MANAGEMENT OF HYPERBILIRUBINEMIA IN THE NEWBORN INFANT 35 OR MORE WEEKS OF GESTATION

AMERICAN ACADEMY OF PEDIATRICS

CLINICAL PRACTICE GUIDELINE

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Goals

- reduce the incidence of severe hyperbilirubinemia and bilirubin encephalopathy
- minimizing the risks of unintended harm such as maternal anxiety, decreased breastfeeding, and unnecessary costs or treatment

Recommendations

1. Promote and support successful breastfeeding.

2. Establish nursery protocols for the identification and evaluation of hyperbilirubinemia.

3. Measure the total serum bilirubin (TSB) or transcutaneous bilirubin (TcB) level on infants jaundiced in the first 24 hours.

Recommendations

4. Recognize that visual estimation of the degree of jaundice can lead to errors, particularly in darkly pigmented infants.

5. Interpret all bilirubin levels according to the infant’s age in hours

6. Recognize that infants at less than 38 weeks’ gestation, particularly those who are breastfed, are at higher risk of developing hyperbilirubinemia and require closer surveillance and monitoring.

Recommendations

7. Perform a systematic assessment on all infants before discharge for the risk of severe hyperbilirubinemia.

8. Provide parents with written and verbal information about newborn jaundice.

9. Provide appropriate follow-up based on the time of discharge and the risk assessment.

10. Treat newborns, when indicated, with phototherapy or exchange transfusion.

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8. Provide parents with written and verbal information about newborn jaundice.

9. Provide appropriate follow-up based on the time of discharge and the risk assessment.

10. Treat newborns, when indicated, with phototherapy or exchange transfusion.

PRIMARY PREVENTION

the AAP recommends breastfeeding for all healthy term and nearterm newborns

RECOMMENDATION 1.0: *Clinicians should advise mothers to nurse their infants at least 8 to 12 times per day for the first several days*

RECOMMENDATION 1.1: *The AAP recommends against routine supplementation of nondehydrated breastfed infants with water or dextrose water*

SECONDARY PREVENTION

1. Blood typing

RECOMMENDATION 2.0: *Clinicians should perform ongoing systematic assessments during the neonatal period for the risk of an infant developing severe hyperbilirubinemia.*

RECOMMENDATION 2.1: *All pregnant women should be tested for ABO and Rh (D) blood types and have a serum screen for unusual isoimmune antibodies.*

RECOMMENDATION 2.1.1: *If a mother has not had prenatal blood grouping or is Rh-negative, a direct antibody test (or Coombs' test), blood type, and an Rh (D) type on the infant's (cord) blood are strongly recommended.*

RECOMMENDATION 2.1.2: *If the maternal blood is group O, Rh-positive, it is an option to test the cord blood for the infant's blood type and direct antibody test, but it is not required provided that there is appropriate surveillance, risk assessment before discharge, and follow-up*

2. Clinical assessment

RECOMMENDATION 2.2: *Clinicians should ensure that all infants are routinely monitored for the development of jaundice, and nurseries should have established protocols for the assessment of jaundice. Jaundice should be assessed whenever the infant's vital signs are measured but no less than every 8 to 12 hours*

RECOMMENDATION 2.2.1: Protocols for the assessment of jaundice should include the circumstances in which nursing staff can obtain a TcB level or order a TSB measurement

3.Laboratory Evaluation

- RECOMMENDATION 3.0: *A TcB and/or TSB measurement should be performed on every infant who is jaundiced in the first 24 hours after birth and timing of a repeat TSB measurement will depend on the zone in which the TcB or TSB falls*
- RECOMMENDATION 3.1*: A TcB and/or TSB measurement should be performed if the jaundice appears excessive for the infant's age*
- RECOMMENDATION 3.2: *All bilirubin levels should be interpreted according to the infant's age in hours*

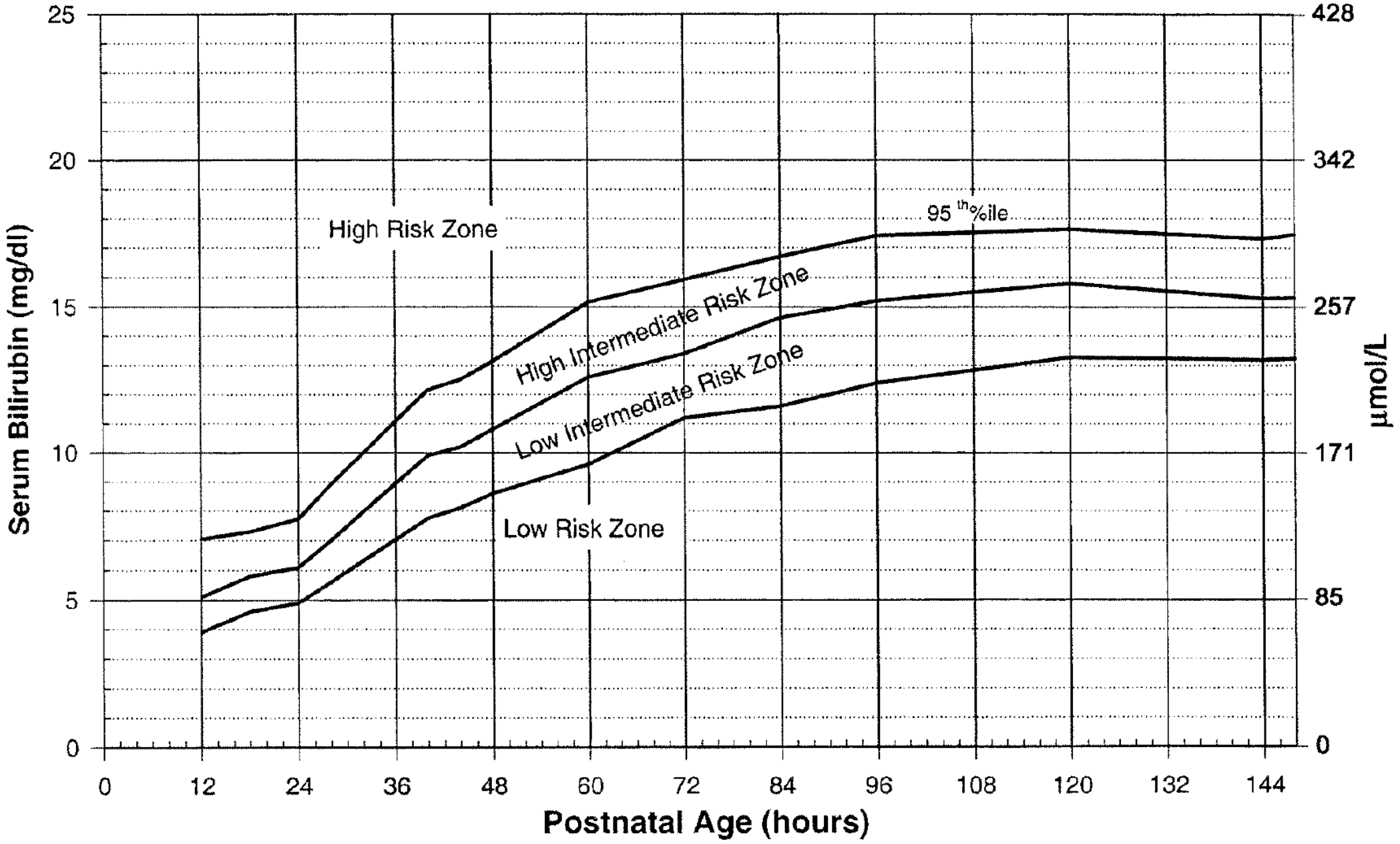
TABLE 1. Laboratory Evaluation of the Jaundiced Infant of 35 or More Weeks' Gestation

