Appendix D Evidence tables

Q1. Which factors affect the relationship between neonatal hyperbilirubinaemia and kernicterus or other adverse outcomes (neurodevelopmental, auditory)?

Bibliographic details	Study type and Evidence level	Patient characteristics	Methodology and interventions	Results	Reviewers Comments
Newman TB; Year: 2000 Country: USA [8]	Study Type: Nested case-control study Evidence Level: II	Cohort of all infants with BW = 2000 grams and GA = 36 weeks born alive at 11 hospitals of a health maintenance organization during a two year period (N = 51,387) <u>Cases:</u> Babies with maximum TSB levels = 428 micromol/L within the first 30 days after birth N = 73 Mean BW: Not reported Mean GA: Not reported Gender: Males = 67.1% Ethnicity: Not reported (only maternal race specified) <u>Controls:</u> Random sample of babies from the cohort with maximum TSB levels = 428 micromol/L N = 423 Mean BW: Not reported Mean GA: Not reported Gender: Males = 54.4% Ethnicity: Not reported (only maternal race specified) For analyses examining the use of phototherapy only, additional random sample of 30 babies with maximum TSB levels of 342 to 426 micromol/L added to	1) Relationship of clinical and demographic factors associated with hyperbilirubinaemia evaluated by bivariate analysis and OR 2) Risk factors significant in the univariate model entered into multiple regression analysis to find independent predictors of hyperbilirubinaemia – both by including and excluding early jaundice cases <u>Early jaundice cases</u> (N = 14) defined as babies with TSB exceeding recommended phototherapy threshold for age during birth hospitalization, those given phototherapy during birth hospitalization, when jaundice noted at less than 20 hours of age and TSB not measured within 6 hrs of that time. 3) Risk index developed by assigning points equal to the OR for risk factors that were significant in the logistic regression model with the exclusion of early jaundice cases, and predictive accuracy compared by the c-statistic	<u>Maternal and prenatal factors associated with significant hyperbilirubinaemia (those with p<0.05 in bivariate analysis)</u> *Maternal factors* - Race, - maternal age, - family HISTORY OF jaundice in a newborn, - vacuum delivery *Neonatal factors* - Male sex, - lower GA, - early jaundice, - cephalohaematoma, - bruising, - breastfeeding at time of discharge <u>Factors independently associated with significant hyperbilirubinaemia from multivariate regression analysis (OR with 95%CI)</u> *All cases (N = 73)* Early jaundice: OR 7.3 (2.8-19) GA (per wk): OR 0.6 (0.4-0.7) Breastfeed only at discharge: OR 6.9 (2.7-17.5) Asian race: OR 3.1 (1.5-6.3) Bruising: OR 3.5 (1.7-7.4) Cephalohaematoma: OR 3.2 (1.1-9.2) Maternal age ≥ 25 yrs: OR 2.6 (1.1-9.2)	Unselected population but exclusion criteria not defined Confounding variables controlled for during multivariate analysis Test & Reference test described adequately Reference test a standard test Blinding – Not reported

		the control group Exclusion criteria: Not defined	(equal to area under ROC curve) <u>Reference standard:</u> Significant hyperbilirubinaemia defined as maximum TSB levels = 428 micromol/L within the first 30 days after birth.	*Cases excluding early jaundice (N = 59)* GA (per wk): OR 0.6 (0.4-0.7) Breastfeed only at discharge: 5.7 (2.1-15.5) Asian race: OR 3.5 (1.7-7.4) Bruising: OR 4.0 (1.8-8.8) Cephalohaematoma: OR 3.3 (1.1-10) Maternal age ≥ 25 yrs: OR 3.1 (1.2-8.1) Family HISTORY OF jaundice: 6.0 (1.0-36.0); p = 0.05 <u>Risk Index scoring</u> 6 points each for exclusive breastfeeding and family HISTORY OF jaundice in a newborn, 4 points each for bruising and Asian race, 3 points each for cephalhematoma and maternal age ≥ 25 yrs, 1 point for male sex, -2 points for black race, and 2(40-GA) <u>Accuracy of Risk Index score in predicting significant hyperbilirubinaemia</u> Overall c-statistic 0.85 *Risk index score < 10* +LR: 0.2 *Risk index score > 10* +LR: 2.2 *Risk index score > 20* +LR: 18.2	

Newman TB et al; Year: 2002 Country: USA [9]	Study Type: Nested case-control study Evidence Level: II	Cohort of all infants with BW = 2000 grams and GA = 36 weeks born alive at 12 hospitals of a health maintenance organization during a four year period (n = 105,384) Cases: Babies with maximum TSB levels = 428 micromol/L within the first 30 days after birth (n = 140) Controls: Random sample of babies from the cohort with maximum TSB levels = 428 micromol/L (n = 631) Exclusion criteria: Babies with conjugated hyperbilirubinaemia	1) Frequency of jaundice noted in the medical record in term and near-term newborns less than 24 hours old 2) Association of jaundice noted in the first 24 hours after birth with the use of phototherapy and risk of developing hyperbilirubinaemia after controlling for confounding variables -	1) Frequency of jaundice noted in newborns within 24 hours of age (Kaplan Meier survival estimates + no. with TSB measured) *Less than 18 hours of age* 3.8% *Less than 24 hours of age* 6.7% 2) Association of jaundice noted within 24 hours of age with risk factors (results of bivariate analysis) No statistically significant difference between the cases and the controls for risk factors ethnicity, sex, gestational age, breastfeeding, cephalhematoma or the birth cohorts Relationship between jaundice noted within 24 hours of birth and phototherapy/ hyperbilirubinaemia (Mantel Haenszel OR with 95%CI) *Phototherapy* Cases: 18.9% Controls: 1.7% M-H OR 10.1 (4.2-24.4) *Hyperbilirubinaemia* Cases: 14.3% Controls: 5.9% M-H OR 2.9 (1.6-5.2)	Nested case-control study Some cases were included in 42290 – should we excluded 42290 Cases and controls taken from comparable populations but exclusion criteria not well defined Confounding variables controlled Methodology described adequately but exact number of babies with jaundice noted in first 24 hours calculated with Kaplan Meier analysis
Kuzniewicz MW et al; Year: 2008 Country: USA	Study Type: Nested case-control study Evidence Level: II	Cohort of all babies with BW = 2000 grams and GA = 34 weeks born alive at hospitals of a health maintenance organization during a 10 year period (n = 285,295).	Cases and controls matched on risk group status (low, medium and high risk based on the hour-specific bilirubin centiles, gestational age and DAT results) and difference between	1) Variables associated with severe hyperbilirubinaemia (those with p<0.1 in bivariate analysis) *Demographic factors* When compared to 40+ weeks	Nested case-control study Cases and controls taken from comparable populations with well defined exclusion criteria Confounding variables controlled Methodology described adequately

[10]		From this cohort 13,843 babies with qualifying TSB level of 291 to 392 micromol/L measured at = 48 hours of age taken as reference population Cases: Babies with maximum TSB levels = 427 micromol/L after the qualifying TSB (n = 62) Mean BW: 3374 ± 527 grams Mean GA: 38.3 + 1.7 weeks Mean age at entry: 71.5 ± 19.4 hours Gender: Males = 58.9% Ethnicity: asian = 27.4% black = 8.1% Controls: Randomly selected sample of babies with maximum TSB levels < 427 micromol/L after the qualifying TSB (4 controls per case, n = 248) Mean BW: 3414 ± 576 grams Mean GA: 37.9 + 1.4 weeks Mean age at entry: 73.1 ± 17.5 hours Gender: Males = 61.3% Ethnicity: asian = 29.8% black = 6.8% Exclusion criteria: infants with resolving jaundice, those where TSB levels not documented after a maximum TSB recording or decline in TSB not recorded, and those with conjugated bilirubin level = 2 MG/DL	their TSB levels and the TSB threshold levels for phototherapy as defined by the AAP 1) Relationship of clinical and demographic factors associated with hyperbilirubinaemia evaluated by bivariate analysis 2) Risk factors significant in the bivariate model (at p<0.1) entered into multiple regression analysis to find independent predictors of hyperbilirubinaemia 3) Predictive accuracy of the final risk factor model evaluated by the c-statistic (equal to area under ROC curve)	GA 38-39 weeks (p = 0.01) GA 34-37 weeks (p = 0.06) birth hospitalization < 48 hours (p = 0.07) *History & physical examination factors* Bruising (p = 0.007) *Laboratory values* Qualifying TSB occurring during birth hospitalization (p = 0.04) TSB increase ≥ 102 micromol/L (p = 0.002) *Interventions* Inpatient phototherapy (p <0.001) Intravenous fluids after qualifying TSB (p = 0.002) exclusive breastfeeding after qualifying TSB (p = 0.005) 2) Factors independently associated with severe hyperbilirubinaemia from multivariate regression analysis (adj OR with 95%CI) GA (compared to 40 weeks as reference) For 38-39 weeks: 3.1 (1.2-8.0); p = 0.02 For 34-37 weeks: 3.7 (0.6-22.7); p = 0.15 Family history of jaundice: 3.8 (0.9-15.7): p = 0.06 Bruising on examination: 2.4 (1.2-4.8); p = 0.02 Exclusive breastfeeding after qualifying TSB: 2.0 (1.03-4.0); p = 0.04 TSB increase of = 102 micromol/day: 2.5 (1.2-5.5); p = 0.02 Accuracy of risk factor model in predicting severe hyperbilirubinaemia c-statistic 0.82 (0.76 to 0.88)	

Keren R et al; Year: 2005 Country: USA [12]	Study Type: Retrospective cohort Evidence Level: II	Infants with BW = 2000 grams if GA = 36 weeks and BW = 2500 grams if GA = 35 weeks participating in the hospital's early discharge programme, and who had both pre and post-discharge TSB levels measured at the phase when ≥ 75% babies had both the samples (n = 899) <u>Group 1</u>: infants with post-discharge TSB > 95th centile on nomogram N = 98 mean BW: 3.4 ± 0.5 kg mean GA: Not reported Gender: males = 54.1% Ethnicity: White = 45.9% Black = 31.6% Asian = 10.2% Hispanic = 3.1% Other = 8.2% <u>Group 2</u>: infants with post-discharge TSB < 95th centile on nomogram N = 801 mean BW 3.3 ± 0.5 kg mean GA: Not reported Gender: males = 52.2% Ethnicity: White = 43.1% Black = 39.9% Asian = 7.7% Hispanic = 4.5% Other = 4.7%	1) Association of risk factors with significant hyperbilirubinaemia derived from univariate analysis (at p<0.2) 2) Multivariate regression analysis used to find factors independently associated with significant hyperbilirubinaemia To calculate risk, birthweight (kg) was transformed by subtracting 2 kg and dividing by 0.5 kg for every 0.5 kg above 2.5 kg 3) Comparison of diagnostic accuracy of the risk factor score (derived from regression modeling) with that of pre-discharge TSB levels in predicting significant hyperbilirubinaemia Pre-discharge TSB levels expressed as risk zone on an hour-specific bilirubin nomogram (High risk > 95th centile, High intermediate risk 76th – 95th centile, Low intermediate risk 40th – 75th centile, Low risk 0 – 40th centile) Significant Hyperbilirubinaemia defined as TSB level > 95th centile on hour-specific nomogram.	<u>Prevalence of significant hyperbilirubinaemia</u> 98/899 (10.9%) <u>1) Factors associated with significant hyperbilirubinaemia</u> *Increased risk* GA < 38 weeks (p = 0.02) GA ≥ 40 weeks (p = 0.12) LGA babies (p = 0.13) higher pre-discharge TSB risk zone > 76th centile (p < 0.001) breastfeeding (p < 0.001) combined breast and bottle feeding (p = 0.02) maternal diabetes (p = 0.17) vacuum extraction (p < 0.001) prolonged rupture (p = 0.08) oxytocin use (p = 0.002) *Decreased risk* SGA (p = 0.04) Parity (p = 0.03) caesarean section (p = 0.18) <u>2) Factors independently associated with significant hyperbilirubinaemia from multivariate regression analysis (OR with 95%CI)</u> Birthweight: 1.5 (1.2-1.9); p = 0.001 GA < 38 weeks: 2.6 (1.5-4.5); p = 0.001 Oxytocin: 2.0 (1.2-3.4); p = 0.005 Vacuum delivery: 2.2 (1.5-3.6); p = 0.003 Exclusive breastfeeding: 2.6 (1.5-4.5); p<0.001 Breast and bottle feeding: 2.3 (1.1-4.9); p = 0.03 <u>Clinical risk index scoring</u>	Retrospective cohort study Unselected population with well defined exclusion criteria Confounding variables controlled Methodology described adequately Blinding – not specified

		Exclusion: admission and treatment in intensive care nursery for neonatal illness and babies requiring phototherapy during birth hospitalization.		Birthweight: 3 points for 2501-3000 grams 6 for 3001-3500 grams 9 for 3501-4000 grams 12 for 4001-4500 grams 15 for 4501-5000 grams GA < 38 weeks: 5 points Oxytocin: 4 points Vacuum delivery: 4 points Exclusive breastfeeding: 5 points Breast and bottle feeding: 4 points <u>3) Predictive accuracy for predicting significant hyperbilirubinaemia</u> RISK FACTOR SCORE c-statistic 0.71 (0.66-0.76) *Risk index score 0-7* +LR: 0.1 *Risk index score 8-11* +LR: 0.4 *Risk index score 12-15* +LR: 0.9 *Risk index score 16-19* +LR: 2.0 *Risk index score 20-23* +LR: 2.6 *Risk index score > 24* +LR: 3.2 PRE-DISCHARGE TSB c-statistic 0.83 (0.80-0.86) *TSB centile 0-40th* +LR: 0.05 *TSB centile 41-75th* +LR: 0.2 *TSB centile 76-95th* +LR: 2.2	

