CLINICAL PRACTICE GUIDELINES

MOH/P/PAK/288.15(GU)

MANAGEMENT OF NEONATAL JAUNDICE

(Second Edition)

Ministry of Health Malaysia

Malaysian Paediatric Association

Perinatal Society of Malaysia

Academy of Medicine Malaysia

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STATEMENT OF INTENT

These clinical practice guidelines (CPG) are meant to be guides for clinical practice, based on the best available evidence at the time of development. Adherence to 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.

These guidelines were issued in 2015 and will be reviewed in 2019 or sooner if new evidence becomes available. When it is due for updating, the Chairman of the CPG or National Advisor of the related specialty will be informed about it. 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 used by MaHTAS will be employed.

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LEVELS OF EVIDENCE

Level	Study design
I	Evidence from at least one properly randomised controlled trial
II -1	Evidence obtained from well-designed controlled trials without randomisation
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group
II-3	Evidence from multiple time series with or without intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees

SOURCE: US / CANADIAN PREVENTIVE SERVICES TASK FORCE 2001

In line with the current development in CPG methodology, the CPG Unit of MaHTAS is in the process of incorporating Grading Recommendations, Assessment, Development and Evaluation (GRADE) into its work process. The quality of each retrieved evidence and its effect size are carefully assessed/reviewed by the CPG Development Group. In formulating the recommendations, overall balances of the following aspects are considered in determining the strength of the recommendations:-

- Overall quality of evidence
- Balance of benefits vs harms
- Values and preferences
- Resource implications
- Equity, feasibility and acceptability

GUIDELINES DEVELOPMENT AND OBJECTIVES

GUIDELINES DEVELOPMENT

The members of the Development Group (DG) for these Clinical Practice Guidelines (CPG) were from the Ministry of Health (MoH) and Ministry of Higher Education. There was active involvement of a multidisciplinary Review Committee (RC) during the process of the CPG development.

The previous CPG entitled Management of Jaundice in Healthy Term Newborns 2003 was used as the basis for the development of the present guidelines. A literature search was carried out using the following electronic databases: Guidelines International Network (G-I-N); Medline via Ovid, Pubmed and Cochrane Database of Systemic Reviews (CDSR) (refer to **Appendix 1** for **Example of Search Strategy**). The inclusion criteria are all literature on neonatal jaundice occurring less than two weeks, regardless of study design. The search was limited to literature published in the last ten years, humans and in English. In addition, 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 were conducted from 29 May 2013 to 23 June 2014. Literature searches were repeated for all clinical questions at the end of the CPG development process allowing any relevant papers published before 31 August 2014 to be included. Future CPG updates will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from the CPG Secretariat.

Reference was also made to other CPG on neonatal jaundice developed by National Collaborating Centre for Women's and Children's Health (2010)/National Institute for Health and Clinical Excellence (NICE) (2010) and American Academy of Pediatrics (2004 and 2009). The CPG was evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) II prior to them being used as references.

A total of 14 clinical questions were developed under different sections. Members of the DG were assigned individual questions within these sections. (Refer to **Appendix 2** for **Clinical Questions**) The DG members met 18 times throughout the development of these guidelines. The literature retrieved was appraised by at least two DG members using Critical Appraisal Skill Programme checklist, presented in evidence tables and further discussed in each DG meetings. All statements and recommendations formulated after that were agreed upon by both the DG and RC. Where evidence was insufficient, the recommendations were made by consensus of the DG and RC. Any differences in opinion were resolved consensually. These guidelines were based largely on

the findings of systematic reviews, meta-analyses and clinical trials, with local practices taken into consideration.

The literature used in these guidelines was graded using the US/ Canadian Preventive Services Task Force Level of Evidence (2001), while the grading of recommendation was done using the principles of GRADE (refer to the preceding page).

On completion, the draft guidelines was reviewed by external reviewers. It was also posted on the MoH Malaysia official website for feedback from interested parties. The draft was finally presented to the Technical Advisory Committee for CPG, and the HTA and CPG Council MoH Malaysia for review and approval.

OBJECTIVES

The objective of the CPG is to provide evidence-based guidance on the management of NNJ, specifically addressing the following:
Diagnosis and Assessment
i. Treatment
ii. Prevention of Severe Jaundice
iii. Referrals and Follow-up

CLINICAL QUESTIONS

Refer to **Appendix 2**

TARGET POPULATION

Inclusion Criteria
- All preterm and term babies with neonatal jaundice

Exclusion Criteria
Babies with:
- Conjugated hyperbilirubinaemia
- Prolonged jaundice (jaundice beyond 14 days in term babies and 21 days in preterm babies)

TARGET GROUP/USER

This CPG is intended to guide those involved in the management of NNJ either in primary or secondary/tertiary care namely:-
i. Medical officers and general practitioners
ii. Family Medicine Specialists
iii. Paediatricians and specialists from related disciplines
iv. Allied health professionals
v. Pharmacists

vi. Students (medical postgraduates and undergraduates, and allied health students)
vii. Parents and carers

HEALTHCARE SETTINGS

Outpatient, inpatient and community settings

GUIDELINES DEVELOPMENT GROUP

Chairperson

Dr. Angeline Wan Seng Lian
Consultant Neonatologist
Hospital Pakar Sultanah Fatimah, Johor

Members (alphabetical order)

Dr. Choo Yao Mun
Senior Lecturer & Consultant Neonatologist
Pusat Perubatan Universiti Malaya
Kuala Lumpur

Dr. Fazila Mohamed Kutty
Consultant Neonatologist
Hospital Serdang, Selangor

Ms. Loong Ah Moi
Nursing Matron
CPG Unit, Health Technology Assessment Section, MoH, Putrajaya

Dr. Marina Mohd Said
Family Medicine Specialist
Klinik Kesihatan Parit Raja, Johor

Dr. Mohd. Aminuddin Mohd. Yusof
Head of CPG Unit
Health Technology Assessment Section
MoH, Putrajaya

Dr. Nazrul Neezam Nordin
Consultant Paediatric Gastroenterologist
Sunway Medical Centre, Kuala Lumpur

Mdm. Noor Haslina Othman
Pharmacist
Hospital Raja Perempuan Zainab II
Kelantan

Dr. Noorzaitun Ariffin
Paediatrician
Hospital Raja Perempuan Zainab II
Kelantan

Dr. Pauline Choo Poh Ling
Consultant Neonatologist
Hospital Tuanku Jaafar
Negeri Sembilan

Dr. Suzaini Mat Daud
Consultant Family Medicine Specialist
Klinik Kesihatan Arau, Perlis

Dr. Tan Hui Siu
Paediatrician
Hospital Teluk Intan, Perak

Dr. Teh Siao Hean
Consultant Paediatrician
Hospital Miri, Sarawak

REVIEW COMMITTEE

The draft guidelines was reviewed by a panel of experts from both public and private sectors. They were asked to comment primarily on the comprehensiveness and accuracy of the interpretation of evidence supporting the recommendations in the guidelines.

Chairperson

Dr. Neoh Siew Hong
Consultant Neonatologist
Hospital Kuala Lumpur, Kuala Lumpur

Members (alphabetical order)

Dr. Aminah Bee Mohd Kassim
Senior Principal Assistant Director
Family Health Development Division
MoH, Putrajaya

Dr. Anna Padmavathy Soosai
Consultant Neonatologist
Prince Court Medical Centre
Kuala Lumpur

Dr. Faridah Aryani Md. Yusof
Senior Principal Assistant Director
Pharmaceutical Services Division
MoH, Selangor

Dr. Hanihaselah Mohd. Saleh
Consultant Family Medicine Specialist
Klinik Kesihatan Bandar Tenggara
Johor

Dr. Jamaluddin Haji Mohamad
Consultant Paediatrician
Hospital Sungai Buloh, Selangor

Datuk Dr. Kuan Geok Lan
Senior Consultant Paediatrician
Hospital Melaka, Melaka

Associate Professor Dr. Lai Nai Ming
Associate Professor of Paediatrics
School of Medicine, Taylor's University
Lakeside Campus Malaysia
Kuala Lumpur

Professor Dr. Rohana Jaafar
Professor of Paediatrics & Senior
Consultant Neonatologist
Pusat Perubatan Universiti Kebangsaan
Malaysia, Kuala Lumpur

Datin Dr. Rugayah Bakri
Deputy Director
Health Technology Assessment Section
MoH, Putrajaya

EXTERNAL REVIEWERS (in alphabetical order)

The following external reviewers provided feedback on the draft:-

Dr. Alvin S M Chang
Consultant, Department of Neonatology
KK Women's and Children's Hospital
Singapore
Adjunct Assistant Professor, Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore and
Adjunct Assistant Professor, DUKE-NUS Graduate Medical School, Singapore

Professor Dr. Jacqueline J Ho
Deputy Dean (Academic Affairs) &
Head of Department of Paediatrics
Honorary Consultant Neonatologist
Penang Medical College
Pulau Pinang

Emeritus Professor Dr. Boo Nem Yun
Senior Professor of Department of Population Medicine and
Deputy Dean for Academic Development and Undergraduate Programmes
Faculty of Medicine and Health Sciences
Universiti Tunku Abdul Rahman, Selangor

Dr. Kok Chin Leong
President, Malaysian Paediatric Asssociation & Consultant Paediatrician
KPJ Puteri Specialist Hospital, Johor

Mdm. Dir Rathna Masni Kamaruddin
Clinical Pharmacist
Hospital Kuala Krai, Kelantan

Dr. Ng Hoong Phak
Senior Consultant Paediatrician
Hospital Umum Sarawak, Sarawak

Dr. Farah Inaz Syed Abdullah
Consultant Neonatologist &
Lactation Consultant
Hospital Kuala Lumpur, Kuala Lumpur

Dr. Rozita Zakaria
Consultant Family Medicine Specialist
Klinik Kesihatan Pasir Gudang, Johor

