Appendix 5- Transfusion Guidelines for infants with NE receiving TH
Inclusion criteria: All patients with NE undergoing TH
Exclusion criteria: Active bleeding*, Code situations

Thrombocytopenia		
Platelet Count (x 10^9/L)**	**Selection**	**Administration Guideline**
<25	Transfuse all	10 ml/kg of irradiated, leukocyte depleted platelets over 2-3 hours
25-49	Transfuse if: • Major Bleed*** in past 48h • Immediately prior to surgical procedure including LP	
50-100	Transfuse if: • Within 24h of major neurosurgical intervention****	

Coagulopathy		
Coagulation lab Parameter	**Selection**	**Administration Guideline**
INR> 2	Transfuse all (clinical discretion possible for borderline cases)	10 ml/kg of FFP over 1-2 hours
Fibrinogen < 150 mg/dl	Transfuse all (clinical discretion possible for borderline cases)	5 ml/kg (not to exceed 1 unit) of Cryoprecipitate over 1 hour

Anemia		
Hematocrit (%)	**Selection**	**Administration Guideline**
≤ 30	Transfuse all	15 ml/kg (in one aliquot) or 20 ml/kg (in two aliquots) of irradiated, leukocyte depleted RBCs over 4 hours (per aliquot) In infants with suspected severe chronic anemia, consider partial exchange
≤ 35	Transfuse if requiring respiratory support including: Mechanical ventilation, CPAP, HNFC or LFNC	

***Active bleeding management is per clinical discretion.** Scant bloody ETT secretions and mild oozing from skin puncture sites typically do not qualify.
**Evaluate actual platelet count at time of decision making. Do not consider "rate of fall" from previous count in decision making. If "rate of fall" is rapid, consider obtaining a repeat platelet count sooner.
***Defined as frank rectal bleeding, pulmonary hemorrhage, major intracranial bleed (ventricular dilation or midline shift, parenchymal hemorrhage, or need for neurosurgical intervention), bleeding associated with hypotension, hypovolemia, or hemodynamic instability requiring volume resuscitation or pRBC Tx
****Per individualized discussion with neurosurgery team.

Supporting Evidence of Transfusion Guidelines for Neonates Receiving Therapeutic Hypothermia

Platelet Transfusion

Thrombocytopenia (defined as a platelet count <150x10^9/L) is common in neonates with perinatal asphyxia with an increased incidence in those undergoing treatment with therapeutic hypothermia (TH) [1-3]. Asphyxia/TH induced thrombocytopenia is typically self-limited (resolving within 3-5 days), mild to moderate (platelet counts between 50 and 100x10^9/L)[2] and likely multifactorial in etiology. Severe asphyxia can result in disseminated intravascular coagulation (DIC) which accounts for many cases of thrombocytopenia in this population. However, some neonates develop thrombocytopenia without concurrent coagulopathy, and studies suggest that decreased platelet production and/or decreased platelet survival following exposure to hypoxia may underlie the thrombocytopenia in these patients [4, 5]. In addition, TH results in a well described inhibition of platelet activation, adhesion and aggregation as well as changes in their surface antigen composition that can lead to their rapid removal from the circulation [6]. Importantly, studies have found that thrombocytopenia secondary to perinatal asphyxia and TH puts infants at increased risk of only *mild bleeding* and factors involved in secondary hemostasis may be more important risk factors for severe hemorrhage [7, 8].

To date, there are no studies comparing platelet transfusion thresholds in infants with perinatal asphyxia undergoing TH. In 2019 the PlaNet-2 Trial was published. This randomized control trial compared liberal and conservative platelet transfusion thresholds in infants <34 weeks' gestational age [9] and found a higher incidence of death and/or major bleeding in the liberal transfusion arm, suggesting that liberal prophylactic platelet transfusions are not without risk in the neonatal population.

Through extrapolation of the best data currently available and considering the often mild and transient nature of perinatal asphyxia- and TH-induced thrombocytopenia and its lack of association with severe hemorrhage, we currently recommend a conservative platelet transfusion threshold of 25x10^9/L in all non-bleeding patients with perinatal asphyxia undergoing TH, with higher platelet transfusion thresholds indicated for specific high risk populations as outlined in the guideline.

