Letter to Practitioners

Last Revised February 2024

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.

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. At the bottom of this letter, we also provide QR codes which you may utilize to access the complete list of citations for these recommendations, a Clinical Decision Support Tree, and a more thorough Provider Primer covering monitoring and treatment for this nuanced disease.

- 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)
  - Cell free fetal DNA (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] and our Allo Hope Foundation website[2] provide instructions for sending sample.
  - 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]
  - Amniocentesis should be considered less optimal for determining the fetal antigen status as it can trigger an enhanced antibody reaction, increasing maternal antibody titer.[3,4]
- For patients with a history of second trimester demise due to HDFN or for patients with markedly elevated initial titers, 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).[5,5]
- 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 after a critical titer is reached (any for Kell, 16 for all other clinically significant antibodies). 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] It is best not to alter the course of treatment based on an MoM measured after steroid administration.
- 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.
- 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.[10] 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.
- 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 further information. Please utilize the codes below for follow-on resources and www.allohopefoundation.org for our complete resource repository.

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Scan code below for provider resources on our website:

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Scan code below for a complete Provider Primer:

Scan code below to view a web version of this letter:

1REFERENCES

[1]https://www.sanquin.org/products-and-services/diagnostics/non-invasive-fetal-blood-group-genotyping

2[2]https://allohopefoundation.org/library/cffdna/

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