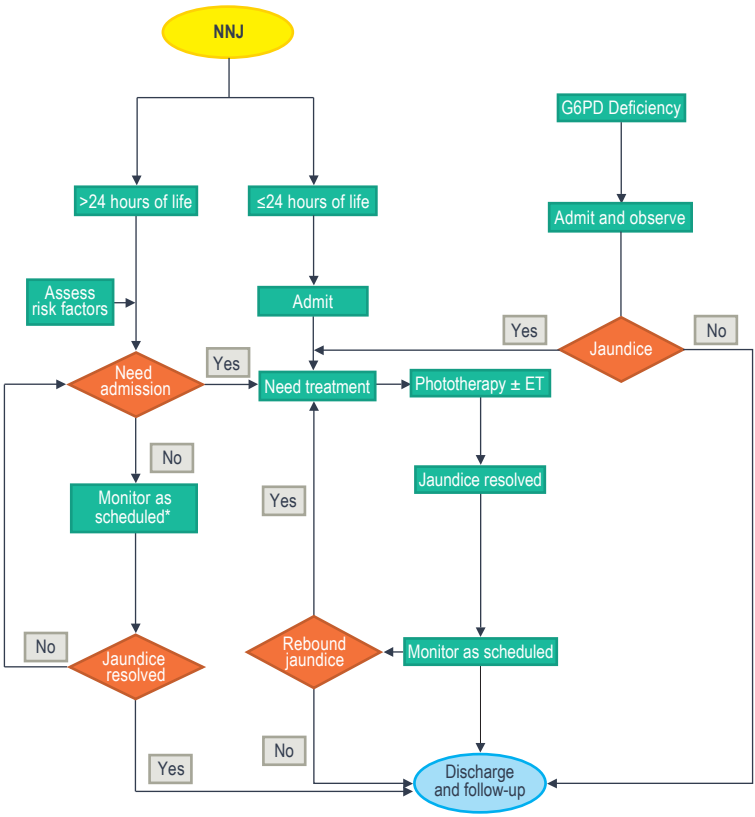
Dr. Irene Cheah Guat Sim
Senior Consultant Neonatologist
Hospital Kuala Lumpur, Kuala Lumpur

Dr. See Kwee Ching
President, Perinatal Society of Malaysia &
Consultant Neonatologist
Hospital Sungai Buloh, Selangor

Dr. Japaraj Robert Peter
Maternal Fetal Medicine Specialist &
Consultant Obstetrics & Gynecology, &
Head, Department of O & G
Hospital Raja Permaisuri Bainun, Perak

Dr. Syahnaz Mohd Hashim
Lecturer & Family Medicine Specialist
Department of Family Medicine
Universiti Kebangsaan Malaysia
Medical Centre, Kuala Lumpur

ALGORITHM ON MANAGEMENT OF NEONATAL JAUNDICE



*If jaundice persists beyond 14 days in term babies and 21 days in preterm babies, further evaluation for prolonged jaundice is needed.

1. INTRODUCTION

Neonatal Jaundice (NNJ) or neonatal hyperbilirubinaemia is one of the most common medical conditions in newborn babies. All babies have a transient rise in serum bilirubin but only about 75% are visibly jaundiced. Jaundice is clinically detectable when the serum bilirubin levels are >85 µmol/L (5 mg/dl). NNJ is more common among Asian babies and varies with races. There are also other risk factors that may be associated with severe jaundice including prematurity, G6PD deficiency and ABO incompatibility. Due to improving survival rates of preterm babies, and better identification of risk factors over the years, there is a need to address the management of jaundice in this group of babies.

Hyperbilirubinaemia is either unconjugated or conjugated. Without treatment, high levels of unconjugated bilirubin may lead to acute and chronic bilirubin encephalopathy. This may cause to neurodevelopmental problems including athetoid cerebral palsy, hearing loss and visual impairment.

The CPG on the Management of Jaundice in Healthy Term Newborns was developed in 2003 as a guide to clinical practice, based on the best available evidence at that time. Since then, novel techniques in the assessment of NNJ, different modalities of treatment and newer concepts of prevention have been introduced. Based on recent evidence, this CPG aims to assist healthcare providers in clinical decision-making and to provide a standard framework for the management of NNJ in the country.

2. RISK FACTORS

Physiological jaundice in babies:
- is due to excessive bilirubin production (higher haemoglobin content and shorter red blood cell life span in newborn babies) and poor bilirubin clearance (liver immaturity)
- usually appears two to four days after birth, resolving after one to two weeks (three weeks if preterm)
- is not associated with underlying disease and is usually benign

Risk factors of severe NNJ are:-
- prematurity
- low birth weight
- jaundice in the first 24 hours of life
- mother with Blood Group O or Rhesus Negative
- G6PD deficiency
- rapid rise of total serum bilirubin
- sepsis
- lactation failure in exclusive breastfeeding
- high predischarge bilirubin level
- cephalhaematoma or bruises
- babies of diabetic mothers
- family history of severe NNJ in siblings

Physiological jaundice is usually benign and occurs in almost all babies. It can be exacerbated by certain conditions such as inadequate intake, cephalohaematoma and bruises. However, high levels of bilirubin can lead to bilirubin encephalopathy. Therefore, it is important to identify babies at risk of severe hyperbilirubinaemia and adverse neurodevelopmental sequelae. Babies are more likely to develop severe hyperbilirubinaemia if they have any of the following factors:

i. Low gestational age/late preterm

NNJ is common among babies delivered <37 weeks of gestation ($p<0.0001$).[1 - 2, level II-2] Babies born at 38 to 39 weeks gestation have higher risk for developing severe NNJ compared with babies of ≥40 weeks gestation (OR=3.12, 95% CI 1.21 to 8.03).[3, level II-2]

ii. Low birth weight

In extremely low birth weight (ELBW) babies, an increasing level of unconjugated bilirubin increases mortality and risk of adverse neurodevelopmental outcomes (moderate to severe cerebral palsy, blindness, severe bilateral central hearing loss or poor mental developmental or psychomotor developmental index) (OR=1.18, 95% CI 1.02 to 1.38).[4, level II-2]

iii. Visible jaundice in the first 24 hours of life

Jaundice developing within the first 24 hours after birth is an important risk factor for severe hyperbilirubinaemia.[5 - 6]

iv. Mother with Blood Group O or Rhesus Negative

Babies with rhesus incompatibility have increased risk of bilirubin encephalopathy.[7, level III] Babies with ABO incompatibility and a positive direct Coombs test have a greater risk for adverse outcome than those with a negative test (OR=4.5, 95% CI 1.3 to 15.4).[8, level II-2]

v. G6PD deficiency

In a study of babies with total serum bilirubin (TSB)>20 mg/dL (>340 μmol/L), G6PD-deficient babies had higher peak TSB levels ($p<0.001$), were more likely to require phototherapy ($p=0.004$) or exchange transfusion (ET) ($p<0.01$) and had a higher mortality rate ($p<0.05$) compared to non-G6PD-deficient babies.[1, level II-2; 8, level II-2]

vi. Rapid rise of total serum bilirubin (TSB)

Babies with a rapid rise of TSB greater than 6 mg/dL/day (103 μmol/L/day) are at risk of developing severe hyperbilirubinaemia (OR=2.94, 95% CI 1.46 to 5.92).[3, level II-2]

vii. Presence of sepsis

In a study among babies >34 weeks, proven sepsis greatly increased the risk of bilirubin toxicity (OR=20.6. 95% CI 4.9 to 87.5).[7, level III]

viii. Excessive weight loss

Excessive body weight loss in the first three days after birth is a predictor for significant hyperbilirubinaemia.[9, level II-2]

Refer to **Subchapter 5.1** on **Weight loss**

ix. Exclusive breastfeeding

Using multivariate analysis, exclusive breastfeeding is a significant predictor of TSB ≥25 mg/dL (425 μmol/L) with OR=2.03 (95% CI 1.03 to 3.99).[3, level II-2]

Refer to **Chapter 12** on **Impact of breastfeeding**

x. High predischarge bilirubin level

A high predischarge bilirubin level is a predictor for development of significant hyperbilirubinaemia with AUC ranging between 0.86 and 0.88.[10 - 11, level II-2]

Refer to **Nomogram** in **Appendix 5**.

xi. Cephalhaematoma or bruises

Babies with cephalhaematomas or bruises are at risk for NNJ.[3, level II-2; 6]

xii. Babies of diabetic mothers

Macrosomic babies of diabetic mothers are at risk factor for NNJ.[12]

xiii. Family history of severe NNJ in siblings

A history of severe NNJ or ET among other siblings increases the risk for severe hyperbilirubinaemia although it is not statistically significant.[3, level II-2; 11, level II-2]

There is no good quality evidence on maternal consumption of traditional herbs as a risk factor for NNJ.

A Malaysian study found that less than 50% of the mother included in this study had good knowledge and awareness about the risks and complications of NNJ. Although a majority of them (88.7%) knew that jaundiced babies needed blood tests to monitor the severity of jaundice, only 27.1% of them were aware that putting jaundiced babies under the sun could result in dehydration and worsening of jaundice.[13, level III]

Recommendation 1

- Risk factors* for developing severe jaundice in babies need to be identified during the antenatal and postnatal period.
- Health education on neonatal jaundice should be given during antenatal and postnatal visits.

*Refer to the **preceding text**.

3. RELATIONSHIP BETWEEN BILIRUBIN LEVEL, ACUTE BILIRUBIN ENCEPHALOPATHY AND KERNICTERUS

Acute Bilirubin Encephalopathy (ABE)
ABE results in changes of mental (behavioural) status and muscle tone during the neonatal period when the baby is having hyperbilirubinaemia. These include drowsiness, poor feeding and hypotonia followed by hypertonia affecting extensor muscles in particular, resulting in retrocollis and opisthotonos.[14]

Classic kernicterus
Classic kernicterus may be seen in babies who survive from ABE. The manifestations of ABE include dystonia, athetoid cerebral palsy, paralysis of upward gaze, and sensorineural hearing loss. Post-mortem icteric (yellow) staining of the basal ganglia, specifically the globus pallidus is the hallmark of this condition.[14]

Bilirubin-Induced Neurologic Dysfunction (BIND)
BIND is a wider spectrum of disorders that not only includes classic kernicterus and ABE, but also less severe forms of neuropathy, including auditory neuropathy, fine and gross motor incoordination, gait abnormalities, fine tremors, exaggerated extrapyramidal reflexes and behavioural problems.[14]

Kernicterus is a rare condition due to severe neonatal hyperbilirubinaemia. It is associated with a high mortality, and survivors usually suffer sequelae such as athetoid cerebral palsy, intellectual disability and high frequency hearing loss. Preventing and treating severe neonatal hyperbilirubinaemia is crucial to prevent kernicterus.

