GRADE TABLES

GRADE TABLE 1: INFANT FORMULA SUPPLEMENTATION (MIXED FEEDING) COMPARED TO EXCLUSIVE HUMAN MILK FOR PREVENTION OF SEVERE HYPERBILIRUBINEMIA

Bibliography: Chen C-F, Hsu M-C, Shen C-H, Wang C-L, Chang S-C, Wu K-G, et al. Influence of breast-feeding on weight loss, jaundice, and waste elimination in neonates. Pediatr Neonatol. 2011;52(2):85–92.

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With exclusive human milk	**With mixed feeding**		**Risk with exclusive human milk**	**Risk difference with mixed feeding**
Severe hyperbilirubinemia (assessed with: TSB concentration ≥ 256.5 µmol/L)											
241 (1 observational study)	very serious [a]	not serious	serious [b]	not serious	none	⨁◯◯◯ VERY LOW	35/161 (21.7%)	7/80 (8.8%)	**RR 0.40** (0.19 to 0.87)	217 per 1,000	**130 fewer per 1,000** (176 fewer to 28 fewer)
Need for phototherapy											
241 (1 observational study)	very serious [a]	not serious	serious [c]	not serious	none	⨁◯◯◯ VERY LOW	36/161 (22.4%)	7/80 (8.8%)	**RR 0.39** (0.18 to 0.84)	224 per 1,000	**136 fewer per 1,000** (183 fewer to 36 fewer)
Bilirubin levels on Day 4 (assessed with: TSB in µmol/L)											
54 measurements (1 observational study)	very serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	30	24	-	The mean bilirubin levels on Day 4 was **225.72**	MD **41.04 lower** (65.67 lower to 16.41 lower)

EXPLANATIONS:

a. Possibility for selection bias as participants were not selected from the same population, outcome measurements may have been measured with error as TSB levels were taken on day 3 and day 4 for some but not all participants, there is also missing and selective outcome data as TSB levels for all days are not provided nor is the time-point when "severe hyperbilirubinemia" is determined.

b. Severe hyperbilirubinemia is a surrogate outcome for kernicterus warranting a downgrade of one level

c. Severe hyperbilirubinemia is defined as 256.5 µmol/L and is the threshold used to re-admit all infants for phototherapy regardless of when their bilirubin levels were measured. We would not admit an infant whose bilirubin levels were near 256.5 µmol/L on days 3 or 4 but rather would consider treatment for infants whose bilirubin levels were above 300 µmol/L.

GRADE TABLE 2: EXCLUSIVE INFANT FORUMULA SUPPLEMENTATION COMPARED TO EXCLUSIVE HUMAN MILK FOR PREVENTION OF SEVERE HYPERBILIRUBINEMIA

Bibliography: Chen C-F, Hsu M-C, Shen C-H, Wang C-L, Chang S-C, Wu K-G, et al. Influence of breast-feeding on weight loss, jaundice, and waste elimination in neonates. Pediatr Neonatol. 2011;52(2):85–92.

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With exclusive human milk	**With exclusive formula**		**Risk with exclusive human milk**	**Risk difference with exclusive formula**
Severe hyperbilirubinemia (assessed with: TSB concentration ≥ 256.5 µmol/L)											
233 (1 observational study)	very serious [a]	not serious	serious [b]	not serious	none	⨁◯◯◯ VERY LOW	35/161 (21.7%)	3/72 (4.2%)	**RR 0.19** (0.06 to 0.60)	217 per 1,000	**176 fewer per 1,000** (204 fewer to 87 fewer)
Need for phototherapy											
233 (1 observational study)	very serious [a]	not serious	serious [c]	not serious	none	⨁◯◯◯ VERY LOW	36/161 (22.4%)	3/72 (4.2%)	**RR 0.19** (0.06 to 0.59)	224 per 1,000	**181 fewer per 1,000** (210 fewer to 92 fewer)
Bilirubin levels on Day 4 (assessed with: TSB in µmol/L)											
52 measurements (1 observational study)	very serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	30	22	-	The mean bilirubin levels on Day 4 was **225.72** µmol/L	MD **58.14 µmol/L lower** (87.46 lower to 28.82 lower)

EXPLANATIONS

a. Possibility for selection bias as participants were not selected from the same population, outcome measurements may have been measured with error as TSB levels were taken on day 3 and day 4 for some but not all participants, there is also missing and selective outcome data as TSB levels for all days are not provided nor is the time-point when "severe hyperbilirubinemia" is determined.

b. Severe hyperbilirubinemia is a surrogate outcome for kernicterus warranting a downgrade of one level.

c. Severe hyperbilirubinemia is defined as 256.5 µmol/L and is the threshold used to re-admit all infants for phototherapy regardless of when bilirubin levels were measured. We would not admit an infant whose bilirubin levels were near 256.5 µmol/L on days 3 or 4 but rather would consider treatment for infants whose levels were above 300 µmol/L.

