Improving the Management of Hyperbilirubinemia in a Limited-Resource Area

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Chapter 1
Introduction

Bilirubin Metabolism

Jaundice is a common clinical finding in the newborn infant. Visible jaundice is seen in approximately one third of all newborn infants. In most cases, clinical jaundice represents a transient elevation of serum bilirubin due to increased bilirubin production and incomplete maturation of bilirubin metabolism and excretion. In some cases, however bilirubin levels may increase to reach potentially dangerous levels.

Bilirubin is the principal breakdown product of heme. Its main source (75%) is hemoglobin from senescent red cells, a smaller amount (25%) is derived from ineffective red cell production and other heme-containing proteins. The first step in heme degradation is the extraction of carbon monoxide from the heme ring by the enzyme heme oxygenase, producing biliverdin. The enzyme heme oxygenase is widespread available in many tissues, like brain, liver, spleen, and kidney. Biliverdin is converted into water-insoluble, unconjugated bilirubin by biliverdin reductase (1) (Figure 1).

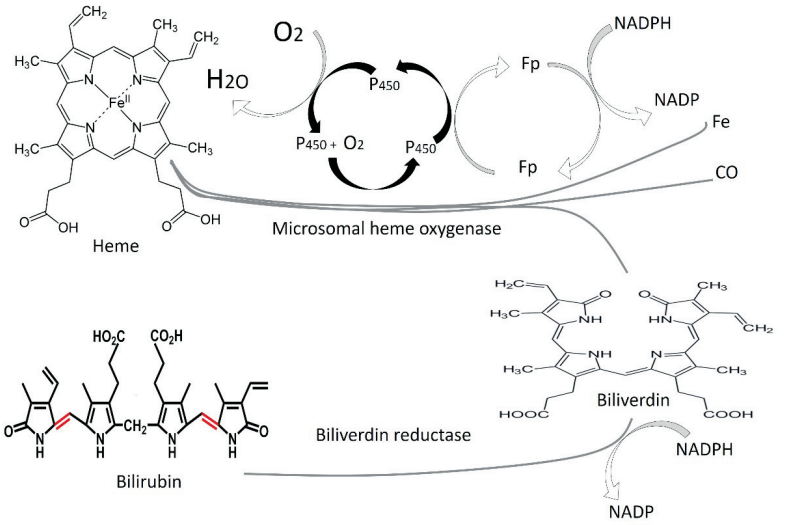

Figure 1. Heme degradation and synthesis of Bilirubin Reproduced from (1), with permission

Unconjugated bilirubin in serum is almost exclusively the 4Z and 15Z isomer, bound to albumin and transported to the liver. The apparent

lipophilic nature of unconjugated bilirubin is explained by the intramolecular hydrogen bonds between the carboxyl and lactam groups of bilirubin. Unconjugated bilirubin, bound and transported by albumin, adheres with ligandin (Y-protein) and hepatocellular surface receptor in the liver to get engulfed into the intracellular compartment (2). Inside the cell compartment, another enzyme, Uridine-di-phosphate-glucuronosyl-transferase (UDPGT), mediates the conjugation process of bilirubin to form, in newborn infants, bilirubin monoglucuronide which is water soluble. When fully mature, the conjugating system catalyses the addition of a second glucuronide molecule to form diglucuronide. Conjugated bilirubin is water-soluble, unlike its precursor. It is also known as direct bilirubin and is secreted in bile by the MRP2 transporter. Via the gall bladder, it passes to the gastrointestinal tract to be discarded with the stool. In the gastro-intestinal tract bilirubin may undergo another route to be re-absorbed and re-enter the bloodstream instead of getting lost via the stool. To return into bloodstream, direct bilirubin is reversely converted into indirect bilirubin once again by β-glucuronidase. This process of re-absorption and re-uptake in the liver is called enterohepatic circulation (3) (Figure 2).

