

PRACTICE GUIDELINES

GUIDELINES ON EVALUATION AND MANAGEMENT OF NEONATAL JAUNDICE

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CHILD HEALTH, SINGAPORE**

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FOREWORD

Neonatal jaundice is a common physiological process that occurs in most newborns. However, jaundice can be significantly elevated in some babies and cause severe morbidity like kernicterus. Historically we have different phototherapy targets for high risk and normal risk babies, with different targets depending on the age of the child. This has led to different practices over the years with various institutions having different phototherapy thresholds. The College of Paediatrics and Child Health and the Chapter of Neonatology have initiated a workgroup to develop a National Neonatal Jaundice Guidelines, and unify a common management plan based on serum bilirubin levels. The recent development of transcutaneous bilirubinometer has also allowed for non-invasive bilirubin screening and guidelines are developed on the use.

I would like to congratulate Professor Samuel Rajadurai for leading this workgroup consisting of several experienced paediatricians, neonatologists, paediatric gastroenterology specialists, general physicians in polyclinics and nurses. They have worked tirelessly to develop this national guideline and I look forward to the successful implementation of this project.

DR LIEW WOEI KANG

President

College Of Paediatrics and Child Health, Singapore

This guideline has been divided into **two sections**:

- **Section 1:** Refers to early neonatal jaundice in the first 2-3 weeks of life
- **Section 2:** Refers to prolonged neonatal jaundice after 2-3 weeks of life

SECTION (1)

GUIDELINES ON EVALUATION AND MANAGEMENT OF EARLY NEONATAL JAUNDICE

(FIRST 2-3 WEEKS OF LIFE)

SCOPE OF GUIDELINES

Objectives and Target patient group to which it applies

This clinical practice guideline provide a framework for all healthcare professionals responsible for the care of newborn babies with jaundice

1. Neonates born at 35 weeks gestation or more AND
2. Birth weight of 2000g or more.

The objective of the guidelines is to help detect and manage optimally significant hyperbilirubinaemia and to prevent very high levels of bilirubin, which can be harmful if not treated.

STATEMENT OF INTENT

This clinical guideline is based on the best available evidence at the time of development and not intended as a substitute for appropriate clinical judgement. The interpretation and application of the guideline to the newborn infant remains the responsibility of the individual clinician.

STATEMENT OF THE EVIDENCE BASE OF THE GUIDELINES

The evidence base in this guideline is based on recommendation from the American Academy of Pediatrics Subcommittee on hyperbilirubinemia guidelines on 'Management of hyperbilirubinemia in the newborn infant 35 or more'⁽¹⁾ and the 'United Kingdom's National Institute of Clinical Excellence (NICE) clinical guidelines on management of jaundice in newborn under 28 days of age'⁽²⁾; and it has been adapted to local needs. The evidence base of prolonged neonatal jaundice guideline is drawn mainly from the NICE clinical guidelines⁽²⁾ and ESPGHAN/NASPGHAN guidelines⁽³⁾

A. INTRODUCTION

BACKGROUND

Neonatal Jaundice (NNJ) or hyperbilirubinaemia is one of the commonest conditions in the neonatal period. It is clinically detectable when the serum bilirubin levels are over 85 $\mu\text{mol/L}$. Approximately 60% of term neonates and 85% of preterm neonates will develop jaundice, mostly as physiological jaundice which is usually benign. However, jaundice can be pathological when serum bilirubin levels rise rapidly or in the presence of risk factors, with the risk of causing irreversible brain injury. It is important therefore, to identify those neonates at risk of severe neonatal hyperbilirubinemia and manage them early in order to prevent the onset of bilirubin induced neurologic dysfunction (BIND) and kernicterus.¹

B. DEFINITIONS USED IN THE GUIDELINES

- (1) **Hyperbilirubinemia:** An elevation of the serum bilirubin (SB) to a level > 205 $\mu\text{mol/L}$.
- (2) **Moderate Hyperbilirubinemia:** An elevation of the SB to a level above the threshold for phototherapy for the given age
- (3) **Severe or extreme Hyperbilirubinemia:** An elevation SB to a level above the threshold for exchange transfusion.^(2,4,5)

C. EARLY NEONATAL JAUNDICE

1.1 BILIRUBIN TOXICITY AND KERNICTERUS

The relationship between the bilirubin levels and neurotoxicity is a complex one. However, the risk of developing bilirubin neurotoxicity increases with severe or extreme hyperbilirubinaemia. Unconjugated bilirubin that is not bound to albumin (free bilirubin) is a potential toxin that can cross the blood brain barrier and cause necrosis and apoptosis. Substances such as sulpha group, ceftriaxone, free fatty acids and some of the Chinese herbs viz. Chuen-Lin, Ngan-Huang and Yin-Chen⁽⁶⁾ have been known to displace bilirubin from its bound form and promote entry into the brain. Hence the above should be avoided by the lactating mother and the infant during the first month of life. The blood brain barrier is more vulnerable in preterm infants rather than in the full-term. The brain regions affected by bilirubin toxicity include the basal ganglia, cerebellum, white matter and the brainstem nuclei of the auditory and oculomotor nerves. The bilirubin deposited in the brain results in bilirubin-induced neurologic dysfunction (BIND)^(4,7).

The neurologic manifestations of bilirubin toxicity reflect the areas of the brain that are most often affected. The clinical syndromes described as the manifestations of bilirubin neurotoxicity are Acute Bilirubin Encephalopathy (ABE) and Kernicterus (Chronic Bilirubin Encephalopathy). ABE results in changes in mental status and muscle tone during the early neonatal period in the presence of extreme hyperbilirubinaemia. The clinical signs may be subtle and include lethargy, poor suck, hypotonia, and high pitched cry. This may be followed by hypertonia, opisthotonus, retrocollis and seizures. Severely affected infants may die from intractable seizures or respiratory failure⁽⁴⁾.

Kernicterus refers to the chronic and permanent sequelae of bilirubin

neurotoxicity that generally manifests during the first year of life. Majority of the infants with kernicterus have had features suggestive of ABE during the neonatal period. The late clinical signs of kernicterus include choreoathetoid cerebral palsy, dystonia, sensorineural hearing loss, limitation of upward gaze and dental enamel dysplasia.

1.1.1. Factors influencing the risk of bilirubin neurotoxicity and kernicterus

In Singapore, kernicterus used to be the leading cause of neonatal mortality and neurodevelopmental disability in the 1950s and 1960s. As a result of investigational research by late Emeritus Professor Wong Hock Boon revealed that 43% were due to red cell G6PD deficiency and 25% due to liver immaturity⁽⁹⁾. A Kernicterus Surveillance Programme in 1964 and a mass Newborn Screening Programme for G6PD Deficiency in 1965 were established, and since then deaths from kernicterus fell from 150 in 1950s to just 5 cases in 1977. This devastating disorder has virtually been eliminated in Singapore since 1990s^(10–12).

