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Original Article

Severe Hyperbilirubinemia in Term and Late Preterm Newborns: An Evidence-Based Clinical Practice Guideline Adapted for The Use in Egypt Based on The 'Adapted ADAPTE' Methodology

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Abstract

Background: The presented evidence-based clinical practice guideline (CPG) is proposed as a National CPG using an evidence-based and formal CPG adaptation methodology. **The purpose of this study** was to adapt the international CPGs' recommendations for term and late preterm neonates with severe hyperbilirubinemia to suit the healthcare system in the Egyptian context. This CPG provides a framework for prediction, prevention and management of severe hyperbilirubinemia in newborn infants of 35 or more weeks of gestation. The quality of evidence and strength of recommendations are indicated. The guideline adaptation group was chosen from various Egyptian Universities. There was an active involvement of a Multidisciplinary Review Committee following a standardized process. The Neonatology Guideline Adaptation Group (NGAG) was assigned individual health questions to cover the different sections of the required CPG. A literature search for source CPGs was carried out. The NGAG studied several guidelines. Critical appraisal was done by AGREE II (Appraisal of Guidelines for Research and Evaluation) Instrument to rate and select the appropriate guidelines. **Results**: The NGAG decided to adapt mainly the American Academy of Pediatrics Guideline (2004, 2009 & 2011) and for the questions which were not answered; the best and most relevant evidence available was used. Implementation tools were sought for to facilitate the application of the adapted CPG. **Conclusion:** The finalized CPG offers healthcare providers with applicable evidence-based guidance for severe neonatal hyperbilirubinemia in the Egyptian context. The Adapted ADAPTE method emphasized the value of collaborative clinical and methodological expert groups' efforts for adaptation of national guidelines.

Key words: Guidelines; bilirubin; hyperbilirubinemia; kernicterus, newborn

Introduction

Neonatal jaundice refers to yellow discoloration of the skin and sclera of newborn babies [1]. It is generally considered a benign self-limiting condition, affecting more than 60% of healthy term and 80% of preterm infants [2,3] . However, in some cases, severe neonatal hyperbilirubinemia (SNH) can lead to irreversible brain damage and kernicterus [4]. Surviving infants may acquire long-term neuro-developmental sequelae such as chorioathetoid cerebral palsy, sensorineural hearing loss, and growth and developmental delays. Acute bilirubin encephalopathy (ABE) and chronic bilirubin encephalopathy (CBE) are largely preventable if severe hyperbilirubinemia is identified early and treated promptly with effective phototherapy or, when indicated, exchange transfusion. In a recent systematic review in which severe neonatal hyperbilirubinemia was defined as that associated with acute bilirubin encephalopathy, exchange transfusion or death. The incidence of severe neonatal hyperbilirubinemia per 10,000 live births was found to be highest in the African region at 667.8, compared to 4.4/10, 000 in the Americans [5].

In Egypt, the numbers are not known; however in a recent study on 4000 well full-term newborns screened for jaundice, 1.9% had bilirubin levels in the high-risk zone on the Bhutani nomogram. This means that, in a population with 2.5 million new births per year a large group could be at risk for severe hyperbilirubinemia and its sequelae [6].

In the neonatal intensive care of Cairo university Children’s hospital, in 2011, 44/249 admitted jaundiced newborns not only had extreme hyperbilirubinemia, but presented with moderate to severe bilirubin encephalopathy and in a recently published follow up study in the same Neonatal Intensive Care Unit (NICU), 23/202 babies admitted with severe hyperbilirubinemia had abnormal

neurological examination at follow up [7, 8].

The root causes for these shocking numbers within the Egyptian community include parental ignorance of the risk of severe jaundice, absence of timely follow up for jaundiced newborns, as well as delay in proper intervention [9].

While tactics to prevent and treat severe neonatal hyperbilirubinemia must be sensitive to cultural and resource variations, the universality of root causes suggest that a common strategy should be applied to make kernicterus a very rare event throughout the world. A systematic approach should be developed in Egypt whereby newborn infants are monitored for risk of hyperbilirubinemia and prompt interventions followed to prevent acute bilirubin encephalopathy and kernicterus [9].

Clinical Practice Guidelines (CPGs) are tools for improving the quality and safety of healthcare services using a standardized process [10]. They are produced by a systematic review of the evidence and assessment of the benefit versus the harm of various care options resulting in statements that optimize patient's care [11]. The production of clinical practice guidelines using this approach is both costly and time consuming. Adaptation of CPG is a valid and efficient alternative to de novo development especially in resource-limited countries. It also provides a means to expedite the process and has been acknowledged by the World Health Organization (WHO) to advance guideline production. To date in Egypt there does not exist a standardized national CPG for the prediction, prevention and management of severe neonatal hyperbilirubinemia.

The aim of this work was to use the Adapted ADAPTE method of Alexandria University to provide an evidence-based CPG tailored to the needs of the Egyptian healthcare context that can be applied at all healthcare levels from outpatients to NICU settings, in order to prevent long-

term morbidity and mortality from severe neonatal hyperbilirubinemia.

Definitions used in this Guideline:

- **Kernicterus**: is the pathological finding of deep-yellow staining of neurons and neuronal necrosis of the basal ganglia and brainstem nuclei; and clinically associated with chronic bilirubin encephalopathy [12].
- **Acute bilirubin encephalopathy (ABE):** a clinical syndrome, that occurs in the presence of severe hyperbilirubinemia, presenting with various combinations of decreased feeding, lethargy, hypotonia and/or hypertonia, high-pitched cry, retrocollis, opisthotonus, setting sun sign, fever, seizures, and death [12].
- **Chronic bilirubin encephalopathy (CBE):** a clinical tetrad that occurs after the history of severe hyperbilirubinemia consisting of (1) a movement disorder consisting not only of athetosis and dystonia, but may also include spasticity and hypotonia, (2) auditory dysfunction consisting of sensory neural hearing loss or auditory dys-synchrony, (3) oculomotor impairments especially impairment of up-gaze, but also lateral gaze impairments including strabismus, and (4) dental enamel hypoplasia of the deciduous teeth [12].
- **Severe neonatal hyperbilirubinemia (SNH):** a total serum bilirubin (TSB) concentration greater than 20 mg/dL in the first 72 hours of life [12].
- **Critical or extreme hyperbilirubinemia**: a TSB concentration greater than 25 mg/dL during the first 28 days of life [12].

Methods

This study is part of a major project by the Egyptian Pediatric Clinical Practice Guidelines Committee (EPG) which was formulated by members of the Departments of Pediatrics from multiple Egyptian Universities. EPG is currently affiliated to the Supreme Council of the Egyptian University Hospitals (http://epg.edu.eg). The committee is

guided by a formal CPG adaptation methodology: The "Adapted ADAPTE" [13].