GRADE TABLE 3: LACTATION SUPPORT COMPARED TO NO LACTATION SUPPORT FOR THE PREVENTION OF SEVERE HYPERBILIRUBINEMIA

Bibliography: Nilsson IMS, Strandberg-Larsen K, Knight CH, Hansen AV, Kronborg H. Focused breastfeeding counselling improves short- and long-term success in an early-discharge setting: A cluster-randomized study. Matern Child Nutr [Internet]. 2017;13(4). Available from: http://www.ncbi.nlm.nih.gov/pubmed/28194877

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With exclusive human milk	**With exclusive formula**		**Risk with exclusive human milk**	**Risk difference with exclusive formula**
Need for phototherapy											
2800 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	42/1143 (3.7%)	27/1657 (1.6%)	**RR 0.44** (0.28 to 0.71)	37 per 1,000	**21 fewer per 1,000** (from 26 fewer to 11 fewer)

EXPLANATIONS

a. For the outcome of phototherapy, there is no indication of the cutoff threshold that was used to determine the initiation for phototherapy, in either the intervention or control facilities. What constitutes usual care in these facilities is also unclear.

GRADE TABLE 4: DELAYED CORD CLAMPING COMPARED TO EARLY CORD CLAMPING FOR THE PREVENTION OF SEVERE HYPERBILIRUBINEMIA

Bibliography: McDonald SJ, Middleton P. Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. Cochrane database Syst Rev. 2013 Apr 16;(2):CD004074; Hutton EK, Hassan ES. Late vs early clamping of the umbilical cord in full-term neonates: systematic review and meta-analysis of controlled trials. JAMA. 2007 Mar 21; 297(11):1241-52.

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With exclusive human milk	**With exclusive formula**		**Risk with exclusive human milk**	**Risk difference with exclusive formula**
Need for phototherapy											
2324 (7 RCTs)	not serious	not serious [a]	not serious	not serious [b]	none	⨁⨁⨁⨁ HIGH	31/1131 (2.7%)	52/1193 (4.4%)	**RR 1.59** (1.03 to 2.46)	27 per 1,000	**16 more per 1,000** (from 1 more to 40 more)
Incidence of clinical jaundice (undefined)											
2098 (6 RCTs)	not serious	not serious [c]	not serious	serious [d]	none	⨁⨁⨁◯ MODERATE	97/977 (9.9%)	129/1121 (11.5%)	**RR 1.16** (0.90 to 1.49)	99 per 1,000	**16 more per 1,000** (from 10 fewer to 49 more)
Bilirubin levels at or after 72 hours (assessed with: TSB in µmol/L)											
91 (2 RCTs)	not serious	not serious	not serious	not serious [e]	none	⨁⨁⨁⨁ HIGH	36	55	-	The mean bilirubin level at or after 72 hours was **122.59**	MD **18.27 umol/L higher** (2.47 lower to 39 higher)

EXPLANATIONS

a. Results from the meta-analysis showed that heterogeneity was not statistically significant (Heterogeneity Chi2 = 5.41, df = 6 (P = 0.49); I2 = 0.0%).
b. Although there are less than 300 events the large sample size and narrow 95% CI around the absolute effect (2-26) led us to judge the outcome as precise.
c. Results from the meta-analysis showed that heterogeneity was not statistically significant (Heterogeneity Chi2 = 5.02, df = 5 (P = 0.41); I2 = 0.0%).
d. Imprecision was rated serious because there were less than 300 events in each group and the 95% CI of the risk ratio (RR) and the risk difference were not narrow indicating imprecise results.
e. Despite the small sample size, the results are considered precise because the course of action would not differ if the upper or the lower boundary of the CI represented the truth: for infants 72 hours of age or older, phototherapy would not be started even if the true bilirubin levels were 101.86 µmol/L (39 lower) or 143.33 µmol/L (2.47 higher).

GRADE TABLE 5: DELAYED CORD CLAMPING COMPARED TO EARLY CORD CLAMPING AMONG CESAREAN-BORN ABO—ALLOIMMUNIZED INFANTS

Bibliography: Ghirardello S, Crippa BL, Di Francesco E, Consonni D, Colombo L, Fumagalli M, te Pas AB, Mosca F. Delayed cord clamping increased the need for phototherapy threatment in infants with ABO alloimmunization born by caesarean section: A retrospective study. Frontiers in Pediatrics. 2018 Sep 19; 6(241):1-6.

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Immediate cord clamping among high-risk infants	**With Delayed**		**Risk with Immediate cord clamping among high-risk infants**	**Risk difference with Delayed**
Need for phototherapy											
336 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	43/192 (22.4%)	53/144 (36.8%)	**RR 1.64** (1.17 to 2.31)	224 per 1,000	**143 more per 1,000** (38 more to 293 more)
Rates of hospital readmission											
336 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	3/192 (1.6%)	5/144 (3.5%)	**RR 2.22** (0.54 to 9.15)	16 per 1,000	**19 more per 1,000** (7 fewer to 127 more)
Maximum bilirubin levels (assessed with: TSB in µmol/L)											
336 (1 observational study)	not serious	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	192	144	-	The mean max bilirubin levels was **194.9** umol/L	MD **25.7 umol/L higher** (11.94 higher to 39.46 higher)

EXPLANATIONS

a. Imprecision was rated serious because there were less than 300 events in each group and the 95% CI of the risk ratio (RR) were not narrow indicating imprecise results.

b. The wide confidence interval around the mean difference in peak bilirubin levels suggests that the true value of difference between groups is uncertain; given the gestational ages and the presence of risk factors among the infants included in the study the upper and lower boundaries of the 95% CI could suggest different clinical courses of care.