With modern neonatal care and early recognition and optimal management of hyperbilirubinaemia, the incidence of kernicterus is very rare in developed nations with a reported incidence of 0.4 to 2.7 per 100,000 live births in term and late preterm infants above 35 weeks gestation⁽⁷⁻⁹⁾. Extreme hyperbilirubinemia with SB levels over 425 µmol/L was reported to be associated with increased risk of Bilirubin Induced Neurologic Dysfunction (BIND) in term and late preterm infants. The risk increased to 1 in 8 with SB levels over 500 µmol/L⁽⁹⁾. Factors disrupting the blood brain barrier may further promote the deposition of bilirubin into the brain tissue resulting in acute bilirubin encephalopathy (ABE)⁽¹⁾ and they are mentioned below.

1.1.2. Risk factors for bilirubin neurotoxicity

- G6PD deficiency
- Isoimmune haemolytic anaemia (e.g. ABO or Rh incompatibility & others)
- Prematurity
- Perinatal asphyxia
- Sepsis
- Acidosis
- Temperature instability
- Hypoalbuminaemia, defined as serum albumin less than 30 g/L

1.2 PHYSIOLOGICAL JAUNDICE (NON-PATHOLOGICAL HYPERBILIRUBINEMIA)

Physiological jaundice is caused by a number of mechanisms including increased bilirubin production, red blood cell (RBC) volume and ineffective erythropoiesis and also contributed by decreased RBC survival, defective uptake of bilirubin from plasma, decreased conjugation and hepatic excretion. It often appears 2 - 3 days after birth. The serum bilirubin (SB) level rises to a peak of 105 – 140 $\mu\text{mol/L}$ by day 3 to 5 in most full-term infants; in some infants a level up to 205 $\mu\text{mol/L}$ is not uncommon. The jaundice often resolves in the first two weeks of life in term infants whereas in preterm infants resolution of jaundice may take up to three weeks. It is benign and not associated with underlying disease nor requires any specific treatment.

1.3 PATHOLOGICAL JAUNDICE

Certain group of infants are more prone to pathological hyperbilirubinaemia and should be monitored for jaundice more closely. This group includes preterm / low birth weight infants, G6PD deficiency, ABO / Rhesus incompatibility, inadequate breast feeding, infants of diabetic mothers, and infants with polycythaemia and cephalohematoma. The occurrence of visible jaundice during the first

24 hours of age should be considered pathological until proven otherwise. For the purpose of clinical management and risk stratification of neonatal jaundice please refer to Table 3.

1.4 G6PD DEFICIENCY

Earlier studies during the 1960s showed that G6PD deficiency occurred in 2.5% of overall Singapore's population, and affected newborns are at risk for severe neonatal hyperbilirubinaemia and kernicterus^(10,11). Analysis of data from 22,830 newborns at the National University Hospital revealed an overall incidence of 1.62% G6PD deficiency, with 3.15% in males and 0.11% in females. A distinct racial variation in the incidence of G6PD deficiency was also observed in this study amongst male infants (Chinese 3.94%, Malays 2.95% and Indians 0.66%). Intermediate deficiency was most frequently identified (1.83%) in Chinese female infants⁽¹²⁾. Over the past 4 decades, neonatology units in local restructured hospitals have monitored affected newborns for 14 to 21 days after birth as inpatients because of the risk of severe hyperbilirubinemia. This practice is unique to Singapore and originated from the Kernicterus Surveillance Programme. Subsequent studies done in the local population revealed that in G6PD deficient babies, significant hyperbilirubinaemia usually occurred during the first week of life only and up to 43% to 55% of infants never developed hyperbilirubinemia. Hence the duration of hospitalisation has been cautiously reduced to 7 days from early 2000 and currently to the first 3 days. After discharge, these infants are closely monitored for jaundice and anaemia on an outpatient basis, either in the polyclinics or hospital setup during the first 14 days of life. Such an evidence-based early discharge of these high risk infants has decreased the social, emotional and financial burden of G6PD deficiency in Singapore and facilitated breast feeding and maternal - infant bonding without any reported case of Kernicterus⁽¹²⁻¹⁶⁾.

1.5 ETHNICITY

Even among the Asians racial factor is an important contributory factor for hyperbilirubinaemia. A local study a multi-ethnic cosmopolitan community suggested that Chinese race is a significant risk factor for jaundice and phototherapy, especially so if exclusively breastfed as compared against Malay or Indian ethnic groups. Chinese neonates who were totally breastfed had a higher risk for jaundice [adjusted odds ratio (OR) = 1.64; 95% confidence intervals (CI), 1.11-2.44; $P < 0.014$], and phototherapy (adjusted OR = 2.75; 95% CI 1.77-4.27; $P < 0.001$) compared to those supplemented with, or totally formula fed⁽¹⁷⁾.

1.6 UGT1A1 GENETIC POLYMORPHISMS

In the hepatocytes, the enzyme uridine diphospho-glucuronate glucuronyltransferase (UGT1A1) catalyses the conjugation of bilirubin with glucuronic acid, resulting in more water soluble forms of conjugated bilirubins that are excreted in the bile. Inherited deficiencies and polymorphisms of the conjugating enzyme gene (UGT1A1) can cause severe hyperbilirubinemia⁴. In addition, a mutation in the UGT1A1 gene that is common among the East Asians contributes to an increased risk of severe hyperbilirubinemia in the absence of haemolysis. This may predispose to kernicterus if untreated. A study in Singapore has shown genetic polymorphisms, such as the G71R mutation in the UGT1A1 liver enzyme which is responsible for bilirubin conjugation, are associated with a higher risk of prolonged jaundice and the need for phototherapy⁽¹⁸⁾.