				TSB centile > 95th +LR: 9.4	

Seidman DS et al; Year: 1999 Country: Israel [13]	Study Type: Prospective cohort study Evidence Level: II	Healthy full term infants with GA = 37 weeks born at two hospitals N = 1177 mean BW 3247 ± 453 grams mean GA 39.8 ± 1.3 weeks Gender: Males = 47.3% Ethnicity: Not reported Exclusion: ABO or Rh incompatibility and a positive direct Coombs' test G-6PD deficiency.	1) Association of various factors with jaundice derived from multiple regression analysis 2) Comparison of diagnostic accuracy of various tests for predicting hyperbilirubinaemia Test: TSB measured within first 8 to 24 hrs of life and repeated daily for the next 4 days Reference standard: Hyperbilirubinaemia defined as TSB >171 micromol/L at day 2 >239 micromol/L at day 3 >291 micromol/L at day 4-5 Analysis: Association between various factors and jaundice calculated from multiple regression analysis using Odds ratios with 95%CI, and these factors used for modelling in predicting hyperbilirubinaemia	1) Factors associated with jaundice after comparing Group 1 vs. Group 2 (n = 1,177) *Day 1 TSB (per 17 micromol/L)* OR: 3.1 (95%CI 2.4 to 4.1) *Change in TSB from day 1 to day 2 (per 17 micromol/L)* OR: 2.4 (95%CI 1.9 to 3.0) *Maternal age (per year)* OR: 1.1 (95%CI 1.0 to 1.2) *Mat education (per year)* OR: 0.8 (95%CI 0.7 to 0.9) *Maternal blood type O* OR: 2.9 (95%CI 1.5 to 5.8) *Full breastfeeding* OR: 0.4 (95%CI 0.2 to 0.9) *Day 1 TSB > 85 micromol/L* OR: 36.5 (95%CI 15.9 to 83.6) 2) Prediction of hyperbilirubinaemia *Prediction by Day 1 TSB only (threshold value > 85 micromol/L)* Sensitivity: 63.1% Specificity: 94.2% *Prediction by all model variables without Day 1 TSB* Sensitivity: 57.9% Specificity: 90.4% *Prediction by all model variables* Sensitivity: 81.8% Specificity: 82.9%	Unselected population No differences at baseline between the two groups Test & Reference test described in detail Reference test a standard one Blinding – Not reported Confounding factors adjusted for during modelling Data not available to calculate PPV or NPV. Raw figures not available

Keren R et al; Year: 2008 Country: USA [14]	Study Type: Prospective cohort study Evidence Level: II	Infants managed exclusively in the well infants nursery of an urban tertiary care hospital with GA = 36 weeks and BW = 2000 grams or GA = 35 weeks and BW = 2500 grams N = 812 mean BW 3.3 ± 0.5 kg GA < 38 weeks: 13.4% Gender: males = 49.4% Ethnicity: White = 33.5% Black = 53.2% Asian = 9.8% Other = 3.4% Since the population in the area was predominantly black, stratified sampling scheme used to get a representative sample. Group 1: Infants with significant hyperbilirubinaemia (N = 48) Group 2: Infants without significant hyperbilirubinaemia (N = 703) Exclusion: babies transferred to the intensive care nursery for any reason Babies who received intravenous antibiotics for concern for sepsis.	1) Factors associated with significant hyperbilirubinaemia in univariate analysis entered into regression modeling for clinical risk factor model 2) Comparison of diagnostic accuracy of three tests in predicting significant hyperbilirubinaemia by the c-statistic (mathematically equal to area under ROC curve) Test 1: Pre-discharge bilirubin measured either by TcB or TSB at < 52 hrs of age, and expressed as risk-zone on hour specific nomogram. Daily TcB levels recorded using BiliChek, and TSB performed if TcB above 75th centile on hour-specific nomogram or TcB reading = 205 micromol/L TSB value taken for analysis when both TcB and TSB done. Test 2: Clinical risk factors assessed by review of hospital charts for maternal race, intended method of feeding, GA, history of previous infant with jaundice, clinical assessment of jaundice, G-6PD deficiency. Test 3: Combination of pre-discharge bilirubin risk zone and clinical	Prevalence of significant hyperbilirubinaemia 48/751 (6.4%) – 61 had an incomplete follow-up 1) Association of factors with significant hyperbilirubinaemia (Univariate analysis) (n = 812) *Factors increasing risk* Pre-discharge bilirubin – high risk zone OR: 147 (95%CI 34-639) high-intermediate risk zone OR: 21 (95%CI 4.9-93.0) GA < 38 weeks OR: 9.2 (95%CI 4.4-19.0) intended breastfeeding OR: 2.2 (95%CI 1.0-4.5) intended breast + bottle feeds OR: 3.7 (95%CI 1.6-8.6) Grade 4 or higher degree of clinical jaundice OR 6.0 (95%CI 2.1 to 17) *Factors decreasing risk* Black race OR 0.43)95%CI 0.23-0.80) Maternal history of smoking OR: Not reported Factors significant in multivariate analysis model (p<0.05) GA<38 weeks OR 19 (95%CI 6.3- 56) Mother's plan of exclusive breastfeeding: OR 3.7 (95%CI 1.1- 13) Black race: OR 0.22 (95%CI 0.08- 0.61) Grade 4 or higher jaundice observed clinically: OR 1.7 (95%CI 1.2-2.6) Female sex: OR 3.2 (95%CI 1.2-8.4) 2) Predictive ability of the three tests in predicting significant hyperbilirubinaemia (multivariate regression)	Unselected population (stratified sampling) with well defined exclusion criteria Baseline characteristics of two groups not compared Confounding variables controlled Methodology described adequately Blinding – not specified

			risk factors. <u>Reference standard:</u> Bilirubin levels (TcB or TSB) measured on day 3-5 on both hospitalized and discharged babies (at home) using similar method as in Test 1, and Significant Hyperbilirubinaemia defined as bilirubin levels exceeding or within 17 micromol/L of the hour-specific phototherapy treatment thresholds.	*Test 1: Pre-discharge bilirubin risk zone* c-statistic 0.88 (95% 0.85 to 0.91) *Test 2: Clinical risk factors (final model had 5 factors – GA, intended method of feeding, black race, extent of jaundice and gender)* c-statistic 0.91 (95% 0.86 to 0.97) *Test 3: Combination model (pre-discharge risk zone + clinical factors of GA and % weight loss)* c-statistic 0.96 (95% 0.93 to 0.98) *Test 3 vs. Test 1* p-value for difference< 0.01 *Test 3 vs. Test 2* p-value for difference = 0.15 *Test 2 vs. Test 1* p-value for difference = 0.35	
Gale R; Year: 1990 Country: Israel [15]	Study Type: Nested case-control study Evidence Level: II	Term babies > 37 weeks delivered during a 5 year period in a university hospital (n = 10,122) <u>Test group</u>: Term babies who developed serum bilirubin levels = 221 micromol/L N = 1154 mean BW 3192 $\pm$ 508 grams mean GA 39.3 $\pm$ 1.5 weeks Gender: Not reported Ethnicity: Not reported <u>Comparison group:</u> every tenth admission randomly selected from the group of with serum bilirubin levels < 221	1) Association of various factors with high serum bilirubin levels by comparing test group with comparison group (univariate analysis) 2) Step-wise regression analysis done to control for confounding variables	<u>1) Factors associated high bilirubin levels (at p<0.01 during univariate analysis)</u> Male sex (p =0.001) maternal diabetes (p = 0.01) maternal PIH (p = 0.005) previous sibling with hyperbilirubinaemia (p < 0.001) delivery by caesarean section (p < 0.001) vacuum or forceps delivery (p < 0.001) epidural anaesthesia (p = 0.001) mother with blood type O (p < 0.001) first delivery (p < 0.001) cephalohaematoma (p = 0.003) short gestation (p = 0.01) lower birth weight (p = 0.01) lower birth order (p = 0.01)	Cases and controls taken from comparable populations with exclusion criteria not well defined Confounding variables controlled Methodology not described adequately Blinding – not specified

		micromol/L N = 1154 mean BW 3257 ± 444 grams mean GA 39.9 ± 1.35 weeks Gender: Not reported Ethnicity: Not reported Exclusion: Not defined		2) Factors independently associated with high TSB levels (adj OR with 95%CI) Maternal age > 35 years: Adj OR 1.7 (95%CI 1.3-2.3) Male sex: Adj OR 1.4 (95%CI 1.2-1.7) Primipara: Adj OR2.7 (95%CI 2.1-3.5) Previous sibling with jaundice: Adj OR 2.3 (95%CI 1.9-2.8) Early gestation (with 40 weeks as reference): For 37 weeks Adj OR 4.5 (95%CI 3.2-6.3) For 38 weeks Adj OR 2.1 (95%CI 1.6-2.8) Vacuum extraction: Adj OR 3.0 (95%CI 2.1-4.4)	
Khoury MJ et al; Year: 1988 Country: USA [16]	Study type: Retrospective study Evidence level: II	Offspring of 1,669 male US Army veterans who entered the Army between 1965 and 1971 and who participated in a nationwide study of veterans' health (N = 3,301, 580 sib-ships with one sibling, 1,089 sib-ships with two or more siblings) Exclusion: babies who had a different mother's name from the rest of the sibling relationship (paternal half sibs), stillbirths, babies with records showing evidence of haemolytic disease of newborn.	1) Univariate analysis to find association of maternal and infant variables with hyperbilirubinaemia (peak TSB levels = 205 micromol/L) 2) Multiple logistic regression analysis to find factors independently associated with hyperbilirubinaemia 3) Recurrence risk of hyperbilirubinaemia by sibling order and degree of hyperbilirubinaemia in the first child before and after controlling for confounding variables *TSB levels for degree of jaundice* Mild: = 205 micromol/L Moderate: 205 to 257	Rate of hyperbilirubinaemia in first child of a sibling relationship 83/1669 (5.0%) 1) Association of factors with hyperbilirubinaemia Prematurity (GA<37 weeks) (OR 2.2) black race (OR 0.37) breast-feeding (OR 2.1) neonatal asphyxia (OR 1.8) 2) Factors independently associated with hyperbilirubinaemia Year of birth (after 1975 vs. before 1975): Adj OR1.49 (95%CI 1.03-2.15) Prematurity (GA<37weeks): Adj OR 2.4 (95%CI 1.4-3.9) Breastfeeding: Adj OR 1.9 (95%CI 1.3-2.7) 1-minute Apgar score: Adj OR1.7	Retrospective study Selected population with well defined exclusion criteria Confounding variables controlled Methodology not described adequately

			micromol/L Severe: = 257 micromol/L	(95%CI 1.0-2.9) <u>3) Risk of recurrence of hyperbilirubinaemia</u> *Unadjusted OR with 95%CI* 3.1 (1.4-6.8) *Adjusted OR with 95%CI* For Mild jaundice 2.7 (1.8-4.1) For Moderate jaundice 4.1 (1.5-10.8) For Severe jaundice 12.5 (2.3-65.3)	
Beal AC et al; Year: 2005 Country: USA [17]	Study type: Cross-sectional survey Evidence level: III	Mothers of babies with GA = 35 weeks discharged from well baby nursery of a health system organization during 22 month period (N = 866) Exclusion: BW<2000 grams, GA<35 weeks, babies who stayed = 3 days in an intensive care nursery, babies with TSB = 171 micromol/L in the first 24 hours.	Maternal and neonatal data extracted from the organization's database and maternal race categorized into 7 categories – American Indian, Asian, African American or black, Hispanic, Middle Eastern or Arabic, Caucasian or white, and Others Computerized telephonic survey conducted to collect further information from mothers about their experience of breastfeeding, neonatal care, hyperbilirubinaemia detection, interventions and education, and racial ancestry for mother, father and newborn (allowing = 5 responses for ancestry of each)	<u>Response rate</u> Total eligible = 3021 Contacted = 1248 Completed survey = 866 <u>Agreement between Medical record documented maternal race vs. Mother self-reported race</u> White: 64.1% Black: 69.6% Hispanic: 97% Middle Eastern: 50% Asian: 35% American Indian: 0% Others: 4.3% <u>Relationship between newborn's, mother's and father's first-named race for newborns reported to be = 2 races</u> First-named race same for all = 40.9% Newborn and mother's race same =	Population not representative Poor response rate

				22.6% Newborn and father's race same = 24.7% All 3 races different = 10.8%	
Murki S et al; Year: 2001 Country: India [19]	Study type: Prospective study Evidence level: II	Term (37 completed weeks) neonates with severe non-haemolytic jaundice. The inclusion criteria were TSB > 308 micromol/L, absence of hemolysis absence of major malformations. <u>Kernicterus group:</u> babies with stage II bilirubin encephalopathy characterized by presence of opisthotonus, rigidity and sun-setting of eyeballs N = 14 mean BW 2402 ± 525 grams mean GA 37.8 ± 0.8 weeks Gender: males = 71.4% Ethnicity: Not reported <u>Non-kernicterus group:</u> babies without features of bilirubin encephalopathy N = 50 mean BW 2654 ± 446 grams mean GA 38.1 ± 1.02 weeks Gender: males = 54% Ethnicity: Not reported	Diagnosis of haemolysis was based on positive direct Coomb's test, peripheral blood smear, reticulocyte count, plasma hemoglobin and packed cell volumes. Exchange transfusion was done whenever total serum bilirubin level reached 342 micromol/L.	<u>Baseline comparison of two groups (kernicterus vs. non-kernicterus group)</u> Higher number of kernicterus infants delivered vaginally (93% vs. 74%, $p < 0.05$) oxytocin use was higher in non-kernicterus group (26% vs. 42%, $p < 0.05$) *Neonatal risk factors* No statistically significant difference (at $p < 0.05$) between the two groups for sex distribution mean gestational age mean birth weight % of small for date (SFD) history of birth asphyxia pH at admission weight loss *Laboratory parameters* Mean max TSB levels: Kernicterus: 542 ± 171 micromol/L Non-kernicterus: 438 ± 79 micromol/L p = 0.002 Free bilirubin levels: Kernicterus: 25.5 ± 10.1 nmol/L Non-kernicterus: 19.9 ± 6.9 nmol/L p = 0.006 Bilirubin/albumin ratio: Kernicterus: 0.14 ± 0.05 Non-kernicterus: 0.11 ± 0.03 p = 0.05	Selected population with small sample size Comparison of baseline characteristics done Methodology not clearly explained Confounding variables controlled (partially)

