

SPECIAL FEATURE

Israel guidelines for the management of neonatal hyperbilirubinemia and prevention of kernicterus

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Despite publication of guidelines for the prevention and management of hyperbilirubinemia in term and late-preterm newborn infants, kernicterus, although rare, continues to occur. Guidelines written for use in one country may not always be universally appropriate. Bearing this in mind, a committee appointed by the Israel Neonatal Society has formulated a set of guidelines, based on those of the American Academy of Pediatrics (2004), but adapted to the realities of the Israeli scene. The guidelines include methods of surveillance of jaundice, prediction of jaundice, assessment of risk factors, discharge planning and post-discharge follow-up, in addition to therapeutic guidelines including indications for phototherapy, exchange transfusion and the use of intravenous immune globulin. Availability of these guidelines to the international community may offer direction to physicians of other countries who may be setting up guidelines for use in their own communities.

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Introduction: why another set of guidelines?

Bilirubin encephalopathy and kernicterus

Neonatal jaundice is a common occurrence and appears in about 60% of newborns.¹ Usually serum total bilirubin (STB) concentrations will remain within the range that will not be a source of danger to the infant. Occasionally, the rate of bilirubin production may exceed the ability of the body to eliminate bilirubin resulting in imbalance between the processes that may lead to hyperbilirubinemia.² In extreme cases, the hyperbilirubinemia may exceed the binding ability of serum albumin and free, or unbound, bilirubin is formed. Unbound bilirubin may cross the blood–brain barrier and penetrate brain cells, especially the basal ganglia, causing usually irreversible

damage. In its acute form, this condition is known as bilirubin encephalopathy. Bilirubin-induced neurologic dysfunction may result in a chronic form of athetoid cerebral palsy known as kernicterus.^{3–5}

In recent years, there has been a greater awareness of this condition than before.^{5–7} Updated recommendations of the American Academy of Pediatrics (AAP) for the management of hyperbilirubinemia have been widely publicized.⁸ The AAP asserts that were its guidelines adhered to, kernicterus would be largely preventable. However, kernicterus continues to occur. Recently published cases emanate from countries with advanced medical care services, including the United States,^{5,6} Canada,^{9,10} Holland,¹¹ Denmark,¹² Italy,¹³ the United Kingdom,¹⁴ New Zealand,¹⁵ Germany¹⁶ and South Africa.¹⁷ The proposed reasons for the continued appearance of kernicterus include adoption of a more liberal policy toward neonatal jaundice, earlier discharge of mother–infant dyads prior to the STB peaking, an increase in the number of breastfeeding neonates, the assumption, subsequently disproved,¹⁸ that increased hemolysis is essential for kernicterus to occur and the practice of managing hyperbilirubinemia in late-preterm infants (34^{0/7} to 36^{6/7} weeks gestation) as if they were term counterparts.¹⁹

Frequently, the severe hyperbilirubinemia or bilirubin encephalopathy does not occur during, but rather following, the birth hospitalization.^{5,6,12,14} Identifiable predischarge predictive risk factors of impending extreme icterus may be absent. The emphasis in the prevention of extreme hyperbilirubinemia may therefore lie equally in the resolute post-discharge follow-up of all neonates as in abiding by guidelines for the institution of phototherapy or performing of exchange transfusion.

Why does Israel need its own guidelines?

Different countries or geographic areas may have local customs or traditions with the potential of either exacerbating or dampening the risk of hyperbilirubinemia.²⁰ One example of an exacerbating factor, relevant to Israel, is that of glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, prevalent in a large population subset of Sephardic Jews.^{21–23} Contributing to diminished risk is the demand of Jewish ritual law that

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circumcision be performed on the eighth day of life to a baby who is medically healthy. Some degrees of neonatal jaundice, but not necessarily at dangerous STB concentrations, may be interpreted by various religious authorities as a sign of ill health disallowing circumcision. As a result, many members of Israeli society are highly aware of the concept of neonatal jaundice and families tend to be compliant with instructions to return for repeat bilirubin testing. Frequently, the routine visit of a ritual circumcisor (mohel) may be instrumental in identifying a hyperbilirubinemic newborn whose jaundice would otherwise not have been recognized by the parents. The short distances between towns and cities ensure that most Israeli families can reach a laboratory within little more than 1 h travel. On the other hand, refusal of some members of the ultraorthodox community to travel on the Jewish Sabbath as well as closure of many laboratories and Well Baby Clinics on that day may delay access to some medical services. Although most newborns are discharged at or around 48 h, it is to our advantage that hospital-based neonatologists are not pressured by health-care providers to discharge all neonates according to a fixed schedule, and late-preterm babies or babies at high risk for developing hyperbilirubinemia may, on occasion, be kept for observation for an additional day or two, as deemed necessary.