This CPG is prepared using the Adapted ADAPTE method of Alexandria University that was based on the ADAPTE Manual and Resource Tool Kit version 2.0, released by the ADAPTE Collaboration in 2009 [13-15]. This formal CPG adaptation process consists of three phases (i.e., set-up, adaptation, and finalization) and 24 steps with modifications in the steps and tools to suit the local healthcare context in health systems with limited resources like Egypt.

Guidelines adaptation methodology

Phase 1 (Set Up):

The topic of severe neonatal hyperbilirubinemia was chosen as a priority because it has been proven that with implementation of CPG in the western world the incidence of chronic bilirubin encephalopathy has declined dramatically compared to the numbers seen in low- and middle income countries. The patient population included in this CPG was late preterm and term newborns diagnosed with indirect hyperbilirubinemia or at risk for severe hyperbilirubinemia meeting the following criteria; age ≤ 28 days, weight ≥ 2.5 kg and GA ≥35 weeks. Preterm neonates and neonates with cholestasis were excluded from this CPG. This adapted CPG is intended for use by neonatologists, pediatricians, family physicians, physician assistants, advanced practice nurses in outpatient, home visits, inpatient, and NICU settings.

The guideline adaptation group was chosen from multiple Egyptian universities. There was active involvement of a Multidisciplinary Review Committee including clinicians (academic faculty staff and consultant pediatricians and neonatologists) and CPG methodologists.

Phase 2 (Adaptation):

The NGAG included 23 Professors of Neonatology in addition to Professors of

Pediatrics and a general pediatrician who are experts in evidence-based CPG adaptation methodologies. Clinical questions are identified, using the PIPOH model, including questions for risk factors, prevention, prediction, diagnosis, and treatment (Table 1). The PIPOH model includes the target patient population (P), intervention(s) (I), professionals and clinical specialties (P), outcomes (O), and healthcare settings or context (H). The literature search was conducted using MEDLINE/PubMed and Google Scholar portals. The Appraisal of Guidelines for Research and Evaluation Instrument (AGREE II) [16] was used to appraise the eligible Source CPGs. AGREE II is considered the gold standard for quality assessment of CPG. It is a reliable tool that consists of 23 items organized in six domains. The neonatology guideline adaptation group (NGAG) studied several CPGs using the criteria of the AGREE II. The American Academy of Pediatrics (AAP) (2004 [17], 2009[18], 2011 [19] CPGs, NICE (2010 [20] , 2016 [21] CPGs, the Australian (Queensland, 2017) [22] CPG as well as Canadian Pediatric Association (2018) [23] CPG were considered. The first draft of the adapted CPG marks the last step of this phase.

Phase 3 (Finalization phase): In phase 3, the first draft of the adapted CPG is finalized after assessing whether it is acceptable and applicable to the Egyptian healthcare context. The draft was then disseminated to a panel of external reviewers of topic experts. Afterwards, the feedback of reviewers was revised and discussed within the NGAG with consideration of the national healthcare context. The finalized version of the adapted CPG included relevant practical implementation tools and strategies.

Ethical approval

Ethics approval and consents: are not applicable in this context.

Results

We identified 19 clinical questions using the PIPOH model. We studied several source original CPGs for prediction,

prevention and management of severe neonatal hyperbilirubinemia. Based on the results of the AGREE II appraisal and in-depth content review, there was a consensus among the members of the NGAG to adapt the AAP CPGs (2004, 2009 & 2011) [18-20] to answer the 19 clinical questions posted. For questions not answered within the chosen source, the group searched for other most relevant evidence available providing its grading and reference. The AGREE II ratings of the AAP CPG were 96% (domain 1: scope and purpose), 90.7% (domain 2: stakeholder involvement), 97.9% (domain 3: rigor of development), 98 (domain 4: clarity and presentation), 72.2% (domain 5: applicability), 97.2% (domain 6: editorial independence), 88.8 % (overall assessment 1), and the overall assessment 2 showed that NGAG recommended its use in practice. The summary recommendations of the adapted CPG are highlighted in Table 1. A set of CPG implementation tools were attached to the finalized adapted CPG. These tools were developed and revised by the NGAG group to be used by healthcare providers and families of neonates for education and awareness, so that the tools would be effective in our community. Implementation tools are shown in Appendices 1-5. The most important of which were the summary of recommendations, the discharge card for the parents that shows the possible risk for developing severe jaundice in their babies and the time of follow up. The algorithm for the management of a case presenting with neonatal jaundice, the decision making graphs as well as how to make phototherapy most effective. Future updates to this adapted CPG will review and consider any evidence published after our cut-off date.

Key to Evidence: The evidence presented in this CPG is categorized according to the categorization of the AAP Steering Committee on Quality Improvement and Management [17]

Table 1: Health Questions

Question 1	How can SNH be prevented among newborns with gestational age ≥ 35 weeks and ≥ 2.5 kilograms?
Question 2	What are the risk factors for SNH to be assessed in every newborn?
Question 3	What is the feeding counselling required for mothers to decrease risk of severe neonatal hyperbilirubinemia?
Question 4	How to monitor and assess babies for neonatal jaundice?
Question 5	What is the best method of predicting SNH among babies ≥ 35 weeks gestation and ≥ 2.5 kg (safe, cost effective)?
Question 6	When should TSB or TcB be measured? How a bilirubin level is interpreted using the hour-specific nomogram?
Question 7	What message should parents know before discharge from maternity hospital?
Question 8	What should be included in the formal assessment of babies with gestational age ≥35 weeks and weight >2.5 kg presenting with neonatal hyperbilirubinemia?
Question 9	When and how to assess for ABE?
Question 10	What is the schedule of follow up for the jaundiced newborn after leaving maternity?
Question 11	When to order other investigations for neonatal jaundice? Which tests to order?
Question 12	What are the different modalities of treatment of neonatal hyperbilirubinemia?
Question 13	What is the best method of administering phototherapy?
Question 14	When to discontinue phototherapy and how to monitor for rebound hyperbilirubinemia?
Question 15	When is exchange transfusion indicated? How is it performed? How to avoid its complications?
Question 16	Is there a role for IVIG use?
Question 17	Is there a role for other medicines in the treatment of neonatal hyperbilirubinemia?
Question 18	What information should be given to parents during hospitalization and before discharge?
Question 19	How to follow up the baby with severe hyperbilirubinemia after discharge?