D. RECOMMENDATIONS

I. IDENTIFICATION AND ASSESSMENT OF NEONATAL JAUNDICE

(1) Care for all babies

1. Babies with any of the risk factors mentioned above, who are likely to develop significant hyperbilirubinaemia should be identified early and monitored more closely for neonatal jaundice
2. In all babies
 - a. Risk factors for increased likelihood of neonatal jaundice should be assessed
 - b. All babies should be examined for jaundice at every opportunity in the first week of life.
 - c. Visual inspection of baby for jaundice should be done preferably in natural light.
 - d. Visual inspection alone should not be relied upon to estimate severity of jaundice
3. All babies with clinically suspected jaundice in the first two weeks of life should have a transcutaneous or serum bilirubin measured to estimate severity of jaundice
4. Babies with higher risk of developing jaundice should be examined more frequently
5. **In all babies with visible jaundice occurring at *less than 24 hours old*, serum bilirubin measurement must be done urgently and appropriate treatment commenced as soon as possible.**

(2) Measurement of Bilirubin levels

i. Total Serum Bilirubin (SB) measurements

1. ***Measurement of Total Serum Bilirubin (SB) remains the gold standard for diagnosis and monitoring of neonatal jaundice in newborn infants, regardless of the age and gestation.***
2. SB measurement is based on the analysis of plasma or serum samples using spectro-photometry. This technique requires a neonatal blood sample usually from a capillary heel-prick.
3. SB levels must be taken in the following situations (refer to Figure 1; Annex 1):
 - a. Babies who are visibly jaundiced at less than 24 hours of age (early onset)
 - b. Babies who are born at less than 35 weeks gestational age (preterm)
 - c. Babies who are receiving phototherapy or received phototherapy in the past 24 hours.
 - d. Whenever transcutaneous bilirubin (TcB) screening exceeds phototherapy threshold or above 250 $\mu\text{mol/L}$
 - e. Whenever transcutaneous bilirubinometer (TcB) is unavailable
4. Both venous and capillary TSB results should be considered equivalent measures.
5. *Total serum bilirubin (SB) levels should be used to determine management and conjugated (direct) bilirubin levels should not be subtracted from total bilirubin when making management decisions for neonatal jaundice.*

ii. Transcutaneous Bilirubin (TcB) Measurements

Transcutaneous Bilirubinometry (TcB) is a helpful screening tool that can aid in the evaluation of the jaundiced neonate when it is used by trained healthcare professionals. TcB does not replace clinical evaluation of the jaundiced neonate when making treatment decisions.

First trialled in a Singapore hospital⁽¹⁹⁾ in 1982, TcB is based on the principle of directing light into the skin of a neonate and measuring the intensity of the specific wavelength that is returned. The number of wavelengths used is variable in different transcutaneous bilirubinometers. The meter analyses the spectrum of optical signal reflected from the neonatal subcutaneous tissues. These optical signals are converted to electrical signals by a photocell, which are analysed by a microprocessor to generate a bilirubin value.

Numerous non-randomised published studies⁽²⁰⁻²³⁾ had reported on the diagnostic accuracy and clinical effectiveness of using TcB for predicting SB. The studies differed in terms of the model of transcutaneous bilirubinometer (JM-101®, JM-102®, JM-103®, BiliCheck®, Bilicare®), site of applying the optic head (forehead, sternum, back), and patient demography. In screening with TcB, the sensitivity and negative predictive value (NPV) are more important than the specificity and positive predictive value respectively. This is because low sensitivity of a screening test caused by false negative results would miss cases needing treatment.

The 3 large unpublished studies⁽²⁴⁻²⁶⁾ that were performed locally using Minolta JM 103 bilirubinometer yielded higher sensitivity than that reported from the west. In a study paired SB and TCB values obtained with from 311 inpatient babies <96 hours of age, revealed that all babies meeting age specific SB based phototherapy criteria could be identified with a TCB that was 90% of the phototherapy criteria and could yield a 50% reduction in the

rate for doing a SB with a sensitivity of 100%, specificity 60% and zero False negative rates⁽²⁴⁾. Comparison of 1072 paired SB and TCB values from a cohort of 484 three to fourteen day old infants showed TCB values that were 90% of the SB based Phototherapy criteria yielded accuracy and sensitivity rates of 90% and 100% respectively. ROC curves for SB's of 220, 260 and 300 on Days 3, 4 and >4 respectively showed that all cases could be identified with a very low (<15%) false positive rate if the TCB cut offs were 90% of the respective TSB values⁽²⁵⁾. A study of 759 infants 1-15 days old, showed very good TcB vs. SB correlation using both BiliCheck® as well as JM103® bilirubinometers, over forehead and sternum. (Correlation co-efficients- JM103® sternum $r = 0.894$, JM103®-Forehead $r = 0.877$, BiliCheck®-Forehead $r = 0.847$; BiliCheck®-Sternum $r = 0.867$, $p < 0.001$)⁽²⁶⁾.

TcB is useful for serial monitoring of jaundice in neonates who are *not* receiving phototherapy, particularly in an outpatient setting. ***The main goal of TcB measurement is to identify jaundiced neonates who require SB measurement*** and thereby reduce the number of invasive tests required for TSB measurement.

The advantages of using TcB for screening neonatal jaundice include the accuracy, non-invasive measurement, rapid reading, repeatability, reliability, competency and cost effectiveness in terms of reduction in blood sampling in about 60% of infants. The main pitfall of transcutaneous bilirubinometry lies in the risk of under-reading the true SB (*false negative*) which may lead to missed opportunity for SB sampling and therefore early treatment. This is especially pertinent in the first few days of life when jaundice is still on the rise, such that a correct decision to repeat screening 24 hours later based on a (falsely) low TcB may lead to sudden increase in bilirubin levels above treatment thresholds the next day.

Eligibility Criteria for Transcutaneous Bilirubinometry (TcB) Screening

1. Babies born at ≥ 35 weeks gestational age
2. Babies up to 14 days old.

Note that TcB is not recommended for screening the following groups of neonates and total serum bilirubin must be taken instead:

1. Visibly jaundiced babies who are less than 24 hours old
2. Preterm babies who are born at 34 weeks gestational age or less
3. Babies with significant oedema or capillary perfusion issues
4. Unwell babies
5. Babies who are on phototherapy or received phototherapy within the last 24 hours
6. Babies with TcB values more than 250 $\mu\text{mol/L}$ regardless of age

Several reports including two large local studies suggested that TcB may under- or over-estimate the serum bilirubin measurement by a margin of up to $\pm 30\mu\text{mol/L}$. While over-estimation of the true bilirubin value leads to unnecessary and painful heel-prick sampling but with no impact to long-term outcome, it is more essential for a healthcare professional to minimize risk of under-estimating bilirubin increases.

The following principles should be followed when using TcB as a screening modality:

- Blood sampling for SB is required whenever TcB screening reaches or exceeds 80% of age-based phototherapy thresholds that were based on serum levels.
- The decision to initiate phototherapy must be based on the SB (not TcB) result.

- When a neonate is already undergoing phototherapy, further monitoring of jaundice should be based on SB (and not TcB) results to guide decision-making for continuation or discontinuation of phototherapy.

Using transcutaneous bilirubinometer

- Some bilirubin meters require daily calibration. Users are advised to refer to manufacturer’s recommendations when using this equipment
- The calibration record should be kept with the machine. Before the first use , the calibration record should be checked
- TcB measurements could be done in sternum or forehead. Measurement over Sternum is the preferred site as it gives better correlation with SB⁽²⁶⁾.

