

## Intensive Care Nursery House Staff Manual

# Hemolytic Disease of the Newborn

**INTRODUCTION and DEFINITION:** Hemolytic Disease of the Newborn (HDN), also known as erythroblastosis fetalis, isoimmunization, or blood group incompatibility, occurs when fetal red blood cells (RBCs), which possess an antigen that the mother lacks, cross the placenta into the maternal circulation, where they stimulate antibody production. The antibodies return to the fetal circulation and result in RBC destruction.

**DIFFERENTIAL DIAGNOSIS** of hemolytic anemia in a newborn infant:

- Isoimmunization
- RBC enzyme disorders (*e.g.*, G6PD, pyruvate kinase deficiency)
- Hemoglobin synthesis disorders (*e.g.*, alpha-thalassemias)
- RBC membrane abnormalities (*e.g.*, hereditary spherocytosis, elliptocytosis)
- Hemangiomas (Kasabach Merritt syndrome)
- Acquired conditions, such as sepsis, infections with TORCH or Parvovirus B19 (anemia due to RBC aplasia) and hemolysis secondary to drugs.

### ISOIMMUNIZATION

#### **A. Rh disease (Rh = Rhesus factor)**

- (1) **Genetics:** Rh positive (+) denotes presence of D antigen. The number of antigenic sites on RBCs varies with genotype. Prevalence of genotype varies with the population. Rh negative (d/d) individuals comprise 15% of Caucasians, 5.5% of African Americans, and <1% of Asians. A sensitized Rh negative mother produces anti-Rh IgG antibodies that cross the placenta. Risk factors for antibody production include 2<sup>nd</sup> (or later) pregnancies\*, maternal toxemia, paternal zygosity (D/D rather than D/d), feto-maternal compatibility in ABO system and antigen load.
- (2) **Clinical presentation** of HDN varies from mild **jaundice** and **anemia** to **hydrops fetalis** (with ascites, pleural and pericardial effusions). Because the placenta clears bilirubin, the chief risk to the **fetus is anemia**. Extramedullary hematopoiesis (due to anemia) results in **hepatosplenomegaly**. Risks during labor and delivery include **asphyxia** and **splenic rupture**. **Postnatal problems** include:
 

<b>Asphyxia</b>	<b>Pulmonary hypertension</b>
<b>Pallor</b> (due to anemia)	<b>Edema</b> (hydrops, due to low serum albumin)
<b>Respiratory distress</b>	<b>Coagulopathies</b> (↓ platelets & clotting factors)
<b>Jaundice</b>	<b>Kernicterus</b> (from hyperbilirubinemia)
<b>Hypoglycemia</b> (due to hyperinsulinemia from islet cell hyperplasia)	
- (3) **Laboratory Findings** vary with severity of HDN and include:
 

<b>Anemia</b>	<b>Hyperbilirubinemia</b> †
<b>Reticulocytosis</b> (6 to 40%)	↑ <b>nucleated RBC count</b> (>10/100 WBCs)
<b>Thrombocytopenia</b>	<b>Leucopenia</b>
+ <b>Direct Antiglobulin Test</b> ‡	<b>Hypoalbuminemia</b>
<b>Rh negative blood type</b> ‡	<b>Smear:</b> polychromasia, anisocytosis, no spherocytes

\*HDN can occur in 1<sup>st</sup> pregnancy, but this is uncommon.

‡Cord blood bilirubin >4 mg/dL indicates severe isoimmunization.

‡With severe HDN, high quantities of antibody may block Rh antigen site resulting in an Rh+ infant typing as Rh- and having a negative Direct Antiglobulin test.

**(4) Intra-uterine Transfusion (IUT):** When iso-immunization is severe, IUTs are given to the fetus to prevent hydrops fetalis and fetal death. After multiple IUTs, most of the baby's blood will be Rh negative donor blood. Therefore, the Direct Antiglobulin test will be negative, but the Indirect Antiglobulin Test will be positive. After IUTs, the cord bilirubin is not an accurate indicator of rate of hemolysis or of the likelihood of the need for post-natal exchange transfusion.

**B. Minor Blood Group Incompatibility** is uncommon, occurs in ~0.8% of pregnant women and usually with E, c, Kell, Kidd or Duffy. Clinical presentation is similar to Rh disease. Anti-Kell disease may be severe due to hemolysis or erythroid suppression. Lewis antigen stimulates only IgM production, so maternal antibody screen may be positive, but fetus is not affected.

**C. ABO Incompatibility**

**(1) Genetics:** With maternal blood types A and B, isoimmunization does not occur because the naturally occurring antibodies (anti-A and -B) are IgM, not IgG. In type O mothers, the antibodies are predominantly IgG, cross the placenta and can cause hemolysis in the fetus. The association of a type A or B fetus with a type O mother occurs in ~15% of pregnancies. However, HDN occurs in only 3%, is severe in only 1%, and <1:1,000 require exchange transfusion. The disease is more common and more severe in African-American infants. Unlike Rh, ABO disease can occur in first pregnancies, because anti-A and anti-B antibodies are found early in life from exposure to A- or B-like antigens present in many foods and bacteria.