Table 2: Key Recommendations

CPG Source	Recommendations	Level of Evidence
PRIMARY PREVENTION of severe hyperbilirubinemia:		
o During antenatal care:		
AAP 2004-2009-2011	All pregnant women should be tested for ABO and Rh (D) blood types. An antibody titer should be performed for mothers with suspected incompatibility. All mothers with Rh-incompatibility should receive Anti D prophylaxis	2
o Following delivery: Support breast feeding		
AAP 2004-2009-2011	Clinicians should advise mothers to nurse their infants at least 8 to 12 times per day for the first several days.	3
AAP 2004-2009-2011	Routine supplementation of breastfed infants with water or dextrose water is **NOT** recommended.	2
2 SECONDARY PREVENTION OF SNH:		
AAP 2004-2009-2011	All infants should be routinely monitored for the development of jaundice, and all nurseries should have established protocols for the assessment of jaundice.	4
AAP 2004-2009-2011	If a mother has not had prenatal blood grouping or is Rh-negative, a direct antibody test (Coombs' test), blood type, and Rh type on the infant's (cord) blood are strongly recommended.	2
AAP 2004-2009-2011	If the maternal blood is group O, check the infant's blood type and direct antibody test, unless bilirubin measurement and risk assessment using Bhutani nomogram is done together with close follow-up.	3

DIAGNOSIS of RISK for severe hyperbilirubinemia and use of Bhutani nomogram (Appendix fig 1):		
AAP 2004-2009-2011	Before discharge from maternity hospital, every newborn should be assessed for the risk of developing 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.**	3
AAP 2004-2009-2011	Combining a pre-discharge measurement of TSB or TcB with clinical risk factors (gestational age/ Rh- or ABO incompatibility) will provide the most accurate risk assessment for SNH.	3
AAP 2004-2009-2011	A TSB measurement should be performed on **every** infant who is jaundiced in the first 24 hours after birth (**Figure** 1). The need for and timing of a repeat TSB measurement will depend on the zone in which the TSB falls on the nomogram (**Figure** 1), the age of the infant and the evolution of hyperbilirubinemia.	3
GPP	If repeat TSB shows a rate of rise >0.2 mg/dL/hour, this baby should be considered high risk and persistent values above this rate require urgent intervention.	4
AAP 2004-2009-2011	A TcB and/or TSB measurement should be performed if the jaundice appears excessive for the infant's age or if there is any doubt about the degree of jaundice exists.	4
AAP 2004-2009-2011	Visual estimation of bilirubin levels from the degree of jaundice can lead to errors, particularly in darkly pigmented infants	3
AAP 2004-2009-2011	All bilirubin levels should be interpreted according to the infant's age in hours (Figure 1.).	3

Instructions to parents before discharge from maternity hospital		
AAP 2004-2009-2011	All maternity hospitals should provide written information for parents at the time of discharge, which should include an explanation about neonatal jaundice, the need to monitor infants for jaundice, and advice on how monitoring should be done.	4

Follow up of a baby for jaundice after discharge from maternity hospital (appendix Fig 4a,b,c):		
AAP 2004-2009-2011	All infants should be examined by a qualified health professional in the first few days after discharge to assess the infant's wellbeing and the presence or absence of jaundice. The timing and location of this assessment is determined by the length of stay in the nursery, pre-discharge TcB or TSB, presence or absence of risk factors for severe hyperbilirubinemia and risk of other neonatal problems.	3
AAP 2004-2009-2011	Follow-up should be provided for some newborns discharged before 48 hours, **2 follow up visits** may be required, the first visit between 24 and 72 hours and the second between 72 and 120 hours. Clinical judgment should be used in determining follow up. (It is essential to ensure a protocol for the assessment of jaundice during these follow up visits especially in rural Egypt).	3
AAP 2004-2009-2011	Earlier or more frequent follow-up should be provided for those who have risk factors for hyperbilirubinemia , whereas those discharged with few or no risk factors can be seen after longer intervals	3
AAP 2004-2009-2011	If appropriate follow-up cannot be ensured in the presence of elevated risk for developing severe hyperbilirubinemia, it may be necessary to delay discharge until appropriate follow-up can be ensured or the period of greatest risk has passed (72-96 hours).	4

AAP 2004-2009-2011	Follow-up assessment should include the infant's weight and percent change from birth weight, adequacy of intake, pattern of voiding and stooling, and the presence or absence of jaundice.	3
AAP 2004-2009-2011	Clinical judgment should be used to determine the need for a bilirubin measurement. If there is any doubt about the degree of jaundice, the TSB or TcB level should be measured.	3
AAP 2004-2009-2011	Assessment for acute bilirubin encephalopathy should be done in every severely jaundiced baby or any jaundiced baby with risk factors for neurotoxicity using **modified BIND score** (**appendix table I**)	4

Diagnosis of the cause of jaundice:		
AAP 2004-2009-2011	The possible cause of jaundice should be sought in an infant requiring phototherapy or whose TSB is rising rapidly (i.e., crossing percentiles) and is not explained by the history and physical examination.	3
AAP 2004-2009-2011	Infants who have an elevation of direct reacting (or conjugated) bilirubin should have a urine analysis and culture. Additional laboratory evaluation for sepsis should be performed if indicated by history and physical examination.	3
AAP 2004-2009-2011	If the direct reacting (or conjugated) bilirubin is elevated, additional evaluation for the causes of cholestasis is recommended.	4
AAP 2004-2009-2011	It is an option to measure the serum albumin level and consider an albumin level of less than 3.0 g/dL as a risk factor for lowering the threshold for phototherapy use.	4

Treatment of neonatal hyperbilirubinemia:		
AAP 2004-2009-2011	In using the guidelines for phototherapy and exchange transfusion, the direct reacting (or conjugated) bilirubin level should **NOT** be subtracted from the total.	4
AAP 2004-2009-2011	If the TSB is at a level at which exchange transfusion is recommended 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 directed to a hospital pediatric service for intensive "crash-cart" Phototherapy, to avoid delay in initiation of treatment.	3

A) Phototherapy (appendix fig 2):		
AAP 2004-2009-2011	All nurseries and NICUs treating infants should have the necessary equipment to provide intensive phototherapy	4
AAP 2004-2009-2011	Recommendations for phototherapy treatment are given in **Figure 2**. If the TSB does not fall or continues to rise despite intensive phototherapy, it is likely that hemolysis is occurring.	3
AAP 2004-2009-2011	In breastfed infants on conventional phototherapy, it is recommended that, if possible, breastfeeding should be continued while withholding phototherapy for the duration of the feed, provided TSB is not rising.	3
AAP 2004-2009-2011	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 is dehydrated.	2
AAP 2004-2009-2011	Routine intravenous fluids are **NOT** necessary for term or near term infants receiving phototherapy unless there is evidence of dehydration.	3
AAP 2004-2009-2011	Monitoring TSB for infants receiving intensive phototherapy: • If TSB ≥ 25 mg/dL, repeat	3