GRADE TABLE 6: POSTPARTUM HOME VISITS COMPARED TO NO POSTPARTUM HOME VISITS FOR THE PREVENTION OF SEVERE HYPERBILIRUBINEMIA

Bibliography: Gagnon AJ, Edgar L, Kramer MS, Papageorgiou A, Waghorn K, Klein MC. A randomized trial of a program of early postpartum discharge with nurse visitation. Am J Obstet Gynecol. 1997 Jan;176(1 Pt 1):205–11; **Paul IM**, Phillips TA, Widome MD, Hollenbeak CS. Cost-effectiveness of postnatal home nursing visits for prevention of hospital care for jaundice and dehydration. Pediatrics. 2004 Oct;114(4):1015–22; **Bashour HN**, Kharouf MH, AbdulSalam AA, El Asmar K, Tabbaa MA, Cheikha SA. Effect of postnatal home visits on maternal/infant outco*mes in Syria: A randomized controlled trial. Public Health Nurs. 2008;25(2):115–25.

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With no home visits	**With home visits**		**Risk with no home visits**	**Risk difference with home visits**
Incidence of severe hyperbilirubinemia (undefined)											
172 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	5/97 (5.2%)	2/75 (2.7%)	**RR 0.52** (0.10 to 2.59)	52 per 1,000	**25 fewer per 1,000** (46 fewer to 82 more)
Rates of hospital readmission											
2967 (1 observational study)	serious [c]	not serious	serious [d]	not serious	none	⨁◯◯◯ VERY LOW	73/2641 (2.8%)	2/326 (0.6%)	**RR 0.22** (0.05 to 0.90)	28 per 1,000	**22 fewer per 1,000** (26 fewer to 3 fewer)
Incidence of jaundice (undefined)											
573 (1 RCT)	serious [e]	not serious	serious [f]	serious [b]	none	⨁◯◯◯ VERY LOW	99/293 (33.8%)	92/280 (32.9%)	**RR 0.97** (0.77 to 1.23)	338 per 1,000	**10 fewer per 1,000** (78 fewer to 78 more)
Exclusive breastfeeding rates											
757 (2 RCTs)	not serious	not serious	serious [g]	not serious	none	⨁⨁⨁◯ MODERATE	97/394 (24.6%)	124/363 (34.2%)	**RR 1.42** (1.14 to 1.76)	246 per 1,000	**103 more per 1,000** (34 more to 187 more)

EXPLANATIONS

a. Unclear how "Severe hyperbilirubinemia" was defined. Substantial risk of bias due to missing outcome data as a result of post-randomization exclusions: 360 participants were enrolled in the study yet outcome data is available for only 172.

b. Evidence is considered imprecise due to number of events and confidence interval that includes the null.

c. This outcome was judged to be at serious risk of bias because the two groups were not matched on any baseline demographic characteristics and home visits were provided at the discretion of the hospital physician

d. Evidence is considered indirect due to differences in the intervention (1 home visit) offered in the study and the Ontario midwifery standard of care which is a minimum of 3 home visits in the first week.
e. Not blinded: Participants, care providers, and to a lesser extent, outcome assessors were aware of study arm allocation. Knowledge of allocation may have influenced this subjective outcome. Other possible sources of bias: Not clear how randomization sequence was generated.
f. The outcome of "jaundice" is considered a proxy outcome, as it is not defined in the study protocol and so its significance or relevance to the outcomes of interest to this guideline is unclear. The evidence is further downgraded for indirectness due to likely differences between low-resource and ON setting and access and content of care. In particular, not clear whether control group (no home visits) would have received care similar to Ontario, where post-discharge follow-up with family doctor or pediatrician is standard for infants who are not under the care of a midwife. Also, the schedule of home visits may be different than what is offered by Ontario midwives.
g. The evidence is downgraded for indirectness as one study contributing 63% of the weight to the meta-analysis took place in Syria and it is not clear whether control group (no home visits) would have received care similar to Ontario, where post-discharge follow-up with family doctor or pediatrician is standard for infants who are not under the care of a midwife. Also, the schedule of home visits was different than what is offered by Ontario midwives.

GRADE TABLE 6: SUNLIGHT COMPARED TO PHOTOTHERAPY FOR PREVENTION OF SEVERE HYPERBILIRUBINEMIA

Bibliography: Cremer RJ, Perryman PW, Richards DH. Influence of light on the hyperbilirubinaemia of infants. Lancet. 1958;1(7030):1094–7.

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With conventional phototherapy	**With sunlight**		**Risk with conventional phototherapy**	**Risk difference with sunlight**
Need for exchange transfusion											
24 (1 observational study)	serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	2/11 (18.2%)	0/13 (0.0%)	**RR 0.17** (0.01 to 3.23)	182 per 1,000	**151 fewer per 1,000** (180 fewer to 405 more)
Decrease in bilirubin levels (assessed with TSB in µmol/L)											
32 (1 observational study)	serious [d]	not serious	serious [b]	not serious	none	⨁◯◯◯ VERY LOW	12	20	-	The mean decrease in bilirubin levels was **75.6** umol/L	MD **9.8 umol/L lower** (40.03 lower to 20.43 higher)

EXPLANATIONS

a. Possibility of performance bias as there were systematic differences between the durations of exposure to light provided to both groups.
b. The preterm population under study does not directly respond to the CPG's focus on healthy term infants.
c. The study's small sample size and very low event rates result in an estimate of association regarding the need for exchange transfusion which is imprecise
d. Risk of bias is very serious because of the differences in the number of times bilirubin measurements were measured between the two groups, missing outcome data from two infants whose bilirubin measurements were not taken, as well as the systematic differences between the durations of exposure to light provided to both groups that may have influenced the declines in bilirubin levels observed in the study.

