Arab Republic of Egypt
Egyptian Pediatric Clinical Practice Guidelines Committee (EPG)
Pediatric Neonatology Group

Evidence-Based Egyptian Clinical Practice Guidelines to Predict, Prevent and Manage Severe Hyperbilirubinemia in Term and Late Preterm Newborns

SECOND EDITION

March 2025

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2004, 2009, 2011, 2022

Front page

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Contact information of the guideline adaptation group

http://epg.edu.eg/#contact-us.
guidelinescommittee@gmail.com.

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Authorship group and Editorial Board

Egyptian Pediatric Clinical Practice Guidelines Committee (EPG) *(Subcommittee for revision and update of the guideline)*		
Name	**Affiliation, Country / Primary location [work]**	**Contribution**
Afaf Abd El-Wahab Korraa	MD, Professor of Pediatrics and Neonatology, Al-Azhar Girls University	Revision of previous guideline version. Modification of the guideline according to the most updated evidence, revision of implementation tools for easy application
Ahmed Mahmoud Youssef	MD, Fellow of Pediatrics, General Organization For Teaching Hospitals and Institutes (GOTHI). Lecturer of Pediatrics, Faculty of Medicine, Modern University for Technology and Information (MTI), Egypt	Final revision of the whole document including scientific parts & editing Revision & update of the methodology part. Presentation of the updated guidelines in WHO template.
Iman Fathy Iskander	MD, Professor of Pediatrics and Neonatology, Cairo University	Revision of previous guideline version. Modification of the guideline according to the most updated evidence, revision of implementation tools for easy application

Egyptian Pediatric Clinical Practice Guidelines Committee (EPG) *Guideline Development/ Adaptation Group (subgroup of original guideline)*		
Name	**Affiliation, Country / Primary location [work]**	**Contribution**
Afaf Abd El-Wahab Korraa	MD, Al-Azhar Girls University	All members contributed in: Search for original guidelines, formulate health questions, write recommendation statements with level of evidence, (adapt previous clinical practice guidelines)
Ahmed Mahmoud Youssef	MD, Fellow of Pediatrics, GOTHI Lecturer of Pediatrics, Faculty of Medicine, MTI University, Egypt	
Dina Essam Rabie	MD, Ain Shams University/AFCM	
Effat Hussein Assar	MD, Benha University	
Eman Almorsy Ahmed	MD, Al-Azhar girls University	
Ghada Ibrahim Gad	MD, Ain Shams University	
Hala Mohamed Fouad	MD Cairo University/MUST	
Hisham Abdel Samie Awad	MD, Ain Shams University	

Hossam Eldeen Abd Allah Mohamed	MRCPCH, Military Medical Academy	
Iman Fathy Iskander	MD, Cairo University/AFCM	
Mohammed Ezzat Abdelshafy	MSc, AFCM	
Mohamed Salah Eldin Abdel Kader	MD MUST	
Mosallam Mohamed Nasser	MD, Al-Azhar Boys University	
Nafisa Hassan Refat AbdelAziz	MD, Assuit University	
Nouran Bayoumi AbdAllah	MD, Suez Canal University	
Osama Abouelfotoh Zaki Elfiky	MD, Benha University	
Safaa Shafik Imam	MD, Ain Shams University	
Sameh Tawfik Amer	MD, Military Medical Academy	
Suzan Samir Ahmed	MD, Suez University	
Walaa Alsharany Abuelhamd	MD, Cairo University/AFCM	
Zahraa Mohamed Ezz-Eldin	MD, Cairo University	

Egyptian Pediatric Clinical Practice Guidelines Committee (EPG)
(Guideline Methodologists subgroup)

Name	Affiliation, Country / Primary location [work]	Contribution
Prof. Ashraf Abdel Baky	Professor of Pediatrics Ain Shams University, Egypt Founder and Chair of EPG	Overseeing the development process of the guidelines, training and education of new members, revision of the final draft, and organizing online meetings of GDG
Dr. Yasser Sami Amer	1. Pediatrics Department and Clinical Practice Guidelines and Quality Research Unit, Quality Management Department, King Saud University Medical City, Riyadh, Saudi Arabia; 2. Research Chair for Evidence-Based Health Care and Knowledge Translation, King Saud University, Riyadh, Saudi Arabia; 3. Chair, Adaptation Working Group, Guidelines International Network (GIN), Perth, Scotland	Overseeing the development t process of the guidelines, training and education of new members, participating in writing up the methodology of adaptation process, guideline appraisal, and revision of the final draft

	4. Department of Internal Medicine, Ribeirão Preto Medical School, University of São Paulo (FMRP-USP), Ribeirão Preto, São Paulo, Brazil.	
Dr. Tarek Omar	MD, Alexandria University	Overseeing the development process of the guidelines, and revision of the final draft.
Dr. Nesreen Kamal	MD, Cairo University	Overseeing the development process of the guidelines, and revision of the final draft.
Dr. Ahmed Mahmoud Youssef	MD, Fellow of Pediatrics, GOTHI Lecturer of Pediatrics, Faculty of Medicine, MTI University, Egypt	Participated in multiple steps of the guideline adaptation process, Writing the methodology of adaptation process and revised the whole document.
Dr. Samar Fathy	Lecturer of Pediatrics, Faculty of Medicine, Modern University for Technology and Information (MTI), Egypt	Participated in writing the methodology of adaptation process and revised the whole document.

External Reviewers Group (ERG)	
Name	**Affiliation, Country / Primary location [work]**
***External Reviewer (s) for Clinical Content* (original guideline version)**	
Prof. Abdel Latef Abd Elmoaz	Professor of Pediatrics, Former Head of the Neonatal Unit-Assuit University
Prof. Ali Afia	Professor of Pediatrics, Former Head of the Neonatal Unit -Al Azhar University
Prof. Hesham Abdel-Hady	Professor of Pediatrics, Head of the Neonatal Unit-Mansoura University
Prof. Mohamed Fathallah	Professor of Pediatrics, Former Head of the Neonatal Unit -Ain Shams University
Prof. Nahed Fahmy	Professor of Pediatrics, Former Head of the Neonatal Unit- Cairo University
***External Reviewer for Clinical Content* (updated guideline version)**	
Prof. Iman Khaled Eyada	Professor of Pediatrics, Former Head of the Neonatal Department - Cairo University
International Peer Reviewers	
Prof. Vinod Bhutani	MD, FAAP - Professor of Pediatrics and Neonatology, Stanford University, USA
Prof. John Watchco	MD, FAAP – Professor of Pediatrics, Gynecology and Obstetrics, University of Pittsburgh, USA

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ABBREVIATIONS

AAP	American Academy of Pediatrics
ABE	Acute bilirubin encephalopathy
ABO	ABO blood group type
ABR	Auditory brainstem response
ADAPTE	The International Collaboration for Guideline Adaptation
AGREE II	Appraisal of Guidelines, Research and Evaluation II
B/A ratio	bilirubin/ albumin ratio
BCSH	British Committee for Standards in Hematology
BIND	Bilirubin induced neurologic dysfunction
BN	Bilirubin nomogram
CBE	Chronic bilirubin encephalopathy
CEBCPGs	Center for Evidence Based Clinical Practice Guidelines
CMV	Cytomegalovirus
CPG	Clinical Practice Guideline
CGAG	Clinical guideline adaptation group
DAT	Direct anti-globulin test
DOB	Date Of Birth
EBCPG	Evidence based clinical practice guidelines
EBM	Evidence-Based Medicine
ENHG	Egyptian Neonatal Hyperbilirubinemia Group
ETCO2	End tidal carbon monoxide
FBC	Full blood count
G6PD	Glucose 6 phosphate dehydrogenase
GA	Gestational age
GDG/GAG	Guideline Development/ Adaptation Groups
GOTHI	General Organization For Teaching Hospitals and Institutes
GPP	Good practice point
HDFN	Hemolytic disease of the fetus and newborn
IUTs	Intrauterine transfusions
IVIG	Intravenous immunoglobulin
LEDs	Light-emitting diodes
LFTs	Liver function tests
M-BIND	Modified bilirubin-induced neurologic dysfunction score
MCHC	Maternal child health center
MMA	Military Medical Academy
MTI	Modern University for Technology and Information
MUST	Misr University for Science & Technology
NICUs	Neonatal Intensive Care Units
NJ	Neonatal jaundice

NPCPGC	National Pediatric Clinical Practice Guidelines Committee
PIPOH	Population, Intervention, Professionals, Outcomes and outcome measures, Healthcare setting and context
PT	Phototherapy
RBC	Red blood cell
RC	Review Committee
RCTs	Randomized controlled trails
Rh (D)	Rhesus Factor blood type D
SBR	Serum Bilirubin
SNH	Severe neonatal hyperbilirubinemia
SNHL	Sensorineural hearing loss
SNJ	Severe neonatal jaundice
SpO2	Oxygen saturation
T4	Free tetra-iodothyronine
TcB	Transcutaneous bilirubinometry
TSB	Total serum bilirubin
TSH	Thyroid stimulating hormone

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Preface

Neonatal jaundice (NJ) or Neonatal hyperbilirubinemia is one of the main reasons for hospital readmission during the first month of life. NJ is usually benign, but in some cases can progress to severe hyperbilirubinemia, acute bilirubin encephalopathy (ABE) and kernicterus/chronic bilirubin encephalopathy (CBE). Surviving infants may acquire long-term neuro-developmental sequelae such as athetoid cerebral palsy, sensorineural hearing loss and gross developmental delays. ABE and CBE are largely preventable if severe neonatal hyperbilirubinemia (SNH) is identified early and treated promptly with effective phototherapy or, for hazardous cases, exchange transfusion.

In Egypt, SNH and acute bilirubin encephalopathy are still being reported in numbers that cannot be ignored. Multiple factors predispose to this condition. Maternal knowledge that NJ is common and disappears with time gives a false sense of security that affects their attitude and behaviour. They seek help late and often receive wrong family advice that poorly impacts correct management. On the other hand, barriers to access appropriate medical care in remote areas coupled with multiple non-evidence-based opinions in the management of NJ among physicians may result in mismanagement of such cases either by underestimation or in some cases, overestimation of the condition. Underestimation of the risk of neonatal jaundice causes poor surveillance for severe hyperbilirubinemia, delayed implementation of treatment and increases the risk of kernicterus, while overestimation leads to unindicated NICU admission, unnecessary separation of mother and baby, interruption of breastfeeding and increased financial burden to both families and governorates.

The availability of national guidelines to, prevent and manage SNH will help bridge the gaps and serve as a guide for clinicians and parents, providing them with a correct understanding of NJ and the actions needed to prevent SNH, ABE and irreversible kernicterus.

The authors have strived to adapt available international guidelines to deliver **Egyptian guidelines for the prediction, prevention, and management of SNH in term and late preterm newborns ≥35 weeks gestation,** that are specific for our circumstances in Egypt to be used by neonatologists, paediatricians, primary healthcare physicians as well as nurses, rural health workers, obstetricians and blood bankers in Egypt. It is hoped that these guidelines will help establish a systematic practice that will be universal all over Egypt and improve the outcome of new-borns at risk of severe hyperbilirubinemia with the aim of preventing kernicterus.

The Authorship Group

OVERVIEW MATERIAL

Adapted Guideline release date:

Original guideline 2018, updated on March 2025.

Status:

Adapted (using ADAPTE Manual and resource Tool kit version 2.0, released by the ADAPTE Collaboration in 2009 [1] and the adapted ADAPTE approach of Alexandria University. [2]

Print and electronic sources:

Available upon request from the **Egyptian Pediatric Clinical Practice Guideline Committee (EPG).**

Adapter:

Egyptian Pediatric Clinical Practice Guideline Committee (EPG) – Neonatology group.

Update team:

Prof. Afaf Koraa, Prof. Iman Iskander, and Dr. Ahmed Youssef and the methodologists.

Main source of the adapted guideline:

1- AAP: American Academy of Pediatrics, **(2004[3], 2009[4], 2011[5] , 2022[6]).**
2- References from high quality researches.

Executive summary

Introduction:

A practical guideline for Prediction, Prevention and Management of Severe Hyperbilirubinemia in Term and Late Preterm Newborns has been adapted to fit the Egyptian healthcare system. This process of customizing existing evidence-based clinical practice guidelines for local contexts offers a practical alternative to creating new ones from scratch, potentially enhancing their usefulness while conserving resources. This guideline aims to provide practical guidance for Prediction, Prevention and Management of Severe Hyperbilirubinemia in Term and Late Preterm Newborns in Egypt, as well as the adaptation methods employed to create Egyptian National Guideline for Prediction, Prevention and Management of Severe Hyperbilirubinemia in Term and Late Preterm Newborns using the Adapted ADAPTE method. The entire adaptation process, encompassing the setup, adaptation, and finalization phases, is thoroughly described. This involved a guideline adaptation group (GAG) and an external review group by experts in clinical content.

The finalized adapted CPG provides pediatricians and healthcare workers in the field of neonatology in Egypt with practical, evidence-based guidance for Prediction, Prevention and Management of Severe Hyperbilirubinemia in Term and Late Preterm Newborns. This initiative underscores the effectiveness of the Adapted ADAPTE method and emphasizes the significance of collaboration between clinical and methodological experts in adapting national guidelines.

Guideline's development and methods:

- After reviewing all the inclusion and exclusion criteria and quality appraisal results, the GDG/ GAG recommended using the following source original clinical practice guidelines (CPGs):

Clinical practice guideline revision: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. AAP 2022.

- We conducted Adolopment for these guidelines: (Adoption and Development):
  - Adoption for most of the guideline recommendations.
  - Development of Good Practice Statements.

Guideline registration:

Will be registered in: http://www.guidelines-registry.org.

Recommendations and Good Practice Statements (GPS):

- All pregnant women should be tested to determine their ABO blood group and Rh (D) type and receive an antibody screen to determine the need for Rh (D) immunoglobulin (RhIG) and to assess the potential for isoimmune hemolytic disease of the fetus or newborn. **SoR: GPS**
- If the maternal antibody screen is positive or unknown because the mother did not have prenatal antibody screening, the infant should have a direct antiglobulin test (DAT) and the infant's blood type should be determined as soon as possible using either cord or peripheral blood. **SoR: Strong**
- If the maternal blood group is unknown, testing for maternal and infant blood group as well as DAT is essential in any case of early jaundice. **SoR: GPS**
- Clinicians should promote frequent breastfeeding on demand and recommend starting within the first hour after birth and should provide breastfeeding support for all mothers. **SoR: GPS**
- Oral supplementation with water or dextrose water should NOT be provided to prevent hyperbilirubinemia or decrease bilirubin concentrations. **SoR: Strong**
- All infants should be visually assessed for jaundice at least every 12 hours following delivery until discharge. **TSB or TcB should be measured as soon as possible for infants noted to be jaundiced < 24 hours after birth. SoR: GPS**
- TcB or TSB should be measured for **ALL** babies between 24 and 48 hours after birth or before discharge if that occurs earlier. **SoR: Conditional**
- If appropriate follow up cannot be arranged for an infant recommended to have an outpatient follow up bilirubin measure, **discharge may be delayed. SoR: Conditional**
- Before discharge, all families should receive **WRITTEN and VERBAL EDUCATION about neonatal jaundice**. **SoR: GPS**
- Beginning at least 12 hours after birth, if discharge is being considered, the difference between the bilirubin concentration measured closest to discharge and the phototherapy threshold at the time of the bilirubin measurement should be calculated and used to determine follow-up appointments. **SoR: conditional**
- Infants with risk factors for hyperbilirubinemia (Table-8) as determined by history of risk factors, family history, examination and laboratory results require closer monitoring than infants without risk factors. **SoR: GPS**
- Elevated TSB in a formula fed infant or late onset jaundice should raise the possibility of G6PD. **SoR: GPS**
- Use TSB as the definitive test to guide phototherapy and escalation-of-care decisions, including exchange transfusion. **SoR: GPS**
- Decisions to initiate phototherapy or escalate care are guided by the gestational age, the TSB, and the presence of risk factors for bilirubin neurotoxicity (Table-9). **SoR: GPS**
- A TSB measurement should be performed on **every** infant who is jaundiced in the first 24 hours after birth. **SoR: Strong**

- TSB should be measured if TCB exceeds or is within 3 mg /dl of phototherapy treatment threshold or if TcB is ≥ 15mg/dL. **SoR: Conditional**
- If more than 1 TcB or TSB measure is available, the rate of increase of bilirubin may be used to identify infants at higher risk of subsequent hyperbilirubinemia. A rapid rate of increase (≥ 0.3 mg/dL per hour in the first 24 hours or ≥ 0.2 mg/dL per hour thereafter) is exceptional and suggests hemolysis. In this case, a DAT should be performed if not previously done. **SoR: Conditional**
- The formal assessment of babies with gestational age ≥35 weeks presenting with indirect neonatal hyperbilirubinemia:
    - History and family history (risk factors for hyperbilirubinemia and risk factors for neurotoxicity)
    - Clinical examination (general / signs of neurotoxicity (BIND score).
    - Laboratory assessment:
        - Complete blood count and reticulocyte count.
        - TSB
        - Maternal and child blood group and Rh.
        - DAT test.
        - Further investigations as required. **SoR: GPS**
- Assessment for acute bilirubin encephalopathy should be done in every jaundiced baby with risk factors for neurotoxicity (Table-9) or any severely jaundiced baby using modified BIND score. **SoR: Conditional**
- For breastfed infants who are still jaundiced at 3-4 weeks of age and for formula fed infants who are still jaundiced at 2 weeks of age, the total and direct reacting or (conjugated) bilirubin concentration should be measured to identify possible pathologic cholestasis. **SoR: Conditional**
- 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 (Table-11). **SoR: Stong**
- All nurseries and NICUs treating infants should have the necessary equipment to provide intensive phototherapy (Table-12). **SoR: Conditional**
- Intensive phototherapy is recommended at the TSB threshold in (Figures-4 & 5) on the basis of gestational age, hyperbilirubinemia neurotoxicity risk factors and age of infant in hours. **SoR: GPS**
- The direct reacting or conjugated bilirubin value should not be subtracted from the total bilirubin value when determining management. **SoR: GPS**
- 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 (max 20 minutes). **If TSB is approaching escalation of care level, the infant should not come out of phototherapy to feed**, as this is a medical emergency. **SoR: Strong**

