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**Author:** Rath, Mirjam Eva Aafke  
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Chapter 13

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In 1932 Diamond et al. reported that hemolysis of fetal and neonatal red blood cells (RBCs) resulted in extramedullary hematopoiesis causing hepatosplenomegaly and a high proportion of erythroblasts in the circulation. Since this description of the pathophysiologic mechanism of alloimmune HDFN, then called erythroblastosis fetalis, numerous discoveries in prenatal and postnatal care have led to a significant decrease in perinatal morbidity and mortality. However, currently there are still several aspects of the pathogenesis, management and outcome of alloimmune HDFN that require further investigation.

Pathogenesis

The cause of late hyporegenerative anemia is still unclear. The following mechanisms have been suggested: intramedullary destruction of RBC precursors and of circulating reticulocytes by RBC antibodies, bone marrow suppression from IUTs, and inappropriate low erythropoietin production for the degree of anemia. Burk et al. showed anti-D antibody bound to Rh D positive erythrocytes in the bone marrow in an infant with a high persistent antibody titer. When antibody titer was fallen to 1:64 at eleven weeks, the first evidence of peripheral reticulocyte survival was observed. Late hyporegenerative anemia was already described before the introduction of IUT in 1963 and thereafter was also observed in infants who were not treated with IUT. Dallacasa et al. reported that reticulocyte counts, hemoglobin and erythropoietin (EPO) levels were similar in IUT and non-IUT treated neonates with Rh D alloimmune HDFN. In contrast, in a study by De Boer et al. the percentage of neonates requiring top-up transfusions was significantly higher for IUT-treated neonates than non-IUT-treated neonates with Rh HDFN. Studies that measured EPO-levels conclude differently on whether EPO-levels are appropriate for the degree of anemia or not. Several small studies and casuistic reports suggest that neonates with alloimmune HDFN may benefit from treatment with recombinant human erythropoietin (rhEPO) to reduce the risk of delayed anemia and subsequent need for top-up transfusions. However, other authors found that rhEPO may be less effective than expected. Pessler et al. suggested that rhEPO might be ineffective when antibody titers are high. This theory from Pessler sounds plausible since RhEPO in these neonates will produce erythrocytes that can be covered by circulating antibodies and subsequently destructed.

Future randomized controlled trials on the effectiveness of rhEPO in preventing late anemia should be stratified for antibody titer, hemoglobin levels, and gestational age.
Management

Antenatal period
Several pharmacological antenatal management options for alloimmune HDFN deserve further study, including phenobarbital, IVIg and corticosteroids.

Phenobarbital
Antenatal maternal administration of phenobarbital (30 mg 3 times a day for 7-10 days) significantly reduced the need for ET in neonates with HDFN due to RBC alloimmunization in a recent retrospective study by Trevett et al.17 In neonates with and without antenatal maternal administration of phenobarbital, ET was performed in 9% and 52%, respectively (p=<0.01). Phenobarbital has been shown to improve the capability of the neonatal liver to conjugate and eliminate bilirubin. Because of the immaturity of the hepatic conjugation pathways, premature infants are at greater risk of requiring ET for hyperbilirubinemia. Mainly premature infants were included in the study by Trevett et al. (mean gestational age in ET and no-ET group 33.0 and 35.4 weeks, respectively). Although the effect of phenobarbital remained significant in reducing the need for ET after Trevett et al. adjusted for gestational age, antenatal maternal administration of phenobarbital might be more effective in premature infants with alloimmune HDFN.17

IVIg
Several case series and retrospective studies show that antenatal maternal administration of IVIg improves perinatal outcome in Rh D and Kell HDFN.18-30 Only Chitkara et al. concluded after studying the effect of maternal IVIg in 5 cases with alloimmune HDFN, that this treatment does not appear useful in Rh D HDFN.31 Suggested mechanism of action of maternal administration of IVIg include: decrease of maternal antibodies by suppression of production or enhanced clearance, competitive inhibition of anti-D transport to the fetus and the inhibition of phagocytosis of fetal antibody-coated red cells by the fetal reticuloendothelial system. Maternal administration of IVIg can not compete with the excellent outcome of IUT treatment but may play an additional role in early hydrops that developed before the 18th week and less eligible for IUT. Fetal administration of IVIG is another option. A great advantage of fetal administration compared with maternal administration is the lower cost since IVIg is dosed per kilogram of body weight. For that reason fetal infusion of IVIg has also been studied.32-34 Although the case report of Alonso et al. and the case series of Kiplani et al. showed promising results32,34, a small RCT including 20 fetuses with severe Rh D HDFN by Dooren et al. showed no significant differences in the
transfusion requirements or clinical outcome. However the dose used in this trial was too low to reach reliable conclusions on the effect.\textsuperscript{33}

**Corticosteroids**

Labor is often induced in pregnancies that are complicated by red cell alloimmunization because of the risks of an additional necessary IUT. Late preterm (34 0/7 to 36 6/7 weeks of gestation) and early term (37 0/7 to 38 6/7 weeks of gestation) births are therefore no exception. Recent studies show that late preterm and early term births have a higher rate of morbidity, especially relating to respiratory function and long-term neurodevelopmental outcome, than infants born at 39 weeks of gestation.\textsuperscript{35,36} In line with this, it should be evaluated if there is a role for maternal administration of corticosteroids to prevent respiratory complications at birth in infants with alloimmune HDFN. A Cochrane review published in 2006 showed that antenatal corticosteroids significantly reduced the rate of respiratory distress syndrome in neonates (without HDFN) born between 33 0/7 and 34 6/7 weeks of gestation (RR 0.53, 95\% CI 0.31 to 0.91, 2 RCTs, 434 infants), but not in neonates born between 35 0/7 and 36 6/7 weeks of gestation (RR 0.61, 95\% CI 0.11 to 3.26, 1 RCT, 189 infants).\textsuperscript{37} In 2011 a randomized placebo-controlled trial by Porto et al. showed that 12 mg Betamethasone for two consecutive days at 34 0/7 to 36 6/7 weeks of non-HDFN pregnancy does not reduce the incidence of respiratory disorders in neonates.\textsuperscript{38} However, the risk of jaundice requiring phototherapy was significantly lower in the group treated with antenatal corticosteroids (RR 0.63, 95\% CI 0.44 to 0.91).\textsuperscript{38} This finding makes it especially interesting to study the effectiveness of antenatal corticosteroids in neonates with alloimmune HDFN who nearly all require phototherapy.

