Champlain Maternal Newborn Regional Program
Programme régional des soins à la mère
et au nouveau-né de Champlain

Newborn Hyperbilirubinemia

A Self–Learning Module

2013 (Updated July 2015)

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Introduction

By completing this self-learning module, the learner will obtain the knowledge and skills to perform a systematic approach to assessment, and management of jaundice, as well as prevention of severe neonatal hyperbilirubinemia. Through proper screening, identification of risk factors for severe hyperbilirubinemia and appropriate use of phototherapy/treatment modalities, the health care team can make a difference and contribute to decreasing a newborn's risk of neonatal encephalopathy.

Objectives

1. Summarize the mechanisms of bilirubin production and clearance (physiologic mechanism).
2. Identify newborns at risk for developing severe hyperbilirubinemia and bilirubin encephalopathy.
3. Identify prevention strategies for at-risk newborns.
4. Describe a systematic process to screen for, assess and monitor neonatal hyperbilirubinemia.
5. Describe the recommended treatment modalities for hyperbilirubinemia.
6. Summarize the current consensus guidelines for screening, early intervention, treatment and follow-up of newborns ≥ 35 weeks gestation at risk for hyperbilirubinemia.

1. Types of Jaundice

	DESCRIPTION
PHYSIOLOGIC	• Normal process occurs in the first few days of life • Benign process • Self-limiting • Resolves by end of first week • Requires no treatment
BREASTFEEDING	• Occurs in first few days of life • Related to decreased breast milk intake and decreased frequency of feeding • May also be related to altered liver conjugation and bilirubin clearance due to inadequate caloric intake • Prompt early initiation of breastfeeding and frequent, short unsupplemented feeding of colostrum and breast milk will prevent exaggeration of early physiologic jaundice
BREAST MILK	• Late onset jaundice beginning after 5th day of life, more uncommon • Peaks during second or third week and continues for several weeks • Caused by increased reabsorption of unconjugated bilirubin, perhaps due to unidentified factor in human milk
PATHOLOGIC	• Jaundice arising from pathologic process(es) which appears within first 24 hours after birth • Characterized by rapidly rising serum bilirubin and or elevated ***direct*** bilirubin concentration (>34 micromols/L or >20% of total serum bilirubin) • Combination of factors: a) **increased production** (polycythemia, sepsis, bruising) b) **decreased excretion** (bowel obstruction, poor feeding, acidosis)

2. Bilirubin Metabolism

2.1 Bilirubin Production

Bilirubin is a product of the breakdown of the heme portion of hemoglobin that occurs when red blood cells are destroyed. Normally, bilirubin is excreted through the body after passing through the liver, spleen, kidneys and the gastrointestinal tract.

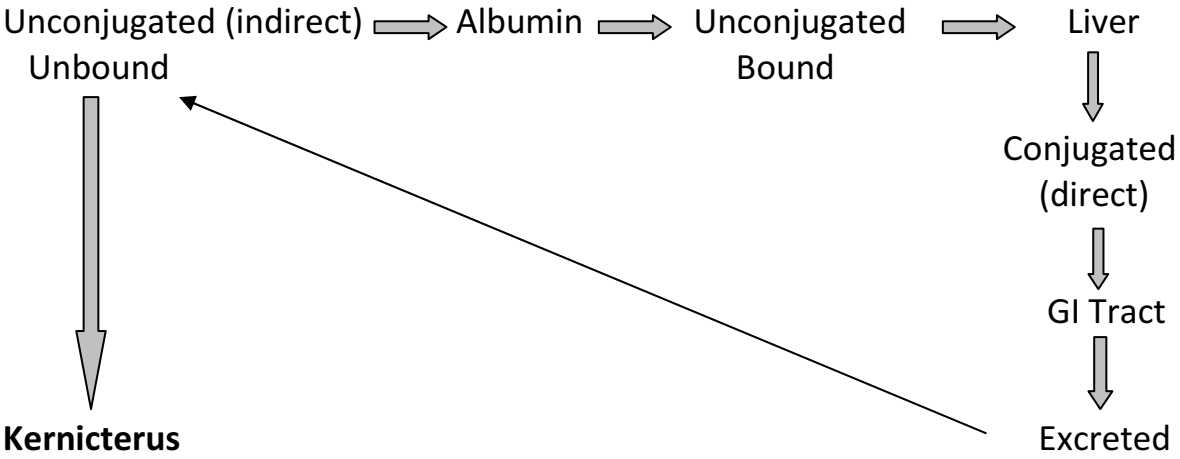
2.2 Types of Bilirubin

There are two types of bilirubin circulating in the blood stream, ***unconjugated*** and ***conjugated***.

Unconjugated* bilirubin** (or ***indirect* bilirubin**) can be found in circulating blood either bound to albumin or not. It is fat-soluble and therefore more potentially toxic since it can bind to the tissues. Most of the ***unconjugated bilirubin is bound to albumin and transported to the liver. There, it is converted to glucuronic acid aided by uridine diphosphate glucuronosyl transferase (UDGT) to produce conjugated bilirubin. Once it becomes conjugated, it is sent to the gut for excretion via the biliary system. The unbound, unconjugated bilirubin is most likely to cross the blood-brain barrier and settle in the tissues where it can cause temporary or permanent neurological damage. Once it settles in the brain, it is there forever. The unbound bilirubin is difficult to measure but it is thought that it is directly related to the amount of unconjugated bilirubin.

***Conjugated* bilirubin** (or ***direct* bilirubin**) is water-soluble and therefore is a more stable and non-toxic form. This allows it to be easily excreted from the body in urine and stool. Elevated levels of conjugated bilirubin may indicate evidence of liver disease.

2.3 Conversion and Elimination of Bilirubin



3. Factors Affecting Bilirubin Metabolism

3.1 Increased Production

Any disorder which causes an increase in the number of red blood cells such as polycythemia, will lead to an increase in the amount of bilirubin produced as these cells breakdown. If there is a decreased amount of albumin available, there will be decreased binding capacity and conversion of indirect to direct bilirubin in the liver resulting in more indirect bilirubin that could potentially cross the blood-brain barrier or settle in the tissues. Bruising will also increase the breakdown of RBCs and increase bilirubin levels.

