for organ transplant patients who received alemtuzumab, for leukemia patients who received HLA-selected platelets or donations from first or second degree relatives, bone marrow or peripheral stem cell donors within 7 days of harvest, patients with Hodgkin Lymphoma, patients treated with purine analogue medications, and in neonates receiving exchange transfusion if time permits.

Lastly, according to Canadian Blood Services, irradiated blood cells should be used in intrauterine transfusions, neonates who have previously undergone intrauterine transfusions, neonatal ECMO, Low birth weight or pre-term infants, granulocyte transfusion, patients with congenital T-lymphocyte immunodeficiency syndromes, hematopoietic stem cell transplants, hematopoietic stem cell donors 7 days prior to or during harvest, patients with Hodgkin’s disease, patients on treatment with purine analogues, alemtuzumab, and anti-thymocyte globulin, patients undergoing chemotherapy or radiotherapy for

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malignancy or solid tumors, patients undergoing solid organ transplantation, transfusions from a biologic relative, and transfusions from HLA-matched blood components.⁸³

Based on these national guidelines and considering the devastating consequences of GVHD, local experts recommend a conservative approach that includes all patients with known or suspected malignancy in light of their high potential for receiving qualifying immunosuppressive therapy and the risk/benefit ratio of using irradiated products. In addition, they recommend broadening the recommendation to infants up to 3 months corrected gestational age since the diagnosis of congenital immunodeficiency may be delayed.

Risk of irradiation of RBCs is hyperkalemia and time to irradiate (around 30 minutes); therefore, the risk of TAGVHD should be balanced against these risks. To minimize this risk of hyperkalemia, irradiated RBCs should be as fresh as possible (<7 days old) and should be transfused within 24 hours of irradiation.⁸¹

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Washed PRBCS

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GRADE</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of severe or recurrent allergic transfusion reactions</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>Severe IgA deficiency</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>During massive blood transfusions of long-stored blood</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

Blood transfusions are known to alter humoral and cellular immunity in patients. Washing RBCs before transfusion is one way to help prevent alteration in immunity by removing substances such as antibodies, plasma proteins, and cytokines. In addition, washing can reduce the level of electrolytes in particular potassium that may be harmful to some patients. Although washed RBCs have the benefit of reducing some immunomodulatory effects of transfusion, it also carries the risk of damaging RBCs during the process which increases susceptibility to hemolysis. Washing is also more time and resource intensive adding approximately one hour of product preparation time and resulting in approximately 10-20% less RBCs.

Based on the recommendations of several International guidelines, washed RBCS are indicated for patients with severe or recurrent allergic or febrile reactions to PRBCs, and severely IgA-deficient patients (usually defined as patients with IgA levels of <0.07 g/L) for whom red cells from an IgA deficient donor are not available. Even then, most IgA deficient patients do not react to blood transfusions. In extreme emergency, transfusion with standard blood components should not be withheld even in patients with IgA deficiency or if there is a history of severe transfusion reaction, but these patients should be monitored carefully.

Washed RBCs can also be beneficial for large volume transfusions such as massive transfusion protocols, cardiopulmonary bypass/ECMO circuits, or exchange transfusions when the blood has been stored for greater than 7-10 days. When RBCs are stored, there is an increase in [K+] by 1 mEq/day, meaning potassium increases from 3 mEq/L at the time of donation to 45 mEq/L if RBCs are stored for 42 days. There are about 7 mEq of K+ for every one unit of blood given, so the risk of hyperkalemia in small-volume transfusions is negligible and washing is therefore not required. However, in the rare situation where large volume transfusion is required, washing PRBCs or using fresh PRBCS (stored < 7-10 days) can prevent hyperkalemia.

There are also debates whether washed RBCs are more beneficial in patients undergoing cardiac surgeries. A systematic review that included three small, similar trials comparing washed and unwashed RBCs had inconclusive results. Overall, there is insufficient evidence to determine whether washed RBCs improve outcomes in fetal, neonatal, or pediatric patients.

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Sickledex Negative

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GRADE</th>
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<tbody>
<tr>
<td>Patients with Hb SS disease</td>
<td>Strong</td>
</tr>
<tr>
<td>Neonates with non-emergent large volume transfusion</td>
<td>Strong</td>
</tr>
</tbody>
</table>

**Patients with Sickle cell disease**

Sickle cell disease is an inherited disorder characterized by the presence of hemoglobin S. Hb-S exists in a homozygous state (S/S) known as sickle cell disease or in a heterozygous state (S/A) know as sickle cell trait. Under conditions of low oxygen tension, red cells with hemoglobin S are less deformable and cause microvascular obstruction.

There are a variety of ways to detect HbS, but the quickest way is use the sickledex solubility test, which can detect levels of HbS of >10% in about 15 minutes. Sickledex testing is an effective way to screen for blood donors with both sickle cell disease and sickle cell trait.

According to the literature and local experts, patients with sickle cell disease should be transfused with blood from donors who are sickledex negative. Using blood from donors with sickle cell trait would reduce the efficacy of small volume transfusions and exchange transfusions and thus should be avoided unless there is an urgent need for blood.

**Neonates receiving large volume transfusions**

Ideally neonates receiving large volume red cell transfusions such as those on ECMO, Cardiopulmonary bypass or receiving exchange transfusions should receive sickle dex negative units. This recommendation is based on case reports of acidotic/hypoxic neonates with organ ischemia due to intravascular sickling after a large volume transfusion. In addition the presence of sickle trait may potentially reduce the efficacy of leukoreduction as thus increase the risk of CMV transmission. Practitioners must balance these potential concerns against the risk of delays in transfusion especially as there is no data on the incidence of sickle cell trait in the donor population and the risk of a neonate-receiving unit as part of a large volume transfusion is probably very low with an estimated 100,000-140,000 sickle positive units a year in the US blood supply.

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99. Sawyer, A, Wesel, Goss’s (2017) Comparison of transfusion thresholds during neonatal extracorporeal membrane oxygenation Transfusion. 57 (9) 2115-2120

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