Common Hematologic Problems in the Newborn Nursery

Jon F. Watchko, MD

KEYWORDS
- Hyperbilirubinemia
- Hemolysis
- Anemia
- Polycythemia
- Thrombocytopenia
- Rh disease
- G6PD deficiency

KEY POINTS
- Early clinical jaundice or rapidly developing hyperbilirubinemia are often signs of hemolysis, the differential diagnosis of which commonly includes immune-mediated disorders, red-cell enzyme deficiencies, and red-cell membrane defects.
- Knowledge of the maternal blood type and antibody screen is critical in identifying non-ABO alloantibodies in the maternal serum that may pose a risk for severe hemolytic disease in the newborn.
- Moderate to severe thrombocytopenia in an otherwise well-appearing newborn strongly suggests immune-mediated (alloimmune or autoimmune) thrombocytopenia.

INTRODUCTION

Hematologic problems often arise in the newborn nursery, particularly those related to the red blood cell (RBC), the primary focus of this review. Their timely identification is important to ensure appropriate care of the neonate. Common RBC disorders include hemolytic disease of the newborn, anemia, and polycythemia. Another clinically relevant hematologic issue in neonates to be covered herein is thrombocytopenia. Disorders of white blood cells will not be reviewed.

RED BLOOD CELL

Clinical signs of an RBC disorder in the immediate newborn period are jaundice (hemolysis), pallor (anemia), and plethora (polycythemia). Of these RBC disorders, hemolysis is the most frequently encountered and often heralded by early-onset jaundice.

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(<24 hours of age). In the current era of birth hospitalization, bilirubin screening using total serum bilirubin (TSB) or transcutaneous bilirubin (TcB) measurements, an elevated hour specific bilirubin greater than 75% on the Bhutani nomogram also is a marker for hemolysis. Although there are many diagnostic considerations in the interpretation of RBC disturbances in the neonatal period, a systematic approach based on mechanism(s) of disease highlighted herein make this process more straightforward.

HEMOLYTIC DISEASE OF THE NEWBORN

Catabolism of RBC-derived heme produces bilirubin that results in jaundice, the most prevalent clinical condition requiring evaluation and management in neonates. Although hepatic and gastrointestinal immaturities that limit bilirubin clearance contribute to neonatal jaundice, it is increasingly clear that accelerated RBC turnover (hemolysis) plays a pivotal role in the risk for subsequent severe hyperbilirubinemia. Moreover, hemolysis potentiates the risk of bilirubin neurotoxicity and treatment interventions are therefore recommended at lower TSB levels when hemolysis is present. Pediatricians must therefore have a strong working knowledge of hemolytic disorders to properly care for the jaundiced neonate. These conditions are outlined in Box 1 and include immune-mediated disorders, red-cell enzyme defects, red-cell membrane abnormalities, and, for completeness but exceedingly rare in neonates, hemoglobinopathies.

Immune-Mediated Hemolytic Disorders

Immune-mediated disorders are the most common cause of hemolysis in neonates and should be suspected when there is (1) a heterospecific mother-infant pair in which

<table>
<thead>
<tr>
<th>Box 1</th>
<th>Hemolytic conditions in the neonate</th>
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<tbody>
<tr>
<td>1. Immune-mediated (positive direct Coombs test)</td>
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<tr>
<td>a. Rhesus blood group: Anti-D, -C, -c, -e, -E, Cw, and several others</td>
<td></td>
</tr>
<tr>
<td>b. Non-Rhesus blood groups: Kell, Duffy, Kidd, Xg, Lewis, MNS, and others</td>
<td></td>
</tr>
<tr>
<td>c. ABO blood group: Anti-A, -B</td>
<td></td>
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<tr>
<td>2. Red blood cell (RBC) enzyme defects</td>
<td></td>
</tr>
<tr>
<td>a. Glucose-6-phosphate dehydrogenase (G6PD) deficiency</td>
<td></td>
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<tr>
<td>b. Pyruvate kinase deficiency</td>
<td></td>
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<tr>
<td>c. Others</td>
<td></td>
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<tr>
<td>3. RBC membrane defects</td>
<td></td>
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<tr>
<td>a. Hereditary spherocytosis</td>
<td></td>
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<td>b. Elliptocytosis</td>
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<tr>
<td>c. Stomatocytosis</td>
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<tr>
<td>d. Pyknocytosis</td>
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<tr>
<td>e. Others</td>
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<tr>
<td>4. Hemoglobinopathies</td>
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</tr>
<tr>
<td>a. alpha-thalassemia</td>
<td></td>
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<tr>
<td>b. gamma-thalassemia</td>
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the infant expresses a red-cell antigen(s) foreign to the mother, (2) the presence of a maternal antibody directed to the infant RBC antigen, (3) and a positive direct Coombs test in the neonate indicating maternal antibody bound to the infant RBC. An initial priority in evaluating every newborn is therefore knowledge of the maternal blood type and the maternal antibody screen. The latter deserves specific comment and emphasis.