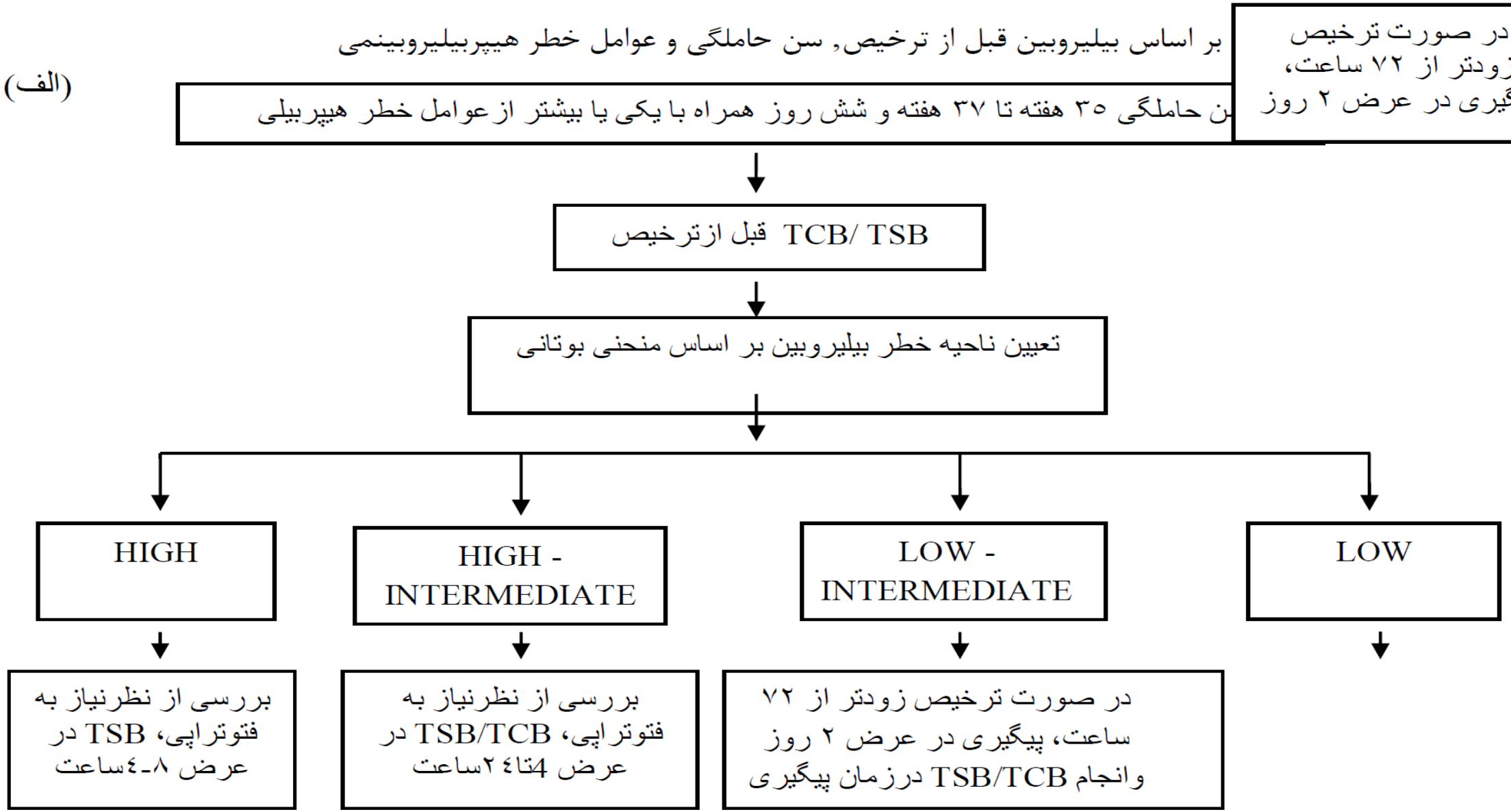
Indications	Assessments
Jaundice in first 24 h	Measure TcB and/or TSB
Jaundice appears excessive for infant's age	Measure TcB and/or TSB
Infant receiving phototherapy or TSB rising rapidly (ie, crossing percentiles [Fig 2]) and unexplained by history and physical examination	Blood type and Coombs' test, if not obtained with cord blood Complete blood count and smear Measure direct or conjugated bilirubin It is an option to perform reticulocyte count, G6PD, and $ETCO_c$, if available Repeat TSB in 4–24 h depending on infant's age and TSB level
TSB concentration approaching exchange levels or not responding to phototherapy	Perform reticulocyte count, G6PD, albumin, $ETCO_c$, if available
Elevated direct (or conjugated) bilirubin level	Do urinalysis and urine culture. Evaluate for sepsis if indicated by history and physical examination
Jaundice present at or beyond age 3 wk, or sick infant	Total and direct (or conjugated) bilirubin level If direct bilirubin elevated, evaluate for causes of cholestasis Check results of newborn thyroid and galactosemia screen, and evaluate infant for signs or symptoms of hypothyroidism

ارزیابی آزمایشگاهی نوزادان دچار زردی با سن حاملگی ۳۵ هفته و بیشتر و مداخلات درمانی:

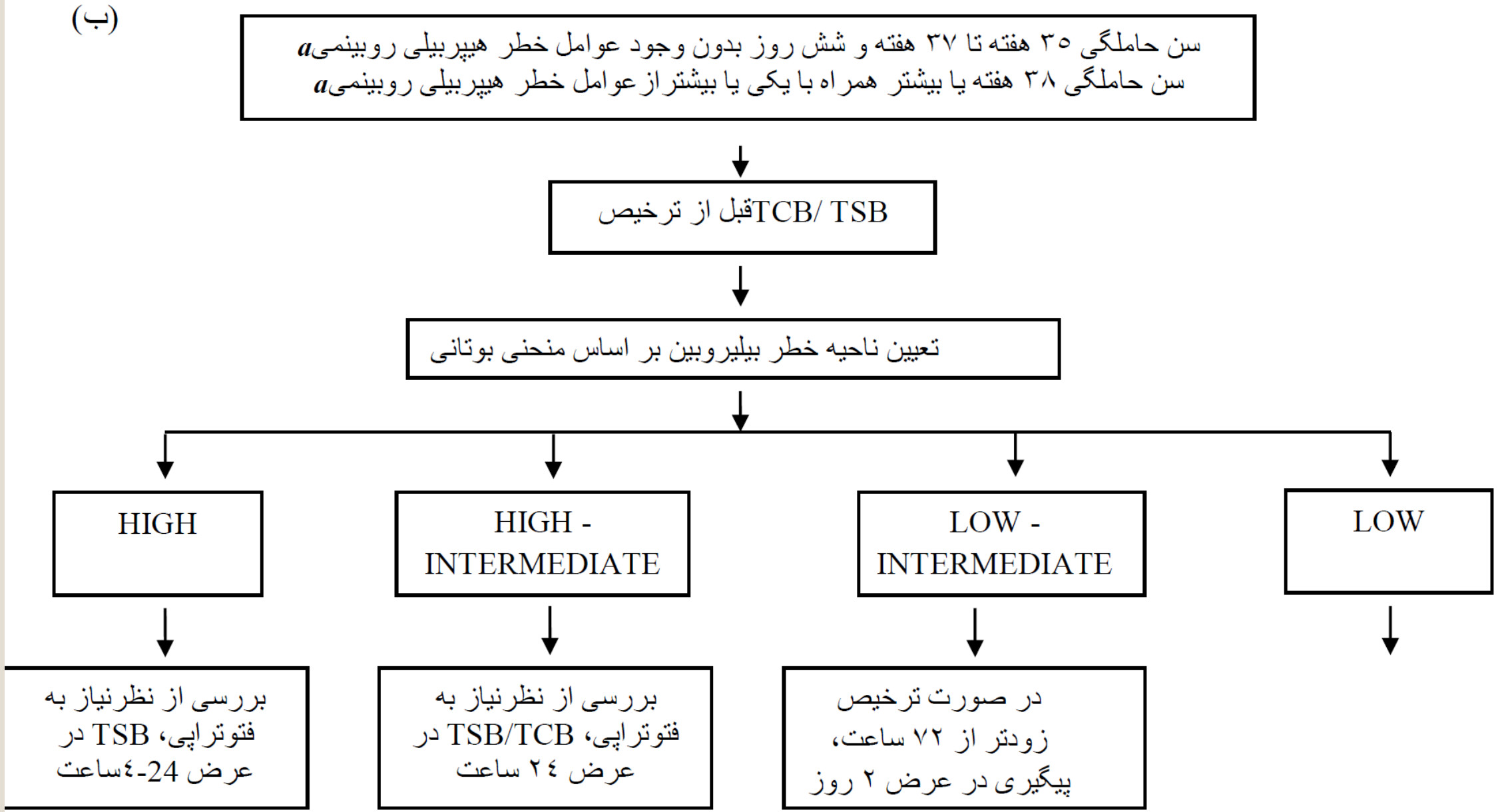
اندیکاسیون	ارزیابی ها
زردی در ۲۴ ساعت اول	چک TsB یا TcB
زردی به نسبت سن نوزاد بیشتر به نظر میرسد	چک TsB یا TcB
نوزاد در حال دریافت فتوتراپی , و یاافزایش سریع بیلیروبین توتال (به طوری که از صدک پیش بینی شده بر اساس جدول بوتانی بگذرد و زردی با توجه به شرح حال و معاینه فیزیکی قابل توجیه نباشد)	آزمایشات الزامی:تعیین گروه خون و انجام تست کومبس,CBC/diff, لام خون محیطی, بیلی روبین مستقیم آزمایشات اختیاری:رتیکولوسیتG6PD,
عدم پاسخ به فتوتراپی, و یا غلظت بیلی روبین به حد تعویض خون برسد	رتیکولوسیتG6PD,
افزایش بیلیروبین مستقیم	آزمایش کامل ادرار و کشت ادرار, ارزیابی سپسیس بر اساس شرح حال یا معاینه بالینی
ادامه زردی در هفته سوم تولد یا بعد از آن, و یا بد حال بودن نوزاد	اندازه گیری بیلی روبین تام و مستقیم, ارزیابی از نظر علل کلستاز در صورت افزایش بیلی روبین مستقیم, کنترل نتایج آزمایش تیروئید و نتیجه غربالگری گالاکتوزمی, ارزیابی نوزاد از نظر علایم و نشانه های هیپوتیروئیدی

Total serum billirubin:TsB ;Transcutaneous billirubin:TcB;Glucose 6 phosphate dehydrogenase:G6PD

