Hyperbilirubinemia in Term and Late Pre-Term Infants (≥ 35 weeks) Clinical Pathway

Toolkit

Provincial Council *for* Maternal *and* Child Health

building a brighter future

December 2017

Introduction

Hyperbilirubinemia in the newborn, also referred to as neonatal jaundice, is a result of the diminished ability to conjugate and excrete an excess of bilirubin in the blood of the neonate (Mosby, 2009). Hyperbilirubinemia is a common condition affecting approximately 60% of term and 80% of pre-term babies in the first week of life (National Institute for Health and Clinical Excellence, 2010); (American Academy of Pediatrics Provisional Committee for Quality Improvement and Subcommittee on Hyperbilirubinemia, 2004). In most of these infants the condition will resolve without any need for intervention. However, for some, there is a risk of developing severe hyperbilirubinemia which can lead to acute bilirubin encephalopathy (kernicterus). Severe hyperbilirubinemia has been on the rise in North America and Europe, with increasing frequency in term and near-term infants (Manning D, 2007). This is a troublesome finding as severe hyperbilirubinemia is largely preventable.

As mentioned above, the diagnosis of hyperbilirubinemia is one that affects a large number of neonates. Hyperbilirubinemia is often mild and can be managed without medical intervention. Medical intervention is required for serious cases of hyperbilirubinemia, some of which can be prevented when early screening and systematic monitoring are in place.

Population Definition

This clinical pathway can be applied to newborns born at 35 weeks gestation and above.

Objectives

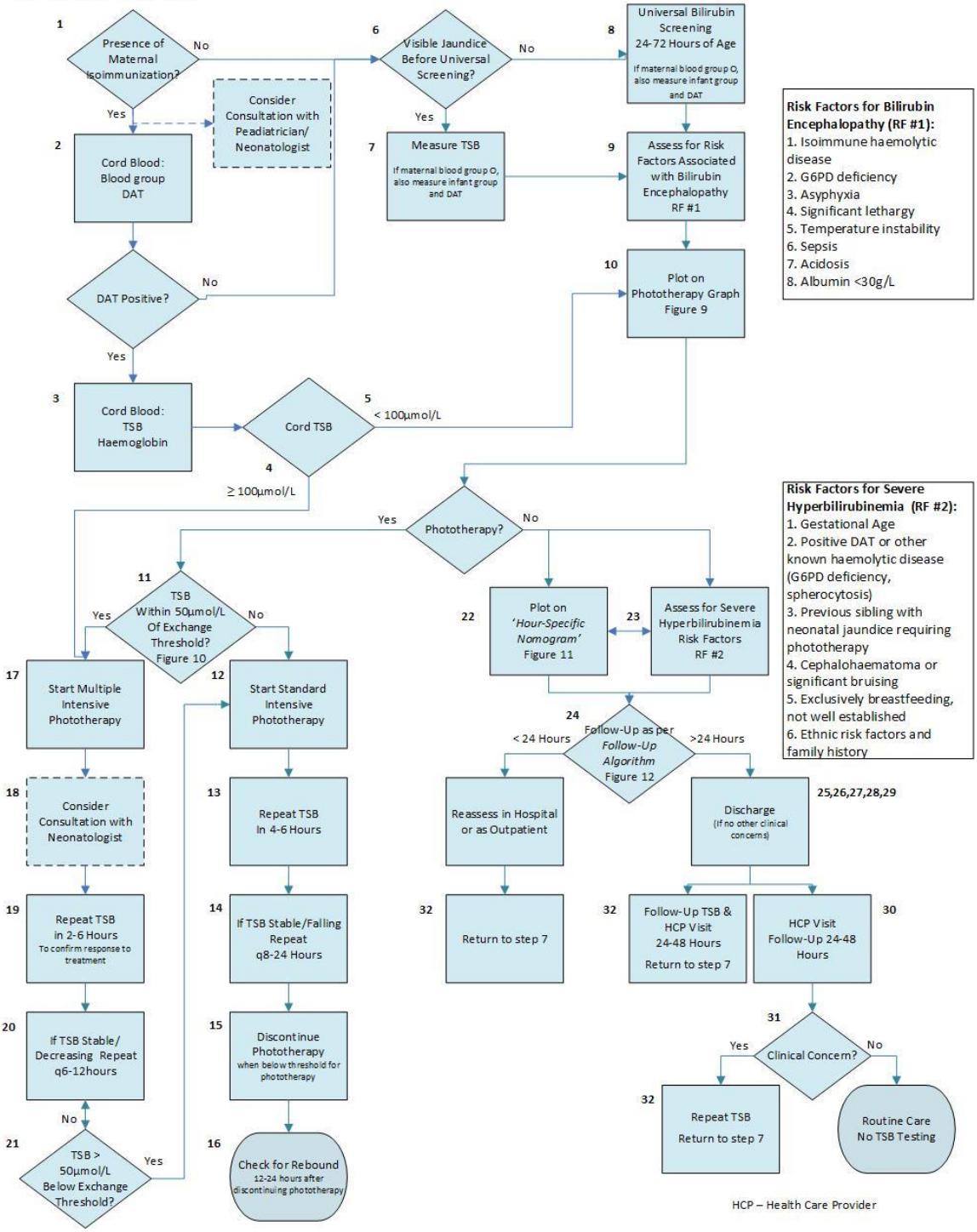
The key objectives of the Hyperbilirubinemia in Term and Late Pre-Term Infants (≥ 35 weeks) Clinical Pathway are to:

- 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

This toolkit serves as a complement to the Clinical Handbook for Hyperbilirubinemia in Term and Late Pre-Term Infants (≥ 35 weeks). The toolkit details the clinical pathway and the tools clinicians can use to implement the Clinical Pathway.

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

Total Serum Bilirubin (TSB) = Unconjugated/Indirect Bilirubin + Conjugated/Direct Bilirubin
DAT = Direct Anti-Globulin Test
HCP – Health Care Provider



Clinical Pathway Instructions and Recommendations

Legend:

AAP = American Academy of Pediatrics Guidelines	CPS = Canadian Paediatric Society Guidelines	NICE = National Institute for Clinical Evidence Guidelines

For a description of the levels of evidence used in each guideline, please see Appendix A.

	Instructions	Recommendations	Support For Recommendations
UNIVERSAL SCREENING			
1	**Identify newborns of mothers with red cell antibodies (isoimmunization)**	- All mothers should be tested for blood type (ABO and Rh(D)) and screened for red cell antibodies during pregnancy - If mother not tested during pregnancy, cord blood should be sent for blood group and DAT - Significance of various antibodies differs - Consultation with a neonatologist or paediatrician suggested due to risk of bilirubin encephalopathy	AAP Guidelines (Quality B: benefits exceed harms), CPS Grade D) CPS
2	**Newborns of mothers with red cell antibodies should have blood group evaluation and direct anti-globulin test (DAT)**	- Significance of various antibodies differs - Further evaluation, closer follow-up and earlier therapy may be required - Consultation with a paediatric haematologist or neonatologist suggested	CPS
3	**Measure cord blood for haemoglobin and TSB**	- Measurement of haemoglobin and bilirubin from cord blood suggested as part of initial evaluation for DAT positive infants of mothers with red cell antibodies	CEAG Consensus
4	**If cord TSB level ≥ 100µmol/L**	- Critical value, suggestive of need for exchange transfusion - Multiple intensive phototherapy should be initiated without delay, while continuing pathway **(Step # 17)** and initiating consult **(Step #18)**	NICE
5	**If cord TSB level <100µmol/L**	- Plot bilirubin on ***Phototherapy Graph*** **(Figure 1, Step # 10)**, using time = 0 hours - Isoimmunization is a risk for bilirubin encephalopathy	

	Instructions	Recommendations	Support For Recommendations
		- If gestation 35-37+6 weeks, use the "high risk" line (lowest position on graph, brown line) - If gestation 38 weeks or more, use the "medium risk" line (middle position on graph, blue line)	
6	**Clinically assess for jaundice routinely during newborn care**	- If visibly jaundiced at 24 hours of age or less, do a blood smear, blood group screen, DAT, and test for G6PD deficiency - Jaundice might appear clinically at any time in the newborn period - Jaundice in the first 24 hours is more likely to be significant/pathologic, so multiple clinical assessments in the first 24 hours are recommended - Clinical assessment of jaundice should continue at every well newborn check through the newborn period, before and after universal bilirubin screening - In case of early discharge (prior to 24 hours) or births outside of hospital, parents need to be made aware of the potential for jaundice and understand when to contact health care provider prior to universal bilirubin screening at 24-72 hours.	AAP (Quality D: benefits vs harms exceptional) (8-12 hours) NICE (every opportunity in the first 72 hours) CPS (repeatedly in the first 24 hours, at a minimum 24-48 hours) CEAG Consensus CEAG Consensus
7	**Measure TSB in all newborns who appear clinically jaundiced in their first 24 hours of life, include blood group and DAT if mother's blood group is O (if not done previously)**	- Further evaluation may be required to determine etiology of early jaundice (see **Step# 6**) - Blood group and DAT useful in assessing risk for haemolysis and risk factor for severe hyperbilirubinemia	AAP (Quality C benefits exceed harms), CPS (Grade D), NICE
8	**If not required earlier because of clinical jaundice, TSB should be obtained (CPS Grade C) at the same time as newborn screening (between 24-72hours of age), include blood group and DAT if mother's blood group is O**	- For early discharge babies, arrangements should be made for outpatient bilirubin measurement - Blood group and DAT useful in assessing risk for haemolysis and risk factor for severe hyperbilirubinemia	CEAG Consensus
9	**Assess for presence of any Bilirubin Encephalopathy Risk Factors (RF #1)**	- **Bilirubin Encephalopathy Risk Factor (RF #1)** determination, along with gestational age, is used to identify the low/medium/high treatment	AAP (Reproduced in CPS)

