

NEONATAL MEDICAL CONDITIONS

3 HYPERBILIRUBINAEMIA AND NEONATAL JAUNDICE

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3 Hyperbilirubinaemia and Neonatal Jaundice
Neonatal Postnatal
Clinical Guidelines
King Edward Memorial Hospital
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ABBREVIATIONS

CBR	Conjugated bilirubin	ABO	Blood Group type A, B, O
SBR	Serum bilirubin	DAT	Direct Antibody Test
TcB	Transcutaneous bilirubin	Rh	Rhesus
UBR	Unconjugated bilirubin	PTx	Phototherapy
G6PD	Glucose-6-phosphate dehydrogenase deficiency		

KEY POINTS

1. All neonates with clinically identifiable **jaundice <24 hours of age should be considered high risk** and have a SBR performed immediately to determine a 'baseline' and need for phototherapy. Haemolysis is the commonest cause.
2. The AAP Guideline graph for commencing and ceasing phototherapy can be found with the Jaundice QRG in the Post-natal ward guidelines. All infants who are commenced on phototherapy should have a direct antibody test (DAT) and repeat SBR performed within 24 hours (or earlier, depending on risk factors).
3. Neonates born to Rh(-) mothers in whom red cell antibodies have been identified during the pregnancy, or who have not had antenatal blood group screening performed, should have a blood group and DAT performed on cord blood.
4. When assessing the need for phototherapy using the SBR, the total serum bilirubin level (i.e. SBR) value should be plotted on the appropriate graph and interpreted against the baby's age in hours from birth. The conjugated bilirubin fraction should not be subtracted from the total. In cases where the conjugated bilirubin is >20 µmol/L or the fractional component is >20% this should be considered pathological jaundice until proven otherwise and management should be discussed with the Paediatric consultant / senior registrar on call.
5. Hyperbilirubinaemia may be managed using phototherapy, exchange transfusion or pharmacological means, of which phototherapy is the preferred method. The rate of rise of SBR in many instances is of greater value than the absolute value in determining the need for escalation of therapy, including the consideration for admission to SCN/NICU for exchange transfusion. In general, infants at high risk for haemolysis should initially have a SBR performed on at least two occasions 4-6 hours apart in order to obtain an accurate assessment of the 'rate of rise'. Bilirubin levels rising ~10µmol/L/Hr represent aggressive haemolysis and require SCN admission, maximal phototherapy and consideration for exchange transfusion.
6. Neonates in whom 'physiological' jaundice is considered to be present, may be managed on the post-natal wards, with attention to adequate feeding and hydration state. Following cessation of phototherapy (if required), delay of discharge pending SBR testing to exclude 'rebound' is unnecessary, providing ongoing clinical evaluation for jaundice can occur over subsequent days (i.e. either via visiting midwifery service, or outpatient SBR testing).
7. Sunlight exposure is NOT recommended for the management of hyperbilirubinaemia since it is an uncontrolled source of multiple wavelengths of light, only a limited spectrum of which is appropriate for management of jaundice. Sunburn is a risk and parents should be discouraged from using this approach.

RISK FACTORS

High Risk:

- J Jaundiced at <24hrs
- A A sibling who needed PTx as a baby, Antibodies (to minor antigens)
- U Unrecognised haemolysis
- N Non-optimal feeding / sucking
- D Deficiency of G6PD
- I Infection, In-utero transfusion
- C Cephalhaematoma or bruising
- E Ethnicity (e.g. East Asian, Mediterranean, African), Early delivery (preterm)

BACKGROUND INFORMATION

Jaundice occurs in ~60% of term newborns and 85% of preterm infants as a result of elevated serum bilirubin levels. Hyperbilirubinaemia may be unconjugated (i.e. lipid soluble, pre-hepatic phase) or conjugated (i.e. water soluble, post hepatic conjugation) in nature. Unconjugated hyperbilirubinaemia whose onset precedes 24 hours of life, or is prolonged beyond 14 days should be considered pathological until proven otherwise. Conjugated hyperbilirubinaemia represented by an absolute value of 20 $\mu\text{mol/L}$ or >20% of the total serum bilirubin (SBR) is always pathological and must be investigated in consultation with senior Paediatric staff. Phototherapy is indicated in unconjugated hyperbilirubinaemia to prevent acute bilirubin encephalopathy and kernicterus (chronic bilirubin encephalopathy) arising as a consequence of deposition in the basal ganglia and certain brainstem nuclei. Charted guidelines exist for the initiation of phototherapy in infants with and without other risk factors and the American Academy of Paediatrics (AAP) guideline used at KEMH is available by clicking 'QRG' in the Jaundice Section of these guidelines.

