

CLINICAL PRACTICE GUIDELINES

FEBRUARY 2003

MOH/P/PAK/62.03 (GU)

MANAGEMENT OF JAUNDICE IN HEALTHY TERM NEWBORNS



MINISTRY OF HEALTH MALAYSIA



ACADEMY OF MEDICINE

Statement of Intent

This clinical practice guideline is meant to be a guide for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily ensure the best outcome in every case. Every health care 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.

Review of the Guidelines

This guideline was issued in 2003 and will be reviewed in 2005 or sooner if new evidence becomes available

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ACKNOWLEDGEMENT

With deepest gratitude and appreciation to the following:

All members of the expert committee for their contribution in drawing up this guideline

The Ministry of Health Malaysia and Academy of Medicine for their collaboration and cooperation

All those who had provided valuable input and feedback

The secretariat for their patience, support and services rendered.

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GUIDELINES DEVELOPMENT AND OBJECTIVES

2.1 Guidelines Development

The workgroup comprised a group of paediatricians. This guideline are based on the best available current evidence and adapted from the recommendations of the American Academy of Paediatrics and The Collage of Family Physician of Canada practice guidelines the local situation.

2.2 Objectives

The aim of these guidelines is to assist health care providers in clinical decision makingby providing well-balanced information on the management of jaundice in newborns. It is also hoped to standardize clinical management.

2.3 Clinical Question

The clinical questions of these guidelines is how Jaundice in newborns been treated and also prevented?

2.4 Target Population

These guidelines are developed to apply to all healthy newborns with jaundice

2.5 Target Group

These guidelines are developed for all health care providers.

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LEVELS OF EVIDENCE SCALE

Level	Strength of evidence	Study design
1	Good	Meta-analysis of RCT, Systematic Review
2	Good	Large sample RCT
3	Good to Fair	Small sample RCT
4		Non- randomized controlled prospective trial
5	Fair	Non- randomized controlled prospective trial with historical control
6	Fair	Cohort studie
7	Poor	Case-control studies
8	Poor	Non-controlled clinical series, descriptive studies multi centre
9	Poor	Poor Expert committees, consensus, case reports, anecdotes

SOURCE: ADAPTED FROM CATALONIAN AGENCY FOR HEALTH TECHNOLOGY ASSESSMENT (CAHTA), SPAIN

SUMMARY

Jaundice is apparent clinically when the level of bilirubin in the serum rises above $85 \mu\text{mol/L}$ (5mg/dl). While in-utero, unconjugated bilirubin is cleared by the placenta resulting in a cord serum bilirubin level usually of $35 \mu\text{mol/L}$ (2mg/dl) or less. However, after birth, the level of jaundice is depend on the type of jaundice present. Continuation elevation of serum bilirubin can result in kernicterus.

When newborns present with jaundice, the following clinical assessment need to be carried out like taking history, physical examination, and assessment of severity of jaundice. If any of the following signs and symptoms: jaundice below umbilicus, jaundice up to soles of feet, rapid rise of serum bilirubin $> 8.5 \mu\text{mol/L/hr}$, prolonged jaundice > 14 days, family history of haemolytic disease/kernicterus and clinical symptoms of sepsis are present that kernicterus need to be referred for hospital management.

The choice of treatment for jaundice are phototherapy and exchange transfusion; for breastfeeding jaundice, continuation of frequent breast feeding and supplementing breast-feeding with formula, with or without phototherapy, can be considered.

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1. INTRODUCTION

1.1 What is Jaundice?

Jaundice is apparent clinically when the level of bilirubin in the serum rises above $85\mu\text{mol/l}$ (5mg/dl). While in-utero, unconjugated bilirubin is cleared by the placenta, resulting in a cord serum bilirubin level usually of $35\mu\text{mol/L}$ (2mg/dl), or less. However, after birth, the level of jaundice, i.e. physiological jaundice is a reflection of the bilirubin load to the liver, rate of hepatic excretion (liver maturity) and ability of the serum binding protein to retain the bilirubin within the plasma. The great variation in individual responses to a bilirubin load prevents the definition of a specific level as physiological jaundice - levels beyond which therapy has been shown to do more good than harm (Maisels, 1985). The pattern of physiological jaundice also varies with other factors like prematurity, ethnicity.