GRADE TABLE 7: INFANT MASSAGE COMPARED TO NO MASSAGE FOR PREVENTION OF SEVERE HYPERBILIRUBINEMIA

Bibliography: Dalili H, Sheikhi S, Shariat M, Haghnazarian E. Effects of baby massage on neonatal jaundice in healthy Iranian infants: A pilot study. Infant Behav Dev. 2016;42(PG - 22-6):22–6; **Chen J**, Sadakata M, Ishida M, Sekizuka N, Sayama M. Baby massage ameliorates neonatal jaundice in full-term newborn infants. Tohoku J Exp Med. 2011;223(2):97–102; **Seyyedrasooli A**, Valizadeh L, Hosseini MB, Asgari Jafarabadi M, Mohammadzad M. Effect of vimala massage on physiological jaundice in infants: a randomized controlled trial. J Caring Sci. 2014;3(3):165–73

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With conventional phototherapy	**With sunlight**		**Risk with conventional phototherapy**	**Risk difference with sunlight**
Bilirubin levels (assessed with TcB in µmol/L)											
92 (2 RCTs)	very serious [a]	not serious	not serious	not serious [b]	none	⨁⨁◯◯ LOW	47	45	-	The mean bilirubin levels was **194.60** umol/L	MD **31.55 umol/L lower** (43.48 lower to 19.63 lower) [c]

EXPLANATIONS

a. Inadequate and unclear sequence generation and allocation concealment, lack of blinding of parents and researchers, and incomplete and selective outcome reporting.
b. Total sample size: 92 participants. Despite small sample, mean difference standard deviations do not cross null.
c. Data from a third study (n = 43) could not be meta-analyzed but results are consistent with the pooled data suggesting that bilirubin levels on day four were slightly lower among infants who received infant massage than those who did not.

GRADE TABLE 8: VISUAL ASSESSMENT (JAUNDICE: YES OR NO?) VS. TSB FOR THE SCREENING OF SEVERE HYPERBILIRUBINEMIA

Bibliography: Riskin A, Abend-Weinger M, Bader D. How accurate are neonatologists in identifying clinical jaundice in newborns? Clin Pediatr (Phila). 2003 Mar;42(2):153–8.

Certainty assessment							Summary of Findings						
№ of participants (studies)	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Publication bias**	**Test accuracy Quality of evidence**	**Thresholds**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**True Positive**	**False Positive**	**False negative**	**True negative**
Diagnostic Accuracy (assessed with true positive, false positive, false negative, true negative)													
317 (1 cross-sectional study)	not serious	very serious [a]	not serious	not serious	none	⊕⊕◯◯ LOW	68 µmol/L	0.37 (0.32-0.42)	0.96 (0.87-1.0)	117	2	200	52
							204 µmol/L	0.81 (0.58-0.95)	0.71 (0.66-0.76)	17	102	4	248

EXPLANATIONS

a. Indirectness was rated very serious because the outcomes presented in this study are proxy outcomes; the study did not report the down-stream consequences of receiving a false positive or a false negative response therefore we are uncertain if any infants developed severe hyperbilirubinemia in this sample. Moreover, this study purposefully chose to examine bilirubin levels which are not clinically significant - with this data alone we cannot be certain how accurate visual assessment is at detecting severe hyperbilirubinemia. All other GRADE criteria were rated not serious.

GRADE TABLE 9: VISUAL ASSESSMENT (CEPHALOCAUDAL PROGRESSION) VS. TSB FOR THE SCREENING OF SEVERE HYPERBILIRUBINEMIA

Bibliography: Aprillia Z, Gayatri D, Waluyanti FT. Sensitivity, Specificity, and Accuracy of Kramer Examination of Neonatal Jaundice: Comparison with Total Bilirubin Serum. Compr child Adolesc Nurs [Internet]. 40(sup1):88–94. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29166181

Certainty assessment							Summary of Findings						
№ of participants (studies)	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Publication bias**	**Test accuracy Quality of evidence**	**Thresholds**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**True Positive**	**False Positive**	**False negative**	**True negative**
Diagnostic Accuracy (assessed with true positive, false positive, false negative, true negative)													
102 (1 cross-sectional study)	serious [a]	serious [b]	not serious	not serious	none	⊕⊕◯◯ LOW	Positive Kramer Zone	0.71 (0.51-0.87)	0.92 (0.83-0.97)	20	6	8	68

a. Risk of bias was rated serious as the study categorizes infants as having a 'positive' or 'negative' TSB results without providing information on the thresholds used to determine a 'positive' result.

b. Indirectness was rated serious because the outcome data presented in this study are proxy outcomes; the study did not report the down-stream consequences of receiving a false positive or a false negative response therefore we are uncertain if any infants developed severe hyperbilirubinemia in this sample.

