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REVIEW

Icterus Neonatorum in Near-Term and Term Infants

An overview

Rehan Ali, *Shakeel Ahmed, Maqbool Qadir, Khalil Ahmad

اليرقان الوليدي في الرضَّع الناضجين والقريبين من النضوج

نظرة عامة

ريحان علي، شاكيل أحمد، مقبول قادر، خليل أحمد

الملخص: اليرقان الوليدي هو اللون الأصفر في الجلد و/أو صُلْبَة العين عند الأطفال حديثي الولادة بسبب ترسب مادة البيليروبين في الأنسجة. اليرقان الفسيولوجي يكون خفيفا عادة بسبب البيليروبين اللا مُقْتَرن ويصيب جميع المواليد الجدد تقريبا. ترتفع مستويات اليرقان الفسيولوجي ما بين 5 و 6 ملغ / ديسيلتر (86–103 مايكرو مول / لتر) عند 72 إلى 96 ساعة من العمر، ولا تتجاوز 17 حتى 18 ملغ / ديسيلتر (291–308 مايكرو مول / لتر). لكن مستويات البليروبين قد لا تصل إلى ذروتها حتى اليوم السابع من العمر عند الرضّع الآسيويين أو عند الرضّع الذين يولدون قبل الأوان (في الأسبوع 35–37 من الحمل). وتعتبر مستويات البيليروبين اللا مُقْتَرن التي تكون أعلى مما ذُكر حالة مرضية وتحدث في مجموعة متنوعة من الظروف. تم في هذه الورقة مراجعة المظاهر السريرية وعلاج اليرقان الفسيولوجي عند الرضع الأصحاء، الناضجين والقريبين من النضوج، وكذلك سمية البيليروبين والوقاية من اليَرَقان النَوَوِيّ، ومناقشة الآلية المرضية والمسببات المرضية لهذا الاضطراب على انفراد.

مفتاح الكلمات: الوليد، يرقان، ارتفاع البيليروبين.

ABSTRACT: Neonatal jaundice is the yellowish discoloration of the skin and/or sclerae of newborn infants caused by tissue deposition of bilirubin. Physiological jaundice is mild, unconjugated (indirect-reacting) bilirubinaemia, and affects nearly all newborns. Physiological jaundice levels typically peak at 5 to 6 mg/dL (86 to 103 µmol/L) at 72 to 96 hours of age, and do not exceed 17 to 18 mg/dL (291–308 µmol/L). Levels may not peak until seven days of age in Asian infants, or in infants born at 35 to 37 weeks' gestation. Higher levels of unconjugated hyperbilirubinaemia are considered pathological and occur in a variety of conditions. The clinical features and management of unconjugated hyperbilirubinaemia in healthy near-term and term infants, as well as bilirubin toxicity and the prevention of kernicterus, are reviewed here. The pathogenesis and aetiology of this disorder are discussed separately.

Keywords: Newborn; Icterus; Hyperbilirubinaemia; Jaundice.

There has been an increase in the number of near-term and term infants reported with acute bilirubin encephalopathy, which has resulted in an increase in the number of readmissions of infants to hospitals. This can partially be attributed to shorter postpartum hospital stays, and limited post-natal follow-up. To prevent kernicterus, clinicians need to understand the physiology of bilirubin production and excretion, and develop a systematic approach to the causes and management of neonatal icterus. This issue is highlighted here with specific relation to near-term and term newborns.

Epidemiology

Nearly all newborn infants have a total serum bilirubin (TSB) value greater than 1 mg/dL (17.1 µmol/L), which is at the upper limit of normal for an adult. Most newborns appear clinically jaundiced.