In hemolytic jaundice, serum bilirubin levels exceed physiological levels and can be due to sepsis and inherited hemolytic diseases like glucose 6 - phosphate dehydrogenase (G6PD) deficiency, ABO and Rh isoimmunisation.

Prolonged jaundice refers to jaundice persisting beyond the first two weeks of life in the term neonate, and causes include late onset breast milk jaundice, congenital hypothyroidism and other rare inherited conditions.

Babies with breast milk jaundice have prolonged levels of unconjugated bilirubin in otherwise healthy infants, and β glucuronidase in the breast milk appears to be an important factor in this condition. There are two types of Neonatal Jaundice associated with breastfeeding, the first known as breastfeeding jaundice is related to inadequate nursing on the breast resulting in dehydration and otherwise physiological jaundice becoming more intense; and the second is breastmilk jaundice which is associated with prolonged jaundice extending beyond the first two weeks of life. One or more substances like enzyme (glucuronidase), 3 alpha, and 20 beta pregnanediol in breastmilk is thought to be may be responsible for

breastmilk jaundice. (Kuhr, 1982 [*Level 6*]; Adam, 1985; Maisels, 1986, Saigal, 1982; De Carvalho, 1981) [*Level 7*]

1.2 What Can Go Wrong In Jaundice?

Elevated serum bilirubin can result in kernicterus, when unconjugated bilirubin is deposited in the cell wall of neurons in basal ganglia, brain stem and cerebellum resulting in cell death. Kernicterus is associated with a high mortality, and survivors usually suffer sequelae like athetoid cerebral palsy, high frequency hearing loss, paralysis of upward gaze and dental dysplasia. The factors influencing bilirubin toxicity in the brain cells of the neonate are complex and incompletely understood. There is no specific level of total serum bilirubin above which Kernicterus can be predicted to happen.

1.3 Causes Of Neonatal Jaundice (NNJ)

The following are the recognised causes of NNJ:

- Haemolysis due to ABO or Rh isoimmunisation, G6PD deficiency, hereditary spherocytosis, drugs
- Sepsis - septicaemia, meningitis, UTI, intra-uterine infection
- Polycythaemia
- Physiological jaundice & idiopathic jaundice
- Breastfeeding and Breastmilk jaundice.

1.4 Factors Affecting Severity of NNJ

The following factors are said to affect the severity of jaundice

- Dehydration
- Large weight loss after birth
- Extravasation of blood, cephalohaematoma, contusion
- Swallowed maternal blood
- Infant of diabetic mother

- Acidosis
- Asphyxia
- GI tract obstruction: increase in enterohepatic circulation

1.5 G6PD Deficiency

G6PD deficiency is an inherited disorder of the red blood cell, inherited in an x-linked recessive manner – males are affected while the females are carriers. G6PD is an enzyme essential in keeping glutathione in the reduced state that in turn is vital to maintain the integrity of the red cell membrane. In G6PD deficiency the red blood cells are prone to haemolysis when exposed to oxidants or when certain foods or herbs are ingested. A list of drugs and herbs that can precipitate haemolysis is provided in the appendix (Luzzato, 1992).

The incidence of G6PD deficiency varies among the various ethnic groups as follows - Chinese 3.1%, Malay 1.4%, and Indian 0.2% (Robinson et al., 1976). These results were obtained by using a fluorescent screening method, that had been found to be as sensitive and specific as other screening tests (Fairbanks & Fernandez 1969).

