

Guidelines for detection, management and prevention of hyperbilirubinemia in term and late preterm newborn infants (35 or more weeks' gestation) – Summary



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ABSTRACT

Hyperbilirubinemia is very common and usually benign in the term newborn infant and the late preterm infant at 35 and 36 completed weeks' gestation. Critical hyperbilirubinemia is uncommon but has the potential for causing long-term neurological impairment. Early discharge of the healthy newborn infant, particularly those in whom breastfeeding may not be fully established, may be associated with delayed diagnosis of significant hyperbilirubinemia. Guidelines for the prediction, prevention, identification, monitoring and treatment of severe hyperbilirubinemia are presented.

For more information, please refer to the full text position statement at <www.cps.ca/english/publications/FetusAndNewborn/>.

BACKGROUND AND EPIDEMIOLOGY

Definitions of terms as used in this statement

- Kernicterus – the pathological finding of deep-yellow staining of neurons and neuronal necrosis of the basal ganglia and brainstem nuclei.
- Acute bilirubin encephalopathy – a clinical syndrome, in the presence of severe hyperbilirubinemia, of lethargy, hypotonia and poor suck, which may progress to hypertonia (with opisthotonos and retrocollis) with a high-pitched cry and fever, and eventually to seizures and coma.
- Chronic bilirubin encephalopathy – the clinical sequelae of acute encephalopathy with athetoid cerebral palsy with or without seizures, developmental delay, hearing deficit, oculomotor disturbances, dental dysplasia and mental deficiency (1).
- Severe hyperbilirubinemia – a total serum bilirubin (TSB) concentration greater than 340 $\mu\text{mol/L}$ at any time during the first 28 days of life.
- Critical hyperbilirubinemia – a TSB concentration greater than 425 $\mu\text{mol/L}$ during the first 28 days.

The prevention, detection and management of jaundice in term and late preterm newborn infants remains a challenge (2-4). Sixty per cent of term newborns develop jaundice, and 2% exceed a TSB concentration of 340 $\mu\text{mol/L}$ (5). The incidence of acute encephalopathy is much lower, recent

data (6) suggesting an incidence of approximately one per 10,000 live births; the incidence of chronic encephalopathy has been estimated to be between one per 50,000 live births and one per 100,000 live births (6-9). Acute encephalopathy does not occur in full-term infants whose peak TSB concentration remains below 340 $\mu\text{mol/L}$ and is very rare unless the peak TSB concentration exceeds 425 $\mu\text{mol/L}$, above this level the risk for toxicity progressively increases (10). Two-thirds of patients with chronic encephalopathy had a recorded peak TSB concentration that exceeded 600 $\mu\text{mol/L}$ (11).

Prevention of acute bilirubin encephalopathy requires appropriate clinical assessment, interpretation of TSB concentration and treatment, which must involve the entirety of the systems involved in the provision of health care and community support.

Several factors that increase the risk of severe hyperbilirubinemia have been identified, including: visible jaundice at younger than 24 h of age, visible jaundice before discharge at any age, gestation less than 38 weeks, sibling with severe hyperbilirubinemia, visible bruising, cephalhematoma, male sex, maternal age older than 25 years of age, ethnic background (Asian or European), and exclusive and partial breastfeeding. These risk factors are all very common and are, thus, of limited usefulness for directing surveillance, investigation or therapy by themselves, but can be useful in combination with timed TSB analysis.

METHODS OF STATEMENT DEVELOPMENT

Literature searches were last updated in January 2007. The hierarchy of evidence from the Centre for Evidence-Based Medicine (Table 1) (12) was applied. The reference lists of recent publications were also examined (9).

CAN SEVERE HYPERBILIRUBINEMIA BE ACCURATELY PREDICTED?