Instructions		Recommendations	Support For Recommendations
		threshold lines on the ***Phototherapy Graph*** **(Figure 1)** - Assess for: 1. Isoimmune haemolytic disease *Blood group evaluation and DAT Recommended* 2. G6PD deficiency *At risk infants (ethnic origin, family history) and infants with severe jaundice should be screened for G6PD deficiency* 3. Asphyxia *Apgar 0-3 beyond 5 min AND cord pH<7.0* 4. Significant lethargy *Impacting on feeding ability and not clearly related to maternal/neonatal medications* 5. Temperature instability *Requiring external warming at time of measurement* 6. Sepsis *On antibiotics for clinical signs of sepsis, not simply because of maternal GBS status* 7. Acidosis *Current status, not isolated low cord pH* 8. Albumin <30g/L *If measured for clinical reasons*	CPS (Grade D)
10	**Plot TSB on *Phototherapy Graph* (Figure 1) to determine need for phototherapy**	• Determination of treatment line depends on gestational age at birth as well as presence of **Bilirubin Encephalopathy Risk Factors (RF #1)** from **Step #9**. • Use the "high risk" line (lowest position on the graph, brown line) for 35-37 weeks plus 6 days gestation and one or more risk factors from **Step #9** • Use the "medium risk" line (middle position on graph, blue line) for 35-37 weeks plus 6 days gestation and NO risk factors from **Step #9** OR baby	AAP (Reproduced in CPS)

	Instructions	Recommendations	Support For Recommendations
		was born at 38 weeks or greater gestation and one or more of the risk factors from **Step #9**. • Use the "low risk" line (highest position on the graph, green line) if baby was born at 38 weeks or greater gestation and has NO risk factors from **Step #9** - Plot on ***Phototherapy Graph*** **(Figure 1)** using TSB (unconjugated + conjugated) and age in hours at the time that the bilirubin was measured.	AAP
	PHOTOTHERAPY – YES		
11	**If phototherapy indicated determine if TSB is within 50µmol/L of the exchange transfusion line on *Exchange Transfusion Graph* (Figure 2)**	- Plot TSB bilirubin on ***Exchange Transfusion Graph*** **(Figure 2)** and refer to same risk line as was used for the ***Phototherapy Graph*** **(Figure 1)**	NICE
12	**If no in Step #11, start Standard Intensive Phototherapy**	- Use dose of 30 uW/cm^2/nm minimum - Irradiance does not need to be measured every time but regular calibration checks of equipment are required according to manufacturer's instructions - Expose maximal skin surface to the lights - Diaper may be left on - Using clinical judgment, short breaks (up to 20-30 minutes q3h) for breastfeeding and other care may be allowed - If using a phototherapy blanket it should remain in place during breaks for feeding and care - Continue lactation and breastfeeding support - Weigh baby daily and monitor urine and stool output - Supplementation of breastfed infants with water or dextrose water is not recommended. - If supplementation is considered, preference is expressed breast milk	AAP, CPS (Grade D) AAP AAP, CPS, NICE AAP, CPS AAP(Quality C: benefits exceed harms), CPS (Grade A), NICE, CEAG Consensus CEAG Consensus NICE NICE, CEAG Consensus AAP, CPS (Grade B), NICE

