Excellent Neonatal HDFN Care Practices

The following constitutes a list of management, intervention and support practices which reflect the available peer-reviewed literature and expert clinical opinion for the neonatal management of Hemolytic Disease of the Fetus and Newborn (HDFN). This list is meant to serve as a resource for families navigating HDFN and their care providers. Medical decisions should be made in consultation with a clinician specialist who is familiar with each specific case. Each HDFN baby is affected differently. Treatment will be modified based on the unique clinical presentation.

Diagnosis of HDFN

- If HDFN in the newborn is known or suspected, delivery at a Level 3 or Level 4 NICU is recommended.
- The infant's antigen status should be determined before birth whenever possible based on paternal genetics, testing fetal DNA in mom's blood (cffDNA), or amniocentesis. If the infant's antigen status was not determined before birth, they should be treated as if they have HDFN until proven otherwise through negative Direct Antiglobulin Test (DAT) and absence of symptoms.
- Delayed cord clamping (30-60 seconds) has been shown to increase starting hemoglobin and may reduce the need for neonatal exchange or top-up transfusion in the HDFN neonate with history of intrauterine transfusion.
- Immediately at delivery in cases where the mother is known to have red cell antibodies or a negative blood type, cord blood should be sent for type, DAT (also called Direct Coombs Test, DCT), CBC (for hemoglobin/hematocrit) and bilirubin levels.
- A positive DAT test indicates HDFN, which can present as aggressive hyperbilirubinemia and delayed onset hemolytic anemia (both manifesting differently than newborn jaundice and iron deficiency anemia).
- Infants who have received intrauterine transfusions may have nearly 100% donor blood at birth and DAT may therefore be negative despite severe HDFN.
- The DAT result can sometimes be falsely negative in instances where the mother has low antibody levels, anti-Dia, anti-Dib, anti-Jsa, and anti-Wra; and additionally false negative results do sometimes occur. In the absence of obvious clinical presentation of HDFN, following bilirubin for the first week of life and hemoglobin/hematocrit weekly for the first four weeks of life may be pertinent in some cases of a negative DAT but where the clinician feels that HDFN may be possible due to neonatal presentation, maternal antibody status or a homozygous paternal antigen phenotype.
- Infants with history of intrauterine transfusion may have inaccurate newborn blood typing and newborn screen results which change once the donor blood has been replaced over time. These tests may need to be repeated several weeks after the infant's last blood transfusion for accurate results.

Monitoring

- Close monitoring of bilirubin per AAP guidelines for management of hyperbilirubinemia in neonates with neurotoxicity risk factors will apply to infants with HDFN.
  - Measure total serum bilirubin (TSB) immediately at birth, every 4 hours 2 times, then every 12 hours 3 times.
  - Continue monitoring TSB daily through the first week of life and until TSB trends downwards without phototherapy for two consecutive draws.
  - If phototherapy is indicated, bilirubin should be monitored more frequently until levels fall below the treatment threshold and for 24 hours after phototherapy discontinuation.
- Late hemolytic anemia may occur until three months of age.
  - Monitor hemoglobin/hematocrit and reticulocyte counts weekly for the first six weeks and then as applicable for the first three months. Increasing hemoglobin/hematocrit (or stable normal values) for two consecutive draws after six weeks are good indicators that HDFN has resolved.
  - Reticulocyte counts can be a helpful indicator of the infant's ability to generate new red blood cells. A reticulocyte count near zero indicates hypo regenerative anemia, a common consequence of HDFN and transfusion dependence. Continued monitoring to ensure active reticulocytosis is an important aspect of monitoring the neonatal HDFN disease course.
- It is necessary to assure referral to pediatric hematology or, in less severe cases, a pediatrician knowledgeable in HDFN monitoring prior to discharge with proper transfer of fetal and neonatal health history. Follow-up should occur 24-48 hours after discharge.
- Breastfeeding is safe in babies with HDFN if baby is stable enough for oral feedings. Supplementation may be needed to provide extra calories to promote stooling, and ridding the body of bilirubin.