Department of Paediatrics and Child Health, Aga Khan University Hospital, Karachi, Pakistan
**Corresponding Author e-mail: shakeel.ahmed@aku.edu*

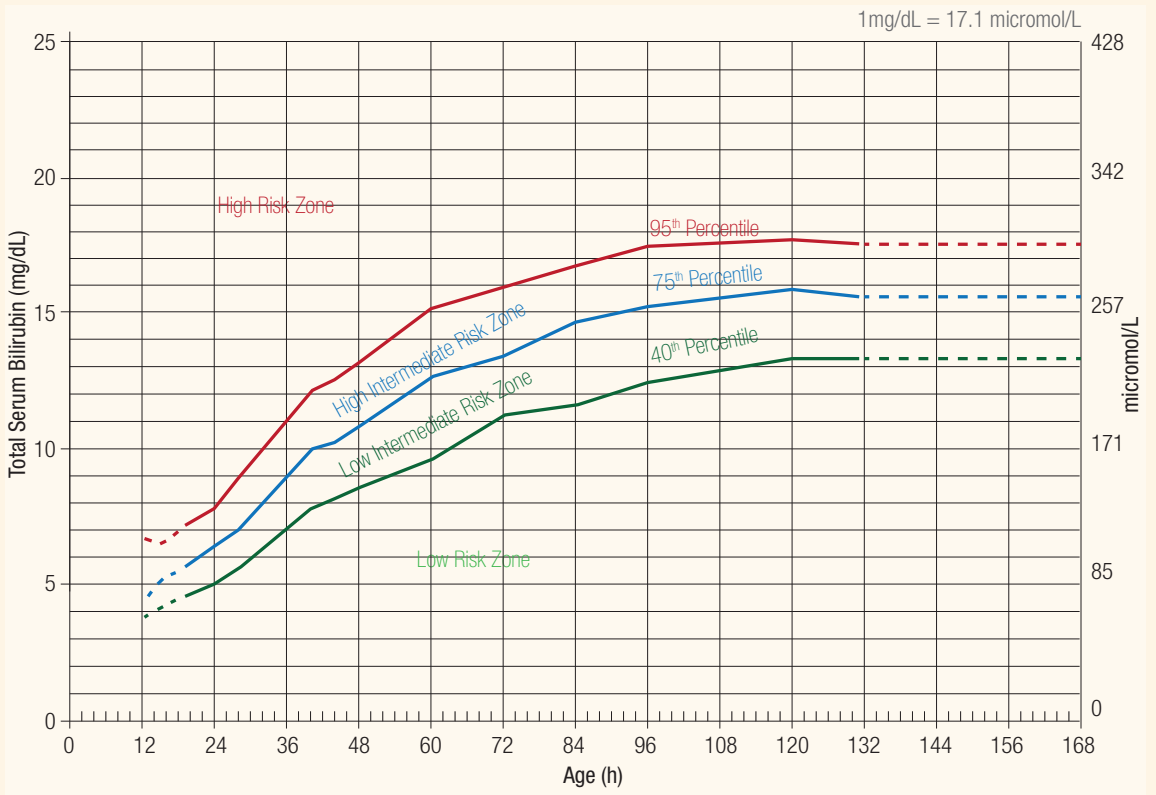

Figure 1: Hour specific nomogram (adapted from Bhutani *et al.*[1])

Pathologic hyperbilirubinaemia occurs when the TSB exceeds the hour-specific 95th percentile using the published nomogram in Figure 1.[1] The nomogram was developed for a racially diverse population in Philadelphia in which nearly 60% were breastfed. Infants were excluded if they had haemolytic conditions or required phototherapy before 60 hours to control rapidly rising TSB levels.

However, rates of hyperbilirubinaemia vary substantially between centres because of racial differences, haemolytic conditions, and breastfeeding practices. In a multinational study, the proportion of infants with TSB levels at or above the 95th percentile at 30 hours ranged from approximately 5% in Hong Kong and China, to 40% in Kobe, Japan.[2]

Clinical Features

Risk factors for the development of jaundice in near-term infants were obtained from clinical histories. They included gestational age of 35 to 37 weeks; polycythaemia; assisted deliveries through such methods as vacuum or forceps instrumentation; trauma during labour or delivery; maternal diabetes; Asian race; blood group incompatibility; poor breastfeeding practices, or a previous sibling with jaundice.[3]

Visual inspection of skin colour can be used to detect jaundice, but it is not a reliable method to assess the level of bilirubin or identify infants at risk for rapidly rising bilirubin levels, especially in those with dark skin.[4] The examination should be performed with adequate ambient light. Pressing on the skin with a finger reduces local skin perfusion and may facilitate detection of jaundice.