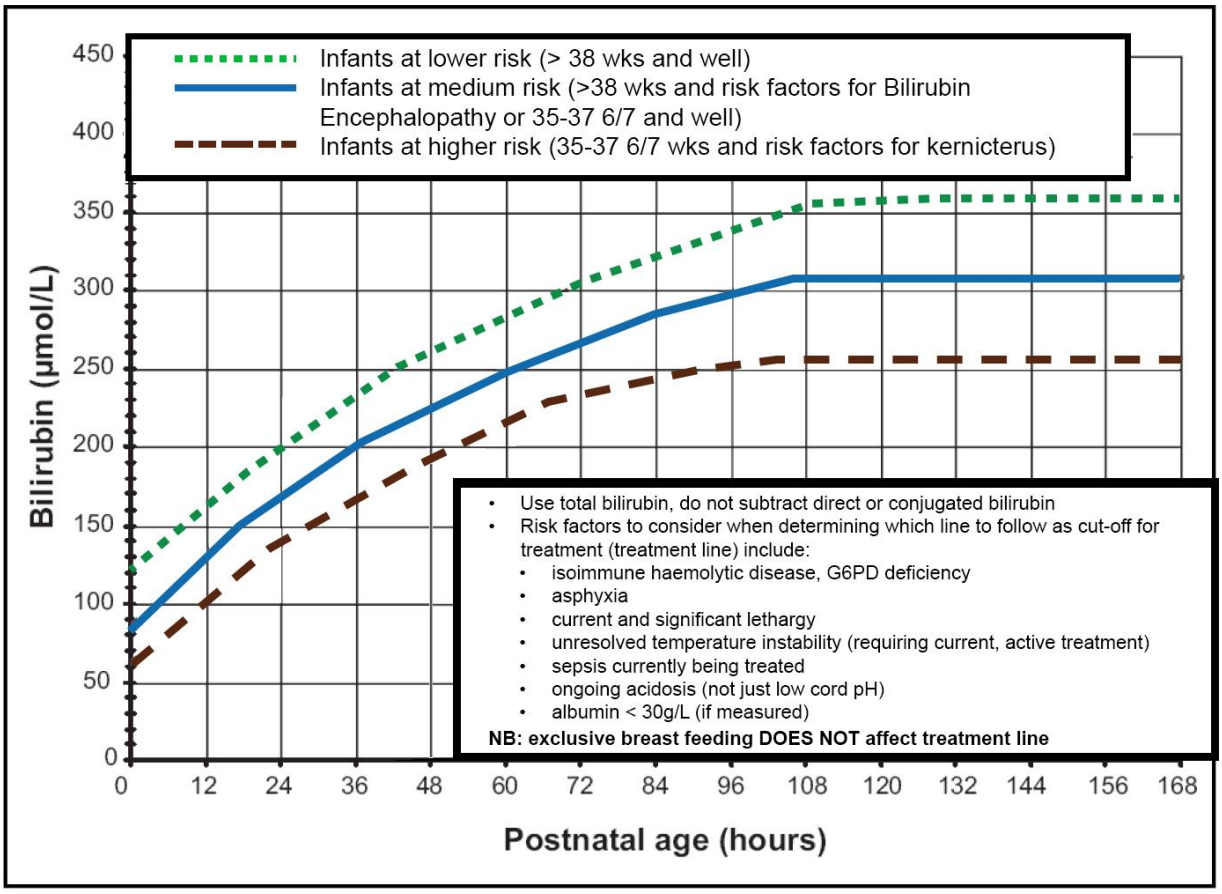
	Instructions	Recommendations	Support For Recommendations
			CEAG Consensus
13	**Repeat TSB in 4-6 hours**	- Use clinical judgment including consideration of **Severe Hyperbilirubinemia Risk Factors (RF #2)** and height of TSB to determine patient specific timing of repeat	AAP, NICE
14	**If TSB is stable/falling continue to repeat TSB q8-24 hours while on phototherapy**	- Use clinical judgment considering **Severe Hyperbilirubinemia Risk Factors (RF #2)** , response to therapy and height of TSB to determine patient specific timing of repeat	CEAG Consensus, considering: NICE (q6-12hr)
15	**Discontinue phototherapy when TSB is below threshold for phototherapy initiation**		CEAG Consensus
16	**Check TSB for rebound 12-24 hours after discontinuing phototherapy**	- Patient does not need to remain in hospital if outpatient follow-up can be ensured.	CEAG Consensus, considering: NICE (12-18 hr) AAP (clinical assessment or repeat TSB within 24 hours)
17	**If YES in Step #11, start Multiple Intensive Phototherapy**	- Add a phototherapy blanket under the infant to increase exposed surface area (i.e. double surface phototherapy) - Remove diaper - Do not interrupt phototherapy for feeding or other care - Supplemental fluids, oral or IV, should be administered in infants at elevated risk of requiring an exchange transfusion - Continue lactation/feeding support - Weigh baby daily and monitor urine and stool output	CPS AAP, CPS AAP, NICE CPS (Grade A) NICE NICE, CEAG Consensus
18	**Consider immediate consult with neonatologist (CPS Grade B)**	- IVIG or exchange transfusion may be indicated - Exchange transfusion should only be performed in tertiary level NICUs	AAP(Quality B: Benefits Exceeds Harms, Quality D: Benefits vs Harms Exceptional), CPS (Grade A), NICE AAP (Quality D: Benefits vs Harms Exceptional), CPS
19	**Repeat TSB in 2-6 hours to confirm response to treatment**	- Use clinical judgment including considering **Severe Hyperbilirubinemia Risk Factors (RF**	CPS , NICE (4-6 hrs)