Israel has not escaped from the scourge of kernicterus. A few unpublished cases have been encountered and the committee is aware of two new cases in 2007 alone. It is of interest that all these occurred following discharge from the birth hospitalization. In an attempt to limit future cases of hyperbilirubinemia and prevent further cases of kernicterus, the Israel Neonatal Society recently appointed this committee to formulate a set of guidelines oriented to the Israeli situation. The Israeli guidelines are based on those of the AAP but adapted to the realities Israeli society. In preparing these guidelines, we aimed to prepare guiding principles which, in our opinion, provided they are adhered to by neonatologists, pediatricians and family doctors in the community should prevent many cases of extreme hyperbilirubinemia (STB ≥ 25 mg per 100 ml).⁵ Frequently, there were few scientific data on which to base these guidelines and the recommendations are based, to a large extent, on our own and others' clinical experience and practice.

In what ways are the Israeli guidelines different from those of the AAP?

Because of good parental compliance, short distances and universal enrollment of all citizens in one of four sick funds offering medical insurance coverage, we can be relatively certain that a newborn invited for a repeat bilirubin test will actually return for testing. For those newborns who had a predischarge STB performed, we based our follow-up recommendations for detecting subsequent hyperbilirubinemia on the position of the STB result on the hour of life-specific bilirubin nomogram. In those infants who have had more than one STB determination, the bilirubin trajectory may be

assessed as an adjunct to the actual STB point on the curve. G-6-PD screening, and not only G-6-PD testing in cases of hyperbilirubinemia, is highly recommended as an option in high-risk subsets of the population. Predischarge transcutaneous bilirubinometry (TcB), where available, is suggested to quantify visual assessment of jaundice, or in lieu of universal predischarge STB testing. Indications for phototherapy are similar to those of the AAP, except that we have been somewhat more conservative in not allowing the STB to exceed 19.0 mg per 100 ml even in term neonates with no risk factors, without instituting phototherapy. This decision was taken because there is no clinically available bedside test for the rapid diagnosis or exclusion of hemolysis. As isoimmunization outside direct antibody titer (DAT)-positive ABO heterospecificity (for example, anti-c or anti-e) may be severe with rapid increases in STB, we have allowed for a shorter trial period of phototherapy in these cases than we have for the ABO setup, prior to administering intravenous immune globulin (IVIG). Finally, we suggest an approach for the infant with jaundice prolonged for more than 10 to 14 days. This shorter time frame has been adopted because current recommendations suggest that, in cases of biliary atresia, the Kasai operation be performed optimally at age ≤ 30

Table 1 Major differences between AAP (2004) guidelines and the Israel guidelines

| | <i>AAP</i> | <i>Israel</i> |
|--|---|---|
| Follow-up based on | Age at discharge + presence of risk factors + risk of other neonatal problems | Standard 2–3 days post-discharge + presence of risk factors + position of STB on nomogram and assessment of bilirubin trajectory |
| G-6-PD determination: | Test in evaluation of hyperbilirubinemic newborn | Test in evaluation of hyperbilirubinemic newborn + option to screen population or subsets of population at high risk for G-6-PD deficiency |
| <i>Upper limit for commencing phototherapy</i> | | |
| In otherwise healthy, risk-free term newborns | 21.0 mg per 100 ml | 19.0 mg per 100 ml |
| IVIG administration | 4 h trial of phototherapy | 4 h trial of phototherapy in DAT-positive, ABO heterospecificity, shorter time in other isoimmunizations. |
| Direct bilirubin determination in otherwise healthy infant | 3 weeks | 10–14 days |

Abbreviations: AAP, American Academy of Pediatrics; DAT, direct antibody titer; G-6-PD, glucose-6-phosphate dehydrogenase; IVIG, intravenous immune globulin; STB, serum total bilirubin.

days.^{24,25} Some differences between the AAP guidelines and the Israeli approach are summarized in Table 1.