2. MANAGEMENT OF NEONATAL JAUNDICE (NNJ)

2.1 History:

The following information needs to be obtained:

- Age of onset, rate of progress of jaundice (both clinically and also if serial serum bilirubin (SB) results are available)
- Previous infants with NNJ, kernicterus, neonatal death, G6PD deficiency
- Mother's blood group (from antenatal history)
- Gestation: although term gestation is taken as 37 completed weeks,

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infants born at 37- 38 weeks of gestation are more prone to hyperbilirubinaemia, the incidence of hyperbilirubinaemia increasing with decreasing gestational age (Friedman et al., 1987, Linn et al., 1985, Maisals, 1988).

- Presence of symptoms such as apnoea, difficulty in feeding, feed intolerance and temperature instability.

2.2 Physical examination

- General condition-whether ill-looking or lethargic, presence of hypotonia, or abdominal distension.
- Pallor, presence of cephalohaematoma/subaponeurotic haematoma, petechiae, purpura, ecchymosis, and hepatosplenomegaly

2.3 Clinical Assessment of the Severity of Jaundice

When a neonate is jaundiced, the yellow discoloration of skin first appears on the face and it progresses to the trunk, to the palm of the hand, and then the sole of the feet-ie cephalo-caudal progression. The intensity of yellow discoloration also correspondingly increases from the face caudally as the severity of jaundice increases. Jaundice can be detected by blanching the skin of the neonate with digital pressure exposing the colour of the underlying skin. The severity of neonatal jaundice is assessed clinically using Kramer's chart based on dermal zones of neonatal jaundice, where the levels of serum bilirubin correlate with the area of skin that is jaundiced, as indicated in the table 1 below. This is applicable to full term infants with jaundice not due to all hemolytic conditions included Rh incompatibility.

Table 1: correlation between levels of serum bilirubin with the area of skin that is Jaundiced

Area of body	Range of indirect bilirubin mg/dl(μ mol/L)
Head & neck	4 - 8 (68 - 135)
Upper trunk	5 - 12 (85 - 204)
Lower trunk and thigh	8 - 16 (136 - 272)
Arms & lower legs	11 - 18 (187 - 306)
Palms and soles	> 18 (>306)

(NB: It may be difficult to assess jaundice in dark skinned infants).

2.4 When Should A Neonate Be Referred For Hospital Management? (When To Get Worried?)

The following are indications for referral:

- Jaundice below umbilicus, corresponding to serum bilirubin of 12-15 mg/dl (200-250 μ mol/L).
- Jaundice up to level of the sole of the feet - likely to need exchange transfusion.
- Jaundice within 24 hours of life.
- Rapid rise of serum bilirubin of more than 8.5 μ mol/L/hour (>0.5 mg/dl/hour).
- Prolonged jaundice of more than 14 days - other causes/conditions need to be excluded e.g. neonatal hepatitis, biliary atresia.
- Family history of significant haemolytic disease or kernicterus
- Clinical symptoms/signs suggestive of other diseases e.g. sepsis.

2.5 Investigations for NNJ Include:

- Total serum bilirubin - sufficient in most cases
- Unconjugated & conjugated fractions in specific conditions eg prolonged NNJ
- Infant's blood group, maternal blood group (if not already known)
- Direct Coomb's test
- G6PD status (if not already known)
- Full blood count
- Reticulocyte count
- Peripheral blood film (if hereditary spherocytosis suspected)
- Blood culture, Urine microscopy and culture (if infection is suspected)

2.6 Transcutaneous Bilirubinometry

This is an instrument measuring bilirubin level using spectrophotometry. While there is good correlation between transcutaneous serum bilirubin readings and serum bilirubin levels in term infants over the range of 10-13mg/dl (175 – 225 μ mol/L), at higher serum bilirubin levels, it has higher negative predictive values, and is thus better for screening purposes. Transcutaneous bilirubinometry had been said is sensitive and cost effective. However, gestational age of infants, sites of reading, phototherapy, and skin pigmentation can potentially affect the reliability of the readings. There is inadequate evidence to advocate the use of Transcutaneous bilirubinometry

