Hemolytic diseases of the new borne

A French midwife was the first to report hemolytic disease of the newborn (HDN) in a set of twins in 1609. In 1932, Diamond and colleagues described the relationship among [fetal hydrops](http://emedicine.medscape.com/article/974571-overview), jaundice, anemia, and erythroblasts in the circulation, a condition later called erythroblastosis fetalis. Levine later determined the cause after Landsteiner and Weiner discovered the Rh blood group system in 1940. In 1953, Chown subsequently confirmed the pathogenesis of Rh alloimmunization to be the result of passage of Rh-positive fetal RBCs after transplacental hemorrhage into maternal circulation that lacked this antigen.

Pathophysiology

Genetics

Although the Rh antibody was and still is the most common cause of severe hemolytic disease of the newborn (HDN), other alloimmune antibodies belonging to Kell (K and k), Duffy (Fya), Kidd (Jka and Jkb), and MNSs (M, N, S, and s) systems do cause severe HDN.[[4](javascript:void(0);)]The Rh blood group system uses Fisher-Race nomenclature, and the Rh gene complex consists of 3 genetic loci each with 2 major alleles. They code for 5 major antigens denoted by letters, C, c, E, e, and D. Rh blood group antigens are inherited as determined by at least 2 homologous but distinct membrane-associated proteins. Two separate genes (RhCE and RhD), located on the short arm of chromosome 1, encode Rh proteins. Each gene is 10 exons in length, and a 96% homology between these genes is observed.

After the initial exposure to a foreign antigen, B-lymphocyte clones that recognize the RBC antigen are established. The maternal immune system initially produces antibodies of the immunoglobulin M (IgM) isotype that do not cross the placenta and later produces antibodies of the IgG isotype that traverse the placental barrier. Predominant antibody subclass appears to be IgG1 in one third of individuals whereas a combination of IgG1 and IgG3 subclasses are found in the remaining individuals.

IgG3 is more efficient in binding to reticuloendothelial cells and causing hemolysis because of its longer hinge region. This is termed the primary response and is dose dependent (documented in 15% of pregnancies with 1 mL of Rh-positive cells in an Rh-negative individual compared with 70% of pregnancies after 250 mL). A repeat exposure to the same antigen rapidly induces the production of IgG. This secondary immune response can be induced with as little as 0.03 mL of Rh-positive RBCs.

The risk of Rh immunization after the delivery of the first child to a nulliparous Rh-negative mother is 16% if the Rh-positive fetus is ABO compatible with its mother, 2% if the fetus is ABO incompatible, and 2-5% after an abortion. The ABO-incompatible RBCs are rapidly destroyed in the maternal circulation, reducing the likelihood of exposure to the immune system. The degree of Rh sensitization of the mother is directly related to the amount of fetomaternal hemorrhage (ie, 3% with < 0.1 mL compared with 22% with >0.1 mL).

After sensitization, maternal anti-D antibodies cross the placenta into fetal circulation and attach to Rh antigen on fetal RBCs, which form rosettes on macrophages in the reticuloendothelial system, especially in the spleen. These antibody-coated RBCs are lysed by lysosomal enzymes released by macrophages and natural killer lymphocytes and are independent of the activation of the complement system.

Reticulocytosis is noted when fetal Hb deficit exceeds 2 gm/dl compared with gestational age norms. Tissue hypoxia develops as fetal anemia becomes severe. When the hemoglobin (Hb) level drops below 8 g/dL, a rise in umbilical arterial lactate occurs. When the Hb level drops below 4g/dL, increased venous lactate is noted. Hydrops fetalis occurs when fetal Hb deficit exceeds 7 g/dL and starts as fetal ascites and evolves into [pleural effusions](http://emedicine.medscape.com/article/1003121-overview) and generalized edema. The various mechanisms responsible for hydrops are hypoalbuminemia secondary to depressed liver function, increased capillary permeability, iron overload secondary to hemolysis, and increased venous pressures due to poor cardiac function.[[8](javascript:void(0);)]

Prolonged hemolysis leads to severe anemia, which stimulates fetal erythropoiesis in the liver, spleen, bone marrow, and extramedullary sites, such as the skin and placenta. In severe cases, this can lead to displacement and destruction of hepatic parenchyma by erythroid cells, resulting in dysfunction and hypoproteinemia. Destruction of RBCs releases heme that is converted to unconjugated bilirubin. Hyperbilirubinemia becomes apparent only in the delivered newborn because the placenta effectively metabolizes bilirubin. HDN due to Kell sensitization results in hemolysis and suppression of erythropoiesis because the Kell antigen is expressed on the surface of erythroid progenitors. This leads to severe fetal disease at a lower maternal antibody titer than in Rhesus disease.