Table 1 shows TcB cut-off readings to trigger TSB measurement in **NORMAL** risk neonates (based on 80% of the phototherapy & exchange transfusion threshold)

Normal Risk (based on 80% of values)	
Age	TcB value
0 - 12 hours	80
13 - 24 hours	120
25 - 36 hours	160
37 - 48 hours	180
49 - 72 hours	200
73 - 96 hours	220
97-120 hours	220
121 hours - 7 days	240
8 – 14 days	≥250

Table 2 shows TcB cut-off readings to trigger TSB measurement in **HIGH risk neonates** (based on 80% of the phototherapy & exchange transfusion threshold)

High Risk (based on 80% of value)	
Age	TcB
0 - 12 hours	80
13 - 24 hours	120
25 - 36 hours	140
37 - 48 hours	160
49 - 72 hours	180
73 - 96 hours	200
97- 120 hours	200
121 hours - 7 days	220
8 – 14 days	240

II. MANAGEMENT OF NEONATAL JAUNDICE

(1) Risk Stratification in Neonatal Jaundice

Certain group of infants are at a higher risk of severe hyperbilirubinemia and should be more closely monitored and early treatment with phototherapy should be considered (refer to Figure 1; Annex 1).

For management purposes, neonates with jaundice are classified into “normal risk” and “high-risk or at-risk” babies

Table 3 Risk Stratification in neonatal jaundice

Normal Risk	High risk for severe hyperbilirubinemia
Any baby who is not in the “at-risk” category*	<ol style="list-style-type: none">1. Visible jaundice within 24 hours of age2. G6PD deficiency & other haemolytic conditions3. ABO incompatibility * <i>defined as Mother Blood Group O, Baby Blood Group A/B, AND DCT positive or maternal “Anti-A” or “Anti-B” IgG antibody titres ≥ 128.</i>4. Rhesus incompatibility5. Rapidly rising serum bilirubin ($>103 \mu\text{mol/L}$ per day)6. Late preterm (35-36 weeks)7. Asphyxia (Apgar ≤ 5 at 1 and 5 min)8. Family history of severe NNJ in siblings needing exchange transfusion9. Inadequate breast feeding plus weight loss $\geq 10\%$10. IUGR infants with Birth Weight 2000 - 2500 <p><i>* NB: If mother’s group & antibody titres unknown, manage the baby as ‘High Risk’ until the results are available</i></p>

*The following group of infants in the second week of life (8-14 days of age) could be considered as normal risk

1. Mother's group & antibody titres still unknown
2. Exclusive breast feeding who had weight loss $\geq 10\%$ & regained normal weight

(2) Investigation For Underlying Disease

Apart from clinical examination and assessment of the hydration (breastfeeding) status, babies with significant hyperbilirubinaemia must be assessed for an underlying aetiology. The following tests are considered as first line investigations:

1. Total serum bilirubin measurement
2. Blood groups of Mother and Baby (antibody titres in mother)
3. Direct Coomb's test (DCT) for baby
4. G6PD screening (if not done earlier)
5. Full blood count including haemoglobin, haematocrit, reticulocytes, blood film

In jaundiced babies who are unwell, further investigations will be necessary depending on the suspected cause, for example: sepsis work-up where infection is suspected.

(3) Management: Information To Parents

1. All Parents or carers should be offered information about neonatal jaundice that is tailored to their needs and expressed concerns.
2. Parents should be informed
 - a. factors that influence the development of significant hyperbilirubinaemia

- b. how to check the baby for jaundice
 - c. what to do if they suspect jaundice
 - d. the importance of recognising jaundice in the first 24 hours and of seeking urgent medical advice
 - e. the importance of checking the baby's nappies for dark urine or pale chalky stools
 - f. the fact that neonatal jaundice is common, and reassurance that it is usually transient and harmless
 - g. reassurance that breastfeeding can usually continue
 - h. exposing baby to sunlight is not a recommended treatment option for neonatal jaundice
 - i. Parents should be advised against using herbs as some of them can aggravate jaundice.
3. Parental communication must be documented in writing or electronically.

(4) Management: Decision For Phototherapy Or Exchange Transfusion

Phototherapy is the mainstay in the management of neonatal jaundice. Phototherapy involves exposure of as much of the baby's skin as possible with blue fluorescent or LED lights to induce a photochemical reaction that transforms bilirubin into lumirubin isomers that are less lipophilic and more water-soluble for urinary excretion. The most effective phototherapy wavelengths are in the 460 - 490 nm range where bilirubin most strongly absorbs light. Irradiance of at least 30 $\mu\text{W}/\text{cm}^2/\text{nm}$ has been recommended⁽⁴⁾. During phototherapy administration, an opaque mask should shield the eyes, avoiding occlusion of the nostrils. Depending on the SB values, the risk factors and the rapidity of rise of bilirubin, 3 methods of phototherapy are commonly administered viz. single blue phototherapy, double blue

phototherapy and intensive phototherapy.

The principles of managing jaundice are:

- Total serum bilirubin levels (SB) should be used to make decisions about management of jaundice
- Conjugated bilirubin levels should not be subtracted from total bilirubin when making decisions
- SB levels should be regularly monitored while on phototherapy, depending on the severity of jaundice

i. Management of Jaundice

a. Phototherapy - Treatment Thresholds

In neonates with significant jaundice, phototherapy and/or exchange transfusion should be considered when the bilirubin levels exceed the age specific threshold as mentioned in this table:

Table 4 shows total serum bilirubin thresholds for phototherapy & exchange transfusion in normal risk neonates

Serum bilirubin thresholds in the Normal Risk infant		
Age	Phototherapy	Exchange Transfusion
0 - 12 hours	100	200
13 - 24 hours	150	250
25 - 36 hours	200	300
37 - 48 hours	225	350
49 - 72 hours	250	350
73 – 96 hours	275	375
97 - 120 hours	275	400
121 hours - 7 days	300	400
8 – 14 days	325	425

Table 5 shows total serum bilirubin thresholds for phototherapy & exchange transfusion in high risk neonates

Serum bilirubin threshold in the HIGH Risk infant		
Age	Phototherapy	Exchange Transfusion
0 - 12 hours	100	200
13 - 24 hours	150	250
25 - 36 hours	175	275
37 - 48 hours	200	300
49 – 72 hours	225	325
73 – 96 hours	250	350
97 – 120 hours	250	350
121 hours - 7 days	275	375
>7 – 14 days	300	375

Single Blue Phototherapy

- The exposure of one plane of body surface (e.g. either the baby’s front or back) to the phototherapy light
- Regularly turning the baby helps to maximise the exposure of all surfaces
- Repeat serum bilirubin levels should be done 12-24 hours after initiation of single blue phototherapy depending on clinical condition.
- **Babies who are on phototherapy should be offered frequent breastfeeding (additional 20-30 ml/kg/day) to prevent dehydration**

Double Blue Phototherapy

- Double Blue phototherapy is *simultaneous exposure of two body surface planes (Front & Back) to two separate sets of blue lights.*
- Ensure the baby is adequately hydrated.