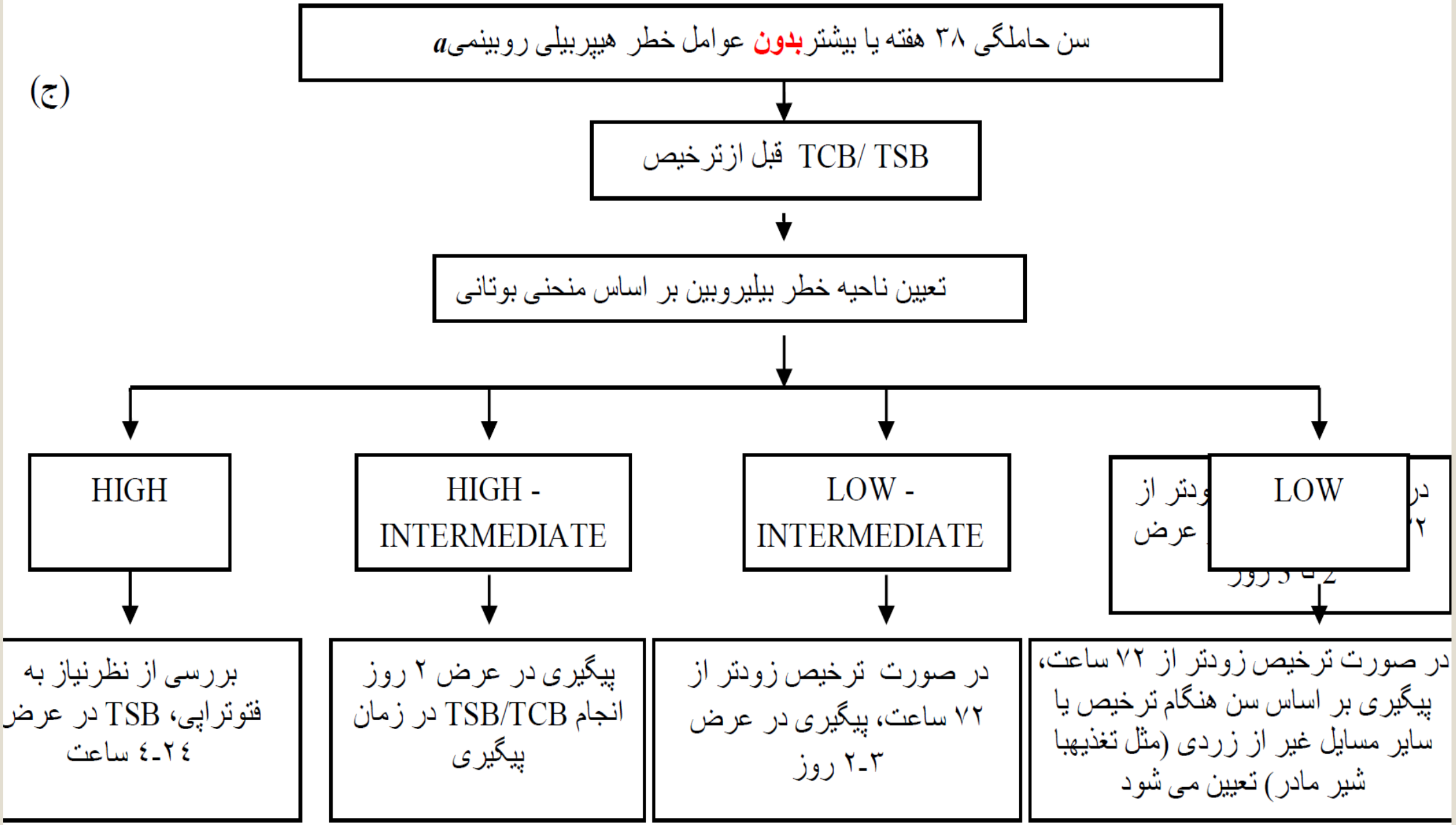

Serum Bilirubin (mg/dl)
25
20
15
10
5
0
428
342
257
171
85
0
µmol/L
High Risk Zone
95 th%ile
High Intermediate Risk Zone
Low Intermediate Risk Zone
Low Risk Zone
0
12
24
36
48
60
72
84
96
108
120
132
144
Postnatal Age (hours)


(الف)
بر اساس بیلیروبین قبل از ترخیص, سن حاملگی و عوامل خطر هیپربیلیروبینمی
ن حاملگی ۳۵ هفته تا ۳۷ هفته و شش روز همراه با یکی یا بیشتر ازعوامل خطر هیپربیلی
در صورت ترخیص زودتر از ۷۲ ساعت، پیگیری در عرض ۲ روز
TCB/ TSB قبل ازترخیص
تعیین ناحیه خطر بیلیروبین بر اساس منحنی بوتانی
HIGH
HIGH - INTERMEDIATE
LOW - INTERMEDIATE
LOW
بررسی از نظرنیاز به فتوتراپی، TSB در عرض ۸-٤ساعت
بررسی از نظرنیاز به فتوتراپی، TSB/TCB در عرض 4تا٢٤ساعت
در صورت ترخیص زودتر از ۷۲ ساعت، پیگیری در عرض ۲ روز وانجام TSB/TCB درزمان پیگیری

(ب)


سن حاملگی ۳۵ هفته تا ۳۷ هفته و شش روز بدون وجود عوامل خطر هیپربیلی روبینمی*a*
سن حاملگی ۳۸ هفته یا بیشتر همراه با یکی یا بیشتر از عوامل خطر هیپربیلی روبینمی*a*
TCB/ TSBقبل از ترخیص
تعیین ناحیه خطر بیلیروبین بر اساس منحنی بوتانی
HIGH
HIGH - INTERMEDIATE
LOW - INTERMEDIATE
LOW
بررسی از نظرنیاز به فتوتراپی، TSB در عرض 24-٤ساعت
بررسی از نظرنیاز به فتوتراپی، TSB/TCB در عرض ٢٤ ساعت
در صورت ترخیص زودتر از ۷۲ ساعت، پیگیری در عرض ۲ روز

(ج)


سن حاملگی ۳۸ هفته یا بیشتر بدون عوامل خطر هیپربیلی روبینمی a
TCB/ TSB قبل از ترخیص
تعیین ناحیه خطر بیلیروبین بر اساس منحنی بوتانی
LOW
LOW - INTERMEDIATE
HIGH - INTERMEDIATE
HIGH
در صورت ترخیص زودتر از ۷۲ ساعت، پیگیری بر اساس سن هنگام ترخیص یا سایر مسایل غیر از زردی (مثل تغذیهبا شیر مادر) تعیین می شود
در صورت ترخیص زودتر از ۷۲ ساعت، پیگیری در عرض ۲-۳ روز
پیگیری در عرض ۲ روز انجام TSB/TCB در زمان پیگیری
بررسی از نظرنیاز به فتوتراپی، TSB در عرض ۲۴-۴۸ ساعت

ریسک فاکتورهایی که احتمال بروز هیپر بیلیروبینمی شدید را پیش گویی می کن عبارتند از:

۱- تغذیه انحصاری با شیر مادر بخصوص اگر تغذیه به خوبی انجام نشود و یا کاهش وزن بیش از ۸ الی ۱۰ درصد

۲- وجود بیماری همولیتیک ایمون یا غیر ایمیون

۳- سابقه ایکتر در فرزند قبلی

۴- سفال هماتوما و یا کبودی شدید

۵- نژاد اسیای شرقی

4.Cause of Jaundice

RECOMMENDATION 4.1: The possible cause of jaundice should be sought in an infant receiving phototherapy or whose TSB level is rising rapidly (ie, crossing percentiles [Fig 2]) and is not explained by the history and physical examination

RECOMMENDATION 4.1.1: Infants who have an elevation of direct-reacting or conjugated bilirubin should have a urinalysis and urine culture. Additional laboratory evaluation for sepsis should be performed if indicated by history and physical examination

- RECOMMENDATION 4.1.2: *Sick infants and those who are jaundiced at or beyond 3 weeks should have a measurement of total and direct or conjugated bilirubin to identify cholestasis . The results of the newborn thyroid and galactosemia screen should also be checked in these infants*

- RECOMMENDATION 4.1.3: *If the direct-reacting or conjugated bilirubin level is elevated, additional evaluation for the causes of cholestasis is recommended*

- RECOMMENDATION 4.1.4: *Measurement of the glucose-6-phosphate dehydrogenase (G6PD) level is recommended for a jaundiced infant who is receiving phototherapy and whose family history or ethnic or geographic origin suggest the likelihood of G6PD deficiency or for an infant in whom the response to phototherapy is poor*

- RECOMMENDATION 5.1: *Before discharge, every newborn should be assessed for the risk of developing severe hyperbilirubinemia, and all nurseries should establish protocols for assessing this risk. Such assessment is particularly important in infants who are discharged before the age of 72 hours*

- RECOMMENDATION 5.1.1: *The AAP recommends 2 clinical options used individually or in combination for the systematic assessment of risk: predischarge measurement of the bilirubin level using TSB or TcB and/or assessment of clinical risk factors. Whether either or both options are used, appropriate follow-up after discharge is essential*

TABLE 2. Risk Factors for Development of Severe Hyperbilirubinemia in Infants of 35 or More Weeks' Gestation (in Approximate Order of Importance)