NOTE: This protocol focusses on unconjugated hyperbilirubinaemia and its management, since this is the problem most commonly encountered on the post-natal ward. All cases where conjugated hyperbilirubinaemia are suspected clinically (e.g. pale stools, very dark urine, 'green-yellow' jaundice) should be discussed urgently with senior Paediatric staff.

ACUTE AND CHRONIC BILIRUBIN ENCEPHALOPATHY (KERNICTERUS)

Acute Bilirubin Encephalopathy

The acute manifestations of bilirubin toxicity may be observed in the first weeks after birth and include;

- Hypotonia
- Poor feeding
- High pitched cry
- Lethargy

Progression of symptoms may occur;

- Hypertonicity with opisthotonus or retrocollis
- Seizures
- Impaired conscious state, coma

Kernicterus - Chronic Bilirubin Encephalopathy

Kernicterus is a pathological diagnosis whereby unconjugated bilirubin is deposited in the basal ganglia and brainstem nuclei. The clinical picture is unremitting and the pathological changes are permanent in nature, resulting in chronic neurological impairment, neuro-cognitive delay and dysfunction of motor control and tone. Neurological features include;

- Athetoid cerebral palsy
- Sensori-neural deafness
- Seizures
- Developmental delay
- Oculomotor dysfunction
- Neuro-cognitive impairment

DIAGNOSTIC EVALUATION

Timing of Onset

Early onset (<24 hours) and aggressive jaundice

Jaundice occurring within the first 24 hours of life should always be considered pathological. Haemolysis resulting from major or minor blood group antigen incompatibility is the most common cause of early and aggressive haemolysis. Early aggressive phototherapy, admission to SCN and consideration for exchange transfusion may be necessary. In circumstances where the risk of haemolysis is significant (e.g. known Rh-isoimmunisation in utero or elevated titres to red cell minor antigens), collect:

1. Serum bilirubin level and direct antibody test (DAT) should be collected from cord blood (cord blood tube).
2. FBP (0.5mL EDTA) should also be collected but must be from a venous or capillary sample not cord blood.

SBR should be monitored initially every 4-6 hours using the appropriate chart to determine the 'rate of rise', to determine the appropriate amount of phototherapy, and if necessary, to prepare for the possibility of IVIG administration or exchange transfusion. An increase in SBR of 10µmol/L per hour is considered significant and is likely to necessitate multiple-lamp phototherapy, IVIG and potentially exchange transfusion. All infants in this category should be discussed with the Paediatric consultant on call as a matter of urgency.

Causes of early jaundice include;

- Haemolysis
 - Rhesus Iso-immunisation
 - Minor red cell antigen incompatibility
 - ABO incompatibility
- Sepsis
- Rarer causes
 - Red cell enzyme defects (e.g. G6PD)
 - Red cell membrane defects (e.g. hereditary spherocytosis)
 - Crigler-Najjar Syndrome

Jaundice between 24 hrs and 14 days

Jaundice occurring after the first 24 hours and lasting less than 14 days is most commonly physiological in nature. Causes of hyperbilirubinaemia with onset during this period include;

- Physiological jaundice

- Haemolysis
- Breakdown of extravasated blood
- Sepsis
- Polycythaemia

Prolonged or Late Onset Jaundice (>10-14days)

Jaundice in which the onset is relatively late (i.e. >10 days), or is prolonged should be considered pathological until possible aetiological factors have been excluded. Unconjugated hyperbilirubinaemia may occur in isolation, or in association with elevated conjugated bilirubin (e.g. idiopathic neonatal hepatitis, TORCH infections). Causes of prolonged or late-onset jaundice include;