- Indication: TSB within 50 $\mu\text{mol/L}$ of the exchange transfusion level or if the rate of rise of SB > 5 $\mu\text{mol/L}$ per hour.
- Repeat serum bilirubin measurement should be done 6 hours after initiation of double blue phototherapy

Intensive phototherapy

- *Intensive phototherapy maximises the exposure of all body surfaces in 4 planes* (Front, Back, right & left sides).
- Blue light should preferably be used.
- Indication: Total SB level within 25 $\mu\text{mol/L}$ of the exchange transfusion level; While exchange transfusion is being arranged (on an average it takes about 4-6 hours in many hospitals) always start the baby on intensive phototherapy.
- Correct dehydration & ensure adequate hydration
- Repeat serum bilirubin measurement should be done 3- 4 hours after initiation of phototherapy and until the SB has started to fall

Home Phototherapy

It is an option to provide conventional phototherapy at home for healthy term infants with hyperbilirubinaemia at SB levels 35-50 $\mu\text{mol/L}$ below the threshold for phototherapy (refer Table 4) and this should be done only by a specialist Paediatrician or Neonatologist. Appropriate advice including extra breast milk or formula intake to prevent dehydration should be given and the baby reviewed 24 hours later. This mode of therapy should not be used in any infant with risk factors.

b. Guidelines for Exchange Blood Transfusion

Exchange transfusion needs to be *considered* when:

- SB level reaches the threshold for an exchange transfusion and is **not decreasing** after hydration & intensive phototherapy for 4 – 6 hours

- There is associated anaemia from haemolysis
- SB level reaches the threshold for an exchange transfusion and there are factors that disrupt the blood brain barrier (e.g. acidosis, asphyxia, sepsis, hypoalbuminemia of <30 g/L), temperature instability or prematurity, significant hemolysis due to G6PD deficiency or isoimmune haemolytic disease of the newborn). In such a situation the HIGH RISK criteria for exchange transfusion need to be followed.

When multiple risk factors are present in an infant with extreme hyperbilirubinemia (e.g. prematurity AND isoimmune haemolytic disease or sepsis), professional clinical judgement by a specialist Paediatrician or Neonatologist should be sought in making treatment decisions in exchange transfusion. Early exchange transfusion may be considered in such infants.

Exchange transfusion should be considered as an *urgent treatment* under the following circumstances:

- In babies with high levels of bilirubin and who demonstrate any of the clinical features of acute bilirubin encephalopathy **and/or**
- If TSB level is **85mmol/L above** the exchange transfusion threshold
- Adequate hydration and intensive phototherapy should continue until and during exchange transfusion.

(5) Adjunct Treatment Modalities

i. Intravenous Immunoglobulin (IVIG)

A systematic review of the use of high dose IVIG has shown to reduce significantly the need for exchange transfusions with RR 0.28 (95%CI 0.17-0.47) with a number needed to treat (NNT) of 2.7 (95% CI = 2.0 – 3.8). It is recommended to consider intravenous immunoglobulin (IVIG) infusion (at a dose of 500 mg/kg over 4 hours) as an adjunct to

continuous double blue / intensive phototherapy in babies with iso-immunization from Rhesus or ABO haemolytic disease where SB level continues to rise by more than $8.5 \mu\text{mol/L/hour}^{(27)}$.

SECTION (2)

GUIDELINES ON EVALUATION AND MANAGEMENT OF PROLONGED NEONATAL JAUNDICE

(AFTER 2-3 WEEKS OF LIFE)

SCOPE OF GUIDELINES

Objectives

This guideline is to assist healthcare professionals in clinical decision making by providing well-balanced information on the management of prolonged neonatal jaundice. It is also intended to standardize clinical management by providing a systematic approach to this common condition.

Target patient group to which it applies

Infants with prolonged jaundice in the neonatal period: This guideline is not meant for the management of jaundice during the first 14 days of life which is covered in the earlier section on neonatal jaundice.

STATEMENT OF INTENT

This clinical guideline is meant to be a guide for clinical practise based on best available evidence at the time of development. It is not intended as a substitute for clinical judgement. The interpretation and application remain the responsibility of the individual clinician.

STATEMENT OF THE EVIDENCE BASE OF THE GUIDELINES

The evidence base in this guideline is drawn mainly from the NICE clinical guidelines ⁽¹⁾ and ESPGHAN/NASPGHAN guidelines ⁽²⁾.

A. INTRODUCTION

Jaundice defined as yellow discolouration of the skin, sclera and mucous membranes is a sign of hyperbilirubinaemia (total serum bilirubin more than $17\mu\text{mol/L}$).

B. DEFINITIONS USED IN THE GUIDELINES

Prolonged neonatal jaundice (hyperbilirubinaemia) is defined as:

1. Visible jaundice in infants with a gestational age of 37 weeks or lasting more than 14 days.
2. Visible jaundice in infants with a gestational age of less than 37 weeks lasting more than 21 days.
3. Conjugated hyperbilirubinaemia (CH) as direct bilirubin $\geq 20\mu\text{mol/L}$.

A list of the possible causes (not exhaustive) of prolonged jaundice is listed in Table 6. Persistent jaundice is more common in breast-fed infants compared to formula fed infants. Clinicians should be aware of the possibility of cholestasis in all cases of prolonged jaundice although testing at 2-weeks old will detect cholestasis in relatively few.

Providing there are no features in the history or on clinical examination that suggest a pathological cause (in particular, the urine and stool colour are normal and the baby is thriving), screening can be safely deferred until 3 weeks of age. However diagnosis of breast milk jaundice remains a diagnosis of exclusion. If jaundice persists beyond 3 weeks, further investigations as listed below are warranted.

Table 6 Differential diagnosis of Jaundice in Newborns and Young Infants***Unconjugated hyperbilirubinemia**

Increased production of bilirubin	<ul style="list-style-type: none"> • Physiological jaundice • Haemolysis: ABO or Rh incompatibility, erythrocyte membrane or enzyme defects (e.g. G6PD deficiency), Polycythaemia • Cephalohematoma • Infection: Sepsis, UTI
Decreased hepatocellular uptake or conjugation	<ul style="list-style-type: none"> • Prematurity • Congenital hypothyroidism • Breast milk jaundice • Drugs • Gilbert syndrome and Crigler-Najjar syndrome

Conjugated hyperbilirubinemia

Obstruction of biliary system	<ul style="list-style-type: none"> • Inspissated bile plug syndrome • Choledochal cyst • Biliary atresia • Alagille syndrome and other non syndromic bile duct hypoplasia
Systemic conditions	<ul style="list-style-type: none"> • Infection: Sepsis, UTI, CMV infection & other TORCH organisms • Acute liver injury: ischemia, hypoxia • Parenteral nutrition – associated cholestasis
Metabolic liver diseases	<ul style="list-style-type: none"> • Metabolic liver disease: Citrin deficiency, Tyrosinaemia, A1-antitrypsin deficiency, Galactosaemia, Mitochondrial

	hepatopathies
Defect of bile acid synthesis or transport	<ul style="list-style-type: none"> • Bile acid synthesis defect • PFIC-1, BESP defect, MDR3 defect

PFIC-1=progressive familial intrahepatic cholestasis-1;

TORCH=toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus and herpes simplex; UTI=urinary tract infection.