	Instructions	Recommendations	Support For Recommendations
		#2) and height of TSB to determine patient-specific timing of repeat test	
20	**If TSB stable or decreasing continue to repeat q6-12h**	- Use clinical judgment **Severe Hyperbilirubinemia Risk Factors (RF #2)** , response to therapy and height of TSB to determine patient specific timing of repeat	NICE
21	**When TSB is more than 50µmol/L below exchange transfusion threshold return to Step # 12**		NICE
PHOTOTHERAPY – NO			
22	**If phototherapy not indicated, plot the TSB on the *Hour-Specific Nomogram* (See Figure 3)**	- Use the infant's age in hours at the time of blood draw - Use TSB (unconjugated + conjugated)	AAP, CPS (Grade D) CPS (Grade B)
23	**Assess for presence of any Severe Hyperbilirubinemia Risk Factors (RF #2)**	- The following risk factors are used to determine timing of repeat testing and clinical follow-up in **Step #24** : 1. Gestational age < 38 weeks (the lower the gestational age, the greater the risk) 2. Positive DAT or other known haemolytic disease (G6PD deficiency, spherocytosis) 3. Previous sibling with neonatal jaundice requiring phototherapy 4. Cephalohaematoma or significant bruising 5. Exclusive breastfeeding, particularly if infant is not feeding effectively and weight loss is excessive (> 8-10% weight loss from birth weight) 6. Ethnic risk factors refer to populations with a higher risk of g6pd deficiency. These include those of east or west Asian decent as well as Mediterranean and Middle Eastern populations. It is also important to collect a full family history.	AAP (Quality C: Benefits Exceeds Harms) CPS AAP, CPS, NICE, Maisels (Maisels MJ, 2009) AAP, Maisels AAP, CPS, NICE AAP, CPS AAP, CPS, NICE Maisels AAP, CPS, Maisels
24	**Consult *Follow-Up Algorithm* (Figure 4) for management**	- Use algorithm to determine: - If repeat TSB measurement is indicated	Maisels

	Instructions	Recommendations	Support For Recommendations
	and follow-up according to pre-discharge TSB	- Recommended timing of repeat TSB - Recommended timing of clinical follow-up	
25	**Arrange follow-up TSB measurement, if indicated**	- Setting of follow-up may vary depending on community resources. Refer to recommendations regarding *Community Follow-Up Care and Monitoring*, page 40	CPS AAP (Quality-C: Benefits Exceed Harms), NICE, Maisels
26	**If appropriate follow-up cannot be ensured in the presence of elevated risk for developing severe hyperbilirubinemia, delay discharge**	- Discharge should be delayed until appropriate follow-up can be ensured or the period of greatest risk has passed (72-96 hours).	AAP (Quality-D: Benefits vs Harms Exceptional)
27	**Provide lactation evaluation and support for all breastfeeding mothers**		CPS (Grade D) Maisels
28	**Any infant discharged before 24 hours should be assessed by an HCP within 24 hours**	- Health care provider conducting the assessment needs to have access to testing and treatment facilities.	CPS (Grade D)
29	**The infant's parent/guardian should be provided with written and verbal instructions regarding the infant's follow-up and the timing of that follow-up** (Refer to recommendations regarding *Discharge Documentation*, page 21)	- Include general information regarding jaundice, the importance of repeat TSB (if indicated) and clinical follow-up.	Adapted from AAP (Quality D: Benefits vs Harms Exceptional)
30	**The follow-up assessment should include** - Infant's weight and % change from birth weight - Adequacy of intake - Pattern of voiding and stooling - Presence or absence of visible jaundice	- Expectations: - Weight loss should be no more than 10% of birth weight - 4 to 6 wet diapers and 3 to 4 stools per day by the fourth day - Stools in breastfed infants should have changed from meconium to mustard yellow - Consider observing breastfeeding to assess effectiveness	AAP (Grade C)
31	**Clinical judgment should be used to determine the need for TSB measurement**	- If there is any doubt about the degree of jaundice, the TSB level should be measured.	AAP (Grade C)

	Instructions	Recommendations	Support For Recommendations
		- Visual estimation of bilirubin levels can lead to errors, especially in darkly pigmented infants.	
32	**Any repeat TSB measurements should be plotted in this algorithm in same manner as the initial TSB**	- To determine the need for phototherapy, need for further TSB measurements, and timing of clinical follow-up	

Phototherapy Graph



Adapted with permission from the Champlain Maternal Newborn Regional Program (Champlain Maternal Newborn Regional Program, 2012)