- 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. **SoR: Strong**
- Routine intravenous fluids are NOT necessary for term or near-term infants receiving phototherapy unless there is evidence of dehydration or if TSB is approaching escalation of care threshold. **SoR: Strong**
- For hospitalized infants, TSB should be measured **within 12 hours** after starting phototherapy. The **timing** of the initial TSB measurement after starting phototherapy and the frequency of monitoring during phototherapy **should be guided by the age of the child, the presence of hyperbilirubinemia neurotoxicity risk factors, the TSB concentration and TSB trajectory. SoR: GPS**
- For infant requiring phototherapy measure the hemoglobin concentration, hematocrit, or complete blood count to assess the presence of anemia and **to provide a base line** in case subsequent anemia develops. **SoR: GPS**
- **Evaluate the underlying cause** or causes of hyperbilirubinemia:
    - In infants who require phototherapy by obtaining a DAT.
    - In infants whose mother had a positive antibody screen.
    - Or whose mother is blood group O, regardless of Rh status.
    - Or whose mother is Rh (D) negative. **SoR: GPS**
- **G6PD activity should be measured in:**
    - Any infant with jaundice of unknown cause whose TSB:
        - increases despite intensive phototherapy.
        - increases suddenly
        - increases after an initial decline or who requires escalation of care.
    - Any infant who requires escalation of care. **SoR: GPS**
- Monitoring TSB for infants receiving intensive phototherapy without signs of ABE:
    - If TSB ≥ 25 mg/dL, repeat TSB within 2–3 h.
    - If TSB 20–25 mg/dL, repeat within 3–4 h.
    - If TSB <20 mg/dL repeat in 4–6 h.
    - If TSB continues to fall, repeat in 8–12 h.
    - Consider exchange transfusion if TSB is not decreasing or is moving closer to the level for exchange transfusion. **SoR: Strong**
- Discontinuing phototherapy is an option when TSB has decreased by at least 2 mg / dL below the hour specific threshold at the initiation of phototherapy. A longer period of phototherapy is an option if there are risk factors for rebound hyperbilirubinemia (e.g. Gestational age < 38 weeks, age < 48 hours at the start of phototherapy, hemolytic disease. **SoR: Conditional**
- Repeat bilirubin measurement after phototherapy is based on the risk of rebound hyperbilirubinemia. Risk factors are:

    - Infants who received phototherapy before 48 hours.
    - Infants who had a positive DAT.
    - Infants who had known or suspected hemolytic disease.
    - Infants with risk for hyperbilirubinemia and hyperbilirubinemia neurotoxicity risk factors (Table-8 and 9). **SoR: GPS**
- In the presence of one of the above risk factors: TSB should be measured for rebound at 6-12 hours after phototherapy discontinuation. All other infants should be followed up for TSB after 24 hours of discontinuation of phototherapy. **SoR: GPS**
- Care should be escalated when an infant's TSB reaches or exceeds the escalation of care threshold **defined as 2 mg /dl below the exchange transfusion threshold.** The direct reacting or conjugated bilirubin value should not be subtracted from the total bilirubin value when determining management. **SoR: GPS**
- For infants requiring escalation of care, blood should be sent STAT for total and direct reacting serum bilirubin, a complete blood count, serum albumin, serum chemistries and blood type and cross match. **SoR: GPS**
- Infants requiring escalation of care should receive intravenous hydration and emergent intensive phototherapy. A neonatologist should be consulted about urgent transfer to a NICU that can perform an exchange transfusion. **SoR: Conditional**
- TSB should be measured at least every 2 hours during the escalation period. Once the TSB is lower than the escalation of care threshold, continue phototherapy according to the bilirubin level. **SoR: GPS**
- Intravenous immunoglobulin (IVIG) (0.5-1 g/kg over 2 hours) may be provided to **infants with isoimmune hemolytic disease (i.e., positive DAT) whose TSB reaches or exceeds the escalation of care threshold**. This dose can be repeated in 12 hours. **SoR: Conditional**
- **Urgent exchange transfusion** should be performed for infants with **signs of intermediate or advanced stages of acute bilirubin encephalopathy (Table-10). SoR: Conditional**
- **An urgent exchange transfusion** should be performed for infants if **the TSB ≥ the exchange transfusion threshold (Figure-7 and 8).** If while preparing for exchange transfusion but before starting the exchange transfusions, a TSB concentration is below the exchange transfusion threshold and the infant does **NOT show signs or intermediate or advanced stages of ABE,** then the exchange transfusion may be deferred while continuing intensive phototherapy and following TSB every 2 hours until the TSB is below the escalation of care threshold. **SoR: Conditional**
- Use the following medications with caution in a baby with hyper-bilirubinemia as they may cause bilirubin to be displaced from albumin binding sites and increase the risk of ABE:
    - Konakion.
    - Digoxin.

    - Diazepam.
    - Salicylates.
    - Diuretics e.g., furosemide and hydrochlorothiazide.
    - Ceftriaxone.
    - Ibuprofen.
    - Sulfamethoxazole such as in trimethoprim/sulfamethoxazole (cotrimoxazole). **SoR: Conditional**
- **The use of any of the following medications for the treatment of hyperbilirubinemia is NOT RECOMMENDED** (Phenobarbitone, Agar, Clofibrate, albumin, charcoal, cholestyramine, D penicillamine, glycerine, riboflavin, homeopathy, and metalloporphyrins). **SoR: Conditional**
- 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. **SoR: Conditional**
- Infants who required exchange transfusion or those who exhibit neurological abnormalities with history of neonatal jaundice require regular neurological follow up. **SoR: Conditional**
- Infants with isoimmunization are at risk of severe anemia after several weeks (up to 8-12 weeks of age); Repeat hemoglobin measurement should be performed at two weeks if it was low at discharge and at four weeks if it was normal. **SoR: Conditional**
- Infants suspected to have G6PD deficiency (elevated TSB in formula infants or late onset jaundice) should be tested at 3 months of age. **SoR: Conditional**

INTRODUCTION

Neonatal jaundice (NJ) refers to yellow discoloration of the skin and sclera of newborn babies [7]. It is generally considered a benign self-limiting condition, affecting more than 60% of healthy term and 80% of preterm infants [8,9]. However, in some cases, severe neonatal hyperbilirubinemia (SNH) can lead to irreversible brain damage and kernicterus [10]. Surviving infants may acquire long-term neuro-developmental sequelae such as cerebral palsy, sensorineural hearing loss, intellectual difficulties or gross developmental delays. Acute bilirubin encephalopathy (ABE) and Chronic bilirubin encephalopathy (CBE) are largely preventable if SNH is identified early and treated promptly with effective phototherapy, or, if indicated, exchange transfusion.

In a recent systematic review in which SNH was defined as that associated with acute bilirubin encephalopathy, exchange transfusion or death; the incidence of SNH 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 Americas [11]. 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 / year, a large group could be at risk for SNH and its sequelae[12]. In the NICU of Cairo university Children's hospital, in 2009, 44/249 admitted jaundiced newborns not only had extreme hyperbilirubinemia, but presented with moderate to severe bilirubin encephalopathy [13] and in a recently published follow up study in the same NICU, all 23/202 babies admitted with SNH had abnormal neurological examination at follow up[14]. The root causes for these shocking numbers within the Egyptian community include parental ignorance [15] of the risk of severe jaundice, absence of timely follow up for jaundiced newborns, as well as delay in proper intervention. [15,16]

While tactics to prevent and treat severe neonatal hyperbilirubinemia must be sensitive to cultural and resource variations, the universality of root causes suggests 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 should be monitored for risk of hyperbilirubinemia and prompt interventions should be followed to prevent acute bilirubin encephalopathy and kernicterus.

Definitions:

Acute bilirubin encephalopathy (ABE): A clinical syndrome in the presence of severe hyperbilirubinemia that consists of decreased feeding, lethargy, variable abnormal tone (hypotonia and/or hypertonia), high-pitched cry, retrocollis and opisthotonus, setting sun sign, fever, apnea, seizures, and death. [17, 18]

Chronic bilirubin encephalopathy (CBE): A clinical tetrad that occurs after the history of severe hyperbilirubinemia consisting of:

(1) A movement disorder consisting of not only 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.

(4) Dental enamel hypoplasia of the deciduous teeth. [19]

Kernicterus: The pathological finding of deep-yellow staining of neurons and neuronal necrosis of the basal ganglia and brainstem nuclei clinically associated with chronic bilirubin encephalopathy. [17,19]

Escalation of care: The intensive care that some infants with elevated or rapid increasing bilirubin concentration require to prevent the need for an exchange and possibly prevent kernicterus. [6]

Critical or, Extreme hyperbilirubinemia: A TSB concentration greater than 25 mg/dL during the first 28 days of life. [18,19]

Rebound Hyperbilirubinemia: Is defined as a TSB concentration that reaches the phototherapy threshold for the infant's age within 72-96 hours of discontinuing phototherapy. [6,20]

Prolonged unconjugated jaundice: Infants 7 days or older with a persistently elevated TSB within 2 mg/dL of the phototherapy threshold may have prolonged indirect hyperbilirubinemia, which can be confirmed by measuring serum direct-reacting or conjugated bilirubin (i.e., a fractionated bilirubin measure) in addition to total bilirubin. [6]

Intensive phototherapy: Requires a narrow spectrum LED blue light with an irradiance of at least 30 mW/cm2 per nm at a wavelength around 475 nm. [6]

STATEMENT OF INTENT

These evidence-based clinical practice guidelines are meant to be guides for clinical practice. The aim of the development of these national guidelines is to provide standardization of the management of neonatal jaundice in Egypt for the prevention of kernicterus. The guidelines were formulated based on those of the American Academy of Pediatrics [3-5] after being evaluated by AGREE II, and adapted to match the realities of the Egyptian society. These guidelines may not necessarily guarantee the best outcome in every case. Every healthcare provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally. This is the second edition of these guidelines after an update based on the most recent AAP [6] guideline has been completed. These guidelines will be reviewed in 2029 or sooner if new evidence becomes available. When it is due for updating, the Chairman of the Egyptian pediatric clinical practice guidelines committee (EPG) or National Advisor of the Egyptian Neonatal Hyperbilirubinemia Group will be informed. A discussion will be done on the need for a revision including the scope of the revised CPG. A multidisciplinary team will be formed and the latest systematic review methodology will be employed.

SCOPE AND PURPOSE

Disease condition:

Neonatal hyperbilirubinemia in late preterm ≥35 weeks and term neonates.

Guideline category:

- Prediction.
- Prevention.
- Management.

Clinical specialty:

- Pediatricians.
- Neonatologist.
- Obstetricians.
- Family physicians.

Intended users:

This evidence base CPG is intended to guide those involved in the management of neonatal hyperbilirubinemia either in primary or secondary/tertiary care namely:

- Medical officers and general practitioners.
- Family medicine specialists.
- Pediatricians, neonatologists and specialists from related disciplines (Nurses and rural health workers).
- Obstetricians.
- Parents and care-givers.

GUIDELINES OBJECTIVES

The objectives of this Clinical Practice Guideline is to provide evidence-based guidance on the prediction, prevention and management of severe neonatal hyperbilirubinemia (SNH) specifically adjusted to the customs of the Egyptian community and to integrate it with the already existing health care system to prevent the occurrence of acute bilirubin encephalopathy and kernicterus through the following:

- Detection of high-risk groups and prediction of severe hyperbilirubinemia.
- Targeted follow-up of risk groups.
- Early diagnosis and timely intervention for severe hyperbilirubinemia.

Target Population:

Inclusion and exclusion criteria:

Inclusion criteria:

Newborns with diagnosis of indirect hyperbilirubinemia or at risk for development of severe hyperbilirubinemia meeting the following criteria:

- Age ≤ 28 days.
- GA ≥35 weeks.

Exclusion criteria:

- Neonate with cholestasis.
- Age >28 days.
- GA <35 weeks GA.

Healthcare Settings:

- Community settings: maternal child health care center (MCHC).
- Hospitals (maternity and children hospitals whether University, Governmental of Private): Outpatient, inpatient, neonatal intensive care units (NICUs) settings.

HEALTH QUESTIONS (PIPOH Format)

Patient population (P):

- **Gender:** both genders.
- **Age group:** Neonates ≥ 35 weeks gestational age.
- **Disease/Condition:** Neonatal indirect hyperbilirubinemia.
- **Comorbidity:** Apparently well but may have blood group incompatibility (e.g. Rh, ABO), G6PD deficiency, spherocytosis…

Intervention (I):

- **Prediction:** Screening for blood group incompatibility and possible hyperbilirubinemia.
- **Diagnosis:**
  a) Screening tests: Visual inspection, transcutaneous bilirubinometry (TcB), other screening modules (Bilitool). [21]
  b) Diagnostic tests: total serum bilirubin (TSB) and other diagnostic tests as indicated.
- **Treatment:**
  a) Medical: non pharmacological (phototherapy), +/- pharmacological therapy (IVIG). [6]
  b) Interventional: Crash-cart phototherapy, [6,22] Exchange transfusion. [6,23]

Professionals (P):

- Medical officers at maternal child health centers.
- General practitioners.
- Family medicine specialists.
- Pediatricians, neonatologists, and specialists from related disciplines (Nurses and rural social health workers).
- Obstetricians.
- Parents and caregivers.

Outcomes (O):

- **Primary outcome:** prevention and treatment of severe neonatal hyperbilirubinemia (SNH) aiming for prevention of bilirubin encephalopathy and kernicterus.
- **Secondary outcome:** Decrease variation of practice, improve patient safety, enhance provider-parent communication, and establish birthing facility and institutional policies.

Health care settings (H):

- **Type:** all (primary, secondary, and tertiary).
- **Health care sector:** government, non-governmental organization, national insurance and private hospitals.

GUIDELINES ADAPTATION METHODOLOGY

- This guideline was adapted (using ADAPTE Manual and resource Tool kit version 2.0, released by the ADAPTE Collaboration in 2009[1] and the adapted ADAPTE approach of Alexandria University. [2]
- The guideline adaptation group was chosen from various Egyptian Universities & General Organization for Teaching Hospitals and Institutes (GOTHI). There was active involvement of a Multidisciplinary Review Committee (RC) during the process of this guideline revision and finalization.
- A literature search was carried out using the following electronic databases: PubMed and Cochrane Database of Systematic Reviews.
- The search was limited to literature published in the last ten years, the reference lists of all retrieved literature and guidelines were searched to further identify relevant studies. Experts in the field were also contacted to identify relevant studies. All searches for the first edition were conducted from April 2018 to June 2018.
- Clinical questions were developed under different sections of the disease. The clinical guideline adaptation group (CGAG) were assigned individual questions within these sections. They met 5 times throughout the development of these guidelines. The literature retrieved was appraised by CGAG using Critical Appraisal Skill Program checklist, presented in the evidence tables and further discussed in each CGAG meetings.
- The CGAG studied several guidelines. The AAP (**2004[3], 2009[4], 2011[5])** guidelines, NICE (**2010[24], 2016[25]**) guidelines, the Canadian Pediatric Association **(2018)** [26] guidelines as well as the Australian (Queensland,**2017**)[27] guidelines were considered.
- Critical appraisal was done by AGREE II (Appraisal of Guidelines, Research and Evaluation)[28], to rate and select the appropriate guidelines and decide the one to work with.
- The final decision for the first edition was to adapt the AAP guidelines (2004, 2009, and 2011) [3-5].
- Answers for the PIPOH questions were searched for in the AAP guidelines [3-5]. If the answers were not found, the group searched for other evidence providing it's grading and reference.
- References for the first edition were mainly made to the CPG on neonatal jaundice developed by American Academy of Pediatrics (2004, 2009, and 2011). [3-5]

- Literature searches were repeated for all clinical questions at the end of the CPG adaptation process allowing any relevant papers published before to be included. Future CPG updates will consider evidence published after this cut-off date.

Updating of this guideline:

Following the release of the recent AAP guideline 2022 [6], and since that included several differences in the practice, a reviewing committee including Prof. Afaf Koraa, Prof. Iman Iskander, and Dr. Ahmed Youssef were selected to work on the revision of the original adapted guideline to match the recent AAP version and prepare this updated document.

Guideline Development/ Adaptation Group meetings:

Over the past year, the update was completed through 5 physical meetings and regular virtual meetings. Due to the extensive scope of the guideline, EPG was responsible for overseeing the review process. The timetable and objectives of each meeting were clearly defined. GDG/ GAG meetings were also attended by members of the methodologists group. Working rules for each contributor type were outlined by the chair at the start of each meeting.

Declarations of interests:

Prospective members of the GDG/ GAG were asked to fill in and sign the standard WHO declaration of interest and confidentiality undertaking forms. All guideline members and methodologists were also asked to fill in and sign the standard WHO declaration-of-interests.

Members of the external review group will be asked to fill in and sign the standard WHO declaration-of-interests form before the peer review process.

Evidence for the guideline

We used the GRADE system (Grading of Recommendations, Assessment, Development and Evaluation) for assigning the quality of evidence and strength of recommendations that includes the following definitions [29]. Informed by the evidence required for the GRADE Evidence to Decision (EtD) framework (s) was (were) done while considering changing strength of recommendations according to availability of some resources in the recommendations (both ETD and changing strength of recommendation were not done in this guideline).

Description of the interpretation of the GRADE four levels of certainty of evidence:

Table-1: Classification of the Quality of Evidence:

High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect.

GRADE EtD's contextual factors, criteria and considerations that link to the strength of recommendations:

Criteria and Considerations:

1. Benefits and harms: When a new recommendation is developed, desirable effects (benefits) need to be weighed against undesirable effects (risks/harms), considering any previous recommendation or another alternative. The larger the gap or gradient in favor of the desirable effects over the undesirable effects, the more likely that a strong recommendation will be made.
2. Certainty of the evidence about the effects: The higher the certainty of the scientific evidence base, the more likely that a strong will be made.
3. Values and preferences: If there is no important uncertainty or variability in how much people value the main outcomes, it is likely that a strong recommendation will be made. Uncertainty or variability around these values that could likely lead to different decisions, is more likely to lead to a conditional recommendation.
4. Economic implications: Lower costs (monetary, infrastructure, equipment or human resources) or greater cost-effectiveness are more likely to support a strong recommendation.

5. Equity and human rights: If an intervention will reduce inequities, improve equity or contribute to the realization of human rights, the greater the likelihood of a strong recommendation.
6. Feasibility: The greater the feasibility of an intervention to all stakeholders, the greater the likelihood of a strong recommendation.
7. Acceptability: If a recommendation is widely supported by health workers and program managers and there is widespread acceptance for implementation within the health service, the likelihood of a strong recommendation is greater.

Table-2: Classification of the Strengths of Recommendations:

Strong	The desirable effects of an intervention clearly outweigh the undesirable effects (or vice versa), so most patients should receive the recommended course of action.
Conditional	There is uncertainty about the trade-offs. The clinician and patient need to discuss the patient's values and preferences, and the decision should be individualized.

Developing good practice statements:

The GDG/ GAG also developed good practice statements for this guideline, which are actionable messages relevant to the guideline questions. The justification for each good practice statement was carefully considered by the GDG/ GAG with an emphasis that they are clearly needed. Good practice statements were developed, guided by the following GRADE criteria:

1- Message is really necessary with regard to actual healthcare practice.

2- Have large net positive consequence (relevant outcomes and downstream consequences) (GRADE EtD domains).

3- Collecting and summarizing the evidence is a poor use of time and resources.

4- Include a well-documented, clear rationale connecting indirect evidence.

5- Are clear and actionable statements.

The GDG/ GAG collectively drafted and finalized good practice statements with relevant justifications and remarks to help with their interpretation, with close support and input from the consultant and guideline methodologists.

