Excellent maternal alloimmunization/HDFN care practices

The following constitutes a list of management, intervention and support practices which reflect the available peer-reviewed literature and expert opinion for the management of maternal red blood cell alloimmunization causing hemolytic disease of the fetus and newborn (HDFN). This list is meant to serve as a resource as patients are selecting a care provider, and as a criterion which members of the Allo Hope Foundation (AHF) use to recommend doctors amongst our patient base.

<u>Diagnosis and monitoring</u>

- Offers antigen phenotype or genotype testing for baby's father
- Facilitates cffDNA testing to patients with D, K, C, c, E and Duffy (Fya) antibodies when fetal antigen status is unknown. cffDNA testing is currently available in the U.S at BilliontoOne (Unity Screen)(100% sensitivity/specificity, 99.9% precision)[1]
- Offers paternal testing and cffDNA testing to avoid amniocentesis for fetal antigen determination if possible. For fetal antigens not available for testing through cffDNA, amniocentesis after 15 weeks in patients with critical titers and unknown fetal antigen status may be indicated. In these cases the placenta is avoided at time of amniocentesis to prevent further alloimmunization[1,2]
- Offers temporizing treatment options such as IVIG +/- plasmapheresis to patients with previous severely affected pregnancies or extremely high titers[3]
- Weekly MCA Doppler scans for women with critical titers (any for Kell, 16 for all other antibodies; 4 IU/ml for anti-D in UK)[4]
- Checks antibody titers every 4 weeks until 28 weeks, then every 2 weeks thereafter or if titers are rising, until titers reach critical value[3]
- Middle cerebral artery (MCA) Doppler scans start by 18 weeks for women with critical titers[5]
- Receptive to starting MCA Doppler scans as early as 15 weeks for women with previously affected pregnancies or high titers[6]
- MCA Doppler Peak Systolic Velocity (PSV) value in multiples of the median (MoM) nearing 1.5 results in prompt re-scan, followed by cordocentesis and IUT if levels remain or exceed 1.5 MoM[7]
- Institutes antenatal testing (non-stress test or biophysical profile) at least weekly from 32 weeks gestation until delivery in all alloimmunized pregnancies[8]

Intervention

Note that a clinician without extensive history in performing an IUT may still be an excellent provider for an alloimmunized patient and should remain highly recommended, given that they facilitate prompt referral to a more experienced center for IUTs should the need arise.

If the clinician does perform IUTs, such a clinician:

- ! Performs IUT promptly after a MoM of 1.5 or higher after confirming anemia via cordocentesis, independent of the presence of hydrops[9]
- ! Has demonstrated competence in performing IUTs (previous research has indicated that initial competence is reached at 30-50 IUTs total and an average of 10 IUTs annually[10,11] or is supervised during procedure by an MFM who meets the aforementioned criteria for competence)
- ! Performs IUTs in an operating room or in a delivery room with immediate access to operating room (a joint decision with the patient)[12]
- ! Uses fetal paralytic medication during IUTs as indicated[1212]
- ! Offers IV sedative to mother during IUTs[13]
- ! Does not bring starting hemoglobin/hematocrit up by more than three times the starting value during IUTs in patients < 24 weeks gestation [13] In these cases, clinician repeats IUT in 48 – 72 hours to achieve normal fetal hematocrit
- ! Offers follow-up ultrasound the day after IUT[12,13]
- ! Once IUTs begin, they are continued at reasonable intervals with final IUT at approximately 35 weeks gestation[12,13]

Delivery and postpartum

- ! Delivers by 37-38 weeks in all alloimmunized pregnancies where the fetus is known to or may have antigen in question independent of antibody titer[14]
- ! Provides patients with a quick and easy way to communicate with their care team during their pregnancy
- ! Has a method of ensuring appropriate follow-up care for newborn after birth; this may entail, for example referral to pediatric hematology before discharge or sending printed instructions for the mother to deliver to their pediatrician

The Allo Hope Foundation provides this checklist as a resource to patients and as a transparent criterion by which AHF staff, board members and volunteers use to determine whether to recommend a doctor to a nearby patient. Only doctors who attest that they follow these practices and who are additionally recommended by multiple patients will be recommended. The Allo Hope Foundation and its staff, board

members and volunteers are never incentivized financially or by any other means to recommend a doctor. AHF is not liable for any outcomes that result from the recommendation of a specific doctor.

1Alford B, Landry BP, Hou S, Bower X, Bueno AM, Chen D, Husic B, Cantonwine DE, McElrath TF, Carozza J, Wynn J. Validation of a Non-invasive Prenatal Test for Fetal RhD, C, c, E, Kell and FyA Antigens. medRxiv. 2023 Mar 20:2023-03.

2 Royal College of Obstetricians & Gynaecologists. The Management of Women with Red Cell Antibodies during Pregnancy. Green-top Guideline No. 65. May 2014.

3 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.

4 Zimmermann R, Durig P, Carpenter Jr RJ, Mari G. Longitudinal measurement of peak systolic velocity in the fetal middle cerebral artery for monitoring pregnancies complicated by red cell alloimmunisation: a prospective multicentre trial with intention-to-treat. BJOG: an international journal of obstetrics and gynaecology. 2002 Jul 1;109(7):746-52.

5 Mari G, Norton ME, Stone J, Berghella V, Sciscione AC, Tate D, Schenone MH, Society for Maternal-Fetal Medicine (SMFM. Society for Maternal-Fetal Medicine (SMFM) Clinical Guideline# 8: the fetus at risk for anemia–diagnosis and management. American journal of obstetrics and gynecology. 2015 Jun 1;212(6):697-710.

6 Mari G, Adrignolo A, Abuhamad AZ, Pirhonen J, Jones DC, Ludomirsky A, Copel JA. Diagnosis of fetal anemia with Doppler ultrasound in the pregnancy complicated by maternal blood group immunization. Ultrasound in Obstetrics and Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology. 1995 Jun 1;5(6):400-5.

7 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.

8 Moise Jr KJ. Management of rhesus alloimmunization in pregnancy. Obstetrics & Gynecology. 2008 Jul 1;112(1):164-76.

9 Klumper FJ, van Kamp IL, Vandenbussche 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.

10 Lindenburg IT, Wolterbeek R, Oepkes D, Klumper FJ, Vandenbussche FP, Van Kamp IL. Quality control for intravascular intrauterine transfusion using cumulative sum (CUSUM) analysis for the monitoring of individual performance. Fetal diagnosis and therapy. 2011;29(4):307-14.

11 Urbaniak SJ, Greiss MA. RhD haemolytic disease of the fetus and the newborn. Blood reviews. 2000 Mar 1;14(1):44-61.

12 Zwiers C, van Kamp I, Oepkes D, Lopriore E. Intrauterine transfusion and non-invasive treatment options for hemolytic disease of the fetus and newborn–review on current management and outcome. Expert review of hematology. 2017 Apr 3;10(4):337-44.

13 Moise, Jr, K. Direct Fetal Transfusion. Glob. libr. women's med., (ISSN: 1756-2228) 2011;DOI10.3843/GLOWM.10213

14 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.