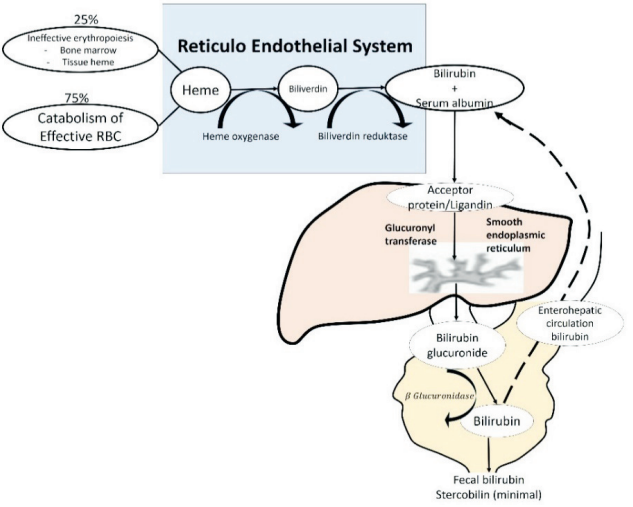

Figure 2. Bilirubin metabolism Reproduced from (3), with permission

There are several explanations for the increased incidence of jaundice in newborn infants. First, an increased production of bilirubin. Fetal red cells

have a shorter life span compared to adult red cells, 70-90 days compared to 115-120 days. Fetal red cells contain fetal haemoglobin, HbF, that can bind oxygen at low oxygen levels. After birth, oxygen tension increases and red cells with fetal haemoglobin are replaced by more mature red cells. Higher than physiological breakdown of red cells can be due to blood group incompatibility, like ABO and Rhesus incompatibility and sepsis in the newborn. Alterations in cell membrane structure like sickle cell deformity and spherocytosis also cause a decreased red cell life span. Secondly, the process involved in bilirubin metabolism are not yet fully developed during the first days after birth. This maturation process can take a few days. Another factor is the lower albumin level seen in newborn infants. Finally, the enterohepatic circulation might be increased due to the absence of a normal gastro-enteral bacterial flora. An overview of potential causes of in neonatal jaundice is shown in Table 1.

Neonatal hyperbilirubinemia

The term hyperbilirubinemia is applied to conditions in which the newborn shows evidence of clinical jaundice that appears earlier than expected, increases above the expected limits of normal accumulation of unconjugated bilirubin in the circulation for age, or persists beyond the point at which spontaneous resolution of physiologic jaundice is expected. Physiological jaundice is characterized by a jaundice that has a peak in term born infants at the third or fourth day after birth and remains below a level that might cause damage to the infant. The peak in bilirubin levels in preterm infants is seen at an earlier age than in term infants. Most neonatal hyperbilirubinemia appears to be an exaggeration of the normal unconjugated bilirubin concentration in the circulation, most cases present only a mild departure from the statistical limits of normal. A large study conducted in the USA between 1959 and 1966 showed that bilirubin levels above 15 mg/dl were found in 4% of infants with a weight above 2500 g and in 17% in infants with a birth weight below 2500 g (4). There are many causes for neonatal hyperbilirubinemia, as outlined in table 1. A structured approach to investigate the cause of hyperbilirubinemia is indicated, given the high number of causes for the hyperbilirubinemia. Mild hyperbilirubinemia is more frequently seen in breastfed compared with formula fed infants. The maximal bilirubin level is reached 1-2 day later in the breastfed

infant. A potential cause for the breastfed jaundice might be a lower fluid intake during the first days after birth. Various studies observed signs of dehydration in breastfed infants in early life. Another cause may be an increased entero-hepatic circulation due to a low milk intake and consequent constipation. Breastfeeding jaundice, mostly occurring in the first week of life, is associated with a depletion in calory intake and/or inadequate feeding frequency which result in increased bilirubin reabsorption in intestines, which can be prevented by advocating mothers to routinely nurse the newborn. Meanwhile, breast milk jaundice, with later onset and a more protracted course, is more relatable to breast milk abnormal factors.