We have used the Reporting Items for Practice Guidelines in Healthcare (RIGHT) extension for adapted guidelines (RIGHT-Ad@pt Tool) as a reporting checklist for this guideline adaptation process as recommended by the EQUATOR network.

SUGGESTED HEALTH QUESTIONS

A. Prevention:

1. How can SNH be prevented among newborns with gestational age ≥ 35 weeks with possible isoimmune hemolytic disease?
2. What is the feeding counselling required for mothers to decrease risk of severe neonatal hyperbilirubinemia among newborns with gestational age ≥ 35 weeks?
3. How to screen for neonatal jaundice among healthy neonates with gestational age ≥ 35 weeks in the maternity unit?
4. What message should parents of newborns with GA ≥ 35 weeks, receive before discharge from maternity hospital? What is the time of primary care follow up?
5. What are the risk factors for SNH and how to identify them in every newborn with gestational age ≥ 35 weeks?
6. How to identify need for treatment for babies with gestational age ≥ 35 weeks presenting with indirect neonatal hyperbilirubinemia?

B. Assessment:

7. What should be included in the formal assessment of babies with gestational age ≥35 weeks presenting with indirect neonatal hyperbilirubinemia?
8. When and how to assess for ABE among newborns with gestational age ≥ 35 weeks presenting with indirect neonatal hyperbilirubinemia?
9. How to suspect and evaluate elevated conjugated bilirubin concentration, for newborns with gestational age ≥ 35 weeks presenting with neonatal hyperbilirubinemia?

C. Treatment:

10. In babies ≥ 35 weeks gestation with neonatal hyperbilirubinemia receiving phototherapy:
    a. When should intensive phototherapy be prescribed?
    b. What is the breastfeeding recommendation for babies under phototherapy?
    c. How should babies under phototherapy be monitored?
    d. When should phototherapy be discontinued?
    e. How to monitor for rebound hyperbilirubinemia following discontinuation of phototherapy?
11. In babies ≥ 35 weeks gestation with neonatal hyperbilirubinemia requiring escalation of care,
    a. What is the threshold for escalation of care?
    b. What is the approach for escalation of care?
12. In babies ≥ 35 weeks gestation with neonatal hyperbilirubinemia, when is exchange transfusion indicated?

13. Which drugs can increase the risk of bilirubin neurotoxicity, in newborn with gestational age ≥ 35 weeks suffering from hyperbilirubinemia?
14. Which drugs are NOT recommended for treatment of neonatal hyperbilirubinemia, in newborn with gestational age ≥ 35 weeks?

D. Discharge:

15. How to follow up the baby≥ 35 weeks' gestation with severe hyperbilirubinemia after discharge from the NICU?

Key to Evidence Statement

The evidence presented in this guideline is categorized according to the categorization of the Steering Committee on Quality Improvement and Management, which categorizes evidence quality in to 4 levels:

1. Well conducted meta- analyses, systematic reviews of well-designed, randomized, controlled trials or diagnostic studies on relevant populations.
2. Randomized, controlled trials or diagnostic studies with minor limitations; overwhelming, consistent evidence from observational studies.
3. Observational studies (case-control and cohort design).
4. Expert opinion, case reports, reasoning from first principles.

Evidence to recommendations: Considerations

The GDG/ GAG was guided by the results of the AGREE II appraisals of the eligible CPGs and thoroughly reviewed the recommendations of the original source WHO CPGs in consideration of local contextual factors related to the national Egyptian health system like burden of the disease, equity, acceptability, feasibility, and other relevant factors. The GDG decided through an informal consensus process to adopt most recommendations. Also, GDG/ GAG develops group of good practice statements to improve acceptability and feasibility.

Recommendations

Table-3: Recommendation statements with level of evidence & strength of recommendations:

Source guideline	Recommendation	QoE	SoR
A. Prevention of severe hyperbilirubinemia:			
Before Delivery:			
Q1: How can SNH be prevented among newborns with gestational age ≥35 weeks with possible isoimmune hemolytic disease?			
ACOG (30) **Vats and Watchco** (31)	All pregnant women should be tested to determine their ABO blood group and Rh (D) type and receive an antibody screen to determine the need for Rh (D) immunoglobulin (RhIG) and to assess the potential for isoimmune hemolytic disease of the fetus or newborn.	**Very low**	**GPS**
AAP 2022	If the maternal antibody screen is positive or unknown because the mother did not have prenatal antibody screening, the infant should have a direct antiglobulin test (DAT) and the infant's blood type should be determined as soon as possible using either cord or peripheral blood (Figure-1).	**Moderate**	**Strong**
Erdeve O (32)	If the maternal blood group is unknown, testing for maternal and infant blood group as well as DAT is essential in any case of early jaundice.	**Very low**	**GPS**
Following delivery:			
Q2: What is the feeding counselling required for mothers to decrease risk of severe neonatal hyperbilirubinemia among newborns with gestational age ≥ 35 weeks?			
Chen et al (33)	Clinicians should promote frequent breastfeeding on demand and to start within the first hour after birth and should provide breastfeeding support for all mothers.	**Very low**	**GPS**
AAP 2022	Oral supplementation with water or dextrose water should NOT be provided to prevent hyperbilirubinemia or decrease bilirubin concentrations.	**Moderate**	**Strong**
Q3: How to screen for neonatal jaundice among healthy neonates with gestational age ≥ 35 weeks in the maternity unit?			
AAP 2022	All infants should be visually assessed for jaundice at least every 12 hours following delivery until discharge. **TSB or TcB should be measured as soon as possible for infants noted to be jaundiced < 24 hours after birth.**	**Very low**	**GPS**
AAP 2022	TcB or TSB should be measured for **ALL** babies between 24 and 48 hours after birth or before discharge if that occurs earlier.	**Low**	**Conditional**
AAP 2022	If appropriate follow up cannot be arranged for an infant recommended to have an outpatient follow up bilirubin measure, **discharge may be delayed.**	**Very low**	**Conditional**
Monitoring for hyperbilirubinemia:			

Q4: What message should parents of newborns with GA ≥ 35 weeks, receive before discharge from maternity hospital? What is the time of primary care follow up?			
AAP 2022	Before discharge, all families should receive **WRITTEN and VERBAL EDUCATION about neonatal jaundice**. (implementation tool)	**Very low**	**GPS**
AAP 2022	Beginning at least 12 hours after birth, if discharge is being considered, the difference between the bilirubin concentration measured closest to discharge and the phototherapy threshold at the time of the bilirubin measurement should be calculated and used to guide follow-up appointments.	**Low**	**Conditional**
Q5: What are the risk factors for SNH and how to identify them in every newborn with gestational age ≥ 35 weeks?			
AAP 2022	• Infants with risk factors for hyperbilirubinemia (Table-8) as determined by history of risk factors, family history, examination and laboratory results require closer monitoring than infants without risk factors do. • Elevated TSB in a formula fed infant or late onset jaundice should raise the possibility of G6PD.	**Very low**	**GPS**
Q6: How to identify need for treatment for babies with gestational age ≥ 35 weeks presenting with indirect neonatal hyperbilirubinemia?			
AAP 2022	• Use TSB as the definitive test to guide phototherapy and escalation-of-care decisions, including exchange transfusion. • Decisions to initiate phototherapy or escalate care are guided by the gestational age, the hour-specific TSB, and the presence of risk factors for bilirubin neurotoxicity (Table-9)	**Very low**	**GPS**
AAP (2004,2009,2011)	• A TSB measurement should be performed on every infant who is jaundiced in the first 24 hours after birth.	**Moderate**	**Strong**
AAP 2022	TSB should be measured if TCB exceeds or is within 3 mg /dl of phototherapy treatment threshold or if TcB is ≥ 15mg/dL.	**Low**	**Conditional**
AAP 2022	If more than one TcB or TSB measure is available, the rate of increase may be used to identify infants at higher risk of subsequent hyperbilirubinemia. A rapid rate of increase (≥ 0.3 mg/dL per hour in the first 24 hours or ≥ 0.2 mg/dL per hour thereafter) is exceptional and suggests hemolysis. In this case, perform a DAT if not previously done.	**Very low**	**Conditional**
B- Assessment:			
Q7: What should be included in the formal assessment of babies with gestational age ≥35 weeks presenting with indirect neonatal hyperbilirubinemia?			
Porter and Dennis (34)	• History and family history (risk factors for hyperbilirubinemia and risk factors for neurotoxicity). (Table-9)	**Very low**	**GPS**

	• Clinical examination (general / signs of neurotoxicity (BIND score). • Laboratory assessment: ➢ Complete blood count and reticulocyte count. ➢ Maternal and child blood group and Rh. ➢ DAT test. Further investigations as required.		
Q8: When and how to assess for ABE among newborns with gestational age ≥ 35 weeks presenting with indirect neonatal hyperbilirubinemia?			
AAP (2004,2009,2011)	Assessment for acute bilirubin encephalopathy should be done in every jaundiced baby with risk factors for neurotoxicity (Table-9) or any severely jaundiced baby using modified BIND score. (Table-10)	**Low**	**Conditional**
Q9: How to suspect and evaluate elevated conjugated bilirubin concentration, for newborns with gestational age ≥ 35 weeks presenting with neonatal hyperbilirubinemia?			
AAP 2022	For breastfed infants who are still jaundiced at 3-4 weeks of age and for formula fed infants who are still jaundiced at 2 weeks of age, the total and direct reacting or (conjugated) bilirubin concentration should be measured to identify possible pathologic cholestasis.	**Very low**	**Conditional**
AAP 2004-2009-20011	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. (Table-11).	**Moderate**	**Strong**
C- Treatment of neonatal hyperbilirubinemia:			
Phototherapy:			
Q10: In babies ≥ 35 weeks gestation with neonatal hyperbilirubinemia receiving phototherapy:			
AAP 2004-2009-2011	All nurseries and NICUs treating infants should have the necessary equipment to provide intensive phototherapy. (Tables-12)	**Low**	**Conditional**
Q10-A: When should phototherapy be prescribed?			
AAP 2022	• Intensive phototherapy is recommended at the TSB threshold in (Figures-4 & 5) on the basis of gestational age, hyperbilirubinemia neurotoxicity risk factors and age of infant in hours. • The direct reacting or conjugated bilirubin value should not be subtracted from the total bilirubin value when determining management.	**Very low**	**GPS**
Q10-B: What is the breast feeding recommendation for babies under phototherapy?			
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 (max 20 minutes). **If TSB is approaching escalation of care level, the infant should not come out of phototherapy to feed**, as this is a medical emergency	**Moderate**	**Strong**

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.	**Moderate**	**Strong**
AAP 2004-2009-2011-2022	Routine intravenous fluids are NOT necessary for term or near term infants receiving phototherapy unless there is evidence of dehydration or if TSB is approaching escalation of care threshold.	**Moderate**	**Strong**
Q10-C: How should babies under phototherapy be monitored?			
AAP 2022	For hospitalized infants, TSB should be measured within 12 hours after starting phototherapy. The timing of the initial TSB measurement after starting phototherapy and the frequency of monitoring during phototherapy should be guided by the age of the child, the presence of hyperbilirubinemia neurotoxicity risk factors, the TSB concentration and TSB trajectory.	**Very low**	**GPS**
AAP 2022	For infant requiring phototherapy measure the hemoglobin concentration, hematocrit, or complete blood count to assess the presence of anemia and **to provide a base line** in case subsequent anemia develops. • **Evaluate the underlying cause** or causes of hyperbilirubinemia: - In infants who require phototherapy by obtaining a DAT. - In infants whose mother had a positive antibody screen. - Or whose mother is blood group O, regardless of Rh status. - Or whose mother is Rh (D) negative. • **G6PD activity should be measured in:** - Any infant with jaundice of unknown cause whose TSB increases despite intensive phototherapy. - Whose TSB increases suddenly? - Or increases after an initial decline or who requires escalation of care.	**Very low**	**GPS**
AAP 2004-2009-2011	Monitoring TSB for infants receiving intensive phototherapy without signs of ABE: • If TSB ≥ 25 mg/dL, repeat TSB within 2–3 h. • If TSB 20–25 mg/dL, repeat within 3–4 h. • If TSB <20 mg/dL repeat in 4–6 h. • If TSB continues to fall, repeat in 8–12 h. Consider exchange transfusion if TSB is not decreasing or is moving closer to the level for exchange transfusion.	**Moderate**	**Strong**
Q10-D: When should phototherapy be discontinued?			
AAP 2022	Discontinuing phototherapy is an option when TSB has decreased by at least 2 mg / dL below the hour specific threshold at the initiation of phototherapy. A longer	**Low**	**Conditional**

	period of phototherapy is an option if there are risk factors for rebound hyperbilirubinemia (e.g. Gestational age < 38 weeks, age < 48 hours at the start of phototherapy, hemolytic disease.		
Q 10-E: When to monitor for rebound hyperbilirubinemia following discontinuation of phototherapy?			
AAP 2022	Repeat bilirubin measurement after phototherapy is based on the risk of rebound hyperbilirubinemia. Risk factors are: - Infants who received phototherapy before 48 hours - Infants who had a positive DAT. - Infants who had known or suspected hemolytic disease. Infants with risk for hyperbilirubinemia and hyperbilirubinemia neurotoxicity risk factors. (Table-8 and 9).	**Very low**	**GPS**
Kaplan M et al (35)	In the presence of one of the above risk factors: TSB should be measured for rebound at 6-12 hours after phototherapy discontinuation. All other infants should be followed up for TSB after 24 hours of discontinuation of phototherapy.	**Very low**	**GPS**
Q11: Escalation of care: In babies ≥ 35 weeks gestation with neonatal hyperbilirubinemia requiring escalation of care,			
Q11-A: What is the threshold for escalation of care?			
AAP 2022	Care should be escalated when an infant's TSB reaches or exceeds the escalation of care threshold **defined as 2 mg /dl below the exchange transfusion threshold** (figures-7 & 8). The direct reacting or conjugated bilirubin value should not be subtracted from the total bilirubin value when determining management.	**Very low**	**GPS**
Q11-B: What is the approach for escalation of care? (Figure-6) [6]			
APP 2022	For infants requiring escalation of care, blood should be sent STAT for total and direct reacting serum bilirubin, a complete blood count, serum albumin, serum chemistries and blood type and cross match.	**Very low**	**GPS**
APP 2022	Infants requiring escalation of care should receive intravenous hydration and emergent intensive phototherapy. A neonatologist should be consulted about urgent transfer to a NICU that can perform an exchange transfusion.	**Low**	**Conditional**
AAP 2022	TSB should be measured at least every 2 hours during the escalation period. Once the TSB is lower than the escalation of care threshold, continue phototherapy according to the bilirubin level.	**Very low**	**GPS**
AAP 2022	**IVIG:** Intravenous immunoglobulin (IVIG) (0.5-1 g/kg over 2 hours) may be provided to **infants with isoimmune hemolytic disease (i.e. positive DAT) whose TSB**	**Low**	**Conditional**

	reaches or exceeds the escalation of care threshold. This dose can be repeated in 12 hours.		
Exchange Transfusion:			
Q12: In babies ≥ 35 weeks' gestation with neonatal hyperbilirubinemia, when is exchange transfusion indicated?			
AAP 2022	**Urgent exchange transfusion** should be performed for infants with **signs of intermediate or advanced stages of acute bilirubin encephalopathy** (Table-10)	**Low**	**Conditional**
AAP 2022	**An urgent exchange transfusion** should be performed for infants if **the TSB ≥ the exchange transfusion threshold**. (Figures-7 & 8) If while preparing for exchange transfusion but before starting the exchange transfusions, a TSB concentration is below the exchange transfusion threshold and the infant **does NOT show signs or intermediate or advanced stages of ABE**, then the exchange transfusion may be deferred while continuing intensive phototherapy and following TSB every 2 hours until the TSB is below the escalation of care threshold.	**Low**	**Conditional**
Drugs (adjuvant therapy):			
Q13: Which drugs can increase the risk of bilirubin neurotoxicity, in newborns with gestational age ≥ 35 weeks suffering from significant hyperbilirubinemia?			
GPP	Use the following medications with caution in a baby with hyper-bilirubinaemia as they may cause bilirubin to be displaced from albumin binding sites and increase the risk of ABE: • Konakion. • Digoxin. • Diazepam. • Salicylates. • Diuretics e.g. furosemide and hydrochlorothiazide. • Ceftriaxone. • Ibuprofen. Sulfamethoxazole such as in trimethoprim/sulfamethoxazole (cotrimoxazole).	**Low**	**Conditional**
Q14: Which drugs are NOT recommended for the treatment of neonatal hyperbilirubinemia in newborns with gestational age ≥35 weeks?			
GPP	**The use of any of the following medications for the treatment of hyperbilirubinemia is NOT recommended:** (Phenobarbitone, Agar, Clofibrate, albumin, charcoal, cholestyramine, D penicillamine, glycerine, riboflavin, homeopathy, metalloporphyrins).	**Low**	**Conditional**
D- Follow up after discharge:			
Q15: How to follow up the baby≥ 35 weeks gestation with severe hyperbilirubinemia after discharge from the NICU?			

Expert opinion (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.	**Low**	**Conditional**
Expert opinion (GPP)	Infants who required exchange transfusion or those who exhibit neurological abnormalities with history of neonatal jaundice require regular neurological follow up.	**Low**	**Conditional**
Expert opinion (GPP)	Infants with isoimmunization are at risk of severe anemia after several weeks (up to 8-12 weeks of age); Repeat hemoglobin measurement should be performed at two weeks if it was low at discharge and at four weeks if it was normal. Infants suspected to have G6PD deficiency (elevated TSB in formula infants or late onset jaundice) should be tested at 3 months of age.	**Low**	**Conditional**

Detailed Recommendations

Table-4: Detailed Recommendations:

Detailed Recommendations

A. Prevention of severe hyperbilirubinemia:

Before Delivery:

Q1: How can SNH be prevented among newborns with gestational age ≥35 weeks with possible isoimmune hemolytic disease?

- **All pregnant women should be tested for ABO and Rh (D) blood types. An antibody titer should be performed for mothers with suspected incompatibility**.
- If the mother was not screened for anti-erythrocyte antibodies during pregnancy, evaluation and treatment should occur shortly after delivery.
- The American College of Obstetricians and Gynecologists recommends that pregnant women be tested to determine their ABO blood group and Rh (D) type and receive an antibody screen to determine the need for Rh (D) immunoglobulin (RhIG) and to assess the potential for isoimmune hemolytic disease of the fetus or newborn. [29]
- **If the maternal antibody screen is positive or unknown because the mother did not have prenatal antibody screening, the infant should have a direct antiglobulin test (DAT) and the infant's blood type should be determined as soon as possible using either cord or peripheral blood**. (Aggregate Evidence Quality Grade B, Recommendation). [29,30]
- The DAT helps to identify infants at risk for hyperbilirubinemia attributable to hemolysis. DAT negative infants may be managed with usual care.
- Mothers who received RhIG can have a positive antibody screen for anti-Rh (D), and RhIG can cause a positive DAT (anti Rh [D]) in the infant but generally **no hemolysis**. [36]
- If the maternal blood type is Rh (D) negative, the Rh type of the infant should be determined to assess the need for administration of RhIG to the mother.
- If the maternal blood is O positive and the maternal antibody screen is negative, it is an option to test the cord blood for the infant's blood type and/or DAT. [30]

Following delivery:

Q2: What is the feeding counselling required for mothers to decrease risk of severe neonatal hyperbilirubinemia among newborns with gestational age ≥ 35 weeks?