In North America and Europe, the estimated incidence of kernicterus ranges from 0.4 to 2.7 cases per 100,000 live births among term and late preterm babies.[15, level III] In a Danish study, the incidence of acute advanced and chronic bilirubin encephalopathy among babies more than 35 weeks was 0.6 per 100 000 live births (95% CI 0.1 to 1.7).[16, level III]

Risk factors for bilirubin neurotoxicity are isoimmune hemolytic disease, G6PD deficiency, asphyxia, sepsis, acidosis and albumin <3.0mg/dL.[6] The risk may be increased by a prolonged exposure to a certain TSB level. Due to limited published data, it is not possible to provide specific recommendations for intervention based on the duration of hyperbilirubinaemia.[12]

The exact bilirubin concentration associated with kernicterus in the healthy term babies is unknown.[8, level II-2; 16, level III] The risk of acute advanced and chronic bilirubin encephalopathy among term and late

preterm babies increases with higher TSB level.[7 - 8, level II-2; 16 - 17, level III; 18, level II-2] ABE can occur with lower TSB levels in the presence of neurotoxicity risk factors such as sepsis and rhesus incompatibility.[7, level II-2]

- The relationship between exact bilirubin level, ABE and kernicterus in healthy term babies is unknown. However, the risk increases with higher TSB levels.
- ABE can occur with lower TSB levels in the presence of other risk factors.

4. METHODS OF DETECTING JAUNDICE AND ASSESSING ITS SEVERITY

TSB measurement is the gold standard for detecting and determining the level of hyperbilirubinaemia. Visual assessment using Kramer's rule is still widely practised. Newer, non-invasive methods like transcutaneous bilirubinometry have been introduced and are gaining wide acceptance.

i. Transcutaneous bilirubinometer (TcB)

The transcutaneous bilirubinometer is a hand-held device that measures the amount of bilirubin in the skin.

- Many studies, including a large health technology assessment, showed a significant correlation (r ranging from 0.75 to 0.95) between bilirubin measurements taken by TcBs (BiliCheck and JM 103), with TSB measurements, in both term and preterm babies. However, the TcBs tended to overestimate or underestimate the bilirubin concentration when compared to TSB.[19, level II-2; 20 - 23, level III] Overestimation can lead to unnecessary invasive investigations and treatment. Underestimation, on the other hand, can lead to missing babies at risk for developing severe hyperbilirubinaemia.

- TcB measurements have good correlation (r ranging from 0.85 to 0.97) with TSB measured by different types of chemistry analysers.[24 - 26, level III] However the mean differences between the TcB and TSB levels vary with each method [24 - 25, level III] and TcB measurement sites (sternum or forehead).[25, level III]

- Mean differences between TcB measurements and TSB levels are large when the bilirubin levels exceed 205 µmol/L (12 mg/dL).[19, level II-2; 26 - 27, level III]

- There has not been any major adverse effect associated with the use of BiliCheck and JM-103 devices.[19, level II-2]

- JM-103 as compared to Bilicheck offers some practical advantages. It does not require any disposable material, has better accuracy in identifying TSB levels >12 mg/dL (205 µmol/L), and is less time consuming.[28, level III]

- Phototherapy affects the accuracy of TcBs in detecting jaundice.[29 - 31, level III] The correlation is better between TSB levels and TcB measurements obtained from the areas unexposed to the phototherapy as compared to the exposed areas.[29 - 30, level III]

ii. Icterometer

The icterometer is a non-invasive instrument which can be used as a screening tool for NNJ. There is no good quality evidence to indicate its reliability.

iii. Visual assessment

Visual assessment of jaundice is based on the assessment of the extent and severity of yellow discolouration of the skin. It is performed by blanching the skin with slight finger pressure and noting the underlying colour of the skin. Jaundice is usually visible when bilirubin levels are about 5 - 7 mg/dL (86 - 120 μmol/L) and progresses from head to toe as the level of bilirubin rises. Kramer's rule describes the relationship between serum bilirubin levels and the progression of skin discolouration (refer to **Table 1** and **Figure 1**).

Visual assessment is not reliable in monitoring jaundice for babies on phototherapy.

Table 1. Visual Assessment of Neonatal Jaundice (Kramer's rule)

Area of the Body	Level	Range of Serum Bilirubin	
		μmol/L	mg/dL
Head and neck	1	68 - 133	4 - 8
Upper trunk (above umbilicus)	2	85 - 204	5 - 12
Lower trunk and thighs (below umbilicus)	3	136 - 272	8 - 16
Arms and lower legs	4	187 - 306	11 - 18
Palms and soles	5	≥306	≥18

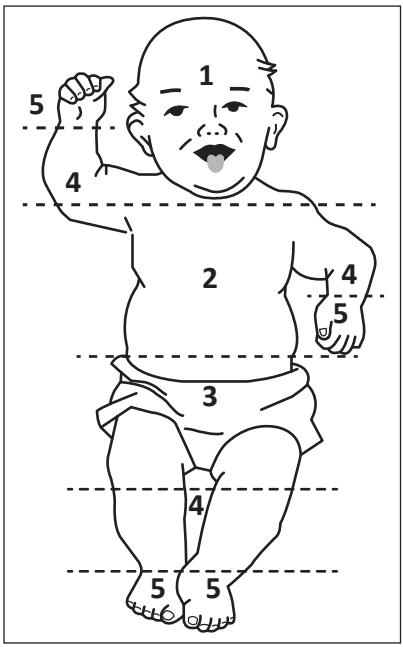


Figure 1. Visual Assessment of Neonatal Jaundice (Kramer's rule)

Source: Kramer LI. Advancement of dermal icterus in the jaundiced newborn. Am J Dis Child. 1969 Sep;118(3):454-8

- Nurses' visual assessment of jaundice extent moderately correlates with TSB and is better in non-black compared to black babies, although the difference is not significant. [r_s=0.55 & 0.45 respectively (p=0.13)]. However, correlation is weak (r_s=0.29) among babies born before 38 weeks of gestation.[32, level III]

- Visual assessment is unreliable as a predischarge screening tool to predict the risk of significant hyperbilirubinaemia.[32 - 33, level III] However, babies with complete absence of jaundice before discharge have a low risk of developing significant hyperbilirubinaemia.[32, level III]

- Trained primary health care workers in a resource poor setting are able to identify jaundiced babies with TSB >255 µmol/L (15 mg/dL) with good sensitivity (83.3%) but poor specificity (50.5%).[34, level II-3]

- TcB is more accurate than visual assessment in detecting hyperbilubinaemia in babies born after 34 weeks of gestation.[19, level II-2; 35, level III] A combination of TcB and visual assessment improves the accuracy as compared to visual assessment alone.[19, level II-2]

Recommendation 2

- All babies should be visually assessed for jaundice at every opportunity.
- Transcutaneous Bilirubinometer (TcB) should be used if jaundice is detected. If TcB levels exceed 200 μmol/L (12 mg/dL), total serum bilirubin (TSB) should be measured.
- When TcB is not available, TSB should be measured in babies with jaundice.
- TcB should not be used to monitor bilirubin levels in babies on phototherapy.

5. ASSESSMENT COMPONENTS

When a baby presents with NNJ, it is important to identify the risk factors and severity of hyperbilirubinaemia, to assess the general condition of the baby and to observe signs of bilirubin toxicity. Proper assessment is needed in deciding on subsequent management.

i. Excessive weight loss

Weight loss ≥7% of birth weight increases the risk of significant hyperbilirubinaemia (OR=1.43, 95% CI 1.03 to 1.99).[36, level II-2]

In exclusively breast-fed babies:

- weight loss ≥8% at day two of life and >11% at day three of life predicts subsequent significant hyperbilirubinaemia [OR=1.45 (95% CI 1.06 to 1.97) and OR=2.01 (95% CI 1.16 to 3.46) respectively].[37, level III]
- weight loss ≥7% is a risk factor for developing severe hyperbilirubinaemia [(TSB >20mg/dL (342 umol/l)] with OR=3.9 (95% CI 1.4 to 10.8).[38, level III]

Recommendation 3

- The adequacy of breastfeeding, weight and hydration status of all babies should be assessed during the first week of life.
  - Babies with weight loss >7% of birth weight should be referred for further evaluation and closely monitored for jaundice.

Parameters to be assessed on adequate breastfeeding are shown as below:-

Assessment of Breastfeeding Adequacy

Parameter	Normal
Urine output	At least 5 - 6 heavy wet nappies in 24 hours
Appearance and frequency of stools	At least 2 in 24 hours; normal appearance
Baby's colour, alertness and tone	Normal skin colour, alert, good tone
Weight	Weight loss not more than 10% of birth weight
Number of feeds in the last 24 hours	At least 8 - 12 feeds
Baby's behaviour during feeds	Generally calm and relaxed
Sucking pattern during feeds	Initial rapid sucks changing to slower sucks with pauses and soft swallowing
Length of feed	Feeding for 5 - 40 minutes at most feeds
End of the feed	Baby lets go spontaneously, or does so when breast is gently lifted
Baby's behaviour after feeds	Content after most feeds

Source: Breastfeeding assessment form (Internet communication, 2 December 2014 at http://www.unicef.org.uk/BabyFriendly/Resources/Guidance-for-Health-Professionals/Forms-and-checklists/Breastfeeding-assessment-form/)

ii. Assessment of ABE

a. Term babies

Serious consequences of NNJ include ABE, choreoathetoid cerebral palsy, hearing impairment and death.[14]

BIND score

BIND score, which was first introduced by Johnson et al. in 1999 (as shown in **Table 2**) quantifies the severity and progression of ABE.

Table 2. Bilirubin-Induced Neurologic Dysfunction

Clinical Signs	**BIND Score**	Date: Time:	Date: Time:
Mental Status			
Normal	0		
Sleepy but arousable; decreased feeding	1		
Lethargy, poor suck and/or irritable/jittery with strong suck	2		
Semi-coma, apnoea, unable to feed, seizures, coma	3		
Muscle Tone			
Normal	0		
Persistent mild to moderate hypotonia	1		
Mild to moderate hypertonia alternating with hypotonia, beginning arching of neck and trunk on stimulation	2		
Persistent retrocollis and opisthotonus - bicycling or twitching of hands and feet	3		
Cry Pattern			
Normal	0		
High pitched when aroused	1		
Shrill, difficult to console	2		
Inconsolable crying or cry weak or absent	3		
TOTAL BIND SCORE			

Advanced ABE (score 7 - 9): urgent bilirubin reduction intervention is needed to prevent further brain damage and reduce the severity of sequelae
Moderate ABE (score 4 - 6): urgent bilirubin reduction intervention is likely to reverse this acute damage
Mild ABE (score 1 - 3): subtle signs of ABE

Note: An abnormal or 'referred' Auditory Brainstem Response (ABR) is indicative of moderate ABE. Serial ABR may be used to monitor progression and reversal of acute auditory damage and could be indicative of the effectiveness of bilirubin reduction strategy.