The maternal antibody screen is a routine test performed at maternal registration on pregnancy diagnosis. The goal of screening is to identify non-ABO alloantibodies in the maternal serum that may pose a risk for hemolytic disease in the newborn. A standard screening panel for alloantibodies is shown in Table 1. In addition, women who are Rh-D negative and have a negative antibody screen at registration will have a repeat screen at 24 to 28 weeks’ gestation before Rhogam (RhD-Ig) administration, and another screen at delivery along with a type and Coombs on the infant to determine the need for postpartum Rhogam. Interpreting the results of the maternal antibody screen by pediatricians is critical in identifying mothers who carry a non-ABO alloantibody, several of which can cause moderate to severe hemolytic disease of the newborn as detailed in Table 2.15,16

Indeed, in addition to the classic Rhesus hemolytic disease of the newborn secondary to Rh-D isoimmunization, alloantibodies directed to non-D Rhesus antigens and a broad range of non-Rhesus blood group antigens are seen. Increasingly, the latter 2 categories comprise a clinically relevant proportion of hemolytic disease of the newborn. Identical maternal and infant blood grouping with respect to the ABO system and Rh-D status (“Rh positive” or “Rh negative”) does not preclude the presence of a clinically significant maternal alloantibody. Only a review of the maternal antibody screen and the direct Coombs test on the infant will uncover such cases.15–17 Indeed, a type and direct Coombs test are indicated at delivery (cord or infant blood) on all infants born to women with potentially significant alloantibodies.17

Table 3 outlines several clinical scenarios in which the maternal antibody screen is positive, accompanied by the likely clinical explanation for the positive screen. It should be readily apparent that the clinical details outlined in each case must be sought out and appreciated by caretakers to identify infants at risk for non-ABO immune-mediated hemolytic disease. The only scenario shown that does not indicate maternal sensitization is that secondary to Rhogam administration. The latter positive anti-D maternal antibody screen finding must be distinguished from the rare occurrence of late Rh-D sensitization by confirming that the mother was anti-D antibody

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**Table 1**

<table>
<thead>
<tr>
<th>Alloantibody</th>
<th>Blood Group</th>
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<tr>
<td>D, C, c, E, e, f, C^W, V</td>
<td>Rhesus</td>
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<tr>
<td>K, k, Kp^a, Js^a</td>
<td>Kell</td>
</tr>
<tr>
<td>Fya, Fyb</td>
<td>Duffy</td>
</tr>
<tr>
<td>Jk^a, Jkb</td>
<td>Kidd</td>
</tr>
<tr>
<td>Xga</td>
<td>Xg</td>
</tr>
<tr>
<td>Le^a, Le^b</td>
<td>Lewis</td>
</tr>
<tr>
<td>S, s, M, N</td>
<td>MNS</td>
</tr>
<tr>
<td>P1</td>
<td>P</td>
</tr>
<tr>
<td>Lu^b</td>
<td>Lutheran</td>
</tr>
</tbody>
</table>
negative before Rhogam administration, and that she did indeed receive the Rhogam. At times, the infant also will have a positive direct Coombs test secondary to maternal Rhogam administration.\textsuperscript{18–20} This finding is generally not thought to indicate a hemolytic risk,\textsuperscript{18–20} albeit one recent case report suggests in rare circumstances it may.\textsuperscript{21} The latter has yet to be confirmed.\textsuperscript{22}