	TSB within 2–3 hours. • If TSB 20–25 mg/dL, repeat within 3–4 hours. • If TSB <20mg/dL, repeat within 4-6 hours. • If TSB continue to fall. Repeat in 8-12 hours. • Consider exchange transfusion if TSB is not decreasing or is moving closer to the level for exchange transfusion	
AAP 2004-2009-2011	When TSB is 13–14 mg/dL discontinue phototherapy. Depending on the cause of the hyperbilirubinemia, it is an option to measure TSB 24 hours after discharge to check for rebound unless there are signs of hemolysis.	3

B) Exchange Transfusion (appendix fig 3):		
Recommendations for exchange transfusion		
AAP 2004-2009-2011	If an exchange transfusion is being considered**,** the serum albumin level should be measured, and the bilirubin/ albumin ratio used in conjunction with the TSB level and other factors in determining the need for exchange transfusion.	4
AAP 2004-2009-2011	Immediate exchange transfusion is recommended in any infant who is jaundiced and manifests signs of intermediate to advanced stages of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonus, fever, high pitched cry) even if the TSB is falling.	4
AAP 2004-2009-2011	Exchange transfusions should be performed only by a team of trained personnel in a neonatal intensive care unit with full monitoring and resuscitation capabilities	4
GPP	A double-volume exchange transfusion should be performed to treat babies whose serum bilirubin level indicates its necessity and/or with clinical features and signs of acute bilirubin encephalopathy.	4

GPP	Use the following medications with caution in a baby with hyperbilirubinaemia as they may cause bilirubin to be displaced from albumin binding sites. • Konakion • Digoxin • Diazepam • Salicylates • Diuretics (e.g., furosemide and hydrochlorothiazide) • Ceftriaxone • Ibuprofen • Sulfamethoxazole such as in trimethoprim/sulfamethoxazole (cotrimoxazole) • Indomethacin • Free fatty acids (Intralipid)	4

C) Intravenous Immunoglobulins (IVIG)		
AAP 2004-2009-2011	In isoimmune hemolytic disease, administration of IVIG (0.5-1 g/kg over 2 hours) is recommended if the TSB is rising despite intensive phototherapy or the TSB level is within 2 to 3 mg/dL of the exchange level. If necessary, this dose can be repeated after 12 hours.	2
	The use of any of the following medications for the treatment of hyperbilirubinemia is NOT indicated: (Phenobarbitone, Agar, Clofibrate, albumin, charcoal, cholestyramine, Dpenicillamine, glycerine, riboflavin, homeopathy, metalloporphyrins).	4
GPP		

Parents information during hospitalization		
AAP 2004, 2009, 2011	Give parents or caregivers information about treatment for hyperbilirubinemia including: *Encourage mothers of jaundiced breastfed babies to breastfeed frequently, and to wake the baby for feeds if necessary. • Provide lactation/feeding support to breastfeeding mothers whose baby is visibly jaundiced. • Reassurance that breastfeeding, nappy-changing can continue in most cases. • Offer parents or caregivers	3

	verbal and written information on phototherapy or exchange transfusion. • Give information about anticipated duration of treatment. • Upon completion of therapy give information about rebound and follow up	

Follow up of newborns with severe hyperbilirubinemia:		
GPP	Any infant with severe neonatal hyperbilirubinemia should receive a hearing screen including brainstem auditory evoked potentials (ABR) for the early diagnosis of auditory dys-synchrony or sensory neural hearing loss and timely intervention.	4
GPP	Infants who required exchange transfusion or those who exhibit neurological abnormalities require regular neurological follow up.	4
GPP	Infants with isoimmunization are at risk of severe anemia after several weeks (up to 8-12 weeks of age); a repeat hemoglobin measurement should be performed at two weeks if it was low at discharge and at four weeks if it was normal.	4

GPP: Good Practice Point (based on the expertise of the NGAG)

Discussion

Jaundice is one of the most common conditions requiring medical attention in Egyptian newborn babies [6]. Because it is so common and usually benign, cases of SNH can easily be missed and mistaken for simple physiological jaundice which is known to occur in 60% of term and 80% of preterm babies in the first week of life. The management of neonatal jaundice is a particular challenge to the neonatologist. He/she should learn to avoid over treatment of harmless cases specially with limited resources but at the same time should never miss severe neonatal hyperbilirubinemia which if left untreated can lead to permanent bilirubin-induced neurological damage

[24] . The importance of this work lies in using the Adapted ADAPTE method [13] to expedite the production of this adapted evidence-based CPG, for the use in the Egyptian community, to prevent further increase in the number of kernicterus cases by following the instructions provided to healthcare physicians and other medical personnel that deal with newborns. The presence of the Egyptian pediatric guidelines committee has provided support and has been a facilitator for this project and the inclusion of representative professors from multiple universities all over Egypt has enriched the process bringing in different experiences that were essential for the completion of this work.

The aim of this project was to produce an available evidence-based document that caters to the need and increases the awareness of Egyptian physicians managing newborn babies regarding the risk of developing severe neonatal hyperbilirubinemia and kernicterus and to provide them with a standardized practical framework for the prediction, prevention and management of SHB through the use of this adapted CPG.

Testing the blood group and RH type of the mother can identify risky blood groups; and health education at that point in the antenatal care clinic can raise awareness of the mother to the possible risks her baby may be exposed to if she belongs to a risky blood group. Also, clear instructions regarding breast feeding support as well as date of follow up for jaundice are essential. Education of the mother for red flags her baby might show that require urgent medical advice can allow timely medical intervention that would prevent acute bilirubin encephalopathy which is the consequence of neglected severe neonatal hyperbilirubinemia.

Measuring a predischarge TSB or TcB for newborn infants, and plotting it on the Bhutani hour-specific nomogram [25] provides an excellent guide for timely follow up and for predicting which infants are at increased risk for

developing severe hyperbilirubinemia and its sequelae. Once baby is clinically jaundiced, the CPG encourages mothers to seek medical advice and decision making should be guided according to the clinical examination for signs of acute bilirubin encephalopathy as well as plotting the serum bilirubin on specific graphs to decide whether phototherapy is sufficient or the baby requires exchange transfusion. In the latter case, this newborn should be managed as a medical emergency where intensive phototherapy is started while preparations for exchange transfusion are made using the crash cart approach.