Major risk factors
Predischarge TSB or TcB level in the high-risk zone (Fig 2)[25,31]
Jaundice observed in the first 24 h[30]
Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (eg, G6PD deficiency), elevated $ETCO_c$
Gestational age 35–36 wk[39,40]
Previous sibling received phototherapy[40,41]
Cephalohematoma or significant bruising[39]
Exclusive breastfeeding, particularly if nursing is not going well and weight loss is excessive[39,40]
East Asian race[39]*
Minor risk factors
Predischarge TSB or TcB level in the high intermediate-risk zone[25,31]
Gestational age 37–38 wk[39,40]
Jaundice observed before discharge[40]
Previous sibling with jaundice[40,41]
Macrosomic infant of a diabetic mother[42,43]
Maternal age ≥25 y[39]
Male gender[39,40]
Decreased risk (these factors are associated with decreased risk of significant jaundice, listed in order of decreasing importance)
TSB or TcB level in the low-risk zone (Fig 2)[25,31]
Gestational age ≥41 wk[39]
Exclusive bottle feeding[39,40]
Black race[38]*
Discharge from hospital after 72 h[40,44]

* Race as defined by mother's description.

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- East Asian race[39*]

Minor risk factors

- Predischarge TSB or TcB level in the high intermediate-risk zone[25,31]
- Gestational age 37–38 wk[39,40]
- Jaundice observed before discharge[40]
- Previous sibling with jaundice[40,41]
- Macrosomic infant of a diabetic mother[42,43]
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- Gestational age ≥41 wk[39]
- Exclusive bottle feeding[39,40]
- Black race[38*]
- Discharge from hospital after 72 h[40,44]

5.Hospital Policies and Procedures

- RECOMMENDATION 6.1: *All hospitals should provide written and verbal information for parents at the time of discharge, which should include an explanation of jaundice, the need to monitor infants for jaundice, and advice on how monitoring should be done*

6.Follow-up

- RECOMMENDATION 6.1.1: *All infants should be examined by a qualified health care professional in the first few days after discharge to assess infant well-being and the presence or absence of jaundice. The timing and location of this assessment will be determined by the length of stay in the nursery, presence or absence of risk factors for hyperbilirubinemia (Table 2 and Fig 2), and risk of other neonatal problems*

Timing of Follow-up

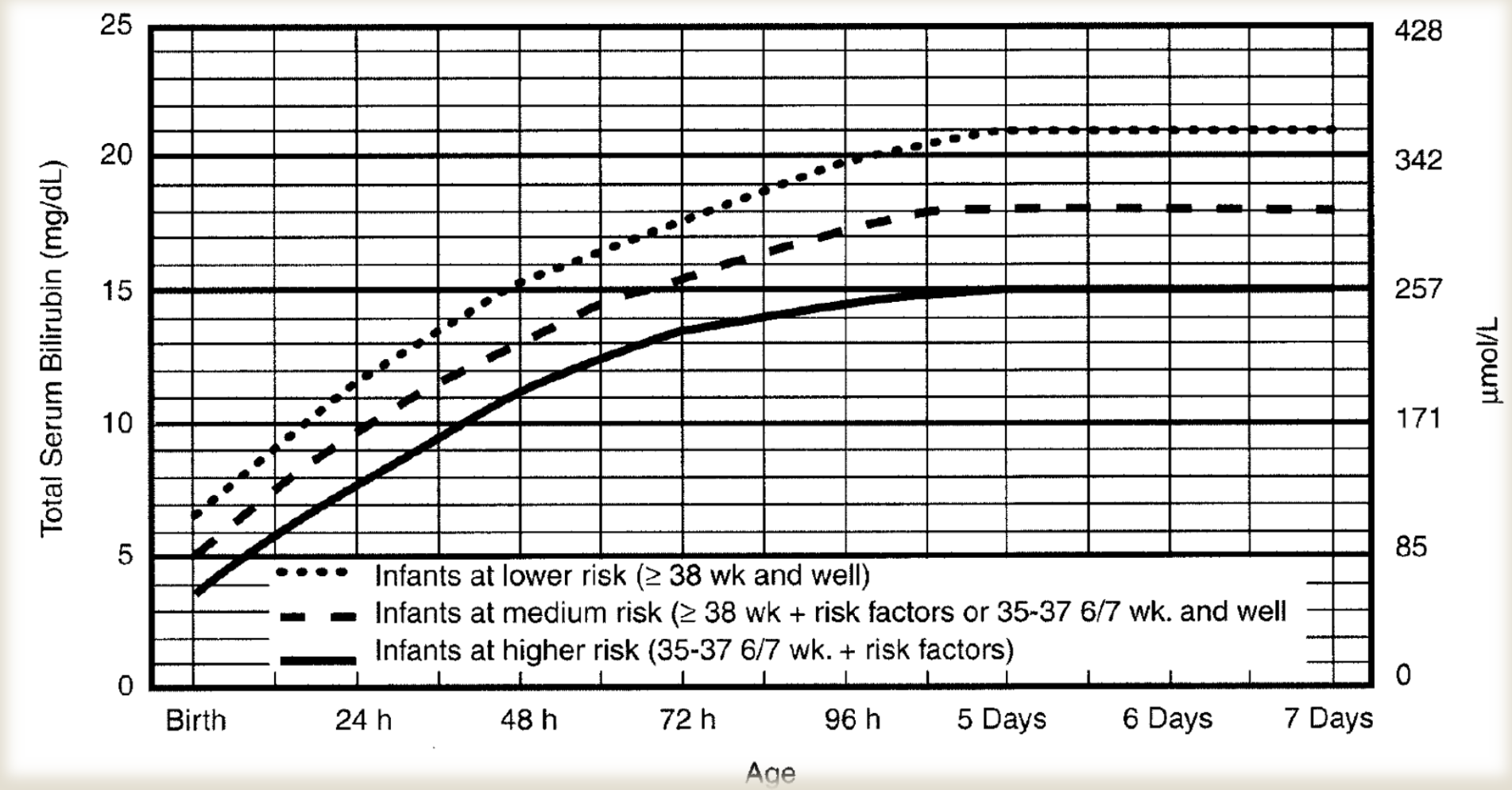
RECOMMENDATION 6.1.2: *Follow-up should be provided as follows:*

Infant Discharged	Should Be Seen by Age
Before age 24 h	72 h
Between 24 and 47.9 h	96 h
Between 48 and 72 h	120 h