Jaundice progresses in a cephalocaudal direction. The face and sclera typically appear icteric when bilirubin levels reach 6 to 8 mg/dL (103 to 137 µmol/L), whereas the entire body, including palms and soles, appears jaundiced at values of 12 to 13 mg/dL (205 to 222 µmol/L).[5] TSB or transcutaneous bilirubin (TcB) levels should be measured in an infant with jaundice detected below the umbilicus.

Physical examination may identify signs that suggest risk for pathological jaundice. They include pallor, enclosed haemorrhage such as cephalhaematoma, and bruising.

Kernicterus

Bilirubin is a potential neurotoxin.[6–7] Unconjugated bilirubin that is not bound to albumin (free bilirubin) can enter the brain and cause focal necrosis of the neurons and glia, resulting in bilirubin encephalopathy, which is also known as kernicterus. The regions most often affected include the basal ganglia and the brain stem nuclei for oculomotor and auditory function, accounting for the clinical features of this condition.[8]

Near-term and term infants are at risk for kernicterus when TSB concentrations exceed 25 to 30 mg/dL (428 to 513 μmol/). However, the relationship between TSB and kernicterus is variable and influenced by other factors such as bilirubin affinity for albumin, which is reduced in premature and sick infants.[9] Most unconjugated bilirubin is normally bound to albumin, resulting in low levels of free bilirubin. High TSB concentrations may exceed the capacity of albumin to bind bilirubin and lead to higher levels of free bilirubin, which may be neurotoxic. Although measurement of free bilirubin concentration would be useful to guide therapy, clinical testing is not universally available.

Drugs such as sulfisoxazole, moxalactam, and ceftriaxone can displace bilirubin from albumin and increase the risk of kernicterus. Acidosis increases movement of bilirubin into tissues and, thus, can contribute to the development of kernicterus.[10]

Kernicterus can occur in healthy term infants. However, infants at increased risk are those who are near term (35 to 37 weeks), breastfed, have haemolytic disease, and are discharged home before 48 hours. To minimise the risk of bilirubin encephalopathy, these infants require close surveillance because the peak TSB levels will be reached after discharge.[7]

Laboratory Evaluation

TSB and the direct-reacting serum bilirubin concentration are measured in infants with jaundice. If the direct-reacting bilirubin is greater than 1.5 to 2.0 mg/dL (26 to 34 μmol/L), causes of cholestatic jaundice should be investigated. The following discussion applies to healthy term and near-term infants with hyperbilirubinaemia. Infants who appear ill or are premature require more extensive evaluation.

The TSB concentration is compared to an hour-specific percentile-based nomogram. TSB levels in a term newborn typically peak at 5 to 6 mg/dL (86 to 103 μmol/L) at 72 to 96 hours of age, and do not exceed 17 to 18 mg/dL (291-308 μmol/L).[1] The peak may not be reached until seven days of age in Asian infants, or in infants born at 35 to 37 weeks' gestation.

Infants with hour-specific values that are greater than or equal to the 95th percentile are at increased risk for the development of clinically significant hyperbilirubinaemia, requiring intervention. In a racially diverse population with a 60% rate of breastfeeding, 95th percentile values for TSB were approximately 8, 10, 12, and 16 mg/dL (137, 171, 205, and 274 μmol/L) at 24, 36, 48, and 72 hours, respectively.[1]

Infants who have TSB values greater than or equal to the 95th percentile, or who are suspected of having haemolytic disease, require subsequent measurement of TSB levels and further evaluation to determine the aetiology of their jaundice. Initial tests that should be obtained are blood type and direct anti-globulin tests, a complete blood count and smear, and a reticulocyte count. The mother's blood type and antibody status usually are known from the prenatal history. If an infant is of Asian origin and the TSB concentration is ≥18 mg/dL (222 μmol/L), glucose-6-phosphate dehydrogenase (G6PD) should be measured.[11] However, G6PD measurements are not universally available, and the results usually are not timely enough to affect clinical decisions.