				<u>Results from multiple logistic regression analysis</u> History of birth asphyxia: OR 8.3 (95%CI 1.2-111.8); p = 0.03 Maximum TSB levels: OR 1.15 (195%CI .04-1.3); p = 0.005 Free bilirubin levels: OR 1.1 (95%CI 1.04-2.2); p = 0.009	
Turkel BS et al; Year: 1980 Country: USA [20]	Study type: Retrospective matched-control study Evidence level: II	All infants with kernicterus found at autopsy. 32 infants identified with kernicterus matched to 32 control infants without kernicterus at autopsy born during the same year, of like gestational age, weight and length of survival. A second group of 13 pairs from the large group of 32 pairs were matched for sex as well.	Multiple historical, clinical, and laboratory factors were compared, including therapy sepsis hypothermia asphyxia (Apgar score) haematocrit acidosis hypercarbia hypoxia hypoglycaemia hyperbilirubinaemia	There were no statistically significant differences between the kernicteric and non-kernicteric infants for any of the factors, including peak total serum bilirubin levels. The multivariate analysis failed to determine a group of factors associated with increased risk for kernicterus.	It was difficult to separate infants with and without kernicterus at autopsy on the basis of the clinical factors evaluated. Some cases of kernicterus may have been missed due to the variables of relying on identification in fixed or fresh brains.
Bhutani VK et al; Year:2006 Country: USA [21]	Study Type: Retrospective study Evidence Level: III	125 of 142 cases of the Pilot Kernicterus Registry met the inclusion criteria. These babies were discharged as healthy and were included for analysis if they exhibited clinical signs of acute bilirubin encephalopathy regardless of total serum bilirubin levels.	Main outcome measures were the comparison of etiology, severity and duration of extreme hyperbilirubinaemia (total serum bilirubin levels >343 micromol/L), response to interventions of intensive phototherapy and exchange transfusion, health care delivery experiences in preterm as compared with term infants.	The total serum bilirubin levels, age at re-hospitalization, and birth weight distribution were similar for late preterm and term infants. Large for gestational age and late preterm infants disproportionately developed kernicterus as compared with those who were appropriate for gestational age and term. Clinical management of extreme of hyperbilirubinaemia, by the attending clinical providers, was not impacted or influenced by the gestational age,	Late prematurity ($34^{0/7}$ to $36^{6/7}$ weeks) of healthy babies was not recognized as a risk factor for hazardous hyperbilirubinaemia by clinical practitioners.

				clinical signs, or risk assessment. This resulted in severe posticteric sequelae which was more severe and frequent in late preterm infants.	
Newman T Year: 1993 Country: USA 22	Study Type: prospective cohort study Evidence Level: II	The study population included first born white and black babies with birth weight = 2500 grams who survived for at least 1 year and had at least one bilirubin level recorded N = 41,324 Mean BW: 3285 grams Mean GA: 39.3 ± 2.8 weeks Gender: males = 51.3% Ethnicity: White = 51.7% Black = 48.3% Exclusion criteria: Non-singleton babies Birthweight < 2500 or birthweight unknown	Babies had TSB measured between 36 and 60 hours of age (as close to 48 hours as possible) and subsequent sampling was done depending on the initial levels Outcomes intelligence quotient (IQ) assessment by psychologists (using Wechsler Intelligence Scale for Children) at the age of 7 years, neurological examination by paediatric neurologists or specially trained paediatricians at the age of 7 years hearing evaluation performed at 8 years of age using pure-tone audiometry Multiple logistic regression analysis was performed to control for the effect of 11 potential confounding variables	About 1% of the white babies (N = 21,375) had peak TSB level = 342 micromol/L while the proportion among the black babies (N = 19,949) was 0.6%. No statistically significant association was seen between high TSB levels and IQ scores or sensorineural hearing loss. Abnormal neurological examination was reported more commonly in children with high TSB levels (= 342 micromol/L) compared to those with lower TSB levels, but the difference was statistically not significant (4.5% vs. 3.8%; RR 1.2, 95%CI 0.7-2.1). However it was observed that there was a significant linear increase in the risk of 'suspicious' abnormal neurological examination with an increase in the TSB levels (OR 1.12, 95%CI 1.06- 1.2).	Selected population Comparison of baseline characteristics done Confounding variables controlled Partially blinded (some tests)
Boo NY et al; Year:1994 Country: Malaysia 23	Study Type: Cohort study Evidence Level: II	136 jaundiced term neonates. N = 128 Mean BW: 3022 + 474 grams Mean GA: 39.8 + 0.7 weeks Gender: males = 62.5% Ethnicity: Malays = 50.8% Chinese = 35.9% Indian = 10.9% Others = 2.3%	Hearing loss was based on brain stem-evoked response. Hyperbilirubinaemia defined as TSB > 340 micromol/L	Hearing loss: 28/128 (21.8%) Hearing loss: TSB < 340 micromol/l 13/83 (15.7%) TSB > 339 micromol/l 15/45 (33.3%) p = 0.11 <u>Risk factors for hearing loss</u>	

		8 babies were excluded due to aminoglycoside treatment and congenital anomalies		Severe jaundice which required exchange transfusion (p = 0.038) Earlier age of onset of hyperbilirubinaemia (p = 0.012)	
Oh W et al; Year:2003 Country: USA [24]	Study Type: Retrospective cohort study Evidence Level: II	Extremely low birth weight infants (401–1000 grams) who survived to 14 days of age N = 5,630 mean BW: 789 ± 136 grams mean GA: 26.2 ± 2.1 weeks Gender: Not reported Ethnicity: Not reported Peak bilirubin levels that were recorded beyond the first 14 days of life were excluded.	Demographic and clinical risk factors and serum bilirubin levels during the first 14 days were analyzed with reference to death or adverse neurodevelopmental outcomes at 18 to 22 months' postmenstrual age. Neurodevelopmental variables were Psychomotor Developmental Index (PDI) <70 Mental Developmental Index (MDI) <70 moderate or severe cerebral palsy (CP) hearing impairment (hearing aids), composite category designated as neuro-developmental impairment (NDI). The NDI is defined as infants with any 1 or more of the following: PDI <70, MDI <70, moderate to severe CP bilateral blindness, bilateral hearing impairment requiring amplification.	3,246 infants survived at discharge, 79 died after discharge, and 592 were lost to follow-up. 2575 of 3167 infants were seen in the follow-up clinics with a compliance rate of 81%. Logistic regression analysis showed that various demographic and clinical variables were associated with poor neurodevelopmental outcomes. After adjustment for these risk factor, significant association were found between peak TSB and death or NDI - OR 1.068 (95%CI 1.03–1.11) PDI <70 - OR1.057 (95%CI 1.00-1.12) hearing impairment requiring hearing aids OR 1138 (95%CI 1.00–1.30) There was no significant association between peak TSB and other variables	PSB concentrations during the first 2weeks of life are directly correlated with death or NDI, hearing impairment, and PDI <70 in ELBW infants.

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Q5. How useful are the following tests in predicting neonatal hyperbilirubinaemia?

Prediction of hyperbilirubinaemia (diagnostic accuracy)

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
Knupfer M; Year: 2005 Country: Germany [26]	Study Type: Diagnostic study Evidence Level: II	Healthy babies with GA > 34 weeks cared for in a maternity ward of a University hospital. The study population divided into 3 groups: **Group 1: Term AGA** N = 1100 mean GA 39.6 ± 1.1 weeks mean BW 3562 ± 418 grams Gender: Not reported Ethnicity: Not reported **Group 2: Term SGA** N = 163 mean GA 39.4 ± 1.2 weeks mean BW 2683 ± 274 grams Gender: Not reported Ethnicity: Not reported **Group 3: Preterm** N = 78 mean GA 35.3 ± 0.8 weeks mean BW 2578 ± 437 grams Gender: Not reported Ethnicity: Not reported Exclusion: discharge before 4th postnatal day, significant illness followed by special therapy such as antibiotics,	Test: Umbilical cord bilirubin (UCB) measured within 2 hrs of storage in amber Threshold values < 20 micromol/L 20-30 micromol/L 30-40 micromol/L > 40 micromol/L Reference standard: TcB from forehead every morning for 4 days and laboratory TSB performed if TcB index > 16. Diagnostic accuracy also calculated for predicting TSB levels requiring phototherapy	Mean UCB (micromol/L) Group 1: 32.4 ± 9.2 Group 2: 31.7 ± 9.1 Group 3: 30.9 ± 6.7 Comparison of prevalence of hyperbilirubinaemia in Group 1, 2 and 3 (in %) *With TSB > 250 micromol/L* 10.6 vs. 9.8 vs. 25.6 *With TSB > 300 micromol/L* 3.0 vs. 3.1 vs. 6.4 *Treated with phototherapy* 3.4 vs. 10.4 vs. 47.7 Diagnostic accuracy of UCB (threshold > 30 micromol/L) in predicting TSB > 300 micromol/L **Group 1:** Prevalence: 33/1100 (3.0%) Sensitivity: 32/33 (97%) Specificity: 442/1067 (41.4%) PPV: 32/657 (4.9%) NPV: 442/443 (99.8%) **Group 2:** Prevalence: 5/163 (3.1%)	Unselected population Test and Reference described adequately Reference test a standard one Blinding – Not reported

		CPAP or artificial ventilation		Sensitivity: 5/5 (100%) Specificity: 70/158 (44.3%) PPV: 5/93 (5.4%) NPV: 70/70 (100%) **Group 3:** Prevalence: 5/78 (6.4%) Sensitivity: 5/5 (100%) Specificity: 32/73 (43.8%) PPV: 5/46 (10.9%) NPV: 32/32 (100%) Diagnostic accuracy of UCB (threshold > 30 micromol/L) in predicting need for phototherapy **Group 1:** Prevalence: 40/1100 (3.6%) Sensitivity: 36/40 (90%) Specificity: 439/1060 (41.4%) PPV: 36/657 (5.5%) NPV: 439/443 (99.1%) **Group 2:** Prevalence: 17/163 (10.4%) Sensitivity: 16/17 (94.1%) Specificity: 69/146 (47.3%) PPV: 16/93 (17.2%) NPV: 69/70 (98.6%) **Group 3:** Prevalence: 37/78 (47.4%) Sensitivity: 26/37 (70.3%) Specificity: 21/41 (51.2%) PPV: 26/46 (56.5%) NPV: 21/32 (65.6%)	
Taksande A; Year: 2005 Country: India [27]	Study Type: Diagnostic study Evidence Level: II	Healthy full term babies born in the hospital with GA > 37 weeks and absence of significant illness requiring NICU admission and any congenital malformation. N = 200 mean GA 38.9 ± 2.07 weeks	Test: Umbilical cord bilirubin (UCB) measured at birth Threshold value > 34 micromol/L Reference standard: Laboratory TSB measured after 72 hours	Diagnostic accuracy of UCB (threshold value > 2 mg% or 34 micromol/L) for predicting TSB > 17 mg% or 290 micromol/L Prevalence: 19/200 (9.5%) Sensitivity: 17/19 (89.5%) Specificity: 154/181 (85.1%)	Unselected population Test & Reference test not described in detail Reference test is a standard one Blinding – yes

		mean BW 2555 ± 442 grams Gender: Males = 41% Ethnicity: Not reported Exclusion: babies with ABO or Rh incompatibility, G-6PD deficiency, those who later developed significant illness requiring NICU admission.	TSB > 290 micromol/L taken as hyperbilirubinaemia	PPV: 17/44 (38.6%) NPV: 154/156 (98.7%)	
Knudsen A; Year: 1992 Country: Denmark [28]	Study Type: Diagnostic study Evidence Level: II	Healthy term babies admitted to the newborn nursery. N = 138 median GA 40 weeks - range 38 to 43 median BW 3495 grams - range 2571 to 4456 Gender: Males = 52.2% Ethnicity: Not reported Exclusion: premature babies, sick babies rhesus sensitization.	Test: Umbilical cord bilirubin (UCB) measured at birth Threshold values: ≥ 20 micromol/L ≥ 25 micromol/L ≥ 30 micromol/L ≥ 35 micromol/L ≥ 40 micromol/L Reference standard: Laboratory TSB measured on Day 3 TSB ≥ 200 micromol/L taken as value for hyperbilirubinaemia ROC curve used to find the best cut-off value of UCB.	Diagnostic accuracy of UCB (threshold value > 35 micromol/L) for predicting TSB > 200 micromol/L Prevalence: 28/138 (20.3%) Sensitivity: 20/28 (71.4%) Specificity: 75/110 (68.2%) PPV: 20/55 (36.4%) NPV: 75/83 (90.4%)	Unselected population Test & Reference test described in detail Reference test is a standard one Blinding – Not reported. Reported using Minolta JM to estimate TcB but no details given
Carbonell X; Year: 2001 Country: Spain [29]	Study Type: Diagnostic study Evidence Level: II	Healthy term babies N = 2004 – 610 in phase one + 1394 in phase 2, mean BW 3230 ± 491 grams mean GA 39 weeks Gender: Males = 50.7% Ethnicity Not reported In first phase (N = 610), cord bilirubin (UCB) at birth and TcB	Test: 1. Umbilical cord bilirubin (UCB) measured at birth (threshold value: ≥ 37 micromol/L) ROC curve used to find the best cut-off value of UCB. 2. TSB (in phase 1 & 2) and TcB (phase 1 only) measured at 24 hrs (threshold value for TSB =	Correlation of TcB levels with lab TSB levels for Sternal vs. Forehead site (Pearson correlation coefficient) At < 24 hrs (N = 120) *Sternum Forehead* 0.81 0.77 At 24-48 hrs (N = 126) *Sternum Forehead* 0.89 0.83	Unselected population but no exclusion criterion Test & Reference test described in detail Reference test a standard one Test and reference test carried out within one hour Blinding – Not reported