It is also important to note that infants who are Rh-D positive and delivered to women who are Rh-D negative during the first isoimmunized pregnancy (conversion from negative to positive maternal antibody titer in that pregnancy) are at an approximately 20% risk of developing hemolytic disease of the newborn requiring treatment, including the possibility of an exchange transfusion.\textsuperscript{23} This risk likely holds true for all non-ABO alloantibodies. An infant born of a pregnancy during which maternal antibody conversion occurs will by definition carry the foreign antigen and may have a positive direct Coombs test. Such infants are at risk of hemolytic disease of the newborn, should be monitored closely for the development of severe hyperbilirubinemia, with serial TSB measurements, and should not be discharged early from the birth hospital.

\section*{ABO HEMOLYTIC DISEASE}

Hemolytic disease related to ABO incompatibility is generally limited to mothers who are blood group O and infants of blood group A or B.\textsuperscript{1,7–9,24} Although this association exists in approximately 15% of pregnancies, only a subset of such infants will develop significant hyperbilirubinemia.\textsuperscript{1,7–9,24} Defining which infants will be affected is difficult to predict using standard laboratory screening tests.\textsuperscript{1,7–9,24} Ozolek and colleagues\textsuperscript{24} observed that of infants who are type A or B born to mothers who are blood group O, approximately one-third had a positive direct Coombs test, and of those with a positive direct Coombs test, approximately 15% had peak serum bilirubin levels greater than 12.8 mg/dL. Others have reported a higher percentage (approximately 50%) of hyperbilirubinemia (defined by an hour specific TSB >95% on the Bhutani nomogram) in infants who are type A or B who demonstrate a positive direct Coombs test born to mothers who are type O.\textsuperscript{9,25} Regardless, only a subset evidence symptomatic hemolytic disease.\textsuperscript{1,7–9,24,25}

Infants born of ABO-incompatible mother-infant pairs who have a negative direct Coombs test as a group appear to be at no greater risk for developing hyperbilirubinemia than their ABO-compatible counterparts\textsuperscript{24} and the development of significant hyperbilirubinemia in such neonates should prompt an evaluation for a cause other than isoimmunization.\textsuperscript{26} Similarly, infants who are group A or B born to mothers who

\begin{table}[h]
\centering
\caption{Non-ABO alloantibodies reported to cause moderate to severe hemolytic disease of the newborn}
\begin{tabular}{|l|}
\hline
Within Rh system & Anti-D, -c, -C\textsuperscript{w}, -C\textsuperscript{r}, -C\textsuperscript{w}, -e, -E\textsuperscript{w}, -Ce\textsuperscript{w}, -Ce\textsuperscript{r}, -Rh29, -Rh32, -Rh42, -f, -G, -Go\textsuperscript{a}, -Be\textsuperscript{a}, -Evans, -Rh17, -Hr\textsubscript{a}, -Hr, -Tar, -Sec, -JAL, -STEM \\
\hline
Outside Rh system & Anti-LW, -K, -k, -Kp\textsuperscript{a}, -Kp\textsuperscript{b}, -Jk\textsuperscript{a}, -Js\textsuperscript{b}, -Js\textsuperscript{a}, -Ku, -K11, -K22, -Fy\textsuperscript{a}, -Fy\textsuperscript{b}, -M, -N, -S, -s, -U, -PP, -pk, -Di\textsuperscript{b}, -Far, -MUT, -En\textsuperscript{a}, -Hut, -Hil, -Vel, -MAM, -JONES, -HJK, -REIT \\
\hline
\end{tabular}
\end{table}

Table 3
Interpreting maternal antibody status in Rh-D negative women at delivery

<table>
<thead>
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</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>Yes</td>
<td>Positive</td>
<td>Anti-D</td>
<td>Passive anti-D; Rhogam effect; Unlikely*</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>No</td>
<td>Positive</td>
<td>Anti-D</td>
<td>Late sensitization to Rh-D; Yes</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>No</td>
<td>Positive</td>
<td>Anti-D</td>
<td>Early sensitization to Rh-D; Yes</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>Yes</td>
<td>Positive</td>
<td>Non-D antibody</td>
<td>Late sensitization to non-D antigen; Yes</td>
</tr>
</tbody>
</table>

* At times, the infant will also have a positive direct Coombs test secondary to maternal Rhogam administration. This finding is generally not thought to indicate a hemolytic risk, albeit one recent case report suggests in rare circumstances it may. The latter has yet to be confirmed.
are, respectively, incompatible group B or A, are not likely to manifest symptomatic ABO hemolytic disease and fewer than 1% will have a positive direct Coombs test.  

