Contents

Prenatal Presentation

Alloimmunization occurs when a patient is exposed to foreign red blood cell antigens, and subsequently develops antibodies against one or more foreign antigens. This exposure most commonly occurs through pregnancy, blood transfusion or shared needles. For patients without childbearing potential or who are not currently pregnant, the only clinical impact of this antibody development is the patient's risk for a hemolytic transfusion reaction. It is for this reason that the presence of antibodies is usually discovered during blood group matching in anticipation of transfusion or in early pregnancy during standard first trimester screening.

Clinically significant antibodies have the potential to lyse fetal and newborn red blood cells (RBCs) causing mild to severe hemolysis. This can result in hemolytic disease of the fetus and newborn (HDFN) presenting from mild anemia and icterus to hydrops fetalis, a condition leading to edema and heart failure in the fetus. Though maternal alloimmunization is a serious and nuanced condition, close monitoring and prompt clinical intervention results in a high survival rate for the child of an alloimmunized woman.

Epidemiology and Screening

Alloimmunization occurs in approximately one to two percent of pregnancies [1], though this estimate includes antibodies which are not clinically significant (see HDFN and the clinical impact of specific antibodies for a list of clinically significant antibodies). A recent retrospective observational study by Sánchez-Durán et al. in a large university setting identified maternal antibodies in 337 pregnancies in a fifteen-year period, of which 259 were clinically significant and known to have the potential to cause mild to severe hemolysis. Of these 259, the fetus was determined to be at risk (i.e., the fetus did inherit or had the potential to inherit the antibody's target red blood cell antigen) in 194 [2]. Though RhD immune globulin (RhIG) prophylaxis is standard in developed countries, anti-D remains one of the most frequently identified antibodies (hence the name "Rh Disease") along with anti-Kell (anti-K) and anti-E.

All pregnant patients should receive blood typing and an antibody screen (indirect Coombs test) during their first prenatal visit. The results of these screens present the following options for clinical management:

- Rh positive blood type: no RhD immune globulin prophylaxis needed.
- Rh negative blood type, "weak D" or "partial D" status: patient should receive RhIG prophylaxis between weeks 26 to 28 of pregnancy [3], within 72 hours of any pregnancy bleeding event ≥ 6 weeks (including miscarriage or abortion) [4], or invasive procedure that may cause fetomaternal bleeding, and within 72 hours of birth of an RhD positive fetus.
    - It should be emphasized that a positive antibody screen for RhD that is thought not to be a result of recent RhIG prophylaxis indicates the patient is already sensitized to the RhD antigen, and therefore RhIG prophylaxis is not necessary.

  - A patient with a non-D antibody who is also Rh negative should continue to receive RhIG as scheduled above.

- Negative indirect Coombs test: no further evaluation necessary
- Positive indirect Coombs test: conduct antibody identification and determine antibody titer.
  - A positive indirect Coombs test for anti-D = no RhIG needed.
  - A positive indirect Coombs test for anti-D within 6 months [4] of RhIG administration may be a response related to RhIG and not indicative of true alloimmunization. In this case the titer for anti-D is low (1:2 or 1:4).

Once a patient's antibody type and titer is established, the following sequence must take place to determine whether the fetus is at risk:

- Determine whether the mother has had a child affected by HDFN requiring intervention in a previous pregnancy. If this is the case and paternity is assured to be the same as the previous pregnancy, one should expect a similar or more severe course of HDFN [5].
- Previous history cannot indicate that a fetus will be unaffected. When a mother with a clinically significant antibody presents, she must still be monitored and the fetal antigen status should still be determined unless the paternal testing reveals a homozygous status for the involved antigen.
- If the mother has not had a previously affected pregnancy, determine whether the antibody has the potential to cause HDFN.
- If the antibody does not have the potential to cause HDFN, proceed with routine obstetric care.
- If the antibody does have the potential to cause HDFN and paternity is certain, obtain zygosity testing from the father for the antigen in question. In the case of RhD, genetic testing of the father must be used instead of serology since there is no Rh negative antigen. Serology can be used through most blood banks to determine paternal zygosity through standard serologic testing. Note that while the mother is tested for her antibody and titer, the father is tested for the corresponding antigen (not antibody or titer).
  - If the father is homozygous for the antigen in question (e.g., an EE genotype in the case of an anti-E pregnancy), the fetus is certain to be at risk.
  - If the father is heterozygous for the antigen in question (e.g., an Ee genotype in the case of an anti-E pregnancy), or paternity is uncertain, the fetus may be at risk. Options to determine fetal antigen status include:
    - Cell-free DNA testing of maternal blood can determine fetal antigen status for RhD, RhC, Rhc, RhE, and Kell with over 99% accuracy. If cffDNA testing for the antigen in question is not an option in the patient's country, the patient's blood

can be shipped to a country where testing is available. Read more about cffDNA testing.

- Amniocentesis (after 15 weeks gestation) can be presented as an option to the mother in order to definitively determine fetal antigen status, though it is used less frequently due the risk of feto-maternal hemorrhage [5]. If it is undertaken, a transplacental approach should be avoided at all costs. Chorionic villus sampling (CVS) is CONTRAINDICATED due to the elevated risk for feto-maternal hemorrhage and a resulting increase in the maternal titer.
- If cffDNA is not available and the patient does not want to proceed with amniocentesis, the pregnancy can be followed with serial middle cerebral artery peak systolic velocity (MCA-PSV) Doppler ultrasound examinations (see description below) However the clinician must be aware that the MCA-PSV is associated with a 10% false positive rate for the detection of fetal anemia – this could lead to unnecessary invasive fetal procedures.

- If the father is negative for the antigen in question (e.g., an ee genotype in the case of an anti-E pregnancy) and paternity is certain, the fetus is not at risk. No further testing or specialized ultrasound exams are indicated. The issue of certain paternity should be documented in the medical record.

Read more about the necessary and optional laboratory assessments for the mother, father, and fetus.

Monitoring During Pregnancy

If the mother is alloimmunized against an antibody known to cause HDFN. and paternal antigen testing determines that the fetus may inherit the corresponding antigen (i.e., the fetus is "at risk"), antibody titers must be drawn at four-week intervals until 28 weeks, then every two weeks until they reach a critical titer (1:16 or 16 in most institutions, 1:4 or 4 for Kell). The critical titer reflects the threshold at which the antibody is capable of causing anemia requiring intervention in-utero. Important caveats include:

- A Kell alloimmunized pregnancy has the potential to result in severe fetal and neonatal outcomes even below critical titers. This is because anti-Kell has the potential to lyse developing cells in the fetal bone marrow in addition to mature red cells. Proceed with noninvasive testing beginning at a titer of 4 at 18 weeks of gestation[5], or earlier in the case of high titers or a previous history of severe HDFN.
- A woman with a previously affected fetus or newborn is at significant risk of recurrence with increasing severity regardless of titer due to an anamnestic maternal antibody response that may occur as the result of feto-maternal hemorrhage at the time of the previous delivery. For this reason, MCA-PSV should be used to monitor the fetus instead of titers alone. Obtaining titer is not necessary more than once in early pregnancy to determine if the patient is a candidate for

immunomodulation with IVIG and/or plasmapheresis. This patient should begin MCA-PSV Doppler ultrasounds at 16 to 18 weeks of gestation[15]. While rare, severe anemia requiring IUT has been reported as early as 15 weeks in subsequent pregnancies. MCA-PSV determinations are possible and reference values are available as early as 12 weeks gestation[7].