Bilirubin toxicity

Unconjugated bilirubin is toxic to the central nervous system of the newborn infant. Clinically, two types of bilirubin toxicity exist, acute and late. The exact mechanism of this toxicity is unknown (5). The direct association between severe unconjugated hyperbilirubinemia and neurological damage, called kernicterus, was first demonstrated convincingly in 1952 by the studies of Hsia (6) and Mollison (7) in 1954. If an infant with kernicterus passes away in the neonatal period, coronal sectioning of the brain reveals a yellow colorization of the hippocampus and the basal ganglia. A study from Mollison from 1954 showed an increased incidence of kernicterus in infants with haemolytic disease and a bilirubin level above 19 mg/dl. The clinical manifestations of acute bilirubin toxicity are usually seen in the first week of life and include lethargy, poor feeding, high pitched cry, vomiting and hypotonia. Later, irritability, hypotonia, opisthotonos and seizures are seen. Late effects in survivors include severe neurological sequelae, hearing loss, paralysis of upward gaze and dental dysplasia.

The susceptibility of infants to develop bilirubin toxicity seems dependent on several factors. Term infants with brain damage, for instance due to perinatal hypoxia, are more vulnerable. There are also indications that the presence of haemolytic disease increases the risk for neurological damage. Preterm infants are more susceptible for bilirubin toxicity than full-term infants. Despite many studies, there are no clear cut-off values that can distinguish between bilirubin levels that are safe and that are dangerous. Hypoalbuminemia can be one of the risk factors of bilirubin neurotoxicity due to increasing levels of free bilirubin. Under circumstances

at physiological pH, bilirubin is water in-soluble. Hence, bilirubin must be metabolized in the liver, i.e., conjugated, in order to be disposed of. Due to the high affinity of albumin for unconjugated bilirubin (8), it is bound by albumin throughout the circulation and carried to the liver (9). Neurological damage is the result of the small fraction of unconjugated bilirubin that does not bind to albumin, so-called free bilirubin. Free bilirubin may cross the blood-brain barrier and result in neurotoxicity. Free bilirubin, normally present at levels at less than 0.1% of total plasma bilirubin (10), is able to pass through the blood-brain barrier and disrupt several essential cellular functions leading to neuronal cell death (10, 11). The ratio of total bilirubin and albumin is therefore considered being among the parameters representing free bilirubin circulating within the blood vessels. An albumin level of less than 3g/dl is considered to be related to a lower effect of phototherapy (11).

Treatment of hyperbilirubinemia

Because the risk that bilirubin levels may cause cerebral damage in case of high plasma levels, methods are developed to reduce bilirubin levels or to prevent them to reach dangerous levels. In the past administration of albumin to bind unconjugated bilirubin and the administration of phenobarbitone have been used, but they showed little or no effect. Nevertheless, albeit not useful in acute management, administering phenobarbitone seems rewarding as adjunct therapy in exaggerated unconjugated hyperbilirubinemia and some other conditions such as Gilbert's syndrome. Albumin can be taken into account in settings of albumin level less than 3 mgdL and administered before exchange transfusion. Presently, there is one method to prevent and two methods to treat hyperbilirubinemia. The method to prevent hyperbilirubinemia is Phototherapy. Blue light (425-475 nm) converts unconjugated bilirubin into isomeric and more water-soluble forms that can be excreted from the liver without conjugation. The production of photo-bilirubin depends on the intensity and wavelength distribution of light, the distance to the skin and the amount of skin exposed. Phototherapy is both used to prevent bilirubin to reach dangerous levels and to reduce levels that might be dangerous (12). Another method to rapidly decrease toxic bilirubin levels is an exchange transfusion where the blood of the infant is exchanged with blood from a healthy donor (13).

Guidelines for prevention and treatment of hyperbilirubinemia

Although no clear cut-off values for the discrimination between dangerous and non-dangerous bilirubin levels exist, guidelines have been developed to assist health care workers dealing with newborn infants when to start phototherapy or to consider an exchange transfusion (14). Guidelines have mainly been developed for high income countries, while hyperbilirubinemia is more frequent in low-middle-income countries (LMICs). The guidelines developed for high income countries might not be applicable to LMICs as options to monitor the bilirubin level and methods to deliver prevention and treatment might be limited in middle- and low-income countries. Guidelines especially developed for these countries therefore are needed (15).