FFP and Cryoprecipitate Transfusion:

Coagulopathy is a common finding in infants with birth asphyxia undergoing TH with an estimated incidence of 12-43% [10-12], and aberrations in the PT, PTT, INR, and Fibrinogen prompt transfusions in both non-bleeding and bleeding infants. The coagulopathy is due to both the hypoxic event and the subsequent treatment. Hypoxia/ischemia can result in disseminated intravascular coagulation (DIC) causing consumption of the coagulation factors and therapeutic hypothermia slows the enzymatic activity of factors in the coagulation cascade [6, 13, 14]. Studies investigating the association of clinical bleeding and coagulopathy in this population found that fibrinogen <150mg/dL and an INR>2 could discriminate between neonates with and without clinical bleeding [7, 8].

Interpretations of standard studies of coagulation (PT, PTT, INR) in this population are complicated by both developmental hemostasis and limitations inherent in laboratory testing. Developmentally, healthy infants have a baseline prolongation of the PT/PTT compared to adult reference ranges due to the infant's unique but appropriately balanced hemostatic system [15-17]. Thus, it is unclear if abnormalities in coagulation measured *in vitro* reflect *in vivo* failures of hemostasis. To further complicate the interpretation of these tests, patient samples are run at room temperature rather than the cooler temperatures achieved *in vivo* in infants undergoing TH [13].

There is very limited data to guide the transfusion of FFP and cryoprecipitate in this population and in infants in general. Very few studies in adults or infants investigating the use of FFP or cryo assess bleeding risk as the study outcome, but one adult study found no difference in subsequent bleeding risk in critically ill adults regardless of randomization to the transfused vs non-transfused group [18]. Additionally, there is a lack of evidence that prophylactic transfusions of FFP in non-bleeding patients are even successful in correcting laboratory markers of coagulopathy, let alone altering bleeding risk [19]. Studies of FFP in neonates have found no utility of transfusion to decrease neonatal mortality, prevent IVH, or support cardiovascular status [15, 20, 21]. In addition to the questionable utility of both FFP and cryo transfusions to alter bleeding risk, there is also concern for potential harm due to strong associations with transfusion related acute lung injury (TRALI), transfusion transmitted infection (specifically prion disease), fluid overload, and allergic reactions [15, 18].

In the absence of strong evidence-based data, the guidelines have been created to guide transfusion practices in this population. The authors note that more restrictive transfusion practices would be reasonable in an otherwise well, non-bleeding infant per clinician discretion. Specific considerations have been outlined regarding the volume of cryoprecipitate transfusion in effort to limit infant exposure to multiple donors (a single cryo unit from one donor is approximately 15-20mL in volume).

Packed Red Blood Cell (pRBC) Transfusion Guideline: Background and Supporting Evidence

There is very little data describing the incidence and consequences of anemia and pRBC transfusion in infants with perinatal asphyxia undergoing TH. One study described significantly increased rates of anemia in infants with asphyxia compared to healthy controls on day 3-4 of life [22]. This increased incidence is most likely related to acute perinatal blood loss resulting in asphyxia/ischemia, in cases such as placental abruption, fetal-maternal hemorrhages, and umbilical cord rupture. A separate study evaluating the correlation of hematologic parameters in infants with perinatal asphyxia found that infants with a worse prognosis had lower hemoglobin values or a more pronounced decrease in levels over the first 96 hours of life compared to those with a more favorable prognosis [23].

There is no data to guide transfusion practices in term infants, let alone term infants with asphyxia undergoing TH. Four studies have investigated pRBC transfusion practices in premature infants, including the most recent ETTNO and TOP trials [24, 25]. Both trials found

no difference in the incidence of severe neurodevelopmental deficits at 24 months when using restrictive vs. liberal transfusion thresholds in the premature population. The British Society of Haematology has published expert opinion guidelines suggesting that in term infants the hemoglobin should be maintained above 10g/dL (Hct~33%) in the first week of life and above 7.5g/dL (Hct~25%) after [26].

Extrapolating from the best available evidence in newborns and published guidelines, the pRBC transfusion guideline has been created for term infants with NE undergoing TH, taking into account the infant's respiratory support requirements.

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