Hemolysis associated with ABO incompatibility exclusively occurs in type-O mothers with fetuses who have type A or type B blood, although it has rarely been documented in type-A mothers with type-B infants with a high titer of anti-B IgG. In mothers with type A or type B, naturally occurring antibodies are of the IgM class and do not cross the placenta, whereas 1% of type-O mothers have a high titer of the antibodies of IgG class against both A and B. They cross the placenta and cause hemolysis in fetus.

Hemolysis due to anti-A is more common than hemolysis due to anti-B, and affected neonates usually have positive direct Coombs test results. However, hemolysis due to anti-B IgG can be severe and can lead to exchange transfusion. Because A and B antigens are widely expressed in various tissues besides RBCs, only a small portion of antibodies crossing the placenta are available to bind to fetal RBCs. Recent analysis of IgG subclass in ABO incompatible direct coombs positive neonates showed IgG2 was predominent antibody which is poorly transferred across placenta and less efficient in causing hemolysis while IgG1 was noted in 22% of neonates and as a group had similar rate of hemolysis and severity of hyperbilirubinemia.[[9](javascript:void(0);)]

In addition, fetal RBCs appear to have less surface expression of A or B antigen, resulting in few reactive sites; hence the low incidence of significant hemolysis in affected neonates. This results in hyperbilirubinemia as a predominant manifestation of incompatibility (rather than anemia), and peripheral blood film frequently reveals a large number of spherocytes and few erythroblasts, unlike what is seen in Rh incompatibility (erythroblastosis fetalis), in which blood film reveals a large number of nucleated RBCs and few spherocytes.[[10](javascript:void(0);)]

## Etiology

In the absence of a positive direct Coombs test result, other causes of pathologic jaundice should be considered,[[11](javascript:void(0);)] including intrauterine congenital infections; erythrocyte membrane defects (eg, hereditary spherocytosis, hereditary elliptocytosis, hereditary pyropoikilocytosis); RBC enzyme deficiencies (eg, glucose-6-phosphate dehydrogenase [G6PD] deficiency, [pyruvate kinase deficiency](http://emedicine.medscape.com/article/957918-overview), triosephosphate isomerase deficiency); and nonhemolytic causes (eg, enclosed hemorrhages, [hypothyroidism](http://emedicine.medscape.com/article/922777-overview), GI obstruction, and metabolic diseases).

Similarly, hydrops can occur from nonimmune hematologic disorders that cause anemia, such as hemoglobinopathies (eg, α-thalassemia major), cardiac failure due to dysrhythmia, congenital heart defects, and infections (eg, [syphilis](http://emedicine.medscape.com/article/969023-overview), [cytomegalovirus [CMV]](http://emedicine.medscape.com/article/963090-overview), parvovirus[[12](javascript:void(0);)]).

* Common causes of hemolytic disease of the newborn
  + Rh system antibodies
  + ABO system antibodies
* Uncommon causes: Kell system antibodies
* Rare causes
  + Duffy system antibodies
  + MNS and s system antibodies
* No occurrence in hemolytic disease of the newborn
  + Lewis system antibodies
  + P system antibodies
* An infant born to an alloimmunized mother shows clinical signs based on the severity of the disease. The typical diagnostic findings are jaundice, pallor, hepatosplenomegaly, and fetal hydrops in severe cases. The jaundice typically manifests at birth or in the first 24 hours after birth with rapidly rising unconjugated bilirubin level. Occasionally, conjugated hyperbilirubinemia is present because of placental or hepatic dysfunction in those infants with severe hemolytic disease. Anemia is most often due to destruction of antibody-coated red blood cells by the reticuloendothelial system, and, in some infants, anemia is due to intravascular destruction. The suppression of erythropoiesis by intravascular transfusion (IVT) of adult Hb to an anemic fetus can also cause anemia. Extramedullary hematopoiesis can lead to hepatosplenomegaly, portal hypertension, and ascites.
* Anemia is not the only cause of hydrops. Excessive hepatic extramedullary hematopoiesis causes portal and umbilical venous obstruction and diminished placental perfusion because of edema. Increased placental weight and edema of chorionic villi interfere with placental transport. Fetal hydrops results from fetal hypoxia, anemia, congestive cardiac failure, and hypoproteinemia secondary to hepatic dysfunction. Commonly, hydrops is not observed until the Hb level drops below approximately 4 g/dL (Hct < 15%).[[8](javascript:void(0);)] Clinically significant jaundice occurs in as many as 20% of ABO-incompatible infants.