GRADE TABLE 10: VISUAL ASSESSMENT (CEPHALOCAUDAL PROGRESSION TO THE MID-ABDOMEN) VS. TSB FOR THE SCREENING OF SEVERE HYPERBILIRUBINEMIA

Bibliography: Kaplan M, Shchors I, Algur N, Bromiker R, Schimmel MS, Hammerman C. Visual screening versus transcutaneous bilirubinometry for predischarge jaundice assessment. Acta Paediatr. 2008 Jun;97(6):759–63.

Certainty assessment							Summary of Findings						
№ of participants (studies)	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Publication bias**	**Test accuracy Quality of evidence**	**Thresholds**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**True Positive**	**False Positive**	**False negative**	**True negative**
Diagnostic Accuracy (assessed with true positive, false positive, false negative, true negative)													
346 (1 cross-sectional study)	serious [a]	serious [b]	not serious	not serious	none	⨁⨁◯◯ LOW	TSB ≥ 75th percentile	0.84 (0.64-0.95)	0.81 (0.76-0.85)	21	62	4	259

EXPLANATIONS:

a. Risk of bias was rated serious due to incomplete data; not all infants received TSB testing (reference standard) resulting in detection bias.

b. Indirectness was rated serious because the outcome data presented in this study are proxy outcomes; the study did not report the down-stream consequences of receiving a false positive or a false negative response therefore we are uncertain if any infants developed severe hyperbilirubinemia in this sample.

GRADE TABLE 11: VISUAL ASSESSMENT (RISK ZONES) VS. TSB MEASUREMENT FOR THE SCREENING OF SEVERE HYPERBILIRBUINEMIA

Bibliography: Riskin A, Tamir A, Kugelman A, Hemo M, Bader D. Is visual assessment of jaundice reliable as a screening tool to detect significant neonatal hyperbilirubinemia? J Pediatr. 2008 Jun;152(6):782–7, 787.e1–2.

Certainty assessment							Summary of Findings						
№ of participants (studies)	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Publication bias**	**Test accuracy Quality of evidence**	**Thresholds**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**True Positive**	**False Positive**	**False negative**	**True negative**
Diagnostic Accuracy (assessed with true positive, false positive, false negative, true negative)													
1129 (1 cross-sectional study)	not serious	serious [a]	not serious	serious [b]	none	⊕⊕◯◯ LOW	Zone A	0.89 (0.87-0.90)	0.59 (0.55-0.64)	2627	230	338	337
							Zone B	0.43 (0.38-0.47)	0.89 (0.88-0.90)	195	331	263	2743
							Zone C	0.34 (0.25-0.45)	0.97 (0.96-0.98)	32	101	62	3337
							Zone D	0.13 (0.02-0.40)	1.00 (0.99-1.00)	2	14	13	3503

EXPLANATIONS:

a. Indirectness was judged to be serious because the population enrolled in the study included late preterm infants and infants with hemolytic disease which is beyond the scope of this guideline.

b. Imprecision was rated serious due to the wide confidence intervals of sensitivity in Zones C + D which include 0 meaning that visual assessment may not identify any infants at higher risk.

GRADE TABLE 12: CLINICAL RISK FACTOR SCORING SYSTEM VS PRE-DISCHARGE TSB RISK ZONE FOR THE PREDICTION OF SEVERE HYPERBILIRUBINEMIA

Bibliography: Keren R, Bhutani VK, Luan X, Nihtianova S, Cnaan A, Schwartz JS. Identifying newborns at risk of significant hyperbilirubinemia: a comparison of two recommended approaches. Arch Dis Child. 2005;90:415-421.

Certainty assessment							Summary of Findings						
№ of participants (studies)	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Publication bias**	**Test accuracy Quality of evidence**	**Thresholds**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**True Positive**	**False Positive**	**False negative**	**True negative**
Diagnostic Accuracy													
884 (1 cohort study)	not serious	very serious [a]	not serious	not serious	none	⊕⊕◯◯ LOW	≥ 8	0.98 (0.93-1.0)	0.13 (0.11-0.16)	95	682	2	105
							≥ 12	0.86 (0.77-0.92)	0.41 (0.38-0.45)	83	464	14	323
							≥ 16	0.54 (0.43-0.64)	0.76 (0.72-0.79)	52	192	45	595
							≥ 20	0.22 (0.14-0.31)	0.92 (0.90-0.94)	21	65	76	722
							≥ 24	0.02 (0.00-0.07)	0.99 (0.99-1.0)	2	5	95	782

EXPLANATIONS:

a. The quality of evidence for diagnostic accuracy was rated low as indirectness was judged to be very serious for two reasons. First, the clinical risk factor score is not relevant to midwifery scope of practice as they consider multiple risk factors in a clinical assessment. Second, the outcomes presented in this study are proxy outcomes; the study did not report the down-stream consequences of receiving a false positive or a false negative response therefore we are uncertain if any infants developed severe hyperbilirubinemia in this sample.

GRADE TABLE 13: TRANSCUTANEOUS BILIMETRE (TcB MEASUREMENTS) VS TSB FOR THE SCREENING OF SEVERE HYPERBILIRUBINEMIA

Bibliography: Institute of Health Economics. Transcutaneous Bilirubinometry for the Screening of Neonatal Hyperbilirubinemia. Edmonton, Alberta; 2013.