- **Breast milk is the best means of nutrition for the newborn.**
- It is contraindicated to supplement infants with anything other than mother's own milk in the absence of a specific clinical indication**.**
- Jaundice in breastfed infants falls into 2 main categories, depending on its timing of onset:
  - Suboptimal intake can lead to hyperbilirubinemia, the so called "breastfeeding jaundice," which typically peaks on days 3 to 5 after birth and is frequently associated with excess weight loss. it is more correctly described as "**suboptimal intake hyperbilirubinemia**"[37] Breastfeeding fewer than 8 times per day has been associated with higher TSB concentrations. [33] Low milk and low caloric intake contribute to decreased stool frequency and increased enterohepatic circulation of bilirubin.[37]
  - Hyperbilirubinemia that persists with adequate human milk intake and weight gain is referred to as "breast milk jaundice" or the "**breast milk jaundice syndrome**." This cause of prolonged unconjugated hyperbilirubinemia, which can last up to 3 months, is almost

always non-pathologic and not associated with direct or conjugated hyperbilirubinemia. which can last up to 3 months. [38]

- Clinicians should promote breastfeeding support for all mothers and breast milk feeding within the first hour after birth with frequent feeding on demand (i.e., at least 8 times in 24 hours [33]. Evidence of adequate breastfeeding includes the following:
  - Normal weight loss by hour of age and delivery method. Maximum weight loss by day 3 is on average 5% - 10% of the birth weight then they begin to gain 15 to 30 g daily, regaining birthweight by 10 to 14 days of age.
  - Appropriate urine output and transitional stooling (Four to six thoroughly wet diapers in 24 hours and the passage of 3 to 4 stools per day by the fourth day).
  - Absence of maternal discomfort, and audible swallowing as the mother's milk volumes increase. [40]
- Loss of >10% of the birth weight by day 3, suggests inadequacy of intake. [40]
- Breastfed infants who are adequately hydrated should not routinely receive supplementation with commercially available infant formula. [39]

Q3: How to screen for neonatal jaundice among healthy neonates with gestational age ≥ 35 weeks in the maternity unit?

- **All infants should be visually assessed for jaundice at least every 12 hours following delivery until discharge. TSB or TcB should be measured as soon as possible for infants noted to be jaundiced.**
- Although jaundice before 24 hours of age may not have an identifiable cause, [41] when a cause is identified, it is most likely to be a hemolytic process. The consequences of missing early jaundice attributable to significant hemolysis justify TSB or TcB measurement. This recommendation for visual assessment DOES NOT replace the need to obtain at least 1 screening TSB or TcB.

- **The TcB or TSB should be measured between 24 and 48 hours after birth or before discharge if that occurs earlier. (Aggregate Evidence Quality Grade C, Recommendation).**
- TcB measurements are valid and reliable when used as a screening test to identify infants who require a TSB measurement.[42] This may result in a reduction in blood draws and easier follow up of neonatal jaundice [43] There is a good correlation between TcB measures and TSB concentrations, with the TSB generally within 3 mg/dL of the TcB among newborn infants with TSB concentrations<15 mg /dl. [44]

- **TSB should be measured if the TcB exceeds or is within 3 mg/dL of the phototherapy treatment threshold or if the TcB is ≥15 mg/dL. (Aggregate Evidence Quality Grade C, Recommendation)**

- **If more than 1 TcB or TSB measure is available, the rate of increase may be used to identify infants at higher risk of subsequent hyperbilirubinemia.[45] A rapid rate of increase (≥0.3 mg/dL per hour in the first 24 hours or ≥0.2 mg/dL per hour thereafter) is exceptional [46] and suggests hemolysis. In this case, perform a DAT if not previously done. (Aggregate Evidence Quality Grade D, Option)**
- If available, measurement of end tidal carbon monoxide production, corrected for ambient carbon monoxide (ETCOc), is a potentially useful method for quantifying hemolysis.[47] Carbon monoxide is produced in equimolar amounts with bilirubin when heme is catabolized to bilirubin.

- **If appropriate follow up cannot be arranged for an infant recommended to have an outpatient follow up bilirubin measure, discharge may be delayed. (Aggregate evidence Quality Grade D)**
- Once a spontaneous decline in TcB or TSB over at least 6 hours is noted, the risk of subsequent hyperbilirubinemia is low and it is not necessary to obtain additional bilirubin measurements unless there are worrying signs.

Monitoring for hyperbilirubinemia:

Q4: What message should parents of newborns with GA ≥ 35 weeks, receive before discharge from maternity hospital? What is the time of primary care follow up?

- In the antenatal clinic, expecting mothers should be offered information about neonatal jaundice especially those with risk of incompatibility. Information should be provided through verbal discussion backed by a handout. Care should be taken to avoid causing unnecessary anxiety to parents or caregivers. [48]
- Before discharge, all families should receive written and verbal education about neonatal jaundice. Parents should be provided written information to facilitate post-discharge care, including the date, time, and place of the follow-up appointment and, when necessary, a prescription and appointment for a follow-up TcB or TSB. Birth hospitalization information, including the last TcB or TSB and the age at which it was measured, and DAT results (if any) should be transmitted to the primary care provider who will see the infant at follow-up. (Aggregate Evidence Quality Grade X, Strong Recommendation)
- The timing of pediatric primary care follow-up be based on the difference between the bilirubin concentration and the phototherapy threshold at the time of bilirubin measurement to determine the interval between discharge and follow-up and the need for additional TSB or TcB measurements. This approach incorporates both gestational age and other hyperbilirubinemia neurotoxicity risk factors. [45]
- If appropriate follow-up cannot be arranged for an infant recommended to have an outpatient follow-up bilirubin measure, discharge may be delayed. (Aggregate Evidence Quality Grade D, Option).
- For infants who required phototherapy before nursery discharge, the timing of follow-up bilirubin testing after discontinuing phototherapy should be based on the risk of rebound hyperbilirubinemia. In most instances, a follow-up bilirubin concentration should be obtained at least 12 hours, and preferably 24 hours, after phototherapy is discontinued to allow for sufficient time for rebound hyperbilirubinemia. [35]

Q5: What are the risk factors for SNH and how to identify them in every newborn with gestational age ≥ 35 weeks?

- Infants with risk factors for hyperbilirubinemia (Table-8) require closer monitoring than infants without risk factors. Determining the presence of these risk factors requires examining the infant, assessing laboratory data, and obtaining a family history of blood disorders or neonatal jaundice.

Laboratory assessment:

  - Complete blood count and reticulocyte count.
  - Maternal and child blood group and Rh.
  - DAT test.
  - Further investigation as required Identification of predisposing factors.

- Before discharge, every newborn should be assessed for the risk of developing significant hyperbilirubinemia (Table-8), and all nurseries should establish protocols for assessing this risk. This is particularly important in infants who are discharged before the age of 72 hours.
- These risk factors should be explained to the mother before discharge so she can attend timely follow-up and understand the need for additional clinical and laboratory evaluation.

Q6: How to identify need for treatment for babies with gestational age ≥ 35 weeks presenting with indirect neonatal hyperbilirubinemia?

- **Visual estimation of bilirubin levels:**
  - Visual estimation is routinely used to guide decisions about obtaining TCB or TSB measures a term-born outpatients 3 or more days old, for whom treatment thresholds are high enough that distinguishing between milder degrees of jaundice is not important. However, all infants should have at least 1 TCB or TSB measured. [6]

- **Estimation of bilirubin level either by skin (TcB) or TSB measured in the laboratory:**
  - TcB (Bili-Check) devices measure the yellowness of reflected light transmitted from the skin and use an algorithm to predict the TSB level from the objective measurement of skin color. Although TcB measurements do not directly assess bilirubin levels, they are valid and reliable when used as a screening test to identify infants who require a TSB measurement [42] Using TcB measures in this way may result in a reduction in blood draws. [43] Implementing universal TcB screening during the nursery stay and at subsequent public health nurse visits has been associated with a reduction in both blood draws and the likelihood of having a TSB level ≥20 mg/dL. [46]
  - There is a good correlation between TcB measures and TSB concentrations, with the TSB generally within 3 mg/dL of the TcB among newborn infants with TSB concentrations <15 mg/dL. [43-46]
  - The magnitude and direction of the average difference between TcB measures and TSB concentrations may depend on skin melanin concentration and the instrument used to measure TcB. For example, Bili-Chek instruments may underestimate TSB at higher levels (e.g., above about 15 mg/dL) in infants with greater skin melanin concentration by an average of about 1 to 2 mg/dL. In contrast, JM instruments may overestimate the TSB infants with greater skin melanin concentration by an average of about 0.7 to 2.5 mg/dL. [49] The recommendations for the use of TcB measures takes into account the degree of uncertainty related to skin melanin concentration. [46,49]
  - **TcB is NOT recommended in case of:** [50]
    - Making a treatment decision.
    - Prolonged jaundice.
    - Conjugated hyperbilirubinemia.
    - During or after phototherapy.
    - Following an exchange transfusion.

- **Plot total serum bilirubin on Hour-Specific Phototherapy Nomogram and Exchange Nomogram:** (www.bilitool.org or www.peditools.org/bili2022) [6]
  - TcB is resorted to if TSB is not available.
  - The early onset of jaundice (detectable < 24 hours of age) is a risk factor for severe hyperbilirubinemia requiring early treatment. [6]
  - Babies who develop jaundice in the first 24 hours of life, usually due to hemolysis, are at risk of developing SNH and acute and chronic bilirubin encephalopathy. [41]
  - The risk of jaundice in the first 24 hours of life is higher in babies 35 to 36 weeks' gestation. [41]

- **In Egypt where babies are discharged early (before 12 hours from delivery), assessment of jaundice should be performed by nurses or health workers during postpartum home visits at Days 2,4,7 of life or in the Maternal Child health center (MCHC) during the administration of first dose of Hepatitis B vaccine on day 1 of life.**

B- Assessment:

Q7: What should be included in the formal assessment of babies with gestational age ≥35 weeks presenting with indirect neonatal hyperbilirubinemia?

- History and family history (risk factors for significant hyperbilirubinemia and neurotoxicity risk factors (Table-9).
- Clinical examination (Modified BIND SCORE). [51]
- Laboratory assessment:
  - Complete blood count and reticulocyte count.
  - Maternal and child blood group and Rh.
  - DAT test.
- Further investigation as required.

Q8: When and how to assess for ABE among newborns with gestational age ≥ 35 weeks presenting with indirect neonatal hyperbilirubinemia?

- ABE may occur in the first days of life and causes a temporary alteration in neurologic state. [52-55]
- The risk and severity of ABE increase with rising bilirubin level.
- Neurotoxicity risk factors include: [6] (Table-9)
  - Isoimmune hemolytic disease, G6PD Deficiency, or other hemolytic conditions.
  - Sepsis.
  - Significant clinical instability in the past 24h.
  - Preterm < 38 wks.
  - Sepsis.
  - Clinical instability and Albumin Level <3.0 Mg/dl.
- Clinical presentation of ABE is subtle and non-specific initially and manifests with poor feeding. This progresses to high pitched cry, high temperature and lethargy. Subsequently disturbance in neurobehavioral state, hypertonia, retrocollis and opisthotonus may occur. [53]
- The modified bilirubin-induced neurologic dysfunction scale (M-BIND) [51] is a 12-point score, incorporating eye abnormalities with the original BIND score [53] to assess bilirubin induced neurological damage in an objective manner (Table-10). It facilitates diagnosis of ABE as well as monitors the neurological progress in neonates with severe hyperbilirubinemia.
- Any infant with evidence of acute bilirubin encephalopathy should have an **immediate exchange transfusion**. [56]
- Severe neonatal hyperbilirubinemia is a medical emergency that should be handled promptly to prevent ABE. **Severely jaundiced babies should NOT be allowed to wait.**

Q9: How to suspect and evaluate elevated conjugated bilirubin concentration, for newborns with gestational age ≥ 35 weeks presenting with neonatal hyperbilirubinemia?

- For breastfed infants who are still jaundiced at 3-4 weeks of age and 2 weeks for formula -fed infants, the total and conjugated bilirubin concentration should be measured to identify possible pathologic cholestasis. [57]
- Infants who have an elevation of direct reacting or conjugated bilirubin should have a urine analysis and culture. Additional laboratory evaluation for sepsis and other possible causes should be performed if indicated by history and physical examination. [58]
- Infection:

- C-reactive protein (may be false negative near onset of infection).
- Blood culture–unwell baby of any age.
- Urine–microscopy and culture.
- Investigate for congenital infections if there are other indications, e.g. clinical signs of suggestive history, severe jaundice, elevated conjugated bilirubin, thrombocytopenia (Toxoplasmosis, Rubella, Cytomegalovirus (CMV) Herpes simplex virus, Syphilis).

- Inborn errors of metabolism: if baby looks unwell and the jaundice is severe, e.g. galactosemia, tyrosinemia.
- Liver disease:
  - Albumin (decreased levels result in poor bilirubin binding capacity and risk of bilirubin toxicity).
  - Liver function tests (LFT) as liver enzymes may be increased, e.g. in congenital infections, inborn errors of metabolism.
  - If the direct reacting or conjugated bilirubin is elevated, additional evaluation for the causes of cholestasis is recommended.

C- Treatment of neonatal hyperbilirubinemia:

Phototherapy:

Q10: In babies ≥ 35 weeks gestation with neonatal hyperbilirubinemia receiving phototherapy:

Q10-A: When should phototherapy be prescribed? [4, 5, 59]

- In using the guidelines for phototherapy and exchange transfusion (Figures-4, 5, 9 & 10), the direct reacting (or conjugated) bilirubin level should not be subtracted from the total bilirubin.
- Measurement of direct bilirubin is not accurate and there is a large variability between labs. There is no harm to treat according to total bilirubin if the direct portion is < 50% of total. In unusual situations in which the direct bilirubin level is 50% or more of the total bilirubin, there are no good data to provide guidance for therapy, and consultation with an expert in the field is recommended. [6]
- All nurseries and services treating infants should have the necessary equipment to provide intensive phototherapy (appendix).
- Intensive phototherapy means an irradiance >30 μW/cm^2 per nm at a wavelength around 475 nm.
- Recommendations for phototherapy treatment are given in Table-14 & Figures-4 & 5.
- Do not use phototherapy in babies unless indicated.
- The amount of irradiance received by infants is higher directly below the light source than at the periphery.
- If the TSB does not fall or continues to rise despite intensive phototherapy, it is likely that hemolysis is occurring. Examine baby daily for signs of ABE.

Q10-B: What is the breast-feeding recommendation for babies under phototherapy?

- Factors affecting phototherapy, side effects, precautions, dose and equipment (phototherapy appendix-).
- In breastfed infants who require phototherapy, it is recommended that, breastfeeding **should be continued** unless there is a clear contraindication.

- Feeding should be maintained during phototherapy to promote bilirubin clearance and avoid dehydration. Interrupting phototherapy for breastfeeding does not impact the overall effectiveness of phototherapy if it is otherwise appropriately used. [60] These interruptions should be minimized if the bilirubin concentration is approaching the need to escalate care.
- If a breastfed infant's intake is inadequate as proven by weight loss > 10% of the birth weight or the infant is dehydrated while on phototherapy, supplementation with expressed breast milk or formula is appropriate.
- Poor feeding leads to reduced caloric intake and dehydration resulting in elevated TSB.
- Intravenous fluids are NOT necessary for term or near-term infants receiving phototherapy unless there is evidence of dehydration not corrected by adequate oral intake. [6]

Q10-C: How should babies under phototherapy be monitored ?

- **For infants receiving intensive phototherapy:** [4]
  - If TSB ≥ 25 mg/dL, repeat TSB within 2–3 h.
  - If TSB 20–25 mg/dL, repeat within 3–4 h.
  - If TSB <20 mg/dL repeat in 4–6 h. If TSB continues to fall, repeat in 8–12 h.
- For infant requiring phototherapy measure the hemoglobin concentration, hematocrit, or complete blood count to assess the presence of anemia and to provide a baseline in case subsequent anemia develops. [6]
- Evaluate the underlying cause or causes of hyperbilirubinemia in infants who require phototherapy by obtaining a DAT:
  - In infants whose mother had a positive antibody screen.
  - Or whose mother is blood group O, regardless of Rh status.
  - Or whose mother is Rh (D) negative.
- **G6PD activity should be measured in:** [6]
  - Any infant with jaundice of unknown cause whose TSB increases despite intensive phototherapy.
  - Whose TSB increases suddenly.
  - Or increases after an initial decline or who requires escalation of care.

Q10-D: When should phototherapy be discontinued?

- **The decision to discontinue phototherapy is based on balancing the desire to minimize exposure** to phototherapy and separation of mothers and infants against the desire to avoid a rebound in TSB following phototherapy.
- **Discontinuing phototherapy is an option when the TSB has decreased by at least 2 mg/dL below the hour-specific threshold at the initiation of phototherapy. A longer period of phototherapy is an option if there are risk factors for rebound hyperbilirubinemia.**
- Rebound hyperbilirubinemia is defined as a TSB concentration that reaches the phototherapy threshold for the infant's age within 72 to 96 hours of discontinuing phototherapy. Risk factors for rebound hyperbilirubinemia include [35]
  - Gestational age < 38 weeks.
  - Age <48 hours at the start of phototherapy.
  - Infants who had a positive DAT.
  - Hemolytic disease.

- **Higher TSB at the time of phototherapy discontinuation in relationship to the phototherapy threshold.**

Q 10-E: When to monitor for rebound hyperbilirubinemia following discontinuation of phototherapy?

- Repeat bilirubin measurement after phototherapy is based on the risk of rebound hyperbilirubinemia.
- **Risk factors are:**
  - Infants who received phototherapy before 48 hours.
  - Infants who had a positive DAT.
  - Infants who had known or suspected hemolytic disease.
  - Infants with risk for hyperbilirubinemia and hyperbilirubinemia neurotoxicity risk factors. (Tables-9)
- In the presence of one of the above risk factors TSB should be measured for rebound at: 6-12 hours after phototherapy discontinuation and the day after
- All other infants should be followed up for TSB after 24 hours.
- It is an option to measure TcB instead of TSB if it has been at least 24 hours since phototherapy was stopped. [61]

Q11: Escalation of care: In babies ≥ 35 weeks gestation with neonatal hyperbilirubinemia requiring escalation of care,

Escalation of care refers to the intensive care that some infants with elevated or rapidly increasing bilirubin concentrations need to prevent the need for an exchange transfusion and possibly prevent kernicterus. [6]

Q11-A: What is the threshold for escalation of care?

- The escalation-of-care threshold is 2 mg/dL below the exchange transfusion threshold.
- The direct-reacting or conjugated bilirubin value should not be subtracted from the total bilirubin value when determining management.