Adapted: Johnson L, Bhutani VK, Karp K, et al. Clinical report from the pilot USA Kernicterus Registry (1992 to 2004). J Perinatol. 2009 Feb;29 Suppl 1:S25-45

BIND score or assessment of ABE was done in the following studies:

- In the Pilot USA Kernicterus Registry of 125 babies, 8% had subtle ABE, 20% had moderate ABE and 70% had advanced ABE.[39, level III]
- In a Canadian study of 258 babies with severe hyperbilirubinaemia [TSB >425 μmol/L (>25 mg/dL)], 32 babies had neurological abnormalities, in which six had intermediate or advanced bilirubin encephalopathy.[17, level III]
- In a study on term and late preterm babies with severe hyperbilirubinaemia [TSB >25 mg/dL (428 μmol/L)], pretreatment BIND score >6 was a good predictor of bilirubin encephalopathy at the time of death or discharge.[7, level III]
- In a recent Chinese study of term babies, 12%, 72% and 16% had subtle, moderate and severe ABE respectively during admission. The severity of ABE correlated significantly with the peak TSB level (p=0.03), bilirubin encephalopathy at the time of discharge (p=0.028) and death (p=0.000).[40, level III]

The AAP 2004 guidelines recommends immediate ET in any infant who is jaundiced and manifests the signs of the intermediate to advanced stages of ABE even if the TSB is falling.[12]

Recommendation 4

- Bilirubin-Induced Neurologic Dysfunction score may be used in babies with severe neonatal jaundice to assess the severity and progression of acute bilirubin encephalopathy.

b. Preterm babies

Acute manifestations of bilirubin toxicity are often subtle and indistinct in preterm babies. Auditory Brainstem Response (ABR) is a useful method to detect and monitor the progression of ABE in this group of babies.[41 - 43]

In a small study of eight preterm babies with athetoid cerebral palsy, none showed features of classical ABE during the neonatal period. However, ABR measurements were abnormal in seven of the eight babies.[44, level III]

In the pilot USA Kernicterus Registry, symptomatic apnoeic events were reported in 50% of the late preterm babies with kernicterus.[45, level III]

Preterm babies with abnormal ABR measurements associated with hyperbilirubinaemia have more apnoea (p=0.0009), more bradycardia (p=0.02), require longer continuous positive airway pressure support (p=0.007) and longer duration of methylxanthine use (p=0.002).[46, level II-2]

- ABR is a useful method to detect and monitor the progression of ABE especially in preterm babies.
- Preterm babies with ABE tend to have more frequent apnoea.

iii. Blood tests

a. Yield of tests

There is limited evidence on the role and yield of tests in babies with NNJ. Clinical expertise is required to guide decision-making in this area. In a study of babies admitted for phototherapy and received full laboratory evaluation (complete blood count, blood cultures, electrolytes, liver function test including total and direct bilirubin, direct Coombs test and qualitative G6PD activity test), only 11.7% of them had abnormal results. These were either a positive direct Coombs test, high reticulocyte count or G6PD deficiency. Therefore, there was no clinical benefit in conducting a full laboratory evaluation to identify possible causes of severe hyperbilirubinaemia except in:[47, level III]

- early onset jaundice (<48 hours from birth) ($p<0.001$)
- rising TSB despite phototherapy

Recommendation 5

- In babies with severe hyperbilirubinaemia, early-onset neonatal jaundice (<24 hours) or rapid rise of TSB (>8.5 µmol/L/h or >0.5 mg/dL/h), further laboratory evaluation may be required to ascertain underlying cause and extent of haemolysis. This may include:
  - G6PD testing (if not screened)
  - mother's and baby's blood groups
  - a direct Coombs test
  - a full blood count ± peripheral blood picture
  - a reticulocyte count
  - a septic workup (if infection is suspected)

b. G6PD measurements

Malaysia has a universal newborn G6PD screening programme since the 1980s. The Beutler's modified fluorescent spot test (FST) method is used as a screening method but it detects only cases with G6PD <30% of normal levels.[48 - 49] The mean level of G6PD enzyme activity of normal babies in Malaysia was quoted as 8.4 IU/g Hb by Boo et al.[50]

The detection rates for G6PD deficiency with severe hyperbilirubinaemia (TSB >300 µmol/L or 18 mg/dL) are 13.1% by FST and 19.6% by enzyme assay (with cut-off level of <8.5 IU/g Hb defined as G6PD deficiency). In addition, almost 10% of babies with normal FST has low enzyme level of <8.5 IU/g Hb (false negative). Significant predictors of severe hyperbilirubinaemia include G6PD enzyme levels of <8.5 IU/g Hb (OR=5.3, 95% CI 2.4 to 11.4)[49, level II-2]

Recommendation 6
- All babies should be screened for Glucose-6-phosphate dehydrogenase (G6PD) deficiency. The results should be reviewed within 24 hours.
- G6PD enzyme assays may be considered in babies suspected to have G6PD deficiency but with normal/indeterminate Fluorescent Spot Test.

c. Bilirubin/albumin ratio (B/A ratio)

Bilirubin in the plasma is bound to the albumin, and the portion of unbound bilirubin (UB) is presumed to leave the intravascular space readily and crosses the intact blood-brain barrier. The measurement of this unbound bilirubin is complex and not available commercially. There have been studies looking into B/A ratio as a surrogate measurement of unbound bilirubin (UB).[51]

The AAP 2004 guidelines states that B/A ratio can be used as an adjunct to the TSB level in the decision for ET.[12] On the contrary, NICE guidelines 2010 does not recommend the use of B/A ratio in the management of neonatal hyperbilirubinaemia.[5]

A Dutch multi-centre randomised controlled trial (BARTrial) showed no difference in the neurodevelopmental outcome at 18 - 24 months for preterm babies <32 weeks treated according to their B/A ratio in conjunction with TSB levels when compared to babies treated based on TSB levels alone.[52, level I]

In a study of babies >35 weeks gestation, B/A ratio correlated with UB concentrations <0.6mg/dL ($p<0.0001$). The B/A ratio was underestimated when the concentrations were >0.6 mg/dL (the UB phototherapy threshold for Japan).[53, level III]

There is not enough evidence to support the use of bilirubin/albumin ratio in the management of NNJ.

d. Unbound bilirubin (UB) or free bilirubin

Bilirubin-induced neurotoxicity depends on a complex interplay between the developing brain, UB concentration and duration of CNS exposure. UB concentration depends on:[51, 54]
- albumin concentration
- bilirubin production/elimination mismatch
- bilirubin-albumin binding affinity (k)
  - this affinity depends on gestation, postnatal age, clinical condition (acidosis/hypoxia/sepsis) and competing substrate.

UB concentration is better than TSB in predicting bilirubin-induced neurotoxicity.

- In both preterm and term babies, UB is a better predictor of ABR than TSB (OR=3.3, 95% CI 1.8 to 6.1).[55, level II-2]
- In ELBW babies, UB significantly predicts death and various neurodevelopmental outcomes in both stable and unstable infants. However, TSB predicts these outcomes only in unstable infants.[4, level II-2]

Currently, the measurement of UB is not commercially available and the threshold for neurotoxic UB concentration is not known.

6. INDICATIONS FOR TREATMENT

Guidelines for phototherapy and ET for babies ≥35 weeks gestation are as shown in **Table 3**.

Table 3. TSB Levels for Phototherapy and ET in Babies ≥35 Weeks Gestation

Age	LOW RISK ≥38 weeks and well		MEDIUM RISK ≥38 weeks with risk factors or 35 - 37 weeks + 6 days and well		HIGH RISK 35 - 37 weeks + 6 days with risk factors	
Hours of life	Conventional Phototherapy - TSB in mg/dL (μmol/L)	ET - TSB in mg/dL (μmol/L)	Conventional Phototherapy - TSB in mg/dL (μmol/L)	ET - TSB in mg/dL (μmol/L)	Conventional Phototherapy - TSB in mg/dL (μmol/L)	ET - TSB in mg/dL (μmol/L)
<24*						
24	9 (154)	19 (325)	7 (120)	17 (291)	5 (86)	15 (257)
48	12 (205)	22 (376)	10 (171)	19 (325)	8 (137)	17 (291)
72	15 (257)	24 (410)	12 (205)	21 (359)	10 (171)	18.5 (316)
96	17 (291)	25 (428)	14 (239)	22.5 (385)	11 (188)	19 (325)
>96	18 (308)	25 (428)	15 (257)	22.5 (385)	12 (205)	19 (325)

a. Start intensive phototherapy at TSB of 3 mg/dL (51 μmol/L) above the level for conventional phototherapy or when TSB increasing at >0.5 mg/dL (8.5 μmol/L) per hour.
b. Risk factors are isoimmune haemolytic disease, G6PD deficiency, asphyxia and sepsis.

* Jaundice appearing within 24 hours of life is abnormal and needs further evaluation.

The AAP exchange transfusion guidelines for babies ≥35 weeks gestation recommend:

i. ET if baby shows signs of ABE or if TSB ≥5 mg/dL (85 μmol/L) above the ET levels.
ii. ET if TSB rises to ET levels despite intensive phototherapy in hospitalised babies.
iii. For readmitted babies without signs of ABE, if the TSB is above the ET levels, repeat TSB every 2 - 3 hours and consider ET if it remains above the levels indicated after intensive phototherapy for six hours.

Modified: American Academy of Pediatrics Subcommittee on Hyperbilirubinaemia. Management of hyperbilirubinaemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2004 Jul;114(1):297-316. Erratum in: Pediatrics. 2004 Oct;114(4):1138)

For babies <35 weeks gestational age, refer to **Appendix 3**.

7. PHOTOTHERAPY

Phototherapy is the mainstay of treatment in NNJ. There are many types of devices that can be used to provide phototherapy such as fluorescent tubes, Light Emitting Diode (LED), fibreoptic and halogen bulbs.