The preparation not only of the adapted CPG but also the attached implementation tools, though tedious is essential. Implementation tools facilitate the use of this adapted CPG. The Arabic explanation of jaundice and its sequelae in a small flyer that parents can receive on discharge, facilitates communication with the parents and also increases awareness to the importance of follow up and the risks of severe jaundice. Other tools, like the summary of recommendations when printed on a small card and made available in every nursery as well as the decision charts can make the life of physicians much easier and facilitate correct decision making.

Limitations: Although the achievement of producing this adapted Egyptian CPG for the prediction, prevention and management of SNH newborns is a huge one; there are limitations to its effectiveness in reducing the number kernicterus cases in our community. These include the limited financial resources required for the wide dissemination of the CPG, and for the continuous medical training and workshops essential for neonatal healthcare providers to be effective in its application in Egypt. The difficult collaboration with Obstetric colleagues which is essential for educating the mothers during antenatal care regarding risky blood groups and the seriousness of neglecting early neonatal jaundice and

the importance of close follow up after delivery. Also, resources are required for providing points of care, bilirubin measuring devices, affordable phototherapy and training personnel on how to make it more effective.

Conclusions

Using the Adapted ADAPTE method facilitated the production of an adapted evidence-based CPG for the predication, prevention and management of severe neonatal hyperbilirubinemia in late preterm and term newborns in prompt time, and with the required implementation tools. The effectiveness of this CPG should be assessed by monitoring the impact of the use of these CPGs in the reduction of cases of kernicterus that still occur in our country.

Summary of Key Recommendations

1. Increase awareness of mothers, during antenatal care, about the risks of severe neonatal jaundice especially if her blood group is Rh-negative or O and/or her indirect Coombs' test is positive.
2. Early promotion of successful frequent breastfeeding.
3. Protocols for monitoring and assessment of the risk for severe neonatal hyperbilirubinemia using the bilirubin nomogram should be present in all nurseries including bilirubin measurement (TcB or TSB) and the risk factors for neurotoxicity.
4. Blood group testing of mothers and infants as well as direct Coombs' test should be performed in every baby who appears jaundiced in the first 24 hours of life. If there is no mother-infant Rh or ABO incompatibility and Coombs' test is negative, other causes of hemolysis should be sought for (e.g. G6PD).
5. Every infant jaundiced in the first 24 hours should have total serum bilirubin (TSB) measurement and be managed accordingly.
6. If treatment is required, it should be based on TSB (do NOT subtract the direct fraction)
7. All bilirubin levels should be interpreted according to the infant's age in hours using the bilirubin nomogram and an appropriate follow-up date based on the time of discharge and the risk assessment; all should be arranged and written in a follow-up card.
8. Initiate phototherapy as soon as possible. Avoid any delay.
9. In isoimmune hemolytic disease (ABO or Rh-incompatibility) administration of

intravenous immunoglobulin (IVIG, 0.5-1 g/kg over 2 hours) is recommended if the TSB is rising despite intensive phototherapy or if the TSB level is within 2 to 3 mg/dL of the exchange level. If necessary, this dose can be repeated after 12 hours.

10. Any baby presenting with severe neonatal jaundice should be examined using the modified BIND score.

11. If there are signs of acute bilirubin encephalopathy or if TSB reaches exchange transfusion level or if the TSB level ≥ 25 mg/dL (428 mol/L), it is a MEDICAL EMERGENCY and the infant should be admitted immediately for intensive "crash-cart" phototherapy, while preparing for possible exchange to avoid delay in initiation of treatment.

12. The use of any of the following medications for the treatment of hyperbilirubinemia in healthy term or late preterm is NOT recommended (phenobarbitone, agar, clofibrate, charcoal, cholestyramine, D-penicillamine, glycerine, riboflavin).

13. Follow up of any baby with severe hyperbilirubinemia should include ABR, a neurological examination and follow up for anemia.

Abbreviations

AAP: American Academy of Pediatrics

ABE: Acute bilirubin encephalopathy

AGREE II: Appraisal of Guidelines for Research and Evaluation Instrument

BIND score: Bilirubin induced neurological damage score

CBE: chronic bilirubin encephalopathy

CPG: clinical practice guideline

EPG: Egyptian Pediatric Clinical Practice Guidelines Committee

NGAG: Neonatal guideline adaptation group

NICU: Neonatal intensive care unit

PIPOH model: population (P), intervention(s) (I), professionals and clinical specialties (P), outcomes (O), and healthcare settings or context (H)

SNH: severe neonatal hyperbilirubinemia

TSB: total serum bilirubin

WHO: World health organization

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Author's contributions

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Iman F. Iskander was the Chair of the NGAG. Afaf A. Korraa, Iman Iskander and Mossallam Nasser have written the first draft of the manuscript. **Ashraf Abdelbaky and Tarek E. Omar** conceptualized and designed the study. **Yasser S. Amer** reviewed the methodology, drafts and the final version of this manuscript. All authors contributed to the data collection, critical appraisal of guidelines and approved the final version of the manuscript.

Conflict of interest

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Availability of Materials

Any relevant material in addition to future revisions and updates will be made available and downloadable from the official website of the Egyptian Pediatrics Clinical Practice Guidelines Committee (http://epg.edu.eg).