Q11-B: What is the approach for escalation of care? (Figure-6) [6]

- Initiating escalation of care is a **medical emergency**. The escalation-of care period starts from the time the infant's TSB result first mandates starting escalation of care and ends when the TSB is below the escalation of care threshold.
- These infants are optimally managed in a neonatal intensive care unit (NICU). If the infant is in an institution that lacks facilities for an emergent exchange transfusion, a neonatologist should be consulted about urgent transfer to a NICU that can perform an exchange transfusion.
- The infant should be admitted directly to the NICU rather than through the emergency department to avoid delaying care.
- For infants requiring escalation of care, blood should be sent STAT .for total and direct reacting serum bilirubin, a complete blood count, serum albumin, serum chemistries and type and cross match.
- Intensive phototherapy and intravenous hydration should be initiated immediately.
- TSB should be measured at least every 2 hours during the escalation period. Once the TSB is lower than the escalation of care threshold, continue phototherapy according the bilirubin level.
- Intravenous immune globulin (IVIG: 0.5 to 1 g/kg) over 2 hours may be provided to infants with isoimmune hemolytic disease (i.e., positive DAT) whose TSB reaches or exceeds escalation of care threshold. The dose can be repeated in 12 hours.

Exchange Transfusion:

Q12: In babies ≥ 35 weeks' gestation with neonatal hyperbilirubinemia, when is exchange transfusion indicated?

- Recommendations for exchange transfusion are given in Figures-7 & 8.
- The aim of an exchange transfusion is to rapidly reduce the TSB by removing small aliquots of blood from the baby and replacing it with donor blood components. [62]
- Recommendations for exchange transfusion are given in Figures-7 & 8.
- **Indications:**
  - Infants with signs of intermediate or advanced stages of acute bilirubin encephalopathy.
  - If the TSB is at or above the exchange transfusion threshold.
  - TSB continues to rise despite intense phototherapy.
  - If the bilirubin albumin ratio exceeds the threshold for GA and risk factors.
- **Post exchange transfusion:**
  - Continue intensive phototherapy.
  - Measure TSB within 2 hours of exchange transfusion.

- **What the indications of IVIG:** [6]
  - Intravenous immune globulin (IVIG; 0.5 to 1 g/kg) over 2 hours may be provided to infants with isoimmune hemolytic disease (i.e., positive DAT) whose TSB reaches or exceeds escalation of care threshold. The dose can be repeated in 12 hour.
  - It acts by blocking Fc receptors on macrophages thereby reducing the breakdown of antibody-coated RBCs and also enhancing the clearance of maternal antibodies. [63]

Drugs (adjuvant therapy):

Q13: Which drugs can increase the risk of bilirubin neurotoxicity, in newborns with gestational age ≥ 35 weeks suffering from significant hyperbilirubinemia?

- Use the following medications with caution in a baby with hyper-bilirubinemia as they may cause bilirubin to be displaced from albumin binding sites and increase the risk of ABE:
  - Synthetic Vitamin K (medadione). [64]
  - Digoxin. [65]
  - Diazepam. [65]
  - Salicylates. [66]
  - Diuretics e.g. furosemide and hydrochlorothiazide. [67]
  - Sulfamethoxazole such as in trimethoprim/sulfamethoxazole (cotrimoxazole). [67]
  - Ceftriaxone. [68]
  - Ibuprofen. [69]

Q14: Which drugs are NOT recommended for the treatment of neonatal hyperbilirubinemia in newborns with gestational age ≥35 weeks?

- There is NO role for the use of the following medications to treat neonatal hyperbilirubinemia (Phenobarbitone, Agar, Clofibrate, albumin, charcoal, and metalloporphyrins). [23]

D- Follow up after discharge:

Q15: How to follow up the baby≥ 35 weeks gestation with severe hyperbilirubinemia after discharge from the NICU?

- Infants requiring exchange transfusion or those who exhibit neurological abnormalities should be referred to a neurological follow-up programs and must have a hearing screen. Their hearing screen should include brainstem auditory evoked potentials. [70]
- Acute bilirubin encephalopathy may progress to athetoid cerebral palsy, deafness and blindness due to paralysis of ocular muscles so neurodevelopmental follow up programs are essential.
- **Hearing assessment:**
  - Babies should have a hearing screen according to local protocols usually after completion of phototherapy.
  - Elevated ABR thresholds may indicate SNHL due to hyperbilirubinemia and require further investigations and treatment.
- Infants with isoimmunization are at risk for severe anemia after several weeks; it is suggested that a repeat hemoglobin measurement be performed at two weeks of age if it was low at discharge and at four weeks if it was normal. [71]
- Antibodies persist for weeks, with continued hemolysis and can cause anemia as late as age 6 months (especially in infants who had received intrauterine transfusions).

External review and Consultation process

No	Names	Scientific degree (Affiliation)	University
Local External Review Panel members (Alphabetical Order)(Original version)			
1	**Prof. Abdel Latef Abd Elmoaz**	**MD**	**Professor of Pediatrics, Former Head of the Neonatal Unit-Assuit University**
2	**Prof. Ali Afia**	**MD**	**Professor of Pediatrics, Former Head of the Neonatal Unit -Al Azhar University**
3	**Prof. Hesham Abdel-Hady**	**MD**	**Professor of Pediatrics, Head of the Neonatal Unit-Mansoura University**
4	**Prof. Mohamed Fathallah**	**MD**	**Professor of Pediatrics, Former Head of the Neonatal Unit -Ain Shams University**
5	**Prof. Nahed Fahmy**	**MD**	**Professor of Pediatrics, Former Head of the Neonatal Unit- Cairo University**
Local External Review Panel member: (Updated version)			
1	**Prof. Iman Khaled Eyada**	**MD**	**Professor of Pediatrics, Former Head of the Neonatal Unit- Cairo University**
International External Reviewer:			
1	**Prof Vinod Bhutani**	**MD, FAAP**	**Professor of Pediatrics and Neonatology , Stanford University USA**
2	**Prof. John Watchco**	**MD, FAAP**	**Professor of Pediatrics, Gynecology and Obstetrics, University of Pittsburgh, USA**

Process of Discussion of the feedback

- The previously mentioned Faculty reviewed the first draft of the adapted guideline and its supporting tools for application and a questionnaire was circulated and recollected, to gather their feedback after reviewing the draft.
- After feedback and meetings with the reviewers, their recommendations were compiled and executed in the presented final adapted EPG document.

The final modifications are based upon available resources, facilities and applicability of these clinical guideline recommendations to the culture and values of Egyptians hoping that the "**Egyptian clinical practice guideline for prediction, prevention and management of neonatal hyperbilirubinemia in term and late preterm newborns "would benefit babies all over Egypt".**

Plan for Scheduled Review and Update

- The panel has decided to review the adapted guideline for updates after 5 years from its last update publication date in 2025, which should be in 2030.
- Review will occur after checking for updates in the source guidelines, consultation of expert opinion on the changes needed for updating according to the newest evidence, recommendations published in this area and the clinical audit and feedback from implementation efforts in local healthcare settings.
- However, in the case of any break through evidence-based recommendations being published before that date, review will occur earlier.

Funding Sources

- The faculty members involved in the adaptation of this EPC volunteered their time. However, their affiliations provided non-financial support throughout the development of this work in terms of utilization of facilities (i.e., medical libraries, websites resources, availability of project management personnel, leadership commitment, technical support, expert methodologists review, administrative support, storage and documentation). This work is not related to any pharmaceutical company.

ADAPTATION PROCESS

The following steps were performed during the adaptation process (Adapte tool kit):

1. Guideline search and retrieval including list of CPGs and whether they were included/excluded, with rationale.
2. Guideline assessments including a summary of results for each assessment (including AGREE II domain scores)
3. Decision process followed by panel.
4. Results and decisions of each evaluation.
5. All these items can be found in the Appendix section of the guideline book.

This guideline was adapted by the Panel named: **Egyptian Neonatal Hyperbilirubinemia Group as one of the pioneer working groups of the Egyptian Pediatric Clinical Practice Guidelines Committee (EPGC).**

For the most part of original guideline was adapted from:

- AAP guideline publication in 2004: Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of gestation. Pediatrics: 114(1); 297-316. http://pediatrics.aappublications.org/content/114/1/297.
- American Academy of Pediatrics in 2009: Hyperbilirubinemia in the Newborn Infant 35 Weeks' Gestation: An Update with Clarifications. Pediatrics: 124(4), 1193-1198.
- American Academy OF Pediatrics 2011: Phototherapy to Prevent Severe Neonatal Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. Pediatrics: 128 (4), e1046-1052.

For the updated guideline, we added the updated AAP guideline:

- American Academy OF Pediatrics 2022: Kemper AR, Newman TB, Slaughter JL, Maisels MJ, Watchko JF, Downs SM, Grout RW, Bundy DG, Stark AR, Bogen DL, Holmes AV. Clinical practice guideline revision: management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2022 Sep 1;150(3): e2022058859.

Implementation Considerations

- It has been demonstrated in a variety of settings that patient care consistent with recommendations in evidence- based guidelines leads to improved outcomes. Guidelines are designed to ensure that all members of a patient's health care team are aware of the goals of treatment and of the different ways of achieving these goals. They help set standards of clinical care, may serve as a basis for audit, and act as a starting point for the education of health professionals and patients.
- However, in order to effect changes in medical practice and consequent improvements in patient outcomes, evidence-based guidelines must be implemented and disseminated at national and local levels. Dissemination involves educating healthcare providers to improve their awareness, knowledge, and understanding of guideline recommendations. It is a part of implementation, which involves the translation of evidence-based guidelines into real-life practice with improvement of health outcomes for the patient. Implementation remains a difficult problem worldwide. Barriers to implementation range from poor infrastructure that hampers delivery of care to remote parts of a country, to cultural factors that make patients reluctant to use recommended medications and lack of use of guidelines

Guideline Implementation Strategies:

- Implementing guidelines in practice that result in successful practice changes and positive clinical impact is a complex undertaking. There are many strategies that can be helpful during implementation, which include the following:
  - Identifying an individual to lead the project who is able to provide dedicated time to implementation. This leader will provide support, clinical expertise and should have strong interpersonal, facilitation and project management skills.
  - Utilizing a systematic approach to planning, implementation and evaluation of the guideline initiative. A work plan is helpful to keep track of activities and timelines.
  - Before a change in practice that can be expected and guideline recommendations implemented, the attitudes, values and beliefs of staff about NNJ must be addressed through a preliminary questionnaire.

Implementation strategies

Table-5: CPG implementation strategies:

Focus of Strategy	Strategies
Practitioners	• Educational meetings: conferences, lectures, workshops or traineeships, grand rounds, seminars, and symposia.
	• Educational materials: Printed or electronic information.
	• Web-based education: Computer-based educational activities.
	• Educational outreach/academic detailing: A trained person meets with providers in their practice setting to provide information with the intention of changing the provider's practice. The information may include feedback on the performance of the provider(s).
	• Audit and feedback: Any summary of clinical provision of health care over a specified period; may include recommendations for clinical action. The information is obtained from medical records, self-assessment check lists, databases or observations of patients. Summary may be targeted at the individual practitioner or the organization.
	• Reminders: The provision of information verbally, on paper or on a computer screen to prompt a health professional to recall information or to perform or avoid a particular action related to patient care.
	• Local opinion leaders: Providers nominated by their colleagues as "educationally influential." In general, such individuals are identified by their peer colleagues, are trained as change agents and operate within their communities to teach and enable change.
	• Patient-mediated interventions: Interventions directed at patients (e.g., mass media campaigns, reminders, education materials) to optimize professional–patient interactions.
	• Practice tools: Tools designed to facilitate behavioural/practice changes, e.g., flow charts.
Patients	• Patient education materials: Printed/electronic information aimed at the patient, consumer, family, caregivers, etc.
	• Mass media campaigns.
	• Reminders: The provision of information verbally, on paper or electronically to remind a patient/consumer to perform a particular health-related behavior.
	• Decision-support tools: Aids designed to facilitate shared decisions by patients and their physicians.

Organizations and regulatory bodies	• Changes to health care teams: Changing tasks or responsibilities of health professionals or compositions of health professional groups.
	• Information and communication technology: Electronic decision support, order sets, care maps, electronic health records, office-based personal digital assistants, etc.
	• Audit and feedback: Any summary of clinical provision of health care over a specified period; may include recommendations for clinical action. The information is obtained from medical records, databases or observations by patients. Summary may be targeted at the individual practitioner or the organization.
	• Administrative procedures / policies.
	• Formularies: Drug safety programs, electronic medication administration records.
	• Financial incentives or penalties: The use of remuneration for the performance of certain functions or actions, e.g., screening procedures in primary care.
	• Mandated practices.

IMPLEMENTATION TOOLS

Education material was prepared for the implementation of the **"Egyptian clinical practice guideline for the prediction, prevention and management of hyperbilirubinemia in term and late preterm newborns".** Each item can be printed out in the form of posters to be hung in different nurseries or NICUs or an information leaflet to be given to parents. Also, it can be utilized within a protocol book of procedures to facilitate its use by physicians in clinics or MCHC.

SUMMARY OF RECOMMENDATIONS:

1. Antenatal orientation of mothers about neonatal jaundice especially if she is of a risky blood group type (Rh negative or O).
2. Early promotion and support of successful breastfeeding.
3. Set protocols for the identification and evaluation of hyperbilirubinemia should be in all nurseries
4. Any infant jaundiced in the first 24 hours should have his total serum bilirubin (TSB) or transcutaneous bilirubin (TcB) level measured.
5. All bilirubin levels should be interpreted according to the infant's age in hours.
6. Infants < than 38 weeks' gestation, particularly those who are breastfed, are at higher risk of developing severe hyperbilirubinemia and require closer surveillance and monitoring.
7. A systematic assessment should be performed on all infants before discharge from maternity hospital for the risk of severe hyperbilirubinemia.
8. Parents should be provided with written and verbal information about newborn jaundice.
9. Appropriate follow-up date based on the time of discharge and the risk assessment should always be arranged and written in a follow up card.
10. Any baby presenting with hyperbilirubinemia should be examined for cause as well as signs of ABE.
11. Prompt treatment of newborns, when indicated, with phototherapy or exchange transfusion should be decided based on TSB (without subtracting direct component).
12. Immediate exchange transfusion is indicated in any baby with signs of ABE.
13. Follow up of any baby with severe hyperbilirubinemia should include ABR, neurodevelopmental follow up and follow up for anemia if cause was hemolytic.

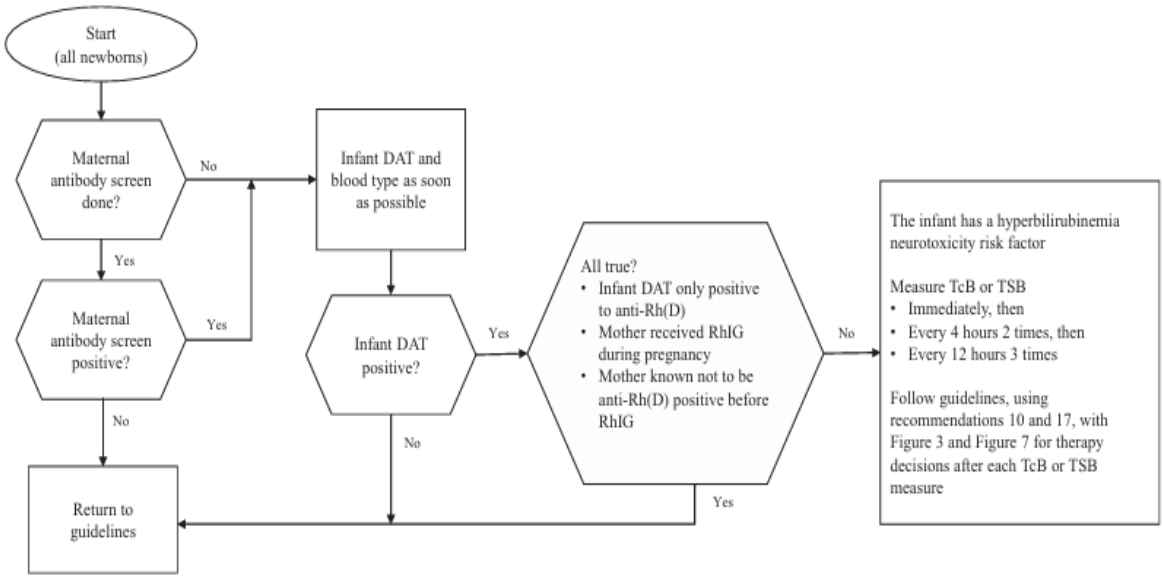
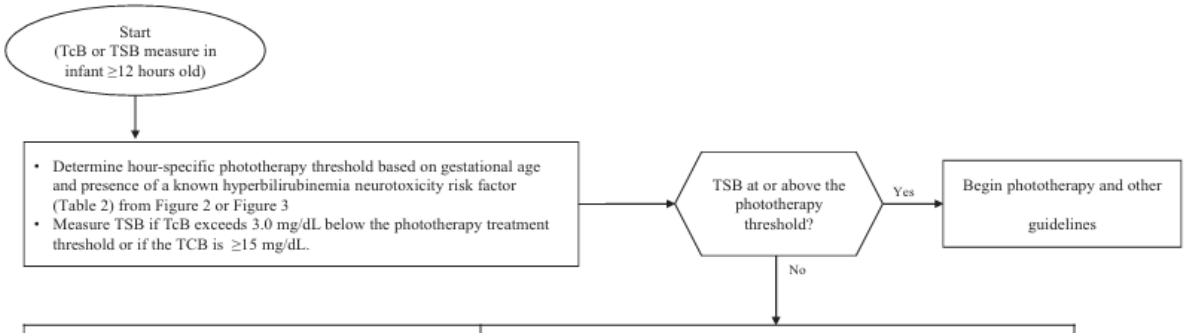


FIGURE 1
Approach to identify newborns with maternal anti-erythrocyte antibodies and to guide early management.[15]

Figure-1: Approach to identify newborns with maternal anti-erythrocyte antibodies and to guide early management (6)



Phototherapy threshold minus TcB or TSB measure		Discharge Recommendations
0.1–1.9 mg/dL	Age <24 hours	Delay discharge, consider phototherapy, measure TSB in 4 to 8 hours
	Age≥24 hours	Measure TSB in 4 to 24 hours[a] Options: • Delay discharge and consider phototherapy • Discharge with home phototherapy if all considerations in the guideline are met • Discharge without phototherapy but with close follow-up
2.0–3.4 mg/dL	Regardless of age or discharge time	TSB or TcB in 4 to 24 hours[a]
3.5–5.4 mg/dL	Regardless of age or discharge time	TSB or TcB in 1– 2 days
5.5–6.9 mg/dL	Discharging <72 hours	Follow-up within 2 days; TcB or TSB according to clinical judgment[b]
	Discharging ≥72 hours	Clinical judgment[b]
≥7.0 mg/dL	Discharging <72 hours	Follow-up within 3 days; TcB or TSB according to clinical judgment[b]
	Discharging ≥72 hours	Clinical judgment[b]

[a]low diagram for infants during the birth hospitalization to determine postdischarge follow-up for infants who have not received phototherapy.
[b]Use clinical judgment and shared decision making to determine when to repeat the bilirubin measure within this 4 to 24 hour time window.
[c]Clinical judgment decisions should include physical examination, the presence of risk factors for the development of hyperbilirubinemia (Table 1) or hyperbilirubinemia neurotoxicity risk factors (Table 2), feeding adequacy, weight trajectory, and family support.