Sharing of responsibilities

In the past, in Israel, the detection and treatment of neonatal jaundice was primarily the responsibility of the neonatologist. Nowadays, with shortening of hospital stay, the monitoring and identification of neonatal jaundice has become a combined responsibility shared between the neonatologist within the confines of the hospital on the one hand, and the family pediatrician or practitioner in the community setting, on the other. Because of the shortening of hospital stay and the sharing of the responsibility of hyperbilirubinemia management between the neonatologist and the community physician, these guidelines should serve not only hospital-based neonatologists, but also Well Baby stations, health fund clinics and private and/or independent physicians.

Providing direction rather than rigid instructions

Our intentions are to provide guidelines and general principles that can be modified according to clinical experience, medical judgment and the individual setting. It is not our objective to enforce strict and rigid instructions upon our colleagues. The committee recognizes that each neonate is a unique entity and, as such, no one set of guidelines may be appropriate for every situation. Risk factors and individual features may be taken into account and appropriately used in modifying an approach to management.

This English language version should not be regarded as binding or having legal implications for Israeli physicians. For this purpose, an official Hebrew language edition will be published by the Israel Medical Association. This version is being written to share our guidelines with colleagues in other countries, and hopefully to suggest direction to those who may be preparing or revising similar protocols for use in their own regions.

Objectives

The guiding principle behind the follow-up and treatment of neonatal jaundice is to prevent extreme hyperbilirubinemia, usually defined as an STB ≥ 25 mg per 100 ml⁵ in an otherwise healthy, term or late-preterm infant, thereby averting the potential for usually irreversible brain damage. The basic principles by which these aims should be achieved include monitoring the development of clinical neonatal jaundice during the birth hospitalization, quantifying the degree of jaundice by determinations of STB or TcB, identification of risk factors for the development of jaundice, formulation of guidelines for the treatment of jaundice, prediction of the development of jaundice following discharge from birth hospitalization and planning for and continuation of surveillance following discharge.

Surveillance for the development of clinical jaundice

It is necessary to monitor infants for the development of jaundice throughout the birth hospitalization and following discharge. Following is a suggested protocol for successful surveillance.

- (1) At the time of admission to the newborn nursery after birth, the admitting nurse should examine the baby to assess the skin color. Should there be a yellow hue a bilirubin test must be performed immediately.
- (2) Ongoing assessment of skin color for the development of jaundice should be performed at least once per nursing shift. In the event in which visible jaundice appears within the first 24 h of life, a bilirubin test must be performed immediately.
- (3) Should jaundice be noted by visual inspection after the first 24 h, the bilirubin value should be quantified by an STB determination or TcB, where available.
- (4) The committee recommends that the nursing staff be allowed to order bilirubin tests at their discretion without the need to await a doctor's instruction.

Interpretation of the serum total bilirubin value

As the STB may increase rapidly during the first days of life, the STB value should be assessed according to the infants' age in hours at the time the bilirubin was sampled. It is recommended that the measured STB concentration should be assessed in conjunction with the percentile value on the hour of life-specific bilirubin nomogram.²⁶ This will make possible comparison of the degree of jaundice from hour to hour, allow for assessment of the bilirubin trajectory over time, and facilitate prediction of the risk of subsequent hyperbilirubinemia. In the event in which the bilirubin percentile be higher than the 75th centile (clinically significant jaundice, intermediate high-risk zone), and certainly if higher than the 95th percentile (hyperbilirubinemia, high-risk zone), that neonate should be closely observed with subsequent STB or TcB measurements, and assessed for the presence of risk factors that may potentially enhance the likelihood of subsequent severe hyperbilirubinemia. In such circumstances, it should also be determined whether the criteria for commencing phototherapy have been met (please see Post-discharge follow-up).

Assessment of risk factors and determination of hemolysis

The presence of risk factors may exacerbate the risk of developing hyperbilirubinemia. It is therefore essential to be aware of and identify potential risk factors. A list of important risk factors can be viewed in Table 2 of the 2004 AAP hyperbilirubinemia guidelines.⁸ Hemolysis is an important risk factor and is thought to enhance the risk of developing bilirubin-induced neurologic dysfunction. However, hematological indices frequently associated with

Table 2 Clinical and laboratory signs suggestive of increased hemolysis

Jaundice appearing within the first 24 h

Positive DAT test in combination with suggestive laboratory evidence

- Decreasing hemoglobin or hematocrit value,
- Increased reticulocyte count,
- Peripheral blood smear suggestive of hemolysis

G-6-PD deficiency in combination with a rapid increase in STB

Increase in the STB >0.2 mg per 100 ml per hour

Abbreviations: DAT, direct antibody titer; G-6-PD, glucose-6-phosphate dehydrogenase; STB, serum total bilirubin.