Despite the difficulty in predicting its development, symptomatic ABO hemolytic disease does occur.  

Hyperbilirubinemia seen with symptomatic ABO hemolytic disease is often detected within the first 12 to 24 hours of life along with jaundice (“icterus neonatorum praecox”) and accompanied by microspherocytosis on peripheral blood smear and an increased reticulocyte count.  

Indeed, of infants who were ABO-incompatible direct Coombs positive who developed a TSB greater than 95% on the Bhutani nomogram, 67% did so within the first 24 hours of life and only 1 of 85 such infants developed hyperbilirubinemia after 48 hours.  

Hyperbilirubinemia in symptomatic ABO hemolytic disease is more often than not controlled with intensive phototherapy alone. Only a few affected infants will develop hyperbilirubinemia to levels requiring exchange transfusion, albeit this must be monitored for.  

Some ABO heterospecific mother-infant pairs hold potential for more severe hemolytic disease than others. O-B heterospecificity is associated with greater hyperbilirubinemia risk than O-A, in particular in mothers and neonates of African origin.  

Although there is some conflicting literature regarding the latter, our recent institutional experience and other reports support the assertion that O-B heterospecificity poses some risk in African American individuals. The last 6 double-volume exchange transfusions we performed for symptomatic ABO hemolytic disease have all been in the context of O-B incompatibility and an African American mother. In each case there were markedly elevated maternal immunoglobulin G (IgG) anti-B titers in the range of 1:1024 to 1:2048, as contrasted with the more typical 1:8 to 1:32 titers in mothers who are type O. None of the affected neonates had coexistent glucose-6-phosphate dehydrogenase (G6PD) deficiency. High-titer anti-B IgG also has been reported in the rare case of ABO hemolytic disease in mothers who are group A.  

During robust hemolysis of any cause, the TSB may continue to rise despite intensive phototherapy. Indeed, if not previously considered, failure of phototherapy to produce a prompt decline in TSB should raise the possibility of an underlying hemolytic condition. It follows that in hyperbilirubinemic newborns with symptomatic ABO hemolytic disease, TSB should be monitored during phototherapy to ensure the TSB does not rise to levels that merit exchange transfusion.  

Routine screening of all ABO-incompatible cord blood has been recommended in the past and remains common practice in many nurseries. The literature, however, suggests that such screening is not warranted given the cost and low yield, consistent with the tenor of recommendations of the American Association of Blood Banks, the American Academy of Pediatrics, and the implementation of universal newborn bilirubin screening during the birth hospitalization. A blood type and direct Coombs test is indicated, however, in the evaluation of any newborn with early jaundice (<24 hours of age) and/or clinically significant hyperbilirubinemia, including those treated with phototherapy.  

Red Blood Cell Enzymopathies  

G6PD and pyruvate kinase (PK) deficiency are the 2 most common red-cell enzyme disorders associated with marked neonatal hyperbilirubinemia. Of these, G6PD deficiency is the more frequently encountered and it remains an important cause of kernicterus worldwide, including the United States, Canada, and the United Kingdom, the prevalence in Western countries a reflection in part of immigration patterns and intermarriage. The risk of kernicterus in G6PD deficiency also relates to the potential for unexpected rapidly developing extreme hyperbilirubinemia in this disorder associated with acute severe hemolysis after exposure to oxidative
stress. Reported hemolytic triggers in neonates include among others naphthalene (moth balls), methylene blue, antimalarials, sulfonamides, maternal ingestion of fava beans (favism by proxy), and infection. This mode of G6PD-deficiency–associated hazardous hyperbilirubinemia can result in kernicterus that may not always be preventable.