Figure-2: Flow diagram for infants during birth hospitalization to monitor jaundice follow up (6)

Table-6: Timing of follow up (unless seen earlier according to nomogram):

Infant Discharged	Should be seen by Age
Before age 24 hours	72 hours
Between 24-47.9 hours	96 hours
Between 48 and 72 hour	120 hours

(AAP guideline, Pediatrics 2004)[3]

Table-7: Risk Factors for Development of significant hyperbilirubinemia: [6]

Risk Factors
• Lower gestational age (ie, risk increases with each additional week less than 40 wk)
• Jaundice in the first 24 h after birth
• Predischarge transcutaneous bilirubin (TcB) or total serum bilirubin (TSB) concentration close to the phototherapy threshold
• Hemolysis from any cause, if known or suspected based on a rapid rate of increase in the TSB or TcB of >0.3 mg/dL per hour in the first 24 h or >0.2 mg/dL per hour thereafter.
• Phototherapy before discharge
• Parent or sibling requiring phototherapy or exchange transfusion
• Family history or genetic ancestry suggestive of inherited red blood cell disorders, including glucose-6-phosphate dehydrogenase (G6PD) deficiency
• Exclusive breastfeeding with suboptimal intake
• Scalp hematoma or significant bruising
• Down syndrome
• Macrosomic infant of a diabetic mother

Table-8: Hyperbilirubinemia neurotoxicity risk factors: [6]

Risk Factors
• Gestational age <38 wk and this risk increases with the degree of prematurity[a]
• Albumin <3.0 g/dL
• Isoimmune hemolytic disease (ie, positive direct antiglobulin test), G6PD deficiency, or other hemolytic conditions
• Sepsis
• Significant clinical instability in the previous 24 h

Table-9: Clinical assessment of neurotoxicity using the Modified BIND score: [51]

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			

Choose one number for each domain. Final score out of 12 (zero: Normal, 1-4: mild encephalopathy, 5-6: moderate encephalopathy, 7-12: severe encephalopathy) [58]

Table-10: Laboratory Evaluation of the Jaundiced Infant of 35 or More Weeks' Gestation: [3]

Indications	Assessments
Jaundice in first 24 hour	Measure TcB and/or TSB and decide according to Table-7
Infant receiving phototherapy or TSB rising rapidly, crossing percentiles (Figure-6), and unexplained by history and physical examination	-Blood type and Coombs' test. - Complete blood count and smear. - Reticulocyte count. - It is an option to perform G6PD (if retics are high and no incompatibility), and $ETCO_2$, if available. - Measure (direct) conjugated bilirubin. - Repeat TSB in 4–24 hour depending on infant's age and TSB level.
TSB approaching exchange levels or not responding to phototherapy	Perform reticulocyte count, G6PD, albumin, ETCO if available and consider exchange transfusion.
Elevated direct-reacting (or conjugated) bilirubin level	Do urinalysis and urine culture. Evaluate for sepsis including TORCH screen if indicated by history and physical examination.
Jaundice present at or beyond age 2 weeks, or sick infant	- Total and direct-reacting (or conjugated) bilirubin level, if direct-reacting bilirubin elevated, evaluate for causes of cholestasis. - Check results of newborn thyroid and galactosemia screen, and evaluate infant for signs or symptoms of hypothyroidism or late onset sepsis.

Table-11: Example of a Clinical Pathway for Management of the Newborn Infant Readmitted for Phototherapy or Exchange Transfusion: [3]

Treatment:

- Use intensive phototherapy and/or exchange transfusion

Laboratory tests:

- TSB and direct-reacting (or conjugated) bilirubin levels.
- Blood type (ABO, Rh).
- Direct antibody test (or Coombs' test).
- Serum albumin.
- Complete blood cell count with differential and smear for red cell morphology.
- Reticulocyte count.
- ETCO (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 week gestation, obtain a type and cross match, 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 (Figures-7 & 8), 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 expressed breast milk or formula. If oral intake is in question, give intravenous fluids.

Parent Information leaflet

الصفراء في الأطفال حديثي الولادة:

ما هى الصفراء فى الأطفال حديثى الولادة ؟

هى عبارة عن حدوث اصفرار ببياض العين و الجلد عند المولود ، وهى حالة قد تتطلب عناية خاصة بحديثى الولادة.

كيف تحدث الصفراء فى حديثى الولادة ؟

تحدث نتيجة زيادة مستوى المادة المسببة للصفراء في الدم عن الحد الطبيعي. و هي مادة تُنتج عند:

- تكسير خلايا الدم الحمراء.
- مشاكل بالكبد (عدم اكتمال نمو الكبد أو وجود التهابات أو اعتلال بالكبد).
- انسداد القنوات المرارية.

ما هى أنواع الصفراء فى حديثى الولادة ؟

1- **الصفراء الفسيولوجية (الطبيعية):**

- هي عادة تظهر بنهاية اليوم الثالث أو الرابع من الولادة وتستمر لمدة عشرة أيام أو أسبوعين من يوم الولادة على الأكثر.
- وتحدث لأن إنزيمات الكبد المسئولة عن التخلص من المادة المسببة للصفراء فى الطفل حديث الولادة تكون غير مكتملة جزئيا .

2- **الصفراء المرضية: وتحتاج لتدخل طبي**

- من أشهر أسبابها: تكسير الدم نتيجة عدم توافق فصيلة دم الطفل مع دم الأم (إذا كان الطفل يحمل فصيلة موجبة والأم تحمل فصيلة سالبة والأب يحمل فصيلة موجبة).
- يحدث ذلك خلال 24 ساعة من الولادة.
- تحدث أيضا نتيجة وجود التهابات أو اعتلال بالكبد أو انسداد القنوات المرارية.

الأطفال الأكثر عرضة للإصابة بصفراء حديثي الولادة:

1- الأطفال المبتسرين (أقل من 9 شهور أو 36 أسبوع حمل).
2- وجود اخ او اخت عانى سابقا من صفراء حديثي الولادة.
3- ناقصي النمو.
4- إذا أصيبت الأم بأي حرارة أو طفح جلدي أثناء الحمل.
5- إذا كانت فصيلة الام 0 أو الأم تحمل فصيلة سالبة والأب يحمل فصيلة موجبة).

أعراض الصفراء فى حديثى الولادة:

- اصفرار بشرة الطفل.
- اصفرار بياض العين.

علامات الخطر:

- ظهور الاصفرار في اليوم الأول من الولادة.
- تحول لون البراز إلى اللون الفاتح المقارب للبياض.
- وجود تشنجات أو تقوس بالضهر.

وعند ظهور أي من هذه العلامات يجب التوجه إلى الطبيب فوراً.

ما هي مضاعفات مرض الصفراء؟

ارتفاع المادة المسببة للصفراء بدم الطفل يؤدي الى وصولها الى أجزاء ومراكز هامة بالمخ ومن ثم حدوث مضاعفات خطيرة مثل:

الاعتلال الدماغي الحاد (الشلل الدماغي): وتكون أعراضه:

- الخمول أو صعوبة الاستيقاظ.
- البكاء عال النبرة.
- قلة الرّضاعة.
- تقوس الرقبة والجسم للوراء.
- تأخر تطور النمو العقلي.
- فقدان السمع.

كيف يتم تشخيص الصفراء في حديثي الولادة:

- قياس نسبة المادة المسببة للصفراء عبر الجلد.
- قياس نسبة المادة المسببة للصفراء في الدم.

علاج الصفراء في حديثي الولادة:

عند ملاحظة الاصفرار على بشرة الطفل يجب التوجه الى الطبيب فورا ويحدد الطبيب طريقة العلاج على حسب نسبة الصفراء في دم الطفل:

1- المتابعة: وتستمر كل 72 ساعة مع استمرار الرضاعة الطبيعية المنتظمة (8:12) مرة يوميا.
2- العلاج الضوئي في الحضانة.
3- تغيير دم الطفل في حالات الارتفاع الشديد لنسبة الصفراء في الدم.
4- فى حالة انسداد القنوات المرارية نتوجه للعلاج الجراحي.

ماذا تفعل بعد خروج الطفل من الحضانة؟

- يجب متابعة الصفراء بعد 24 ساعة.
- يجب عمل فحص للسمع لأي طفل عانى من نسبة صفرا مرتفعة.

معتقدات خاطئة:

- عدم عرض الطفل الأصفر على الطبيب.
- أن حالة الطفل ستتحسن تحت الإضاءة المنزلية المعتادة (اللمبة النيون). أو في الشمس.
- ان الفيتامينات أو الجلوكوز أو الاجار أو الاعشاب علاج للصفراء.
- ان الرضاعة الطبيعية لا يمكن ان تستمر في حالة وجود الصفراء او العلاج الضوئي.

Instructions to parents before discharge from maternity unit:

Parents should be provided with written information to facilitate post discharge care including the date, time and place of follow up appointment and when necessary prescription and appointment for a follow up TcB or TSB.

Birth hospitalization information including the last TcB or TSB and the age at which it was measured and DAT results (if any) should be documented.

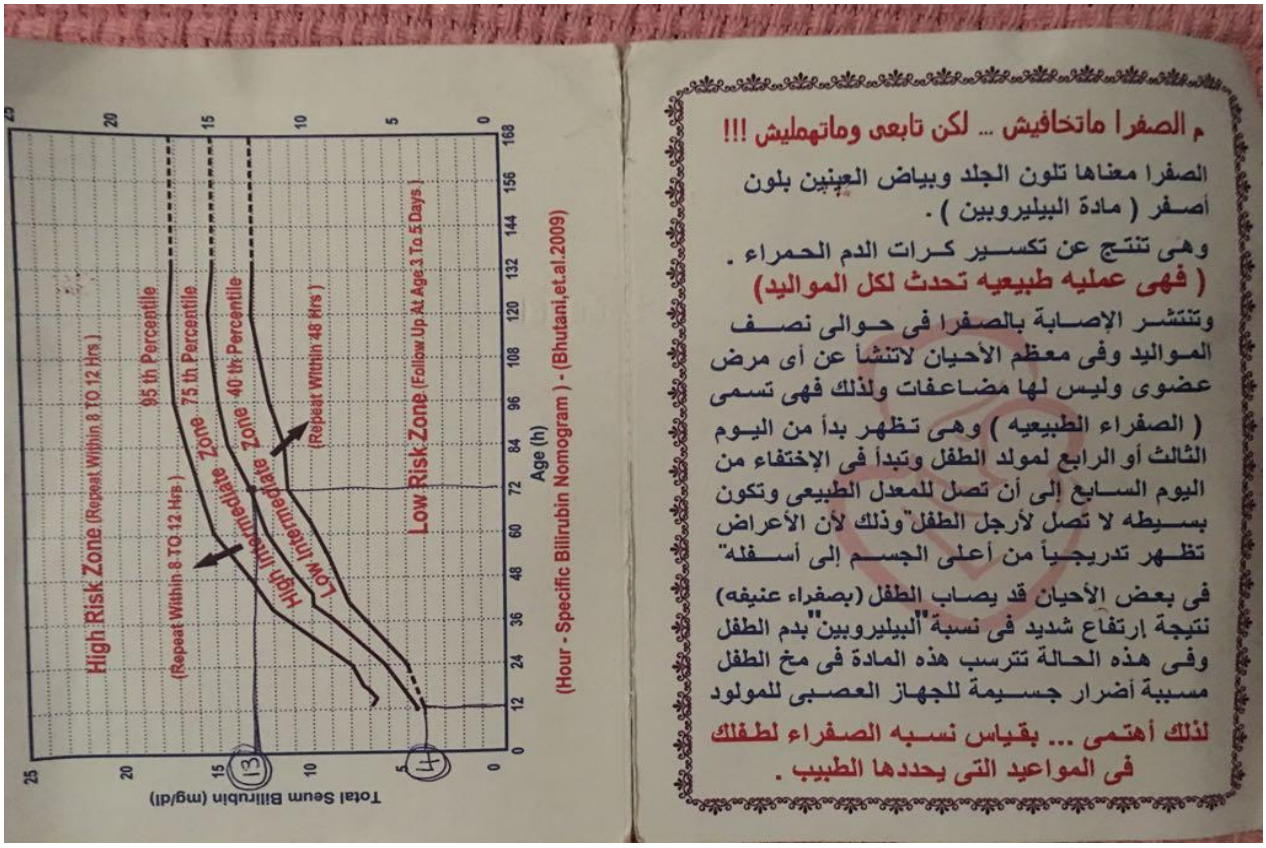


Figure-3: Example of parent card

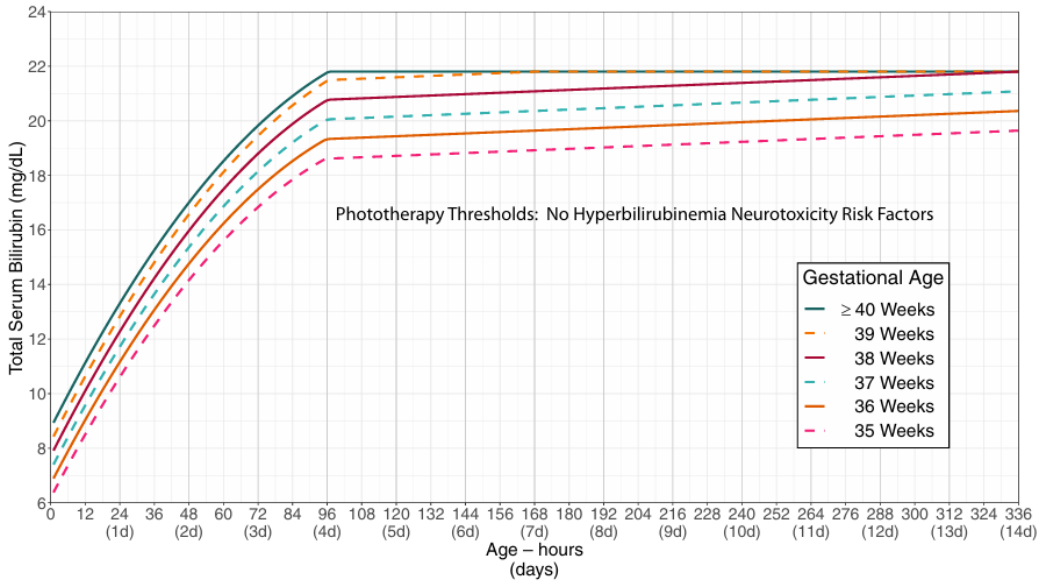
Appendix 1: Phototherapy

Introduction:

Clinical trials have validated the efficacy of phototherapy in reducing excessive unconjugated hyperbilirubinemia, and its implementation has drastically curtailed the use of exchange transfusions. [3] The initiation and duration of phototherapy is defined by a specific range of total bilirubin values based on an infant's postnatal age and the potential risk for bilirubin neurotoxicity. [3] Clinical response to phototherapy depends on the efficacy of the phototherapy device as well as the balance between an infant's rates of bilirubin production and elimination. The active agent in phototherapy is light delivered in measurable doses, which makes phototherapy conceptually similar to pharmacotherapy.

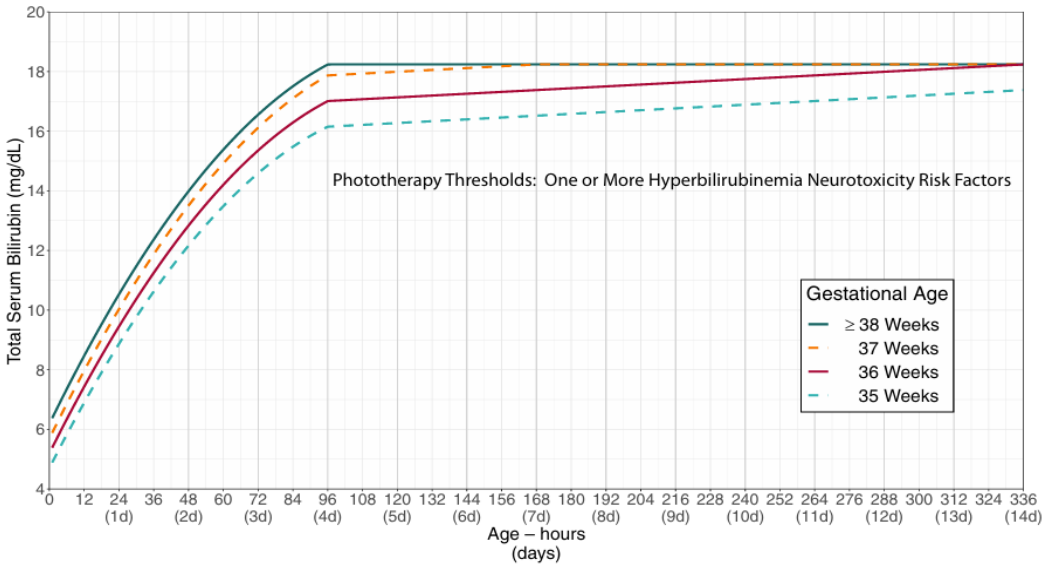
When to start phototherapy [6]:

- If TsB at/above PHOTOTHERAPY THRESHOLD
- If TsB less than 3 mg/dL below PHOTOTHERAPY THRESHOLD but with signs/symptoms of ACUTE HEMOLYSIS.
- Provider may start phototherapy if TsB < 3 mg/dL below threshold in order to prevent readmission.



Phototherapy thresholds by gestational age and age in hours for infants with no recognized hyperbilirubinemia neurotoxicity risk factors other than gestational age. These thresholds are based on expert opinion rather than strong evidence on when the potential benefits of phototherapy exceed its potential harms. Use total serum bilirubin concentrations; do not subtract direct-reacting or conjugated bilirubin from the total serum bilirubin. In rare cases of severe hyperbilirubinemia in which the direct-reacting or conjugated bilirubin exceeds 50% of the TSB, consult an expert. Note that infants <24 hours old with a TSB at or above the phototherapy threshold are likely to have a hemolytic process and should be evaluated for hemolytic disease as described in recommendation 14. Hyperbilirubinemia neurotoxicity risk factors include gestational age <38 weeks; albumin <3.0 g/dL; isoimmune hemolytic disease, glucose-6-phosphate dehydrogenase (G6PD) deficiency, or other hemolytic conditions; sepsis; or any significant clinical instability in the previous 24 hours.