- An extremely high titer found in early pregnancy or previous fetal loss as a result of HDFN may be an indication for intravenous immune globulin (IVIG) treatment and/or plasmapheresis. Though studies examining efficacy of these interventions are limited due the rarity of HDFN and therefore small sample size, results point to a delayed interval to first intrauterine transfusion and higher fetal survival rate [5, 6, 34]. Consider referral to a maternal fetal medicine program with experience offering this treatment. For additional articles relating to IVIG and plasmapheresis, see our additional reading by topic page.

Once a critical titer is reached, titer concentration is no longer indicative of severity of HDFN. Noninvasive testing with MCA-PSV scan should be initiated should be initiated at 16 to 18 weeks gestation [15] and repeated weekly (or more frequently if the MoM is rising or approaching 1.5 multiples of the median (MoM). If needed, indexes exist for MCA-PSV scans as early as 12 weeks [7]. The ideal MCA-PSV scan is performed by trained personnel during a state of fetal rest, in the absence of fetal breathing, and with no or minimal angle correction. Multiple readings should be obtained despite fetal activity level. Correct technique is critical in determination of the MCA-PSV value. The highest MCA-PSV value of at least three assessments should be recorded and used for clinical decision making. Read more about MCA technique here.

Note that the objective of the MCA-PSV scan is to screen for fetal anemia in order to initiate intervention before progression to fetal hydrops. In the early second trimester (less than 24 weeks gestation), fetal hydrops may not be present despite the finding of an elevated MCA-PSV. These fetuses are still profoundly anemic [97]. An MCA-PSV at or above 1.5 MoM for gestational age (calculator available here), indicates possible severe anemia requiring intervention. Some types of steroid administration including oral[8], vaginal[8], or IM administration[9, 35, 36] can affect the fetal blood flow - resulting in undetected fetal anemia. Expert opinion holds that steroid administration has been shown to falsely lower MoM values. Planned delivery or intrauterine transfusion should not be modified based on MoM values observed after administration of steroids. Steroids should only be administered after the decision to transfuse or deliver has been made.

In addition to false lows, MCA scans have a false positive rate of 12%[11]. Potential causes for falsely elevated MoM scores (scan indicates anemia when no anemia is present) include: fetal activity[10], fetal breathing[11], and maternal meals[12]. For this reason, an MCA-PSV closely approaching 1.5 MoM should be reassessed in 2-3 days[5, 15].

Some institutions initiate weekly antenatal testing (non-stress tests and biophysical profiles) at 32 weeks gestation for any at risk pregnancies regardless of titer and MoM [14], and this is suggested in recent UpToDate guidance [5].

Considerations for Subsequent Pregnancies

Though cost is generally a prohibitive factor, options exist to prevent alloimmunization entirely in subsequent pregnancies. This includes:

- In-vitro fertilization (IVF) with preimplantation genetic testing (PDG) in the case of a heterozygous paternal genotype for the offending red cell antigen[32]
- Gestational carrier using an embryo conceived via IVF
- Donor sperm used in intrauterine insemination (IUI) from a donor who does not carry the offending red cell antigen.

To see additional information on alternatives to natural conception visit our Alternatives to Natural Conception page.

If a woman intends to become pregnant again, pregnancy monitoring and potential interventions can be pre-planned with a supportive provider. This may include IVIG and plasmapheresis beginning in the first trimester and assessment for eligibility for inclusion in new clinical trials such as that for nipocalimab. To see additional clinical trials relating to alloimmunization and HDFN, visit our Current Research and Clinical Trials page. For women with previously affected pregnancies requiring IUTs, referral to a specialist with extensive experience in IUTs, IVIG and plasmapheresis may be considered and pre-pregnancy consultation should be initiated.

Interventions During Pregnancy

Noninvasive preventative measures

Plasmapheresis and Intravenous Immunoglobulin (IVIG)

Plasmapheresis or therapeutic plasma exchange (TPE) and intravenous immunoglobulin (IVIG) has been used for over 40 years to lower antibody titers and prevent/reduce fetal hemolysis in cases of extremely high titers or previous pregnancy loss as a result of HDFN. These interventions are most effective when initiated during the first trimester of pregnancy, typically around ten to twelve weeks of gestation. These usually are not effective in reducing fetal anemia once it is present, but these measures have been shown in small studies to reduce the time to initiation of IUT.

The mechanism of action of IVIG is not well-known in this application, though positive results have been demonstrated in small series and one prospective study[23, 24, 34]. This treatment usually initiates at 1g/kg maternal weight every week.

Plasmapheresis (removal of maternal plasma through an apheresis machine) may enhance the efficacy of IVIG, and though IVIG is sometimes instituted alone, plasmapheresis is not often instituted alone[25, 26]. The combination of plasmapheresis and IVIG is typically reserved for the most high-risk cases. A case series of 9 pregnancies using this technique reported reduced antibody titers, IUT initiation at a later

gestation, and no fetal and neonatal fatalities [26]. A common treatment plan for a patient receiving plasmapheresis and IVIG involves initiating several serial plasmapheresis treatments followed by IVIG at ten to twelve weeks' gestation and continuing with weekly IVIG [26], though this treatment should be considered on a case-by-case basis.

For additional articles relating to IVIG and plasmapheresis, see our additional reading by topic page.

Nipocalimab

Phase two clinical trials are currently enrolling for nipocalimab administered via weekly IV infusion in women who have previously had severely affected pregnancies before 24 weeks gestation and who have anti-D or anti-K antibodies (ClinialTrials.gov identifier: NCT03842189).

Invasive Measures

Intrauterine Transfusion (IUT)

After an MCA-PSV at or above 1.5 MoM, the following interventions should be scheduled within 2-3 days [6, 10] and conducted during the same operative session [6]:

- Fetal cordocentesis to determine fetal hemoglobin level (considering MCA-PSV has a false positive rate of 12%)[6, 14, 16]
- If cordocentesis confirms severe anemia represented by hematocrit lower than 30%, or fetal hemoglobin is more than two standard deviations below the mean value for gestational age, initiate intrauterine transfusion in a skilled facility (See UTD Intrauterine Fetal Transfusion of Red Cells [6] for more detailed information). Availability of cross-matched antigen negative blood should be ensured in advance of the session. Phenotypically matching additional clinically significant antigens (such as Duffy, Kidd, MNS) to the mother is recommended and performed at some centers to prevent the formation of new red cell alloantibodies that can result from exposure to donor blood at the time of intrauterine transfusion [17]. Women with one alloantibody are significantly more likely to develop additional antibodies upon exposure [17]. The presence of these new antibodies can further contribute to the development of fetal anemia.
- If cordocentesis identifies hemoglobin is above 30%, obtain another blood sample in one to two weeks depending on the value's closeness to the threshold [6].