		with Minolta JM-102 measured at 24hrs, 48 hrs & 60-96 hrs of life. Additionally TSB done for all at 60-96 hrs. On 169 babies TSB also measured at 24 & 48hrs In second phase (N = 1394), TcB and lab TSB values obtained to find accuracy of TSB and TcB at 24hrs and 48 hrs to predict hyperbilirubinaemia. <u>Prevalence of TSB > 290 micromol/L</u> = 2.9% in phase 1 (18/610) and 3.25% in phase 2 (46/1324) Exclusion: not defined	102 micromol/L and for TcB > 11) 3. TSB and TcB (in phase 1 & 2) measured at 48 hrs (threshold value for TSB = 154 micromol/L and for TcB > 13) TcB reading using Minolta JM 102 at the forehead and the sternum (mean of 3 measurements recorded at each site used for analysis) <u>Reference standard:</u> Laboratory TSB measured on Day 3-4 TSB = 290 micromol/L taken as indicative of hyperbilirubinaemia	At > 48 hrs (N = 412) *Sternum Forehead* 0.94 0.83 <u>Diagnostic accuracy of TcB for detecting TSB > 222 micromol/L</u> Sensitivity: 98% Specificity: 72% <u>Diagnostic accuracy for predicting TSB = 290 micromol/L</u> *Prevalence of TSB = 290 micromol/L* 2.9% in phase 1 (18/610) and 3.25% in phase 2 (46/1324) **1. For UCB (threshold = 37 micromol/L)** Sensitivity: 4/18 (22.2%) Specificity: 537/567 (94.7%) **2. At 24 hours** *For TcB in phase 1 (threshold > 11 Reflectance Units)* Sensitivity: 15/18 (83.3%) Specificity: 368/556 (66.2%) PPV: 15/203 (7.4%) NPV: 368/371 (99.2%) *For TSB in phase 1 (threshold = 102 micromol/L)* Sensitivity: 7/7 (100%) Specificity: 74/162 (45.7%) PPV: 7/95 (7.4%) NPV:74/74 (100%) *For TSB in phase 2 (threshold = 102 micromol/L)* Sensitivity: 25/25 (100%) Specificity: 239/398 (60%) PPV: 25/95 (26.3%) NPV: 239/239 (100%)	

				2. At 48 hours *For TcB in phase 1 (threshold > 13 reflectance units)* Sensitivity: 17/18 (94.4%) Specificity: 288/556 (51.7%) PPV: 17/285 (5.9%) NPV: 288/289 (99.6%) *For TcB in phase 2 (threshold > 13 reflectance units)* Sensitivity: 45/46 (97.8%) Specificity: 262/819 (32.0%) PPV: 45/602 (7.5%) NPV: 262/263 (99.6%) *For TSB in phase 1 (threshold = 154 micromol/L)* Sensitivity: 11/11 (100%) Specificity: 102/158 (64.6%) PPV: 11/67 (16.4%) NPV: 101/102 (100%) *For TSB in phase 2 (threshold = 154 micromol/L)* Sensitivity: 45/46 (97.8%) Specificity: 348/774 (45%) PPV: 45/471 (9.5%) NPV: 348/349 (99.7%)	
Agarwal R; Year: 2002 Country: India [30]	Study Type: Diagnostic study Evidence Level: 1b	All infants with GA > 35 weeks with no significant illness requiring NICU admission for > 12 hours, absence of any major congenital malformations and residing near hospital whose parents agreed to come for follow-up. N = 220 mean GA 38 ± 1.4 weeks mean BW 2827 ± 459 grams Gender: Males = 53.3% Ethnicity: Not reported Exclusion:	Test: TSB at 24 ± 6 hrs after birth – three samples taken and mean of two closest values taken for analysis Threshold value: > 102 micromol/L Reference standard: Laboratory TSB measured on Day 5 when clinical jaundice > 171 micromol/L TSB ≥ 290 micromol/L taken as	Diagnostic accuracy of TSB (threshold value > 102 micromol/L) for predicting TSB = 290 micromol/L (N = 213) Prevalence: 22/213 (10.3%) Sensitivity: 21/22 (95.4%) Specificity: 135/191 (70.7%) PPV: 21/77 (27,3%) NPV: 135/136 (99.3%)	Unselected population Test & Reference test described in detail Reference test a standard one Blinding – yes

		babies requiring NICU admission, Rh hemolysis.	indicative of hyperbilirubinaemia		
Alpay F; Year: 2000 Country: Turkey [31]	Study Type: Diagnostic study Evidence Level: II	All healthy full term newborn babies with GA = 38 weeks. N = 498 mean GA Not reported mean BW Not reported Gender: Not reported Ethnicity: Not reported Exclusion: babies with blood groups A, AB, B and O / Rhesus blood factor incompatibility and a positive direct antiglobulin test result G-6PD deficiency	Test: TSB within first 24 hrs (mean 17.1 hrs) ROC curve used for threshold value with highest sensitivity for predicting hyperbilirubinaemia (threshold value: = 102 micromol/L) Results also given for threshold values = 120 micromol/L and = 137 micromol/L Reference standard: Laboratory TSB measured at 24 hrs interval for next 4 days TSB = 290 micromol/L till Day 5 taken as indicative of hyperbilirubinaemia	Diagnostic accuracy of TSB for predicting TSB = 290 micromol/L (N = 498) *Threshold value = 102 micromol/L* Prevalence: 60/498 (12.0%) Sensitivity: 54/60 (90%) Specificity: 286/438 (65.3%) PPV: 54/206 (26.2%) NPV: 286/292 (97.9%) *Threshold value = 120 micromol/L* Sensitivity: 36/60 (60%) Specificity: 363/438 (82.9%) PPV: 36/111 (32.4%) NPV: 363/387 (97.8%) *Threshold value = 137 micromol/L* Sensitivity: 21/60 (35%) Specificity: 413/438 (94.3%) PPV: 21/46 (45.6%) NPV: 413/452 (91.4%)	Unselected population Test & Reference test described in detail Reference test a standard one Blinding – Not reported
Seidman DS; Year: 1999 Country: Israel [13]	Study Type: Diagnostic study Evidence Level: II	Healthy full term infants with GA = 37 weeks born at two hospitals N = 1177 mean BW 3247 ± 453 grams mean GA 39.8 ± 1.3 weeks Gender: Males = 47.3% Ethnicity: Not reported Exclusion: ABO or Rh incompatibility and a positive direct Coombs' test G-6PD deficiency.	1) Association of various factors with jaundice derived from multiple regression analysis 2) Comparison of diagnostic accuracy of various tests for predicting hyperbilirubinaemia Test: TSB measured within first 8 to 24 hrs of life and repeated daily for the next 4 days Reference standard: Hyperbilirubinaemia defined as TSB >171 micromol/L at day 2	Factors associated with jaundice after comparing Group 1 vs. Group 2 (N = 1177) *Day 1 TSB (per 17 micromol/L)* OR: 3.1 (95%CI 2.4 to 4.1) *Change in TSB from day 1 to day 2 (per 17 micromol/L)* OR: 2.4 (95%CI 1.9 to 3.0) *Maternal age (per year)* OR: 1.1 (95%CI 1.0 to 1.2) *Mat education (per year)* OR: 0.8 (95%CI 0.7 to 0.9)	Unselected population No differences at baseline between the two groups Test & Reference test described in detail Reference test a standard one Blinding – Not reported Confounding factors adjusted for during modelling Data not available to calculate PPV or NPV. Raw figures not available

			>239 micromol/L at day 3 >291 micromol/L at day 4-5 Analysis: Association between various factors and jaundice calculated from multiple regression analysis using Odds ratios with 95%CI, and these factors used for modelling in predicting hyperbilirubinaemia	*Maternal blood type O* OR: 2.9 (95%CI 1.5 to 5.8) *Full breastfeeding* OR: 0.4 (95%CI 0.2 to 0.9) *Day 1 TSB > 85 micromol/L* OR: 36.5 (95%CI 15.9 to 83.6) Prediction of hyperbilirubinaemia *Prediction by Day 1 TSB only (threshold value > 85* micromol/L*)* Sensitivity: 63.1% Specificity: 94.2% *Prediction by all model variables without Day 1 TSB* Sensitivity: 57.9% Specificity: 90.4% *Prediction by all model variables* Sensitivity: 81.8% Specificity: 82.9%	
Stevenson DK; Year: 2001 Country: USA [33]	Study Type: Diagnostic study/cohort Evidence Level: II	Newborns with GA = 35 weeks as determined by best obstetric estimate and enrolled serially from 9 clinical sites (4 domestic and 5 international) within the first 36 hours of life. N = 1895 Mean BW: Not reported Mean GA: Not reported Gender: Males = 49% Ethnicity: Asian/Pacific Islander = 38.9% White = 33.1% Black = 16.4% Hispanic = 3.9% Other = 7.7%	Test: 1. End-tidal CO measurement corrected for inhaled CO (ETCOc) at 30 $\pm$ 6 hrs (threshold value: value > population mean) 2. TSB at 30 $\pm$ 6 hrs (threshold value: TSB = 75th centile) Timing of various TSB measurements: a) at 30 $\pm$ 6 hrs for all babies (Test) b) between 24 - 84 hrs only on clinical grounds c) at 96 $\pm$ 12 hrs for all babies d) till 168 hrs as per study protocol	Prevalence of hyperbilirubinaemia at 30 $\pm$ 6 hrs and 96 + 12 hrs 120/1370 (8.8%) Comparison of ETCOc levels between Group 1 vs. Group 2 (mean + SD) 1.45 $\pm$ 0.47 ppm vs. 1.81 $\pm$ 0.59 ppm ($p<0.001$) Diagnostic accuracy of ETCOc, TSB and combined test in predicting hyperbilirubinaemia - derived from ROC curves - (at 30 $\pm$ 6 hrs) *ETCOc (threshold > population mean)* Sensitivity: 92/120 (76.7%) Specificity: 635/1250 (50.8%) PPV: 92/707 (13.0%)	Unselected population Baseline data presented for total group (1370 (72.3%) completed the study) Test & Reference test described in detail Reference test a standard one Blinding – Not reported Data not given for calculating TP, FP, FN, and TN. Confounding factors adjusted for during modelling

		Exclusion: babies requiring admission to NICU, severe congenital anomalies, babies in incubators, pulmonary disease requiring oxygen or any form of ventilatory support, with BW < 850 grams, and respiratory rates = 10 or = 100 breaths/min. Babies with age-specific TSB = 95th centile either at < 24 hrs, at 30 ± 6 hrs, at 24-84 hrs or at 96 ± 12 hrs exited the study after giving test samples. Also babies with TSB < 40th centile at 96 ± 12 hrs exited.	Reference standard: Lab TSB confirmed hyperbilirubinaemia Hyperbilirubinaemia was defined as Age-specific lab TSB = 95th centile Analysis: Logistic regression analysis models performed for prediction of hyperbilirubinaemia with ETCOc and TSB at 30 ± 6 hrs using multiple variables (bruising, type of feeding, BW, race, maternal diabetes, type of labor, gender, infection, PIH, parity, maternal blood type and Rh status)	NPV: 635/663 (95.8%) *TSB (threshold > 75th centile) after excluding babies with TSB > 95th centile at < 36 hours* PPV: 16.7% NPV: 98.1% *Combined test* PPV: 6.4% NPV: 99.0%	
Okuyama H; Year: 2001 Country: Japan [35]	Study Type: Diagnostic study Evidence Level: II	Full-term infants with GA = 37 weeks and BW = 2500 grams. N = 51 mean BW 3108 ± 327 grams, mean GA 39.3 ± 1.4 weeks Gender: Males = 51% Ethnicity: Not reported Exclusion: subjects with maternal smoking, infants of diabetic mother, haemolytic disease such as blood group incompatibilities, closed space haemorrhage, respiratory distress, polycythemia.	Test: End-tidal CO measurement corrected for inhaled CO (ETCOc) every 6 hrs during the first 72 hrs. (different threshold values at different age) Reference standard: TcB measured every 12 hrs during the first 5 days using JM-102, and serum TSB measured when TcB index = 22 reflectance units Hyperbilirubinaemia defined as TSB = 257 micromol/L ROC curve used for predicting hyperbilirubinaemia	Group 1 vs. Group 2 No statistical differences between the two groups for sex, GA, mode of delivery, Apgar score at 1 min, age at peak TcB, and feeding type. *ETOCc levels* At 6-36 hrs – No statistical difference At 42, 48, 54 and 66 hrs – levels significantly higher in Group 1 Diagnostic accuracy of ETCOc in predicting hyperbilirubinaemia *Threshold 1.6 ppm at 36hrs* Sensitivity: 5/7 (71.4%) Specificity: 27/44 (61.4%) PPV: 5/22 (22.7%) NPV: 27/29 (93.1%) *Threshold 1.8 ppm at 42hrs* Sensitivity: 6/7 (85.7%) Specificity: 35/44 (79.5%)	Unselected population but small sample size Test & Reference test described adequately Reference test a standard test but not done in all babies Blinding – Not reported