3.2 Decreased Conjugation

Conditions such as acidosis and hypoxia can also affect the bilirubin/albumin ratio for binding. The presence of any type of liver disease, metabolic or enzyme disorder will also affect the ability of the body to convert bilirubin to the direct form to allow for excretion. Because bilirubin is changed in the gut to urobilinogen with the assistance of the normal intestinal flora, anything that affects normal gut function can affect the excretion of bilirubin from the body. We know that at birth, the infant's gut is not fully developed so that prematurity and/or any disorder of the bowel, as well as antibiotic therapy, can slow the excretion of bilirubin.

4. Maternal and Newborn Risk Factors for Development of Jaundice

	OVER PRODUCTION	UNDER SECRETION
MATERNAL	– ABO or Rh-incompatibility – Forceps or vacuum extraction – Use of oxytocin in labour (oxytocin binds to albumin) – Mediterranean, Middle Eastern, East Asian, Aboriginal background	– Maternal illness (diabetes mellitus, pre-eclampsia) – Family history of jaundice, anemia, liver disease or splenectomy
INFANT	– Polycythemia – Sepsis – Excessive bruising – Asphyxia, hypoxia, hypothermia, hypoglycaemia, acidosis – Congenital enzyme, metabolic/ endocrine disorders	– Prematurity – GI anomalies – Poor nutrition (dehydration, decreased fluid intake)

These risk factors can also be illustrated by the following mnemonic:

J - Jaundice within 24 hours of birth

A – A sibling who had jaundice as a neonate and required treatment, or an infant who has asphyxia, acidosis, or albumin < 3.0 g/dL

U – Unrecognized haemolysis (ABO, Rh or other blood incompatibility, red cell membrane defects)

N – Newborn born < 37^{+0} weeks gestation

D – Deficiency in glucose-6-phosphate dehydrogenase (G6PD)

I – Infection or infant of a diabetic mother

C – Cephalohematoma/bruising or central hematocrit > 65%

E – East Asian, Mediterranean, Middle Eastern, Aboriginal descent

D – Due to sub-optimal feeding (breast or formula) (CPS, 1999)

5. Bilirubin Encephalopathy (Bilirubin Toxicity)

Normally, hyperbilirubinemia resolves on its own as the infant processes the bilirubin and excretes it. However, in some infants, it can become harmful and will need treatment. If not detected or left untreated and levels rise too high, some of the bilirubin may cross the blood brain barrier and settle into brain tissue where it can cause ***acute bilirubin encephalopathy*** (ABE). This encephalopathy, if not detected early and treated, can develop into ***kernicterus.*** ***Kernicterus*** is a potentially fatal disease and results in permanent injury to specific parts of the brain.

To help quantify the degree of ABE, the Bilirubin-Induced Neurological Dysfunction (BIND) score was developed. It describes three phases of worsening encephalopathy and the clinical signs in each phase:

Initial phase:
- lethargy, decrease in tone or activity

Intermediate phase:
- moderate stupor, irritability and variable activity
- increased tone, some retrocollis/opisthotonus
- minimal feeding, high-pitched cry

Advanced phase:
- deep stupor to coma, hypertonicity
- retrocollis/opisthotonus
- no feeding, shrill cry, seizures, death

6. Screening Steps

The content of this section is based on the Ontario Ministry of Health and Long-Term Care (MOHTLC) Quality-Based Procedure (QBP) titled *Hyperbilirubinemia in Term and Late Pre-Term Infants (≥ 35 weeks)* (2013). The key objectives of the QBP for Hyperbilirubinemia are to:

- ensure all newborns receive bilirubin screening between 24-72 hours of life (if not clinically indicated and performed earlier)
- ensure infants receive systematic bilirubin monitoring as per the treatment graph and risk nomograms recommended by evidence-based guidelines
- utilize health care resources responsibly through avoidance of unnecessary/excessive testing, timely discharge, appropriate outpatient follow-up and minimization of preventable readmission
- reduce the incidence of severe hyperbilirubinemia and acute bilirubin encephalopathy

The Provincial Council for Maternal and Child Health (PCMCH) has developed a toolkit to accompany the MOHLTC's QBP on hyperbilirubinemia. The toolkit details the clinical pathway and the tools clinicians can use to implement the QBP. Further information may be downloaded from the PCMCH website. Information regarding QBPs can be downloaded from the Health System Funding Reform, Quality Based Procedures portion of the MOHLTC webpage.