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Appendix 1

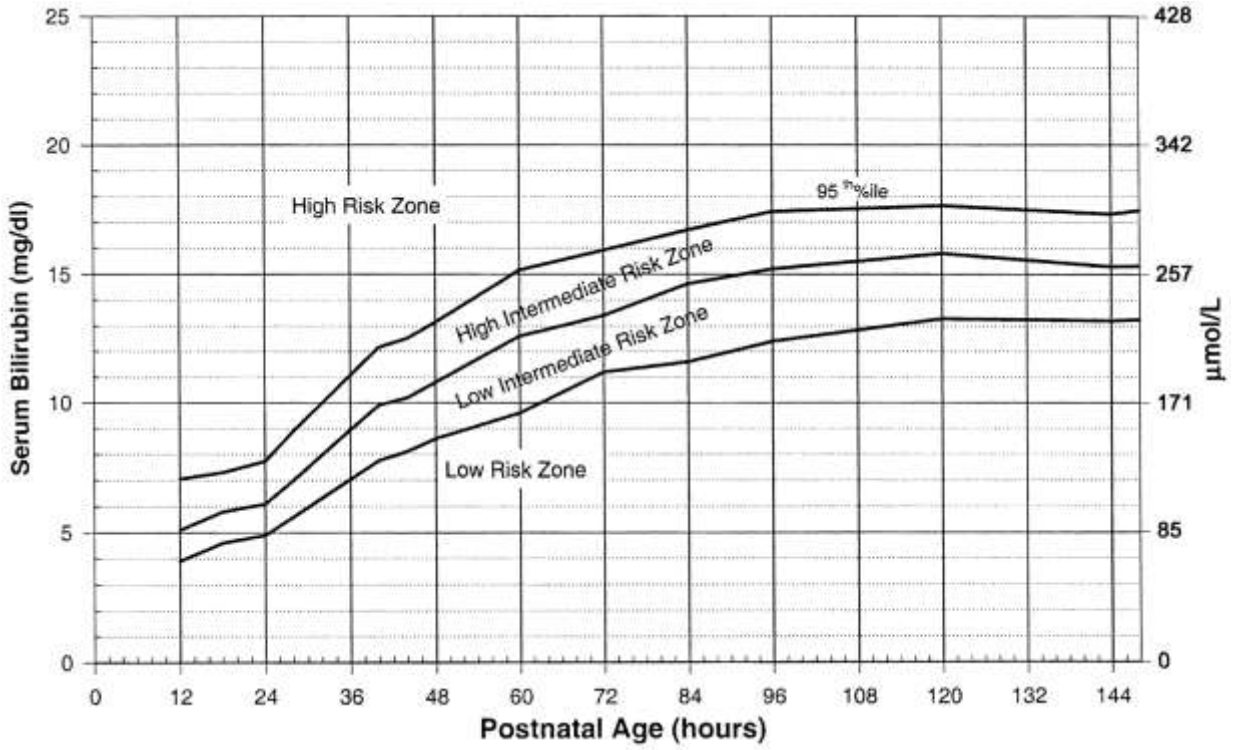
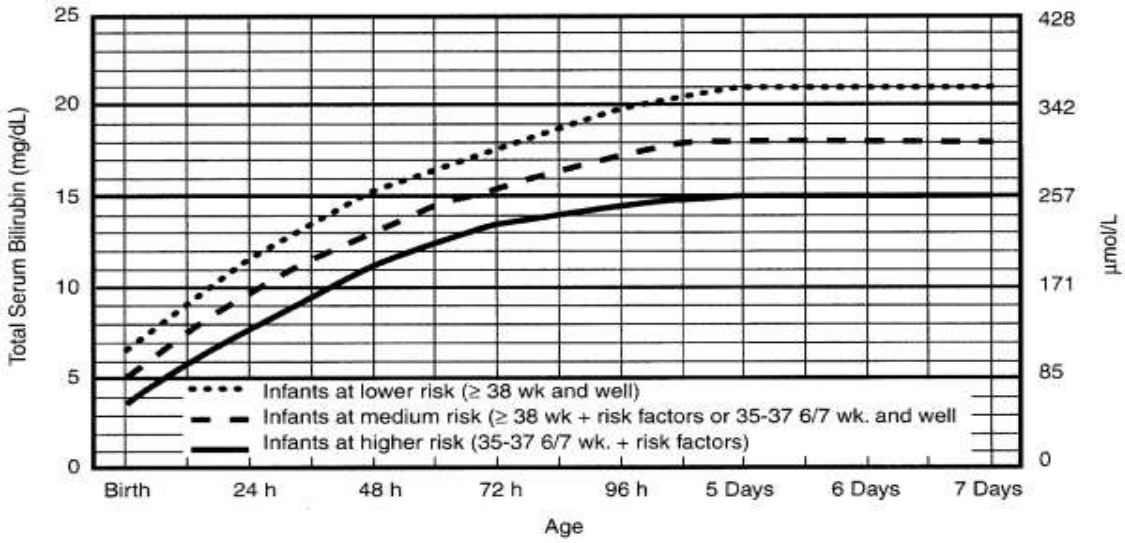


Figure (1): Bilirubin nomogram (BN) [25]

BN shows **3 risk zones** by the percentile tracks, high-risk zone, Intermediate-risk zone, and Low risk zone. The purpose of the BN is to predict which newborn is at high, intermediate, or low risk to develop severe hyperbilirubinemia after discharge from the hospital.

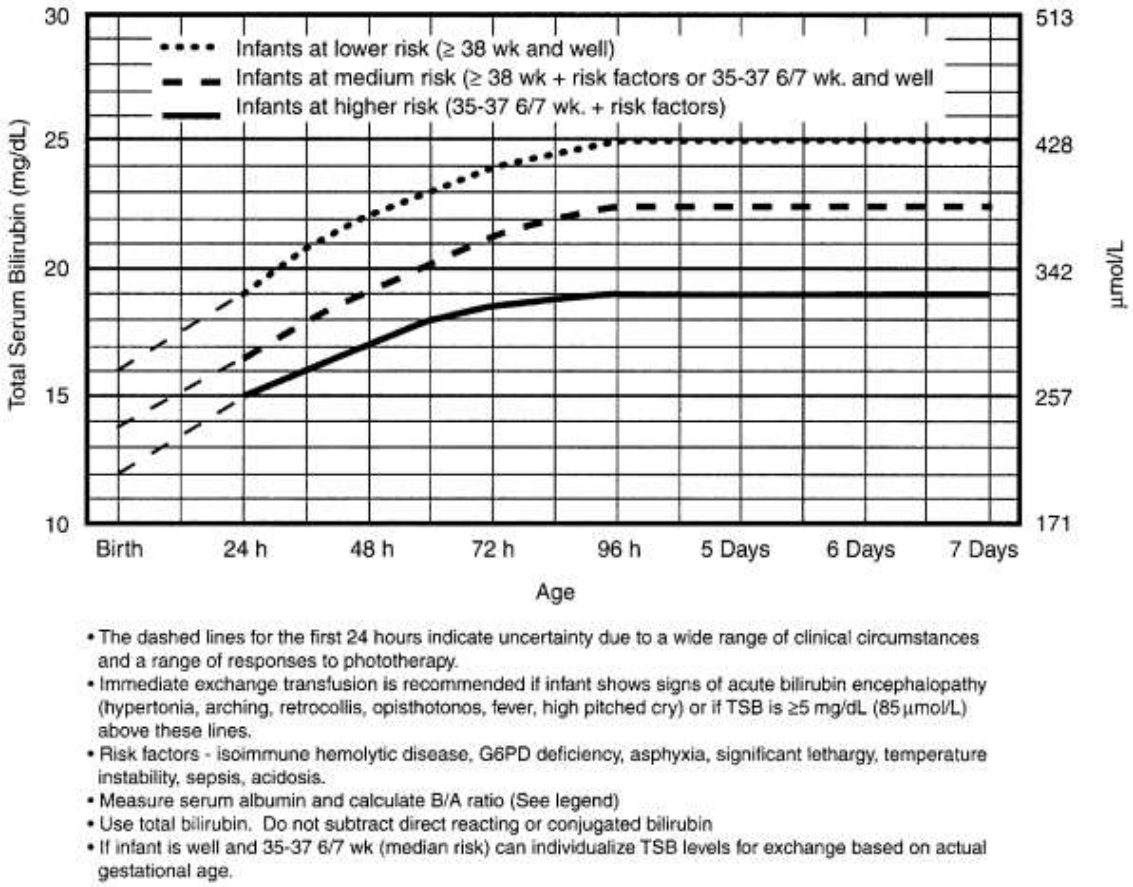
Appendix 2



- 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.