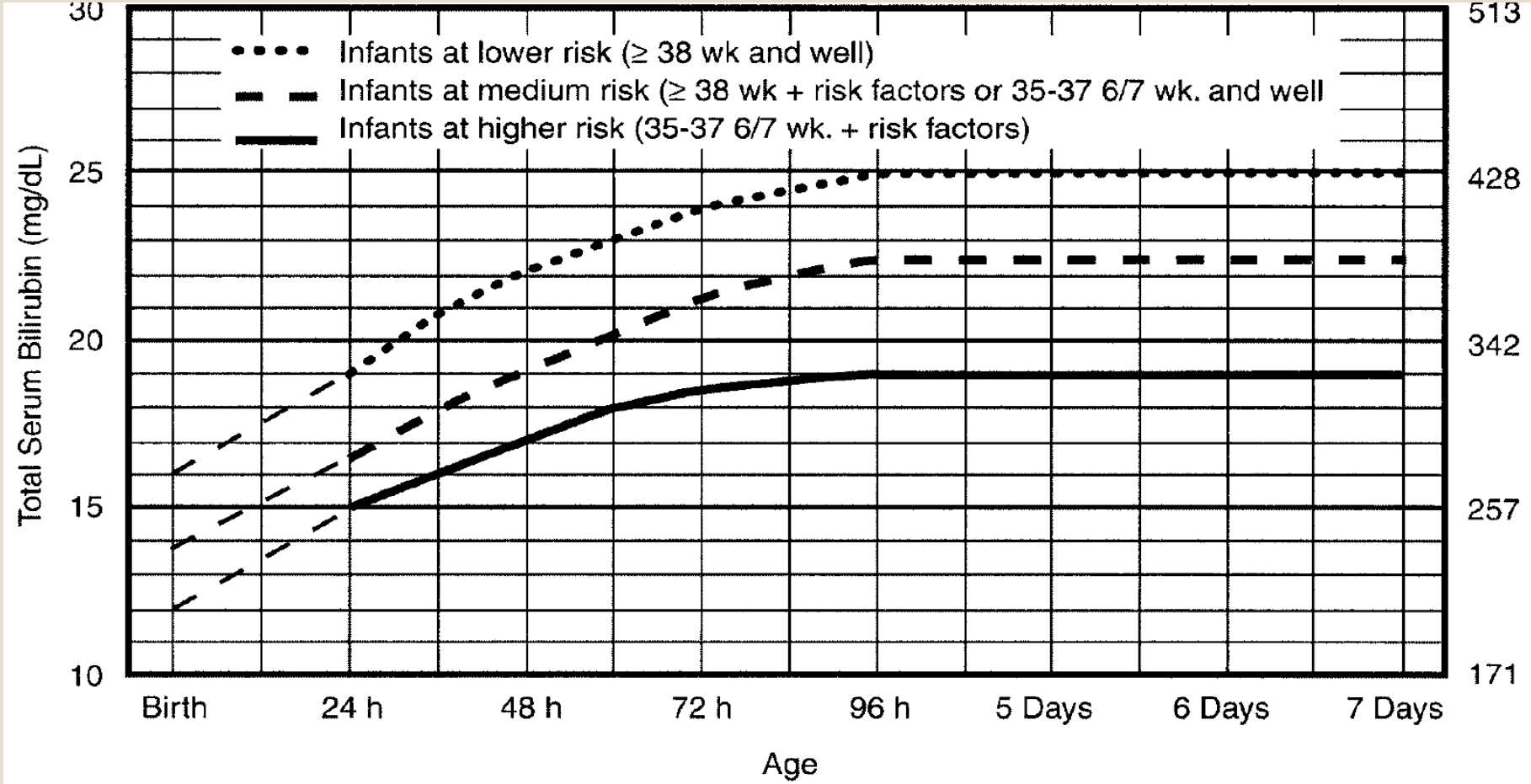
- RECOMMENDATION 6.1.3: *If appropriate follow-up cannot be ensured in the presence of elevated risk for developing severe hyperbilirubinemia, it may be necessary to delay discharge either until appropriate follow-up can be ensured or the period of greatest risk has passed (72-96 hours)*

- RECOMMENDATION 6.1.4: *The follow-up assessment should include the infant's weight and percent change from birth weight, adequacy of intake, the pattern of voiding and stooling, and the presence or absence of jaundice*

7.TREATMENT



- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin < 3.0g/dL (if measured)
- For well infants 35-37 6/7 wk can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wks and at higher TSB levels for those closer to 37 6/7 wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2-3 mg/dL (35-50mmol/L) below those shown but home phototherapy should not be used in any infant with risk factors.



- The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy.
- Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high pitched cry) or if TSB is ≥5 mg/dL (85 µmol/L) above these lines.
- Risk factors - isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis.
- Measure serum albumin and calculate B/A ratio (See legend)
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin
- If infant is well and 35-37 6/7 wk (median risk) can individualize TSB levels for exchange based on actual gestational age.

Treatment

- Use intensive phototherapy and/or exchange transfusion as indicated in Figs 3 and 4 (see Appendix 2 for details of phototherapy use)

Laboratory tests

- TSB and direct bilirubin levels
- Blood type (ABO, Rh)
- Direct antibody test (Coombs')
- Serum albumin
- Complete blood cell count with differential and smear for red cell morphology
- Reticulocyte count
- $ETCO_c$ (if available)
- G6PD if suggested by ethnic or geographic origin or if poor response to phototherapy
- Urine for reducing substances
- If history and/or presentation suggest sepsis, perform blood culture, urine culture, and cerebrospinal fluid for protein, glucose, cell count, and culture

Interventions

- If TSB ≥25 mg/dL (428 μmol/L) or ≥20 mg/dL (342 μmol/L) in a sick infant or infant <38 wk gestation, obtain a type and crossmatch, and request blood in case an exchange transfusion is necessary
- In infants with isoimmune hemolytic disease and TSB level rising in spite of intensive phototherapy or within 2–3 mg/dL (34–51 μmol/L) of exchange level (Fig 4), administer intravenous immunoglobulin 0.5–1 g/kg over 2 h and repeat in 12 h if necessary
- If infant's weight loss from birth is >12% or there is clinical or biochemical evidence of dehydration, recommend formula or expressed breast milk. If oral intake is in question, give intravenous fluids.

For infants receiving intensive phototherapy

- Breastfeed or bottle-feed (formula or expressed breast milk) every 2–3 h
- If TSB ≥25 mg/dL (428 μmol/L), repeat TSB within 2–3 h
- If TSB 20–25 mg/dL (342–428 μmol/L), repeat within 3–4 h. If TSB <20 mg/dL (342 μmol/L), repeat in 4–6 h. If TSB continues to fall, repeat in 8–12 h
- If TSB is not decreasing or is moving closer to level for exchange transfusion or the TSB/albumin ratio exceeds levels shown in Fig 4, consider exchange transfusion (see Fig 4 for exchange transfusion recommendations)
- When TSB is <13–14 mg/dL (239 μmol/L), discontinue phototherapy
- Depending on the cause of the hyperbilirubinemia, it is an option to measure TSB 24 h after discharge to check for rebound

- RECOMMENDATION 7.1.2: *If the TSB is at a level at which exchange transfusion is recommended (Fig 4) or if the TSB level is 25 mg/dL (428 mol/L) or higher at any time, it is a medical emergency and the infant should be admitted immediately and directly to a hospital pediatric service for intensive phototherapy. These infants should not be referred to the emergency department, because it delays the initiation of treatment*