				PPV: 6/15 (40%) NPV: 35/36 (97.2%) *Threshold 1.8 ppm at 48hrs* Sensitivity: 6/7 (85.7%) Specificity: 32/44 (72.7%) PPV: 6/18 (33.3%) NPV: 32/33 (96.9%) *Threshold 1.8 ppm at 60hrs* Sensitivity: 6/7 (85.7%) Specificity: 29/44 (65.9%) PPV: 6/21 (28.6%) NPV: 29/33 (87.9%)	
Bhutani VK; Year: 1999 Country: USA [34]	Study Type: Diagnostic study Evidence Level: II	Birth cohort Term (BW = 2000 grams for = 36 weeks) and near-term AGA (BW = 2500 grams for GA = 35 weeks) newborn babies in a tertiary hospital (N = 13,003) For nomogram N = 2,840 mean BW 3318 ± 457 grams mean GA 38.7 ± 1.3 weeks mean age for pre-discharge sampling 33.7 ± 14.6 hrs Gender: Males = 50.1% Ethnicity: White = 43.4% Black = 41.2% Hispanic = 3.6% Asian = 4.1% Other = 7.7% Exclusion: admission and treatment in intensive care nursery for neonatal illness, positive Coombs' test,	Test: Pre-discharge TSB characterized by postnatal age in hours and measured between 18-72 hrs Reference standard: Hour-specific nomogram or TSB centiles developed from pre and post-discharge TSB values. Post-discharge values obtained on clinical grounds from day 1-6. Data recorded in epochs of: 4 hrs for first 48 hrs, 12 hrs for 48-96 hrs, 24 hrs for age 5-7 days. Predictive ability of pre-discharge TSB levels (given as percentile tracks and risk zones) evaluated for subsequent Significant Hyperbilirubinaemia (defined as TSB level reaching into the high-risk zone or = 95th centile) Threshold zones: High risk zone above 95th percentile, High intermediate risk zone	Prevalence of significant hyperbilirubinaemia *Including both pre and post-discharge TSB* 230/2840 (8.1%) *Post-discharge TSB only* 126/2840 (4.4%) Predictive ability of pre-discharge TSB percentile tracks as risk demarcators for subsequent hyperbilirubinaemia (N = 2840) *Pre-discharge TSB above 95th percentile (N = 172)* Sensitivity: 68/126 (54.0%) Specificity: 2610/2714 (96.2%) PPV: 68/172 (39.5%) NPV: 2610/2668 (97.8%) *Pre-discharge TSB above 75th percentile (N = 528)* Sensitivity: 114/126 (90.5%) Specificity: 2300/2714 (84.7%) PPV: 114/528 (21.6%)	Unselected population Test & Reference test described adequately Reference test a standard test as nomogram developed from lab TSB values Blinding – Not reported

		TSB measured after initiation of phototherapy, babies requiring phototherapy before 60 hrs to control unexplained rapidly rising TSB levels.	between 75th and 95th centile, Low intermediate risk zone between 75th and 40th centile Low risk zone below 40th centile	NPV: 2300/2312 (99.5%) *Pre-discharge TSB above 40th percentile (N = 1084)* Sensitivity: 126/126 (100%) Specificity: 1756/2714 (64.7%) PPV: 126/1084 (11.6%) NPV: 1756/1756 (100%) Likelihood ratio (LR) based on risk zones *High risk zone* +LR: 14.1 *Upper-intermediate risk zone* +LR: 3.2 *Lower-intermediate risk zone* +LR: 0.5 *Low risk zone* +LR: 0	
Romagnoli C; Year: 2005 Country: Italy [36]	Study Type: Diagnostic study Evidence Level: II	Phase 1: Development of nomogram Full term AGA babies delivered by vaginal or caesarean section after uneventful pregnancy, without asphyxia and with no Rh or major ABO incompatibility. N = 438 mean BW 3389 ± 668 grams mean GA 40 ± 1.8 weeks Gender: Males = 51.6% Ethnicity: Not reported Exclusion: congenital anomalies, any illness requiring admission to neonatal intensive care unit, infants with delayed meconium passage,	Test: Laboratory TSB measured between 30-72 hrs on clinical suspicion (single measurement in all babies, two consecutive TSB determinations 12 hrs apart in 514/1244 babies in Hospital A and 175/498 babies in Hospital B) Reference standard: Hour-specific nomogram. TSB curves developed from TSB values measured at 6 hrs of age and then every 4-6 hrs during day and 6-12 hrs during night. Curves of babies with TSB > 205 micromol/L and those with TSB > 205 micromol/L taken	Phase 1: Time of reaching highest TSB values in Phase 1 At 24-48 hrs: 20.3% At 49-72 hrs: 48.4% At 73-96 hrs: 26.0% At 97-120 hrs: 5.3% Phase 2: Predictive ability of Trend 12 and 15 as risk demarcators for subsequent hyperbilirubinaemia **HOSPITAL A** *Prevalence of TSB > 205* micromol/L 230/1244 (18.5%) *Prevalence of TSB > 205 micromol/L* 100/1244 (8.0%)	Unselected population Test & Reference test described adequately Reference test a standard test as nomogram developed from lab TSB values Blinding – Not reported

		hypothermia, hypoglycaemia, cephalohematoma, local bleeding, hemorrhagic disease of newborn, UTI or suspected clinical sepsis. <u>Phase 2: Application of the nomogram</u> Healthy term babies in two hospitals who had TSB estimation between 30-72 hrs due to clinical jaundice Hospital A: N = 1244, mean BW 3299 $\pm$ 447 grams, mean GA 39.2 $\pm$ 1.4 weeks Gender: Males = 56.4% ethnicity: Not reported Hospital B: N = 498, mean BW 3312 $\pm$ 394 grams, mean GA 39.5 $\pm$ 1.3 weeks Gender: Males = 51.8% ethnicity: Not reported	separately, their 1st percentile TSB values determined for each hour of life and connected to form percentile tracks. Predictive ability of TSB levels measured in Phase 2 evaluated for subsequent hyperbilirubinaemia at 24-36 hrs, 37-48 hrs, 49-60 hrs, 61-72 hrs and all together (threshold value – Trend 12 defined as TSB value exceeding the 1st percentile track of babies with TSB > 205 micromol/L, and Trend 15 defined as TSB value exceeding the 1st percentile track of babies with TSB > 256 micromol/L	*Single TSB measurement with Trend 12 as threshold* Sensitivity: 228/230 (99.1%) Specificity: 496/1014 (48.9%) PPV: 228/746 (30.6%) NPV: 496/498 (99.6%) + LR: 1.9 *Single TSB measurement with Trend 15 as threshold* Sensitivity: 100/100 (100%) Specificity: 859/1144 (75.1%) PPV: 100/385 (26.0%) NPV: 859/859 (100%) +LR: 4.0 *Two TSB measurements with Trend 12 as threshold* Sensitivity: 85/85 (100%) Specificity: 217/429 (50.6%) PPV: 85/302 (28.6%) NPV: 217/217 (100%) +LR: 2.0 *Two TSB measurements with Trend 15 as threshold* Sensitivity: 92/92 (100%) Specificity: 355/422 (84.1%) PPV: 92/159 (57.9%) NPV: 355/355 (100%) +LR: 6.3 **HOSPITAL B** *Prevalence of TSB > 12 MG/DL* 129/498 (25.9%) *Prevalence of TSB > 15 MG/DL* 59/498 (11.8%) *Single TSB measurement with Trend 12 as threshold* Sensitivity: 127/129 (98.4%) Specificity: 131/369 (35.5%) PPV: 127/365 (34.8%)	

				NPV: 131/133 (98.5%) + LR: 1.5 *Single TSB measurement with Trend 15 as threshold* Sensitivity: 52/59 (88.1%) Specificity: 344/439 (78.4%) PPV: 52/147 (35.4%) NPV: 344/351 (98.0%) +LR: 4.1 *Two TSB measurements with Trend 12 as threshold* Sensitivity: 54/54 (100%) Specificity: 84/121 (69.4%) PPV: 54/91 (59.3%) NPV: 84/84 (100%) +LR: 3.3 *Two TSB measurements with Trend 15 as threshold* Sensitivity: 23/24 (95.8%) Specificity: 117/151 (77.5%) PPV: 23/58 (40.4%) NPV: 117/118 (99.2%) +LR: 4.3	
Bhutani VK; Year: 2000 Country: USA [37]	Study Type: Diagnostic study Evidence Level: 1b	All term and near-term babies (either = 36 weeks GA and BW = 2000 grams or = 35 weeks and BW = 2500 grams) discharged as healthy from the well baby nursery in a tertiary hospital N = 490, observations=1788, mean BW 3404 ± 518 grams, mean GA 38. 9 ± 1.5 weeks Gender: Not reported Ethnicity: White = 59.1% Black = 29.5%	Test: Pre-discharge TcB reading from the forehead using BiliChek measured between 24 and 72 hours of age. Reference standard: Laboratory TSB measured at same time as TcB, and also sent for HPLC assays. Paired TcB and HPLC TSB values plotted on the hour-specific nomogram. Predictive ability of pre-	Prevalence of significant hyperbilirubinaemia 30/490 (6.1%) Correlation of TcB levels with TSB levels using HPLC (Pearson correlation coefficient, N = 1788 samples) $r = 0.91$, $p < 0.01$ Bland Altman analysis for difference between TSB and TcB MD = -8 micromol/L (95%CI -38.9 to 54.9) Predictive ability of pre-discharge TcB (threshold = 75th centile) for significant	Unselected population but only 1.1% of study population had TSB values > 256 micromol/L Test & Reference test described adequately Reference test a standard test as nomogram developed from lab TSB values Blinding – specified

		Hispanic = 3.5% Asian = 4.5% Others = 3.5% Exclusion: clinical manifestation of sepsis, heart or circulatory disease, respiratory distress, clinical evidence of haemoglobinopathy, initiation of phototherapy.	discharge TcB levels (threshold = 75th centile) evaluated for subsequent significant hyperbilirubinaemia (defined as TSB = 95th centile or in the high-risk zone on the hour-specific nomogram)	<u>hyperbilirubinaemia (N = 419)</u> Sensitivity: 23/23 (100%) Specificity: 349/396 (88.1%) PPV: 23/70 (32.9%) NPV: 349/349 (100%) +LR: 8.4	
Newman TB; Year: 2000 Country: USA [8]	Study Type: Nested case- control study Evidence Level: II	Cohort of all infants with BW = 2000 grams and GA = 36 weeks born alive at 11 hospitals of a health maintenance organization during a two year period (N = 51,387) <u>Cases:</u> Babies with maximum TSB levels = 428 micromol/L within the first 30 days after birth N = 73 Mean BW: Not reported Mean GA: Not reported Gender: Males = 67.1% Ethnicity: Not reported (only maternal race specified) <u>Controls:</u> Random sample of babies from the cohort with maximum TSB levels = 428 micromol/L N = 423 Mean BW: Not reported Mean GA: Not reported Gender: Males = 54.4% Ethnicity: Not reported (only maternal race specified) For analyses examining the use of	1) Relationship of clinical and demographic factors associated with hyperbilirubinaemia evaluated by bivariate analysis and OR 2) Risk factors significant in the univariate model entered into multiple regression analysis to find independent predictors of hyperbilirubinaemia – both by including and excluding early jaundice cases <u>Early jaundice cases</u> (N = 14) defined as babies with TSB exceeding recommended phototherapy threshold for age during birth hospitalization, those given phototherapy during birth hospitalization, when jaundice noted at less than 20 hours of age and TSB not measured within 6 hrs of that time. 3) Risk index developed by assigning points equal to the OR for risk factors that were significant in the logistic regression model with the	<u>Maternal and prenatal factors associated with significant hyperbilirubinaemia (those with p<0.05 in bivariate analysis)</u> *Maternal factors* - Race, - maternal age, - family HISTORY OF jaundice in a newborn, - vacuum delivery *Neonatal factors* - Male sex, - lower GA, - early jaundice, - cephalohaematoma, - bruising, - breastfeeding at time of discharge <u>Factors independently associated with significant hyperbilirubinaemia from multivariate regression analysis (OR with 95%CI)</u> *All cases (N = 73)* Early jaundice: OR 7.3 (2.8-19) GA (per wk): OR 0.6 (0.4-0.7) Breastfeed only at discharge: OR 6.9 (2.7-17.5)	Unselected population but exclusion criteria not defined Confounding variables controlled for during multivariate analysis Test & Reference test described adequately Reference test a standard test Blinding – Not reported

		phototherapy only, additional random sample of 30 babies with maximum TSB levels of 342 to 426 micromol/L added to the control group Exclusion criteria: Not defined	exclusion of early jaundice cases, and predictive accuracy compared by the c-statistic (equal to area under ROC curve) Reference standard: Significant hyperbilirubinaemia defined as maximum TSB levels = 428 micromol/L within the first 30 days after birth.	Asian race: OR 3.1 (1.5-6.3) Bruising: OR 3.5 (1.7-7.4) Cephalohaematoma: OR 3.2 (1.1-9.2) Maternal age ≥ 25 yrs: OR 2.6 (1.1-9.2) *Cases excluding early jaundice (N = 59)* GA (per wk): OR 0.6 (0.4-0.7) Breastfeed only at discharge: 5.7 (2.1-15.5) Asian race: OR 3.5 (1.7-7.4) Bruising: OR 4.0 (1.8-8.8) Cephalohaematoma: OR 3.3 (1.1-10) Maternal age ≥ 25 yrs: OR 3.1 (1.2-8.1) Risk Index scoring 6 points each for exclusive breastfeeding and family HISTORY OF jaundice in a newborn, 4 points each for bruising and Asian race, 3 points each for cephalhematoma and maternal age ≥ 25 yrs, 1 point for male sex, -2 points for black race, and 2(40-GA) Accuracy of Risk Index score in predicting significant hyperbilirubinaemia Overall c-statistic 0.85 *Risk index score < 10* +LR: 0.2 *Risk index score > 10* +LR: 2.2 *Risk index score > 20* +LR: 18.2	
Newman TB; Year: 2005	Study Type: 1) Nested case- control study	**Study 1:** Cohort of all infants with BW = 2000 grams and GA = 36 weeks	**Study 1:** Risk index score developed by assigning points equal to the OR	**Study 1:** Comparison of 1995-96 cohort (N = 51,387) with 1997-98 cohort (N =	Retrospective cohort study Unselected population but exclusion criteria not defined