Fig (2): Guidelines for phototherapy in infants ≥ 35 weeks gestation [17]

Appendix 3



- 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.

Fig (3). Guidelines for exchange transfusion in infants ≥35 weeks' gestation [17]

Appendix 4

Table I: Clinical assessment of neurotoxicity using the Modified (bilirubin induced neurologic dysfunction (BIND) score

CLINICAL SIGN	SCORE	SEVERITY	Date/Time
MENTAL STATUS			
□ Normal	0	None	
□ Sleepy but arousable □ Decreased feeding	1	Mild	
□ Lethargy □ Poor suck and/or □ Irritable/jittery with short-term strong suck	2	Moderate	
□ Semi-coma □ Apnea □ Seizures □ Coma	3	Severe	
Total / 3			
MUSCLE TONE			
□ Normal	0	None	
□ Persistent mild hypotonia	1	Mild	
□ Moderate hypotonia □ Moderate hypertonia □ Increasing arching of neck and trunk on stimulation without spasms of arms and legs and without trismus	2	Moderate	
□ Persistent retrocollis □ Opisthotonus □ Crossing or scissoring of arms or legs but without spasms of arms and legs and without trismus	3	Severe	
Total / 3			
CRY PATTERN			
□ Normal	0	None	
□ High pitched	1	Mild	
□ Shrill	2	Moderate	
□ Inconsolable crying or □ Cry weak or absent in child with previous history of high pitched or shrill cry	3	Severe	
Total / 3			
OCCULOMOTOR OR EYE MOVEMENTS			
□ Normal	0	None, Mild	
□ Sun-setting □ Paralysis of Upward Gaze	3	Severe	
Total / 3			
Total ABE Score / 12			

Final score out of 12 (zero: Normal, 1-4: mild encephalopathy, 5-6: moderate encephalopathy, 7-12: severe encephalopathy) **[12]**

Appendix 5

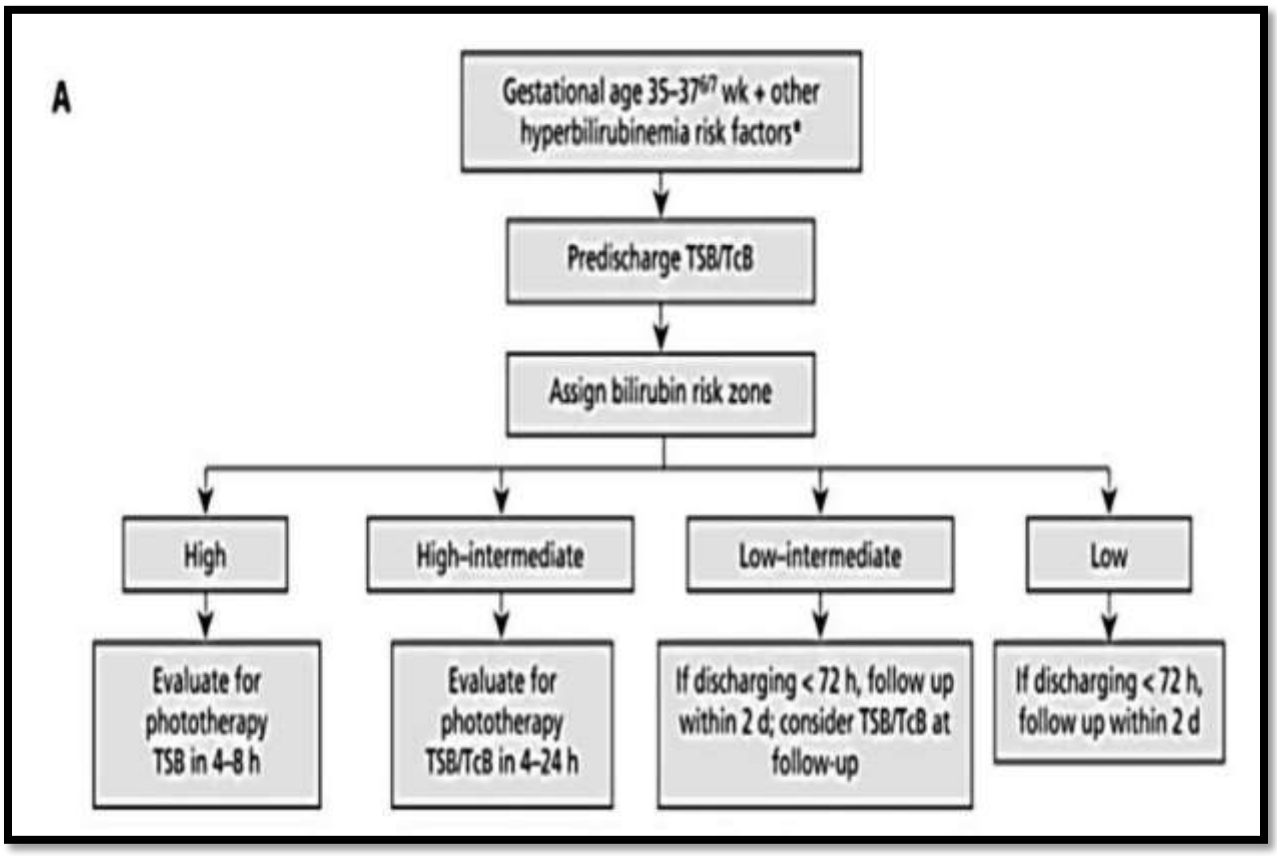


Figure 4 (A): Algorithm for management and follow-up according to pre-discharge bilirubin, gestation, and risk factors [17]