More than 20% of neonates in the United States pilot kernicterus registry, a database of voluntarily submitted information on 125 infants who developed kernicterus between 1992 and 2004, had G6PD deficiency, as contrasted to an estimated 4% to 7% background population prevalence, reflecting the high prevalence of this condition (12.2% for boys; 4.1% for girls) and risk for hazardous hyperbilirubinemia (TSB ≥30 mg/dL) in newborns of black race. The latter belies the fact that black race is associated with a lower risk of TSB in the ranges of 13 to 15 mg/dL, 16 to 19 mg/dL, and ≥20 mg/dL. This apparent discrepancy is best explained by G6PD deficiency itself and its potential to predispose to acute hemolysis, resultant rapid rise in TSB, and hazardous hyperbilirubinemia.

G6PD deficiency is an X-linked enzymopathy affecting hemizygous males, homozygous females, and a subset of heterozygous females (via X chromosome inactivation). Hemolysis in G6PD deficient neonates, however, may be self-limited and overt anemia not necessarily noted, masked by other factors that modulate hemoglobin concentration in the immediate newborn period. Severe jaundice rather than anemia may predominate in the clinical presentation. In other neonates, the combination of G6PD deficiency with hepatic bilirubin conjugation defects of Gilbert syndrome significantly increases the risk of hyperbilirubinemia. Pediatricians must have a high index of suspicion for G6PD deficiency in populations with increased risk (Mediterranean region, Africa, the Middle East, Asia), and in particular the African American neonate, with significant hyperbilirubinemia.

PK deficiency typically presents with jaundice, anemia, and reticulocytosis. Such jaundice may be severe, as reflected by one series in which a full third of affected infants required exchange transfusion to control hyperbilirubinemia and kernicterus in PK deficiency, and is well described. The diagnosis of PK deficiency is often difficult, as the enzymatic abnormality is frequently not simply a quantitative defect, but in many cases involves abnormal enzyme kinetics or an unstable enzyme that decreases in activity as the red cell ages. It is inherited as an autosomal recessive disorder, but notably, most affected individuals are compound heterozygotes; that is, they express 2 different disease-causing alleles: 1 maternal and 1 paternal in origin. The diagnosis of PK deficiency should be considered whenever persistent significant hyperbilirubinemia and a picture of nonspherocytic, Coombs-negative hemolytic anemia is observed, particularly in populations in which consanguinity is prevalent, including newborns of Amish descent and in other remote communities where intermarriage is prevalent.

RED BLOOD CELL MEMBRANE DEFECTS

Establishing a diagnosis of RBC membrane defects is classically based on the development of Coombs-negative hyperbilirubinemia, a positive family history, and abnormal RBC smear, albeit it is often difficult because newborns normally exhibit a marked variation in red-cell membrane size and shape. Spherocytes, however, are not often seen on RBC smears of hematologically normal newborns and this morphologic abnormality, when prominent, may yield a diagnosis of hereditary spherocytosis (HS) in the immediate neonatal period. Given that approximately 75% of families affected with hereditary spherocytosis manifest an autosomal dominant
phenotype, a positive family history can often be elicited and provide further support
for this diagnosis. More recently, Christensen and Henry highlighted the use of an
elated mean corpuscular hemoglobin concentration (MCHC) \( \geq 36.0 \, \text{g/dL} \) and/or
elevated ratio of MCHC to mean corpuscular volume, the latter they term the “neonatal HS index” \(-0.36, \text{likely} >-0.40 \)\(^{28,55} \) as screening tools for HS. An index of greater than 0.36 had 97% sensitivity, greater than 99% specificity, and greater than 99% negative predictive value for identifying HS in neonates. Christensen and colleagues\(^ {28} \) also provided a concise update of morphologic RBC features that may be helpful in diagnosing this and other underlying hemolytic conditions in newborns.

The diagnosis of HS can be confirmed using the incubated osmotic fragility test when coupled with fetal red-cell controls or eosin-5-maleimide flow cytometry. One must rule out symptomatic ABO hemolytic disease by performing a direct Coombs test, as infants so affected also may manifest prominent microspherocytosis. Moreover, HS and symptomatic ABO hemolytic disease can occur in the same infant and result in severe hyperbilirubinemia and anemia.

