Hyperbilirubinemia

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KEYWORDS

• Hyperbilirubinemia • Jaundice • Kernicterus
• Phototherapy • Exchange transfusion

Hyperbilirubinemia is the most common condition requiring evaluation and treatment in newborns.[1] The clinical manifestation of hyperbilirubinemia—jaundice—occurs in 60% of normal newborns and nearly all preterm infants.[2–5] As compared with conditions such as persistent pulmonary hypertension of the newborn and congenital heart disease, which require advanced pharmacologic and technologic treatment strategies, hyperbilirubinemia seems to be overshadowed and may lose the attention it deserves as a condition that has potentially devastating effects. So severe are its consequences that the American Academy of Pediatrics (AAP) issued two practice guidelines[5,6] on the management of hyperbilirubinemia and the Joint Commission issued two sentinel event alerts[7,8] on kernicterus. Nurses must be vigilant when caring for babies with ''just jaundice'' by monitoring bilirubin levels, identifying infants at risk for developing severe hyperbilirubinemia, and implementing prescribed treatment effectively when indicated.

BILIRUBIN SYNTHESIS, TRANSPORT, CONJUGATION, AND EXCRETION

Synthesis

Bilirubin is produced by the breakdown of heme-containing proteins (**Fig. 1**). In newborns, 75% of all bilirubin comes from the catabolism of erythrocyte hemoglobin.[9] The remaining 25% of bilirubin is produced from the breakdown of other proteins, such as myoglobin, cytochromes, catalase, and peroxidases. Bilirubin synthesis starts with the lysis of senescent red blood cells (RBCs) in the reticuloendothelial system. When RBCs are degraded, heme is released from hemoglobin. Heme oxygenase, an enzyme found in most cells of the body except anucleated RBCs, catalyzes the first step in the breakdown of heme, yielding equimolar parts of biliverdin, iron, and carbon monoxide (CO).[10,11] Iron is conserved for new heme synthesis, and most of the CO is excreted by the lungs. From this initial step arise two points that have clinical implications discussed in more detail later: (1) Heme oxygenase is the rate limiting step for bilirubin production; inhibiting heme oxygenase limits the amount of bilirubin produced. (2) CO production is linked to bilirubin synthesis and, if measured, can serve as a proxy for the extent of hemolysis.

Biliverdin, a water-soluble, nontoxic, blue-green pigment is then rapidly converted by a second enzyme, biliverdin reductase, to indirect (unconjugated) bilirubin (4Z-15Z-bilirubin-IXa). This bilirubin isomer is orange-yellow, fat soluble, and not readily excreted in the bile or urine. Each gram of hemoglobin yields 35 mg of bilirubin.[9]

Transport and Hepatic Uptake

When released from the reticuloendothelial system, bilirubin is insoluble in water and must be transformed to a form that the body can excrete. Unconjugated bilirubin binds reversibly with albumin for its journey to the liver, where it is conjugated. The bilirubin-albumin (B/A) complex is vulnerable to separation by factors including metabolic derangements, such as acidosis and hypoxia, hypothermia, infection, and fatty acids. Drugs that decrease B/A binding include salicylates, sulfonamides, sodium benzoate, and indomethacin. The contribution that any of these make to creating severe hyperbilirubinemia is not thoroughly understood. Circulating bilirubin that is not bound to albumin is called ''free bilirubin,'' which is the bilirubin that can enter the brain and cause neuronal injury.