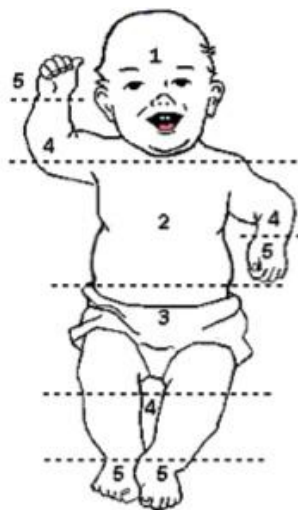
- Ongoing haemolysis (e.g. ABO incompatibility)
- Hypothyroidism (most detected on day 3 via the newborn screening card)
- Sepsis / urinary tract infection
- Breast milk jaundice (peak around day 7-14, duration up to 6 weeks after birth)

Causes of jaundice characterised by either conjugated hyperbilirubinaemia or mixed conjugated and unconjugated hyperbilirubinaemia include;

- TORCH infections (e.g. Toxoplasmosis, Rubella, cytomegalovirus, Herpes Simplex virus)
- Sepsis
- Congenital biliary tract obstruction (e.g. Biliary atresia, choledochal cyst)
- Metabolic disorders (e.g. Hypothyroidism, Galactosaemia, α 1-antitrypsin deficiency)
- Haemochromatosis
- Idiopathic neonatal hepatitis

Clinical Assessment

All newborns should be assessed at least every 8 to 12 hours for jaundice. Appearance and progression tends to occur in a cephalo-caudal manner. Kramer's Rule provides a mechanism for the clinical assessment of jaundice severity by the proportion of the skin involved. Whilst this provides a useful guide, visual estimation of jaundice severity is prone to error, and is particularly difficult in darkly pigmented infants. All infants in whom the severity of jaundice is in question, especially those with risk factors, should have a transcutaneous bilirubin or serum bilirubin measurement performed.



Zone	1	2	3	4	5
Definition	Head and neck	Upper trunk	Lower trunk and thighs	Arms and lower legs	Palms and soles
TSB (micromol/L)	100	150	200	250	>250

Figure 1. Kramer's Rule

INVESTIGATIONS

Categorisation of risk in Neonatal Jaundice

Infants at HIGH RISK for early / aggressive jaundice

Infants at high risk for early and / or aggressive jaundice include those with raised antibody titres to red cell antigens, especially Rhesus and some minor group antigens. Women who are Rh(-) or in whom red cell antibodies have been detected have generally been monitored during pregnancy. Repeated titre results may be available. In severe cases of Rhesus isoimmunisation, intra-uterine blood transfusion may have been administered. These infants are at increased risk for unconjugated hyperbilirubinaemia. The following investigations should be performed:

- Review maternal notes
 - Blood group and Rhesus status
 - Anti-D administration status
 - Presence of any red cell antibodies and changes in titre concentrations
 - Presence of foetal hydrops, pleural/peritoneal effusion, anaemia, cardiac failure
 - Need for intra-uterine blood transfusion
- At birth on cord blood, perform:
 - SBR
 - Direct Antibody Test
- At birth on venous or capillary blood, perform,
 - FBP

A repeat SBR should be performed 4-6 hours later in order to monitor the rate of rise and enable commencement of early phototherapy and preparation for intravenous immunoglobulin or exchange transfusion as necessary.

Jaundice in the late preterm infant

Prematurity is a risk factor for earlier and more severe jaundice. The threshold for investigating and treating jaundice in infants ≤ 37 weeks gestation should be reduced in comparison to term-born infants. This is especially important in the presence of other risk factors, such as sepsis, Rhesus or other group incompatibility. The AAP graph (see QRG) provides a guide for assessing risk and treatment threshold for jaundice in the late preterm infant. The AAP subcommittee for management of hyperbilirubinaemia in neonates considers gestation 35-36 w a *major risk factor* for severe hyperbilirubinaemia, with gestation 37-38 weeks a *minor risk factor*.¹

Infants with risk factors for non-physiological or jaundice potentially resistant to phototherapy