3. TREATMENT

3.1 Phototherapy

The aim of phototherapy is to prevent potentially dangerous bilirubin levels and to decrease the need for exchange transfusion, since phototherapy changes bilirubin into more soluble forms to be excreted in the bile or urine. The effectiveness of phototherapy is affected by the intensity, or irradiance, of the phototherapy light, increased irradiance producing increased effectiveness, until the saturation dose of $40 \mu\text{W}/\text{cm}^2/\text{nm}$ of appropriate light is reached. The minimum irradiance is $6\text{-}12 \mu\text{W}/\text{cm}^2/\text{nm}$. Other factors affecting the effectiveness are the spectrum of light delivered by the phototherapy unit, the surface area of the infant exposed to phototherapy, and the distance of the light source from the baby, the optimum distance being 35 - 50 cm in conventional lights. In addition, overheating of the fluorescent lamps used in phototherapy causes a rapid decay of the phosphor resulting in incorrect emission spectrum of the lamps. Increasing bilirubin concentration has a positive effect on the efficacy of phototherapy. Finally, the postnatal age and gestational age of the infant also has a bearing, phototherapy being most effective in very small preterm infants, and least effective in severely growth retarded full term infants.

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3.1.1 Types of phototherapy

Types of phototherapy	Light wavelength (nm)	Light intensity ($\mu\text{W}/\text{cm}^2/\text{nm}$)	Color/type of bulbs
Conventional phototherapy	425 - 475	6-12	- Many variation - Blue/special blue/ - Day light fluorescent tube - Tungsten- halogen lamps
Fibre optic phototherapy (Biliblanket)	400 - 500	35 (+/- 20%)	Fibreoptic cable containing 2000 -2400 individual acrylic fibres
Intensified phototherapy		26 - 40	High intensity blue over head lamps with lamps placed below infant also Fibreoptic blanket with standard overhead phototherapy Several phototherapy lamps placed around the infant

3.1.2 The methods of providing intensified phototherapy are as follows:

- i. high intensity blue lights (F20 T12 / BB) with 7 overhead lamps, and 4 lamps placed below the infant. To mitigate the alarming blue effect, special blue tubes may be used in the central portion of a standard phototherapy unit with daylight fluorescent tubes on either side.
- ii. combined fibreoptic blanket with standard phototherapy system above, thus increasing the surface area of the infant exposed to light.
- iii. several phototherapy lamps placed around the infant, if a fibreoptic unit is not available.

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- iv. placing a white reflecting surface (e.g. sheet) around the bassinet, so that light is reflected onto the baby's skin when using a single phototherapy unit so as to increase the area of exposure.

3.1.3 Colours of phototherapy light

White light is recommended for non-hemolytic jaundice regardless of gestational age and birth weight, since it is effective, inexpensive, and adequate in most cases (Tan, 1986) [*Level 4*]. Blue light, however provides a more rapid response and shorter duration of treatment (Donzelli, 1995) [*Level 4*]. High intensity blue light is the treatment of choice for infants with rapidly increasing or high venous serum bilirubin not responding to white phototherapy as mentioned above. However, the rebound is greater, and nursing and clinical monitoring is more difficult (Tan, 1992) [*Level 4*]

Phototherapy : Practical considerations.

Position light source 35-50 cm from top surface of the infant (when conventional fluorescent photolight are used)

Expose infant appropriately

Cover infant's eyes

Turn infant every 2 hours

Monitor serum bilirubin levels as indicated

Monitor infant's temperature 4 hourly to avoid chilling or overheating

Allow parental-infant interaction

Turn off light during feeding and blood taking

Measure intensity of phototherapy light periodically using irradiance meters

Discontinue phototherapy when bilirubin is less than threshold levels and has been falling for 24 hours. In infants without haemolytic disease, the average bilirubin rebound after phototherapy is less than 1 mg/dl (17 μ mol/dl). Discharge from hospital need not be delayed in order to observe the infant for rebound, and in most cases, no further measurement of bilirubin is necessary. However, if phototherapy is initiated early and discontinued before the infant is 3 to 4 days old, additional ambulatory follow-up may be necessary