Of other red-cell membrane defects, only hereditary elliptocytosis, stomatocytosis, and infantile pyknoticosis have been reported to exhibit significant hemolysis in the newborn period.\(^ {7,59-61} \) Hereditary elliptocytosis and stomatocytosis are both rare. Infantile pyknoticosis, a transient red-cell membrane abnormality manifesting itself during the first few months of life, is more common. The pyknocyte, an irregularly contracted red cell with multiple spines, can normally be observed in newborns, particularly premature infants, in whom up to approximately 5% of red cells may manifest this morphologic variant. In newborns affected with infantile pyknoticosis, up to 50% of red cells exhibit the morphologic abnormality and this degree of pyknocytosis is associated with jaundice, anemia, and reticulocytosis. Infantile pyknocytosis can cause hyperbilirubinemia that is severe enough to require control by exchange transfusion. Red cells transfused into affected infants become pyknoytic and have a shortened life span, suggesting that an extracorpuscular factor mediates the morphologic alteration. Whatever the mechanism underlying infantile pyknocytosis, the disorder tends to resolve after several months of life. Pyknocytosis also may occur in other conditions, including G6PD deficiency and hereditary elliptocytosis, and these must be excluded before a diagnosis of infantile pyknoticosis is made.

**HEMOGLOBINOPATHIES**

Defects in hemoglobin structure or synthesis are rare disorders that infrequently manifest themselves in the neonatal period. Of these, the alpha-thalassemia syndromes are the most likely to be clinically apparent in newborns. Each human diploid cell contains 4 copies of the alpha-globin gene and, thus, 4 alpha-thalassemia syndromes have been described reflecting the presence of defects in 1, 2, 3, or 4 alpha-globin genes. Silent carriers have 1 abnormal alpha-globin chain and are asymptomatic. Alpha-thalassemia trait is associated with 2 alpha-thalassemia mutations and in neonates is not associated with hemolysis. Alpha-thalassemia trait, however, is common in black populations and can be detected by a low mean corpuscular volume of less than 95 \( \mu^3 \) (healthy infants 100 to 120 \( \mu^3 \)). Hemoglobin H disease results from the presence of 3 thalassemia mutations and can cause hemolysis and anemia in neonates. Hemoglobin H disease results from the presence of 3 thalassemia mutations and can cause hemolysis and anemia in neonates. Homozygous alpha-thalassemia (total absence of alpha-chain synthesis) results in profound hemolysis, anemia, hydrops fetalis, and almost always stillbirth or death in the immediate neonatal period.

The pure beta-thalassemias do not manifest themselves in the newborn period and the gamma-thalassemias are (1) incompatible with life (homozygous form), (2)
associated with transient mild to moderate neonatal anemia if 1 or 2 genes are involved that resolves when beta-chain synthesis begins, or (3) in combination with impaired beta-chain synthesis, associated with severe hemolytic anemia and marked hyperbilirubinemia.64

**DIAGNOSIS OF HEMOLYSIS**

It is increasingly apparent that the diagnosis of hemolysis in neonates remains problematic and hemolytic conditions as a result are underrecognized. Several reports demonstrate that the etiology of extreme (>25 mg/dL) or hazardous (>30 mg/dL) hyperbilirubinemia is often unclear and not identified,10,43,65 when almost assuredly a hemolytic process is an important contributor to its genesis in many if not most cases.4,9,66 Indeed, Christensen and colleagues66 recently reported that when an exhaustive search, including “next-generation” sequencing of a panel of hematologic and hepatic gene variants involved in neonatal hyperbilirubinemia was performed, a specific diagnosis was made in all infants with extreme hyperbilirubinemia (TSB >25 mg/dL) and without exception in this cohort was hemolytic in nature. Because the catabolism of heme derived from red-cell hemoglobin produces equimolar amounts of carbon monoxide (CO) and bilirubin, the point-of-care measurement of end-tidal CO corrected for ambient CO (ETCOc) may prove a useful adjunct in identifying infants with hemolysis at risk for subsequent severe hyperbilirubinemia and in further stratifying phototherapy and exchange transfusion treatment criteria.67,68