increased hemolysis in adults may be unreliable as indicators of increased heme catabolism in neonates.²⁷ G-6-PD-deficient neonates may have acute and severe hemolysis, which is not manifest by decreased hemoglobin or hematocrit or reticulocytosis.²⁸ Bedside determination of end tidal carbon monoxide is no longer available. It may therefore be difficult to determine definitively whether or not increased hemolysis is present. Clinical signs and laboratory evidence suggestive of increased hemolysis are summarized in Table 2. Factors increasing the risk of bilirubin-induced neurologic dysfunction in hyperbilirubinemic neonates include hemolysis, perinatal asphyxia, hypoalbuminemia (<3.0 g per 100 ml) and diminished albumin–bilirubin binding. The latter may be exacerbated, with resultant appearance of unbound bilirubin, by metabolic acidosis, hypothermia, drugs (for example, sulfa, benzyl alcohol), prematurity and sepsis.

Laboratory tests

Routine testing

To identify some of the risk factors for jaundice, few routine tests are recommended.

Blood groups and DAT. In most instances, the mother will have had a blood group and a DAT test performed during the pregnancy.

Rh-negative mother. To determine the need for maternal anti-D globulin (Rhogam) administration, Rh blood typing must be performed. This is usually tested along with ABO blood types and DAT testing. Typing can be done on appropriately stored umbilical cord blood collected in the delivery room after delivery of the placenta.

O blood group mothers. In neonates born to a O blood group mother, it is optional to test blood group and DAT as long as the baby does not become clinically jaundiced. Determination of an O–A or O–B situation in the presence of a positive DAT should alert the caretaker to an increased risk of developing hyperbilirubinemia. Should a neonate born to an O blood group

mother develop hyperbilirubinemia, blood typing and DAT testing should be mandatory.

Other isoimmunization. Should there be a previous history of isoimmunization, or the mother has a known positive DAT, or there be evidence of hemolysis (Table 2), STB unresponsiveness to phototherapy, or a positive DAT in the baby, an antibody screen should be considered.

G-6-PD testing. G-6-PD deficiency is associated with acute hemolytic episodes that may result in extreme hyperbilirubinemia^{28,29} and is a major contributing factor to bilirubin encephalopathy.^{5,9,10,14,30,31} In Israel, G-6-PD deficiency is found in a high percentage of Sephardic Jews whose families immigrated from the Middle East and Asia Minor. North African Jews are affected to a lesser extent, whereas Ashkenazi Jews (Central and East Europe) are minimally affected.^{21,22} In similarity with other affected population groups, in Sephardic Jews, G-6-PD deficiency increases the incidence of neonatal hyperbilirubinemia²³ and may be associated with sudden, unpredictable and exponential increases in the STB.^{28,32,33}

The committee recommends approaching this problem in one of two ways:

- (a) screening of all neonates,
- (b) selective screening of neonates born to Jewish mothers whose families originate in areas associated with a high incidence of the condition among Jews (Kurdistan, Iraq, Iran, Syria, Lebanon, Turkey).

The committee realizes that G-6-PD screening will not prevent all cases of G-6-PD deficiency-associated kernicterus. However, knowledge that their infant is G-6-PD-deficient should hopefully increase parental awareness of the risk of their newborn developing hyperbilirubinemia with the possibility of sudden onset of jaundice and extremely rapid rise in STB. Parents and, especially, nursing mothers, can be warned to avoid potentially dangerous foodstuffs, chemicals or medications, and to refrain from using baby clothes that had been stored in naphthalene-containing mothballs. Knowledge that an infant is G-6-PD-deficient should encourage earlier referral to hospital when necessary and more efficient processing once in hospital.

It is recommended that these screening results become available prior to discharge of the baby from hospital. The rapid turn-around time required may necessitate that G-6-PD screening be performed on a regional basis or alternatively in each individual hospital. Because G-6-PD testing with immediate availability of results is not currently available at all Israeli hospitals, the committee suggests G-6-PD screening as an option, but recommends that individual hospitals work toward initiating a screening program in their institutions. The WHO Working Group recommends a fluorescent technique as the preferred test,³⁴ although other techniques may be

acceptable, as a similar degree of accuracy was found when a commercially available color reduction test was compared with a commercial fluorescent test.³⁵

Suggested tests for neonates with STB value >95th percentile or requiring phototherapy

In many cases, a causal etiology for hyperbilirubinemia will not be found³⁶ and performing a battery of laboratory tests will in most cases not shed further light on the cause of the jaundice. Save for STB monitoring, only a few laboratory tests, summarized in Table 3, are actually indicated for the average hyperbilirubinemic neonate. Liver function tests and direct bilirubin fractionation add little information in the first days of life and should be performed only in cases of persistent or unexplained prolonged jaundice, or in the presence of evidence of disease.

