



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 website¹ and our Allo Hope Foundation website² 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% precision³
 - 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.





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- 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. A MoM of 1.5 or more suggests fetal anemia and requires prompt intervention, *even 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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Sincerely,

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Scan code below for provider resources on our website:



Scan code below for a complete Provider Primer:



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



REFERENCES

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

² <https://allohopefoundation.org/library/cffdna/>

³ Oepkes D, Seaward PG, Vandebussche FP, Windrim R, Kingdom J, Beyene J, Kanhai HH, Ohlsson A, Ryan G; DIAMOND Study Group. Doppler ultrasonography versus amniocentesis to predict fetal anemia. *N Engl J Med*. 2006 Jul 13;355(2):156-64. doi: 10.1056/NEJMoa052855.

⁴ Moise Jr, Kenneth J. RhD alloimmunization in pregnancy: Management. UpToDate. Last updated July 2022. Available at: <https://www.uptodate.com/contents/rhd-alloimmunization-in-pregnancy-management>

⁵ Ruma MS, Moise Jr KJ, Kim E, Murtha AP, Prutsman WJ, Hassan SS, Lubarsky SL. Combined plasmapheresis and intravenous immune globulin for the treatment of severe maternal red cell alloimmunization. *American journal of obstetrics and gynecology*. 2007 Feb 1;196(2):138-e1.

⁶ Mari G, Abuhamad AZ, Cosmi E, Segata M, Altaye M, Akiyama M. Middle cerebral artery peak systolic velocity: technique and variability. *Journal of ultrasound in medicine*. 2005 Apr;24(4):425-30.

⁷ Klumper FJ, van Kamp IL, Vandebussche FP, Meerman RH, Oepkes D, Scherjon SA, Eilers PH, Kanhai HH. Benefits and risks of fetal red-cell transfusion after 32 weeks gestation. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2000 Sep 1;92(1):91-6.

⁸ Zwiers C, Lindenburg IT, Klumper FJ, De Haas M, Oepkes D, Van Kamp IL. Complications of intrauterine intravascular blood transfusion: lessons learned after 1678 procedures. *Ultrasound in Obstetrics & Gynecology*. 2017 Aug;50(2):180-6.

⁹ Urban R, Lemancewicz A, Przepieć J, Urban J, Kretowska M. Antenatal corticosteroid therapy: a comparative study of dexamethasone and betamethasone effects on fetal Doppler flow velocity waveforms. *Eur J Obstet Gynecol Reprod Biol*. 2005 Jun 1;120(2):170-4. doi: 10.1016/j.ejogrb.2004.09.009.

¹⁰ American College of Obstetricians and Gynecologists, Committee on Obstetric Practice, Society for Maternal-Fetal Medicine. Medically indicated late-preterm and early-term deliveries: ACOG Committee Opinion, Number 831. *Obstetrics and gynecology*. 2021 Jul 1;138(1):e35-9.