The use of maternal premedication for IUT varies by center and may include use of local anesthetics, indomethacin/pethidine/promethazine, or spinal epidural analgesia. The prophylactic use of antibiotics or corticosteroids are sometimes used but their necessity is not well-established [18, 19]. Direct injection of fetal medication including atracurium or vecuronium [6, 21] for fetal paralysis is necessary to fetal movement in most cases and has been associated with increased success of the procedure. Some practitioners recommend fentanyl for fetal pain [20] though it is not universally used [22]. Click here for more detailed information about medications during IUTs.

Intrauterine transfusion should be guided by continuous ultrasound and staffed, at minimum, by an experienced maternal fetal medicine (MFM) specialist/perinatologist, seasoned ultrasonographer and one or more operating nurses. A recent article found that training under the supervision of an experienced operator requires 30 – 50 procedures for a physician to gain the skills to perform this procedure. An annual volume of 10 procedures has been proposed to maintain proficiency [98].

Transfusion volume can be calculated using a simplified formula by Giannina et al[29] to attain a final fetal hematocrit of 45% [30, 31]. For IVT, transfusion volume = 0.02 × target increase in fetal Ht per 10% × g of estimated fetal weight, assuming that donor blood hematocrit is approximately 75%. [16] Fetal hemoglobin/hematocrit testing through cordocentesis at the time of intravascular transfusion allows for a precise calculation of transfusion quantity. It is important to note that transfusing too large of a volume of blood can result in fetal loss due to an acute change in blood viscosity and subsequent cardiac failure. This is especially true in the early second trimester fetus (<24 weeks gestation). Fetal hematocrit should never be raised higher than 3x the initial value. A repeat procedure to normalize the fetal hematocrit can be undertaken 48 hours later.

In some centers, an intravascular transfusion is supplemented by an intraperitoneal procedure (IPT) at the same setting. This allows for the slow absorption of blood between procedures in an effort to maintain a more stable hematocrit. The formula for determining the IPT volume is (# weeks gestation – 20) X 10 = volume to be transfused in cc. Blood in the peritoneal reservoir will be absorbed over 7-10 days. IPTs have also been used to successfully correct fetal anemia in severe cases of HDFN that present prior to 20 weeks gestation. In this situation, attempts to gain access to the fetal umbilical cord to perform an intravascular transfusion are associated with as high as a 20% perinatal loss [97].

The goal of an intrauterine transfusion is to maintain the fetal hematocrit above 25% . To this end, some experts will typically transfuse 10 days after the first transfusion, 2 weeks after the second transfusion, and 3 weeks after the third transfusion. Beyond the third transfusion, additional transfusions typically take place at 3-4 week intervals due to suppression of fetal erythropoiesis and the high percentage of donor RBCs which are safe from hemolysis. A second approach to the timing of intrauterine transfusions is to expect a decline in hemoglobin of 0.4 g/dL/day after the first transfusion, 0.3 g/dL/day after the second transfusion, and 0.2 g/dL/day after the third transfusion. This approach requires caution due to a potentially inaccurate fetal hemoglobin immediately after the procedure as a result of fetal fluid shifts, and bleeding from the puncture site[6]. Information regarding the accuracy of MCA-PSV for determining the timing of additional transfusions is mixed, and providers must familiarize themselves with the various data available[61, 62, 63, 64, 65].

Fetal survival has increased in recent years following the incorporation of continuous ultrasound and clinical implementation and discussion of published research techniques. Even so, a large cohort study examining the outcomes of intrauterine transfusion found that 1.8% of fetuses died from the procedure even under the care of an experienced practitioner [16]. Van den Alker et al found that 23% of severely hydropic fetuses had severe thrombocytopenia [81]. Fetal thrombocytopenia increases fetal mortality, especially for severely hydropic fetuses [81]. A copy of Table 1 from Zwiers et al.[16] shows a representative summary of fetal survival after intrauterine transfusion.

Table 1. Overall survival after intrauterine transfusion.

Author, year	N	Hydrops (%)	GA at first IUT[a]	Technique	Preferred puncture site	Overall survival (%)
Somserset, 2006	221	26.9	25 (16–32)	IUST	Liver	90.9
Weisz, 2009	154	11.1	*25.9 (3.2)*	IUET	-	88.9
Tiblad, 2011	284	11.8	-	IUST	Liver	94.1
Johnstone-Ayliffe, 2012	114	13	26 (17–35)	IUST	Liver	93.5
Birchenall, 2013	256	-	30 (16–35.7)	-	Liver or PCI	95.3
Walsh, 2013	242	16	29.1 (19.2–34.4)	-	PCI	95.1
Pasman, 2015	135	14	-	IUST	PCI	100
Sainio, 2015	339	11.5	29 (18–36)	-	Free loop	96.2
Deka, 2016	303	21.6	*26.9 (19.7–33.8)*	-	PCI	96.1
Zwiers, 2016[b]	937	12.9	27 (16–36)	IUST	Liver	97
Overall						***95.5***

N: number of transfusions; GA: gestational age; IUT: intrauterine transfusion; overall survival: live birth rate; IUST: intrauterine single transfusion; IUET: intrauterine exchange transfusion; PCI: placental cord insertion.
[a]weeks, median (range) or *mean (range)*.
[b]result of cohort since 2001 shown.

Additional IUT-related complications include bleeding from the puncture site, cord occlusion, brady- or tachycardia, chorioamnionitis, and preterm premature rupture of the membranes (PPROM) which may require emergency caesarian or lead to maternal and fetal morbidity or mortality [31, 39]. For this reason IUTs performed at or after viability are usually performed in or proximate to an operating suite where delivery may be carried out immediately. Normal neurologic outcome occurs in 94-95.2% of cases after IUTs. Severe hydrops may be associated with a higher risk of impairment [71, 72]. The incorporation of IUT into a provider's clinical practice should be weighed heavily against experience and available resources.

Please contact the Allo Hope Foundation for referral recommendations to an experienced facility if patient need requires. Additional information regarding IUT technique is available here.

After the last IUT, phenobarbital is considered in many institutions to enhance the fetus' liver function and therefore accelerate the breakdown of bilirubin in neonatal circulation. In one study, mothers took 30mg phenobarbital three times daily after their last IUT until delivery. The incidence of exchange transfusion was significantly lower in neonates whose mothers took phenobarbital in advance of delivery [27]. Due to the time required for phenobarbital to work, this intervention was not shown to be efficacious when administered to the neonate after delivery in a randomized controlled trial [28].

Timing of Delivery

In at risk pregnancies with nonsignificant titers or MCA-PSV values consistently below 1.5MoMs, mild to no anemia can be presumed with a scheduled delivery at 37 to 38 weeks gestation [3].

There is an increased risk of false positive (elevated) MCA-PSV values beyond 35 weeks of gestation[10]. It is generally agreed that a high value at or beyond 35 weeks of gestation merits delivery. In a pregnancy requiring IUTs, the final procedure is usually planned at approximately 35 weeks with delivery planned at 37-38 weeks gestation.

Follow additional protocols regarding steroid administration and other preventative treatments in advance of preterm delivery. Be aware that steroid administration has been shown to falsely lower fetal blood velocity [8, 9, 35, 36] and expert opinion holds that steroid administration has been shown to falsely

lower MoM values. Planned delivery should not be modified based on MoM values observed after administration of steroids.