**Intrauterine transfusions**

Although IUTs are performed since the 1960s, there are still some aspects to be taken into consideration for future research in alloimmune HDFN. In our center, IUTs are performed mainly intravascular to treat fetal anemia. However, a combination of intravascular and intraperitoneal IUT might achieve a more stable fetal Ht and a longer interval between transfusions.\textsuperscript{39,41} This topic deserves further study in a randomized controlled trial. Another technical aspect of IUT that requires further investigation is the effect of analgesia on the fetal hormonal and hemodynamic stress response in case of intrahepatic vein needling.\textsuperscript{42}

Further research is also required to evaluate the benefits and harms associated with maternal sedation and fetal paralysis during the procedures.\textsuperscript{43}
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Postnatal period

Exchange transfusions
Recently, an RCT that compared two-stage single-volume ET (TSSV-ET) with single-stage double-volume ET (SSDV-ET) in full-term neonates with HDFN due to Rh or ABO incompatibility showed promising results.44 The mean rebound bilirubin level (measured 3 hours after ET) was significantly lower in the TSSV-ET group compared to the SSDV-ET group (12.7 ± 1.1 mg/dL versus 17.3 ± 1.7 mg/dL, p=<0.001). Also the need for repeated ET was significantly lower in the TSSV-ET group compared to the SSDV-ET group (13.5% versus 32.7%, p=<0.05). In addition, complications of ET (sepsis, NEC, pulmonary hemorrhage) and mortality were not significantly different between both groups. Authors suggested that the beneficial effect of TSSV-ET lies in lowering rebound bilirubin because extravascular bilirubin has more time to distribute to the intravascular space.44 Likewise, antibodies also have a longer period to distribute between the extravascular and intravascular space and consequently a lower antibody titer and duration and severity of late anemia could be expected. However, the authors did not measure the number of top-up transfusions or antibody titers. Future RCTs should preferably include a more homogenous group of neonates (only Rh HDFN or ABO HDFN) and should also measure duration of phototherapy and the number of top-up transfusions to evaluate all possible benefits of TSSV-ET compared to SSDV-ET.

IVIg
Based on the results of the Cochrane review in Chapter 6 it can be concluded that the effectiveness of neonatal administration of IVIg in alloimmune HDN is still controversial. Future research into the role of neonatal administration of IVIg in alloimmune HDN may particularly be warranted in infants for whom ET is considered to be high risk or not available.

Prophylactic antibiotics
In Chapter 4 we demonstrated that leukocytopenia and sepsis are common complications of ET. Whether ET-related removal of leukocytes may play a role in the higher incidence of sepsis after ET deserves further study. However, it might be more interesting to evaluate the role of prophylactic antibiotics to prevent sepsis after ET in alloimmune HDFN because the higher incidence of sepsis is probably caused by manipulating the umbilical venous catheter during ET. A recent Cochrane review on the use of prophylactic antibiotics to reduce morbidity and mortality in neonates with umbilical venous catheters only included one
study which was of poor quality.\textsuperscript{45} This quasi-RCT, performed in 1984, included 23 infants who required ET for hyperbilirubinemia and 6 infants who required partial ET for hematocrit > 0.70.\textsuperscript{46} Although 5 of 15 infants given antibiotics and 5 of 14 control infants having positive blood cultures three days after catheterization, all positive blood cultures were considered contaminated due to lack of clinical and hematological evidence of infection.

\textit{Top-up transfusion and medicaments for late anemia}

The optimal transfusion trigger for top-up transfusions in alloimmune HDN should be taken into consideration for future research. Guidelines for RBC transfusions in neonates vary greatly between and within countries. Possible advantages of restrictive transfusion guidelines are reduction of total transfusions and donor exposure. However, some studies reported worse short-term neurological or long-term neurodevelopmental outcome in those treated with restrictive transfusion guidelines compared to liberal transfusion guidelines.\textsuperscript{57,48}

As previously mentioned in this chapter, RCTs to evaluate the use of rhEPO to prevent late anemia and consequently top-up transfusions are required. RhEPO has been increasingly used in neonates to prevent or reduce neonatal anemia without short or long-term adverse effects and might even work neuroprotective.\textsuperscript{14,49-52}

Another benefit of rhEPO in alloimmune HDN could be lowering ferritin levels in neonates with iron overload/cholestasis. However, studies should monitor ferritin levels to prevent iron deficiency.

Folic acid and Vitamin E are often used in infants with alloimmune HDFN to support erythropoiesis.\textsuperscript{53} However, no high-quality studies are performed so far to evaluate the efficacy of those supplements in reducing the severity of anemia. Further well-designed studies are required.

\textbf{Long term outcome}

There is lack of long-term follow-up studies in alloimmune HDFN. The neurodevelopmental outcome in IUT treated infants with alloimmune HDFN has recently been reported.\textsuperscript{54} However, studies that evaluate long term effects on the immune system and liver function in infants with iron overload and/or cholestasis are warranted.
References


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