Figure-4: Phototherapy thresholds for babies with no neurotoxicity risk factors [6]



Phototherapy thresholds by gestational age and age in hours for infants with any recognized hyperbilirubinemia neurotoxicity risk factors other than gestational age. These thresholds are based on expert opinion rather than strong evidence on when the potential benefits of phototherapy exceed its potential harms. Use total serum bilirubin concentrations; do not subtract the direct-reacting or conjugated bilirubin from the total serum bilirubin. In rare cases of severe hyperbilirubinemia in which the direct-reacting or conjugated bilirubin exceeds 50% of the TSB, consult an expert. Hyperbilirubinemia neurotoxicity risk factors include gestational age <38 weeks; albumin <3.0 g/dL; isoimmune hemolytic disease, glucose-6-phosphate dehydrogenase (G6PD) deficiency, or other hemolytic conditions; sepsis; or any significant clinical instability in the previous 24 hours. See Supplemental Fig 2.

Figure-5: Phototherapy thresholds for babies with neurotoxicity risk factors [6]

Commercial light sources:

A wide selection of commercial phototherapy devices is available in Egypt.

Phototherapy devices can be categorized according to their light source as follows:

- Fluorescent-tube devices that emit different colors (cool white daylight, blue [B], special blue [BB], turquoise, and green) and are straight (F20 T12, 60 cm, 20 W), U-shaped, or spiral-shaped;
- Metal halide bulbs, used in spotlights and incubator lights;
- Light-emitting diodes (LEDs) used with fiber-optic light guides in pads, blankets, or spotlights;
- High-intensity LEDs, used as over- and under-the-body devices. [5]

Standards for phototherapy devices:

Factors to consider in prescribing and implementing phototherapy are:

- Emission range of the light source,
- Light intensity (irradiance):
  - Standard PT units deliver 8–10 W/ cm^2 per nm.
  - Intensive PT requires 30 W/cm^2 per nm, if the level of bilirubin is approaching exchange transfusion only INTENTSIVE phototherapy will be effective.
- Exposed ("treatable") body surface area illuminated
- Reduction in total bilirubin concentration. [5]

Table-12: Factors That Affect the Dose and Efficacy of Phototherapy (PT): [5]

Factor	Mechanism/Clinical Relevance	Implementation and Rationale	Clinical Application
SPECTRUM of light emitted (wave length)	Blue-green spectrum is most effective. At these wavelengths, light penetrates skin well and is absorbed maximally by bilirubin.	Special blue fluorescent tubes or other light sources that have most output in the blue-green spectrum and are most effective in lowering TSB.	Use special blue tubes or LED light source with output in blue-green spectrum for intensive PT.
Spectral IRRADIANCE (in certain wavelength band) delivered to surface of infant	increase irradiance will increase rate of decline in TSB	Irradiance is measured with a radiometer as W/cm^2 per nm. Standard PT units deliver 8–10 W/cm^2 per nm. Intensive PT requires 30 W/cm^2 per nm.	If special blue fluorescent tubes are used, bring tubes as close to infant as possible to increase irradiance. . Note: This cannot be done with halogen lamps because of the danger of burn. Special blue tubes 10–15 cm above the infant will produce an irradiance of at least 35 W/cm^2 per nm.
Spectral POWER(average spectral irradiance across surface area)	increase surface area exposed will increase rate of decline in TSB	For intensive PT, expose maximum surface area of infant to PT.	Place lights above and fiber-optic pad or special blue fluorescent tubes* below the infant. For maximum exposure, line sides of bassinet, warmer bed, or incubator with aluminum foil.
Cause of jaundice	PT is likely to be less effective if jaundice is due to hemolysis or if cholestasis is present. (increase direct bilirubin)		When hemolysis is present, start PT at lower TSB levels. Use intensive PT. Failure of PT suggests that hemolysis is the cause of jaundice. If direct bilirubin is increased, watch for bronze baby syndrome or blistering.
TSB level at start of PT	The higher the TSB, the more rapid the decline in TSB with PT.		Use intensive PT for higher TSB levels. Anticipate a more rapid decrease in TSB when TSB 20 mg/dL (342 mol/L).

PT: phototherapy; LE: light-emitting. *Olympic Bili Bassinet (Olympic Medical, Seattle, WA)

Table-13: Practice considerations for optimal administration of phototherapy: [5]

Checklist	Recommendation	Implementation
Light source (nm)	Wavelength spectrum in 460- 490-nm blue-green light region	Know the spectral output of the light source.
Light irradiance ($W \cdot cm^2 \cdot nm^1$)	Use optimal irradiance: 30 $W \cdot cm^2 \cdot nm^1$ within the 460- to 490-nm waveband	Ensure uniformity over the light footprint area.
Body surface area (cm^2)	Expose maximal skin area	Reduce blocking of light.
Timeliness of implementation	Urgent or "crash-cart" intervention for excessive hyperbilirubinemia	May conduct procedures while infant is on phototherapy.
Continuity of therapy	Briefly interrupt for feeding, parental bonding, nursing care	After confirmation of adequate bilirubin concentration decrease.
Efficacy of intervention	Periodically measure rate of response in bilirubin load reduction	Degree of total serum/plasma bilirubin concentration decrease.
Duration of therapy	Discontinue at desired bilirubin threshold; be aware of possible rebound increase	Serial bilirubin measurements based on rate of decrease.

What decline in the Serum Bilirubin can you expect?

- With extremely high bilirubin (more than 30 mg/dL), and intensive phototherapy, a decline of as much as 10 mg/dL can occur within few hours, and a decrease of at least 0.5 to 1 mg/dL/ hour can be expected in the first 4 to 8 hours.
- On average, for infants >35 weeks' gestation readmitted for phototherapy, intensive phototherapy can produce a decrement of 30% to 40% in the initial bilirubin level by 24 hours after initiation of phototherapy.
- The most significant decline will occur in the first 4 to 6 hours.
- With standard phototherapy systems, a decrease of 6- 20% of the initial bilirubin level can be expected in the first 24 hours.

Safety and protective measures:

- A clinician skilled in newborn care should assess the neonate's clinical status during phototherapy to ensure adequate hydration, nutrition, and temperature control. Clinical improvement or progression of jaundice should also be assessed, including signs suggestive of early bilirubin encephalopathy (ABE).
- The distance of the phototherapy device from the infant should be safely minimized.
- It is important to note that the intensity of light decreases at the outer perimeter of the light footprint and to recognize the effects of physical factors that could impede or obstruct light exposure to have maximum exposure.
- **Temperature should be monitored during phototherapy and a neutral thermal environment ensured.**
- **Baby should be monitored for adequate hydration by daily weighing and as**sessment of wet nappies.
- Phototherapy does not use ultraviolet light and exposure to lights is mostly harmless. Devices must comply with general safety standards.
- The genitalia should be protected from light during phototherapy.
- Give baby eye protection and routine eye care.

Other clinical considerations include:

- Phototherapy is contraindicated in infants with congenital porphyria or those treated with photosensitizing drugs.
- Prolonged phototherapy is associated with increased oxidant stress and lipid peroxidation and riboflavin deficiency.

When should phototherapy be stopped?

- There is no standard for discontinuing phototherapy.
- For infants who are readmitted after their birth hospitalization (usually for TSB levels of 18 mg/dL or higher), phototherapy may be discontinued when the serum bilirubin level falls below 13 to 14 mg/dL.
- Do not delay discharge to observe the infant for rebound.
- If phototherapy is used for infants with hemolytic diseases or is initiated early and discontinued before the infant is 3 to 4 days old, a follow-up bilirubin measurement within 24 hours after discharge is recommended.

Intermittent Versus Continuous Phototherapy:

- **NO rationale for intermittent phototherapy exists.**

- If the infant's bilirubin level is approaching the exchange transfusion zone, intensive phototherapy should be administered continuously until a satisfactory decline in the serum bilirubin level occurs or exchange transfusion is initiated.
- Phototherapy may be interrupted for breastfeeding or brief parental visits as long as the level of bilirubin is not approaching the exchange zone.

Hydration:

- No evidence that excessive fluid administration affects the serum bilirubin concentration.
- If a baby with high bilirubin levels is also mildly dehydrated. This may need supplemental fluid intake to correct the dehydration.
- Encourage frequent breastfeeding but if baby is dehydrated despite frequent breastfeeding, supplement with a milk-based formula, because it inhibits the enterohepatic circulation of bilirubin and should help to lower the serum bilirubin level.
- Routine intravenous fluid or other supplementation (e.g., with dextrose water) of term and near-term infants receiving phototherapy is NOT required or indicated unless there is evidence of dehydration or escalation of care is required. [(6)]

Safety and state of the art use:

PHOTOTHERAPY IS A DRUG like Pharmacotherapy.[(20)]

In order to provide effective PT and improve outcomes, the following rules should be followed:

- Use photons as a drug when prescribing phototherapy.
- Use a narrow-spectrum blue light (450 nm).
- Measure irradiance for specific wavelength.
- Use the least irradiance dose to achieve an efficient decrease in bilirubin load.
- Use phototherapy for the shortest possible time and only when indicated. [(71)]

Complications:

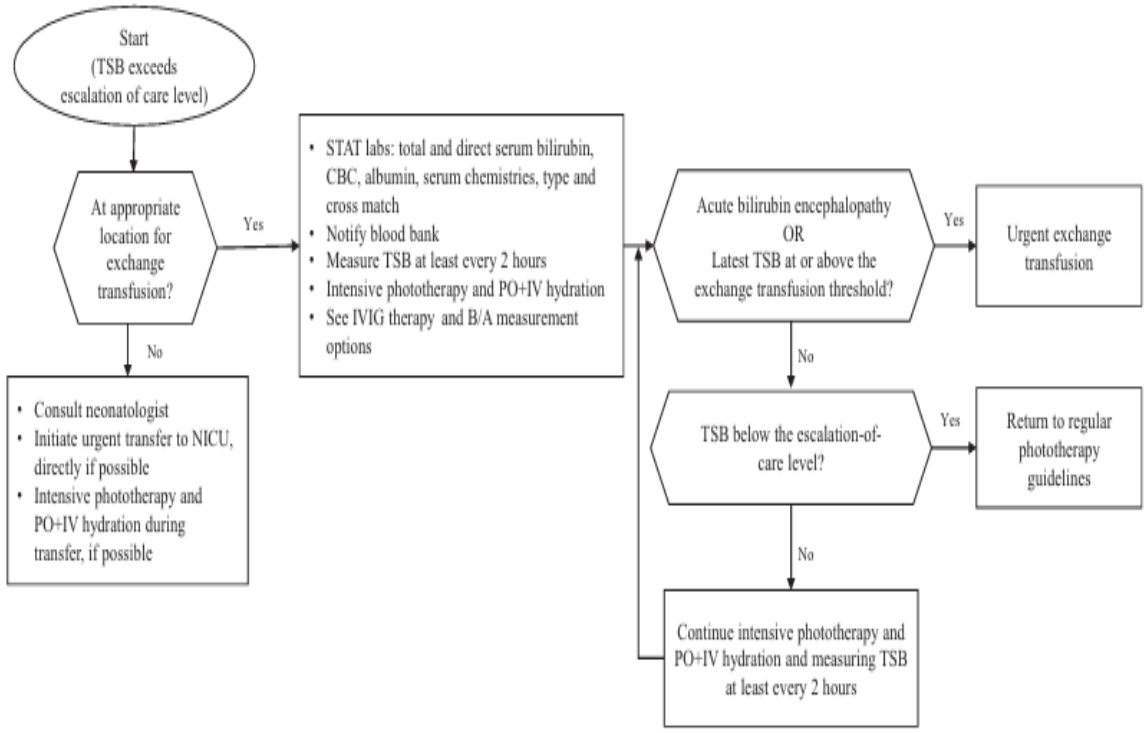
- Phototherapy in hospital separates mother and infant. Eye patching is disturbing to parents.
- Diarrhoea, intestinal hypermotility.
- Temperature instability.
- Phototherapy rash.
- Possible long term effects:
  - Teratogenic effects, one study reported that phototherapy was associated with DNA damage. However, there is no evidence that this effect on DNA at a microscopic level can lead to long-term adverse effects in phototherapy-treated babies.
  - Melanocytic nevus development.
- Infants with cholestatic jaundice may develop a dark, grayish-brown discoloration of the skin, serum, and urine (the bronze infant syndrome). This syndrome generally has had few deleterious consequences, and if there is a need for phototherapy, the presence of direct hyperbilirubinemia should not be considered a contraindication to its use. This is particularly important in sick neonates.
- Rarely, purpura and bullous eruptions have been described in infants with severe cholestatic jaundice receiving phototherapy and severe blistering and photosensitivity during phototherapy have occurred in infants with congenital erythropoietic porphyria.
- Congenital porphyria or a family history of porphyria is an absolute contraindication to the use of phototherapy, as is the concomitant use of drugs or agents that are photosensitizers.

Home phototherapy:

- Home phototherapy should not be used unless there is quality assurance regarding the phototherapy device, the implementation and the monitoring of bilirubin at home. Very close supervision of medical practitioners by a regulator of the process is required to avoid malpractice. Since that is currently not available, it is not recommended to have home phototherapy until these rules are fulfilled.

Escalation of care:

The intensive care that some infants with elevated or rapid increasing bilirubin concentration require to prevent the need for an exchange and possibly prevent kernicterus. (6)



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Approach to escalation of care. The escalation-of-care threshold is 2 mg/dL below the exchange transfusion threshold. IVIG, intravenous immune globulin; B/A, bilirubin to albumin ratio.

Figure-6: Approach to escalation of care

Appendix 2: Exchange Transfusion

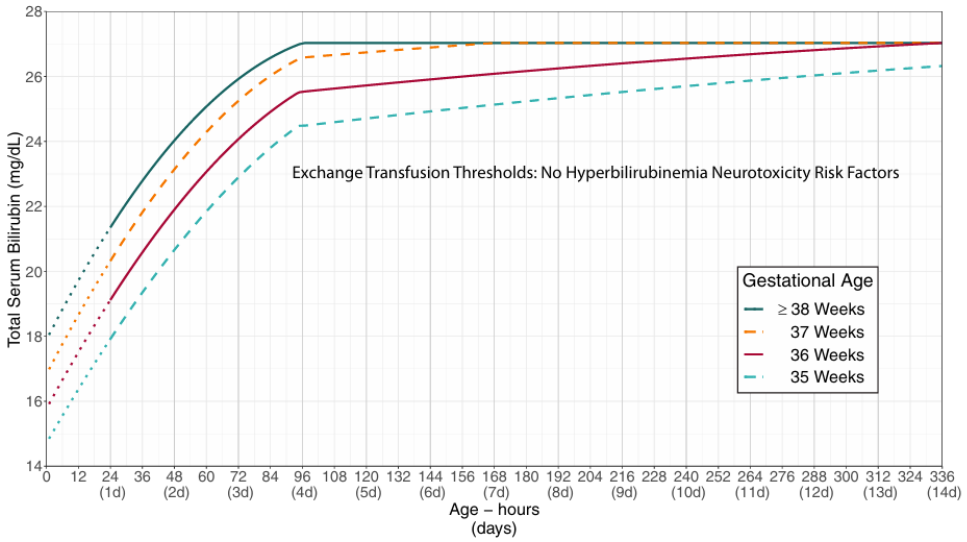
- Exchange transfusion is an intensive invasive procedure and should not be performed in a Level 1 NICU.
- "Exchange transfusion must take place in an intensive care setting with intensive physiological and biochemical monitoring, carried out by staff trained in the procedure following written informed parental consent", cited by British Committee for Standards in Hematology. [72]
- Exchange transfusion is usually carried out by repeatedly exchanging small samples (5-10 ml/kg) of blood through an umbilical venous catheter and replacing with same volumes by compatible blood.
- Neonatal exchange transfusion is becoming an infrequent procedure because severe Rh hemolytic disease of the newborn is becoming increasingly rare due to:
  - Maternal anti-D therapy and intrauterine transfusion of affected fetuses.
  - Maximizing phototherapy use prevents the need for exchange transfusion, even at very high level of TSB.
  - Intravenous immunoglobulin (IVIG) acts by preventing the destruction of sensitized erythrocytes.

Benefits of Exchange Transfusion in severely jaundiced babies:

- Rapidly lowers the serum bilirubin level and reduce the risk of brain damage and kernicterus.
- Corrects anemia and increase the oxygen carrying capacity of the infant's blood.
- Removes damaged and antibody coated red cells.

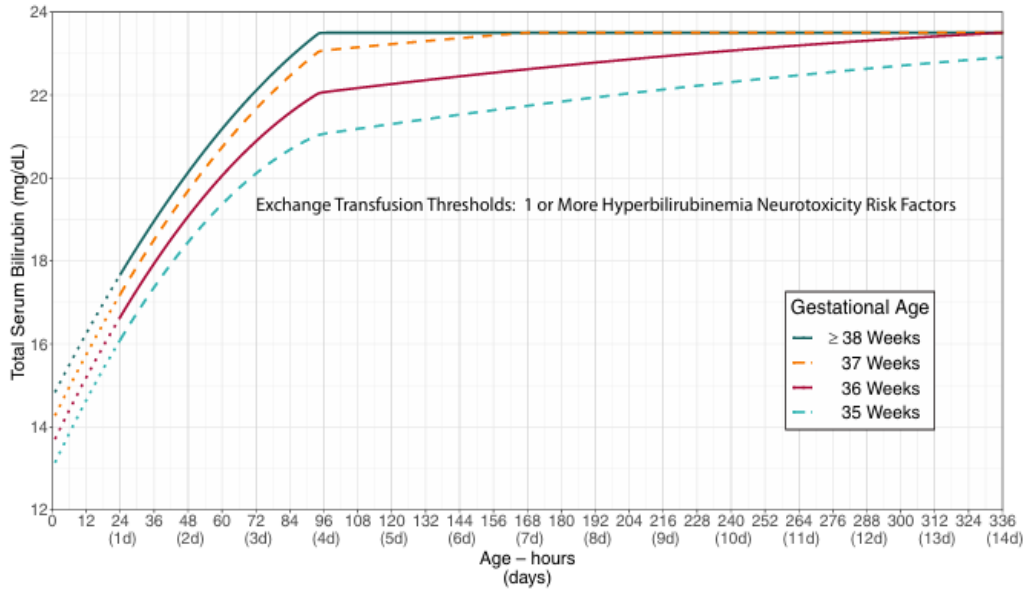
Indication for exchange transfusion in severe hyperbilirubinemia:

- Any baby showing signs of intermediate or advanced stages of acute bilirubin encephalopathy (e.g., hypertonia, arching, retrocollis, opisthotonus, high pitched cry, or recurrent apnea) irrespective of bilirubin level.
- If the TSB is at or above the exchange transfusion threshold.
- If intensive phototherapy is failing to lower TSB and it is approaching exchange level
- If the bilirubin /albumin ratio is:
  - ≥8.0 If the gestational age is ≥38 weeks' gestation and there are no hyperbilirubinemia neuro toxicity risk factors,
  - ≥7.2 If the gestational age is ≥38 weeks' gestation and there is at least 1 hyperbilirubinemia neurotoxicity risk factor,
  - ≥7.2 If the gestational age is 35 through 37 weeks' gestation with no hyperbilirubinemia neurotoxicity risk factor,
  - ≥6.8 If the gestational age is 35 through 37 weeks' gestation and at least 1 hyperbilirubinemia neurotoxicity risk factor. [62]



Exchange transfusion thresholds by gestational age for infants with no recognized hyperbilirubinemia neurotoxicity risk factors other than gestational age. See Fig 4, which describes escalation of care. These thresholds are based on expert opinion rather than strong evidence on when the potential benefits of escalation of care exceed its potential harms. The stippled lines for the first 24 hours indicate uncertainty because of the wide range of clinical circumstances and responses to intensive phototherapy. Use total serum bilirubin concentrations; do not subtract direct bilirubin from the total serum bilirubin. In rare cases of severe hyperbilirubinemia in which the direct-reacting or conjugated bilirubin exceeds 50% of the TSB, consult an expert. Hyperbilirubinemia neurotoxicity risk factors include albumin <3.0 g/dL; isoimmune hemolytic disease, glucose-6-phosphate dehydrogenase (G6PD) deficiency, or other hemolytic conditions; sepsis; or any significant clinical instability in the previous 24 hours. See Supplemental Fig 4.