Effective phototherapy consists of:
- blue light range (400 - 500 nm)
- irradiance of minimum of 15 μW/cm²/nm for conventional phototherapy
- irradiance of minimum of 30 μW/cm²/nm for intensive phototherapy
- distance of the light source not exceeding 30 - 50 cm from the baby

i. Type of phototherapy

a. LED phototherapy

In two meta-analyses, phototherapy based on LED and non-LED light sources showed similar clinical efficacy as measured by duration of phototherapy and rate of decline of TSB in term and late preterm babies.[56 - 57, level I]

In preterm babies, the use of LED has a similar rate of decline but significantly shorter duration of phototherapy compared with a non-LED light source.[57, level I] LED phototherapy does not induce significant alterations on transepidermal water loss and cerebral blood perfusion when compared to conventional phototherapy.[58, level I]

No study reported any major complications of LED phototherapy.[56, level I]

b. Fibreoptic phototherapy

Fibreoptic phototherapy units are less commonly used compared with conventional/LED phototherapy. Common fibreoptic phototherapy units used in studies include Biliblanket and Wallaby II.

A Cochrane systematic review showed that:[59, level I]
- In preterm babies, fibreoptic phototherapy was as efficacious as conventional phototherapy in terms of duration of phototherapy and percentage of serum bilirubin change in 24 hours.
- In term babies, fibreoptic phototherapy was efficacious in reducing serum bilirubin; however its efficacy was less in comparison to conventional phototherapy.
- A combination of fibreoptic and conventional phototherapy was more efficacious compared to conventional phototherapy alone in terms of less ET and less additional phototherapy, although this was not statistically significant.

ii. Methods of administration

Various methods of providing phototherapy have been used in order to maximise the effectiveness of phototherapy especially in babies with high serum bilirubin.

a. Use of reflecting curtains

White reflecting curtains significantly reduces TSB levels after four hours of phototherapy and shortens median duration of phototherapy by 22 hours.[60, level I]

The use of reflecting curtains shortens the duration of phototherapy and achieves a faster reduction of TSB, although these were not statistically significant.[61, level I]

The effectiveness of reflecting curtains in phototherapy depends on the material and type of curtain used. However, the use of curtains may impair observation of the babies.

b. Changing positions during phototherapy

There is no difference in the fall of TSB by changing baby's position (supine/prone vs supine alone) while receiving phototherapy.[62, level I] In clinical practice, the supine position is preferred because the prone position is associated with and increased risk of sudden infant death syndrome.

c. Double vs triple phototherapy

There is no difference in the rate of bilirubin decline and length of hospital stay between double and triple phototherapy in term babies.[63, level I]

Effective phototherapy is achieved with optimal irradiance and adequately exposed body surface area rather than the number of phototherapy units.

d. Overhead vs underneath LED phototherapy

Duration of phototherapy is shorter and rate of decrease in TSB is more rapid in overhead LED compared to underneath LED with no erythema or any other complications in both groups.[64, level II - 1]

e. Aggressive vs conservative phototherapy

There is a reduction in neurodevelopment impairment (especially profound impairment) in aggressive phototherapy on ELBW babies especially ≥750 g, when babies are started on phototherapy at TSB 85 µmol/L (5 mg/dL) in the first week of life and 120 µmol/L (7 mg/dL) during the second week of life.[65, level I] However, there is a need for more vigilance in babies with birth weight under 750 g as there is a higher risk of transepidermal water loss.

f. Prophylactic phototherapy for preventing jaundice

In a Cochrane systematic review, prophylactic phototherapy (i.e. initiation of phototherapy before TSB reached a pre-specified level) in preterm and LBW babies reduced ET by 78%, reduced rate of neurodevelopmental impairment (mainly severe hearing loss and moderate/severe cerebral palsy) at 18 - 22 months by 15% and had lower peak TSB during first seven days of life compared to control group.[66, level I]

g. Fluid management

Presently, there is no good evidence to advocate extra fluids in the management of NNJ.

Recommendation 7

- Phototherapy should be commenced when total serum bilirubin reaches the phototherapy threshold for neonatal jaundice*.
- Irradiance of phototherapy units (non-Light Emitting Diode) should be regularly checked.
- Overhead phototherapy is preferred to underneath phototherapy.
- Babies should be placed in the supine position with adequate exposure.
- Phototherapy should be started at a lower threshold in preterm and low birth weight babies.
- Light Emitting Diode phototherapy is preferred in preterm babies.

*Refer to **Chapters** on **Risk Factors** and **Indications for Treatment**.

Care of babies during phototherapy

- Babies should be regularly monitored for vital signs including temperature and hydration status.
- Babies should be adequately exposed.
- Babies' eyes should be covered to prevent retinal damage.
- Breastfeeding should be continued.

8. EXCHANGE TRANSFUSION

ET is indicated when the TSB is above the recommended levels (refer to **Table 3** and **Appendix 3**).

ET is efficacious in reducing TSB levels by 45%. Amongst those who have undergone ET, 93% have TSB levels below 342 µmol/L (20 mg/dL) after the procedure.[67, level III]

There are various methods used in performing ET. These include femoral vein (FV), umbilical vein (UV), umbilical artery/vein (UA/V) and peripheral artery (radial artery)/peripheral vein. All methods are comparable in terms of efficacy.[68 - 69, level III] With regard to safety, ET via UA/V route have significantly increased incidence of thrombocytopenia when compared to FV and UV.[68, level III]

The blood product used most commonly for ET is citrated fresh whole blood. However, some centres use reconstituted blood products when it is not available. Both citrated fresh whole blood and reconstituted blood products are comparable in terms of efficacy and safety.[70, level III]

Adverse events occur up to 36.7% of patients who have undergone ET.[67, level III; 71 - 72, level III] The adverse events include thrombocytopaenia, hypocalcaemia, hyperkalaemia, apnoea, infection, hypoglycaemia, seizure, catheter malfunction, leg ischaemia, cyanosis, bradycardia, hypotension, renal failure and necrotising enterocolitis.[67, level III; 71 - 73, level III] Mortality has been reported at 2.3%.[73, level III] The rate has declined since 1990s. In recent studies where a standardised ET protocol was adhered to and the procedure attended by experienced personnel, no mortality attributable to the ET procedure was reported.[67, level III; 69, level III; 71 - 73, level III]

Recommendation 8

- Exchange transfusion (ET) should be considered when total serum bilirubin reaches the threshold levels in neonatal jaundice (NNJ).
- ET procedure should follow a standardised protocol and supervised by experienced personnel. Babies undergoing ET should be closely monitored.
- Reconstituted blood products may be used if citrated fresh whole blood is not available for ET in NNJ.

Refer to **Appendix 4** on **Protocol on Exchange Transfusion**.

9. PHARMACOTHERAPY

There is limited good evidence on pharmacotherapy in NNJ.

i. Clofibrate

Clofibrate, an activator of peroxisome proliferator-activated receptors, is a lipid-lowering drug used in patients with hypercholesterolemia. In NNJ, its presumed mode of action is by increasing bilirubin conjugation and secretion.

Clofibrate is efficacious when compared to placebo in unconjugated neonatal hyperbilirubinaemia in terms of the need for phototherapy and ET, duration of phototherapy and peak TSB levels. No major side-effects have been reported.[74 - 76, level I]

In Malaysia, clofibrate is not registered with the Drug Control Authority.

ii. Immunoglobulin

Intravenous immunoglobulin (IVIg) has been used to reduce the rate of haemolysis in babies with rhesus hemolytic disease and other immune hemolytic jaundice. It is a competitive inhibitor for antibodies that causes red cell destruction.

In a meta-analysis of 12 studies, the efficacy of IVIg was inconclusive in both Rh and ABO haemolytic diseases of the newborn as only studies with high risk of bias showed benefit. No mortality or adverse reactions were reported.[77, level I]

iii. Human albumin

It has been postulated that intravenous (IV) human albumin infusion may be protective against bilirubin toxicity by providing more binding sites, thereby reducing the levels of unbound bilirubin. It has also been hypothesised that vascular bilirubin-albumin binding would cause a shift of bilirubin from the extravascular to the intravascular compartment following albumin administration.

In two small studies, babies were administered IV human albumin (20%, 1 g/kg) one hour prior to ET. In the treated group, the mean TSB levels after ET were significantly lower than the control group. The treated group required a significantly shorter duration of phototherapy post-ET.[78, level II-1; 79, level I] The duration of hospital stay was also significantly shorter in the treated group.[78, level II-1] However, the unbound bilirubin was not measured in both studies. Human albumin is a pooled blood product with a risk of blood-borne infection.

iv. Tin-mesoporphyrin

In a Cochrane systematic review, there was no evidence that hyperbilirubinaemia can be effectively prevented or treated with tin-mesoporphyrin, a drug that inhibits bilirubin production through blockage of heme oxygenase.[80, level I]

v. Phenobarbitone

In a meta-analysis of three RCTs of moderate quality, phenobarbitone was efficacious in reducing peak serum bilirubin, duration and need of phototherapy and need of ET in preterm babies with very low birth weight. Further studies are warranted to evaluate adverse effects and neurodevelopmental outcome.[81, level I]

- Further studies are required before clofibrate or its equivalent can be recommended for use in NNJ.
- There is no conclusive evidence to support the use of IVIG, human albumin and phenobarbitone in the management of NNJ.

10. COMPLEMENTARY/ALTERNATIVE MEDICINE

There is no good quality evidence to support the use of complementary/ alternative medicine in the management of babies with NNJ.

11. MONITORING

This chapter is written based on the Paediatric Protocols for Malaysian Hospitals (3rd Edition)[82, level III] and the Integrated Plan for Detection and Management of Neonatal Jaundice[83, level III] developed by MoH Malaysia. The documents were developed via consensus method by experts in the field.

Home visits by community healthcare providers during the postnatal period:[83, level III]

- Home visits should be done for all newborns on day 1, 2, 3, 4, 6, 8, 10 and 20. Special attention for jaundice must be given on day 2, 3 and 4 of life.
- If jaundice is detected, TSB should be measured and managed accordingly.

Recommendation 9

- All babies discharged <48 hours after birth should be seen by a healthcare provider in an ambulatory setting or at home within 24 hours of discharge.
- For babies with severe jaundice admitted for treatment, early follow-up is needed to detect rebound jaundice after discharge.