Timed TSB measurements

Carefully timed TSB measurements can be used to predict the chances of developing severe hyperbilirubinemia. A study (13) in direct antiglobulin test (DAT)-negative term and late preterm infants demonstrated that a timed measurement of TSB concentration at discharge (between 18 h and three days of age) could predict a later TSB concentration greater than 300 $\mu\text{mol/L}$ (evidence level 1b,

TABLE 1
Levels of evidence used in this statement summary

Level	Therapy	Prognosis	Diagnosis
1a	SR (with homogeneity) of randomized controlled trials (RCTs)	SR (with homogeneity) of inception cohort studies	SR (with homogeneity) of level 1 diagnostic studies
1b	Individual RCT (with narrow CI)	Individual inception cohort study with >80% follow-up	Validating cohort study with good reference standards
2a	SR (with homogeneity) of cohort studies	SR (with homogeneity) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity) of level >2 diagnostic studies
2b	Individual cohort study (or low-quality RCT; eg, <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT	Exploratory cohort study with good reference standards;
3a	SR (with homogeneity) of case-control studies		SR (with homogeneity) of 3b and better studies
3b	Individual case-control study		Nonconsecutive study; or without consistently applied reference standards
4	Case series (and poor quality cohort and case-control studies)	Case series (and poor-quality prognostic cohort studies)	Case-control study, poor or non-independent reference standard
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'		

SR Systematic review

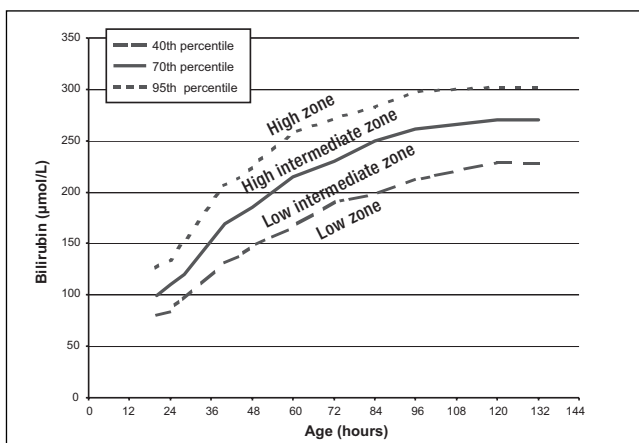


Figure 1) Nomogram for evaluation of screening total serum bilirubin (TSB) concentration in term and late preterm infants, according to the TSB concentration obtained at a known postnatal age in hours. Plot the TSB on this figure, then refer to Table 3 for action to be taken

Figure 1). Combining a timed TSB at less than 48 h of age with gestational age (14) improved the prediction of a subsequent TSB concentration greater than 342 $\mu\text{mol/L}$ (evidence level 2b).

Blood group and Coombs testing

ABO isoimmunization may cause severe hyperbilirubinemia, most commonly in blood group A or B infants born to a mother of group O (15,16). It is therefore recommended to perform a DAT in infants who are clinically jaundiced, or in the high intermediate zone (Figure 1) of mothers who are group O.

The usual antenatal screen for a panel of red cell antibodies occasionally identifies more infrequent antibodies that increase the risk of hemolysis. Infants may require further

testing, closer follow-up and earlier therapy; consultation with a paediatric hematologist or neonatologist is suggested.

Glucose-6-phosphate dehydrogenase (G6PD) deficiency
Newborns with G6PD deficiency have an increased incidence of severe hyperbilirubinemia (evidence level 1b). Testing for G6PD deficiency is advised in boys and girls at increased risk (eg, children of Mediterranean, Middle Eastern, African [17] or Southeast Asian origin) (18,19). G6PD-deficient newborns require intervention at a lower TSB concentration (18); therefore, a test for G6PD deficiency should be considered in all infants with severe hyperbilirubinemia (evidence level 5) (18). Unfortunately, in many centres, it currently takes several days for a G6PD deficiency screening test result to become available. Because G6PD deficiency is a disease with life-long implications, its identification is still of value for the infant.