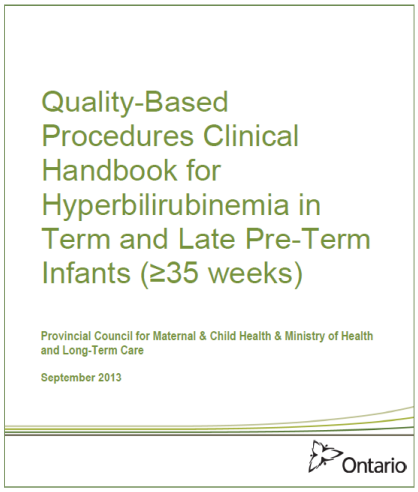
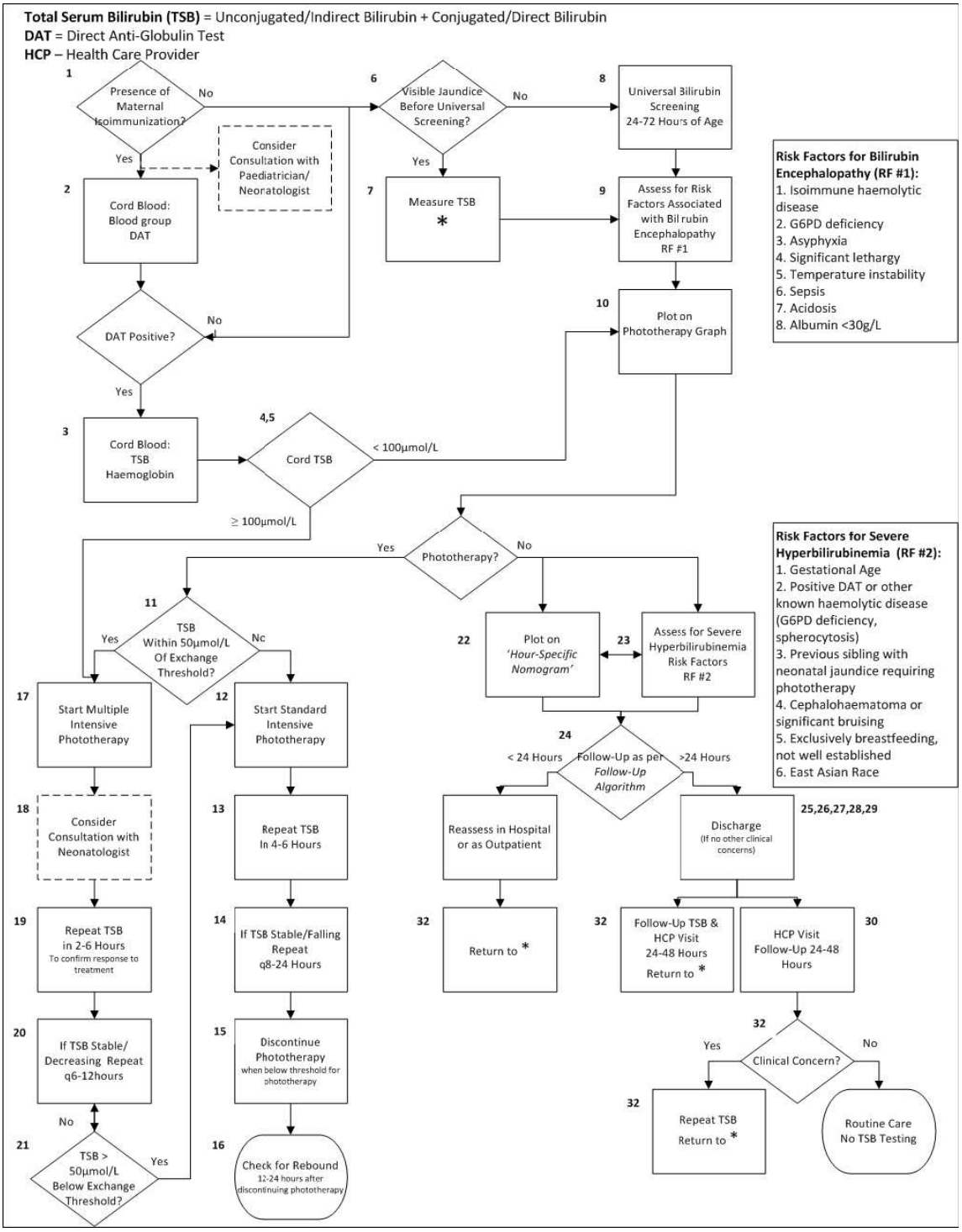


Figure 1. Clinical Pathway for the Management of Hyperbilirubinemia in Term and Late Pre-Term Infants (≥ 35 weeks)

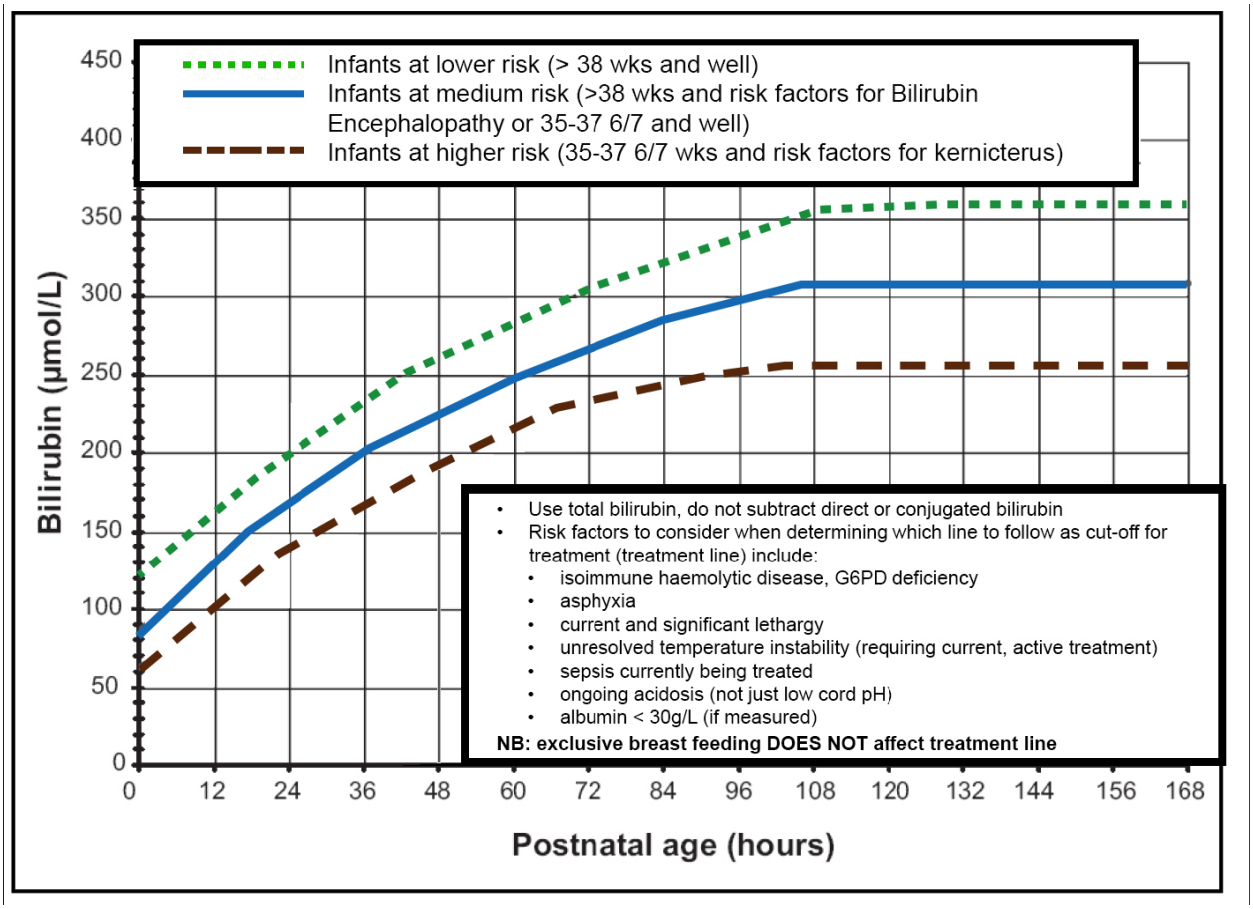


Developed by the PCMCH Hyperbilirubinemia Working Group, 2014

Screening Steps (1 – 32) (Figure 1)