Transcutaneous bilirubinometry may be useful as an adjunct in assessing the need for STB determination. Visual assessment has traditionally been the mainstay of screening for jaundice. However, the AAP Subcommittee on Hyperbilirubinemia warns of the potential inaccuracy of visual assessment.⁸ Furthermore, it has been determined that in newborns with STB concentrations in the range of 10 to 12 mg per 100 ml, jaundice may be difficult to identify.^{37,38} As, at or around 48 h, STB values in this range may lie between the 75th and 95th percentile, visual assessment alone may not be effective in the prediction of subsequent hyperbilirubinemia.²

Technology for the non-invasive assessment of the degree of jaundice in the baby's skin has recently been improved and suitable devices are nowadays available for clinical use. By measuring the color of the babies' skin, and correcting for hemoglobin and pigment, the available equipment offers a reasonable reflection of the serum bilirubin. As an adjunct to in-hospital or predischarge assessment of jaundice, the technique can be used as a screening test, but not as a substitute for STB determination.³⁹⁻⁴¹ Depending on availability, it can be used to follow babies following discharge. As there is as yet little information on the correlation between TcB values and high STB concentrations, TcB values >15 mg per 100 ml should be confirmed with a serum bilirubin test.⁸ Similarly, should there be a discrepancy between the TcB result and the visual appearance of an infant, a blood test should be performed. In most population

Table 3 Laboratory tests that should be performed in the evaluation of a hyperbilirubinemic neonate

1. Complete blood count, reticulocyte count, red-cell morphology
2. Blood group and DAT test (if not already performed)
3. G-6-PD test (if not already performed)
4. Direct bilirubin fraction should the hyperbilirubinemia be persistent or in the presence of hepatic disease or systemic disease with hepatic manifestations

Abbreviations: DAT, direct antibody titer; G-6-PD, glucose-6-phosphate dehydrogenase.

groups, including a sample of babies tested in Jerusalem (Kaplan M and Hammerman C, unpublished data), the TcB reading tends to read lower than the actual PTB value. In each nursery/ laboratory setting, the mean difference and upper limit of range between TcB and STB readings can be determined and used to correct the TcB reading to an estimated STB concentration, or to determine a cutoff point above which an STB determination should be performed. As with STB, the TcB readings should be plotted on the bilirubin nomogram for assessment. Where available, the committee recommends obtaining a TcB reading at least once during the birth hospitalization, preferably close to discharge. As phototherapy causes a bleached appearance of the skin, TcB measurements should not be used in newborns being or having been treated with phototherapy.

Prediction of neonatal hyperbilirubinemia and discharge planning

Neonates are nowadays discharged from birth hospitalization at or around 48 h, and from some Israeli hospitals even earlier. At this time, the STB has not yet peaked and may do so, with resultant hyperbilirubinemia, when the baby is already at home.²⁶ It is therefore of utmost importance, prior to discharge, to estimate the risk of any neonate developing hyperbilirubinemia. On the basis of the AAP recommendations,⁸ the committee recommends use of one of the following two approaches:

- (a) risk assessment in all infants, and an STB test should jaundice become clinically apparent or,
- (b) risk assessment combined with universal predischarge bilirubin testing. Universal bilirubin testing implies a routine STB test on each infant prior to discharge, and estimation of

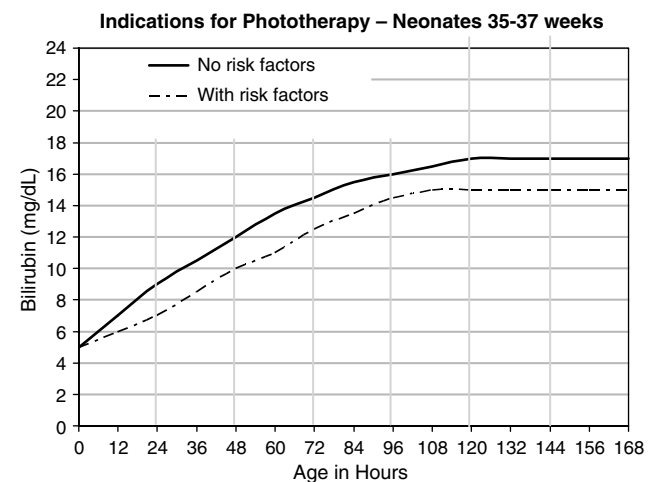


Figure 1 Indications for phototherapy in neonates 35^{0/7} to 37^{6/7} weeks gestation, with and without risk factors. (Graphs are adapted from the recommendations of the AAP.⁸) AAP, American Academy of Pediatrics.