Serum Albumin Levels and the Bilirubin/Albumin Ratio

- RECOMMENDATION 7.1.5*: It is an option to measure the serum albumin level and consider an albumin level of less than 3.0 g/dL as one risk factor for lowering the threshold for phototherapy use*

- RECOMMENDATION 7.1.6: *If an exchange transfusion is being considered, the serum albumin level should be measured and the bilirubin/albumin (B/A) ratio used in conjunction with the TSB level and other factors in determining the need for exchange transfusion*

Acute Bilirubin Encephalopathy

- RECOMMENDATION 7.1.7: *Immediate exchange transfusion is recommended in any infant who is jaundiced and manifests the signs of the intermediate to advanced stages of acute bilirubin encephalopathy61,62 (hypertonia, arching, retrocollis, opisthotonos, fever, highpitched cry) even if the TSB is falling*

Outpatient Management of the Jaundiced Breastfed Infant

- RECOMMENDATION 7.3: *In breastfed infants who require phototherapy (Fig 3), the AAP recommends that, if possible, breastfeeding should be continued. It is also an option to interrupt temporarily breastfeeding and substitute formula. This can reduce bilirubin levels and/or enhance the efficacy of phototherapy.In breastfed infants receiving phototherapy, supplementation with expressed breast milk or formula is appropriate if the infant's intake seems inadequate, weight loss is excessive, or the infant seems dehydrated.*

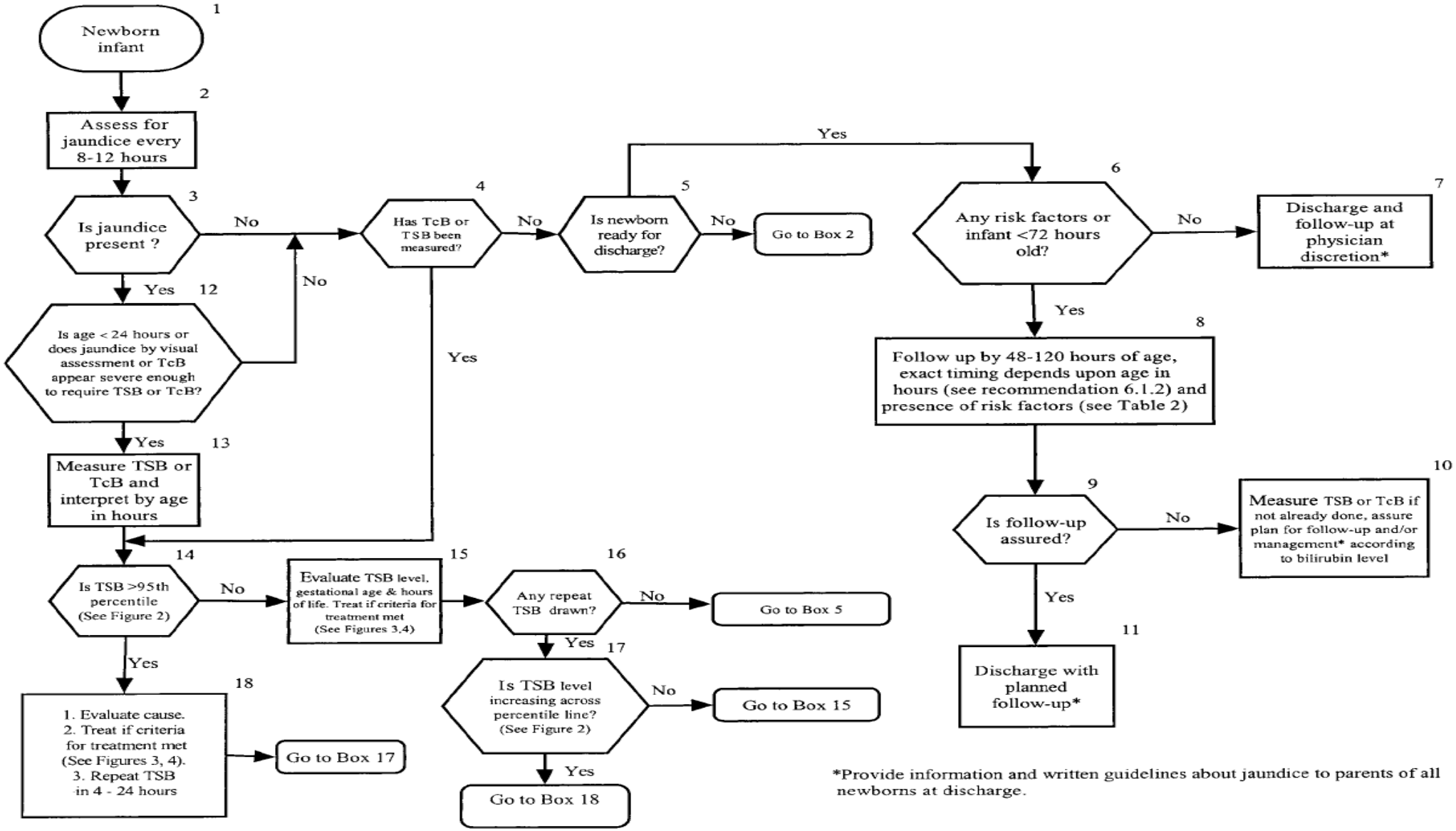
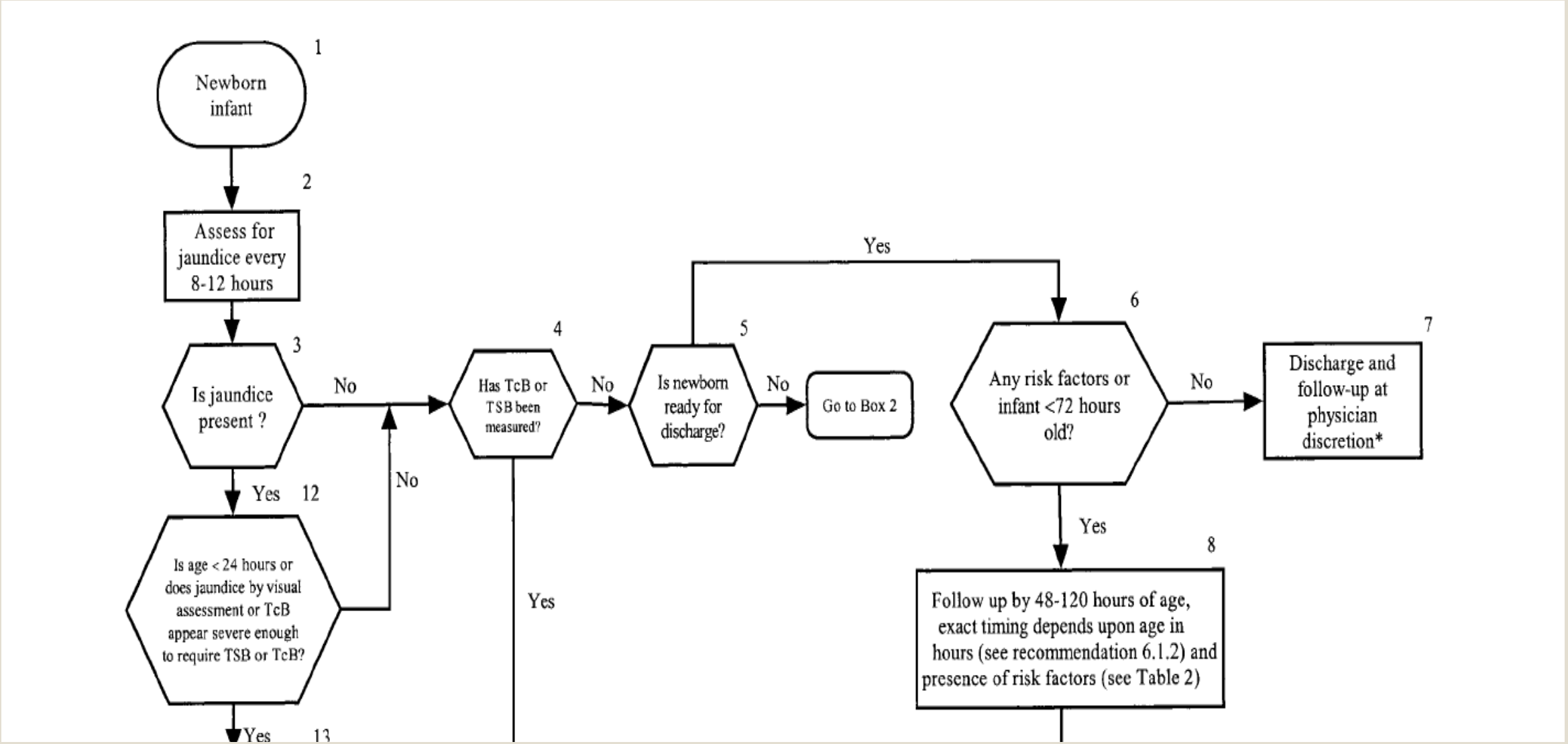