*Adapted & modified from Pan DH (4)

C. RECOMMENDATIONS

I. EVALUATION OF THE INFANT WITH PROLONGED JAUNDICE

(a) Ensure the infant does not have any life-threatening events.

It is important to recognise that prolonged jaundice may be due to sepsis, metabolic conditions and cardiovascular problems (Congestive cardiac failure, haemolytic anaemia, Alagille syndrome).

Assess airway, breathing and circulation and managed patient accordingly.

(b) History:

A thorough history is essential for evaluation:

- Prenatal and infant history- details of neonatal screening and any medications including excess Vitamin K intake.
- Feeding history- breastfeeding, formula-fed or soy formula fed
- Urine colour
- **Stool colour- any pale stools?**
- Weight gain (check birth weight and current weight)
- Any lethargy – sleep/wake/feed cycle
- Bleeding or bruising
- Any seizures or abnormal movements
- Family history- previous or recurrent miscarriages, pruritus
- Maternal fever, rash
- Any maternal medications

- Traditional/Herbal medicine
- History of cardiac conditions and vascular anomalies
- Check Inborn Errors of Metabolism (IEM) screen results from Health booklet if performed

(c) Physical Examination

- Dysmorphic feature
- Any jaundice- this is best observed under natural light
- Pallor
- Hydration status
- Hepatomegaly/Hepatosplenomegaly
- Skin rashes /Petechiae/Purpura
- Cataracts/Nystagmus
- Cardiac examination
- Hypoplastic genitals (Micropenis in Hypopituitarism)
- Direct inspection of stool and urine
- Hypotonia/ Encephalopathy

II. INVESTIGATIONS

Perform the following investigations in babies with prolonged jaundice:

- Liver function test
- Full blood count including haematocrit, blood film & reticulocyte count⁽⁵⁾
- Blood Group determination (Mother and Baby) from health booklet
- Thyroid function test-TSH and Free T4
- Urinalysis, urine reducing substances and culture (where appropriate)
- Check G6PD status
- Check results of IEM screen (if performed).

Consider referral to a paediatrician or neonatal jaundice clinic for the above prolonged jaundice workup.

If the clinics are unable to perform prolonged jaundice workup as above, check total and conjugated bilirubin as a minimum (refer to Figure 1; Annex 1). Any patients with conjugated bilirubin $\geq 20\mu\text{mol/L}$ or **acholic stools** will need early referral to a paediatric jaundice clinic/ paediatric gastroenterologist within a week.

III. RESULTS

- **Conjugated bilirubin $20\mu\text{mol/L}$ or greater is always considered pathological and should be investigated accordingly.** These infants require an urgent referral to the paediatric unit in the hospital to be seen within a week, unless patient is unwell in which case, he/she should be seen immediately. Consider consulting the paediatric gastroenterology team for further management.
- **Haemoglobin:** If there is evidence of anaemia, consider haemolytic jaundice and workup accordingly including Blood film, Direct Coombs test and reticulocytes count.

In order not to delay the diagnosis of baby with biliary atresia, **all babies with jaundice should be seen at least one more time, before the age of 6 weeks.** It is difficult to be absolutely sure that one has excluded biliary atresia if the D 14 blood test showed predominantly elevated indirect bilirubin. It is advisable to continue following up these infants. At 4-6 weeks of age, perform both the total and direct bilirubin as well as check for acholic stools (refer to Figure 2; Annex 2)

D. CONJUGATED HYPERBILIRUBINAEMIA

We defined conjugated hyperbilirubinaemia (CH) as direct bilirubin ≥ 20 $\mu\text{mol/L}$. **All CH is pathological until proven otherwise.** These infants require an urgent referral to the paediatric jaundice clinic/paediatric gastroenterologist to be seen within a week, unless patient is unwell in which case, he/she should be seen immediately.

Sepsis including urinary tract infection in a newborn infant can present as prolonged neonatal jaundice due to unconjugated as well as conjugated hyperbilirubinaemia. Another disorder to be excluded by performing thyroid function tests is congenital hypothyroidism, even if the initial screening test is normal. One needs to be aware that the current screening strategy using cord blood TSH levels may miss 5 – 10% of cases of hypothyroidism.

(1) Citrin Deficiency:

Citrin deficiency is an autosomal recessive inborn error of metabolism with a high prevalence in Asia and is associated with mutations in the SLC25A13 gene. This disorder presents as prolonged conjugated hyperbilirubinaemia due to neonatal intrahepatic cholestasis (NICCD). Local experience has shown that classic galactosaemia is rare in East-Asian infants whilst elevated galactose levels due to NICCD are more common. The carrier frequency for citrin deficiency in China is reported to be one in 65 while the carrier frequency in Singapore is reported to be one in 41. This condition need to be excluded by doing a plasma amino acid as part of the initial jaundice workup. The newborn IEM screening test may be normal, which does not exclude this disorder. Plasma amino acid analyses show significant elevation of citrulline and methionine concentrations. Plasma and urine galactose levels may be elevated and urine for reducing substances is often positive. Early diagnosis of citrin deficiency is crucial in enabling timely intervention to prevent complications, and help the infants to achieve optimal growth and development. Management consists of lactose-free soy milk or special amino acid-based formula, which helps to alleviate the

secondary galactosaemia. In addition these infants are given medium chain triglyceride (MCT) oil and fat soluble vitamin supplements^(32,33).

(2) Biliary Atresia

Biliary atresia (BA) is the most frequent identifiable cause of obstructive jaundice in infants in the first 3 months of life. The prevalence of BA varies from about 1 in 6000 in Taiwan to 1 in 18,000 in Europe. The aetiology of BA is unknown. The infant with BA may be growing well in the first few months of life. A common misconception is that BA babies show early failure to thrive. Up to 30% of infants may pass normal pigmented stools in the first weeks of life with subsequent progression to acholic stools and hepatomegaly⁽³⁰⁾. This pattern of clinical presentation is in keeping with progressive obliteration of extrahepatic bile ducts after birth.