Country: USA [38]	2) Retrospective cohort Evidence Level: II	born alive at 11 hospitals of a health maintenance organization during a two year period (N = 53,997) Cases: Babies with maximum TSB levels = 428 micromol/L within the first 30 days after birth (N = 67) Controls: Random sample of babies from the cohort with maximum TSB levels = 428 micromol/L (N = 208) Mean BW: Not reported Mean GA: Not reported Gender: Not reported Ethnicity: Not reported **Study 2:** All infants with BW = 2000 grams and GA = 36 weeks born alive at 11 hospitals of a health maintenance organization during a four year period, and who had TSB measured at < 48 hrs of age (N = 5,706) Mean BW: Not reported Mean GA: Not reported Gender: Not reported Ethnicity: Not reported Exclusion criteria: Babies developing TSB levels > 342 micromol/L at < 48 hrs	for risk factors significant in the logistic regression model (not including family history of jaundice) with the exclusion of early jaundice cases. Predictive accuracy compared by the c-statistic (equal to area under ROC curve) **Study 2:** Test 1 Partial clinical risk index derived from Risk index in Study 1 by deleting factors family history of jaundice, breastfeeding, bruising and by substituting scalp injury in medical records with cephalohaematoma. Test 2 TSB levels measured at < 48 hrs and classified into 4 age-specific percentile groups < 40th centile, 40th to < 75th centile, 75th to < 95th centile, > 95th centile). The data was then transformed into hour-specific z scores Reference standard Significant Hyperbilirubinaemia defined as maximum TSB levels = 342 micromol/L	53,997) No difference regarding % of babies with TSB level ≥ 342 micromol/L, TSB ≥ 428 micromol/L, age more than 7 days at the time of highest TSB levels, average number of TSB tests per patient, length of hospitalization stay and treatment with phototherapy Accuracy of Modified risk index score (with exclusion of family HISTORY OF jaundice) in predicting significant hyperbilirubinaemia (with 95%CI) *1997-1998 cohort* c-statistic 0.83 (95%CI 0.77 to 0.89) *1995-96 cohort* c-statistic 0.84 (95%CI 0.79 to 0.89) **Study 2:** Prevalence of hyperbilirubinaemia 230/5,706 (4.7%) Risk of developing TSB levels > 342 micromol/L based on TSB percentile group < 40th centile = 0.5 40th to < 75th centile = 0.7 75th to < 95th centile = 3.3 ≥ 95th centile = 13.8 Accuracy of tests in predicting hyperbilirubinaemia (TSB levels = 342 micromol/L *Partial risk index score* c-statistic 0.69	Confounding variables controlled for during multivariate analysis Test & Reference test described adequately Reference test a standard test Blinding – Not reported

				TSB centile group c-statistic 0.79 *TSB z score* c-statistic 0.83 *TSB z score + Partial risk index score* c-statistic 0.86	
Keren R; Year: 2005 Country: USA [12]	Study Type: Retrospective cohort/ diagnostic study Evidence Level: 2	Infants with BW = 2000 grams if GA = 36 weeks and BW = 2500 grams if GA = 35 weeks participating in the hospital's early discharge programme, and who had both pre and post-discharge TSB levels measured at the phase when ≥ 75% babies had both the samples (N = 899) Group 1: infants with post-discharge TSB > 95th centile on nomogram (N = 98, 54% males, mean BW 3.4 ± 0.5 kg) Group 2: infants with post-discharge TSB < 95th centile on nomogram (N = 801, 52% males, mean BW 3.3 ± 0.5 kg) Exclusion: admission and treatment in intensive care nursery for neonatal illness and babies requiring phototherapy during birth hospitalization.	Test 1: Clinical risk factor score derived from regression modelling using the factors found independently associated with significant hyperbilirubinaemia. Test 2: Pre-discharge TSB levels expressed as risk zone on an hour-specific bilirubin nomogram (High risk > 95th centile, High intermediate risk 76th – 95th centile, Low intermediate risk 40th – 75th centile, Low risk 0 – 40th centile) Reference standard: Significant Hyperbilirubinaemia defined as TSB level > 95th centile on hour-specific nomogram. Accuracy of Clinical risk score and pre-discharge TSB risk zone evaluated for predicting significant hyperbilirubinaemia	Prevalence of significant hyperbilirubinaemia 98/899 (11%) Factors associated with significant hyperbilirubinaemia (those with p<0.2 in univariate analysis) *Increased risk* GA < 38 weeks and ≥ 40 weeks, LGA babies, higher pre-discharge TSB risk zone, combined breast and bottle feeding, maternal diabetes, vacuum extraction, prolonged rupture, oxytocin use *Decreased risk* SGA, parity, caesarean section Factors independently associated with significant hyperbilirubinaemia from multivariate regression analysis (OR with 95%CI) Birthweight: 1.5 (1.2-1.9) GA < 38 weeks: 2.6 (1.5-4.5) Oxytocin: 2.0 (1.2-3.4) Vacuum delivery: 2.2 (1.5-3.6) Exclusive breastfeeding: 2.6 (1.5-4.5) Breast and bottle feeding: 2.3 (1.1-4.9) Clinical risk index scoring	Retrospective cohort study Unselected population Test & Reference test described adequately Reference test a standard test Blinding – Not reported

				Birthweight: 3 points for 2501-3000 grams, 6 for 3001-3500 grams, 9 for 3501-4000 grams, 12 for 4001-4500 grams, 15 for 4501-5000 grams GA < 38 weeks: 5 points Oxytocin: 4 points Vacuum delivery: 4 points Exclusive breastfeeding: points Breast and bottle feeding: 4 points <u>Predictive accuracy for predicting significant hyperbilirubinaemia</u> RISK FACTOR SCORE c-statistic 0.71 (0.66-0.76) *Risk index score 0-7* +LR: 0.1 *Risk index score 8-11* +LR: 0.4 *Risk index score 12-15* +LR: 0.9 *Risk index score 16-19* +LR: 2.0 *Risk index score 20-23* +LR: 2.6 *Risk index score > 24* +LR: 3.2 PRE-DISCHARGE TSB c-statistic 0.83 (0.80-0.86) *TSB centile 0-40th* +LR: 0.05 *TSB centile 41-75th* +LR: 0.2	

				TSB centile 76-95th +LR: 2.2 *TSB centile > 95th* +LR: 9.4	
Keren R et al; Year: 2008 Country: USA [14]	Study Type: Prospective cohort study Evidence Level: II	Infants managed exclusively in the well infants nursery of an urban tertiary care hospital with GA = 36 weeks and BW = 2000 grams or GA = 35 weeks and BW = 2500 grams N = 812 mean BW 3.3 ± 0.5 kg GA < 38 weeks: 13.4% Gender: males = 49.4% Ethnicity: White = 33.5% Black = 53.2% Asian = 9.8% Other = 3.4% Since the population in the area was predominantly black, stratified sampling scheme used to get a representative sample. Group 1: Infants with significant hyperbilirubinaemia (N = 48) Group 2: Infants without significant hyperbilirubinaemia (N = 703) Exclusion: babies transferred to the intensive care nursery for any reason Babies who received intravenous antibiotics for concern for sepsis.	1) Factors associated with significant hyperbilirubinaemia in univariate analysis entered into regression modeling for clinical risk factor model 2) Comparison of diagnostic accuracy of three tests in predicting significant hyperbilirubinaemia by the c-statistic (mathematically equal to area under ROC curve) Test 1: Pre-discharge bilirubin measured either by TcB or TSB at < 52 hrs of age, and expressed as risk-zone on hour specific nomogram. Daily TcB levels recorded using BiliChek, and TSB performed if TcB above 75th centile on hour-specific nomogram or TcB reading = 205 micromol/L. TSB value taken for analysis when both TcB and TSB done. Test 2: Clinical risk factors assessed by review of hospital charts for maternal race, intended method of feeding, GA, history of previous infant with jaundice, clinical assessment of jaundice,	Prevalence of significant hyperbilirubinaemia 48/751 (6.4%) – 61 had an incomplete follow-up 1) Association of factors with significant hyperbilirubinaemia (Univariate analysis) (n = 812) *Factors increasing risk* Pre-discharge bilirubin – high risk zone OR: 147 (95%CI 34-639) high-intermediate risk zone OR: 21 (95%CI 4.9-93.0) GA < 38 weeks OR: 9.2 (95%CI 4.4-19.0) intended breastfeeding OR: 2.2 (95%CI 1.0-4.5) intended breast + bottle feeds OR: 3.7 (95%CI 1.6-8.6) Grade 4 or higher degree of clinical jaundice OR 6.0 (95%CI 2.1 to 17) *Factors decreasing risk* Black race OR 0.43)95%CI 0.23-0.80) Maternal history of smoking OR: Not reported Factors significant in multivariate analysis model (p<0.05) GA<38 weeks OR 19 (95%CI 6.3- 56) Mother's plan of exclusive breastfeeding: OR 3.7 (95%CI 1.1- 13)	Unselected population (stratified sampling) with well defined exclusion criteria Baseline characteristics of two groups not compared Confounding variables controlled Methodology described adequately Blinding – not specified

			G-6PD deficiency. Test 3: Combination of pre-discharge bilirubin risk zone and clinical risk factors. Reference standard: Bilirubin levels (TcB or TSB) measured on day 3-5 on both hospitalized and discharged babies (at home) using similar method as in Test 1, and Significant Hyperbilirubinaemia defined as bilirubin levels exceeding or within 17 micromol/L of the hour-specific phototherapy treatment thresholds.	Black race: OR 0.22 (95%CI 0.08- 0.61) Grade 4 or higher jaundice observed clinically: OR 1.7 (95%CI 1.2-2.6) Female sex: OR 3.2 (95%CI 1.2-8.4) 2) Predictive ability of the three tests in predicting significant hyperbilirubinaemia (multivariate regression) *Test 1: Pre-discharge bilirubin risk zone* c-statistic 0.88 (95% 0.85 to 0.91) *Test 2: Clinical risk factors (final model had 5 factors – GA, intended method of feeding, black race, extent of jaundice and gender)* c-statistic 0.91 (95% 0.86 to 0.97) *Test 3: Combination model (pre-discharge risk zone + clinical factors of GA and % weight loss)* c-statistic 0.96 (95% 0.93 to 0.98) *Test 3 vs. Test 1* p-value for difference< 0.01 *Test 3 vs. Test 2* p-value for difference = 0.15 *Test 2 vs. Test 1* p-value for difference = 0.35	
Herschel M; Year: 2002 Country: USA 225	Study Type: Prospective diagnostic study Evidence Level: II	All consecutive babies admitted to the General Care Nursery of a tertiary care city hospital. Mean GA: 38.9 ± 1.4 weeks Mean BW: 3267 ± 480 grams Gender: Males = 47.6%, Ethnicity: black - 82.9%	**Objective 1:** Diagnostic accuracy of DAT Test: Direct Antiglobulin Test (DAT) done on cord blood of all newborn babies. Reference standard: Haemolysis identified by measuring ETCOc levels in all babies at 12 ± 6 hrs	**Objective 1:** Prevalence of DAT positive results 23/659 (3.5%) Accuracy of DAT in detecting haemolysis (ETCOc = 3.2 µl/l) in babies of non-smoking mothers (N = 499) Sensitivity: 10/26 (38.5%) Specificity: 466/473 (98.5%)	Unselected population but exclusion criteria not defined Test and Reference described adequately Reference test a standard one Blinding – Not reported

		white = 9.8% Hispanic = 3.3% Asian = 2% Other = 2% Results given separately for babies with smoking mothers and non-smoking mothers. Exclusion: not defined	and 24 ± 6 hrs. Significant haemolysis defined as ETCOc levels = 95th centile in babies of non-smoking mothers at 12 hrs (= 3.2 µl/l), and among all babies at 24 hrs (= 2.5 µl/l). **Objective 2:** Accuracy of DAT and ETCOc in predicting hyperbilirubinaemia defined as bilirubin reading = 75th centile on the nomogram (TcB readings with BiliChek at the time of discharge or earlier as clinically indicated, and subsequent TSB as deemed necessary)	PPV: 10/17 (58.8%) NPV: 466/482 (96.7%) Accuracy of DAT in detecting haemolysis (ETCOc = 2.5 µl/l) in babies of all mothers (N = 563) Sensitivity: 4/47 (8.5%) Specificity: 504/516 (97.6%) PPV: 4/16 (25.0%) NPV: 504/547 (92.1%) **Objective 2:** Prevalence of hyperbilirubinaemia. In babies of non-smoking mothers 61/499 (12.2%) Accuracy of positive DAT test in predicting hyperbilirubinaemia in babies of non-smoking mothers (N = 499) Sensitivity: 9/61 (14.7%) Specificity: 430/438 (98.2%) PPV: 9/17 (52.9%) NPV: 430/482 (89.2%) Accuracy of ETCOc (threshold = 2.5 µl/) in predicting hyperbilirubinaemia in babies of non-smoking mothers (N = 499) Sensitivity: 17/61 (27.9%) Specificity: 429/438 (97.9%) PPV: 17/26 (65.4%) NPV: 429/473 (90.7%)	
Risemberg HM; Year: 1977 Country: USA [39]	Study Type: Prospective diagnostic study Evidence Level: III	All consecutive newborns of hetero-specific pregnancies (blood group O mothers with babies having blood group A or B) born in two hospitals (N = 91) Mean GA: Not reported Mean BW: Not reported Gender: Not reported	Test 1: Coombs' test done on cord blood of all newborn babies. Test 2: UCB levels measured (threshold value > 68 micromol/L) Reference standard: Severe hyperbilirubinaemia defined as TSB > 274	Prevalence of severe hyperbilirubinaemia 13/91 (14.3%) Prevalence of DAT positive 31/91 (34.1%) Accuracy of positive DAT test in predicting severe hyperbilirubinaemia (N = 91) Sensitivity: 12/13 (92.3%)	Small sample Test and Reference standard not described in details Reference test a standard one Blinding – Not reported