1. Identify newborns of mothers with red cell antibodies (isoimmunization).
2. Newborns of mothers with red cell antibodies should have blood group evaluation and direct anti-globulin test (DAT).
3. Measure cord blood for hemoglobin and total serum bilirubin (TSB).
4. If cord TSB level ≥ 100 µmol/L this is a ***critical value*** and is suggestive of a need for ***exchange*** transfusion. Multiple intensive phototherapy lights should be initiated without delay, while continuing on pathway (step #17) and initiating consult (step #18).
5. If cord TSB level < 100 µmol/L plot bilirubin on ***phototherapy graph:*** Figure 2 *(step #10)* using time=0.
6. Clinically assess for jaundice routinely during newborn care. Jaundice in the first 24 hours is more likely to be significant/pathologic, so multiple clinical assessments in the first 24 hours are recommended.
7. Measure TSB in all newborns that appear clinically jaundiced in their first 24 hours of life.
8. If not required earlier because of clinical jaundice, TSB should be obtained at the same time as newborn metabolic screening (between 24-72 hours of age).
9. Assess for presence of any ***Bilirubin Encephalopathy Risk Factors***. These risk factors along with gestational age are used to identify the low/medium/high treatment threshold lines on the ***phototherapy graph*** (Figure 2).
    - **Risk factors for bilirubin encephalopathy** to consider when determining which line to follow as cutoff for treatment (threshold line) include:
        - isoimmune haemolytic disease
        - G6PD deficiency
        - asphyxia
        - current and significant lethargy
        - unresolved temperature instability (requiring active treatment)
        - sepsis (current treatment with antibiotics)
        - ongoing acidosis (not isolated low cord pH)
        - albumin < 30g/L (if measured)
10. Plot TSB on ***Phototherapy graph*** (Figure 2) to determine need for phototherapy. Determination of the treatment line depends on gestational age at birth as well as presence of bilirubin encephalopathy risk factors from step #9. Plot on phototherapy graph using TSB (unconjugated + conjugated) and age in hours at the time of the bilirubin was measured.

Figure 2. Guidelines for Intensive Phototherapy for Infants ≥ 35 weeks

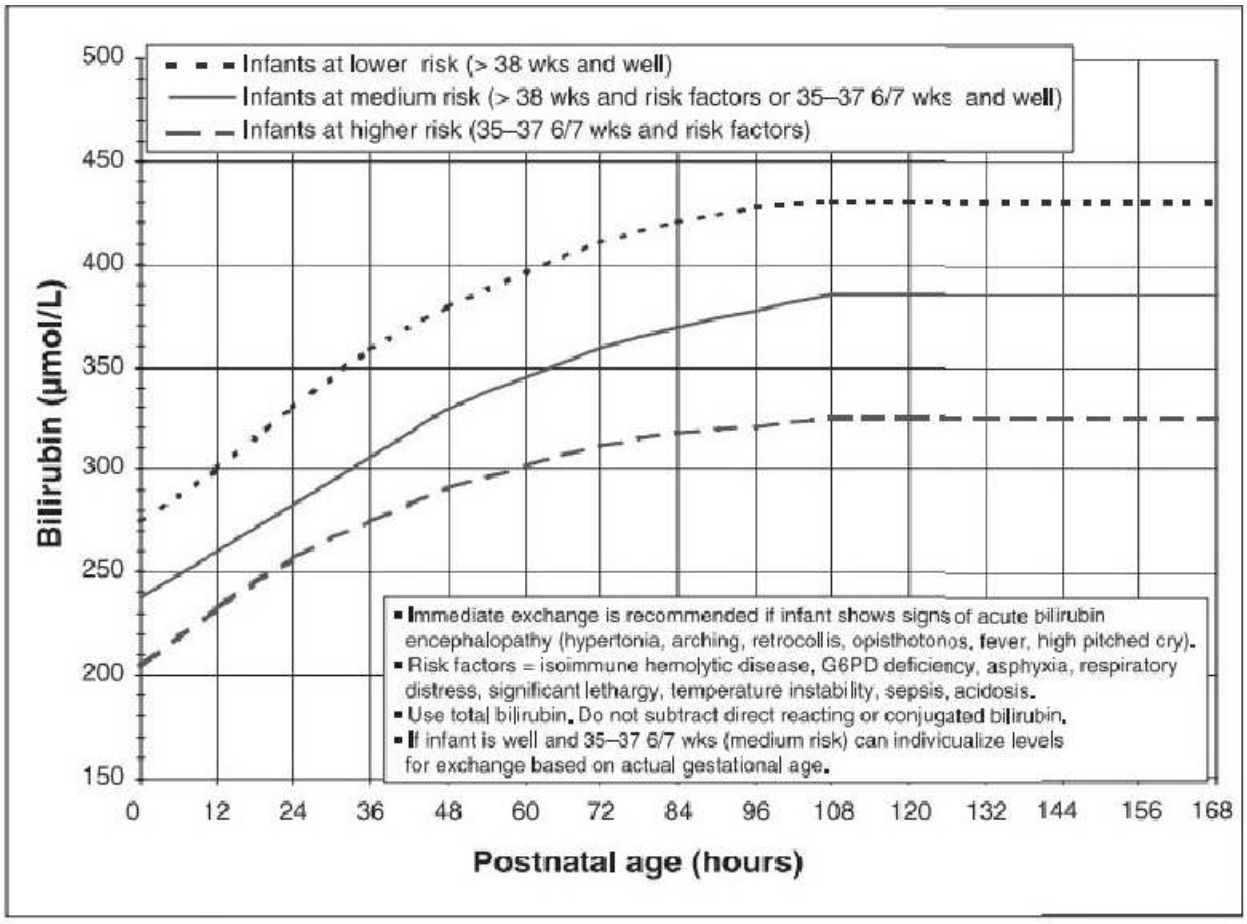


Adapted with permission from the American Academy of Pediatrics - Subcommittee on Hyperbilirubinemia. (2004). Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics, 114*(1), 297-316.