**HEMOLYSIS AND NEUROTOXICITY RISK**

Although bilirubin-induced brain injury is complex and multifactorial in nature,69 the clinical impression that hemolysis potentiates bilirubin neurotoxicity in neonates is long-standing, dating back to the early work on Rh isoimmunization70 and subsequent debates on the TSB treatment thresholds for exchange transfusion in hemolytic and nonhemolytic hyperbilirubinemia.71,72 The neurotoxicity intensifying effect of hemolysis has recently been reaffirmed.10–12 In one such study, Gamaleldin and coworkers11 showed that the TSB threshold for identifying 90% of infants with bilirubin encephalopathy was 25.4 mg/dL (434 μmol/L) in infants with neurotoxicity risk factors (n = 138; primarily hemolytic disorders) as contrasted with 31.5 mg/dL (539 μmol/L) in those without (n = 111).11 The presence of Rh hemolytic disease alone greatly increased the risk for bilirubin encephalopathy (odds ratio 48.6; 95% confidence interval 14–168).11

Other risk factors that might increase the risk of brain damage in an infant who has severe hyperbilirubinemia are shown in Box 2.14 Treatment is recommended at a lower TSB when any of the neurotoxicity risk factors is present.13,14

**Jaundice Evaluation and Management**

The identification, evaluation, and management of neonatal jaundice are outlined in detail in the 2004 American Academy of Pediatrics hyperbilirubinemia practice guideline and is beyond the scope of the current review.13 An update with clarifications published in 2009 highlighted the utility of universal bilirubin screening before birth hospitalization discharge and provided an algorithm for management and follow-up according to the predischarge bilirubin measurement(s), gestation, and risk factors for subsequent severe hyperbilirubinemia.14 Phototherapy and exchange transfusion remain the mainstays of treatment with intervention thresholds based on hour specific TSB measurement, gestation, and risk factors for neurotoxicity.13,14 Phototherapy can be effectively administered in
the newborn nursery, including during rooming-in, skin-to-skin contact, and breast-feeding. Szucs and Rosenman recently highlighted this family-centered method of phototherapy delivery in the mother’s room, another example of which is shown in Fig. 1. Exchange transfusion, on the other hand, because of attendant risks and the need for intensive monitoring during the procedure, must be performed in the neonatal intensive care unit (NICU).

ANEMIA

The causes of neonatal anemia (defined here as a hematocrit at birth <39) are numerous and diagnostically categorized as those secondary to hemolysis, hemorrhage, and impaired RBC production. In the newborn nursery, hemolytic disorders

<table>
<thead>
<tr>
<th>Box 2 Risk factors for bilirubin neurotoxicity</th>
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<tbody>
<tr>
<td>Isoimmune hemolytic disease</td>
</tr>
<tr>
<td>G6PD deficiency</td>
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<tr>
<td>Asphyxia</td>
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<tr>
<td>Sepsis</td>
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<tr>
<td>Acidosis</td>
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<tr>
<td>Albumin less than 3.0 g/dL</td>
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</table>


Fig. 1. Infant receiving family-centered care phototherapy delivery in mother’s room and in skin-to-skin contact with father. Protective eye cover is worn by both the infant and parent.
are the most frequently encountered cause for anemia and any hemolytic condition can lead to anemia. In this regard, practitioners must monitor for progressive anemia in alloimmune-mediated disease and subsequent later need for packed RBC transfusion in the weeks after birth hospitalization discharge.¹

Impaired RBC production is a rare cause of neonatal anemia, with the most frequent current etiology being fetal infection with parvovirus B-19; an important cause of fetal anemia and hydrops fetalis. If the degree of fetal anemia is modest and chronic in nature, such infants may appear otherwise well at birth. Pure RBC aplasia (Diamond-Blackfan anemia) is exceedingly uncommon.

Perinatal hemorrhage is the third diagnostic category and a commonly observed cause of neonatal anemia, particularly that secondary to fetomaternal hemorrhage and twin-twin transfusion syndrome. Like other etiologies, if the degree of anemia is modest and chronic in nature, such infants will not be compromised from a cardiopulmonary standpoint and will appear well without pallor. If fetal-neonatal blood loss is extensive and/or acute (regardless of cause), infants will be ill-appearing and managed in the NICU. The diagnosis of fetomaternal hemorrhage is made using Kleihauer-Betke testing on maternal blood. This test is based on the property of fetal hemoglobin (as opposed to adult hemoglobin) to resist elution from the RBC by strong acid to detect fetal RBCs in the maternal circulation. Twin-twin transfusion syndrome should be suspected in monochorionic twins and is often diagnosed in utero.