Fig 1. Algorithm for the management of jaundice in the newborn nursery.


1
Newborn infant
2
Assess for jaundice every 8-12 hours
3
Is jaundice present ?
No
4
Has TcB or TSB been measured?
No
5
Is newborn ready for discharge?
No
Go to Box 2
Yes
6
Any risk factors or infant <72 hours old?
No
7
Discharge and follow-up at physician discretion*
Yes
8
Follow up by 48-120 hours of age, exact timing depends upon age in hours (see recommendation 6.1.2) and presence of risk factors (see Table 2)
Yes
12
Is age < 24 hours or does jaundice by visual assessment or TcB appear severe enough to require TSB or TcB?
No
Yes
13
Yes

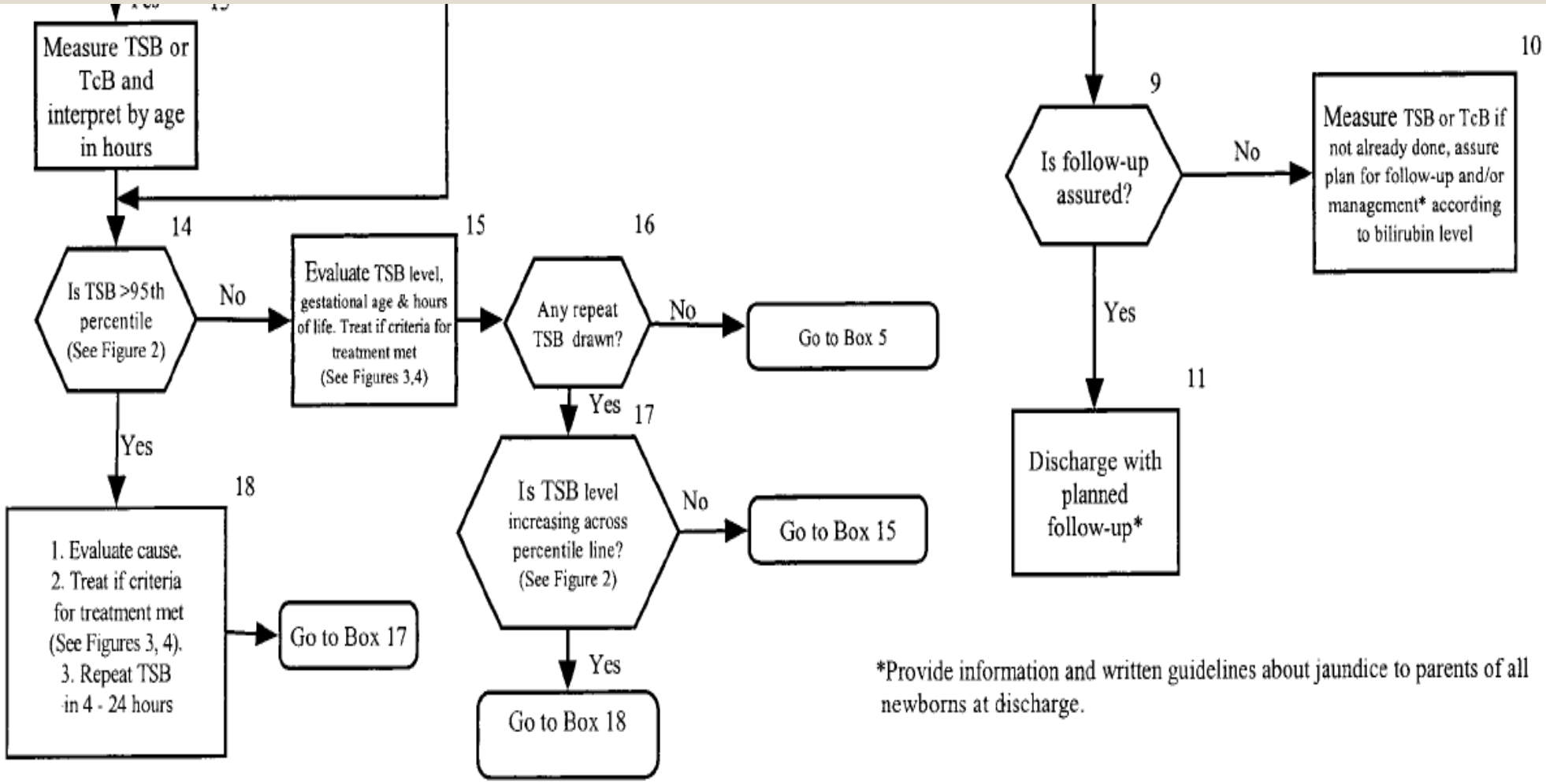


Fig 1. Algorithm for the management of jaundice in the newborn nursery.


با تشکر از توجه شما