11. If phototherapy indicated, determine if TSB is within 50µmol/L of the exchange transfusion line on ***Exchange Transfusion Graph*** (Figure 3).

12. If 'No" in Step #11, start ***Standard Intensive Phototherapy***:
    - Begin with **high intensity** of at least **30 µw/cm²/nm**
    - Expose maximum skin surface; limiting interruptions to 20 minutes every 3 hours

Figure 3. Guidelines for Exchange Transfusion for Infants ≥ 35 weeks

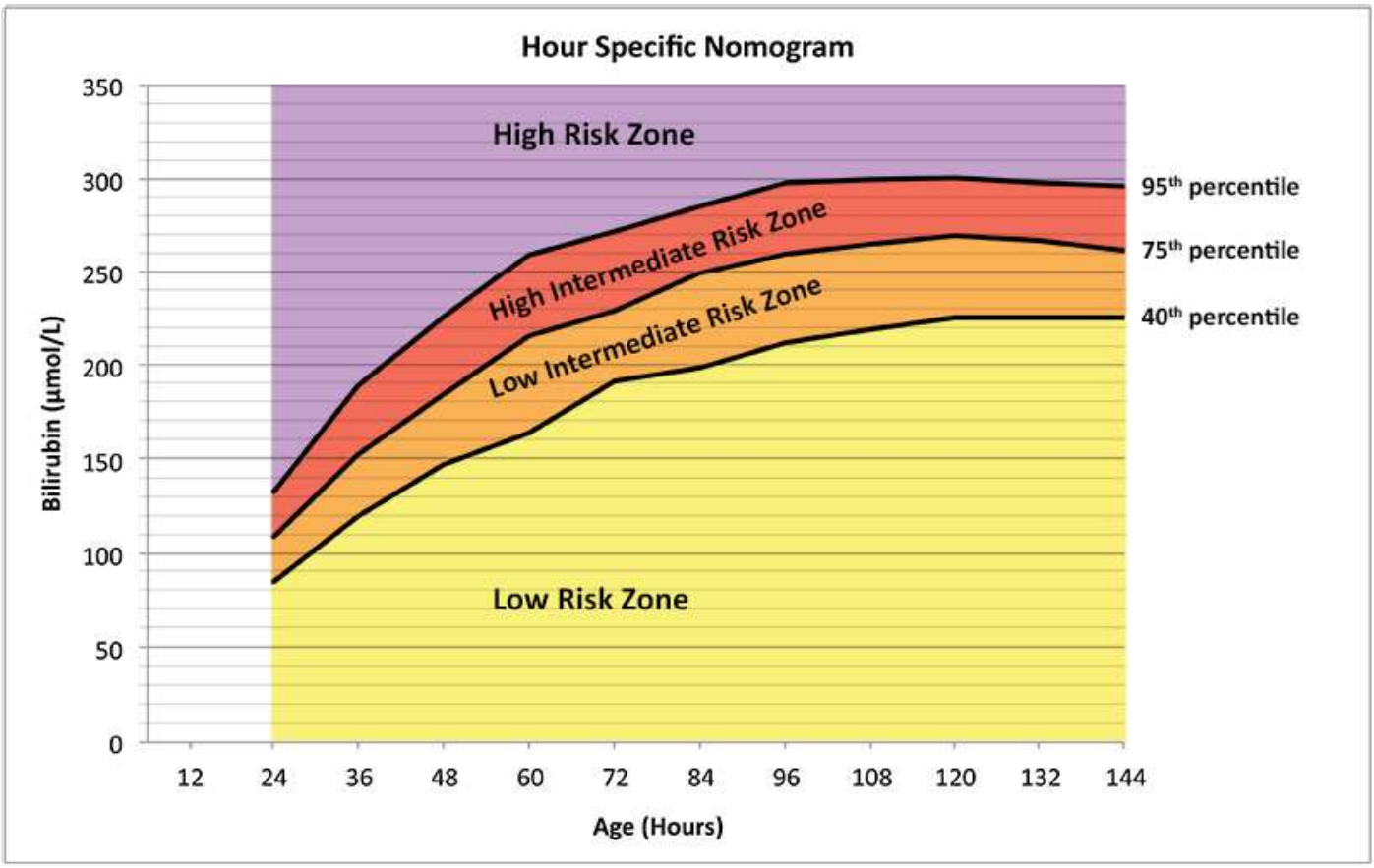


Reproduced with permission from the Canadian Paediatric Society, Fetus and Newborn Committee, 2007 (updated 2011). *Guidelines for detection, management and prevention of hyperbilirubinemia in term and late preterm newborn infants (35 or more weeks' gestation)*.