the subsequent risk of developing hyperbilirubinemia by determining its position on the hour of life-specific bilirubin nomogram (Figure 1). To avoid an additional blood-drawing procedure, the bilirubin test may be performed simultaneously with routine metabolic testing.

The committee realizes that there may be financial or manpower constraints in achieving universal predischarge screening. When available, TcB screening may be a helpful adjunct in predischarge screening. Ease of performance and non-invasiveness may promulgate the incorporation of universal predischarge bilirubin screening into routine practice. The 75th percentile for STB (beginning of the intermediate high-risk zone) may be a useful starting point for determining the need for follow-up bilirubin determinations. As the 75th percentile is about 2 to 3 mg bilirubin higher than the 40th percentile, and a TcB reading may be 2 to 3 mg per 100 ml lower than the STB, a TcB reading >40th percentile on the bilirubin nomogram may be a useful indicator for performing STB measurements.

Predischarge bilirubin testing may be useful to formulate discharge and follow-up plans in Table 4. Guidelines for discharge and post-discharge bilirubin monitoring, based on a predischarge bilirubin test, when performed, appear in the section: Interpretation of the serum total bilirubin value. These guidelines refer to a single STB test. In the event, there is more than one STB result, the relationship of an individual infant's bilirubin trajectory can be compared with that of the bilirubin nomogram to modify prescribed planning. The STB percentile value should be assessed in combination with apparent risk factors.

In those situations where universal bilirubin testing is not being performed, predischarge STB determination may be considered in high-risk situations including G-6-PD deficiency, positive DAT and early discharge (prior to 48 h).

Post-discharge follow-up

Hyperbilirubinemia may develop both in the absence of identifiable risk factors and without clinically significant jaundice having been present at the time of discharge.⁴¹ Many newborns who entered the Kernicterus Registry were readmitted after having been discharged as healthy babies from birth hospitalization.^{5,6} A recent study in Jerusalem demonstrated that 21.6% of all neonates treated with phototherapy had been readmitted, whereas 42% of those readmitted had not been regarded as sufficiently jaundiced to warrant a predischarge bilirubin determination.⁴² Rigorous follow-up of every baby within a few days of discharge would identify many in whom hyperbilirubinemia is developing at home. We recognize that our health services may not yet be completely geared to seeing each and every newborn shortly after discharge, these Well Baby stations do not function on the Sabbath and Jewish holidays and Health Fund Clinics function on an emergency basis

only on these days. Despite these limitations, the committee recommends assessment for the development of jaundice by a health-care professional (Well Baby Clinic, family practitioner of pediatrician) of each baby within 2 to 3 days of discharge.

Guidelines for phototherapy

- (1) The appropriate graphs (Figures 1 and 2) indicating the commencement of phototherapy at any specific age should be chosen according to the following categories:
 - (a) gestational age (i) ≥ 38 weeks or (ii) $35^{0/7}$ to $37^{6/7}$ weeks,
 - (b) presence of (i) one major risk factor or two minor risk factors for hyperbilirubinemia or (ii) absence of risk factors for hyperbilirubinemia.⁸
- (2) It is recommended that at least two STB determinations be performed daily, and more, according to clinical judgment, for any neonate receiving phototherapy.
- (3) Phototherapy should be discontinued when the STB decreases to 12 to 13 mg per 100 ml, or to between the 40th and the 75th percentiles. The lower percentile value should be considered in the presence of risk factors.
- (4) Usually there is no need to discontinue nursing while under phototherapy.
- (5) In the event in which the STB continues to rise despite phototherapy, the intensity of phototherapy may be increased by adding additional banks of lights, placing the infant on a phototherapy mattress, or placing the lights closer to the baby (the latter should not be done if halogen lamps are being used as these may burn the baby if placed too close—see manufacturer's instructions).

