Newborn Critical Care Center (NCCC) Clinical Guidelines

Management of Hemolytic Hyperbilirubinemia

BACKGROUND

Newborns exposed to maternal red cell alloimmunization are at increased risk of hemolytic disease of the fetus and newborn (HDFN). Specific alloantibodies leading to severe disease include Anti-Rh(D), anti-K (anti-K1), anti-Rh(c), and less often Anti-Rh(E). During the fetal period, this may lead to severe anemia, hydrops fetalis, and intrauterine fetal demise, all of which can be reduced with the use of prenatal intrauterine transfusion (IUT). Postnatally, all infants with HDFN remain at risk of anemia and hyperbilirubinemia and thus require special follow-up**.** While most newborns treated with IUT will have an adequate hematocrit at birth, they are at high risk of requiring at least one postnatal transfusion in the first month after birth.[1,2,3] Anemia in infants with HDFN is due to the continued destruction of newly made RBCs by circulating maternal antibodies; if the infant is the recipient of IUT or postnatal transfusion, the suppression of EPO also contributes to anemia. In some cases, the resulting anemia can be severe and lead to failure to thrive and congestive heart failure.

MANAGEMENT OF THE NEWBORN WITH RED CELL ALLOIMMUNIZATION

At Birth*:*

1. Send cord blood for type, Direct Coombs, hematocrit, reticulocyte count, and neobilirubin level. Of note, in IUT recipients, postnatal blood typing will be influenced by the proportion of circulating RBCs from the donor at the time of birth, and thus may not reflect the typing of the newborn's own cells.
2. If the newborn is clinically appropriate for the NBN, notify the provider in the NBN who will be responsible for the infant to ensure prompt follow-up of pending laboratory work.

Initial Management (in NBN or NCCC):

1. Start intensive phototherapy* immediately for cord bilirubin ≥2 mg/dL.
2. If phototherapy is not required at birth, repeat neobilirubin level at 4 and 8 hours after birth, then every 12 hours for three checks (at 20 hours, 32 hours and 44 hours after birth) and then spaced per the provider's discretion.[4]
3. If bilirubin level is at or above the hour-specific phototherapy threshold at any point, begin intensive phototherapy. *

* *Intensive phototherapy implies irradiance in the blue-green spectrum (460-490nm) of at least 30μW/cm² per nm (measured at the infant's skin directly below the center of the phototherapy unit)*

Indications for NCCC Admission:

1. Cord bilirubin ≥ 6 mg/dL or hematocrit < 25%
2. Rate of rise ≥0.3mg/dL/hr despite intensive phototherapy
3. Anticipated need for blood transfusion or exchange transfusion (within 2mg/dL of exchange threshold)

If Admission to NCCC Required for Management of Hyperbilirubinemia:

1. Send blood for ABO/Rh, total and direct bilirubin, Chem10, and albumin.
2. Obtain consent for administration of blood products.
3. Consider administration of intravenous immunoglobulin (IVIG) if the neobilirubin is within 2 mg/dL of the exchange threshold and rising despite intensive phototherapy.[1]
    a. If administered, IVIG 0.5-1g/kg should be given over 2 hours and can be repeated 12 hours later.[1]
4. If double volume exchange transfusion appears imminent, notify Blood Bank immediately, as it takes **at least 4 hours** to screen and modify blood to be used for exchange transfusions.
    a. If TSB drops below the exchange transfusion threshold during preparation for the transfusion and the infant does not display signs of acute bilirubin encephalopathy, exchange transfusion may be deferred with repeat TSB every 2 hours until the infant is below the escalation of care threshold.[4] (*See Exchange Transfusion Guidelines*)
5. Transfusion of pRBCs is often needed in this population, however there are no published trials of transfusion thresholds for infants with red cell alloimmunization.
    a. A research group from the Netherlands with a focus on HDFN uses thresholds of Hgb <10.4 g/dL in the first week of life, <8.8 g/dL in the second week of life, and <7.2 g/dL thereafter.[3]
6. There is insufficient evidence to support the use of recombinant erythropoietin (rhEpo) or its longer-acting analog darbopoeitin to reduce or prevent the need for transfusion in this population.
    a. Of note, the EPO-4-Rh study is underway and examines the effect of darbopoeitin alfa in reducing the need for RBC transfusion in infants with HDFN treated with IUT (NCT03104426; anticipated completion in 2023).
7. For infants with severe HDFN (early anemia requiring transfusion or hyperbilirubinemia requiring exchange transfusion), consult Pediatric Hematology/Oncology.

For additional recommendations on phototherapy and exchange transfusion, refer to the NCCC Phototherapy Guidelines and Exchange Transfusion Guidelines.

DISCHARGE PLANNING FOR ALL NEWBORNS WITH RED CELL ALLOIMMUNIZATION

1. Despite significant anemia, infants with red cell alloimmunization, regardless of IUT status, rarely have iron deficiency and are likely to have iron overload at birth.[5] For this reason, iron supplementation is not recommended.[3,4]
2. Obtain hematocrit with reticulocyte count prior to discharge.
3. Call PCP to notify them of infant's history of HDFN and to ensure that provider is comfortable obtaining frequent labs. There is no evidence to support the cadence of labs, however, it is advised to obtain hematocrit and reticulocyte count weekly until hematocrit is stable and reticulocytes are rising 2 consecutive weeks. This may mean frequent labs up to 3 months of age.
4. Inform parents of the importance of following anemia closely and counsel on the symptoms of severe anemia including pallor, lethargy, and failure to thrive.

References:

1. Millard DD, Gidding SS, Socol ML, et al. Effects of intravascular, intrauterine transfusion on prenatal and postnatal hemolysis and erythropoiesis in severe fetal isoimmunization. *J Pediatr*. 1990;117(3):447-454.
2. Ree IMC, Smits-Wintjens VEHJ, van der Bom JG, van Klink JMM, Oepkes D, Lopriore E. Neonatal management and outcome in alloimmune hemolytic disease. *Expert Rev Hematol*. 2017;10(7):607-616.
3. De Winter DP, Hulzebos C, Van 't Oever RM, De Haas M, Verweij EJ, Lopriore E. History and current standard of postnatal management in hemolytic disease of the fetus and newborn. *Eur J Pediatr*. 2023;182(2):489-500. doi:10.1007/s00431-022-04724-0
4. Kemper AR, Newman TB, Slaughter JL, et al. Clinical Practice Guideline Revision: Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. *Pediatrics*. 2022;150(3).
5. Rath ME, Smits-Wintjens VE, Oepkes D, Walther FJ, Lopriore E. Iron status in infants with alloimmune haemolytic disease in the first three months of life. *Vox Sang*. 2013;105(4):328-333. doi:10.1111/vox.12061