As part of a delivery plan, the MFM should connect the patient with services such as a NICU tour, a consultation with a pediatric hematologist, and a neonatologist after birth. Infants with HDFN should not be discharged from the hospital until a hematology appointment has been made. This will ensure proper follow up care for neonates exposed to maternal alloantibodies.

Pregnancy Outcomes

Among 106 patients in a single center in their first alloimmunized pregnancy with anti-D, 57% did not develop a critical titer. Of those who did develop a critical titer, 54% developed HDFN of any severity, 26% developed severe disease (hydrops, fetal demise, need for IUT), 4% developed moderate disease (need for neonatal exchange transfusion), and 24% developed mild disease (need for phototherapy or simple blood transfusion)[37].

Another recent 15-year retrospective study in a single center observed an IUT rate of 77% among at risk pregnancies with critical titers and MCA-PSV MoM values above 1.5. The average gestational age at birth for this group was 34 weeks. Among those with critical titers but PCA-PSV values below 1.5 MoM, no IUT was required and the average gestational age at birth was 37 weeks [2].

With appropriate monitoring and skilled intervention, fetal survival rate has increased in recent years. The table below provides survival outcomes in a range of populations and treatment circumstances at some of the most experienced fetal centers in the world.

Author, Year	Country, Time period	Population	Treatment summary	Fetal/infant survival rate
Zwiers, 2017	Netherlands, 1988-2015	334 fetuses undergoing 937 intrauterine transfusions in 2001-2015	Fetuses with severe anemia requiring and receiving intrauterine transfusion.	97%
Sanchez-Duran, 2019	Spain, 2002-2017	38 pregnancies with at-risk fetuses and non-critical titers (<16)	Fetuses being monitored through titers every four weeks or every two weeks if rapidly increasing.	100%
Sanchez-Duran, 2019	Spain, 2002-2017	93 pregnancies with at risk-fetuses and critical titers (>16) or Kell pregnancies and MCA-PSV scores below 1.5 MoM	Fetuses being monitored through weekly MCA scans, delivery at 37-39 weeks.	96%
Sanchez-Duran, 2019	Spain, 2002-2017	57 pregnancies with at risk-fetuses and critical titers (>16) or Kell pregnancies of any titer requiring IUTs	Fetuses being monitored through weekly MCA scans and IUTs performed through 34 weeks (or delivery if later).	84%

Tiblad, 2011	Sweden, 1990-2010	84 pregnancies with at-risk fetuses and critical titers (>64) requiring IUTs	Fetuses being monitored through "intermittent" MCA scans requiring subsequent IUTs.	92%
Pasman, 2015	Belgium, 2000-2014	56 pregnancies with reported IUTs due to maternal alloimmunization	Fetuses receiving IUTs.	100%
Dodd, 2018	Australia, New Zealand, Canada, UK, Ireland, Belgium, Argentina, 2009-2013	71 pregnancies with reported IUTs due to maternal alloimmunization	Half of pregnancies being monitored by fetal hematocrit, others by MCA-PSV (no significant difference between groups) and receiving IUTs.	88%
Bondagji, 2012	Saudi Arabia, 2004-2009	84 pregnancies with C/c, D, and/or e antibodies with critical titers at first assessment (>16).	Routine ultrasound and amniocentesis prior to 2007, then MCA-PSV. IUT in 5 cases.	75%
Nardozza, 2007	Brazil, 1995-2004	99 pregnancies with D antibodies and critical titers (>16).	1995-2000: Amniocentesis between 26-28 weeks with subsequent amniocenteses based on results of first exam and ultrasonographic signs of fetal compromise. IUT if moderate to severe anemia prior to 34 weeks. 2001-2004: Weekly MCA PSV. IUT if moderate to severe anemia prior to 34 weeks.	Overall (N=99): 76% 1995-2000 Amnio group (N=74): 73% 2001-2004 MCA group (N-25): 84%

Bondagji NS. Rhesus alloimmunization in pregnancy. A tertiary care center experience in the Western region of Saudi Arabia (32, pg 1039, 2011). SAUDI MEDICAL JOURNAL. 2012 Jun 1;33(6):688-.

Dodd JM, Andersen C, Dickinson JE, Louise J, Deussen A, Grivell RM, Voto L, Kilby MD, Windrim R, Ryan G, MCA Doppler Study Group. Fetal middle cerebral artery Doppler to time intrauterine transfusion in red-cell alloimmunization: a randomized trial. Ultrasound in Obstetrics & Gynecology. 2018 Mar;51(3):306-12.

Nardozza LM, Camano L, Moron AF, Chinen PA, Torloni MR, Cordioli E, Junior EA. Perinatal mortality in Rh alloimmunized patients. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2007 Jun 1;132(2):159-62.

Pasman SA, Claes L, Lewi L, Van Schoubroeck D, Debeer A, Emonds M, Geuten E, De Catte L, Devlieger R. Intrauterine transfusion for fetal anemia due to red blood cell alloimmunization: 14 years experience in Leuven. Facts, views & vision in ObGyn. 2015;7(2):129.

Tiblad E, Kublickas M, Ajne G, Ek S, Karlsson A, Wikman A, Westgren M. Procedure-related complications and perinatal outcome after intrauterine transfusions in red cell alloimmunization in Stockholm. Fetal diagnosis and therapy. 2011;30(4):266-73.

Zwiers C, Lindenburg ITM, Klumper FJ, de Haas M, Oepkes D, Van Kamp IL. Complications of intrauterine intravascular blood transfusion: lessons learned after 1678 procedures. Ultrasound Obstet Gynecol. 2017;50(2):180.

Estimates above reflect the positive impact of close monitoring of titers, frequent MCA-PSV Doppler ultrasound, and prompt initiation of IUTs. Studies reporting lower survival rates also show practice standards not consistent with current recommendations. Note as well the significance of RhIG prophylaxis and the importance of administering during early pregnancy bleeding, at the beginning of the third trimester and within 72 hours of birth to a RhD positive fetus. Bondaghi [42] reported that in Saudi Arabia between 2004 and 2009, failure to administer RhIG was common and 24% of women who were RhD negative became sensitized, a glimpse of the effect of sub-optimal monitoring and management of the RhD negative pregnant woman.

Neonatal Presentation

The risks of HDFN do not end at delivery. Monitoring and management must be just as vigilant after birth as during pregnancy in order to prevent neonatal harm and infant death. Maternal alloantibodies which have crossed the placenta remain in the infant's circulation and can attach to the infant's red blood cells for up to 12 weeks after birth. For this reason, follow-up in newborns whose cord blood confirms the presence of maternal antibodies is essential for several weeks after discharge from the hospital, even in the absence of visible indications of anemia.

Infants with either a positive DAT or who are antigen positive in the case of a DAT exception antibody, and who have signs of anemia, hyperbilirubinemia, or some other consequence of HDFN are considered to be affected by HDFN. It is not required that an infant be treated (via transfusion etc) in order for them to be considered affected and diagnosed with HDFN. Affected infants must be monitored for ongoing and delayed anemia and other signs of HDFN. This poses a unique challenge when consistent, quality care must continue across multiple providers including maternal-fetal medicine specialists, neonatologists, hematologists and pediatricians. Unfortunately many infants do not receive proper monitoring and follow up care for HDFN and preventable infant deaths are still occurring today.