## Differential Diagnoses

* [Acute Anemia](https://emedicine.medscape.com/article/780334-overview)
* [Galactose-1-Phosphate Uridyltransferase Deficiency (Galactosemia)](https://emedicine.medscape.com/article/944069-overview)
* [Parvovirus B19 Infection](https://emedicine.medscape.com/article/961063-overview)
* [Pediatric Atrial Flutter](https://emedicine.medscape.com/article/894226-overview)
* [Pediatric Cardiac Tumors](https://emedicine.medscape.com/article/901147-overview)
* [Pediatric Cytomegalovirus Infection](https://emedicine.medscape.com/article/963090-overview)
* [Pediatric Hydrops Fetalis](https://emedicine.medscape.com/article/974571-overview)
* [Pediatric Hypothyroidism](https://emedicine.medscape.com/article/922777-overview)
* [Pediatric Syphilis](https://emedicine.medscape.com/article/969023-overview)
* Toxoplasmosis
* [Tyrosinemia](https://emedicine.medscape.com/article/949816-overview)

Treatment

* + - The infant should be in the bassinet, and the sides should be lined with white cloth or aluminum foil to expose more surface area. The exposed surface area is increased by the use of 1-2 fiberoptic pads that should be placed under the infant or by the use of BiliBed or Bili-Bassinet, which provides phototherapy from above and below. The diaper should be removed if bilirubin is approaching exchange levels.
    - The serum bilirubin declines by 0.5-1 mg/dL in the first 4-8 hours on intensive phototherapy and should be measured in 2-3 hours to document the effectiveness.
    - If the serum bilirubin level continues to rise despite intensive phototherapy or is within 2-3 mg/dL of exchange level, administer intravenous immunoglobulin (IVIG) at 0.5-1 g/kg over 2 hours and repeat every 12 hours if needed.
    - High-dose IVIG 1 g/kg given early in high-risk neonates with rapid rise of bilirubin level (>0.5 mg/kg/h) and worsening anemia (hemoglobin [Hb] < 2 g/dL) despite intensive phototherapy, is be able to eliminate the need for exchange transfusion and to reduce duration of phototherapy. The number needed to treat (NNT) is 6.[[44](javascript:void(0);)]
  + Phototherapy is indicated in the term infant with hemolytic disease of the newborn immediately after birth due to Rh disease and due to ABO incompatibility as follows:[[45](javascript:void(0);)]
    - Unborn (cord blood): Total serum bilirubin level of more than 3.5 mg/dL
    - Age less than 12 hours: Total serum bilirubin level of more than 10 mg/dL
    - Age less than 18 hours: Total serum bilirubin level of more than 12 mg/dL
    - Age less than 24 hours: Total serum bilirubin level of more than 14 mg/dL
    - Age 2-3 days: Total serum bilirubin level of more than 15 mg/dL
    - Immediately after birth in all preterms who weigh less than 2500 g
* Exchange transfusion removes circulating bilirubin and antibody-coated RBCs, replacing them with RBCs compatible with maternal serum and providing albumin with new bilirubin binding sites. The process is time consuming and labor intensive but remains the ultimate treatment to prevent kernicterus. The process involves the placement of a catheter via the umbilical vein into the inferior vena cava and removal and replacement of 5- to 10-mL aliquots of blood sequentially, until about twice the volume of the neonate's circulating blood volume is reached (ie, double-volume exchange).