		Ethnicity: Not reported Exclusion: Rh incompatible babies	micromol/L at 12-36 hours of age	Specificity: 59/78 (75.6%) PPV: 12/31 (38.7%) NPV: 58/60 (98.3%) Accuracy of UCB levels (threshold > 68 micromol/L) in predicting severe hyperbilirubinaemia (N = 91) Sensitivity: 12/13 (92.3%) Specificity: 78/78 (100%) PPV: 12/12 (100%) NPV: 78/79 (98.7%)	
Chen JY; Year: 1994 Country: Taiwan 42	Study Type: Diagnostic accuracy study Evidence Level: III	Healthy term babies born to blood group O, Rh positive mothers and weighing = 2.5 kg with no evidence of perinatal asphyxia, polycythemia, huge cephalhematoma or infection. (N = 88) Mean GA: Not reported Mean BW: Not reported Gender: Not reported Ethnicity: Not reported Exclusion: not defined	Test 1: Direct Coombs' test from cord blood. Test 2: UCB levels measured threshold value > 68 micromol/L Reference standard: Hyperbilirubinaemia defined as TSB levels = 256 micromol/L) within first 4 days of life and/or early jaundice with TSB levels = 171 micromol/L within 24 hours of birth	Prevalence of DAT positive 14/53 (26.4%) Prevalence of hyperbilirubinaemia 29/53 (54.7%) Diagnostic accuracy of Coombs' test for predicting hyperbilirubinaemia (N = 53) Sensitivity: 13/29 (44.8%) Specificity: 23/24 (95.8%) PPV: 13/14 (92.8%) NPV: 23/39 (59.0%) Diagnostic accuracy of UCB (> 68 micromol/L for predicting hyperbilirubinaemia (N = 53) Sensitivity: 12/29 (41.4%) Specificity: 24/24 (100%) PPV: 12/12 (100%) NPV: 24/41 (58.5%)	Small sample and data derived from results of two groups of babies with blood group A & B only Test & Reference test not described in detail Reference test is a standard one Blinding: none
Sarici SU Year: 2002 Country: Turkey 43	Study type: Prospective diagnostic study Evidence level: III	All full-term babies (GA > 38 weeks) with blood groups A or B born to mothers with blood group O without simultaneous Rhesus blood factor incompatibility. (N = 150) Mean GA: 39.4 ± 1.2 weeks Mean BW: 3212 ± 415 grams	Test: Direct Antiglobulin Test (DAT) on cord blood Reference standard: Total serum bilirubin level (TSB) at 6, 30, 54, 78 and 102 hours Hyperbilirubinaemia was defined	Prevalence of DAT positive 4.4% (6/136) Prevalence of Hyperbilirubinaemia 29/136 (21.3%) Accuracy of DAT in predicting hyperbilirubinaemia (N = 136)	Aim of study was to see if 6hr TSB levels predicted hyperbilirubinaemia No data on 14 babies for clinical or consent reasons Selected sample and test not

		Gender: Males = 50.7% Ethnicity: Not reported	as: TSB ≥ 85 micromol/L and increase of 8.5 micromol/L in first 24 hours Day 2 TSB > 205 micromol/L Day 3 TSB > 256 micromol/L Day 4/5 TSB > 290 micromol/L	Sensitivity: 6/23 (20.1%) Specificity: 107/107 (100%) PPV: 6/6 (100%) NPV: 107/130 (82.3%)	described. Reference is a standard test and was adequately described Blinding: None
Meberg A Year: 1998 Country: Norway [40]	Study Type: Diagnostic Accuracy study Evidence level: III	All babies born in a general hospital. (N = 2,463) Mean GA: Not reported (94.8% were term babies ≥ 27 weeks) Mean BW: Not reported Gender: Not reported Ethnicity: Not reported Exclusion: Stillbirth, death, high-risk deliveries. severe neonatal conditions	Test: Direct Antiglobulin Test (DAT) on cord blood Reference: TSB levels requiring phototherapy according to the Hillingdon Hospital bilirubin chart. Phototherapy indicated at TSB > 350 micromol/L at ≥72 hours for term babies TSB >250 micromol/L at ≥ 120 hours for preterm babies TSB at lower levels for younger babies	Prevalence of DAT positive 4.1% (100/2,463) Prevalence of Hyperbilirubinaemia 139/2,463 (5.6%) Accuracy of DAT in predicting need for phototherapy for hyperbilirubinaemia (N = 2,463) Sensitivity: 20/139 (14.4%) Specificity: 2244/2324 (96.6%) PPV: 20/100 (20.0%) NPV: 2244/2463 (91.1%)	Universal sample Test: not adequately described Reference test is a standard one but not described adequately Blinding: None

Evidence table – Prediction of hyperbilirubinaemia (effectiveness)

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
Petersen JR; Year: 2005 Country: USA [44]	Study Type: Retrospective cohort study Evidence Level: II	Babies with a diagnosis-related group designation indicating 'normal newborn' and admitted in the newborn unit of a tertiary hospital from August 2002 to December 2003. (N = 6603, males 52.9%) Group 1: babies born before TcB introduced – August 2002 to March 2003 (N = 3237, 51.3% males) Group 2: babies born after TcB introduced – May 2003 to December 2003 (N = 3366, 53.2% males) Exclusion: babies who did not fit the criterion of 'normal newborns', and those born in the transitional time – April 2003	Comparison of the number of births, number of vaginal and caesarean deliveries, ethnicity and gender distribution, newborn readmission rates, and number of serum bilirubin measurements between Group 1 vs. Group 2	<u>Comparison of bilirubin testing (values in mean (SD)</u> *Number of monthly admissions* 404.6 (33.2) vs. 420.7 (36.8), p=0.42 *Number of newborns tested monthly* 128.0 (26.1) vs. 152.1 (26.2), p=0.10 *% of newborns tested by TSB levels* 6.4% vs 8.7% p=0.21 *Serum bilirubin measurement per newborn* 1.51 vs. 1.56 p=0.33 *Total bilirubin measurement (TcB +TSB)* 0.37 vs. 0.61 p=0.007 *% of newborns treated with phototherapy* 5.9% vs 7.7% p=0.014 *Newborn readmissions for hyperbil. within 7 days of initial discharge (per 1000 births)* 4.5 vs 1.8 p=0.044	Retrospective cohort study Some of the baseline characteristics compared between the two groups, but information not given for all variables. Confounding variables not adjusted
Ebbesen F; Year: 2002 Country: Denmark	Study Type: Diagnostic study Evidence Level: III	All newborns more than 24 hours old who for clinical reasons had their plasma bilirubin determination during the day, except at weekends. <u>Group 1:</u> Both preterm infants < 35	TcB measurement using BiliChek from forehead, sternum, knee and the foot – mean of 5 measurements from each site taken for data analysis.	<u>Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient, N = 210)</u> **Group 1:** *Forehead*	Unselected population Test & Reference test described adequately Test and reference test carried out within one hour Blinding – not specified

[45]		weeks and sick term and near-term infants in the NICU N = 261 mean BW 2521 grams - range 680 to 4645 grams, mean GA 34.6 weeks - range 25 to 43 weeks postnatal age at 1st TcB: 98.4 - range 48 – 840 Gender: Males = 60.1% Ethnicity: Non-northern European descent = 9% Group 2: Healthy term and near-term infants with GA ≥ 35 weeks in the maternity ward N = 227 mean BW 3362 grams - ange 2170 to 5000 grams mean GA 38.6 weeks - range 35 to 43 weeks postnatal age at 1st TcB: 74.4 - range 48 – 360 Gender: Males = 55.5% Ethnicity: Non-northern European descent = 7% Exclusion: babies already receiving phototherapy or who received phototherapy 6 hours before TSB measurement, with skin infection, purpura, bruising	Reference standard: Laboratory TSB levels taken concurrently with TcB measurement Diagnostic accuracy of TcB from forehead (threshold ≥ 0.70 of phototherapy limit) estimated for predicting TSB levels ≥ phototherapy limits as suggested by the Danish Pediatric Society	r = 0.88, p > 0.05 *Sternum* r = 0.82, p < 0.001 *Knee* r = 0.77, p < 0.001 *Foot* r = 0.51, p < 0.001 On comparing correlation coefficient of forehead with that for sternum, knee and foot, p < 0.001 for each of the comparison **Group 2:** *Forehead* r = 0.87, p > 0.05 *Sternum* r = 0.90, p < 0.05 *Knee* r = 0.83, p < 0.05 *Foot* r = 0.63, p < 0.001 On comparing correlation coefficient of forehead with that for sternum, knee and foot, p < 0.05 for comparison with knee and foot only Diagnostic accuracy of TcB (threshold value > 0.70 times the phototherapy limit) from forehead in detecting TSB > phototherapy limit **Group 1 (N = 504 observations):** Sensitivity: 108/109 (99.1%) Specificity: 177/395 (44.8%) PPV: 108/326 (33.1%) NPV: 177/178 (99.4%) **Group 2 (N = 317 observations):** Sensitivity: 3/3 (100%) Specificity: 254/314 (80.9%) PPV: 3/63 (4.8%) NPV: 254/254 (100%)	Data not given for the mean difference and SD from Bland Altman analysis for TSB - TcB

Samanta S; Year: 2004 Country: UK [46]	Study Type: Diagnostic study Evidence Level: II	All babies > 33 weeks in the postnatal ward of a regional teaching hospital who were due to have blood taken for TSB estimation N = 300 median BW 3295 grams – range 1972 to 4720 median GA 39 weeks – range 33 to 42 median postnatal age: 72 hours – range 24 to 264 Gender: Males = 50% Prevalence of TSB > 250 micromol/L = 55/300 (18.3%) Exclusion: babies who had previously received phototherapy	TcB using BiliChek (site not specified) – single measurement taken. Reference standard: Laboratory TSB levels taken concurrently with TcB measurement Diagnostic accuracy of TcB (various thresholds) estimated by plotting ROC curve.	Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient, N = 300) r = 0.77, p < 0.0001 Bland Altman analysis for difference between lab TSB and TcB MD = -10.6 micromol/L (95%CI -80.0 to +60.0) SD = Not reported Diagnostic accuracy of TcB (threshold value > 195 micromol/L) for detecting TSB > 250 micromol/L Sensitivity: 50/55 (90.9%) Specificity: 162/245 (66.1%) PPV: 50/133 (37.6%) NPV: 162/167 (97%)	Unselected population Test & Reference test described adequately Test and reference test carried out within one hour Blinding – not specified
Briscoe L; Year: 2002 Country: UK [47]	Study Type: Diagnostic study Evidence Level: II	Babies > 34 weeks who were having blood taken for any reason, mostly done for clinical jaundice. N = 303 median BW 3267 grams - range 1800-5008 median GA 39 weeks - range 34-42 median age at presentation: 3 – range 0 to 13 days Gender: Not reported Ethnicity White: 94.7% Prevalence of TSB > 300 micromol/L = 3.3% (10/303) Exclusion: babies who had previously received phototherapy	TcB reading using Minolta JM-102 at the forehead (mean of 3 readings used for analysis) Reference standard: Laboratory TSB levels measured concurrently For diagnostic accuracy: Area under ROC curve calculated for detecting TSB > 249 micromol/L	Correlation of JM-102 with lab TSB levels (Pearson correlation coefficient, N = 303) r = 0.76, p < 0.0001 Diagnostic accuracy of JM-102 for detecting TSB > 249 micromol/L (N = 303) Area under ROC = 0.89 *Predictive accuracy of JM-102 value 19.9 (highest accuracy from ROC curve)* Sensitivity: 86% (81-89%) Specificity: 78% (73-83%) PPV: Not reported NPV: Not reported	Unselected population Test & Reference test described in detail Test and reference test carried out within one hour Blinding – not specified Data not extractable for calculating values of TP, FP, TN & FN