HDFN can manifest itself in a variety of ways, including: hyperbilirubinemia, neutropenia, thrombocytopenia, hemolytic anemia, etc.

Hyperbilirubinemia

The destruction of red blood cells causes the release of bilirubin. In utero the bilirubin is filtered via the placenta; after birth the neonatal liver assumes the role of removing bilirubin. Due to the neonatal liver's immature metabolic pathways [44], high levels of bilirubin can rapidly build up in the neonate's system causing jaundice which can lead to permanent effects such as: bilirubin encephalopathy, kernicterus, cholestasis, and death if not treated properly. A total serum bilirubin level at or above the exchange transfusion level should be considered a medical emergency and intensive phototherapy, IVIG, and preparation for an exchange transfusion should be commenced immediately. Elevated levels of bilirubin have been associated with hearing loss in the neonate. Therefore, newborn screening for hearing loss (standard of care in most states) would appear warranted in children with HDFN. Follow-up screening at 1 and 2 years of age should be considered. Hyperbilirubinemia due to other causes typically peaks during days 1-3 of life, while hyperbilirubinemia due to HDFN tends to peak on days 4-6.

Documents like the American Academy of Pediatrics' Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation exist to help prevent and reduce the complications of hyperbilirubinemia. These guidelines should be followed closely to prevent neonatal harm. Tools such as Peditools provide clinical tools to assist the provider in the management of hyperbilirubinemia. Infants with HDFN should be considered to have "risk factors" when assessing bilirubin levels using standard phototherapy eligibility guidelines [45]. Treatment options for hyperbilirubinemia are discussed in depth on the Infant interventions page and include: phototherapy, IVIG, exchange transfusion, and some clinical trials with tin mesoporphyrin. Phototherapy treatment may result in the development of Bronze Baby Syndrome in infants with elevated direct bilirubin levels. Bronze Baby Syndrome may increase the risk of complications due to hyperbilirubinemia such as Kernicterus [59]. For additional articles relating to the consequences of hyperbilirubinemia listed below, see our additional reading by topic page.

Bilirubin encephalopathy

Infants with HDFN are at higher risk for developing bilirubin encephalopathy. Bilirubin encephalopathy develops when bilirubin moves from the bloodstream into the brain and refers to the acute manifestations of bilirubin toxicity in the first weeks after birth [45]. This condition commonly develops during the first week of life, but can occur as late as the third week [75]. Signs of bilirubin encephalopathy include: extreme jaundice, an absent startle reflex, poor feeding or sucking, lethargy, hypotonia, a high-pitched cry, irritability, and a hyperextended back and neck [75]. Complications of bilirubin encephalopathy include: nerve deafness, damage to the tooth enamel (enamel dysplasia, and discoloration of the teeth), and brain damage.

Kernicterus

While bilirubin encephalopathy refers to the acute manifestation of bilirubin toxicity, kernicterus is the chronic and permanent clinical sequelae of bilirubin toxicity [45]. Kernicterus is NOT associated with any degree of cognitive impairment (mental disability), however survivors are often left trapped in a body that does not function as it should. This disease, listed as one of 27 medical errors that should never happen [73], continues to occur despite being completely preventable. Kernicterus is a spectrum which can include some or all of the following: movement disorders (athetoid cerebral palsy, dystonia, myoclonus that impairs the ability to sleep, vestibular instability), seizures, visual impairments (gaze abnormalities, nystagmus, strabismus, cortical visual impairment), digestive impairment (GERD, reflux, impaired digestion, impaired ability to swallow or eat orally), dental (dental enamel dysplasia or hypoplasia), and hearing impairment (including auditory neuropathy spectrum disorder) [74]. Individuals living with kernicterus are affected to varying degrees. Some live with mild hearing loss, behavioral challenges, and/or clumsiness while other might be mistaken for someone with spastic quadriplegia.

Cholestasis

Cholestasis occurs in up to 13% of infants with HDFN [58]. Cholestasis can be identified with an elevated direct or conjugated bilirubin level. If the direct or conjugated bilirubin is elevated, additional evaluation

for the cause of cholestasis is recommended [45]. When other causes of cholestasis have been ruled out in a DAT positive infant, HDFN as a cause of cholestasis should be strongly considered. This can be due to iron overload from intrauterine transfusions [58], though in rare cases, cholestasis can result from inappropriate iron administration [56]. While cholestasis is most commonly seen with HDFN due to anti-D [58], it can happen with HDFN due to other alloantibodies as well [76, 77].

Bronze Baby Syndrome

This is a rare complication that occurs in infants with cholestatic jaundice where they develop dark, grayish-brown discolored skin, blood, and urine. Infants who have received phototherapy with an elevated direct-reacting or conjugated bilirubin level may develop the bronze-baby syndrome [45, 59]. Bronze baby syndrome has few consequences, but it can be disturbing to parents. Phototherapy is not contraindicated in infants with bronze baby syndrome, however providers should be aware that cholestasis will decrease the efficacy of phototherapy [45]. For this reason, exchange transfusion may be considered at lower levels if intensive phototherapy is not working and the total serum bilirubin (TSB) is high or rising despite phototherapy [45]. It is important that the direct serum bilirubin should not be subtracted from the TSB when making decisions about exchange transfusions [45]. For additional articles relating to bronze baby syndrome, see our additional reading by topic page.

Neutropenia

Neutropenia as a result of maternal alloimmunization has been documented since 1960 and still occurs in 45% of infants with HDFN [80] today. Koenig et al notes that, “the marked increase in erythropoiesis in fetuses with Rh hemolytic disease can be accompanied by a down-modulation of neutrophil and platelet production” [78]. While all hydropic infants in Koenig’s paper were neutropenic, hydrops is not a requirement for neutropenia - even mildly affected infants with HDFN can be neutropenic. Neutropenic infants are at higher risk for infection and may require treatment for neutropenia; Recombinant Human Granulocyte Colony-Stimulating Factor has been used in some cases [79]. Providers should make parents aware of the increased risk and encourage them to take precautions with their children. Neutropenia due to HDFN can persist for a year in some cases. In addition to neutropenia, leukopenia has also been known to occur [95]. For additional articles relating to neutropenia, see our additional reading by topic page.

Thrombocytopenia

Thrombocytopenia is another lesser-known complication of HDFN, affecting 26% of fetuses [81] and infants [82]. Risk factors include IUTs, small for gestational age, and lower gestational age at birth. Hydropic infants are more likely to be thrombocytopenic, though thrombocytopenia occurs in non-hydropic infants as well. Infants with thrombocytopenia experience bruising and bleeding easier than other infants. In severe cases, platelet transfusions are utilized. “Thrombocytopenia is an independent risk factor for perinatal mortality. Mortality in fetuses that were severely thrombocytopenic and severely hydropic was 67%.” [81]For additional articles relating to thrombocytopenia, see our additional reading by topic page.

Anemia

Maternal alloantibodies which have crossed into the fetal circulation remain and can attach to the infant's red blood cells for up to 12 weeks after birth. For this reason, follow-up in newborns whose cord blood confirms the presence of maternal antibodies is essential until hemoglobin is increasing without a blood transfusion for at least two consecutive weeks, even in the absence of visible indications of anemia. Depending on the specific antibody and it's reactions, anemia due to HDFN can manifest itself in one of three ways: early onset anemia, delayed onset anemia, and hyporegenerative anemia. No matter which form of anemia presents, iron is not an acceptable treatment for an infant with HDFN. Improperly monitored and untreated anemia can lead to heart failure and death in infants who are several weeks old. For additional articles relating to all of these types of anemia, see our additional reading by topic page.