Timely diagnosis of BA is important to optimise the outcome of Kasai portoenterostomy (surgical intervention of choice in BA) to re-establish bile flow. If the surgery is performed within 60 days of life, approximately 70% of patients will establish bile flow whilst after 90 days of life, <25% will have bile flow⁽³¹⁾. Early liver transplantation may be necessary in BA patients who did not clear jaundice.

Initial investigations include ultrasound abdomen which should ideally be performed after fasting for 4 hours. Ultrasound may reveal absence or abnormal gall bladder but it is not diagnostic of BA. Ultrasound is more useful in diagnosing choledochal cyst. Radioisotope hepatobiliary excretion studies using an immino-diacetic acid (HIDA scan) has limited specificity and is not used as a standalone test to diagnose BA. Definitively demonstrating bile flow on the other hand may be useful in excluding BA.

Liver biopsy can provide the diagnosis in more than 90% of patients. The classic pathological findings of BA include presence of bile duct proliferation, bile plugs with expansion of portal tracts. Intraoperative

cholangiogram and histology of the bile duct remnant is considered the gold standard investigation of choice for diagnosing BA.

Timely referral and early discussion with a paediatric gastroenterologist/hepatologist cannot be overemphasized for optimal diagnosis and management of biliary atresia.

E. UNCONJUGATED HYPERBILIRUBINAEMIA

(1) Breast-milk Jaundice

The most common cause of unconjugated hyperbilirubinaemia is breast milk jaundice. It can occur in up to a third of breastfed infants and peaks at 2-3 weeks old. Complete resolution may take up to 3 months or longer. Current guidelines advocate continuing breast feeding. It is however important to recognise that breast milk jaundice is a diagnosis of exclusion and any infants presenting with prolonged jaundice will require systematic workup to be performed.

(2) Hemolysis

Several haemolytic disorders may result in anaemia and jaundice. Majority of cases present as early jaundice (within first week of life) although a few may present as prolonged jaundice. The hyperbilirubinaemia from hemolysis is mainly unconjugated. Further investigations including haemoglobin level, reticulocyte counts, blood film, blood group determination and direct coombs test may be necessary as clinically indicated.

F. CONCLUSION

Prolonged neonatal Jaundice is commonly seen in the primary care setting. Cholestatic jaundice represents only a small proportion of prolonged neonatal jaundice. The majority of infants present with unconjugated hyperbilirubinaemia secondary to breastmilk jaundice. and other common causes include urinary tract infection and congenital hypothyroidism. Despite neonatal cholestasis being relatively uncommon, investigation for the aetiologies is important to obviate the grave consequences of missing BA and other treatable disorders such as Citrin deficiency and Choledochal cyst. These conditions may have well-established treatment that is life-saving if diagnosed early. This guideline is developed to provide clinicians with a systematic approach to infants presenting with prolonged jaundice. **It is not intended as a substitute for clinical judgement.** The interpretation and application remain the responsibility of the individual clinician.

G. AUDIT

In order to improve the clinical outcomes it is important to continue to monitor adherence to the guidelines and audit cases of severe hyperbilirubinaemia.

It is recommended to audit the outcome of the following:

1. Referral for Phototherapy
2. Referral for exchange transfusions
3. Cases needing ambulance referrals
4. Cases with SB levels > 360 $\mu\text{mol/L}$
5. Referrals for Prolonged neonatal jaundice

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ANNEX 1

Figure 1: Flowchart showing Management of the newborn infant with visible jaundice