Physiological jaundice usually presents between 24 hours and 7 days of life. Risk factors for more severe jaundice include prematurity, infection, or antibodies to red cell antigens (e.g. ABO incompatibility, minor antigens – Kell, Duffy, c, e, E and others). ABO incompatibility, particularly in the presence of a positive DAT, may produce a more aggressive picture than physiological jaundice, with potential for a more rapid rise in SBR and also a more prolonged resolution phase which may last several weeks. Jaundice resulting from haemolysis of any cause may show a resistance to phototherapy necessitating an increase in the number of phototherapy lights, use of a 'Bili-Blanket' and more frequent monitoring of SBR, feeding and hydration status. Haemolytic causes of jaundice are also more likely to rebound following cessation of phototherapy and a low threshold for testing the SBR in the days following withdrawal of treatment should be maintained.

Glucose-6-Phosphate Dehydrogenase deficiency (G6PD) should be considered in infants in whom the response to phototherapy is poor, or there is a relevant family, ethnic or geographic history. The condition is widespread, being present in approximately 12% of African Americans, and prevalence is higher in the Mediterranean, Middle East, Southeast Asia and Africa.¹

Infants with physiological jaundice on post-natal wards

The majority of infants treated for hyperbilirubinaemia on the post-natal ward will have physiological jaundice. The severity of jaundice may be assessed using Kramer's Rule (see above), with yellow skin changes usually presenting in a head-to-toe fashion as intradermal bilirubin deposition progresses. The maternal blood group is usually available on the neonatal history sheet or iCM. Neither the neonatal blood group, nor the direct antibody test are performed routinely after delivery, however both should be requested if hyperbilirubinaemia reaches a level requiring phototherapy, and in any infant with risk factors for non-physiological jaundice – especially haemolysis resulting from Rh, ABO or minor antigen incompatibility. Testing can be performed on cord blood in the laboratory until day 3. After that time, a blood sample is required from the neonate. In most circumstances, infants requiring phototherapy for physiological jaundice should have a SBR performed at least daily to monitor response.

Transcutaneous Bilirubin Measurement

Transcutaneous measurement of bilirubin in this hospital uses a JM-103 bilirubinometer. TcB measurements may be performed as an initial screen for jaundice in the well, term infant **who is greater than 24 hours of age**. Infants in whom jaundice presents less than 24 hours of age, or where other risk factors are present (e.g. preterm, maternal antibodies, possible sepsis, G6PD risk, etc) should have an SBR performed in the first instance.

Jaundice onset	TcB	Action
<24 hrs	-----	Perform SBR
24-48 hrs	>140 µmol/L	Perform SBR
48-72 hrs	>200 µmol/L	Perform SBR
>72 hrs	>260 µmol/L	Perform SBR

The trans-cutaneous bilirubin is unreliable following the commencement of phototherapy, unless a skin patch has been applied prior to starting lights and this area is used exclusively for TcB measurement (not routinely done at KEMH). An SBR should be performed to track progress once lights are instigated. The frequency with which monitoring should occur varies with the absolute SBR, the expected or actual rate of change of serum bilirubin level, and risk factors present. In general, high risk infants should be monitored 4-6 hourly initially. Low risk infants can be monitored daily.

Use of TcB in the late preterm infant

Several studies have investigated the use of transcutaneous bilirubin measurement in preterm infants. De Luca et al obtained a correlation coefficient of 0.795 (p<0.001) between TcB and SBR measured in 340 preterm infants 30-36 w gestation.⁸ More recently, TcB measurements in preterm infants grouped by gestation 24-28w, 29-31w and 32-34w were highly correlated with SBR values, with a high degree of inter-observer precision.⁹ A number of other studies have provided nomograms for TcB levels in late preterm neonates.¹⁰

At KEMH, the large majority of infants of gestation < 34 w or birthweight <2000gm will be admitted to SCN. Data pertaining to the use of TcB in preterm infants suggests a high level of correlation between TcB and SBR measures, however these infants are also at higher risk. Therefore, infants < 34 w or birthweight <2000gm should have a SBR performed if clinical jaundice is evident.

Serum Bilirubin Measurement

Serum bilirubin measurement should be performed in all infants at high risk of haemolysis, early or aggressive jaundice. Infants at high risk of early haemolysis (e.g. Rh isoimmunisation, haemolysis requiring in-utero transfusion) should have an SBR performed on cord blood initially and then 4 - 6 hourly to determine the rate of rise. Physiological jaundice in a term or near term infant may be monitored with daily SBR.