Early onset anemia

Early onset anemia is anemia that is present at birth or before week 2. This anemia, caused by antibody mediated hemolysis, may be detected during a cord blood sample, or as part of other follow up testing. Infants who are in the NICU may struggle with feeding, failure to thrive, or cardiovascular complications. For these infants it is often not a matter of if they will need a transfusion, but when. Correcting the anemia early (at higher hemoglobin levels) may reduce stress on the infant's body, reduce prematurity issues, and help improve latch for oral feeds. Infants with early onset anemia will have an elevated bilirubin, and a normal or elevated reticulocyte count [44]. It is important to note that while early onset anemia occurs within the first 2 weeks of life, it does not resolve within the first two weeks of life. Early onset anemia can become hyporegenerative anemia and all infants with early onset anemia must be monitored weekly until the hemoglobin is increasing without intervention for 2-3 weeks in a row.

Delayed onset anemia

Delayed onset anemia is anemia that presents between 2-12 weeks of life. This anemia is still caused by antibody mediated hemolysis and may be worsened by a natural decline of hemoglobin levels. It is not uncommon for infants to need their first transfusion at 2-4 weeks of age. Infants with delayed onset anemia may have a normal or elevated bilirubin count, along with a normal or high reticulocyte count [44]. Delayed onset anemia can happen to all infants with HDFN regardless of which antibody the mother has, even if the fetus was not treated with IUTs. Treatment options for infants with delayed onset anemia include folic acid, blood transfusion, and erythropoietin [13, 38].

Hyporegenerative anemia

Hyporegenerative anemia is a unique form of anemia due to HDFN that happens due to a combination of factors. Antibody mediated hemolysis is still in play, however bone marrow suppression either by IUTs and transfusions, or by specific antibody action is a major factor. Antibodies such as anti-Kell and anti-M are known to cause bone marrow suppression making it harder for the infant to regenerate blood cells destroyed by maternal antibodies. These infants usually have a normal bilirubin level along

with a low reticulocyte count, and may also have erythropoietin deficiency [83]. Hyporegenerative anemia is treated via erythropoietin to increase reticulocyte count [33, 69, 70].

A Note Regarding Iron

A special consideration in these infants is the use of iron in HDFN. Infants with HDFN do not suffer from iron-deficiency anemia [49]. A 2013 paper [49] found that ferritin levels are highly elevated at birth in neonates with HDFN. "Iron overload occurred in 70% of neonates at birth and in 50% and 18% at the age of 1 and 3 months, respectively." [49] Do not administer iron supplements without first confirming the ferritin level [49, 50, 51]. Inappropriate administration of iron in infants with HDFN can result in iron overload [46] and adverse events such as cholestasis [56], portal hypertension, coagulopathy abnormal liver enzymes, free-radical damage [57], liver damage, or death. For infants with severe iron overload, chelation therapy with desferrioxamine is an option to prevent or reduce organ damage [51, 52, 53, 54]. Folic acid can be safely given to neonates with HDFN [46]. If hyporegenerative anemia is a concern, Erythropoietin can be used either alone or in combination with desferrioxamine if iron overload is a concern [55]. For additional articles relating to iron, see our additional reading by topic page.

Monitoring the Infant

Lab testing should be carried out when an infant is born to an alloimmunized mother, and any time when HDFN is suspected later (ie cases of unexplained hyperbilirubinemia or anemia). "A rate of rise in bilirubin levels greater than 5 mg/dL/24 h (or >0.5 mg/dL/h) is suggestive of hemolysis in any infant; therefore, clinical jaundice (bilirubin >5 mg/dL needed to be clinically visible) in the first 24 hours strongly suggests a hemolytic process" [85].

Immediately after delivery, a cord blood sample should be obtained for such studies as fetal blood type, hematocrit and direct agglutination test (DAT). An Indirect Agglutination Test (IAT) or antigen phenotype may be considered in the case of maternal alloantibodies that have been shown to yield an affected infant despite a negative DAT. These include anti-C, anti-c, anti-Fya, anti-Good, anti-H, anti-Jra, anti-M, and anti-Mta antibodies. To read more about these exception antibodies see our additional reading by topic page.

Cord blood bilirubin and a complete blood count should be ordered including hemoglobin, hematocrit, neutrophil count, thrombocyte count and reticulocyte count. Even in the absence of a positive DAT/IAT result, it is advised to continue to monitor bilirubin in the infant every four to six hours for at least the first 24 hours of life. If bilirubin levels are higher than expected during the infant's first week of life, repeat the DAT. Establish hemoglobin and hematocrit values at eight to twelve hours of age and until stable. Visible jaundice is a sign that the bilirubin level is rising, but it is a poor predictor of the concentration of bilirubin in circulation or in the brain - neonatal blood testing must occur. Visual assessments are not an acceptable way to monitor or treat an infant with HDFN.

It is important to note that in neonates who received IUTs in utero, the infant's blood type and the state mandated newborn screenings may be incorrect due to the majority of the circulating red cells being

derived from the donor blood used during intrauterine transfusions. Direct agglutination test (DAT) is often negative at birth in these infants as well.

During the first week of life, bilirubin should be checked daily, especially considering that bilirubin due to alloimmunization tends to peak at days four to six. Hemoglobin should be checked at least one additional time in the week after birth [44]. Afterwards, weekly hematocrit and reticulocyte counts should be assessed and simple transfusions initiated if hemoglobin levels fall below 7 gm/dL or sooner if symptoms of anemia are present.

Bilirubin should continue to be checked at least one to two times a week until a steady decrease is certain. Current guidelines state that infants with hemolytic disease of the fetus and newborn are at medium or high risk for developing severe hyperbilirubinemia and its consequences "If phototherapy is used for infants with hemolytic diseases or is initiated early and discontinued before the infant is 3 to 4 days old, a follow-up bilirubin measurement within 24 hours after discharge is recommended." [45] Home phototherapy is not an option for infants with HDFN and readmission may be necessary. In the case of infants who are readmitted for hyperbilirubinemia, a repeat TSB after subsequent discharge is an option [45].

Before discharge a follow up appointment should be scheduled with a pediatric hematologist or other provider. The discharging physician should alert the family pediatrician or pediatric hematologist of the follow up care plan. Pediatricians and parents should be aware that affected infants may develop significant anemia until 12 weeks of life, especially if they received IUTs during pregnancy (see Delayed Onset Anemia on Additional Reading by Topic page). Parents should be educated on the physical signs of anemia and when to return to the hospital if the infant deteriorates between appointments.

Elevated levels of circulating maternal antibodies in the neonatal circulation in conjunction with suppression of the fetal bone marrow production of red cells often results in the need for neonatal red cell "top-up" transfusions after discharge from the nursery. This results in a 1- to 3-month period in which up to 75% of these infants may need "top-up" red cell transfusions [96]. Weekly reticulocyte counts and hematocrit levels should be assessed until a rising reticulocyte count is noted for at least 2 consecutive weeks. The threshold-for-transfusion includes a hematocrit value of less than 30% in the symptomatic infant or less than 20% in the asymptomatic infant have been suggested by some experts. Typically, only one neonatal transfusion is required, although a maximum of up to three has been reported.