END-TIDAL CARBON MONOXIDE

End-tidal measurement of carbon monoxide (CO) corrected for ambient CO (ETCOc) provides a noninvasive assessment of bilirubin production because catabolism of heme results in equimolar quantities of bilirubin and CO.[11–12] Elevated ETCOc values (>2.0 parts per million) can identify infants with increased bilirubin production (most often caused by haemolysis) who require additional evaluation or close monitoring. In one study, the ETCOc value at 30 hours of age exceeded the mean value (1.48 ppm) in 76% of hyperbilirubinaemic infants.[12]

TRANSCUTANEOUS BILIRUBIN MEASUREMENT

Transcutaneous devices that use multi-wavelength spectral reflectance can be used to estimate TSB in order to avoid blood sampling. In contrast to older devices, this method is not affected by skin pigmentation.[13] In one report of a racially and ethnically diverse group of 490 newborns, a close correlation was found between transcutaneous and TSB measurements.

Prevention of Severe Hyperbilirubinaemia

Infants with severe hyperbilirubinaemia are at risk for developing kernicterus, although only a small number will do so (see section on kernicterus above). Timely identification and treatment of infants with severe hyperbilirubinaemia will prevent most cases of kernicterus. Infants at risk require close surveillance and follow-up.[14]

Term and near-term infants should be evaluated for jaundice between 72 and 96 hours of age, the time at which TSB levels typically peak.[1] However, many infants are discharged from the hospital prior to 48 hours of age; these infants should be examined for jaundice by a clinician within one to two days of discharge.

TSB levels are often higher in breastfed than in formula-fed infants. In addition, milk intake may be inadequate until lactation is well established, resulting in volume depletion and weight loss. Increased surveillance is needed for infants born at 35 to 37 weeks' gestation because they are at increased risk for early difficulty with breastfeeding.

Counselling regarding jaundice and breastfeeding should be provided before discharge where the importance of frequent feedings should be emphasised. Lactation consultants and home visits by a nurse may be helpful. Until lactation is well-established in significantly jaundiced infants, it may be helpful to interrupt breast feeding briefly and supplement with formula for a short period (supplementation with water is not recommended).[15]

A root cause analysis of factors contributing to cases of kernicterus identified potentially correctable causes.[15] These include: 1) discharge within 48 hours of birth with no follow-up within 48 hours of discharge; 2) failure to measure the bilirubin concentrations in an infant with jaundice within 24 hours of birth; 3) failure to recognise risk factors for hyperbilirubinaemia; 4) lack of concern regarding the presence of jaundice; 5) delayed measurement of TSB in infants with severe jaundice; 6) delayed initiation of phototherapy in infants with elevated TSB levels, and 7) lack of response to parental concerns regarding jaundice, lethargy, or poor feeding.

PREDICTION OF SEVERE HYPERBILIRUBINAEMIA

A percentile-based nomogram, such as that in Figure 1, can be used to predict the subsequent risk for severe hyperbilirubinaemia.[1] In another report, the combined use of an hour-specific TSB measurement and ETCOc did not improve the predictive ability of an hour-specific TSB alone.[16] However, these clinical devices are not currently available. In this study, in contrast to the report on which the nomogram was based that used TSB alone, 4 of 620 infants with TSB levels in the low risk zone (<40th percentile) at 30 ± 6 hours subsequently developed TSB levels greater or equal to those in the 95th percentile. This finding supports the need for early follow-up of all infants regardless of their risk zone at discharge.

UNIVERSAL SCREENING

Universal screening of infants for TSB levels prior to discharge has been proposed to facilitate identification of infants at high risk for the development of severe hyperbilirubinaemia.[2] Limitations of this approach are the need for blood sampling and the cost of TSB measurement. Use of transcutaneous methods for screening may decrease the need for phlebotomy, and reduce costs.[13,16] An alternative approach is clinical assessment of jaundice before and within one to two days of discharge, and subsequent TSB measurement in jaundiced infants.