Certainty assessment							Summary of Findings						
№ of participants (studies)	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Publication bias**	**Test accuracy Quality of evidence**	**Thresholds**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**True Positive**	**False Positive**	**False negative**	**True negative**
Diagnostic Accuracy: Predicting TSB value-based hyperbilirubinemia													
1946 (6 cross-sectional studies)	serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	265.5 µmol/L	96-100 (CI not reported)	39-90 (CI not reported)	Not reported	Not reported	Not reported	Not reported
Diagnostic Accuracy: Predicting TSB percentile-based hyperbilirubinemia													
1935 (5 cross-sectional studies)	serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	95th percentile	87-100 (CI not reported)	30-88 (CI not reported)	Not reported	Not reported	Not reported	Not reported

a) Included studies were subject to various methodological limitations including concerns that a consecutive or random sample was not enrolled, that blinding was not adequate and that there were inappropriate exclusions at the enrollment or analysis stage.
b) The variability in reported sensitivity and specificity values suggest results were inconsistent across studies.
c) Imprecision cannot be assessed in the study as 95% confidence intervals for the sensitivity and specificity data were not provided

GRADE TABLE 14: UNIVERSAL BILIRUBIN MEASUREMENT COMPARED TO SELECTIVE BILIRUBIN MEASUREMENT FOR SCREENING OF SEVERE HYPERBILIRUBINEMIA

Bibliography: Alkalay AL, Bresee CJ, Simmons CF. Decreased neonatal jaundice readmission rate after implementing hyperbilirubinemia guidelines and universal screening for bilirubin. Clin Pediatr (Phila) [Internet]. 2010 Sep;49(9):830–3; **Bhutani VK**, Johnson LH, Schwoebel A, Gennaro S. A systems approach for neonatal hyperbilirubinemia in term and near-term newborns. J Obstet Gynecol neonatal Nurs JOGNN. 35(4):444–55; **Wickremasinghe AC**, Karon BS, Saenger AK, Cook WJ. Effect of universal neonatal transcutaneous bilirubin screening on blood draws for bilirubin analysis and phototherapy usage. J Perinatol [Internet]. 2012 Nov;32(11):851–5; **Morgan MC**, Kumar GS, Kaiser S V, Seetharam S, Ruel TD. Implementation of a neonatal transcutaneous bilirubin screening programme in rural India. Paediatr Int Child Health [Internet]. 2016 May;36(2):122–6; **Wainer S**, Parmar SM, Allegro D, Rabi Y, Lyon ME. Impact of a transcutaneous bilirubinometry program on resource utilization and severe hyperbilirubinemia. Pediatrics [Internet]. 2012 Jan;129(1):77–86; **Kuzniewicz MW**, Escobar GJ, Newman TB. Impact of universal bilirubin screening on severe hyperbilirubinemia and phototherapy use. Pediatrics. 2009 Oct;124(4):1031–9; **Darling EK**, Ramsay T, Sprague AE, Walker MC, Guttmann A. Universal bilirubin screening and health care utilization. Pediatrics. 2014 Oct;134(4):e1017–24; **Eggert LD**, Wiedmeier SE, Wilson J, Christensen RD. The effect of instituting a prehospital-discharge newborn bilirubin screening program in an 18-hospital health system. Pediatrics. 2006 May;117(5):e855–62; **Mah MP**, Clark SL, Akhigbe E, Englebright J, Frye DK, Meyers JA, et al. Reduction of severe hyperbilirubinemia after institution of predischarge bilirubin screening. Pediatrics. 2010 May;125(5):e1143–8.

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With no universal bilirubin measurement	**With Universal bilirubin measurement**		**Risk with no universal bilirubin measurement**	**Risk difference with Universal bilirubin measurement**
Need for exchange transfusion											
49726 (2 observational studies)	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	4/24661 (0.0%)	5/25065 (0.0%)	**RR 1.31** (0.35 to 4.86)	16 per 100,000	**5 more per 100,000** (from 11 fewer to 63 more)
Incidence of bilirubin concentration ≥ 513 µmol/L (assessed with: TSB or TcB in µmol/L)											
1408759 (3 observational studies)	serious [c]	not serious	serious [d]	serious [e]	none	⨁◯◯◯ VERY LOW	52/459943 (0.0%)	29/948816 (0.0%)	**RR 0.35** (0.19 to 0.65)	11 per 100,000	**7 fewer per 100,000** (from 9 fewer to 4 fewer)
Incidence of bilirubin concentration ≥ 427.5 µmol/L (assessed with: TSB or TcB in µmol/L)											
1510040 (4 observational studies)	serious [c]	serious [f]	serious [d]	not serious	none	⨁◯◯◯ VERY LOW	477/508741 (0.1%)	266/1001299 (0.0%)	**RR 0.42** (0.25 to 0.70)	94 per 100,000	**54 fewer per 100,000** (from 70 fewer to 28 fewer)