**(2) Clinical presentation:** generally less severe than with Rh disease.

**(3) Laboratory findings** that differ from Rh disease:

**Smear:** microspherocytosis

**MCV <95**, microcytic for a newborn (normal for adult)

**Direct Coombs test** is often weakly +.

**MANAGEMENT:**

**A. Preparation prior to delivery** should include:

-**Blood:** type O Rh negative packed RBCs, cross-matched against the mother. For severe HDN, have blood in the Resuscitation Room to correct **severe anemia immediately after birth by partial exchange transfusion (ExTx)**. Anticipate need for later ExTx for hyperbilirubinemia and have additional blood for these.

-**Surfactant**, if infant is preterm.

-**Catheters** (e.g., angiocaths) for immediate drainage of hydropic fluid.

**B. Resuscitation:** At birth, the major problems are **cardiopulmonary** and relate to effects of severe anemia, hydrops and prematurity. Because of the multiple problems with severe HDN, effective resuscitation requires several individuals.

-Obtain **cord blood** for bilirubin (total & direct), albumin, blood type & Rh, Direct Coombs test, CBC, platelets, reticulocyte count and nucleated RBCs.

- If the infant is **hydropic**, **intubate immediately and begin assisted ventilation** with oxygen. If ventilation is difficult, drain pleural and ascitic fluid; during paracentesis, take care to **avoid puncturing the enlarged liver and spleen**.
  - Insert **umbilical arterial (UAC) and venous catheters (UVC)** (See section on Umbilical Catheters, P. 25) and **immediately measure blood pressures, arterial pH and blood gas tensions, hematocrit (Hct) and blood sugar**.
  - Correct metabolic acidosis with **alkali**, but only if giving assisted ventilation (see section on Acid Base Balance, P. 62).
  - Correct anemia**, which is essential for effective resuscitation.
    - If arterial blood pressure is low, give simple transfusion of packed RBCs (*e.g.*, for Hct of 30%, push 10 mL/kg over 5 min; for Hct of 20%, push 10 mL/kg over 5 min, then repeat).
    - Do not infuse packed RBCs or blood through UAC** because of risk of damage to spinal cord from emboli.
    - With normal blood pressure, elevated central venous pressure, metabolic acidosis or hydrops, correct anemia by **partial ExTx** (exchange 20 mL/kg, then repeat hematocrit).
  - Measure blood sugar frequently and correct **hypoglycemia**.
  - Follow **platelet counts**; consider platelet transfusion for counts <50,000.
- (C) **Hyperbilirubinemia** results from continued hemolysis and inability of the neonatal liver to handle a large bilirubin load. **Kernicterus** (bilirubin encephalopathy) results from high levels of indirect bilirubin (**>20 mg/dL in a term infant with HDN**). Kernicterus occurs at lower levels of bilirubin in the presence of **acidosis, hypoalbuminemia, prematurity and certain drugs** (*e.g.*, sulfonamides).
- Measure bilirubin in cord blood and at least q4h for the first 12 to 24h**. Plot bilirubin concentrations over time. A graph for plotting bilirubin over time is available at the unit clerk's desk.
  - Begin **phototherapy** shortly after birth. Although phototherapy may not eliminate the need for ExTx, it may delay ExTx and decrease the number required.
  - Use **ExTx** for hyperbilirubinemia not controlled by phototherapy (see P. 42).
    - Indications** depend upon absolute serum concentration of bilirubin, the rate of rise of bilirubin, gestational age, albumin concentration and acid-base status. In general, perform ExTx for cord bilirubin >5 mg/dL, for a rate of rise of bilirubin >0.7 mg/h, and to prevent bilirubin >20 mg/dL in a term infant, and lower levels in preterm infants (*e.g.*, maintain serum bilirubin <10X the birthweight in kg).
    - Blood** should be reconstituted (to Hct ~40-50%) from fresh, O negative packed RBCs cross-matched against the mother and type-specific fresh frozen plasma.
    - Technique:** About 30 min before ExTx, give albumin 1 g/kg to increase the bilirubin bound to albumin in the circulation and make the ExTx more effective. Exchange **2X the blood volume** (estimate blood volume at 85 mL/kg). Preferred technique is isovolumic ExTx, withdrawing blood from UAC and infusing through UVC (with tip in IVC or low right atrium). **Do not infuse blood through UVC if tip is in portal circulation**. Alternatively, ExTx can be done through a single catheter (UAC or UVC) using aliquots <5% of the

infant's blood volume (*e.g.*, 5 mL/kg). The blood should be warmed and the bag agitated every few minutes (to prevent settling of the RBCs).

•**Complications of ExTx:**

- Hypocalcemia** due to  $\text{Ca}^{++}$  binding by citrate. Give Ca-gluconate 100 mg after every 100 mL of blood exchanged.
- Hypoglycemia**, particularly after the ExTx, due to dextrose load from anti-coagulant of donor blood and hyperinsulinism in HDN.
- Thrombocytopenia** and **granulocytopenia** due to washout with the ExTx.
- Hyperkalemia**, especially with older units of blood.
- Hypothermia**, associated with inadequate warming of blood.

**OUTCOME:**

- (A) **Late anemia:** Antibodies persist for weeks, cause continued hemolysis and can cause anemia as late as age 6 months (especially in infants who had received IUTs). After discharge, follow Hct weekly. Erythropoietin treatment will help prevent severe anemia and further transfusions (see P. 111).
- (B) **Neurological** prognosis is good. Commonest problem is sensorineural hearing loss.