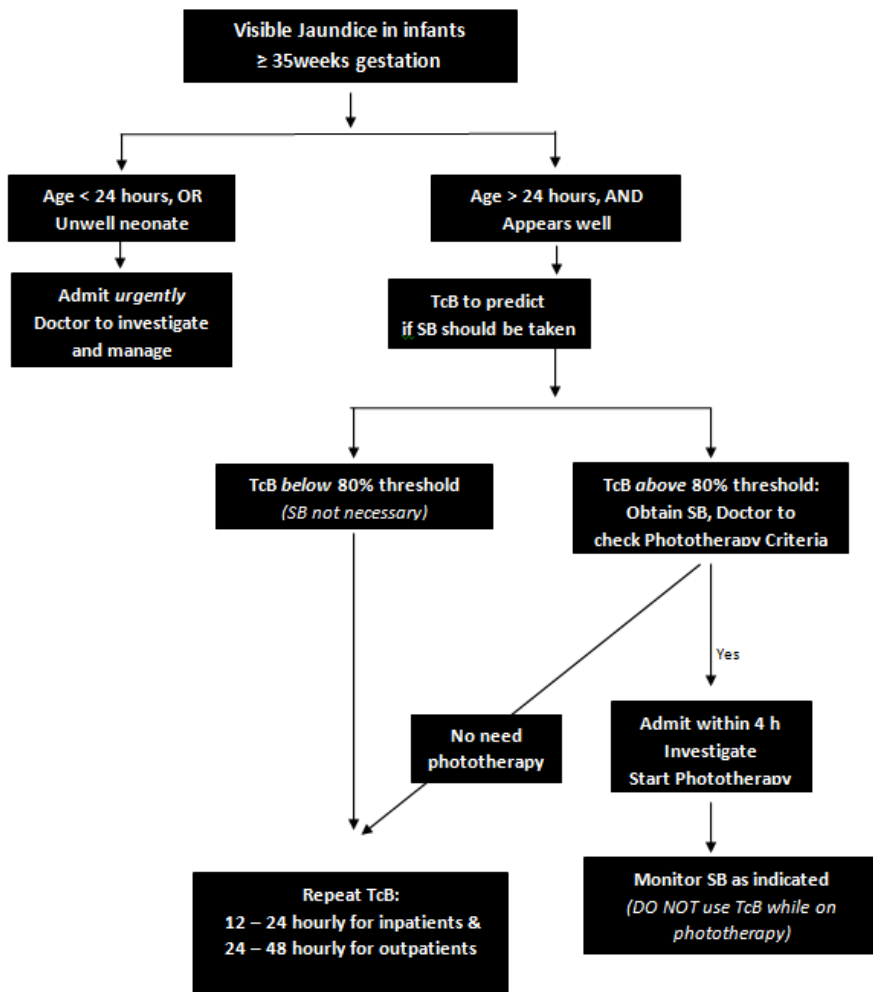


Figure 2: Recommended Screening for Infants with Prolonged Neonatal Jaundice

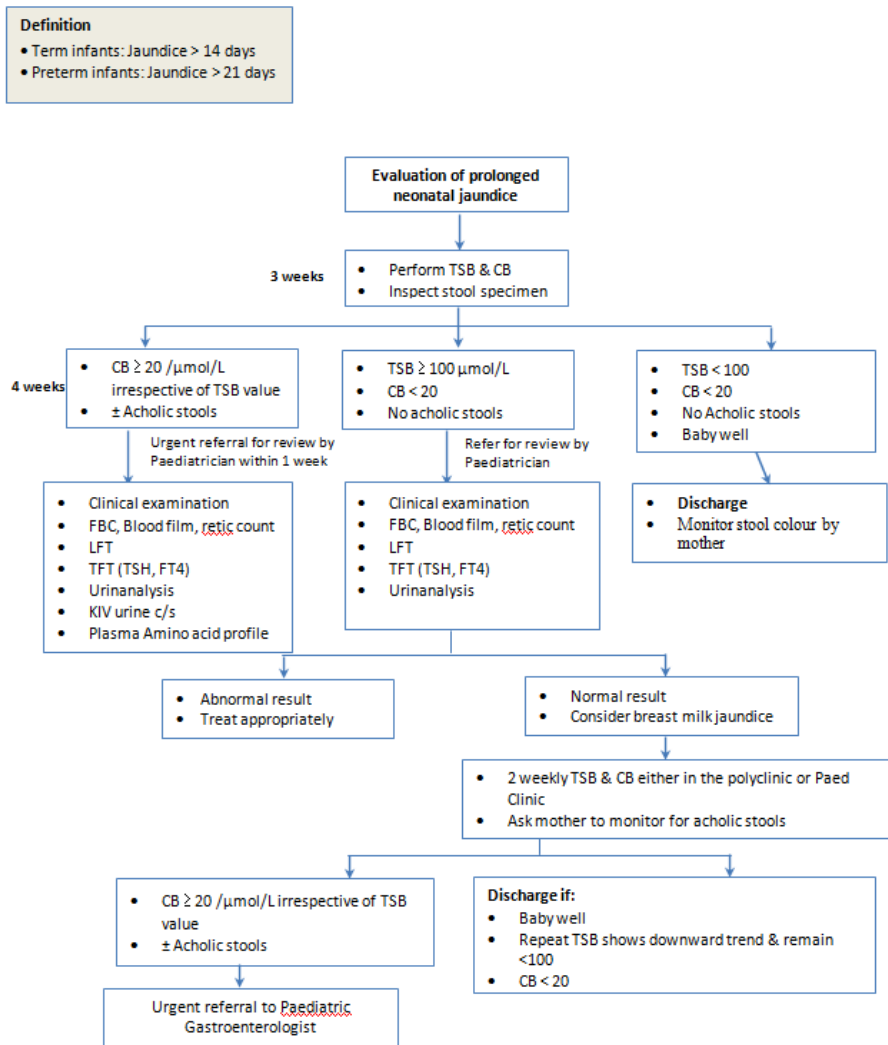
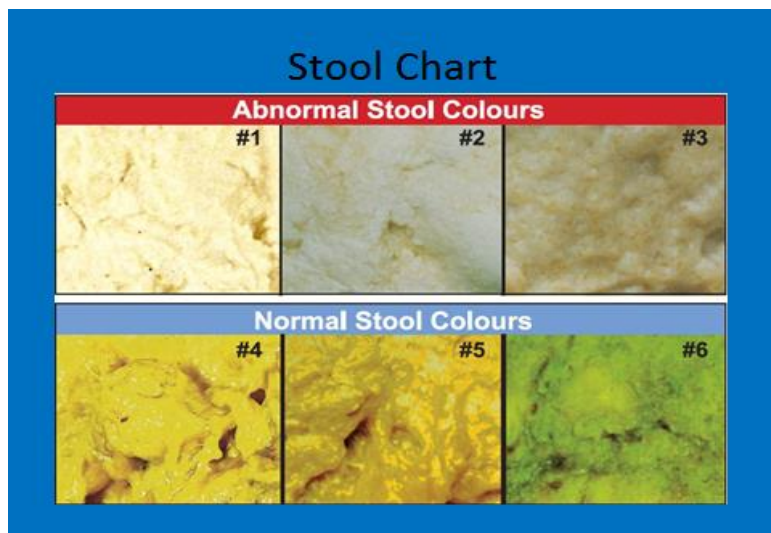


Figure 3: Infant stool colour chart



Criteria for Referral to Hospital from Primary Healthcare

- **Immediate:** to reach hospital within 1 hour, aided by an ambulance transfer if the infant has:
 - Features of an encephalopathy (sensorial and tone disturbances viz. Lethargy, poor suck, hypotonia or hypertonia etc.) in a jaundiced baby (by ambulance)
 - Serum bilirubin exceeds threshold for Exchange transfusion (By ambulance / By car)
- **Urgent:** to reach hospital within 4 hours, through self-arranged transport if:
 - TSB ≥ 300 $\mu\text{mol/L}$ but below ET threshold
 - TSB \geq age specific phototherapy value
 - Features of an illness (temperature instability, poor suck, dehydration), irrespective of the TSB value
- **For babies with Prolonged NNJ:**
 - To follow the nomogram for evaluation of Prolonged NNJ (Refer to Figure 2; Annex 2)
 - Usually it is an semi urgent referral to be seen by a Paediatrician in a week

WORKGROUP MEMBERS

The Singapore Workgroup Committee on Neonatal Jaundice

Members of “*The Singapore Workgroup Committee on Neonatal Jaundice*” comprised paediatricians and neonatologists employed at all three restructured hospitals (KK Women’s and Children’s Hospital, National University Hospital, Singapore General Hospital), one paediatrician practising in the private sector, as well as family medicine doctors from the three polyclinic clusters (National Healthcare Group Polyclinic, National University Polyclinic and SingHealth Polyclinic) in Singapore.

Workgroup Chairman

Adjunct Prof Victor Samuel RAJADURAI

Workgroup Members *(listed in alphabetical order of surname)*

Dr Abdul Haium Abdul Alim, Neonatology, KK Hospital

Cl A/Prof Daisy CHAN Kwai-Lin, Neonatal & Developmental Medicine, Singapore General Hospital

Dr Angelia CHUA Hwee Ling, National Healthcare Group Polyclinic

Assoc Prof Roy JOSEPH, Neonatology, National University Hospital

Dr LIM Kwang Hsien, Kinder Clinic Pte Ltd, Mount Alvernia Hospital

Dr Christina ONG, Paediatrics, KK Hospital

Prof PHUA Kong Boo, Paediatrics, KK Hospital

Prof QUAK Seng Hock, Paediatrics, National University Hospital

Dr Ratnaporn SIRIAMORNSARP, Singhealth Polyclinic

Dr Ruth MingLi ZHENG, National University Polyclinic

Workgroup Secretariat

Ms Ser Hui Wen, Secretariat, College of Paediatrics and Child Health Singapore (CPCHS)

Ms Elise Toh, Secretariat, College of Paediatrics and Child Health Singapore (CPCHS)

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College of Paediatrics and Child Health, Singapore
Academy of Medicine, Singapore
81 Kim Keat Road
#11-00 NKF Centre
Singapore 328836