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Crit Care Nurs Clin N Am 21 (2009) 97–120
doi:10.1016/j.ccell.2008.11.001
0899-5885/08/$ – see front matter

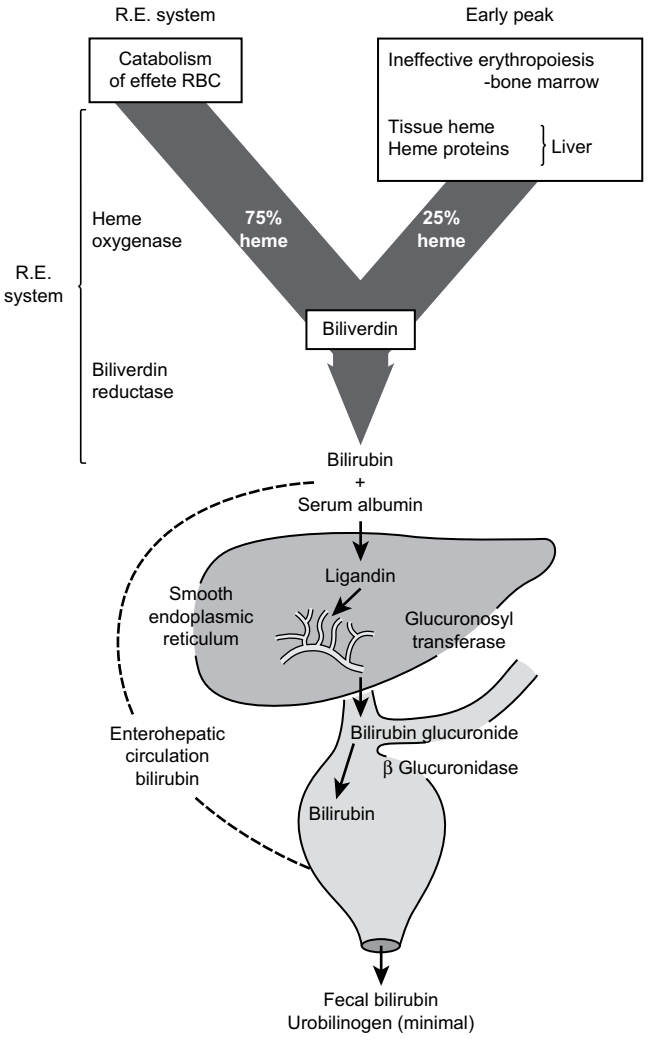

Fig. 1. Bilirubin synthesis, transport, and excretion. *Abbreviations:* RBC, erythrocytes; RE, reticuloendothelial. (*Adapted from* Maisels MJ. Jaundice. In: MacDonald MG, Mullett MD, Seshia MMK, editors. Avery's neonatology: pathophysiology & management of the newborn. 6th edition. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 770; with permission.)

Conjugation

When the B/A complex reaches the plasma membrane of the hepatocyte, bilirubin detaches from albumin and enters the liver cell. Inside the hepatocyte, bilirubin binds with other carrier proteins to be carried into the endoplasmic reticulum for conjugation. Protein Y is the primary carrier; protein Z is used during times of increased bilirubin load to the liver. Conjugation occurs inside the smooth endoplasmic reticulum, where each molecule of bilirubin combines with one or two molecules of glucuronic acid to produce bilirubin monoglucoronide and diglucoronide pigments. In children and adults, approximately two thirds of the monoglucuronides are conjugated to diglucoronides. In neonates, monoglucoronide is the predominate conjugate.[12,13] Conjugated bilirubin is water soluble and can be excreted into the bile and eventually eliminated from the body. Uridine diphosphoglucuronate glucuronosyltransferase (UGT) is the liver enzyme responsible for conjugation and formation of the glururonides. Sufficient supplies of glucose and oxygen are required for proper conjugation to occur.

Excretion

Once conjugated, bilirubin is readily excreted by the hepatocyte into the bile canaliculi as bilirubin mono- or diglucuronide. This water-soluble conjugated bilirubin is then emptied into the small intestine via the common bile duct. Conjugated bilirubin is not absorbed in the small intestine. The mono- and digluronides are relatively unstable molecules, however, and can be converted easily to unconjugated bilirubin and absorbed by the intestine. In the presence of mild alkaline conditions, such as exists in the jejunum and duodenum, and the