12. IMPACT OF BREASTFEEDING

Breast milk provides the best nutrition for babies and its benefits extend beyond basic nutrition. World Health Organization recommends exclusive breastfeeding up to six months of age. There is evidence that breastfeeding is associated with an increased incidence and severity of early NNJ. This may be due to inadequate intake as a result of poor lactation support but the exact mechanism remains unclear. Further details on this issue are available in ABM Clinical Protocol # 22: Guidelines for Management of Jaundice in the Breastfeeding Infant Equal to or Greater Than 35 Weeks' Gestation.[84, level III]

In the USA Kernicterus Registry (1992 - 2004), lactation failure was identified in over 90% of babies discharged on exclusive breastfeeding, with a high incidence of excessive weight loss and dehydration.[39, level III.]

Breastfeeding is significantly associated with neonatal hyperbilirubinaemia,[1, level II-2; 36, level III; 85, level III; 86, level II-3] greater body weight loss,[36, level III; 85, level III; 86, level II-3] higher peak bilirubin level, and longer mean days of phototherapy and hospitalisation.[86, level II-3] It is also associated with reduced urine and stool output on the second and third day of life.[85, level III; 86, level II-3]

In exclusively breastfed babies, those with lower gestational age and greater weight loss percentage are significantly associated with hyperbilirubinaemia.[37, level III]

Recommendation 10

- Breastfeeding, because of its benefits, should be continued in the jaundiced babies.
- Adequate lactation/breastfeeding support should be provided to all mothers, particularly those with preterm babies.
- In breastfed babies with jaundice associated with inadequate intake, excessive weight loss or dehydration, supplementation with expressed breast milk or formula may be considered.

13. PREVENTION OF SEVERE NNJ

Late preterm, G6PD deficiency and isoimmune haemolytic disease (ABO and Rhesus incompatibility) are well known factors for developing severe NNJ. Phototherapy thresholds are lower for babies with these factors (refer to **Chapter** on **Phototherapy**). Predischarge bilirubin screening, clinical risk factor scoring, prophylactic phototherapy and pharmacotherapy are among the strategies studied to prevent severe NNJ.

Predischarge screening involves performing daily TcB screening until discharge; this TcB value is referenced against the AAP hour-specific bilirubin risk-zone nomogram stratified into low-, intermediate- and high-risk zones (refer to **Figure 2**). TcB values ≥12 mg/dL (205 μmol/L) are confirmed with a TSB. Clinical risk factors that have been studied are gestational age (prematurity), the intent to exclusively breastfeed, weight loss in the first two days of life and extent of jaundice.[11, level II-2]

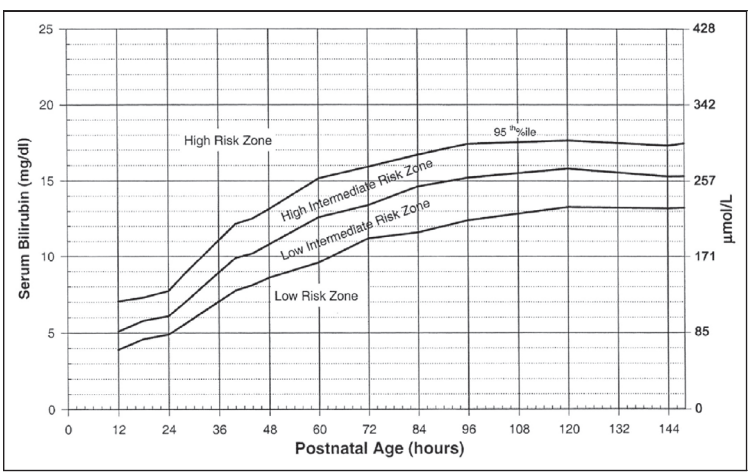


Figure 2. Nomogram for Designation of Risk at ≥36 Weeks' Gestational Age with Birth Weight ≥2000 g or ≥35 Weeks' Gestational Age with Birth Weight ≥2500 g

Source: Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinaemia in healthy term and near-term newborns. Pediatrics. 1999 Jan;103(1):6-14

i. Predischarge bilirubin and clinical risk scoring in both term and late preterm babies

a. Late preterm babies

- The incidence of hyperbilirubinaemia [TSB ≥ 20mg/dL (342 µmol/L)] is reduced by almost 50% with the implementation of predischarge screening programme.[87, level II-3]
- Predischarge screening results in a 0.41% readmission rate for significant hyperbilirubinaemia, almost half of which did not have a predischarge bilirubin determination as they were not deemed sufficiently jaundiced at the time of discharge. The rate for ET is 1:18079.[88, level II-3]
- The AUC for strategies to assess the risk of significant hyperbilirubinaemia are 0.91 (95% CI 0.86 to 0.97) for clinical risk factors, 0.88 (95% CI 0.85 to 0.91) for predischarge bilirubin and 0.96 (95% CI 0.93 to 0.98) for combination of clinical risk factors and predischarge bilirubin. Predischarge bilirubin and gestational age are the two most important factors in predicting the risk of significant hyperbilirubinaemia.[11, level II-2]
- Predischarge bilirubin in combination with gestational age gives a higher predictability of risk in developing significant hyperbilirubinaemia with AUC of 0.90 (95% CI 0.84 to 0.95) compared to 0.86 (95% CI 0.80 to 0.92) if only predischarge bilirubin being used.[10, level II-2]
- Predischarge TSB risk zone gives high predictability of risk in developing significant hyperbilirubinaemia with area AUC of 0.83 (95% CI 0.80 to 0.86) compared to clinical risk factor score alone 0.71 (95% CI 0.66 to 0.76).[89, level II-2]

b. Term babies

- The institution of predischarge bilirubin results in significant reduction of the incidence of bilirubin levels ≥25 mg/dL (425 µmol/L) by 38% and TSB ≥30.0 mg/dL (513 µmol/L) by 65%. However, this reduction in severe hyperbilirubinaemia is associated with a small increase (0.7%) in the use of neonatal phototherapy ($p<0.001$).[90, level II-3]
- Low predischarge bilirubin does not eliminate the risk of readmission. The low risk group (≤40th percentile) has a 4.2% readmission rate while intermediate low risk group (41 - 75th percentile) has a 28% readmission rate. This give a RR for readmission of 7.62 (95% CI 3.23 to 17.96) for intermediate low risk group compared to the low risk group.[91, level III]

ii. Universal predischarge bilirubin screening

- Universal screening for hyperbilirubinaemia reduces readmissions by 61% ($p<0.001$).[92, level II-3]
- The rate of ET after universal screening is 0.12%. Preterm babies have ten times higher risk of ET compared to term babies. All

babies in the high risk zone require ET compared to 28% of babies in the high intermediate zone.[93, level II-2]

iii. Prophylactic phototherapy

- Prophylactic phototherapy during the first day of life for babies with Coombs-positive ABO incompatibility is associated with a decrease in TSB within the first 48 hours of life (p=0.03) but does not result in a sustained clinical benefit.[94, level I]
- Prophylactic phototherapy in preterm and LBW babies reduces the need for ET, peak TSB and the rate of neurodevelopmental disability at 18 - 22 months.[66, level I]

iv. Pharmacotherapy

- Prophylactic oral phenobarbital is not efficacious in reducing the need for phototherapy in G6PD deficient babies.[95, level I]
- The effectiveness of IVIg is not conclusive in ABO and Rh haemolytic diseases of newborn.[77, level I]

v. Monitoring in G6PD deficiency

- Most G6PD deficient babies with birth weight ≥2500 g (76%) would require phototherapy by day four.[96, level II-2]
  - Those with TSB <160 µmol/L (9 mg/dL), on day four of life, with a rise of <30 µmol/L/day (2 mg/dL/day), are unlikely to develop significant hyperbilirubinaemia (TSB >200 µmol/L or 12 mg/dL) requiring phototherapy [NPV of 94.1% (95% CI 83.4 to 97.9)].
  - A TSB ≥160 µmol/L (9 mg/dL) on day four predicts significant hyperbilirubinaemia [PPV of 82.1% (95% CI 70.2 to 90.4)].

Recommendation 11

- Predischarge screening should be used to prevent severe neonatal jaundice (NNJ) in late preterm and term babies.
  - Clinical risk factor assessment or/and predischarge bilirubin levels [transcutaneous bilirubin or total serum bilirubin (TSB)] can be used as predischarge screening.
- Universal predischarge bilirubin screening may be considered for all babies if resources are available.
- All G6PD deficient babies should be admitted and monitored for NNJ during the first five days of life. A TSB should be done if there is clinical jaundice.
- Term G6PD deficient babies with birth weights >2500 g may be discharged earlier on day four of life if the TSB is <160 µmol/L (9 mg/dL), and followed-up closely.

Refer to **Appendix 5** on **Clinical risk factors** and **Algorithm for Predischarge Screening**.
Refer to **Appendix 6** on **Information on Prevention of NNJ.**

14. REFERRAL

This chapter is written based on Paediatric Protocols for Malaysian Hospitals (3rd Edition)[82, level III] and Integrated Plan for Detection and Management of Neonatal Jaundice[83, level III] developed by MoH Malaysia. The documents were developed via consensus method by experts in the field. Extrapolation from evidence in other chapters has also been done.