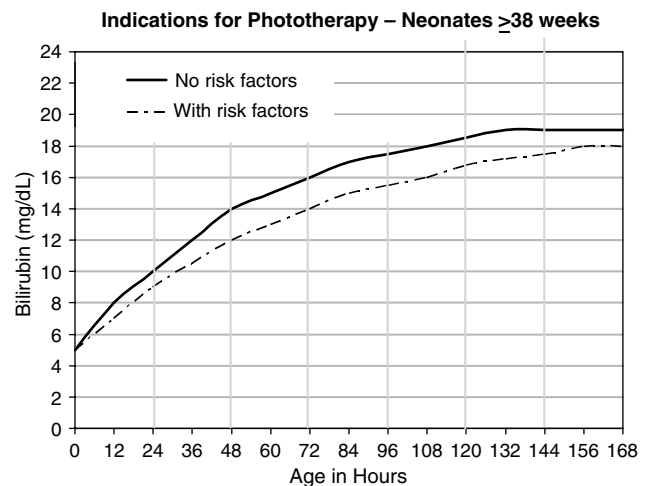


Figure 2 Indications for phototherapy in term neonates $\geq 38^{0/7}$ weeks gestation, with and without risk factors. (Graphs are adapted from the recommendations of the AAP.⁸) AAP, American Academy of Pediatrics.

- (6) The committee does not recommend any specific phototherapy unit. The reader is referred to Appendix 2 of the AAP hyperbilirubinemia statement (2004) for guidelines regarding the effective use of phototherapy, measurement of irradiance and other practical issues.

Follow-up after discontinuation of phototherapy

Post-phototherapy bilirubin rebound has been studied including two Israeli centers.^{43–45} In the absence of hemolysis, rebound did not appear to be a serious phenomenon.⁴³ However, when all newborns requiring phototherapy were evaluated in a Jerusalem population, rebound to levels of STB > 15 mg per 100 ml and even exceeding 20 mg per 100 ml was reported.⁴⁴ Levels of STB reported may be of clinical significance or concern in the presence of hemolysis or additional risk factors. Subgroups at high risk for rebound included neonates with positive DAT, gestational age < 37 weeks and in those in whom phototherapy was commenced within the first 3 days of life. Therefore, in high-risk groups (and possibly in other neonates as well), the STB should be closely monitored following discontinuation of phototherapy. At least 12 h, and preferably 24 h, should elapse to allow sufficient time for the STB to rebound. Usually it is not necessary for the baby to remain hospitalized to observe for rebound, provided the family can be trusted to return for a bilirubin test.

The following guidelines for further follow-up or discharge may be used:

- (1) decrease in post-phototherapy STB; discharge neonate from further follow-up,
- (2) increase in STB in parallel with the bilirubin nomogram; follow-up according to the nomogram in conjunction with Table 2,
- (3) increase in STB more rapidly than expected from the nomogram: repeat within 12 to 24 h according to clinical judgment.

Reinstitution of phototherapy. If the STB were to rebound substantially, phototherapy should be reinstated according to the guidelines in Figure 2, according to the age of the infant at the time of reassessment.

Use of intravenous immune globulin

In conditions of isoimmunization, IVIG has been shown to reduce hemolysis⁴⁶ and to reduce the need for exchange transfusion.⁴⁷ Use of IVIG can be considered in hyperbilirubinemic newborns with a positive DAT and evidence of hemolysis. In some cases, use of IVIG can be considered in the presence of ABO blood group incompatibility (mother blood group O, baby A or B) but negative DAT, provided the jaundice is behaving as if it were of hemolytic nature (see Table 2). However, in such cases, a cause for hemolysis other than isoimmunization should be sought.

Because IVIG is a biological preparation with the potential of complications, and as phototherapy may be successful in containing the rise in STB in many instances of ABO heterospecificity rendering the IVIG unnecessary, the committee recommends a 4-h trial of intensive phototherapy prior to administering IVIG. In cases of non-ABO isoimmunization such as anti-c or anti-e immunization, a shorter trial period of phototherapy may be appropriate. Not all newborns with a positive DAT will necessarily develop hyperbilirubinemia and IVIG should not be administered until it is apparent that hyperbilirubinemia is progressing.

Indications for use of IVIG

The following guideline applies to ABO incompatibility with positive DAT. In cases of non-ABO isoimmunization, IVIG may be used at lower levels of STB, depending on the rate of rise, response or lack thereof to phototherapy and clinical judgment.