Intervention

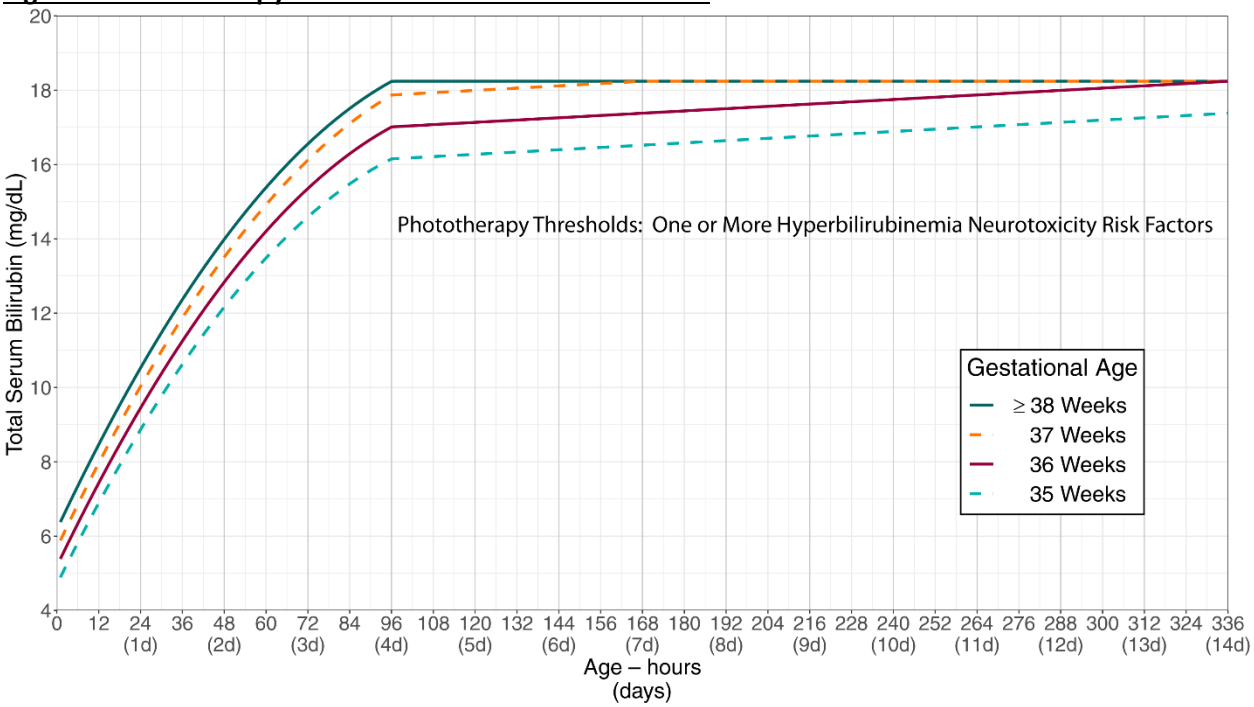
- Hyperbilirubinemia treatment
  - Phototherapy
    - Thresholds are determined by gestational age at birth, age in hours since birth, total serum concentration, and whether there are neurotoxicity risk factors (see AAP guidelines; also provided in Figure A below).
    - Phototherapy discontinuation is possible when TSB has decreased by at least 2 mg/dL below the phototherapy threshold or lower in the case of HDFN.
    - After phototherapy discontinuation, measure TSB 6, 12, and 24 hours after to observe for rebounding hyperbilirubinemia.
  - Double-volume exchange transfusion may be needed if bilirubin reaches a certain threshold. This washes out excess bilirubin as well as maternal antibodies.
    - Escalation of care per AAP guidelines is appropriate if TSB is 2mg/dL below exchange transfusion threshold (begin following TSB every 2 hours alongside aggressive phototherapy and IV hydration) (Figure B below).
    - Intravenous immune globulin (IVIG; 0.5-1 g/kg over 2hrs) may be given in infants whose TSB reaches escalation of care threshold though effectiveness is unclear.
    - Urgent exchange transfusion is needed if TSB is at or above the exchange transfusion threshold or baby is showing signs of intermediate or advanced acute bilirubin encephalopathy: hypertonia, arching, high pitched cry, apnea, neck muscle contractions.