Incidence of bilirubin concentration ≥ 342 µmol/L (assessed with: TSB or TcB in µmol/L)											
481223 (3 observational studies)	serious [c]	serious [g]	not serious	not serious	none	⨁◯◯◯ VERY LOW	7187/379396 (1.9%)	936/101827 (0.9%)	**RR 0.58** (0.47 to 0.71)	1,894 per 100,000	**796 fewer per 100,000** (from 1,004 fewer to 549 fewer)
Need for phototherapy											
408302 (5 observational studies)	serious [h]	serious [i]	serious [d]	not serious	none	⨁◯◯◯ VERY LOW	15037/344769 (4.4%)	4862/63533 (7.7%)	**RR 1.10** (0.64 to 1.90) [j]	44 per 1,000	**4 more per 1,000** (from 16 fewer to 39 more)
Rates of hospital readmission											
115202 (2 observational studies)	serious [c]	serious [k]	not serious	not serious	none	⨁◯◯◯ VERY LOW	334/55770 (0.6%)	252/59432 (0.4%)	**RR 0.58** (0.30 to 1.12) [l]	6 per 1,000	**3 fewer per 1,000** (from 4 fewer to 1 more)

EXPLANATIONS:

a. Risk of bias was judged to be serious because the studies failed to adequately control for confounding variables. For example, infants receiving universal screening also received lactation support which may influence rates of severe hyperbilirubinemia and the requirement for treatment including exchange transfusion.

b. Given that the need for exchange transfusion is a rare event, many event rates are required to gather an understanding of the certainty of the risk of an exchange transfusion. Because this study had few event rates, our confidence in this estimate is limited warranting a rating of serious imprecision.

c. Risk of bias was rated serious because the studies failed to identify or control from confounding factors such as risk factors, rates of breastfeeding, lactation support programs, or parental education.

d. Indirectness was rated serious as the population included in the studies was not limited to healthy term or late-term neonates.

e. Imprecision was rated serious as there were less than 300 events between the two groups.

f. Inconsistency was rated serious as heterogeneity in the meta-analysis was statistically significant (Heterogeneity $Chi^2 = 8.55$, df = 3 (P = 0.04); $I^2 = 65\%$).

g. Inconsistency was rated very serious as heterogeneity in the meta-analysis was statistically significant (Heterogeneity $Chi^2 = 7.94$, df = 1 (P = 0.005); $I^2 = 87\%$).

h. The evidence was judged to be at serious risk of bias because the studies failed to adequately control for confounding variables. For example, infants receiving universal screening also received lactation support which we know may influence rates of severe hyperbilirubinemia and the requirement for treatment including phototherapy.

i. Inconsistency was rated serious as heterogeneity in the meta-analysis was statistically significant (Heterogeneity: $Chi^2 = 423.44$, df = 4 (P < 0.00001); $I^2 = 99\%$).

j. Data from a sixth study (n = 534,103) could not be meta-analyzed but results are consistent with the pooled data suggesting that rates of phototherapy increased after the implementation of universal screening (RR 1.28).

k. Inconsistency was rated serious as study results across the three studies are different: after the implementation of universal screening one study reported a increased rate of readmission to hospital whereas the others reported decreased rates.

l. Data from a third study (n = 534,103) could not be meta-analyzed but results are inconsistent with the pooled data suggesting that rates of readmission to hospital increased after the implementation of universal screening (RR 1.21).

GRADE TABLE 15: FIBREOPTIC PHOTOTHERAPY COMPARED TO CONVENTIONAL PHOTOTHERAPY FOR TREATMENT OF SEVERE HYPERBILIRUBINEMIA

Bibliography: Mills JF, Tudehope D. Fibreoptic phototherapy for neonatal jaundice. Cochrane Database Syst Rev. 2001;(1):CD002060.

Certainty assessment							Summary of findings				
Nº of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With conventional phototherapy	**With Fibreoptic**		**Risk with conventional phototherapy**	**Risk difference with Fibreoptic**
Duration of phototherapy (assessed with: hours)											
330 (4 RCTs)	very serious [a]	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	166	164	-	The mean duration of phototherapy (hours) was **53.8** hours	MD **21.45 hours higher** (16.92 higher to 25.99 higher)
Change in bilirubin concentration over total treatment period (assessed with: % change/day, TSB in µmol/L)											
345 (5 RCTs)	not serious	serious [b]	not serious	not serious	none	⨁⨁⨁◯ MODERATE	The change in bilirubin concentration was 4.82% (p < 0.0005) greater in the conventional phototherapy group than in the fibreoptic phototherapy group.				
Change in bilirubin concentration over first 24 hours of treatment (assessed with: % change/ 24 hours, TSB in µmol/L)											
183 (4 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	The percent change in bilirubin concentration was 4.35% (p = 0.002) greater in the conventional phototherapy group than in the fibreoptic phototherapy group.				

EXPLANATIONS:

a. Three of the four studies contributing 92.8% of the weight to the meta-analysis were found to have major methodological flaws. These studies were not randomized and did not properly conceal the allocation sequence. Furthermore, outcome assessors and study personnel were not blinded to study arm allocation and this outcome is particularly susceptible to bias. While blinding may have been difficult due to the nature of the intervention, the knowledge of study arm may have influenced how long study personnel kept infants under phototherapy lights.

b. Results appear inconsistent; heterogeneity in the meta-analysis of the seven studies was statistically significant (Heterogeneity $Chi^2 = 21.74$, df = 6 (P = 0.001); $I^2 = 72\%$)

GRADE TABLE 16: FORMULA SUPPLEMENTATION (MIXED FEEDING) DURING PHOTOTHERAPY COMPARED TO EXCLUSIVE HUMAN MILK FEEDING DURING PHOTOTHERAPY FOR TREATMENT OF SEVERE HYPERBILIRUBINEMIA

Bibliography: Gulcan H, Tiker F, Kilicdag H. Effect of feeding type on the efficacy of phototherapy. Indian Pediatr. 2007 Jan;44(1):32–6.