Treatments

Phototherapy is the standard treatment for pathologic unconjugated hyperbilirubinaemia.[17] Rare cases of extremely high TSB levels (>25 mg/dl) require an exchange transfusion.

PHOTOTHERAPY

Phototherapy consists of exposing the infant's skin to blue-to-green light in wavelengths ranging from 400–520 nm. It is a safe and efficient method to reduce the toxicity of bilirubin and increase its elimination. Phototherapy detoxifies bilirubin by three mechanisms: structural isomerisation to lumirubin, photoisomerisation to a less toxic isomer, and photooxidation to polar small molecules. These processes are thought to occur in the blood vessels or interstitial spaces of the skin.

Phototherapy with blue light phototherapy converts bilirubin into lumirubin in a process of structural isomerisation that is not reversible.[18] Lumirubin, a more soluble substance than bilirubin, is excreted without conjugation into bile and urine. It is the principal mechanism by which phototherapy reduces the TSB concentration. Phototherapy with blue light phototherapy also converts the stable 4Z, 15Z bilirubin isomer to the 4Z, 15E isomer, which is more polar and less toxic than the common form. Like lumirubin, it is excreted into bile without conjugation. Unlike structural isomerisation to lumirubin, photoisomerisation is reversible, and some of the 4Z, 15E isomer in the bile is converted back into the stable 4Z, 15Z isomer. Photoisomerisation is the second important mechanism to increase bilirubin excretion. TSB photo oxidation reactions convert bilirubin to colourless, polar compounds that are excreted primarily in the urine. This mechanism accounts for a small proportion of bilirubin elimination.[10]

The dose of phototherapy, known as irradiance, times duration determines its efficacy. Irradiance depends upon the intensity of the blue light, its distance from the infant, and the surface area exposed. It usually is expressed for a certain wavelength band (spectral irradiance). Fluorescent blue light typically is used at a dose of approximately 30 μW/cm^2/nm of area exposed. Blue lights are more effective at reducing bilirubin but may interfere with the detection of cyanosis.[17,18] The use of white daylight fluorescent lights/lamps is better than no phototherapy.

Fluorescent lights are placed 15 to 20 cm above the infant. We use light banks with eight alternating white and blue fluorescent bulbs. This combination increases the irradiance but lessens the eye strain for clinicians. Halogen white light lamps are hot and can cause thermal injury. They should be placed at the manufacturer recommended distance from the patient.

Fibre optic blankets generate little heat and can be placed close to the infant and provide higher irradiance than do fluorescent lights.[19] However, blankets are small and rarely cover sufficient surface area to be effective when used alone in near-term and term infants. They can be used as an adjunct to overhead fluorescent or halogen lights. High intensity gallium nitride light emitting diodes (LEDs), such as neoblue, are as effective as conventional fluorescent light phototherapy.[20]

For intensive phototherapy (30 μW/cm^2/nm) of infants with TSB levels greater than 25 mg/dL (428 μmol/L), a bank of special blue lights should be placed 10 to 12 cm from the infant's body to expose the maximum surface area to light. Premature and hypothermic babies should be placed in an open crib or on a warmer. The area covered by the diaper should be minimised and the infant's eyes should be shielded with a blindfold with care taken so that the blindfold does not cover the nose.

Temperature, time of exposure, irradiance (if possible), and the infant's hydration status should all be monitored. Infants should continue oral feedings by breast or bottle. Intravenous hydration is needed only in cases of significant volume depletion. Phototherapy should be continuous, with interruptions only for feeding. If the TSB is at a near toxic level, fibre optic blanket exposure can continue during the feedings.