13. Repeat TSB in 4-6 hours. Use clinical judgment including consideration of ***Severe Hyperbilirubinemia Risk Factors:***
    - gestational age less than 38 weeks (the lower the gestational age, the greater the risk)
    - positive DAT or other known haemolytic disease (G6PD deficiency, spherocytosis)
    - previous sibling with neonatal jaundice requiring phototherapy
    - cephalohematoma or significant bruising
    - exclusively breastfeeding, not well established and excessive weight loss
    - East Asian race

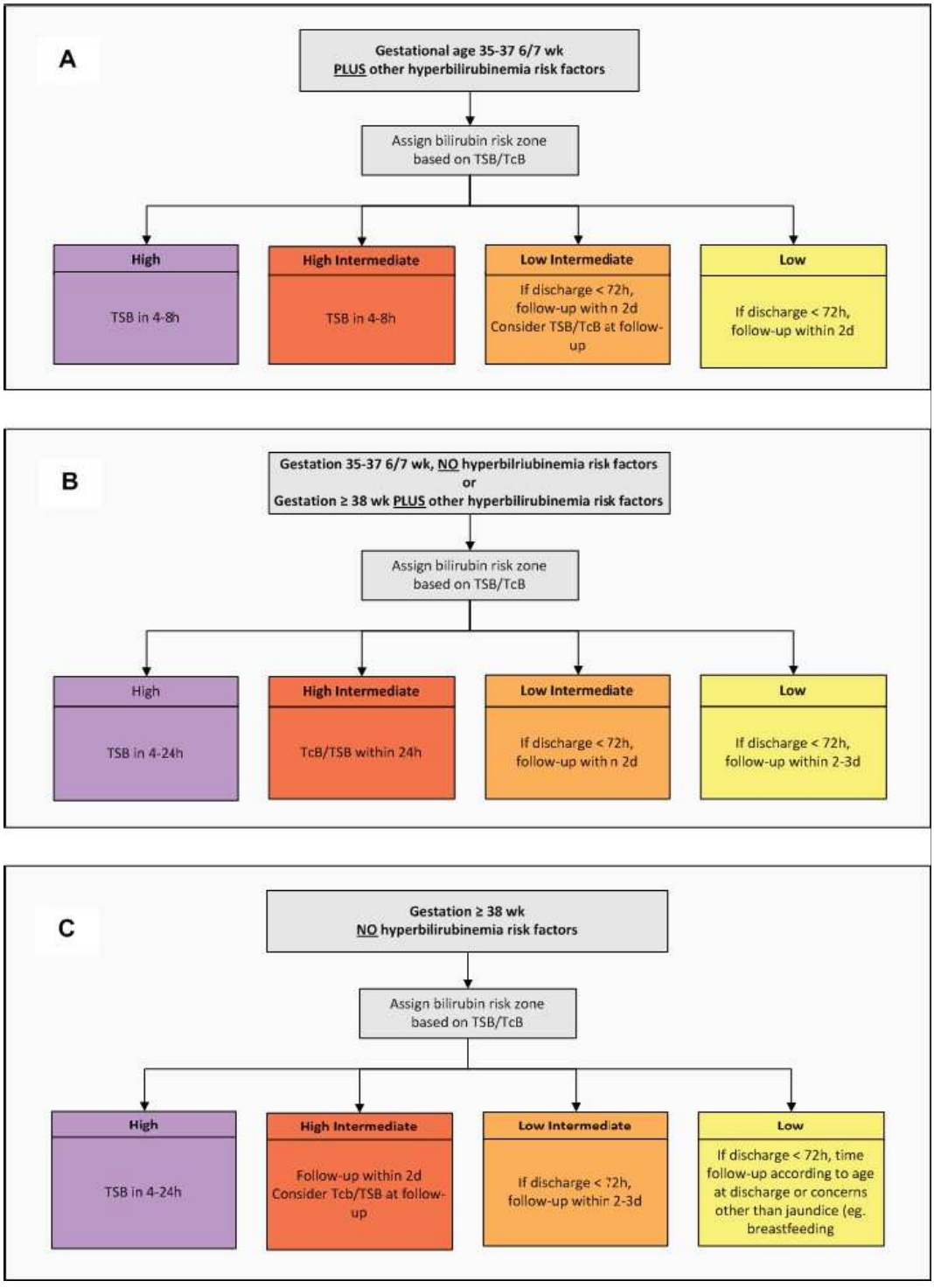
14. If TSB is stable or falling continue to repeat TSB every 8 – 24 hours while on phototherapy.
15. Discontinue phototherapy when TSB is below threshold for phototherapy initiation.
16. Check TSB for rebound 12-24 hours after discontinuing phototherapy.
17. If YES in Step #11, start multiple intensive phototherapy modalities including a phototherapy blanket under the infant to increase exposed surface area. Do not interrupt phototherapy for feeding or other care.
18. Consider immediate consult with neonatologist. IVIG or exchange transfusion may be indicated in specific situations.
19. Repeat TSB in 2-6 hours to confirm response to treatment.
20. If TSB stable or decreasing continue to repeat every 6-12 hours.
21. When TSB is more than 50 µmol/L below exchange transfusion threshold return to step #9.
22. If phototherapy is not indicated, plot the TSB on the ***Hour Specific Nomogram*** (Figure 4).
23. Assess for presence of any ***Severe Hyperbilirubinemia Risk Factors*** (see step #13).
24. Consult ***Follow-up Algorithm*** (Figure 5) for management and follow-up according to pre-discharge TSB.
25. Arrange follow-up TSB measurement, if indicated.
26. If appropriate follow-up cannot be ensured in the presence of elevated risk for developing severe hyperbilirubinemia, delay discharge.
27. Provide lactation evaluation and support for all breastfeeding mothers.
28. Any infant discharged before 24 hours should be assessed by a health care provider within 24 hours. That care provider should have access to testing and treatment facilities.
29. The infants' parent or guardian should be provided with written and verbal instructions regarding the infant's jaundice follow-up and the timing of that follow-up.
30. The follow-up assessment should include confirmation that:
    - Weight loss should be no more than 10% of birth weight
    - 4-6 wet diapers and 3-4 stools per day by the fourth day
    - Stools in breastfed infants should have changed from meconium to mustard yellow
    - Breastfeeding is effective
31. Clinical judgment should be used to determine the need for TSB measurement. Visual estimation of bilirubin levels can lead to errors, especially in darkly pigmented infants.
32. Any repeat TSB measurement should be plotted in this algorithm in the same manner as the initial TSB to identify the need for and timing of further clinical follow-up.

Figure 4. Hour Specific Nomogram



Based on data from Stevenson et al. (2001).

Figure 5. Follow-Up Algorithm



Modeled on Maisels Algorithm (Maisels, 2009), reflecting the findings of the Clinical Expert Advisory Group for the paediatric QBP on Hyperbilirubinemia in Term and Late Pre-Term Infants.