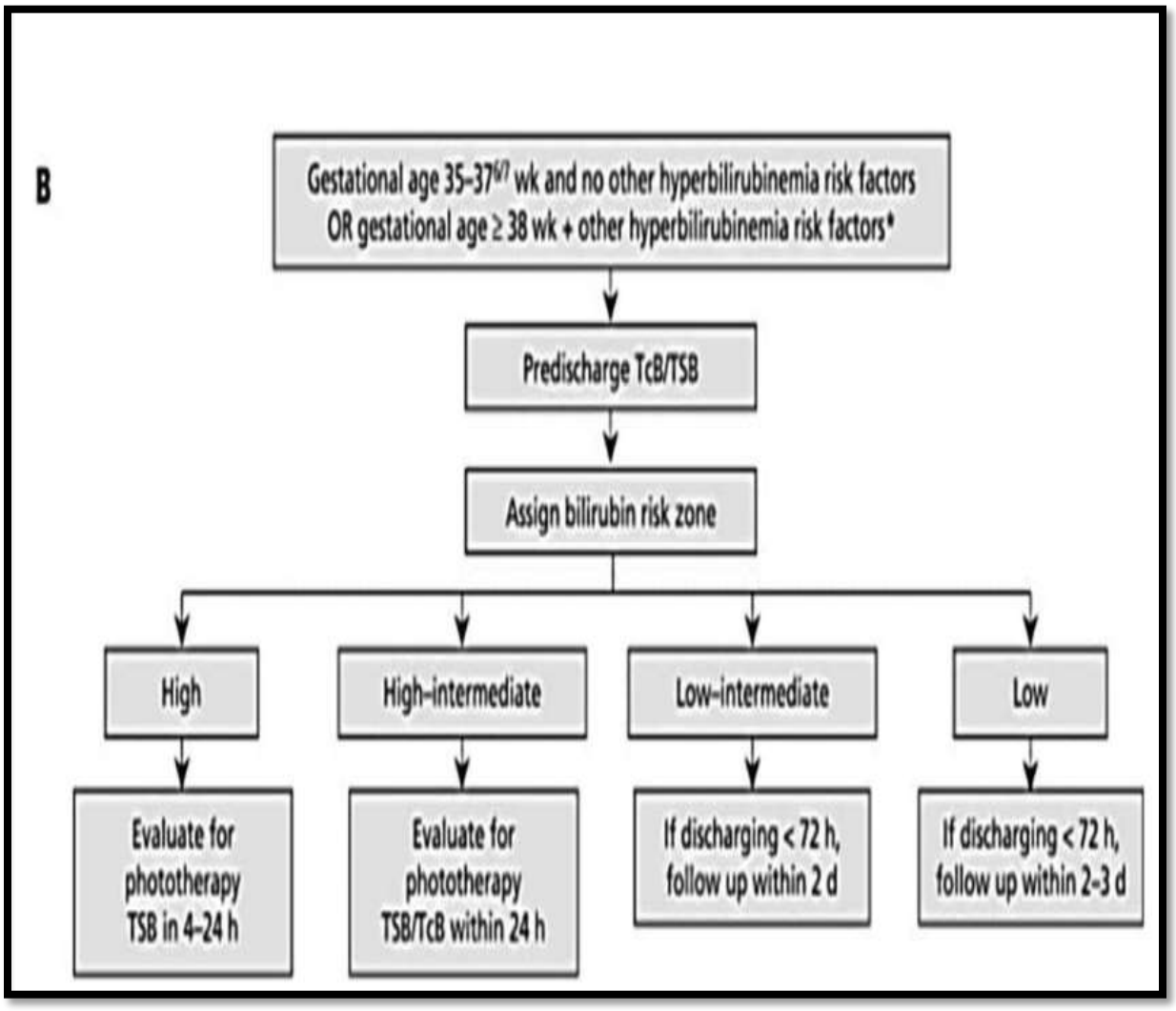


Figure 4 (B): Algorithm for management and follow-up according to pre-discharge bilirubin, gestation, and risk factors [17]

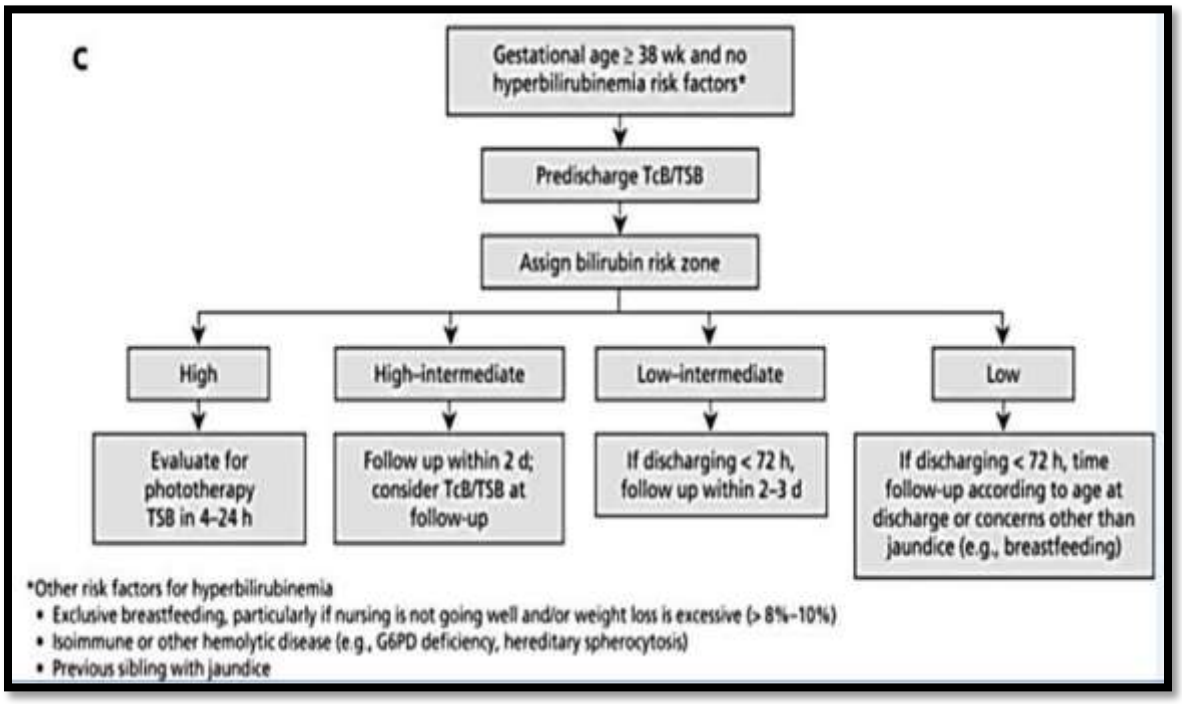


Figure 4 (c): Algorithm for management and follow-up according to pre-discharge bilirubin, gestation, and risk factors [17]

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