    - Treatment with a home phototherapy device is contraindicated as a standalone treatment in infants with HDFN.
- Anemia treatment
    - One or more top-up transfusions may be necessary up to 3-4 months of age even if hemoglobin/hematocrit levels are initially normal in the first few weeks of life, especially if the neonate has received an intrauterine transfusion (IUT) in utero.
    - Transfusion thresholds have not been standardized but generally, RBC transfusions should not be conducted *routinely* for a hemoglobin concentration of ≥7 g/dL in *term* neonates with HDFN who are otherwise well and not requiring respiratory support. RBC transfusion for hemoglobin ≥7 g/dL may be appropriate for term neonates with HDFN based upon the hemoglobin concentration, postnatal age, degree of respiratory support, and overall clinical context.
    - Transfusion thresholds tend to vary by center, however, two centers with specific HDFN expertise and a high case volume employ the following thresholds for red blood cell top-up transfusions with irradiated donor blood in HDFN infants:
        - Leiden University (Netherlands): transfuse at or below 10.4 g/dL (6.5 mmol/L) in the first week of life, below 8.8 g/dL (5.5 mmol/L) in the second week of life, and below 7.2 g/dL (4.5 mmol/L) thereafter.
        - Intermountain Health (U.S.): transfuse at or below Hb of 9 g/dL in first week of life, 8 g/dL in second week of life, 7 g/dL thereafter. At any age, transfuse if Hb is less than 9g/dL and infant is not feeding well or requiring oxygen.
    - If the neonate is clinically stable, proceeding with transfusion should be balanced against the risk of transfusion dependence potentially requiring longer follow-up and/or a higher number of total transfusions.
    - Erythropoietin or darbepoetin has been used as an adjunct treatment for anemia to increase bone marrow production of red blood cells and increase reticulocyte count. In a recent randomized controlled trial, darbepoetin alfa treatment resulted in a significant reduction in erythrocyte transfusion episodes versus standard care.

<u>Special considerations</u>

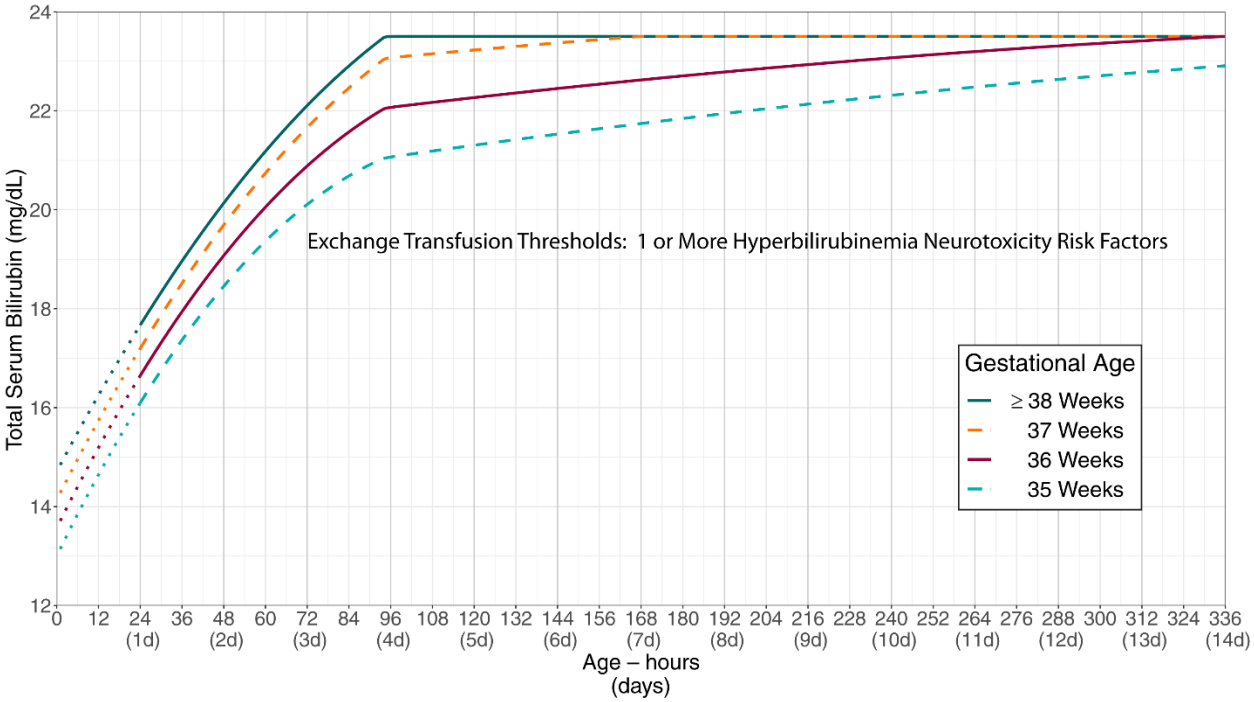
- Blood for transfusion must be cross-matched to the maternal antibody(ies).
- Because infants with HDFN do not have iron deficiency anemia, they do not require iron supplementation. During hemolysis, the iron molecule remains in the bloodstream leading to high iron levels, which is additionally exaggerated in cases where the infant has already received intrauterine or post-birth transfusions with iron rich adult donor blood. 70% of infants with HDFN may have high ferritin levels exceeding the 95th percentile. Administering iron is contraindicated unless a ferritin test has indicated true iron deficiency.
- Thrombocytopenia, neutropenia, and cholestasis can occur in infants with HDFN but are usually self-limiting. Platelet transfusion is sometimes required, though this is rare.
- In addition to weekly CBCs, parents should monitor their baby for signs of anemia (paleness, poor eating, lethargy, increased heart rate, fast breathing). If they begin to show signs, parents should call their pediatrician or take their baby to the emergency room.