The following discussion applies to healthy term and near-term infants. Infants who appear ill or are premature require more aggressive intervention. For healthy term and near-term infants, we initiate phototherapy according to the 2004 practice and parameter recommendations of the American Academy of Pediatrics (AAP) on the management of hyperbilirubinaemia. Phototherapy is started if TSB levels are 15, 18, or 20 mg/dL (257, 308, and 342 μmol/L) at 25 to 48, 49 to 72, or >72 hours after birth, respectively.[2] These values exceed the 95th percentile for hour-specific TSB concentrations, predicting increased risk for developing severe hyperbilirubinaemia after discharge. For this reason, clinicians often initiate treatment for TSB levels that are 2 to 3 mg/dL (34–51 μmol/L) lower than the above values, especially for near term infants (35–37 weeks), or infants with other risk factors.[2]

Infants with clinical jaundice within the first 24 hours of birth frequently have haemolysis. They require immediate evaluation and close surveillance to assess the need for phototherapy. In infants with other causes of increased bilirubin production, such as cephalohaematoma or extensive bruising, or in infants suspected of having conjugation disorders, we start phototherapy when the hour-specific TSB concentration is in a high intermediate risk zone (>75th percentile).

When TSB values are ≥20 mg/dL (342 µmol/L), the measurement should be repeated four to six hours after phototherapy is initiated to assess the response. For lower initial values, TSB should be measured after 24 hours and then once daily while phototherapy continues. However, measurement of serum bilirubin will also depend on the aetiology of the jaundice, rate of rise, etc., and may be indicated more often even when levels are not yet at 20 mg/dL. A decrease in TSB level can be measured as soon as two hours after initiation of treatment. Intensive phototherapy should result in a decline of TSB of at least 1 to 2 mg/dL (17- 34 µmol/L) within four to six hours.[2]

Our centre discontinues phototherapy when the hour-specific TSB level falls to a value less than the 95th percentile, or has decreased 4 to 5 mg/dL (68–86 µmol/L) when measured 18 to 24 hours later. Although the value following discontinuation is known as the rebound bilirubin, typically it is lower than the previous TSB during treatment. In one study of 161 infants with birth weights of more than 1800 grams, the rebound TSB was significantly lower 17 hours after termination of phototherapy (11.5 versus 12.2 mg/dL, 197 versus 209 µmol/L).[21]

Phototherapy is considered safe. Side effects include transient erythematous rashes, loose stools and hyperthermia. Increased insensible water loss caused by enhanced peripheral blood flow may lead to dehydration.

As an alternative to readmission to the hospital, phototherapy can be administered at home. Home phototherapy is less disruptive to the family and can be considered for healthy infants without haemolysis who are feeding well and can be closely followed.

EXCHANGE TRANSFUSION

Exchange transfusion is used to remove bilirubin from the circulation when intensive phototherapy fails. It is especially useful for infants with increased bilirubin production from immune-mediated haemolysis because the circulating antibodies and the sensitised red blood cells also are removed.

An exchange transfusion is performed when severe hyperbilirubinaemia does not respond to intensive phototherapy. According to the AAP practice parameters, an exchange transfusion is indicated in healthy near-term and term infants when TSB levels are greater than or equal to 20 mg/dL (342 µmol/L) at 24 to 48 hours of age, or are at or greater than 25 mg/dL (428 µmol/L) thereafter. Failure of intensive phototherapy occurs if TSB levels do not decrease by 1 to 2 mg/dL (17–34 µmol/L) within four to six hours of initiation of phototherapy. An exchange transfusion also should be performed in infants with high TSB levels as per the nomogram, and in any infant with any signs of bilirubin neurotoxicity.

Exchange transfusion is indicated in cases of haemolysis, especially immune-mediated, if the anaemia is severe and resulting in hydrops, or the TSB is rising rapidly and is expected to reach 25 mg/dL (428 µmol/L) within 48 hours. Exchange transfusions will correct the anaemia without causing circulatory overload and remove maternal antibodies and sensitised erythrocytes. Less severely affected patients can be managed with intensive phototherapy to reduce TSB levels, and transfusions of packed red blood cells to correct the anaemia.