Recommendations

- All mothers should be tested for ABO and Rh (D) blood types and be screened for red cell antibodies during pregnancy (recommendation grade D [Table 2]).
- If the mother was not tested, cord blood from the infant should be sent for evaluation of the blood group and a DAT (Coombs test) (recommendation grade D).
- Blood group evaluation and a DAT should be performed in infants with early jaundice or in the high intermediate zone (Figure 1) of mothers of blood group O (recommendation grade B).
- Selected at-risk infants of Mediterranean, Middle Eastern, African or Southeast Asian origin should be screened for G6PD deficiency (recommendation grade D).
- A test for G6PD deficiency should be considered in all infants with severe hyperbilirubinemia (recommendation grade D).

TABLE 2
Grades of recommendation

A	Consistent level 1 studies
B	Consistent level 2 or 3 studies
C	Level 4 studies
D	Level 5 evidence, or troublingly inconsistent or inconclusive studies of any level

WHO SHOULD HAVE THEIR BILIRUBIN CONCENTRATION MEASURED, WHEN AND HOW?

Clinical assessment of jaundice is inadequate for diagnosing hyperbilirubinemia, particularly in infants with darker skin colour; only 50% of babies with a TSB concentration greater than 128 $\mu\text{mol/L}$ appear jaundiced. The peak TSB concentration usually occurs between three and five days of age, at which time the majority of babies have already been discharged from hospital. Therefore, it is clear that at the usual age of discharge, TSB concentrations in the high zone (Figure 1) cannot be reliably detected by visual inspection, especially in infants with darker skin colour.

It is therefore recommended that either TSB or transcutaneous bilirubin (TcB) concentration be measured in all infants between 24 h and 72 h of life; if the infant does not require immediate treatment, the results should be plotted on the predictive nomogram to determine the risk of progression to severe hyperbilirubinemia. The TSB (or TcB) and the predictive zone should be recorded, a copy given to the family at the time of discharge and follow-up arrangements should be made for infants who are at elevated risk of developing severe hyperbilirubinemia.

If the TSB concentration has not been measured earlier because of clinical jaundice, a TSB measurement should be obtained at the same time of the metabolic screening test to decrease pain and minimize costs; alternatively a TcB measurement should be obtained either at discharge or before 72 h of life (14).

Some of the most severely affected infants require therapy initiation before the time of the screen; sudden increases in TSB concentration may also occasionally occur after the first two to three days (20), particularly in association with excessive postnatal weight loss. Therefore, the institution of a program of universal screening does not replace the need for careful on-going assessment of newborn infants continuing throughout the first weeks of life. Systems to ensure follow-up within recommended intervals after hospital discharge must be in place so that an infant who develops severe hyperbilirubinemia can be identified and treated promptly. This requires, for example, that an infant discharged from hospital within the first 24 h of life be reviewed within 24 h, any day of the week, by an individual with the training to recognize neonatal hyperbilirubinemia, obtain measurement of TSB or TcB without delay and refer the infant to a treatment facility if required. This individual may be from any medical or nursing discipline.

In addition to universal measurement, all newborn infants should be clinically assessed for jaundice repeatedly within

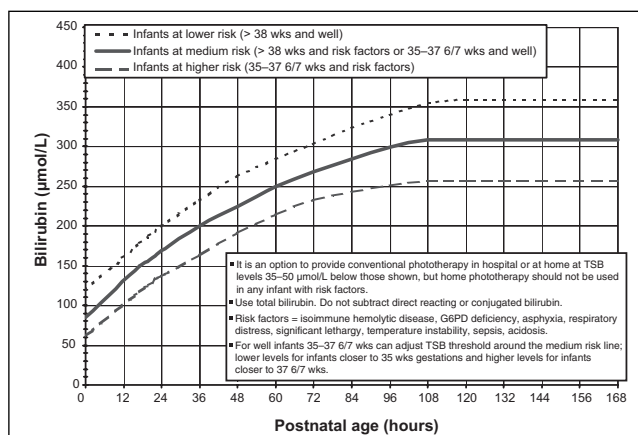


Figure 2) Guidelines for intensive phototherapy in infants of 35 or more weeks' (wk) gestation. These guidelines are based on limited evidence and the levels shown are approximations. Intensive phototherapy should be used when the total serum bilirubin (TSB) concentration exceeds the line indicated for each category. G6PD Glucose-6-phosphate dehydrogenase

the first 24 h and again, at a minimum of 24 h to 48 h later. This should be performed by an individual competent in the assessment of the newborn who can, if necessary, immediately obtain a TSB or TcB measurement and arrange treatment for the infant, whether in hospital or after discharge.