<24 h: Following a 4-h trial of intensive phototherapy, STB > 16 or 2 to 3 mg per 100 ml less than the recommended bilirubin level for performing exchange transfusion (below), whichever comes first.

>24 h: Following a 4-h trial of intensive phototherapy, STB level > 18 or 2 to 3 mg per 100 ml below the level for performing exchange transfusion, whichever comes first.

Dose: 0.5 to 1.0 g per 100 ml by slow intravenous infusion, over 3 to 4 h.

On completion of the infusion, an STB determination should be obtained.

Exchange transfusion

Ideally, in extreme cases (STB > 25 mg per 100 ml), in the presence of clinical signs of bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonus, fever, high-pitched cry), or should there be a multiplicity of risk factors, exchange transfusion should be performed as soon as it is practically feasible. However, the committee is aware that preparation of blood by the blood bank for the exchange transfusion, or preparation of the infant for the exchange, including obtaining venous access, may be time consuming. In such situations, the exchange should be undertaken in as short a time as possible. Intense phototherapy should be provided in the interim. Should the STB decrease to below exchange transfusion levels during the waiting period, it may be prudent to continue intense phototherapy, provided there is a steady decline in the STB concentration. In less acute situations, transfusion should usually be performed after a trial of 3 to 4 h of intense phototherapy. The indications for exchange transfusion in Table 5 are based on those of the AAP,⁸ although in different format. Exchange transfusion is nowadays a rarely performed procedure.⁴⁸ As there may be associated morbidity and mortality,⁴⁹ it should be performed under the direct supervision of a neonatologist and preferably in an intensive care setting.

Table 4 Discharge planning and follow-up program according to the STB percentile at the time of discharge

| Bilirubin percentile | Follow-up plan |
|--|--|
| <40th percentile (low-risk zone) | Discharge from hospital. Clinical assessment at Well Baby Clinic, pediatrician or family practitioner within 2–4 days. |
| 40th–75th percentile (low-intermediate risk zone) | |
| (a) Term infant, no risk factors | Clinical evaluation within 48 h STB according to clinical judgment |
| (b) Premature infant (≤ 37 weeks), or term with risk factors | STB test within 48 h |
| 75th–95th percentile (high-intermediate risk zone) | STB test within 24 h |
| >95th percentile (high-risk zone) | Determine whether meets criteria for phototherapy (see below) |
| | Consider delaying discharge Repeat bilirubin within 6–12 h |

Abbreviation: STB, serum total bilirubin.

In the presence of risk factors, the timing of repeat STB testing or follow-up may be brought forward, according to clinical judgment.

Table 5 Recommendations for exchange transfusion

| Age (h) | ≥ 38 weeks gestation | 35–37 weeks gestation |
|-------------------------------------|---------------------------|-----------------------|
| <i>(A) Hemolytic conditions</i> | | |
| 0–12 | 14 (mg per 100 ml) | 12–13 (mg per 100 ml) |
| 12–24 | 16 | 15 |
| 24–48 | 18 | 16 |
| 48–72 | 20 | 18 |
| 72–96 | 20 | 18 |
| >96 | 20 | 18 |
| <i>(B) Non-hemolytic conditions</i> | | |
| 0–12 | 18 (mg per 100 ml) | 15 (mg per 100 ml) |
| 12–24 | 20 | 18 |
| 24–48 | 20 | 18 |
| 48–72 | 23 | 20 |
| 72–96 | 23 | 20 |
| >96 | 25 | 20 |

Preliminary approach to the infant with prolonged jaundice (> 10 to 14 days)

Although the investigation of the newborn with prolonged jaundice is not integral to the management of neonatal hyperbilirubinemia

or prevention of kernicterus, the following approach for initial workup is supplied.

- (1) Assess infant by gestational age, history, including history of jaundice in siblings, physical examination, nursing or formula feeding, success of nursing, weight gain.
- (2) Maternal and newborn blood group, DAT.
- (3) Fractionate bilirubin (direct and indirect components).
- (4) Send thyroid function tests.
- (5) Urinalysis, urine culture, reducing substances.
- (6) In most cases, initially, there is no need for liver enzyme tests, except in cases in which the direct bilirubin component is high (greater than 20% of the total bilirubin or >2 mg per 100 ml).
- (7) In the event of a persistently high direct bilirubin component, an abdominal ultrasound should be obtained and the baby investigated for causes of cholestatic jaundice.

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