Last Revised April 2025

Dear Provider,

Your patient has been diagnosed with maternal red blood cell alloimmunization, which can cause hemolytic disease of the fetus and newborn (HDFN). They have utilized resources provided by the Allo Hope Foundation, a nonprofit organization led by patients and maternal fetal medicine specialists (MFMs) to provide evidence-based content related to the management and treatment of alloimmunization/HDFN with the objective of achieving zero preventable deaths to HDFN.

Knowing this disease's rarity and being intimately aware of constraints which may prevent practitioners from quickly accessing the most recent resources for management of this disease, we would like to provide a brief list of key aspects of managing a pregnancy such as this.

- Fetal antigen status may be determined to assess whether the fetus is at risk for HDFN. If fetal antigen status is not determined (for example if paternity is unknown, the father of the baby is not available for testing, and/or the patient declines fetal screening or testing for antigen status), the fetus should be assumed to be antigen positive so that the pregnancy can be monitored for development of HDFN. Options for determining the fetal antigen status include:
    - Antigen phenotype (not antibody screen) on father (homozygous result gives conclusive answer)
    - U.S. – cell free fetal DNA (cffDNA) testing for fetal antigen status for D, C, c, E, K, and Duffy (Fya) antigens is currently available in the U.S. at BilliontoOne (Unity Screen) (100% sensitivity/specificity, 99.9% precision)[3]
    - Non-U.S – cffDNA testing for fetal antigen status for D, E, K, C, and c antigens is available through Sanquin Laboratories in Netherlands with 99% sensitivity/specificity – Sanquin website[1] provides instructions for sending sample. Also available in various national laboratories including AU, UK, and Canada.
    - Amniocentesis should be considered less optimal for determining the fetal antigen status as it can trigger an enhanced antibody reaction, increasing maternal antibody titer.[2,3]
- For patients with a history of second trimester demise due to HDFN, history of IUT <24 weeks gestation, or markedly elevated initial titers (≥512 for Anti-D; ≥64 for Anti-K), IVIG with or without plasmapheresis beginning before 13 weeks (usually 10-12 weeks of gestation) should be considered to delay the time to first intrauterine transfusion (IUT).[4,5]
- For elevated initial titers, consider prompt referral or collaboration with an MFM specialist with experience in treating high titer pregnancies with preventative treatments, early MCA Doppler scans and IUTs. The MFMs on the advisory board of the Allo Hope Foundation at the bottom of this letter are available for outreach.
- With skilled ultrasound technicians and fetal interventionists, MCA Doppler ultrasounds and IUTs can begin as early as 15 weeks gestation.[6] If your facility does not offer this but a patient requires it, prompt referral is critical.

- Middle cerebral artery (MCA) peak systolic Doppler measurement should be conducted weekly beginning at 16 weeks or after a critical titer is reached (titer of 4 for Kell, 16 for all other clinically significant antibodies); whichever is later. A value in multiples of the median (MoM) nearing 1.5 requires prompt re-scan within 24 hours. An MoM of 1.5 or more suggests fetal anemia and requires prompt intervention, e*ven if evidence of fetal hydrops is not yet present. Fetal hydrops is often absent in the second trimester fetus even with severe anemia.* Outcomes with IUT decline significantly once hydrops is present.[7,8]
- Administration of antenatal corticosteroids can falsely lower MCA Doppler MoMs in some cases.[9,10] It is best not to alter the course of treatment based on an MoM measured after steroid administration.
- IUTs should be conducted by a clinician who has sufficient experience in the procedure. Previous analyses and Delphi consensus suggest that previous research and Delphi expert consensus has indicated that initial competence is reached at 30-50 IUTs total and an average of 10 IUTs annually,[11,12] or is supervised during procedure by an clinician who meets the aforementioned criteria for competence.
- In the early second trimester fetus, the fetal hematocrit/hemoglobin should not be increased more than three times over the starting measurement at the time of the IUT in an effort to prevent cardiac overload. If after IUT, the fetal hematocrit is still below the normal range, a second IUT can be scheduled 48 – 72 hours later to raise the fetal hematocrit into the normal range.[13]
- Termination of pregnancy is rarely indicated in cases of HDFN as survival rates of > 95% have been reported with IUTs at experienced centers.[9]
- In an at-risk fetus (determined or suspected to have the antigen in question), antenatal testing beginning at 32 weeks and induction at 37-38 weeks is recommended regardless of titer.[14,15] Please utilize our Clinical Decision Support Tree (link below) for a flow diagram.
- Consider offering your patient mental health support resources as significant psychosocial burden is consistently reported in this patient population.[16]
- Integration with the newborn's care team will be essential to ensure proper post-birth monitoring. Regardless of disease severity in-utero or after delivery, delayed onset hemolytic anemia is possible through the first 12 weeks of life and requires weekly follow-up with pediatric hematology to follow serial hematocrits and reticulocyte counts. Some of these infants develop late onset of anemia and require "top-up" transfusions.

All signatories below are available for consultation. Visit www.allohopefoundation.org for a complete clinician resource repository. Email info@allohopefoundation.org with your mailing address to request a free laminated clinical pocket guide for alloimmunization pregnancy management.

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Sincerely,

Juan M. González Vélez, MD PhD
Professor
Russell K. Laros, Jr., MD Endowed Chair in Clinical Obstetrics and Gynecology
Maternal-Fetal Medicine and Reproductive Genetics Division Director
Division of Maternal-Fetal Medicine and Reproductive Genetics | UCSF Department of Obstetrics, Gynecology & Reproductive Sciences
Email: Juan.Gonzalez@ucsf.edu
(267) 207-1923

Kara Beth Markham, MD
Associate Professor of Obstetrics and Gynecology and Maternal Fetal Medicine
University of Cincinnati Medical Center
Cincinnati Children's Fetal Center at the Cincinnati Children's Hospital Medical Center
Cincinnati, OH, USA
markhakb@ucmail.uc.edu
(513) 558-8440

Kenneth J Moise Jr, MD
Professor of Women's Health
Dell Medical School – UT Austin
Director, Comprehensive Fetal Care Center
Dell Children's Medical Center
Austin, TX, USA
kmoise@austin.utexas.edu
(713) 444-7603

Katie Shanahan, RN, MSN, CPNP
Director of Development
Allo Hope Foundation
Stoneham, MA, USA
katie@allohopefoundation.org
978-697-8344

Molly Sherwood
Director of Research
Allo Hope Foundation
Lexington, KY, USA
molly@allohopefoundation.org
(443) 812-5316

Saul Snowise, MD
Carol L. Wells Endowed Chair in Fetal Surgery
Medical Director
Midwest Fetal Care Center
Minneapolis, MN, USA
saul.snowise@allina.com
(713) 557-0616

Thomas Trevett, MD
Georgia Perinatal Consultants
Northside Hospital
Atlanta, GA, USA
thomas_trevett@yahoo.com
(404) 851-8988

Bethany Weathersby, MEd
Founder, Executive Director
Allo Hope Foundation
Tuscaloosa, AL, USA
bethany@allohopefoundation.org
(205) 331-6430

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