POLYCYTHEMIA

Polycythemia (venous hematocrit ≥65%) is seen in infants across a range of conditions associated with active erythropoiesis or passive transfusion.⁷⁶,⁷⁷ They include, among others, placental insufficiency, the infant of a diabetic mother, recipient in twin-twin transfusion syndrome, and several aneuploidies, including trisomy 21.⁷⁶,⁷⁷ The clinical concern related to polycythemia is the risk for microcirculatory complications of hyperviscosity. However, determining which polycythemic infants are hyperviscous and when to intervene is a challenge. Microviscometer measurements on blood are often not clinically available and the generalizability of normative data limited by several variables, including the site and time of sampling. Clinicians therefore screen for the presence of abnormal signs of hyperviscosity several of which are nonspecific and seen in other clinical contexts⁷⁶ and include lethargy, hypotonia, jitteriness, respiratory distress, hypoglycemia, and cyanosis. A hematocrit measurement should be part of the evaluation of infants with these signs to rule out the presence of polycythemia.

The management of the polycythemic neonate remains highly controversial because of the lack of evidence showing that aggressive treatment improves long-term outcome.⁷⁶,⁷⁷ Most recent recommendations suggest limiting partial exchange transfusion to those polycythemic neonates with abnormal signs.⁷⁶,⁷⁷ Partial volume exchange transfusion, if indicated, should be performed as early as possible and done so in the NICU with intensive monitoring. Polycythemia also is associated with increased risk for hyperbilirubinemia.

THROMBOCYTOPENIA

Thrombocytopenia (platelet count <150,000/μL) occurs in fewer than 1% of all newborns and is far more common in sick neonates in the NICU than the otherwise healthy-appearing term or late-preterm neonate in the newborn nursery. Analogous to anemia, the causes of thrombocytopenia can be grouped into (1) increased destruction, (2) loss (consumption), and (3) decreased production. For the otherwise healthy-appearing full-term neonate in the newborn nursery during the birth hospitalization,
the most common etiology is immune-mediated destruction secondary to alloimmune and autoimmunity-mediated mechanisms.\textsuperscript{78,79} Indeed, the classic presentation of such disorders is a term neonate who appears well but manifests petechiae or bruising and has isolated thrombocytopenia.\textsuperscript{78,79}

Neonatal alloimmune thrombocytopenia (NAIT) is often severe (median 19,000/mm\textsuperscript{3}, range 1000–51,000 mm\textsuperscript{3})\textsuperscript{78} and affected newborns are frequently firstborns.\textsuperscript{78} Fetomaternal incompatibility for human platelet antibodies 1a, 5b, and 15b account for 95% of NAIT with HPA-1a the most common.\textsuperscript{78} Such infants are at risk for intracranial hemorrhage and should have neuroimaging to rule out this complication. Monitoring and treatment will require transfer to the NICU.

In contrast, autoimmune-mediated thrombocytopenia results from the passage of maternal antibodies directed to both maternal and infant platelet antigens and is associated with a history of or concurrent maternal thrombocytopenia and the diagnosis of a maternal autoimmune disorder, including among others maternal immune thrombocytopenic purpura, lupus, or other collagen vascular disorder.\textsuperscript{79} In some cases, the maternal diagnosis is first made during the evaluation of her thrombocytopenic neonate.\textsuperscript{79}

Other etiologies of thrombocytopenia encountered in the newborn nursery include congenital intrauterine infection and consumptive processes, such as vascular tumors in Kasabach-Merritt syndrome and renal vein thrombosis.\textsuperscript{78,79} Inherited etiologies include those associated with aneuploidies (eg, trisomy 21), Fanconi anemia, thrombocytopenia absent radii syndrome, and congenital amegakaryocytic thrombocytopenia.\textsuperscript{78,79} Thus, all thrombocytopenic infants in the healthy-infant nursery should have a careful examination for splenomegaly and lymphadenopathy (congenital infection), limb abnormalities, and cutaneous hemangiomas.\textsuperscript{78} Infants with severe thrombocytopenia should be referred to the NICU for evaluation, monitoring, and management.

REFERENCES