Measurement of bilirubin

Estimation of TSB using capillary blood sampling is acceptable (21,22). TcB measurements are also acceptable, however, there are several limitations to TcB measurements – they become unreliable after initiation of phototherapy and may also be unreliable with changes in skin colour and thickness. The results are more accurate at lower levels of bilirubin; therefore, the use of TcB as a screening device is reasonable. The available devices differ in accuracy; the safe use of TcB mandates knowledge of the accuracy of the individual device. The 95% CIs for TSB based on the TcB concentration range from approximately 37 $\mu\text{mol/L}$ to 78 $\mu\text{mol/L}$ (23,24). For example, if the 95% CI is 37 $\mu\text{mol/L}$, then a TcB concentration greater than 37 $\mu\text{mol/L}$ below the intervention line (Figure 2) should be safe (eg, if the intervention at 24 h is at 170 $\mu\text{mol/L}$, then a TcB concentration of less than 133 $\mu\text{mol/L}$ should be safe) (evidence level 1b).

Measurement of conjugated bilirubin

Early neonatal jaundice is generally due to unconjugated hyperbilirubinemia in infants placed on phototherapy; measurement of the conjugated fraction should be considered to detect the uncommon case of an infant with an elevation. However, previous reports on the epidemiology of bilirubin toxicity use the TSB concentration as the standard, which remains the deciding value for phototherapy or other therapies. An infant with persistent jaundice (longer than two weeks) and/or hepatosplenomegaly should have an estimation of conjugated bilirubin fraction. A total conjugated bilirubin concentration greater than 18 $\mu\text{mol/L}$ or greater than 20% of the TSB concentration warrants further investigation (25).

Recommendations

- Either TSB or TcB concentration should be measured in all infants during the first 72 h of life. If not required earlier because of clinical jaundice, TSB should be obtained at the time of obtaining the metabolic screening test; alternatively, a TcB measurement should be obtained either at discharge or, if not yet discharged, before 72 h of life (recommendation grade C).
- If the TSB concentration does not require immediate intervention, the results should be plotted on the predictive nomogram. The results of the TSB measurement, the time at which it was obtained and the zone should be recorded, and a copy given to the parents. Follow-up of the infant should be individualized according to the risk assessment (recommendation grade D).
- Any infant discharged before 24 h of life should be reviewed within 24 h by an individual with experience in the care of the newborn who has access to testing and treatment facilities (recommendation grade D).
- There should be a systematic approach to the risk assessment of all infants before discharge and institution of follow-up care if the infant develops jaundice (recommendation grade D).
- All newborn infants who are visibly jaundiced within the first 24 h of life should have a bilirubin level determined (recommendation grade D).
- Transcutaneous bilirubinometry is an acceptable method; the result should be summed with the 95% CI of the device to estimate the maximum probable TSB concentration (recommendation grade C).
- TSB concentration may be estimated on either a capillary or a venous blood sample (recommendation grade C).
- Infants with severe or prolonged hyperbilirubinemia should be further investigated, including measurement of the conjugated component of the bilirubin (recommendation grade C).

HOW CAN THE RISK OF SEVERE HYPERBILIRUBINEMIA BE REDUCED?