For additional information on infant testing, see necessary laboratory assessments for infants exposed to maternal alloantibodies.

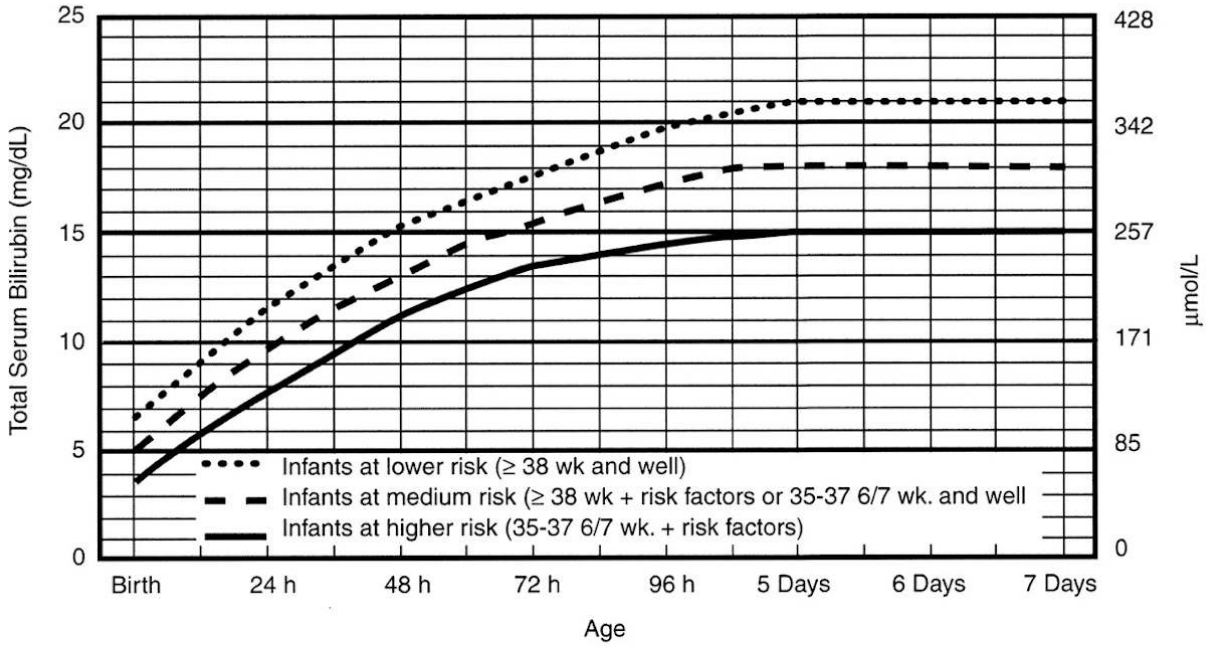
Interventions for the Infant

Interventions for Hyperbilirubinemia

Phototherapy

Intervention for hyperbilirubinemia includes phototherapy based on cord bilirubin, serial determinations, and the rate of rise. A cord bilirubin of ⩾2.05 mg/dL (pre-term) to 2.15 mg/dL (full-term) indicates need for phototherapy [60]. Serum bilirubin should be assessed regularly during phototherapy. It is important to note that infants with HDFN will have rebounding hyperbilirubinemia. When phototherapy is stopped, levels will increase rapidly and the infant will frequently require additional phototherapy. To help prevent this, it is better to use continuous phototherapy vs intermittent phototherapy. Because home phototherapy is not an option for infants with HDFN, a 12 or 24 hour trial without lights before discharge is advisable to reduce hospital readmissions.

Guidelines for phototherapy in hospitalized infants of 35 or more weeks' gestation.



- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin < 3.0g/dL (if measured)
- For well infants 35-37 6/7 wk can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wks and at higher TSB levels for those closer to 37 6/7 wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2-3 mg/dL (35-50mmol/L) below those shown but home phototherapy should not be used in any infant with risk factors.

American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation [published correction appears in Pediatrics. 2004 Oct;114(4):1138]. Pediatrics. 2004;114(1):297–316. doi:10.1542/peds.114.1.297

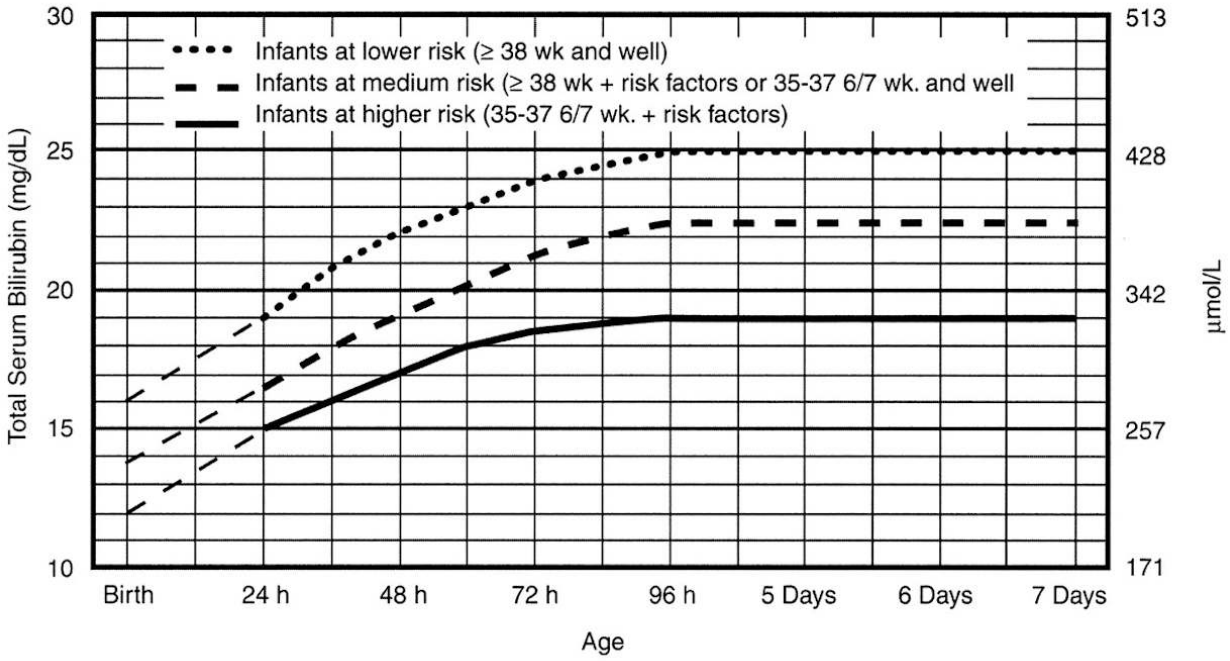
Intravenous Immune Globulin (IVIG)

The implementation of intravenous immune globulin (IVIG) in the newborn is employed by many neonatal units in the treatment of HDFN after birth [46]. IVIG is given when bilirubin levels are rising despite intensive phototherapy, or when levels are approaching the levels necessitating an exchange transfusion. Early studies indicated that high-dose IVIG (0.5g/kg IV immediately after HDFN is confirmed) does reduce serum bilirubin levels and subsequent need for exchange transfusion [47]. A recent meta-analysis confirmed these findings in studies where IVIG doses ranged from 0.5g/kg to 1.5g/kg in one to three administrations [48]. Adverse effects of IVIG can include: fever, allergic reactions, rebound hemolysis, and fluid overload [88]. IVIG can affect the efficacy of some live-virus vaccines for 11-12 months. This can affect administration of the rotavirus vaccine.