MANAGEMENT

Phototherapy

The primary role of phototherapy is to lower the concentration of circulating unconjugated bilirubin to a level at which the risk of central nervous system deposition is minimised, thus avoiding the deleterious consequences of acute and/or chronic encephalopathy. The native form of unconjugated bilirubin is photo-reactive to photons with a wavelength of 450 nm (max) – 510 nm (min). Molecules exposed to this light spectrum undergo three forms of photochemical reaction; configurational isomerisation, structural isomerisation and photo-oxidation. Conversion of the bilirubin *Z*-isomer to the *E*-isomer configuration or re-arrangement of double bonds in one of the pyrrole rings to form lumirubin are likely to be the major mechanisms of action of phototherapy.

As is the case with any clinical intervention, phototherapy is not without its own side effects (e.g. dehydration, temperature dysregulation, bronze baby syndrome) and the benefit / risk profile should be considered on an individual basis when deciding to initiate or continue this management strategy.

Energy Output of Phototherapy Units

Different phototherapy units have different power outputs depending on the age of the instrument and type of light source used. Output is quantified as microwatts per cm² (μW/cm²). Phototherapy aims to deliver light in the blue-green part of the visible spectrum (i.e. ~460-490nm wavelength) at an irradiance of at least 30 μW/cm²/nm in order to decrease serum bilirubin concentrations over a 4-6 hour period. Energy output specifications for the most commonly used phototherapy units are;

Microlite	1450 – 1700 μW/cm ²
Medela (blue/white)	1400 μW/cm ²
Medela (Blue only)	1300 μW/cm ²
Medela (White only)	200 μW/cm ²
Biliblanket	40 – 50 μW/cm ²
6 tube fluorescent	250 – 400 μW/cm ² (Note: these are no longer commonly in use)

Intravenous Immunoglobulin (IVIG) and Exchange Transfusion

Aggressive haemolysis, most frequently occurring in response to Rhesus isoimmunisation or other minor antigen incompatibility, has the potential to elevate serum unconjugated bilirubin levels to dangerous levels within hours of birth. In these cases, the umbilical cord SBR together with a specimen obtained 4-6 hours later, provides a useful indication of the rate of rise of serum bilirubin level and allows planning for preventative strategies such as IVIG administration or exchange transfusion. IVIG is unlikely to prevent the need for a first exchange transfusion, however the need for repeated

transfusion is decreased. A rise in SBR of $\geq 40 \mu\text{mol/L}$ in 4 hrs (i.e. $\sim 10 \mu\text{mol/L}$ per hour) indicates a high risk for exchange transfusion. Infants with risk factors for early and aggressive jaundice should be discussed with the Paediatric consultant / senior registrar *early* for consideration of admission to SCN for monitoring, commencement of phototherapy and possible exchange transfusion.

DISCHARGE PLANNING AND FOLLOW-UP

Infants with aggressive / haemolytic jaundice

Infants in whom aggressive jaundice is present are at risk of rebound hyperbilirubinaemia following withdrawal of phototherapy. Rhesus isoimmunisation and certain minor red cell antigen incompatibilities are risk factors and infants requiring phototherapy for these problems should have lights removed sequentially once stabilisation of the SBR has occurred. An SBR should be performed the day after cessation of phototherapy, and electively post-discharge if there is suspicion that jaundice is again worsening, if there is poor feeding or lethargy. Excessive haemolysis in these circumstances may exaggerate and prolong the normal nadir in Haemoglobin level seen during the first 4-8 weeks of life, on occasion necessitating blood transfusion. Consequently, infants identified as having a haemolytic cause for jaundice should be considered for follow-up in 4 -6 weeks with a FBP and reticulocyte count performed at that time.

Infants with physiological jaundice

Infants considered to have physiological jaundice, who are feeding appropriately and have weight loss within acceptable limits (i.e. less than 10% below birthweight) may be discharged without ongoing monitoring of SBR. Monitoring of skin colour, feeding, weight gain and lethargy should be performed by a visiting midwife (VMS) or child health nurse.

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