7. Assessment of Jaundice

7.1 Physical Assessment

- **Visual assessment:** Jaundice moves from head to toe, with the eyes affected last.

  Serum bilirubin (approx.)
  = 85 micromols/L - When yellow tinge first becomes visible
  = 150 micromols/L - Yellow tinge appears on trunk
  = 200 micromols/L - Yellow tinge appears on legs
  = 250 micromols/L - Eyes (sclera) are affected

- Although visual assessment alone cannot determine the degree of jaundice, a general assessment of the extent of jaundice can be done under bright light. It is important to:
  - Blanch skin to determine underlying colour.
  - Press over a bony prominence for best results (nose, forehead).
  - Check sclera.

  NOTE: For dark skinned infants, the colour of the sclera, conjunctiva and oral mucosa is most reliable indicator of level of jaundice.

  NOTE: Petechiae may indicate underlying sepsis or haemolytic disease.

- **Level of activity:**
  - Increasing levels of unconjugated bilirubin in the brain can lead to decreased levels of consciousness or alertness. Infants may become lethargic and less responsive.

- **Level of hydration:**
  - Monitor intake and output.
  - Adequate hydration is necessary to help maintain enough fluid to help with the absorption and excretion of conjugated bilirubin once it passes through the liver.

- **Stools:**
  - Monitor frequency, type and colour of stools (meconium versus transitional).
  - Unconjugated bilirubin can accumulate in stool and thus has the potential to be reabsorbed.
  - Conjugated bilirubin can also become unconjugated in the gut and become reabsorbed into the blood stream.

7.2 Laboratory Assessment

- Obtain serum bilirubin levels as per algorithm (Figure 2).
- NOTE: When bloodwork is being drawn, phototherapy should be stopped to prevent the sample from being affected by the lights. The total bilirubin should be interpreted according to the infant's age in hours to determine the treatment plan and timing of reassessment.
- Other blood work that may be ordered:
    - Serum albumin - to help determine how much albumin is available for binding
    - CBC and differential – can help determine level of red blood cell destruction, haemolytic anemia, sepsis or polycythemia
    - Direct Antiglobulin Test (DAT) - to look for presence of maternal antibodies in infant's serum. NOTE: Indirect Antibody Test (IAT) is done on maternal serum antenatally
    - G6PD (glucose-6-phosphate dehydrogenase) – helps maintain RBC wall integrity; a deficiency indicates enzyme deficiency and a possible metabolic reason for jaundice

REMEMBER:

It is possible that bilirubin levels could rise once phototherapy is discontinued although current methods of weaning phototherapy from high intensity (intensive) to low intensity (standard) phototherapy can prevent this. A follow-up serum bilirubin should be taken 12-24 hours as per protocol; usually 12–24 hours after therapy is discontinued.

8. Treatment

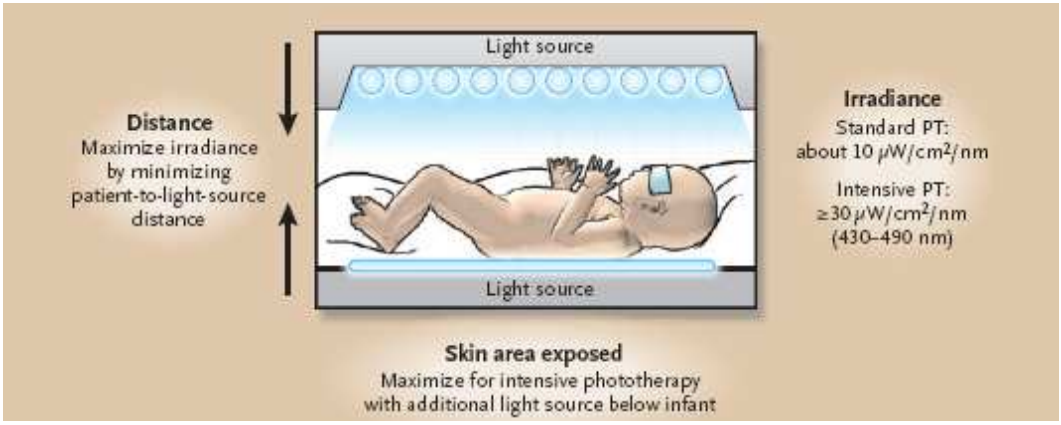
8.1 Phototherapy Principles

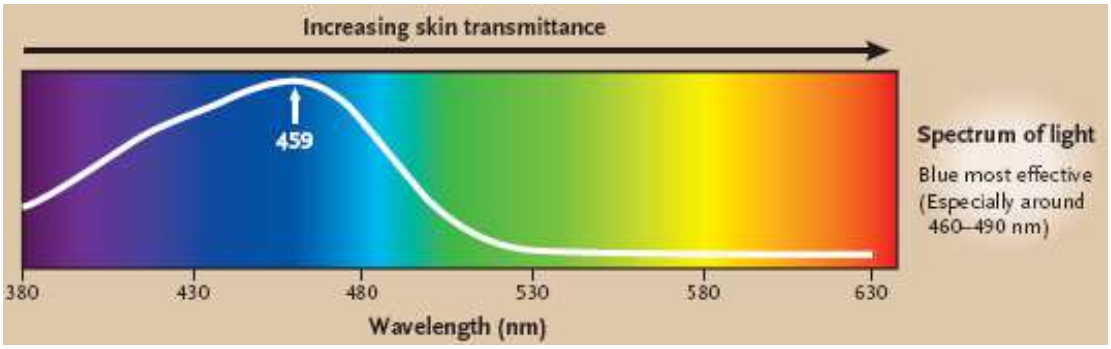
<u>Effectiveness of phototherapy</u> =

Area of skin exposed + **Radiant energy** + **Wavelength** of light used

Phototherapy acts on unconjugated bilirubin to a depth of 2 to 3 mm. Through photoisomerization, fat soluble molecules are reconfigured to water soluble molecules and are excreted by the liver without actual conjugation.