Exchange Transfusion Graph

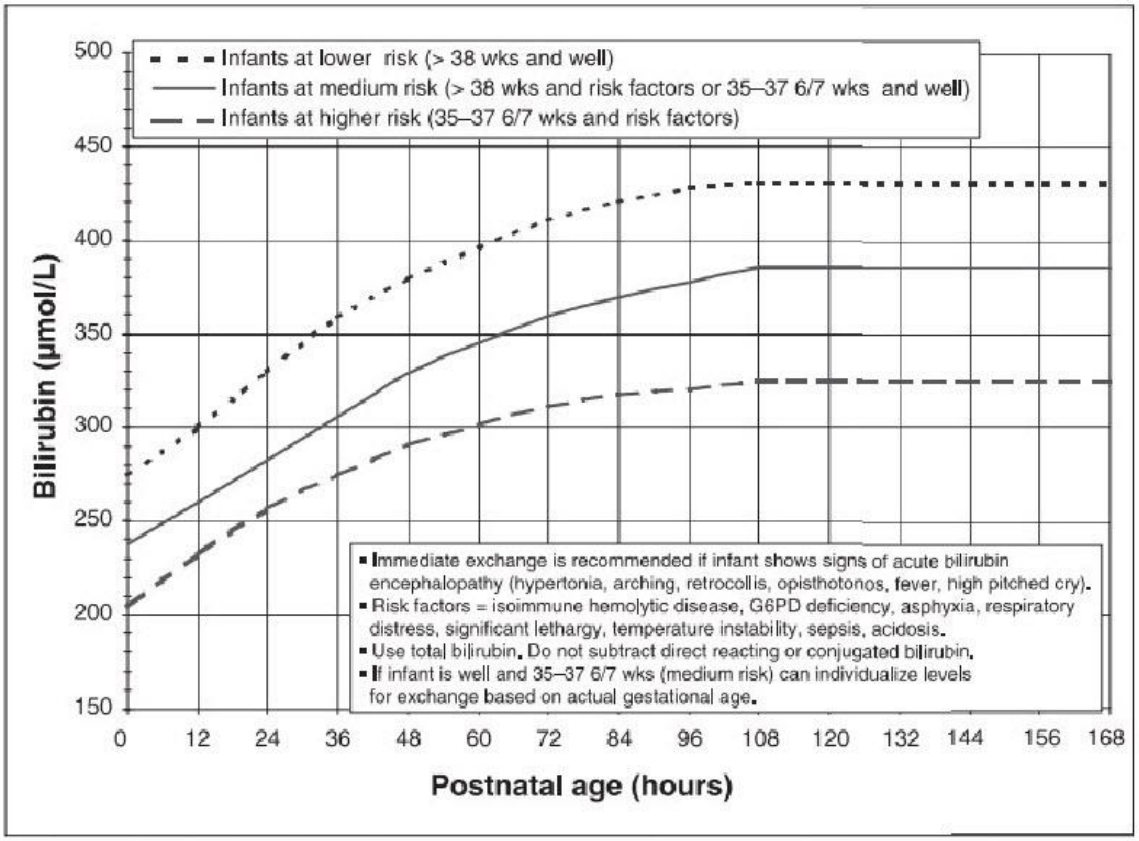
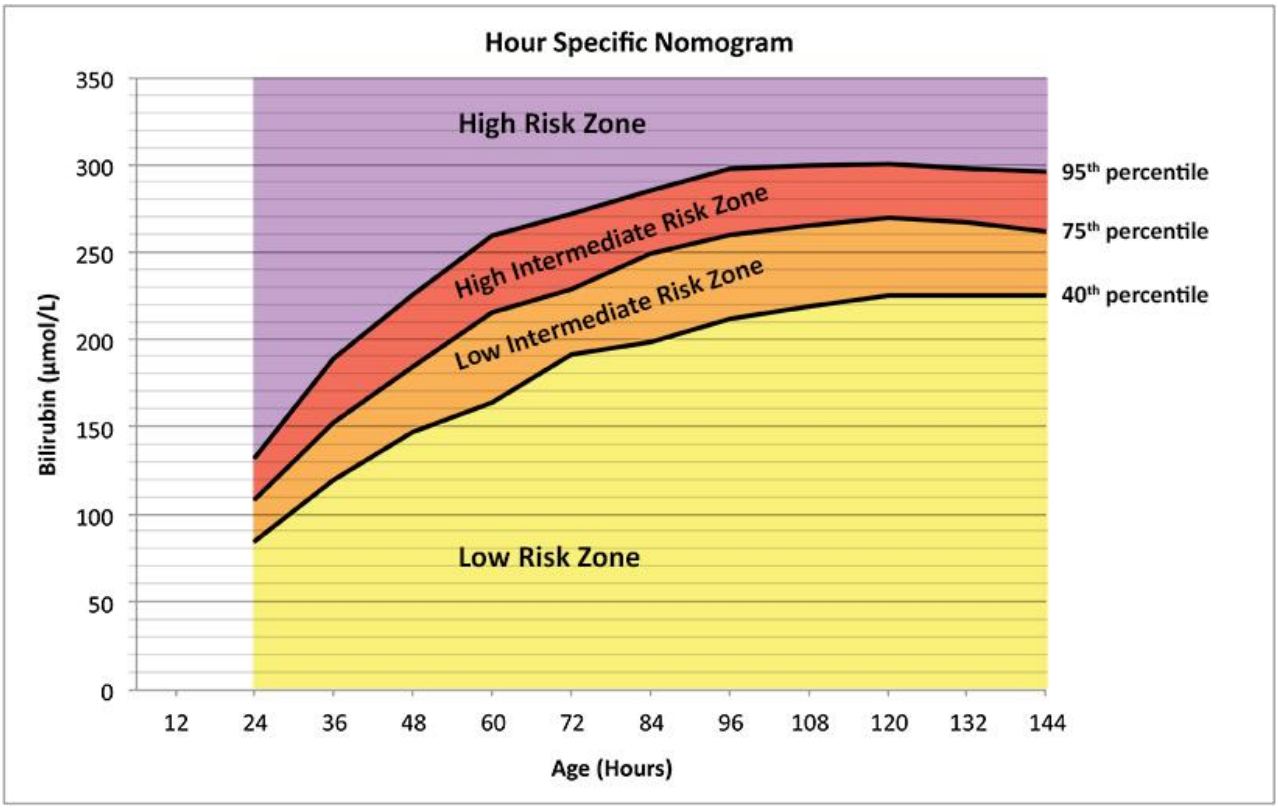