Primary prevention of severe hyperbilirubinemia

Breastfeeding support

Although breastfed infants are at higher risk for developing severe hyperbilirubinemia than formula-fed infants, the known risks of acute bilirubin encephalopathy are very small when weighed against the substantial known benefits of breastfeeding (26). Support of the breastfeeding mother by knowledgeable individuals increases the frequency and duration of breastfeeding, and providing such support is recommended (evidence level 5). Exclusively breastfed infants experience their maximum weight loss by day 3 and lose, on average, 6% to 8% of their birth weight (26). Infants who lose more than 10% of their birth weight should be carefully evaluated by an individual with training

and experience in support of breastfeeding mothers (26) (evidence level 5). Routine supplementation of breastfed infants with water or dextrose water does not prevent hyperbilirubinemia (evidence level 2b) (27).

Prevention of severe hyperbilirubinemia in infants with mild or moderate hyperbilirubinemia

Phototherapy

Phototherapy decreases the progression to severe hyperbilirubinemia in infants with moderate hyperbilirubinemia (evidence level 1a). Its effectiveness is related to the area of skin exposed and the intensity of the light at the skin at the relevant wavelengths (28). Intensity can be increased by using multiple phototherapy units (29) or moving the unit closer to the infant. Phototherapy causes minor increases in transepidermal skin water loss in full-term infants. Side effects include temperature instability, intestinal hypermotility, interference with maternal-infant interaction and, rarely, bronze discoloration of the skin. Phototherapy is perceived by parents as implying that their infant's jaundice is a serious disease (30) (evidence level 2); reassurance of the parents is an important part of their care. Eye patches should be used to protect the developing retina (31).

Fluorescent light sources are most commonly used (32), but their intensity wanes over time; thus, a program of biomedical support for ensuring adequate light intensity is important. Fibre optic phototherapy systems have the advantage of allowing the baby to be breastfed without interruption of phototherapy and eye pads are not required, but the disadvantage is that the peak intensity is lower than in fluorescent systems. Halogen spotlights may also be used, but they must not be placed closer to the infant than the manufacturer's recommendation.

Intensive phototherapy, as recommended by the present position statement summary, implies that a high intensity of light (greater than $30 \mu\text{W}/\text{cm}^2/\text{nm}$) is applied to the greatest possible surface area of the infant. In usual clinical situations, this will imply two phototherapy units, or special high-intensity fluorescent tubes, placed approximately 10 cm from the infant, who can be nursed in a bassinet. Usually the diaper can be left in place. In infants approaching the exchange transfusion threshold, the addition of a fibre optic blanket under the infant can increase the surface area illuminated; the diaper should then be removed (or a phototherapy wavelength-transmitting diaper used instead). The guidelines for therapy (Figure 2) are based on limited direct evidence, but are thought to be the most appropriate currently available standard. Conventional phototherapy – a single bank of fluorescent lights placed above the incubator or bassinet of an infant nursed with a diaper in place – is less effective because both surface area and intensity are reduced; nevertheless, it will have some effect on TSB concentration.

Enteral feeding should be continued to replace missing fluid, supply energy and reduce enterohepatic reuptake of the bilirubin (33).

The recommendations for treatment are determined from Figure 2. These recommendations are as follows:

TABLE 3
Response to results of bilirubin screening

Zone	Greater than 37 weeks' gestation and DAT-negative	35 to 37 6/7 weeks' gestation or DAT-positive	35 to 37 6/7 weeks' gestation and DAT-positive
High	Further testing or treatment required*	Further testing or treatment required*	Phototherapy required
High-intermediate	Routine care	Follow-up within 24 h to 48 h	Further testing or treatment required*
Low-intermediate	Routine care	Routine care	Further testing or treatment required*
Low	Routine care	Routine care	Routine care

*Arrangements must be made for a timely (eg, within 24 h) re-evaluation of bilirubin by serum testing. Depending on the level indicated on Figure 2, treatment with phototherapy may also be indicated. DAT Direct antiglobulin test

- intensive phototherapy for infants with severe hyperbilirubinemia or those at greatly elevated risk of developing severe hyperbilirubinemia.
- in addition, there is an option for conventional phototherapy for those infants with moderately elevated risk and at TSB concentrations of 35 $\mu\text{mol/L}$ to 50 $\mu\text{mol/L}$ below the thresholds (Figure 2).