Structural photoisomerization





Source: Maisels & McDonagh, 2008

- The most effective light sources for degrading bilirubin are those that emit blue-green light in a relatively narrow wavelength range (425 – 490 nanometers).
- When phototherapy is used, the decrease in bilirubin level is proportionately greater in the skin than in the serum. The infant should have as much skin as possible exposed to the lights.
- It is possible to increase the efficacy of treatment by using multiple sources of phototherapy to optimize the amount of skin exposed.
- According to standards of care phototherapy is ordered as either intensive (high) or standard (low) intensity and expressed in nanometers of light.

8.2 Phototherapy Equipment

There are a variety of methods of delivering phototherapy. The method used depends on the equipment availability in each institution. The following are the current recommended methods:

- **Phototherapy Lights**: Deliver light in the narrow spectrum most effective for reducing bilirubin. Their effectiveness depends on the distance from the baby as measured by a specific light meter.
- **Bili Bassinet**: Self-contained unit that combines a mattress area and three phototherapy light units to provide phototherapy and may be used as an adjunct therapy to phototherapy lights, but should not be used as the sole source of therapy.
- **Bili Blanket**: A small fiber optic pad is placed under the infant. It can be used as an adjunct to overhead phototherapy lights but not as the only source of phototherapy. The advantage of a bili blanket is that it can remain in place for breastfeeding, providing continuity of therapy.

8.3 Potential Side Effects of Phototherapy

SIDE EFFECT	SPECIFIC SIGNS / SYMPTOMS	IMPLICATION	ACTION
Altered Activity	• Lethargy or irritability • Decreased eagerness to feed	• May impact parent-infant interaction • May alter fluid and caloric intake	• Observe and support parental efforts and concerns
Altered Fluid Status	• Increased peripheral blood flow • Increased insensible water loss with open bed or warmer	• Increased fluid loss may alter uptake of I.M. medications • Due to increased evaporative water loss, metabolic rates and possible respiratory rate	• Monitor weight and fluid intake/output
Altered GI Function	• Increased number and frequency of watery, greenish-brown stools • Decreased time for intestinal transit • Decreased absorption, retention of nitrogen, water, electrolytes	• Increased water loss leading to risk of dehydration • May be related to increased bile flow thus stimulating GI activity	• Monitor output of stool
Altered Hematological Function	• Increased rate of platelet turnover • Damage to circulating red blood cells with decreased potassium and increased ATP (energy) activity	• May be a problem in infants with low platetets and sepsis • May lead to haemolysis, increased energy needs	• Observe for bruising & petechiae
Ocular Effects	• Lack of sensory input and stimulation • Use of eye patches for prolonged period	• Eye patches increase risk of eye infection, corneal abrasion, increased intracranial pressure (if applied too tight)	• Remove eye patches regularly to promote interaction/stimulus and observe for irritation/signs of infection • Ensure eye patches are in place when lights are used
Skin Changes	• Tanning • Rashes • Burns • Bronze Baby Syndrome	• Due to melanin synthesis • Due to injury to skin mast cells with release of histamine or erythema	• Monitor skin condition at least every 4 hours and report changes to

SIDE EFFECT	SPECIFIC SIGNS / SYMPTOMS	IMPLICATION	ACTION
		• From exposure to shortwave emissions from fluorescent light • Due to decreased hepatic excretion of bilirubin photodegradation by-products	team
Altered Thermal / Metabolic Function	• Increased environmental and body temperature changes • Increased O_2 consumption • Increased respiratory rate • Increased skin blood flow	• Influenced by maturity, caloric intake, heat dissipation from phototherapy unit, air flow, distance from infant to lights	• Monitor temperature, distance from lights • Ensure adequate food/fluid intake

9. Nursing Care

Nursing care of the infant with hyperbilirubinemia is focused on assessment and management of the signs and symptoms of the disease. The main goals of treatment are to reverse the haemolytic process and prevent the development of bilirubin-induced encephalopathy. Most infants with hyperbilirubinemia will require the use of phototherapy to help reduce the amount of unconjugated (indirect) bilirubin. The guidelines included here refer to newborns receiving phototherapy.

9.1 Feeding and Nutrition

- Fluid intake is crucial to treatment success so this is an important factor to consider in caring for an infant with jaundice. Dehydration may be associated with increased serum bilirubin concentrations and intravenous (IV) therapy may be necessary to ensure adequate hydration.
- Breastfeeding should always be strongly encouraged and supported, even when the infant is receiving phototherapy. Although more frequent breastfeeding may be beneficial, it is important to minimize the time that intensive phototherapy is interrupted to 20 minutes within a 3-hour

period. If possible, provide a referral to a Lactation Consultant for a more specific assessment of breastfeeding.

- Accurate recording of intake and output, including stool pattern, is necessary. If the infant is receiving IV therapy, usual standards of care should be followed.

9.2 Skin Care and Thermoregulation

- Skin plays an important role in the regulation of body temperature and serves as a route of water excretion.
- Skin care includes observing colour, rashes and excoriation; cleaning the skin with warm water, especially the perineal area after stooling; changing position every 2 hours. NOTE: Prompt cleansing of perianal area after stooling is important as photo-oxidation of bilirubin results in loose green caustic stools and can result in excoriation.
- Phototherapy is most effective when the exposed skin area is maximized, so infants in isolettes should be exposed as much as possible; otherwise, diapers to catch urine and stool should be used.
- The infant's temperature must be monitored at least every 4 hours to maintain a safe environment.

9.3 Eye Care

- The infant's eyes must be protected from the phototherapy lights to prevent retinal damage. Place the pads correctly over the eyes:
    - Use the appropriate size of the eye pad or prefabricated eye protection.
    - Make sure the eyes are closed first to help prevent corneal abrasion, irritation and/or infection
    - Check frequently to make sure the eye pads remain in place and are not obstructing the nares.
- Eye protection should be removed every 2 to 4 hours and eyes cleansed with normal saline to reduce irritation and promote eye contact, socialization and attachment.

NOTE: Eye patches are not necessary if only the Bili Blanket is being used since the infant's eyes are not directly exposed to the blue lights.

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- Members of the Jaundice Working Group
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