Hydration- there is no evidence to support any influence of excess fluid administration on serum bilirubin concentration. Some infants admitted with high bilirubin levels may also be mildly dehydrated, and may need fluid supplementation. More frequent breastfeeding is recommended because it inhibits the enterohepatic circulation of bilirubin and thus lowers the serum bilirubin level. Other routine supplementation e.g. with dextrose water is not indicated

Once the baby is on phototherapy, visual observation as a means of monitoring is unreliable. Serum bilirubin levels must guide the management.

3.2 Exchange Transfusion (ET)

Bilirubin levels beyond which Kernicterus may occur if an ET is not carried out have not been established. The modality of treatment should be based on the clinical history, risk factors and physical examination of the infants. The table and graph below illustrates the recommended levels for various modalities of treatment adapted from the American Academy of Pediatrics as well as the College of Family Physicians of Canada taking into consideration that Malaysian babies have been known to have higher levels of significant jaundice and consequently at higher risk of developing kernicterus.

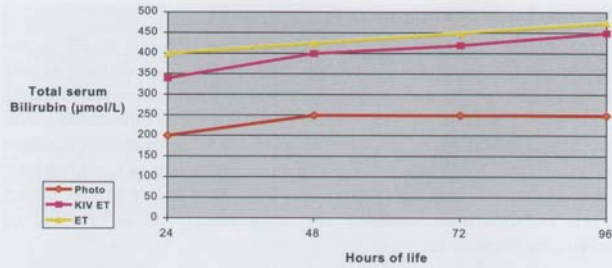
Exchange transfusion is recommended if serum bilirubin levels though declining with intensive phototherapy, persists above the level for exchange transfusion. It is also recommended in those infants whose levels continue to rise to exchange transfusion levels despite being on phototherapy. Cessation of feeds and hydration with intravenous fluids is only recommended when an exchange transfusion is impending.

Table 2: Recommended action levels for management of neonatal jaundice in healthy term newborns

Hours of life	Total Serum Bilirubin levels ($\mu\text{mol/l}$)		
	Phototherapy	ET if Phototherapy fails	ET + Intensive phototherapy
* < 24	-	-	-
24	200	340	400
48	250	400	425
72	250	420	450
>72	>250	450	475

* Term infants who are clinically jaundiced at 24 hrs. of age or less are not considered healthy and require further evaluation.

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Graph 1: Recommended action levels for phototherapy and exchange transfusion in healthy term newborns

(source: level of various modalities of treatment adapted from the American Academy of Pediatrics & College of Family Physicians of Canada)

3.3 Drug Treatment

Phenobarbitone, cholestyramine (Nicolopoulos, 1978, Tan et al., 1984) [Level 7], agar (Harold et al., 1973 [Level 8] Gerard et al., 1983, Caglayan et al., 1993) [Level 7] and vitamin E (Gross, 1979) [Level 8] have been investigated in the past to treat neonatal hyperbilirubinemia, but there is no evidence to support the use of these. More recently tin protoporphyrin and tin mesoporphyrin (Jorge, 1999, [Level 3]; Valaes, 1994 [Level 6]; Kappas 1995 [Level 3] have been used. These competitively inhibit the activity of heme oxygenase, the rate limiting enzyme in heme catabolism, thus reducing the production of bilirubin. Side effects are transient erythema at the site of the intramuscular injection of the metalloporphyrin if concomitant phototherapy is also administered. There is limited knowledge (Cooke, 1999) [Level 8] on long term effects of these drugs and hence they are currently not recommended.