Exchange Transfusion

Exchange transfusion should be conducted if bilirubin reaches or exceeds critical levels as shown below (infants with HDFN are medium or high risk)[45]. A cord bilirubin level of >5 mg/dL, or a rate of rise in serum bilirubin of more than 0.5-1 mg/dL/h is predictive of the ultimate need for exchange transfusion [84]. IVIG may prevent the need for an exchange transfusion if initiated early enough.

Guidelines for exchange transfusion in infants 35 or more weeks' gestation.



- The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy.
- Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high pitched cry) or if TSB is ≥5 mg/dL (85 µmol/L) above these lines.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis.
- Measure serum albumin and calculate B/A ratio (See legend)
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin
- If infant is well and 35-37 6/7 wk (median risk) can individualize TSB levels for exchange based on actual gestational age.

American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation [published correction appears in Pediatrics. 2004 Oct;114(4):1138]. Pediatrics. 2004;114(1):297–316. doi:10.1542/peds.114.1.297

Metalloporphyrins

While phototherapy and exchange transfusions are effective treatments for hyperbilirubinemia after it forms, much can be done to optimize treatment of infants with HDFN to prevent and eliminate the development of kernicterus. Studies are currently underway on a multitude of pharmacotherapeutic agents to prevent or treat neonatal hyperbilirubinemia, including metalloporphyrins. The increased hemolysis occuring in infants with HDFN is associated with increased bilirubin production and a greater risk for neurologic injury. Preventing the formation of bilirubin via heme oxygenase (the rate-limiting enzyme responsible for the production of bilirubin), is possible with both natural and synthetic metalloporphyrins [87]. Clinical studies of SnMP show that it prevents excessive hyperbilirubinemia and reduces the duration and need for phototherapy in both term and near-term infants [86]. The use of metalloporphyrins reduces the risk of Kernicterus and BIND, however side effects such as

photosensitivity and potential inhibition of several other enzymes that have essential roles in metabolism have been known to occur [86]. While multiple metalloporphyrins have been studied in animal models, only two have been studied in human neonates: tin protoporphyrin (SnPP) and tin mesoporphyrin (SnMP). SnPP was highly efficacious, but abandoned due to its photosensitizing properties85. SnMP can be used at lower doses with minimal photoreactivity [87]. Metalloporphyrins are currently being studied and administered on a compassionate basis, particularly in regards to patients with religious objections to blood products [89].

Interventions for Anemia

"Top-up" Transfusions

Elevated levels of circulating maternal antibodies in the neonatal circulation in conjunction with suppression of the fetal bone marrow production of red cells often results in the need for neonatal red cell "top-up" transfusions after discharge from the nursery. This results in a 1- to 3-month period in which up to 75% of these infants may need "top-up" red cell transfusions [96]. Weekly reticulocyte counts and hematocrit levels should be assessed until a rising reticulocyte count is noted for at least 2 consecutive weeks. The threshold-for-transfusion includes a hematocrit value of less than 30% in the symptomatic infant or less than 20% in the asymptomatic infant have been suggested by some experts. Typically, only one neonatal transfusion is required, although a maximum of up to three has been reported.

Erythropoietin

Erythropoietin has been in use since the 1990s as an adjunct treatment for late anemia and to increase a reduced reticulocyte count. In limited single-arm studies and case reports, erythropoietin has been shown to be safe [33, 38] and may reduce the need for transfusion in neonates with HDFN [46, 66, 68, 69, 70]. In one 6-week study of 20 infants with HDFN due to anti-D, the "number of erythrocyte transfusions was significantly lower than that of the control group (1.8 versus 4.2). The reticulocyte counts and Hb levels rose earlier in the treatment group" [13]. This may also be a treatment option for children whose parents object to the use of blood products for religious reasons [67]. For additional articles relating to erythropoietin, see our additional reading by topic page.

Folic Acid

Active hemolysis consumes folate; folate is a key ingredient in erythropoiesis. As a result, folic acid is frequently prescribed for infants with HDFN in order to encourage the creation of new RBCs. Various approaches supplement folic acid at a dosage between 50 µg/day and 300µg/day for 3 months [56].

Recovery and Long-term Outcomes

Infants are generally cleared of HDFN when weekly draws reveal that the hemoglobin or hematocrit is rising for 2-3 weeks in a row. At this point the infant no longer has issues with hyperbilirubinemia, and further blood draws for anemia are no longer necessary. Neutropenia and thrombocytopenia may

persist beyond 12 weeks. In this case, they are simply managed as usual, there is nothing extra needed. The infant can be cleared of HDFN.

Long-term outcomes for infants with HDFN are favorable. The largest predictor of reduced neurological outcomes was the appearance of fetal hydrops [88]. The LOTUS study (the largest cohort study of children who received IUTs) followed 291 children ages 2-17 years old and found that "the overall incidence of neurodevelopmental impairment was 4.8% (14/291)[90]". Previous studies show similar or improved neurological outcomes for infants treated with IUTs. In 1993 Doyle et al reported 35 of 38 infants (92%) treated with IUTs had no sensorineural disability at 2 years of age [91]. In 1998 Hudon looked at 40 infants with HDFN due to anti-D who were treated with IUTs. All 40 showed normal neurodevelopmental outcomes at >5 years of age [94]. In 1999 Grab et. al., also showed no moderate or severe neurological impairment in 35 infants who had received IUTs [93]. This data stands in stark contrast to the findings from Harper et. al. where 22% (4/18) hydropic fetuses treated with IUT had major neurological morbidities or death, and 12% of the surviving infants had major neurologic sequelae [92]. Severe hydrops may be associated with a higher risk of impairment [71, 72]. For infants who did not develop hydrops and who were not treated with IUTs, normal outcomes should be expected.

Considerations for Subsequent Pregnancies

Though cost is generally a prohibitive factor, options exist to prevent alloimmunization entirely in subsequent pregnancies. This includes:

- In-vitro fertilization (IVF) with preimplantation genetic testing (PDG) in the case of a heterozygous paternal genotype for the offending red cell antigen[32]
- Gestational carrier using an embryo conceived via IVF
- Donor sperm used in intrauterine insemination (IUI) from a donor who does not carry the offending red cell antigen.

If a woman intends to become pregnant again, pregnancy monitoring and potential interventions can be pre-planned with a supportive provider. This may include IVIG and plasmapheresis beginning in the first trimester and assessment for eligibility for inclusion in new clinical trials such as that for nipocalimab. To see additional clinical trials relating to alloimmunization and HDFN, visit our Current Research and Clinical Trials page. For women with previously affected pregnancies requiring IUTs, referral to a specialist with extensive experience in IUTs, IVIG and plasmapheresis may be considered and pre-pregnancy consultation should be initiated.