Figure A. Phototherapy thresholds for neonate with HDFN



Copied from Figure 3 of AAP's Hyperbilirubinemia Guidelines (Kemper et al., 2022).

Figure B. Exchange transfusion thresholds for neonate with HDFN



Copied from Figure 6 of AAP's Hyperbilirubinemia Guidelines (Kemper et al., 2022).

Resources

Bilyk, I. Hemolytic Disease of the Fetus and Newborn *(HDFN)*. 2022. Dynamed. https://www.dynamed.com/condition/hemolytic-disease-of-the-fetus-and-newborn-hdfn
Delaney, & Patterson. Postnatal Management of Red Cell Alloimmunization: NCCC Clinical Guidelines. MomBaby. 2019.

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. European Journal of Pediatrics. 2023 Feb;182(2):489-500.

de Winter DP, Verweij EJ, Debeer A, Devlieger R, Lewi L, Verbeeck S, Maurice P, Jouannic JM, Guillemin MG, Mailloux A, Dos Santos MC. Variations and opportunities in postnatal management of hemolytic disease of the fetus and newborn. JAMA network open. 2025 Jan 2;8(1):e2454330.

Garabedian C, Rakza T, Drumez E, et al. Benefits of delayed cord clamping in red blood cell Alloimmunization. Pediatrics. 2016;137(3): e20153236.

Kemper AR, Newman TB, Slaughter JL, Maisels MJ, Watchko JF, Downs SM, Grout RW, Bundy DG, Stark AR, Bogen DL, Holmes AV. Clinical practice guideline revision: management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2022 Sep 1;150(3):e2022058859.

Ree, I. M. C., Smits-Wintjens, V. E. H. J., van der Bom, J. G., van Klink, J. M. M., Oepkes, D., & Lopriore, E. Neonatal management and outcome in alloimmune hemolytic disease. Expert review of hematology. 2017;*10*(7): 607–616.

Ree IM, de Haas M, van Geloven N, Juul SE, de Winter D, Verweij EJ, Oepkes D, van der Bom JG, Lopriore E. Darbepoetin alfa to reduce transfusion episodes in infants with haemolytic disease of the fetus and newborn who are treated with intrauterine transfusions in the Netherlands: an open-label, single-centre, phase 2, randomised, controlled trial. The Lancet Haematology. 2023 Dec 1;10(12):e976-84.

UNC School of Medicine. Management of Hemolytic Hyperbilirubinemia: NCCC Clinical Guidelines. MomBaby. 2023.

van Rossum HH, de Kraa N, Thomas M, Holleboom CA, Castel A, van Rossum AP. Comparison of the direct antiglobulin test and the eluate technique for diagnosing haemolytic disease of the newborn. Practical Laboratory Medicine. 2015 Dec 1;3:17-22.

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