Recommendation 12

- Babies should be referred to secondary/tertiary care when they present with any of the following:-
  - Onset of jaundice within 24 hours of life
  - Rapidly rising total serum bilirubin of greater than 6 mg/dL/day (103 µmol/L/day)
  - Clinical jaundice below umbilicus, corresponding to total serum bilirubin of 12 - 15 mg/dL (205 - 257 µmol/L)
  - Clinical jaundice till the soles of the feet (urgent referral for possibility of exchange transfusion)
  - G6PD deficiency (if not previously hospitalised)
  - Clinical symptoms/signs suggestive of sepsis

15. FOLLOW-UP

The estimated incidence of kernicterus among term and late preterm neonates in North America and Europe is 0.4 to 2.7/100,000 live births while the estimate for ABE is 0.9 to10/100,000 live births.[18, level III; 39, level III; 97 - 98, level III]

A systematic review revealed that the incidence of hearing loss ranged from 13.2% to 83.3% at initial testing and 6.7% to 14.3% at three months' follow-up. The occurrence of ABR abnormalities was high at TSB levels >20 mg/dL (342 µmol/L) but unpredictable at lower levels of TSB. Greater hearing abnormalities were seen with rising TSB levels.[99, level II-2]

Using the parent-completed Ages and Stages Questionnaire, there is no association between non-haemolytic hyperbilirubinaemia and overall development in 1- to 5-year-old children who in the neonatal period had TSB >25 mg/dL (428 µmol/L) with no or only minor neurologic symptoms.[100, level II-2]

Non-haemolytic neonatal hyperbilirubinaemia is not associated with increased risk of cognitive or neuropsychiatric disability in young males at the age of 18 - 20 years.[101, level II-2]

Term babies with haemolytic (ABO or Rh incompatibility or G6PD deficiency) and non-haemolytic hyperbilirubinaemia who are treated aggressively with phototherapy (at TSB >15 mg/dL or 257 µmol/L) or ET (at TSB >20mg/dL or 342 µmol/L) do not show any differences in ABR and reversible mild motor delay/hypotonia at three months old.[102, level II-2]

In ELBW babies, higher peak serum bilirubin levels in the first two weeks of life is associated with risk of:[103, level II-2]

- death or neurodevelopment impairment (OR=1.07, 95% CI 1.03 to 1.11)
- hearing impairment (OR=1.13, 95% CI 1.00 to 1.30)
- lower psychomotor development index (OR=1.05, 95% CI 1.00 to 1.12)

Recommendation 13

- Babies with acute bilirubin encephalopathy should have long-term follow-up to monitor for neurodevelopmental sequelae.
- Term and late preterm babies with TSB >20 mg/dL (342 µmol/L) or exchange transfusions should have Auditory Brainstem Response (ABR) testing done within the first three months of life. If the ABR is abnormal, neurodevelopmental follow-up should be continued.
- Healthy term and late preterm babies with non-haemolytic hyperbilirubinaemia and TSB <25 mg/dL (428 µmol/L) may be followed-up at the primary care level.
- Preterm babies with jaundice should be followed-up for neurodevelopmental sequelae as per follow-up plans for all preterm babies.

16. IMPLEMENTING THE GUIDELINES

It is important to standardise the management of NNJ at all healthcare levels in Malaysia by using an evidence-based CPG. This aims to prevent long-term morbidity and mortality.

16.1 Facilitating and Limiting Factors

Existing facilitators for application of the recommendations in the CPG include:-

1. wide dissemination of the CPG to healthcare providers (hardcopies and softcopies)
2. regular continuous medical education on NNJ to healthcare providers
3. reporting of cases with severe NNJ [TSB ≥20 mg/dL (342 µmol/L)]

Existing barriers for application of the recommendations of the CPG are:-

1. poor assessment of NNJ and limited knowledge on its management
2. insufficient resources in the management of NNJ
3. variation in treatment practice and preferences

16.2 Potential Resource Implications

To implement the CPG, there must be strong a commitment to:-

1. ensure widespread distribution of the CPG to healthcare providers via printed and electronic copies.
2. strengthen training (with adequate funding) of healthcare providers by regular seminars or workshops to ensure information is up-to-date
3. ensure availability of equipment for measuring bilirubin levels and managing NNJ in both health clinics and hospitals
4. ensure empowerment of caregivers via education materials
5. improve the current reporting system to include bilirubin encephalopathy and other related parameters

To assist in the implementation of the CPG, the following is proposed as **clinical audit indicator for quality management**:-

$$\text{Incidence of severe NNJ*} = \frac{\text{Number of babies with severe NNJ* in a month}}{\text{Total number of live births in the same period}} \times 10{,}000$$

*Severe NNJ is defined as TSB ≥20 mg/dL or ≥342 µmol/L

Implementation strategies will be developed following the approval of the CPG by MoH. They are such a Quick Reference and a Training Module.

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APPENDIX 1

EXAMPLES OF SEARCH STRATEGY

The following MeSH terms or free text terms were used either singly or in combination, search was limit to English, human and 2001 to current:-

A. Phototherapy

1. Jaundice, Neonatal/
2. Hyperbilirubinemia, Neonatal/
3. (jaundice adj1 neonat*).tw.
4. (jaundice adj1 newborn*).tw.
5. (hyperbilirubin* adj1 neonat*).tw.
6. (hyperbilirubin* adj1 newborn*).tw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. Phototherapy/
9. (Therap* adj1 light).tw.
10. Phototherap*.tw.
11. Light*.tw.
12. 8 or 9 or 10 or 11
13. 7 and 12
14. Limit 13

B. Exchange Transfusion

1. Jaundice, Neonatal/
2. Hyperbilirubinemia, Neonatal/
3. (jaundice adj1 neonat*).tw.
4. (jaundice adj1 newborn*).tw.
5. (hyperbilirubin* adj1 neonat*).tw.
6. (hyperbilirubin* adj1 newborn*).tw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. Exchange Transfusion, Whole Blood/
9. (Exchange adj1 transfus*).tw.
10. Exchange transfus* whole blood.tw.
11. 8 or 9 or 10
12. 7 and 11
13. Limit 12

C. Pharmacotherapy

1. Jaundice, Neonatal/
2. Hyperbilirubinemia, Neonatal/
3. (jaundice adj1 neonat*).tw.
4. (jaundice adj1 newborn*).tw.
5. (hyperbilirubin* adj1 neonat*).tw.
6. (hyperbilirubin* adj1 newborn*).tw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. Drug Therapy/
9. (drug adj1 therap*).tw.
10. pharmacotherap*.tw.
11. Clofibrate/
12. clofibrate.tw.
13. (chlorophenoxyisobutyrate adj1 ethyl).tw.
14. Immunoglobulins/
15. immunoglobulin*.tw.
16. (globulins adj1 immune).tw.
17. Albumins/
18. albumins.tw.
19. Metalloporphyrins/
20. metalloporphyrins.tw.
21. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. 7 and 21
23. Limit 22

APPENDIX 2

CLINICAL QUESTIONS

1. What are the risk factors for NNJ (including kernicterus)?
2. What is the relationship between bilirubin level, acute bilirubin encephalopathy and kernicterus?
3. What is the accuracy and reliability of various methods of detecting and assessing the severity of NNJ?
4. What should be included in the assessment of NNJ?
5. What are the indications for starting treatment in NNJ?
6. Is phototherapy effective and safe in NNJ?
7. Is exchange transfusion effective and safe in NNJ?
8. How to monitor babies with NNJ?
9. Is pharmacotherapy effective and safe in NNJ?
10. Is complementary/alternative medicine effective and safe in NNJ?
11. What is the impact of breastfeeding in early NNJ?
12. What are the effective and safe measures for preventing severe NNJ?
    **What information and support should be given to parents/carers of babies with NNJ?*
13. When should babies with NNJ be referred to secondary care?
14. How should babies with severe NNJ be followed-up?

APPENDIX 3

TOTAL SERUM BILIRUBIN LEVELS FOR PHOTOTHERAPY AND EXCHANGE TRANSFUSION IN BABIES 23 - 34 WEEKS GESTATION

Age	23 weeks		24 weeks		25 weeks	
Hours of life	Phototherapy - TSB in mg/dL (μmol/L)	ET - TSB in mg/dL (μmol/L)	Phototherapy - TSB in mg/dL (μmol/L)	ET - TSB in mg/dL (μmol/L)	Phototherapy - TSB in mg/dL (μmol/L)	ET - TSB in mg/dL (μmol/L)
<24*						
24	4.1 (70)	7.6 (130)	4.1 (70)	7.9 (135)	4.7 (80)	8.2 (140)
48	5.9 (100)	10.5 (180)	6.5 (110)	10.9 (185)	6.5 (110)	11.1 (190)
72	7.6 (130)	13.5 (230)	8.2 (140)	14.0 (240)	8.8 (150)	14.6 (250)
96	7.6 (130)	13.5 (230)	8.2 (140)	14.0 (240)	8.8 (150)	14.6 (250)

Age	26 weeks		27 weeks		28 weeks	
Hours of life	Phototherapy - TSB in mg/dL (μmol/L)	ET - TSB in mg/dL (μmol/L)	Phototherapy - TSB in mg/dL (μmol/L)	ET - TSB in mg/dL (μmol/L)	Phototherapy - TSB in mg/dL (μmol/L)	ET - TSB in mg/dL (μmol/L)
<24*						
24	4.7 (80)	8.2 (140)	4.7 (80)	8.2 (140)	5.3 (90)	8.8 (150)
48	7.0 (120)	11.7 (200)	7.6 (130)	12.0 (205)	7.6 (130)	12.3 (210)
72	9.4 (160)	15.2 (260)	10.0 (170)	15.8 (270)	10.5 (180)	16.4 (280)
96	9.4 (160)	15.2 (260)	10.0 (170)	15.8 (270)	10.5 (180)	16.4 (280)

Age	29 weeks		30 weeks		31 weeks	
Hours of life	Phototherapy - TSB in mg/dL (μmol/L)	ET - TSB in mg/dL (μmol/L)	Phototherapy - TSB in mg/dL (μmol/L)	ET - TSB in mg/dL (μmol/L)	Phototherapy - TSB in mg/dL (μmol/L)	ET - TSB in mg/dL (μmol/L)
<24*						
24	5.3 (90)	8.8 (150)	5.6 (95)	8.8 (150)	5.9 (100)	9.1 (155)
48	8.2 (140)	12.9 (220)	8.5 (145)	12.9 (220)	9.1 (155)	13.5 (230)
72	11.1 (190)	17.0 (290)	11.7 (200)	17.5 (300)	12.3 (210)	18.1 (310)
96	11.1 (190)	17.0 (290)	11.7 (200)	17.5 (300)	12.3 (210)	18.1 (310)

Age	32 weeks		33 weeks		34 weeks	
Hours of life	Phototherapy - TSB in mg/dL (μmol/L)	ET - TSB in mg/dL (μmol/L)	Phototherapy - TSB in mg/dL (μmol/L)	ET - TSB in mg/dL (μmol/L)	Phototherapy - TSB in mg/dL (μmol/L)	ET - TSB in mg/dL (μmol/L)
<24*						
24	5.9 (100)	9.4 (160)	5.9 (100)	9.4 (160)	6.5 (110)	10.0 (170)
48	9.4 (160)	14.0 (240)	10.0 (170)	14.3 (245)	10.0 (170)	14.6 (250)
72	12.9 (220)	18.7 (320)	13.5 (230)	19.3 (330)	14.6 (240)	20.0 (340)
96	12.9 (220)	18.7 (320)	13.5 (230)	19.3 (330)	14.6 (240)	20.0 (340)

Source: National Collaborating Centre for Women's and Children's Health. Neonatal jaundice. London: NCC-WCH; 2010) for recommended levels of phototherapy and ET

*Jaundice appearing within 24 hours of life is abnormal & needs further evaluation.