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Exclusively chest/breastfed infants	**With Mixed fed**		**Risk with Exclusively chest/breastfed infants**	**Risk difference with Mixed fed**
Duration of phototherapy (assessed with: hours)											
53 (1 observational study)	serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	28	25	-	The mean duration of phototherapy (hours) was **38.6** hours	MD **11.8 hours lower** (17.75 lower to 5.85 lower)
Rate of TSB decrease with a 24 hour period (assessed with: hours)											
53 (1 observational study)	serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	28	25	-	The mean rate of TSB decrease (24 hours) was **68.4** µmol/L	MD **23.94 µmol/L higher** (7.05 higher to 40.83 higher)

EXPLANATIONS:

a. Study authors did not identify or control for confounders such as parity, feeding support, or length or timing of feeding nor did they report on all relevant outcome measures one would anticipate in this review such as need for exchange transfusion.

GRADE TABLE 17: INFANT MASSAGE DURING PHOTOTHERAPY COMPARED TO NO INFANT MASSAGE DURING PHOTOTHERAPY FOR TREATMENT OF SEVERE HYPERBILIRUBINEMIA

Bibliography: **Lin C-H**, Yang H-C, Cheng C-S, Yen C-E. Effects of infant massage on jaundiced neonates undergoing phototherapy. Ital J Pediatr. 2015 Nov 25;41:94; **Eghbalian F**, Rafienezhad H, Farmal J. The lowering of bilirubin levels in patients with neonatal jaundice using massage therapy: A randomized, double-blind clinical trial. Infant Behav Dev [Internet]. 2017;49:31–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28688960

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With no massage and phototherapy	**With massage and phototherapy**		**Risk with no massage and phototherapy**	**Risk difference with massage and phototherapy**
Bilirubin levels on day 3 (assessed with: TSB in µmol/L)											
142 (2 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	72	70	-	The mean bilirubin levels (TSB, infants without IV hydration, day 3) was **0**	MD **31.03 lower** (41.1 lower to 20.96 lower)

EXPLANATIONS:

a. Across the two studies there were concerns due to missing information about randomization and allocation concealment.

GRADE TABLE 18: SKIN TO SKIN CONTACT DURING PHOTOTHERAPY COMPARED TO CONTINUOUS PHOTOTHERAPY FOR TREATMENT OF NEONATAL HYPERBILIRUBINEMIA

Bibliography: Samra NM, El Taweel A, Cadwell K, NM. S, A. ET, K. C. The effect of kangaroo mother care on the duration of phototherapy of infants re-admitted for neonatal jaundice. J Matern Neonatal Med. 2012 Aug;25(8):1354–7; **Goudarzvand L**, Dabirian A, Nourian M, Jafarimanesh H, Ranjbaran M. Comparison of conventional phototherapy and phototherapy along with Kangaroo mother care on cutaneous bilirubin of neonates with physiological jaundice. J Matern Fetal Neonatal Med [Internet]. 2017 Nov 27;1–5.

Certainty assessment							Summary of findings				
№ of participants (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With continuous phototherapy	**With Intermittent kangaroo care during phototherapy**		**Risk with continuous phototherapy**	**Risk difference with Intermittent kangaroo care during phototherapy**
Duration of phototherapy (assessed with: hours)											
50 (1 observational study)	not serious [a]	not serious	not serious	not serious [b]	none	⨁⨁◯◯ LOW	22	28	-	The mean duration of phototherapy (hours) was **100.86** hours	MD **32.72 hours lower** (52.54 lower to 12.9 lower)
Bilirubin levels (assessed with: TSB in µmol/L)											
50 (1 observational study)	not serious [a]	not serious	not serious	serious [c]	none	⨁◯◯◯ VERY LOW	22	28	-	The mean bilirubin levels (TSB) was **263.6** µmol/L	MD **2 µmol/L lower** (20.14 lower to 16.14 higher)
Duration of hospitalization (assessed with: days)											
70 (1 RCT)	serious [d]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	35	35	-	The mean duration of hospitalization was **3.03** days	MD **0.94 days lower** (0 to 0)

EXPLANATIONS

a. Intervention group was convenience sample of newborns whose parents were able and willing to come to NICU to provide kangaroo care between PT sessions until jaundice resolved. While kangaroo care and usual care groups were similar at baseline in terms of mode of delivery, sex, GA at delivery and suspected cause of jaundice (physiologic vs breastfeeding-associated), it's possible the kangaroo care group may have had socioeconomic or other advantages that could possibly explain some of the differences observed between groups, however no evidence of confounding was noted.

b. Despite a small sample size, imprecision was not rated as serious because the confidence interval around the mean difference was sufficiently narrow, indicating precise results.

c. Confidence interval around mean difference suggests that true value of difference between groups is uncertain.

d. This study has been downgraded on risk of bias due to selective outcome reporting, as the study did not include important information on standard deviation.