A useful tool is available on-line at <<http://bilitool.org>> for deciding whether intensive phototherapy would be recommended by these guidelines.

Interrupting breastfeeding

Interrupting breastfeeding as part of hyperbilirubinemia therapy is associated with an increase in the frequency of stopping breastfeeding by one month (evidence level 2b) (30). Continuing breastfeeding in jaundiced infants receiving phototherapy is not associated with adverse clinical outcomes (34).

Intravenous immunoglobulin

Intravenous immunoglobulin (IVIG) at a dose of either 500 mg/kg or 1 g/kg reduces bilirubin concentrations in newborns with immune hemolytic jaundice (35,36) and reduces the need for exchange transfusion (evidence level 1a). These studies only included infants at high risk of requiring an exchange transfusion. IVIG should therefore be given to infants with predicted severe disease based on antenatal investigation and to those with an elevated risk of progressing to exchange transfusion.

Supplemental fluids

Nondehydrated infants with severe jaundice appear to have a reduced risk of progressing to exchange transfusion if they receive extra fluids, either intravenous or orally (37,38) during intensive phototherapy (evidence level 1b). There is a concern that offering supplemental oral fluids may interfere with the eventual duration of breastfeeding (39,40) (evidence level 2b). The frequency of exchange transfusion in the studies supporting supplemental fluids, noted above, was very high (37). In breastfed infants, therefore, extra fluids are indicated for, but should be restricted to, those infants with an elevated risk of requiring exchange transfusion (evidence level 1b).

Recommendations

- A program for breastfeeding support should be instituted in every facility where babies are delivered (recommendation grade D).

- Routine supplementation of breastfed infants with water or dextrose water is not recommended (recommended grade B).
- Infants with a positive DAT who have predicted severe disease based on antenatal investigation or an elevated risk of progressing to exchange transfusion based on the postnatal progression of TSB concentration should receive IVIG at a dose of 1 g/kg (recommended grade A).
- A TSB concentration consistent with increased risk (Figure 1 and Table 3) should lead to enhanced surveillance for the development of severe hyperbilirubinemia, with follow-up within 24 h to 48 h, either in hospital or in the community, and repeat estimation of TSB or TcB concentration in most circumstances (recommended grade C).
- Intensive phototherapy should be given according to the guidelines shown in Figure 2 (recommended grade D).
- Conventional phototherapy is an option at TSB concentrations 35 $\mu\text{mol/L}$ to 50 $\mu\text{mol/L}$, lower than the guidelines in Figure 2 (recommended grade D).
- Breastfeeding should be continued during phototherapy (recommended grade A).
- Supplemental fluids should be administered, orally or by intravenous infusion, in infants receiving phototherapy who are at elevated risk of progressing to exchange transfusion (recommended grade A).

HOW SHOULD SEVERE HYPERBILIRUBINEMIA BE TREATED?

Phototherapy

An infant who presents with severe hyperbilirubinemia or who progresses to severe hyperbilirubinemia despite initial treatment should receive immediate intensive phototherapy. Bilirubin concentration should be checked within 2 h to 6 h of initiation of treatment to confirm response. Consideration of further therapy should commence and preparations for exchange transfusion may be indicated. Supplemental fluids are indicated, and IVIG should be given in the DAT-positive infant.

Exchange transfusion

If phototherapy fails to control the rising bilirubin concentration, exchange transfusion is indicated to lower TSB concentration. Exchange transfusion should be considered when the TSB exceeds the thresholds on Figure 3 (despite