Figure-7: Exchange transfusion threshold by gestational age for infants with no recognized hyperbilirubinemia neurotoxicity risk factors



Exchange transfusion thresholds by gestational age for infants with any recognized hyperbilirubinemia neurotoxicity risk factors other than gestational age. See Fig 4, which describes escalation of care. These thresholds are based on expert opinion rather than strong evidence on when the potential benefits of escalation of care exceed its potential harms. The stippled lines for the first 24 hours indicate uncertainty because of the wide range of clinical circumstances and responses to intensive phototherapy. Use total serum bilirubin concentrations; do not subtract direct bilirubin from the total serum bilirubin. In rare cases of severe hyperbilirubinemia in which the direct-reacting or conjugated bilirubin exceeds 50% of the TSB, consult an expert. Hyperbilirubinemia neurotoxicity risk factors include albumin <3.0 g/dL; isoimmune hemolytic disease, glucose-6-phosphate dehydrogenase (G6PD) deficiency, or other hemolytic conditions; sepsis; or any significant clinical instability in the previous 24 hours. See Supplemental Fig 5.

Figure-8: Exchange transfusion threshold by gestational age for infants with any recognized hyperbilirubinemia neurotoxicity risk factors[6]

Table-14: B/A Ratio at which Exchange Transfusion should be considered: [6]

- The bilirubin/ albumin ratio can be used with TSB level to help determine need for exchange transfusion.
- The bilirubin/ albumin ratio threshold for exchange transfusion, measured as TSB (measured in mg/ dL) divided by serum albumin (measured in g/dL), varies by gestational age and risk.
- An exchange transfusion may be considered if the bilirubin albumin ratio is:
  - ≥8.0 if the gestational age is ≥38 weeks' gestation and there are no hyperbilirubinemia neuro toxicity risk factors
  - ≥7. 2 if the gestational age is ≥ 38 weeks' gestation and there is at least 1 hyperbilirubinemia neurotoxicity risk factors
  - ≥7.2 if the gestational age is 35 through 37 weeks' gestation with no hyperbilirubinemia neurotoxicity risk factors
  - >6.8 if the gestational age is 35 through 37 weeks' gestation and at least 1 hyperbilirubinemia neurotoxicity risk factors.

Use of IVIG: [6]

Intravenous immunoglobulin (IVIG) 0.5-1 g/kg over 2 hours:
Provide to **infants with isoimmune hemolytic disease (i.e. positive DAT) whose TSB reaches or exceeds the escalation of care threshold**. This dose can be repeated in 12 hours.

Table-15: Procedures for Exchange Transfusion:

Steps	Preparation for exchange transfusion
1	Parent/care giver Information and consent Informed parental consent about the procedure and risks of exchange transfusion should be obtained and documented wherever possible. This should be a written consent.
2	**Order the blood :** **Which blood group to use?** • Cross-matched washed packed red blood cells mixed with thawed adult fresh-frozen plasma to a hematocrit approximating 40% is preferred for exchange transfusions. The additional albumin-containing fresh frozen plasma that infants receive by keeping the hematocrit close to 40% will augment bilirubin removal. [72-74]. • Use blood group O packed RBCs (with low titer hemolysins) Rh negative or Rh identical with the neonate suspended in AB plasma for exchange transfusion. • **If not found** then: if ➢ Rh isoimmunization: use Rh negative and blood group O or blood group of the baby suspended in AB plasma. Cross matched with the baby's and mother's blood. ➢ ABO incompatibility: Rh compatible and blood group O (not that of the baby), suspended in AB plasma, cross matched with baby's and mother's blood. ➢ Other conditions: baby's group and Rh type, cross matched with the baby's and mother's blood. **Use a double-volume exchange transfusion**: • Do not perform a single volume exchange.

	• A double volume exchange transfusion will exchange approximately 80% of the infant's blood volume:(2 x 80 mls / Kg = 160 / per Kg = double volume blood exchange) **Red Blood Cell Requirements:** • 5 days old or less. • Negative for any antigens to which the mother or baby has antibodies. • Irradiated – use within 24 hours. Irradiation is a MUST if the infant has had a previous intrauterine transfusion and is preferable for all exchange transfusions if no delay will occur. • CMV negative. • Plasma reduced with HCT 40%. • It should be warmed to 37^{o}c immediately before transfusion by a blood warmer. (Not to be transfused straight from 4^{0}C)
3	**Gain intravenous access:** • Central via the umbilical vein. • Or a combination of central and peripheral lines. • Any central line should have its position confirmed by X-ray prior to procedure and checked for patency.
4	**Prepare equipment:** **Make a check list with the following before starting exchange:** • Continuous cardio-respiratory monitoring equipment, including SpO_2, and temperature should be available and resuscitation equipment. • Blood sugar monitoring available. • Exchange Transfusion tray. • Blood: do not collect blood until ready to begin exchange. • Protective clothing - Sterile gowns, gloves and masks. • Blood warmer and extension set. • Blood giving set with appropriate 170-200-micron filter. • Stand for blood. • Laboratory bottles = Full blood count x 2, urea and electrolytes x 2 including calcium and glucose. Blood culture x 2, capillary gas for pH x 2, (x 2 = pre and post specimens required). • 2 ml, 5 ml, 10 ml and 60 ml syringes and needles. • Ventilator and intubation equipment, also suction equipment. (available if needed) • Sharps bin box. • High stools for doctor and nurse as the procedure up to 3 hours. • Timing device for timing infusion and withdrawal of aliquots.
5	Ensure a neonatal screening blood spot has been taken prior to procedure.
6	A minimum of 2 staff are required for the procedure (senior doctor and trained nurse).
Steps	**Management prior to exchange transfusion**
1	• Nurse the infant in the radiant overhead heater if available, in the intensive care nursery with continuation of phototherapy.
2	• Monitor heart rate, respiratory rate, oxygen saturation, blood pressure and temperature, a baseline set of observations including general color and tone and blood sugar should be documented before the procedure starts.

3	• Stop enteral feeds one hour before the procedure, leaving the nasogastric tube on free drainage, (to reduce the risk of necrotizing enterocolitis).
4	• Recheck TSB and check blood sugar (and effect of treatment) prior to picking up blood.
5	• Set up the blood warmer. Using aseptic non touch technique when appropriate.
6	• Collect and <u>check the blood</u> with another trained member of staff. • Warm the blood in a towel if warmer is not available. • Do not place blood on servo heater. Prime tubing.
7	• Establish volume of aliquots prior to commencement • Aliquots usually tolerated for exchange transfusion: ➢ <1500 grams: 5 ml ➢ 1500-2490 grams :10 ml ➢ 2500 grams – 3500 : 15 ml
8	Bloods tests, blood sugar and a starting set of observations are recorded
Steps	**Management during Exchange Transfusion**
1	Define responsibility: • Senior doctor (person A) is responsible for infusing and withdrawing an equal amount of blood. • Person B is responsible for the accurate recording of blood input and withdrawal on the Exchange Transfusion Fluid Chart (Table-17).
2	• One member of staff (person A) flushes the input line with sodium chloride, connects the blood giving set, and connects the first syringe to the withdrawal line. Start by withdrawal of aliquot send to lab, and continue to infuse and withdraw equal amounts so that an equal rate is maintained. • Person B records this. • Small aliquots exchanged at a slower rate are usually better tolerated by infants with cardiovascular instability. The time for each in/out should be around 4-10 minutes (withdrawal and infusion of blood should be performed at the same rate). In and out aliquots are repeated sequentially until desired volume for exchange is reached. In and out aliquots should be said out load, so that Person B recording the procedure can keep an accurate tally. • A timer may be used for guiding speed of aliquots.
3	• Whilst the exchange transfusion is in progress, the volume of blood exchanged in and out is recorded in the fluid balance chart with the Time.
4	• <u>The first aliquot of blood removed should be sent for estimation of full blood count, (FBC), differential, urea and electrolytes (U&Es), liver function tests, split bilirubin, Ca, hematocrit and glucose</u>. • In severe cases consider: - coagulation screen, glucose 6-phosphate dehydrogenase (G6PD).
5	• This process of administration and withdrawal continues until the agreed volume of blood has been exchanged or the condition of the baby determines cessation. • <u>At the end of the procedure the infant's fluid balance should be in deficit of one aliquot</u>.

6	• The last withdrawn blood should be sent for blood sugar, urea and electrolytes, bilirubin - total + direct, FBC, hematocrit, magnesium, calcium, blood gases and consider coagulation screen.
7	• Continuously observation is required for ➢ Any signs of deterioration including cyanosis, pallor, abdominal distension, vomiting and blood in stools ➢ Record heart rate, respirations, temperature, oxygen saturation and blood pressure every 15 minutes, any changes in these should be reported immediately. ➢ Signs of hypocalcaemia - Tachycardia, irritability, seizures. ➢ Monitor capillary blood glucose every 30 minutes. ➢ All lines should be monitored for extravasation, blanching, erythema, leaking and edema.
8	• Aim for procedure should take 2 hours (no longer than 3 hours). • On completion of the exchange transfusion, the lines are again flushed with NaCl.
9	• Disposal of equipment –in accordance with local policy.
10	• Documentation – ALL the procedure should be documented including: ➢ All transfusion records, timing, accurate fluid balance, observation, samples taken and their results. ➢ Also any untoward reaction, corrective measures taken and outcomes.
11	• The baby should be left in a comfortable position and parents informed that the procedure has been completed and the condition of the baby.
12	• Stop the procedure immediately and review if there are any concerns or untoward reactions.
13	• Do NOT routinely administer intravenous calcium. [23]
Steps	**Management following exchange transfusion**
1	• Continue intensive phototherapy after exchange, checking serum bilirubin as required.
2	• Take blood pressure at completion of procedure. • Continue to monitor vital signs hourly for 6 hours or as the condition of the baby indicates. • After this time, and if stable and within normal limits routine observations may be recommenced.
3	• Measure TSB level within 2 hours and manage according to threshold graphs (Figures-7 & 8). • Continue to monitor CBC and reticulocytes.
4	• Monitor the blood sugar 1, 2 and 4 hours after exchange regularly according to condition for rebound hypoglycemia.
5	• Observe catheter sites for bleeding/signs of infection.
6	• Observe urine for blood, observe stools for blood.
7	• **Feeding:** ➢ Observe for abdominal distension, and for signs of feed intolerance, gastric aspirate and vomiting.

	➢ Commence feeds on medical advice, but not before 3 hours post-exchange transfusion.
8	• Neonatal screening must not be taken until 4 days after the exchange as blood transfusion will invalidate all the tests.
9	• All infants should receive regular audiology testing as they are at risk of hearing loss due to the severely raised serum bilirubin levels.

Risks/Complications of exchange transfusion

There is a 5% risk of complication [3]

Exchange Transfusion Reaction:

- Tachycardia or bradycardia.
- Respiratory Distress.
- Dramatic changes in blood pressure.
- Temperature irregularity.
- Rash.
- Cyanosis or pallor.
- Hypoglycemia
- Hypocalcaemia (treatment see below)
- Cardiac Arrhythmias.
- Heart failure (fluid overload).

Other risk/complications:

- Administration of incorrect blood product.
- Volume overload.
- Hemodynamic instability.
- Acid base instability.
- Apnea.
- Electrolyte imbalances (hypocalcaemia, hypoglycemia, hypomagnesaemia).
- Convulsions.
- Hypotension (volume depletion).
- Embolism (air/thrombus).
- Graft versus host reaction.
- Infection.
- Necrotizing enterocolitis.
- Temperature instability.
- Thrombocytopenia.
- Thrombosis.
- Intraventricular hemorrhage.

Table-16: Exchange Transfusion Fluid Chart: [24]

Name	
DOB	
Hospital no	

Aliquot Number	Time	IN		OUT		Total Balance (in/out)
		aliquot mls	Total mls	aliquot mls	Total mls	
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
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24						
25						

Glossary for unfamiliar terms (after ADAPTE)

1. Acceptability

Is the extent to which the users are likely to adopt a recommendation, based on internal qualities such as clarity, comprehensiveness, and logical reasoning and on external factors such as the burden imposed on the process and system of care, patient and providers attitudes and beliefs, and patients' needs, expectations, and preferences.

2. Adaptation (of guidelines)

Is the systematic approach to considering the use and/or modification of (a) guidelines(s) produced in one cultural and organizational setting for application in different context? Adaptation can be used as an alternative to de novo guideline development or for customizing (an) existing guideline(s) to suit the local context.

3. Adoption (of a guideline)

Is the acceptance of a guideline as a whole after the assessment of its quality, currency, and content? When health care providers (or other users of recommendations) adopt a guideline, they feel committed to change their practices in accordance with the recommendations of the guideline.

4. Applicability

Is the extent to which the users are able to put a recommendation into practice, based on internal qualities such as a clearly defined eligible patient population that matches the population to which the intervention is targeted in the local setting and external factors such as the availability of the necessary knowledge, skills, provider time, staff, equipment, and other resources.

Applicability is sometimes taken as a synonym for feasibility:

- Feasibility of the acquisition of necessary skills and knowledge.
- Feasibility of the necessary increase in provider time, staff, equipment, and so on.

5. Culture

Culture represents the norms and values of a specific group, community, or population.

6. Diffusion

Is a passive means of transferring knowledge; it is not directed towards a target audience (e.g. publication of articles in medical journals).

7. Dissemination

Is more active than diffusion in that it targets a specific audience and involve tailoring the information for that audience (e.g. of dissemination strategies include targeted mailings, presentations, and press conferences.

8. Evidence-based principles

Evidence-Based Medicine (EBM) has been defined as — the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of EBM means integrating individual clinical expertise with the best available external clinical evidence from systematic research.

9. Evidence tables

Are summaries of the most salient information from studies identified in the systematic review. The elements of evidence tables are dependent on the types of information in studies related to a particular

topic but might include information such as the article reference, the study type (e.g. RCT or Cohort), the number of patients and their characteristics, and the intervention, comparison arms, outcome measures, and effect sizes.

10. Guideline or Clinical Practice Guideline (CPG)

Systematically developed statements about specific health problems, intended to assist practitioners and patients in making decisions about appropriate health care.

11. Guideline consistency

Agreement between the evidence and the recommendations, based on the:

- Comprehensiveness of the study search and selection process,
- Coherence between the results of the studies and their interpretation by the guideline authors, and
- Transparency between interpretation and recommendations.

12. Guideline content

In the 'ADAPTE Manual and Resource Toolkit for Guideline Adaptation' document, guideline content refers to the recommendations in the source guidelines.

13. Guideline currency

A CPG may be considered up to date ―when (no) new information on interventions, outcomes, and performance justifies updating (it).

14. Guideline quality

By quality of clinical practice guidelines, we mean the confidence that the potential biases of guideline development addressed adequately and that the recommendations are both internally and externally valid and are feasible for practice. This process involves taking into account the benefits, harms and costs of the recommendations, as well as the practical issues attached to them. Therefore, the assessment (of quality) includes judgments about the methods used for developing the guidelines, the content of the final recommendations, and the factors linked to their uptake.

15. Guideline topic

In the ADAPTE Manual and Resource Toolkit for Guideline Adaptation' document, the topic refers to the theme of the guideline, as described in the guideline title, for a targeted population (disease and patients) and intervention. The purpose, the audience, and the setting intended for the guideline, although not necessarily explicitly stated in the title, are also part of the topic. A guideline on a given topic may contain more than one health question.

16. Health question or clinical question or key question

Is a precisely described health issue (e.g. clinical, professional practice or public health) relating to the topic of the guideline? Guideline may include one or more questions.

17. Implementation

Implementation includes methods to promote the uptake of research findings into routine healthcare in both clinical and policy contexts and hence to improve the quality and effectiveness of healthcare. It includes the study of influences on healthcare professional and organizational behavior.

18. Intra-class correlations

Intra-class correlations provide a measurement of the extent to which two or more raters agree when rating the same set of things. It is a reliability index and is typically a ratio of the variance of interest over the sum of the variance of interest plus error.

19. Recommendation

Any statement that promote or advocate a particular course of action in clinical care.

20. Stakeholder

A stakeholder is an individual, group and/or organization with a stake in your decision to implement a guideline. Stakeholders include individuals or groups who will be directly or indirectly affected by the implementation of a guideline.

21. Source guideline

In the ADAPTE Manual and Resource Toolkit for Guideline Adaptation' document, source guideline refers to those guidelines selected to undergo assessments of quality, currency, content, consistency, and acceptability/applicability and upon which an adapted guideline may be based.

Limitation of the guidelines:

- Most of the recommendation statements from one source & many recommendations of low strength of evidence (GPS)
- No data registry in Egypt about neonatal jaundice.
- The guidelines directed only for term and late preterm newborns

Suggestions:

- It is essential to have data registry about neonatal jaundice cases and cases with BIND.

Further research needs:

- To study the actual effectiveness of IVIG in arresting hemolysis and progression of severe hyperbilirubinemia
- To prepare guidelines for premature babies.
- To study the safety, practicality and efficacy of home phototherapy remain a research priority.

Monitoring and evaluating the impact of the guideline:

- Research should be directed toward methods for disseminating the information contained in this guideline to increase awareness on the part of physicians, residents, nurses, and parents concerning the issues of neonatal hyperbilirubinemia and strategies for its management.
- In addition, monitoring systems should be established to identify the impact of these guidelines on the incidence of acute bilirubin encephalopathy and kernicterus and the use of phototherapy and exchange transfusions.

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Annexes

Declaration of Conflict of Interests:

The members of the guideline development/ adaptation group and the external review group have no academic, financial, or competing interests to declare and none of them were involved in the development of the original source guideline (s).

Annex Table 17: Results of the AGREE II assessment of the source guidelines:

AGREE II/ CPGs	**Percentage**
Domain 1 (Scope)	81 %
Domain 2 (Stakeholder)	76 %
Domain 3 (Rigour)	83 %
Domain 4 (Clarity)	88 %
Domain 5 (Applicability)	68 %
Domain 6 (Independence)	80 %
Overall assessment.	78 %
Recommend for use (Overall assessment)	Yes with modifications