Hyperbilirubinemia in low-middle-income countries

It is estimated that 60-80% of cases of hyperbilirubinemia with mortality and long-term morbidity worldwide are found in low-middle income countries (16,17). A study that evaluated the burden of severe neonatal jaundice worldwide found that the highest incidence of neonatal jaundice was found in Africa (667.8 infants per 10,000 live birth), followed by South-east Asia (251.3 infants per 10,000), Eastern Mediterranean (155.7), Western Pacific (9.4), Americas (4.4) and European region at 3.7 per 10,000 live births (18). A recent study showed that exchange transfusions are presently hardly done in high income countries, while they are performed regularly in developing countries. The use of early and intense phototherapy has diminished the need for exchange transfusions in the developed countries (19).

There are several explanations for these differences in incidence of hyperbilirubinemia worldwide. The health care facilities in high income countries are well developed and well equipped to detect and treat neonatal jaundice early on. In these countries, patients can be seen in the first days after birth by experienced and well-equipped health care workers. Jaundice can be detected at an early stage and treatment can be given when needed (20). Guidelines for the early detection and treatment of hyperbilirubinemia are available in most countries. In low-middle income countries it is more difficult to detect jaundice at an early stage, follow-up of infants is often difficult or impossible and methods to measure bilirubin

levels are not available. There might also be a lack of adequate devices to treat hyperbilirubinemia. Secondly, the incidence of sepsis and dehydration is much higher in low-middle income countries compared to high income countries. Both diseases increase the risk for hyperbilirubinemia. The incidence of G6PD deficiency is also much higher in low-income countries, while the methods to detect this disease are frequently lacking. Thirdly, guidelines how to prevent and treat hyperbilirubinemia in developing countries are lacking (15,16,21). Finally, due to a lack of facilities, diseases in the mother such as blood group antagonism and infections are much more frequent. These diseases in the mother increase the risk for hyperbilirubinemia in the newborn (22,23).

The general aim of the studies described in this thesis is to find methods to decrease the burden of neonatal hyperbilirubinemia in Indonesia. To reach that goal, we try to find an answer on the following questions.

1. How is the knowledge of and adherence to guidelines on the prevention and treatment of neonatal hyperbilirubinemia among health care workers in East Java, Indonesia?
2. What is the knowledge regarding neonatal hyperbilirubinemia and the relevant guidelines among pediatric residents in Indonesia?
3. Can we improve the use of and adherence to a new Indonesian guideline for the detection and treatment of hyperbilirubinemia by a web-based application?
4. Is a bed-side system to measure total serum bilirubin reliable enough to be used in Indonesia?
5. How is the current practice of the use of phototherapy in East Java, Indonesia?
6. Can we use transcutaneous measured bilirubin to predict neonatal hyperbilirubinemia in Indonesia?

Table 1. (Risk Factors for Development of Hyperbilirubinemia and Bilirubin-induced Neurotoxicity)

	Risk Factors of Hyperbilirubinemia		Risk Factors of Bilirubin-Induced Neurotoxicity
1	Predischarge TSB* or TCB** level	1	Infection - UTI*** - Sepsis - Meningitis
2	Jaundice observed in the first 24 hours	2	Birth Asphyxia
3	Gestational Age/prematurity	3	Albumin <3.0g/dL
4	Previous sibling with jaundice	4	Severe hypothermia (Tc< 36°C for > 6 hours)
5	Exclusive breastfeeding (if nursing is not going well or dehydration and weight loss is excessive)	5	Respiratory failure (RDS, pneumonia, meconium aspiration syndrome)
6	Race	6	Prolonged acidosis (pH < 7.20 for > 6 hours)
7	Diabetic Mother	7	Severe hypoglycemia (glucose < 45 mg/dl for > 12 hours)
8	Primipara (mother who give the first birth)	8	Severe hemolysis
9	Maternal Age > 25 years		
10	Male gender		
11	Hemolytic Disease - ABO incompatibility - Rh**** - G6PD***** - Sickle Cell Disease		
12	Birth Trauma		
13	Metabolic Disorder		
14	Drugs: - Streptomycin - Sulfa - Benzyl alcohol - Chloramphenicol		
15	Early Discharge		

Legends: *** TSB= Total Serum Bilirubin; ** TCB= Transcutaneous Bilirubin; ***UTI= Urinary Tract Infection; ****Rh= Rhesus; *****G6PD= Glucose-6 Phosphate dehidrogenase**

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