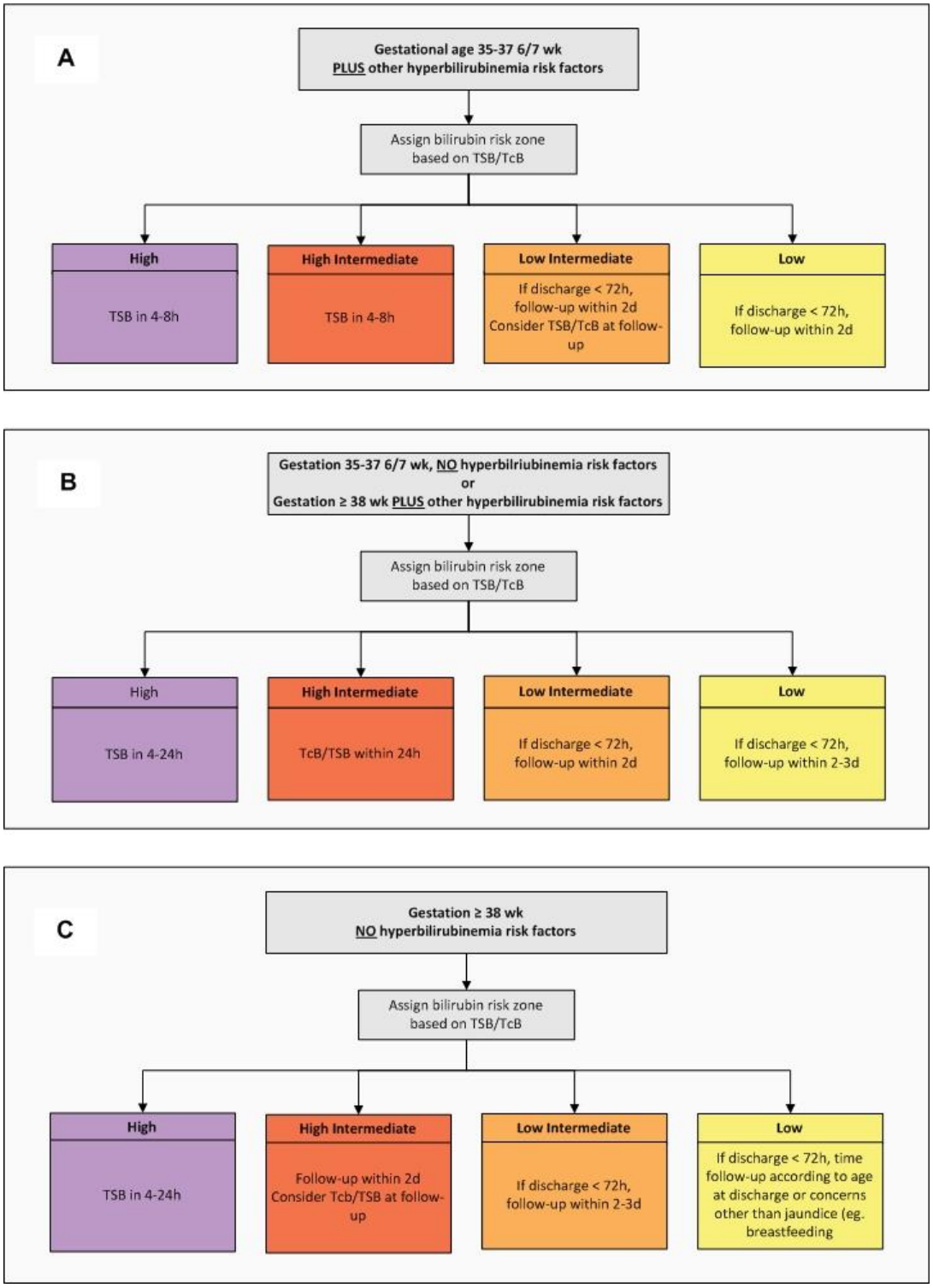
Figure 3) *Guidelines for exchange transfusion in infants of 35 or more weeks' gestation. These guidelines are based on limited evidence and the levels shown are approximations. Exchange transfusions should be used when the total serum bilirubin (TSB) concentration exceeds the line indicated for each category*