A double-volume exchange transfusion removes approximately twice the infant's circulating blood volume (blood volume is approximately 80 to 90 mL/kg), replacing it with appropriately cross-matched fresh or reconstituted (from packed red blood cells and fresh frozen plasma) whole blood. The procedure involves placement of a central catheter and the subsequent removal and replacement of the maximum amount of blood that should be withdrawn at any one time (approximately 5 ml per Kg body weight). Most of the bilirubin is extravascular; as a result, an exchange transfusion removes approximately 25% of the total body bilirubin.[22] An infusion of albumin (1 g/kg) one to two hours before the procedure moves more extravascular bilirubin into the infant's circulation, allowing removal of more bilirubin.[23]

After the procedure, TSB levels typically fall to approximately half of the pre-exchange value, and

then increases to approximately two-thirds of that level as the extravascular and vascular bilirubin re-equilibrate. A double volume exchange transfusion replaces approximately 85% of the infant's red blood cells.

The risks of exchange transfusions result from the use of blood products and from the procedure itself. Possible complications include blood-borne infection, thrombocytopenia, coagulopathy, graft-versus-host disease, necrotising enterocolitis, portal vein thrombosis, electrolyte abnormalities, cardiac arrhythmias, and sudden death.[24]

Most complications occur in sick infants and are rare in healthy infants. In a retrospective review of 15 years of experience at two academic medical centres, one of 81 healthy infants developed necrotising enterocolitis after exchange an transfusion, and none died.[22]

Pharmacological Agents

Pharmacological agents, including intravenous immunoglobulin (IVIG), phenobarbital, and metalloporphyrins can be used to inhibit haemolysis, increase conjugation and excretion of bilirubin, or inhibit the formation of bilirubin. However, IVIG is currently used only to treat unconjugated hyperbilirubinaemia.

INTRAVENOUS IMMUNOGLOBULIN

Intravenous immunoglobulin IVIG (500 mg/kg per dose IV over two hours) may reduce the need for exchange transfusions in infants with haemolytic disease caused by Rh or ABO incompatibility.[23] The mechanism is uncertain, but IVIG is thought to inhibit haemolysis by blocking antibody receptors on red blood cells.

PHENOBARBITAL

Phenobarbital increases the conjugation and excretion of bilirubin and decreases postnatal TSB levels when given to pregnant women or infants; however, prenatal administration of phenobarbital may adversely affect cognitive development and reproduction.[24] As a result, phenobarbital is not used to treat indirect hyperbilirubinaemia. There are exceptional circumstances, like prolonged jaundice in Gilbert's syndrome, where it might be useful.

METALLOPORPHYRINS

Synthetic metalloporphyrins, such as tin mesoporphyrin (SnMP), reduce bilirubin production by competitive inhibition of heme oxygenase.[25] In one report, for example, term and near-term infants with G6PD deficiency given SnMP at approximately 27 hours of age had lower and earlier peak TSB values than did control infants with and without G6PD deficiency.[11] No treated infant required phototherapy, compared to 31% and 15% in the controls with and without G6PD deficiency, respectively. However, metalloporphyrins are not available for clinical use.

Conclusion

The following recommendations only apply to healthy term and near-term infants. Infants who appear ill, are premature, or have evidence of haemolysis require more intensive evaluation and management.

Infants should be assessed for jaundice at 24 to 48 hours of age and prior to hospital discharge. Measurement of serum or transcutaneous bilirubin concentration is preferred. Alternatively, the infant can be assessed by visual inspection and a measurement of TSB levels should be obtained in those who appear jaundiced.

TSB values should be compared to an hour-specific nomogram to predict the risk of subsequent development of clinically significant hyperbilirubinaemia. Infants at high risk require increased surveillance.

Infants discharged within 48 hours of birth require a follow-up evaluation within 24 to 48 hours of discharge. Infants at high risk for the development of significant hyperbilirubinaemia should be evaluated within 24 hours of discharge. In addition, parents should also be told to return immediately if the infant becomes visibly more jaundiced or develops any sort of neurological symptom.

Lactation counselling should be provided for breastfeeding mothers. Near-term (35 to 37 weeks) infants are at greater risk of receiving inadequate fluid and nutrition, and require increased surveillance.

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