APPENDIX 4

PROTOCOL FOR EXCHANGE TRANSFUSION

ET should preferably be done in Neonatal Intensive Care Unit (NICU) or in a place where adequate resuscitation equipment is available. Babies should be placed in an open bed radiant warmer where possible.

i. Preparation of Baby

- Obtain written informed consent from parent/caregiver.
- Ensure resuscitation equipment and medications are available.
- Stabilise and maintain temperature, pulse rate, blood pressure, oxygen saturation and respiration.
- Obtain peripheral venous access for maintenance fluids.
- Apply gentle restraint and nurse in comfortable position.
- Continue feeding, omit only the last feed before ET. If less than four hours from last feed, empty gastric contents by orogastric tube before ET.

The procedure should be performed under aseptic technique using gloves, gown and mask.

ii. Type of Blood to be Used

- Rh isoimmunisation: ABO compatible, Rh negative blood
- Other conditions: Cross-match with baby's and mother's blood
- In emergencies if blood type unknown: 'O' Rh negative blood

iii. Pre-ET Blood Investigations

- Full blood count including differential
- Bilirubin (total, direct and indirect) level
- Blood culture and sensitivity via peripheral venous blood
- Others as indicated

iv. Procedure for ET

- Volume to be exchanged is two times the baby's total blood volume (2 x 80 mls/kg).
- Use fresh whole blood <5 days old (preferably irradiated) or reconstituted packed red blood cells and fresh frozen plasma in a ratio of 3:1.
- Take baseline observations (either via monitor or manually) and record down on the Neonatal Exchange Blood Transfusion Sheet.

The following observations are recorded every 15 minutes:

- Heart rate
- Blood pressure
- Respiratory rate
- Oxygen saturation
- Skin temperature

v. Methods of ET

- One Catheter Push-pull Technique – Umbilical Venous Catheter (Refer to Malaysian Paediatric Protocol 3rd Edition for details)
- Two Catheter Push-pull Technique – Isovolumetric or Continuous Technique

In	Out
Umbilical vein	Umbilical artery
Peripheral vein	Peripheral artery
Peripheral vein	Umbilical artery

vi. Post-ET Management

- Maintain intensive phototherapy.
- Monitor vital signs: hourly for 4 - 6 hours and 4 hourly subsequently.
- Monitor capillary blood sugar: hourly for 2 hours following ET.
- Check serum bilirubin: 4 - 6 hours after ET.
- Maintain strict input and output record.
- Monitor appearance of abdomen and lower limbs with routine observations (3 - 4 hourly) for 24 hours.
- Listen for bowel sounds.
- Commence feeds after 3 - 4 hours if clinically stable, abdomen is soft and not for repeat ET.
- Observe for signs of feed intolerance: gastric aspirate, vomiting, abdominal distension.

vii. Post-ET Blood Investigations

- Full blood count including differential
- Bilirubin (total, direct and indirect) level
- Capillary blood sugar
- Serum electrolyte and calcium
- Others as indicated

Modified: Hussain Imam MI, Ng HP, Thomas T, editors. Malaysian Paediatric Protocol for Malaysian Hospitals 3rd Edition. Putrajaya; MoH: c2012)

Refer to the above protocol for more details.

APPENDIX 5

CLINICAL RISK FACTORS AND ALGORITHM FOR PREDISCHARGE SCREENING

A. Clinical risk factors to be considered with predischarge TcB or TSB levels:

1. isoimmune (ABO or Rhesus) haemolytic disease, G6PD deficiency or other haemolytic diseases
2. exclusive breastfeeding, if nursing is not going well, and/or weight loss is >8 - 10%
3. previous sibling with jaundice
4. cephalhaematoma or significant bruising
5. East Asian race

Nomogram for Predischarge Screening

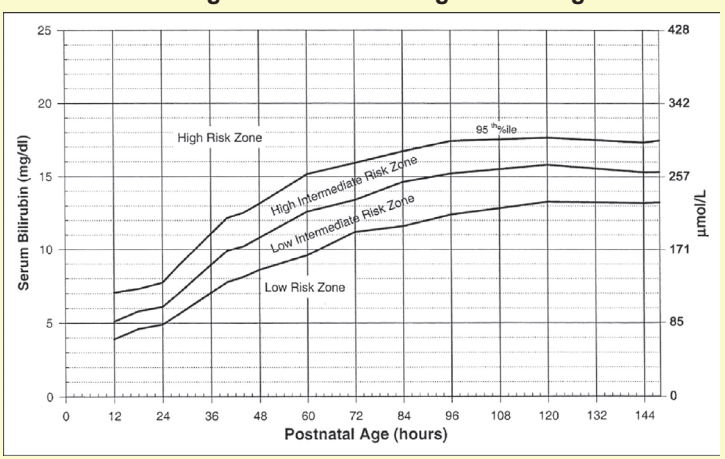

Figure 3. Nomogram for Designation of Risk at ≥36 Weeks' Gestational Age with Birth Weight ≥2000 g or ≥35 Weeks' Gestational Age with Birth Weight ≥2500 g

1. Babies with gestational age 35 – 37 weeks WITH clinical risk factors in (A) and predischarge TcB/TSB in the following risk zones:

Predisc arge Tcb/TSB Risk Zone	Action	Interval to repeat TSB
High Risk	• Check TcB/TSB against phototherapy guidelines • Start phototherapy as needed	4 - 8 hours
High Intermediate Risk	• Check TcB/TSB against phototherapy guidelines • Start phototherapy as needed	4 - 24 hours
Low Intermediate Risk	If discharging in <72 hours, follow-up within two days	Within two days at follow-up
Low Risk	If discharging in <72 hours, follow-up within two days	If jaundiced at follow-up

2. Babies with gestational age 35 – 37 weeks with NO clinical risk factors in (A) OR with gestational age ≥38 weeks WITH clinical risk factors in (A) and predischarge TcB/TSB in the following risk zones:

Predischarge Tcb/T B Risk Zone	Action	Interval to repeat TSB
High Risk	• Check TcB/TSB against phototherapy guidelines • Start phototherapy as needed	4 - 24 hours
High Intermediate Risk	• Check TcB/TSB against phototherapy guidelines • Start phototherapy as needed	24 hours
Low Intermediate Risk	If discharging in <72 hours, follow-up within two days	If jaundiced at follow-up
Low Risk	If discharging in <72 hours, follow-up within two days	If jaundiced at follow-up

3. Babies with gestational age ≥38 weeks with NO clinical risk factors in (A) and predischarge TcB/TSB in the following risk zones:

Predischarge Tcb/TSB Risk Zone	Action	Interval to repeat TSB
High Risk	• Check TcB/TSB against phototherapy guidelines • Start phototherapy as needed	4 - 24 hours
High Intermediate Risk	Follow-up in two days	Two days
Low Intermediate Risk	If discharging in <72 hours, follow-up in 2 – 3 days	If jaundiced at follow-up
Low Risk	If discharging in <72 hours, follow-up in 2 - 3 days	If jaundiced at follow-up

Adapted: Maisels MJ, Bhutani VK, Bogen D, et al. Hyperbilirubinemia in the newborn infant > or =35 weeks' gestation: an update with clarifications. Pediatrics. 2009 Oct;124(4):1193-8

APPENDIX 6

INFORMATION ON PREVENTION OF NNJ

A. Parents and carers[13, level III]

Advice that should be given to parents/carers during antenatal and postnatal visits include:

1. Look for jaundice daily during the first week of life.
2. Check the naked baby for jaundice in bright and preferably natural light, by blanching the skin with gentle finger pressure over the chest.
3. Presence of jaundice needs to be confirmed by healthcare providers; blood tests may be required.
4. Jaundice in the first 48 hours of life needs urgent review by healthcare providers.
5. Continue breastfeeding even if the baby is jaundiced. Contact a healthcare provider for assistance with breastfeeding if needed.
6. Untreated jaundice may lead to deafness and brain damage.
7. Phototherapy is a safe and effective form of treatment for neonatal jaundice.
8. Traditional and alternative methods of treating jaundice are unproven and likely to be ineffective.
9. Exposing the baby to sunlight as a form of treatment may be harmful due to dehydration and sunburn.

B. Healthcare providers

Healthcare providers should take note on the following in NNJ management:

1. Antenatal education should include NNJ.
2. Routine postnatal visits should include the detection of NNJ.
3. Effectiveness of breastfeeding should be assessed during postnatal visits. Individualised lactation support and help should be given to breastfeeding mothers.

LIST OF ABBREVIATIONS

µmol/L	micromol/litre
ABR	Auditory Brainstem Response
AAP	American Association of Pediatrics
ABE	Acute Bilirubin Encephalopathy
ABO	ABO blood group system
AUC	area under the curve
B/A	Bilirubin/Albumin
BIND	bilirubin-induced neurologic dysfunction
CI	confidence interval
cm	centimeter
CPG(s)	clinical practice guidelines
DG	Development Group
dL	deci
ELBW	extremely low birth weight
ET	exchange transfusion
FST	fluorescent spot test
FV	femoral vein
g	gramme
G6PD	Glucose-6-phosphate dehydrogenase
Hb	haemoglobin
IU	international unit
IV	intravenous
IVIg	intravenous immunoglobulin
kg	kilogramme
LBW	low birth weight
LED	light emitting diode
mg	miligramme
ml	mililitre
MoH	Ministry of Health
NICE	National Institute for Health and Clinical Excellence
nm	nanometre
NPV	negative predictive value
OR	odds ratio
PPV	positive predictive value
r	correlation coefficient
rs	Spearman's rank correlation coefficient
RC	Review Committee
Rh	Rhesus blood group system
RR	relative risk
TcB	Transcutaneous Bilirubinometer
TSB	total serum bilirubin
UA/V	umbilical artery/vein
UB	Unbound Bilirubin
UV	umbilical vein
vs	versus

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Malaysia Health Technology
Assessment Section (MaHTAS)
Medical Development Division,
Ministry of Health Malaysia
Level 4, Block E1, Precinct 1
Federal Government
Administrative Centre
62590, Putrajaya, Malaysia