Hour Specific Nomogram



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

Follow-Up Algorithm



Modeled on Maisels' Algorithm (Maisels MJ, 2009), reflecting the findings of the Clinical Expert Advisory Group.

Appendix A – Description of Levels of Evidence

Organization	Canadian Paediatric Society (CPS)	
Guideline Name	Guideline for Detection, Management and Prevention of Hyperbilirubinemia in Term and Late Preterm Newborn Infants	
Evidence Grading Method	Oxford Centre for Evidence-Based Medicine – Levels of Evidence (Centre for Evidence Based Medicine, 2013)	
Grades	A: Consistent level 1 studies	1a – SR (with homogeneity) of RCTs 1b – Individual RCT (with narrow confidence interval) 1c – All or none
	B: Consistent level 2 or 3 studies	2a – SR (with homogeneity) of cohort studies 2b – Individual cohort study 2c – "Outcomes" research 3a – SR (with homogeneity) of case-control studies 3b – Individual case-control studies
	C: Level 4 studies	4 – Case-series (and poor quality cohort and case-control studies)
	D: Level 5 evidence or troublingly inconsistent or inconclusive studies of any level	Expert opinion without explicit critical appraisal or based on physiology, bench research or "first principles"

Organization	American Academy of Pediatrics (AAP)	
Guideline Name	Management of Hyperbilirubinemia in the Newborn Infant 25 or More Weeks of Gestation	
Evidence Grading Method	AAP Steering Committee on Quality Improvement and Management (American Academy of Pediatrics Steering Committee on Quality Improvement and Management, 2004)	
Grades	A: Well designed, RCTs or diagnostic studies on relevant populations	Preponderance of Benefit or Harm: Strong Recommendation Balance of Benefit and Harm: Option
	B: RCTs or diagnostic studies with minor limitations overwhelmingly consistent evidence from observational studies	Preponderance of Benefit or Harm: Strong Recommendation/ Recommendation Balance of Benefit and Harm: Option
	C: Observational studies (case control and cohort design	Preponderance of Benefit or Harm: Recommendation Balance of Benefit and Harm: Option
	D: Expert opinion case reports, reasoning from first principals	Preponderance of Benefit or Harm: Option Balance of Benefit and Harm: No Recommendation
	X: Exceptional situations where validating studies cannot be performed and there is clear preponderance of benefit or harm	Preponderance of Benefit or Harm: Strong Recommendation/ Recommendation

Organization	National Institute for Clinical Evidence (NICE)	
Guideline Name	Neonatal Jaundice	
Evidence Grading Method	NICE Clinical Guideline Development Methods (National Institute for Clinical Evidence, 2013) **Used to rate studies, but not to assign a grade to a recommendation**	
	For Intervention Studies	
	1++	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
	1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
	1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
	2++	High-quality systematic reviews of case–control or cohort studies; high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
	2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
	2-	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
	3	Non-analytical studies (e.g. case reports, case series)
	4	Expert opinion, formal consensus
	For Diagnostic Tests	
	Ia	Systematic review (with homogeneity) of level-1 studies
	Ib	Level-1 studies
	II	Level-2 studies systematic reviews of level-2 studies
	III	Level-3 studies systematic reviews of level-3 studies
	IV	Consensus, expert committee reports or opinions and/or clinical experience without explicit critical appraisal; or based on physiology, bench research or 'first principles'