3.4 Breastfeeding and Jaundice

1. Interruption of breastfeeding in healthy term newborns is discouraged and frequent breast-feeding (at least 8-10 times every 24 hours) should be continued.
2. Supplementation of breast-feeding with formula with or without phototherapy can be considered. Supplementing with water or dextrose water does not lower bilirubin level in jaundiced, healthy, breast-feeding infants (Nicoll., 1982) [Level 8]

Table 3. Treatment Options for Jaundiced Breast-fed Infants

Observe
Continue breast-feeding; administer phototherapy
Supplement breast-feeding with formula with or without phototherapy

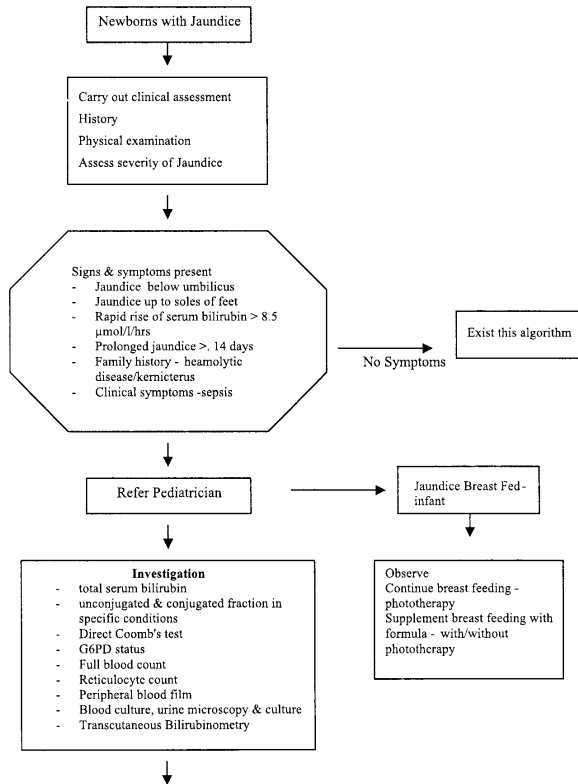
4 PREVENTIVE MEASURES FOR SEVERE NNJ

1. Maternal prenatal testing should include ABO and Rh(D) typing. When the mother is Rh-negative, a direct Coombs' test, ABO blood type, and an Rh(D) type on the infant's (cord) blood are recommended (American Academy of Pediatrics, 1992, Ministry of Health Malaysia, 1999).
2. All infants must have a glucose-6-phosphate dehydrogenase (G6PD) screening done on cord blood (Ministry of Health Malaysia, 1999). The results of G6PD screening must be known before discharge and special management is indicated for those infants found deficient (Ministry of Health Malaysia, 2000).
3. Infants whose mothers are of O blood group and infants with a strong family history of severe neonatal jaundice should be observed for at least 24 hours in the ward. If earlier discharge is necessary, arrangements must be made for these infants to be reviewed the following (Ministry of Health Malaysia, 1999).

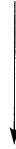
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4. Mothers must be assisted and provided support to manage breastfeeding successfully before discharge.
5. Approximately one third of healthy breast-fed infants have persistent jaundice after 2 weeks of age (Alonso, 1991). A measurement of total and direct serum bilirubin should be obtained and a history of dark urine or light stools should be sought. If the history, physical examination and direct bilirubin results are normal, continued observation is appropriate
6. Parents must be alerted to the significance of early onset (within 24 hours) and severe jaundice and advised that in these situations medical attention is necessary.
7. Follow-up should be provided to all neonates discharged less than 48 hours after birth by a health care professional in an ambulatory setting, or at home within 2-3 days of discharge (Seidman et al., 1995, Catz et al., 1995)

5. Algorithm Management of Jaundice in Healthy Terms Newborns



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Measure infant Total Serum Bilirubin



Hours of life	Total Serum Bilirubin Levels ($\mu\text{mol/l}$)		
	Phototherapy	ET if Phototherapy Fails	ET + Intensive Phototherapy
* < 24	-	-	-
24	200	340	400
48	250	400	425
72	250	420	450
>72	>250	450	475

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