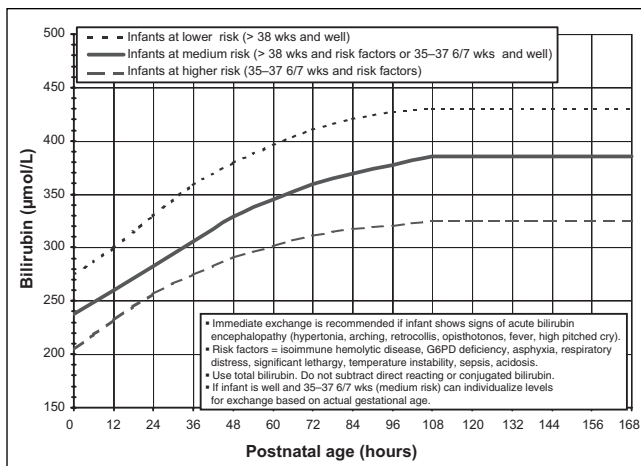


Figure 3) Guidelines for exchange transfusion in infants of 35 or more weeks' (wk) gestation. These guidelines are based on limited evidence and the levels shown are approximations. Exchange transfusions should be used when the total serum bilirubin (TSB) concentration exceeds the line indicated for each category. G6PD Glucose-6-phosphate dehydrogenase

adequate intensive phototherapy). Preparation of blood for exchange transfusion may take several hours, during which time intensive phototherapy and supplemental fluids should be used and IVIG (in case of isoimmunization). If an infant presents for medical care and is already above the exchange transfusion line, then immediate consultation with a referral centre is required. Repeat measurement of the TSB concentration just before performance of the exchange is reasonable, as long as therapy is not thereby delayed. In this way, some exchange transfusions may be avoided. Exchange transfusion is a procedure with substantial morbidity that should only be performed in centres with the appropriate expertise under the supervision of an experienced neonatologist.

An infant with clinical signs of acute bilirubin encephalopathy should have an immediate exchange transfusion (evidence level 4).

Recommendations

- Infants with a TSB concentration above the thresholds (Figure 3) should have immediate intensive phototherapy, and should be referred for further investigation and preparation for exchange transfusion (recommendation category B).
- An infant with clinical signs of acute bilirubin encephalopathy should have an immediate exchange transfusion (recommendation category D).

Follow-up

Routine newborn surveillance, whether in hospital or after discharge, should include assessment of breastfeeding and jaundice every 24 h to 48 h until feeding is established (usually on the third or fourth day of life). All jaundiced infants, especially high-risk infants and those who are exclusively breastfed, should continue to be closely monitored until feeding and weight gain are established and the TSB

concentration starts to fall. Community services should include breastfeeding support and access to TSB or TcB testing. Infants with isoimmunization are at risk for severe anemia after several weeks; it is suggested that a repeat hemoglobin measurement be performed after two weeks if it was low at discharge, and at four weeks if it was normal (evidence level 5). Infants requiring exchange transfusion or those who exhibit neurological abnormalities should be referred to regional multidisciplinary follow-up programs. Neurosensory hearing loss is of particular importance in infants with severe hyperbilirubinemia, and their hearing screen should include brainstem auditory evoked potentials.

Further investigations

The occurrence of severe hyperbilirubinemia mandates an investigation of the cause of hyperbilirubinemia. Investigations should include clinically pertinent history of the baby and the mother, family history, description of the labour and delivery, and the infant's clinical course. A physical examination should be supplemented by laboratory investigations (conjugated and unconjugated bilirubin levels; direct Coombs test; hemoglobin and hematocrit levels, and complete blood cell count including differential count, blood smear and red cell morphology). Investigations for sepsis should be performed if warranted by the clinical situation.

Recommendations

- Adequate follow-up should be ensured for all infants who are jaundiced (recommendation grade D).
- Infants requiring intensive phototherapy should be investigated for determination of the cause of jaundice (recommendation grade C).

CONCLUSION

Severe hyperbilirubinemia in relatively healthy term or late preterm newborns (greater than 35 weeks' gestation) continues to carry the potential for complications from acute bilirubin encephalopathy and chronic sequelae. Careful assessment of the risk factors involved, a systematic approach to the detection and follow-up of jaundice with the appropriate laboratory investigations, along with judicious phototherapy and exchange transfusion when indicated, are all essential to avoid these complications.

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The recommendations in this statement do not indicate an exclusive course of treatment or procedure to be followed. Variations, taking into account individual circumstances, may be appropriate. Internet addresses are current at time of publication.