Hemolysis in Preterm Neonates

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KEYWORDS

• Bilirubin • Anemia • Prematurity • End-tidal carbon monoxide • Haptoglobin
• Next-generation DNA sequencing

KEY POINTS

- Identifying hemolysis in premature neonates can be more difficult than in term neonates; recommendations for identifying hemolysis are presented.
- When hemolysis is recognized in a premature neonate, caregivers should be alerted to the possibility of (1) a relatively rapid rise in total serum/plasma bilirubin, (2) hyperbilirubinemia that is relatively slow to abate with phototherapy, and (3) hyperbilirubinemia that is likely to rebound after phototherapy is discontinued.
- The bilirubin load a preterm neonate receives from a donor red blood cell transfusion is influenced by the percentage of donor cells lysed during storage before the transfusion.
- The genetic conditions that cause hemolytic jaundice in term neonates, such as erythrocyte cytoskeletal protein mutations and enzymatic defects, also occur in premature neonates.

WHAT IS HEMOLYSIS?

When erythrocytes emerge from the marrow (or, in preterm infants, from the liver and the marrow) into the blood, they typically remain in circulation for a certain number of days. This length of time is known as the red blood cell (RBC) life span.[1,2] In adults, the RBC life span is 100 to 120 days.[3,4] In term neonates, it is approximately 60 to 80 days.[5] In preterm infants, the RBC life span is shorter still and is likely shorter in

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proportion to gestational age (GA); however, the details of this relationship remain unclear.[3–7] The definition of hemolysis is an RBC life span significantly shorter than it should be and associated with increased bilirubin production.[1,2]

The process of natural termination of the RBC life span in circulation is a physiologic process known as senescence. In contrast, hemolysis is a pathologic shortening of the RBC life span due to a wide range of conditions, including genetically based abnormalities in RBC structure or function,[8] antibodies attached to erythrocytes leading to premature removal, or issues extrinsic to RBCs. These issues include physical disruption; injury by infectious agents, temperature, or chemicals; or injury by disruption from tethering on fibrin strands as occurs in disseminated intravascular coagulation (DIC). Extravasation of blood into tissues is another cause of hemolysis that is encountered in bruising, cephalohematoma, subgaleal hemorrhages, or intraventricular hemorrhages because the RBCs in the environment of tissues are metabolized much more rapidly than had they remained in circulation.

The consequence of any hemolytic process is bilirubin load that is larger than normal. This is because heme is metabolized to bilirubin.[9,10] Conceptually, the bilirubin load is the amount of bilirubin that must be taken up by hepatocytes, conjugated, and excreted. When hemolysis produces an excessive bilirubin load, which cannot be metabolized efficiently by normally functioning bilirubin metabolic mechanisms, the total serum/plasma bilirubin (TB) concentration rises and may result in hemolytic jaundice that could be associated with hemolytic anemia.[11–13]

When hemolysis is recognized as the cause of jaundice and/or anemia in a preterm infant, caregivers should be aware of the possibility that (1) TB can rise rapidly, (2) the hyperbilirubinemia may be somewhat slow to fall with phototherapy, and (3) the hyperbilirubinemia is more likely to rebound after phototherapy is discontinued.[9,10]

HOW IS HEMOLYSIS RECOGNIZED IN A JAUNDICED PRETERM INFANT?

In neonates, a set of laboratory tests can be used to identify the presence of a hemolytic process, although they are often limited by their individual specificity.[14] Unfortunately, when applied to preterm infants, these tests all have additional limitations compared with their use in term neonates. **Table 1** lists the tests typically used to diagnose hemolysis in infants and children, and reviews the pitfalls or problems when applying these tests to preterm neonates.

When heme is metabolized to bilirubin, equimolar amounts of carbon monoxide (CO) is generated and exhaled.[11] Therefore, measuring the end-tidal or exhaled breath CO concentration, corrected for inhaled CO (ETCOc) provides a quantitative measurement of the hemolytic rate.[11,12,15,16] It was previously reported that in term neonates the upper reference range level of ETCOc during the first week after birth is 1.7 ppm but in preterm infants this upper range value is not yet known.[15,16] Also, preterm infants might have tachypnea, and the presently available ETCOc monitor (CoSense, Capnia Inc, Redwood Shores, CA, USA) does not consistently provide data if the respiratory rate exceeds 60 breaths per minute. Also, the present instrumentation is not usable for neonates on mechanical ventilation or continuous positive airway pressure.

Many of the tests used to identify hemolysis have not been specifically validated in preterm infants. Values for reticulocytes, immature reticulocyte fraction, and nucleated RBCs are definitely different in preterm than in term neonates, and they vary with GA at birth and with postnatal age.[17,18]

Erythrocyte morphology, judged by light microscopy, is challenging in preterm infants because the erythrocytes tend to have greater percentages of abnormal forms than those found in term neonates. However, careful examination for the presence