Bhutani VK; Year: 2006 Country: USA [48]	Study Type: Observational study Evidence Level: III	All babies born from 01 January 1990 to 31 December 2000 who were discharged from the well-baby nursery of a tertiary hospital as term and near-term healthy babies. N = 31,059 mean BW: 3318 ± 457 grams mean GA: 38.7 ± 1.3 weeks Gender: Males = Not reported Ethnicity: White = 43.5% Black = 39.1% Asian = 6.9% Hispanic = 4.5% Exclusion: low BW preterm babies admitted to the well-baby nursery babies admitted to and treated in the intensive care nursery for any neonatal illness	Incremental hospital systems approach in the management of neonatal hyperbilirubinaemia studied with different clinical approaches at different phases: Phase 1: selective pre-discharge TSB measurements (1990-1992) Phase 2: universal TSB measurement at the time of metabolic screening with an authority given to nurses (after in-service workshops and training) to obtain bilirubin estimation at their own discretion (1993-95) Phase 3: universal TSB screening along with post-discharge follow-up based on the hour-specific nomogram (1996-98) Phase 4: organized institutional systems-based management of newborn jaundice (1999-2000) Phase 5: impact of the complete approach assessed in 2001-2003. Under the systems-based approach all babies had pre-discharge bilirubin estimation (TSB or TcB) and follow-up care for jaundice was given either at the hospital (more than 85% cases) or at home within 24-48 hours of discharge. Other components of the approach included lactation support services, counselling and information to parents on the clinical course and rare risk of neurotoxicity, and close follow-up of jaundiced babies based on their hour-specific bilirubin	Incidence of adverse outcomes for term and near-term infants in the well baby nursery *Hospital-based intensive phototherapy* Phase 1: 3.6% Phase 2: 4.5% Phase 3: 5.4% Phase 4: 2.5% Phase 5: 1.3% *Exchange transfusion (in risk)* Phase 1: 1:2137 Phase 2: 1:1322 Phase 3: 1:1637 Phase 4: 1:3198 Phase 5: 1:11995 *Number of readmissions* 14 per 1000 well baby infants discharged in 1994 to 5.5 per 1000 in 2001-2003. Results in babies (6 – 72 hours of age) with ABO incompatibility (N = 553) *High risk zone or TSB >95th centile (N = 55 or 9.9%)* Phototherapy: 54.5% Exchange Transfusion: 5.4% Length of stay: 3.3 days *Intermediate risk zone or TSB 40th-74th centile (N = 233 or 42.1%)* Phototherapy: 22.7%, Exchange Transfusion: 0% Length of stay 2.6 days *Low risk zone or TSB < 40th centile (N = 265 or 48.0%)* Phototherapy: 2.6%	Non-comparative observational study Time periods of different clinical approaches overlapping. Confounding variables not adjusted

			levels. A clinical evaluation for jaundice severity was mandatory for all babies at about the age of 4 days, along with subsequent follow-up of at-risk infants at age 7 days and 2 weeks.	Exchange Transfusion: 0% length of stay: 2.36 days	
Eggert LD; Year: 2006 Country: USA [49]	Study Type: Retrospective cohort study Evidence Level: II	Retrospective cohort study to determine the effectiveness of a pre-discharge bilirubin screening program instituted in December 2002. All babies delivered at = 35 weeks gestation within a private health care organization involving 18 hospitals during two time periods: **Group 1:** before the program started from 01 March 2001 to 31 December 2002, **Group 2:** after the program started from 01 January 2003 to 31 December 2004. Exclusion: Not defined	Pre-discharge bilirubin screening program started in December 2002 to measure bilirubin levels in every baby either at the recognition of jaundice or before discharge from hospital. Two hospitals used TcB (BiliChek) levels while others used TSB. Bilirubin levels plotted on the hour-specific nomogram and levels = 40th centile notified to the relevant health care provider and baby managed according to his/her discretion. After first 3 months percentile tracks of the nomogram modified since a large number of babies had bilirubin levels in the high or intermediate-high zones	<u>Incidence of severe hyperbilirubinaemia</u> *TSB levels <u>></u> 342 micromol/L* Group 1 - 1:77 Group 2 - 1:142 p<0.0001 *TSB levels <u>></u> 428 micromol/L* Group 1 - 1:1522 Group 2 - 1:4037 p<0.005 *TSB levels <u>></u> 513 micromol/L* Group 1 - 1:9742 Group 2 - 1:17494 p=0.24 <u>Incidence of hospital readmissions for hyperbilirubinaemia</u> Group 1 - 0.55% Group 2 - 0.43% p<0.005	Retrospective cohort study with exclusion criteria not defined Baseline characteristics of the two groups not compared Confounding variables not adjusted
Madan A Year: 2004 Country: USA [50]	Study type: Retrospective observational study Evidence level: III	All babies (N = 4,450) of which those born to blood type O or Rh negative mothers (N = 2,443) Mean GA: Not reported Mean BW: Not reported Gender: Not reported Ethnicity: Asian = 45.9% White = 36.8%	Test: Direct Antiglobulin Test (DAT) on cord blood. Reference standard: phototherapy / re-admission for phototherapy	<u>Prevalence of DAT positive</u> 7.9% (193/2,443) <u>Rate of phototherapy:</u> among DAT positive cases was 18.6% (36/193). <u>Rates for re-admission for phototherapy</u>: among tested babies: 1.1% (26/2,443) among untested babies : 0.9% (19/2,097)	Data not reliable: authors reported not determining the number of DAT negative who were treated for jaundice before readmission Sample: Selective Blinding: None

		Exclusion criteria: None		Odds Ratio (OR): 1.18 (95% CI 0.65 – 2.13)	
Leistikow EA Year: 1995 Country: USA [51]	Study type: Health economics study Evidence level: III	All patients in Neonatal Intensive Care Unit; babies with clinical jaundice; babies with Rh negative mothers and/or positive maternal antibody screenings; no available maternal blood Mean GA: Not reported Mean BW: Not reported Gender: Not reported Ethnicity: Not reported Exclusion: Not reported	Test: Direct Antiglobulin Test (DAT) on cord blood. Reference standard: Readmission for jaundice	Prevalence of DAT positive: Not reported Percentage of babies tested Among universal testing (2,253/4,003) 56.3% among selective testing (1,048/4,498) 23.3% Rate of readmission for hyperbilirubinaemia among universally tested babies 0.4 (15/4,003) among selectively tested babies 0.3 (15/4,498) Odds Ratio (OR) 1.12 (95% CI 0.56 – 2.30)	Small study No definition on readmission for hyperbilirubinaemia given Sample: Non-selective Blinding: None
Madlon-Kay DJ Year: 1992 Country: USA [52]	Study type Retrospective cohort study: Evidence Level: III	All babies in normal nursery cared for by family practice service were included (N = 301) Sample was split between those tested automatically (N = 113) and those tested selectively (N = 188) Mean GA: 39.4 weeks Mean BW: 3344 grams Gender: Males = 50.5% Ethnicity: White = 44.5% Black = 16.3% Asian = 17.9% Other = 21.3% Exclusion criteria: babies in intensive care	Test: Direct Antiglobulin Test (DAT) on cord blood. Reference standard: Need for phototherapy (no clear definition)	<u>Overall Prevalence of DAT positive</u> 9.0% (27/301) Overall rate of phototherapy 12/301 (3.9%) Rates of phototherapy among universally tested babies 4/113 (3.5%) among selectively tested babies 8/188 (4.3%) Odds Ratio (OR) 0.83 (95%CI: 0.24 – 2.81) Rates of readmission for phototherapy among universally tested babies 2/113 (1.8%) among selectively tested babies 1/188 (0.5%)	Small sample Test and reference standard not described in details Blinding: None

				Odds Ratio (OR) 3.36 (0.32 – 37.58)	

Q2. What is the best method of recognizing hyperbilirubinaemia?

Evidence table – Recognition

Bibliographic details	Study type & Evidence level	Patient characteristics	Test, Reference Standard, Threshold for a positive test	Results	Reviewers Comments
Riskin A; Year: 2008 Country: Israel [53]	Study Type: Diagnostic study Evidence Level: Ib	Healthy full term and late pre-term babies (≥ 35 weeks) examined for clinical jaundice before discharge (days 2 to 5 of life) in a hospital N = 1,129, total observations = 3,532, mean BW 3298 ± 462 grams, mean GA 39.5 ± 1.4 weeks, mean time of assessment 62 ± 24 hours (median 55 hours; range 9 to 252 hours) Gender: Males = 52.3% Ethnicity Majority reported as Ashkenazi or Sephardic Jews (73%) or Arabs (26%) Exclusion: babies with < 50 observations, visual assessment done after starting phototherapy	Test: Visual assessment of jaundice (BiliEye) by experienced observers (total 23 observers – 5 neonatologists and 17 nurses, mean experience 11.4 ± 10.2 yrs). No. of observations per observer were record in 1,195 encounters with a mean of 3.0 ± 1.8 observers. The observers were identified by code numbers and unaware of laboratory TSB values and BiliEye values made by other observers. Reference standard: Laboratory TSB levels within 1 hr Analysis: After determining correlation between BiliEye and lab TSB, the values were grouped into risk zones according to Bhutani nomogram. Accuracy of BiliEye in determining TSB levels (or degree of hyperbilirubinaemia) evaluated. Ability of BiliEye to detect significant hyperbilirubinaemia	Correlation of visual assessment of TSB levels with lab TSB (Pearson correlation coefficient, N = 3532 observations) *All observers* Weighted r = 0.75, p<0.001 kappa (weighted) = 0.363 *Each observer separately (range)* r = 0.51 to 0.88 kappa = 0.11 to 0.52 Accuracy of BiliEye for determining TSB values (after grouping Zones B, C & D together versus Zone A) Sensitivity: 337/567 (59.4%) Specificity: 2627/2965 (88.6%) PPV: 337/675 (49.9%) NPV: 2627/2857 (91.9%) *False negative rate of BiliEye* Zone A: 230/2857 (8.1%) Zone C + D: 67/109 (61.5%) Zone D only: 13/15 (86.7%) Difference between BiliEye and laboratory TSB values *All observers*	Unselected population with defined exclusion criterion Test & Reference test described in detail Test and reference test carried out within one hour Blinding – yes Funding: None specified

			(defined as zones C+D on nomogram) analyzed by ROC curve – after correcting for postpartum age and GA	MD = 0.11 ± 2.17 *Each observer separately* P < 0.001 for both the mean values and absolute values Diagnostic accuracy of BiliEye in detecting hyperbilirubinaemia Area ROC = 0.82 *Best AROC* 0.93 for observations at > 60 hours in babies ≥ 37 weeks GA *Worst AROC* 0.64 for observations at < 36 hours 0.61 for babies < 37 weeks	
Moyer VA; Year: 2000 Country: USA [54]	Study Type: Diagnostic study Evidence Level: II	Full-term healthy babies (BW > 2000 grams and GA> 36 weeks) in well-newborn nursery of an urban public hospital, in whom TSB was measured because of clinical jaundice, Rh-negative mother or positive maternal Coomb's test. N = 122, GA: > 36 weeks BW > 2,000 grams mean age = 2 days (range 8 to 168 hours) Gender: Males = 54.1% Ethnicity Not reported Exclusion: babies having previous TSB determination and under phototherapy	Visual observation by two experienced staff (paediatric residents, paediatric nurse practitioners, paediatric physicians) regarding a) Subjective assessment of presence/absence of icterus at different sites b) Estimated TSB levels Reference standard: Laboratory TSB levels within 1 hr	Agreement between observers on presence/absence of icterus at different sites (Weighted Kappa with 95%CI) Face & neck: 0.16 (-0.02 to 0.34) Neck to nipple line: 0.15 (0.01 to 0.29) Nipple line to umbilicus: 0.23 (0.09 to 0.38) Umbilicus to groin: 0.19 (0.05 to 0.34) Upper legs: 0.20 (0.06 to 0.35) Weighted K not statistically significant for other sites – Lower legs, Soles, Arms, Palms, Tip of nose and palate Correlation of estimated TSB levels with lab TSB (Pearson correlation coefficient) Observer 1: r = 0.43 Observer 2: r = 0.54	Unselected population Reference test not described adequately Test and reference test carried out within one hour Blinding – yes Funding: Not reported

				Accuracy of clinical icterus in lower chest (nipple line to umbilicus) in detecting TSB > 205 micromol/L (N = 243 observations) Sensitivity: 97.1% (67/69) Specificity: 19.0% (33/174) PPV: 32.2% (67/208) NPV: 94.3% (33/35)	
Madlon-Kay DJ; Year: 2001 Country: USA [55]	Study Type: Diagnostic study Evidence Level: II	Newborn babies delivered in a hospital with follow-up visit at home by Home Health Nurses. (N = 164, mean GA: Not reported mean BW: Not reported mean age at assessment 6.4 ± 2.5 days) Gender: Not reported Ethnicity (nurse determination) white = 60% black = 18% Asian = 6% Hispanic = 7% Other = 9% Exclusion: babies who were in intensive care nursery or received phototherapy, Also babies whose mothers lived more than 10 miles from hospital or were not proficient in English Babies examined by 12 home health nurses.	1) Clinical assessment by nurses with their usual method (e.g blanching skin, judging degree of yellowness with caudal progression, looking for jaundice at sclera, gums, nose) 2) Caudal progression of jaundice alone as assessed by nurses 3) Ingram Icterometer reading from nose Threshold for diagnostic accuracy – reading ≥ 2.5 Reference standard: Laboratory TSB levels within 1 hr	TSB levels (micromol/L) *All babies (N = 164)* Mean (sd) 125 (80) Range: 12 to 345 *Babies assessed to be jaundiced by nurses (N = 82)* Mean (sd): 180 (68.4) *Babies assessed not to be jaundiced by nurses (N = 82)* Mean (sd): 72 (46) Comparison 1: *Correlation of estimated TSB levels with lab TSB (Pearson correlation coefficient, N = 82 where sampling done)* r = 0.61, p < 0.01 Comparison 2: *Correlation of estimated TSB levels with lab TSB (Pearson correlation coefficient, N = 82 where sampling done)* r = 0.47, p < 0.01 *Accuracy of test (caudal progression to nipple line) in detecting TSB > 205 micromol/L (N = Not reported)* Sensitivity: 76%	Unselected population Test & Reference test described in detail Test and reference test carried out within one hour Blinding – not specified Data not extractable for calculating exact values of TP, FP, TN & FN Funding: Ramsey Foundation

				Specificity: 60% <u>Comparison 3:</u> *Correlation of estimated TSB levels with lab TSB (Pearson correlation coefficient, N = 82 where sampling done)* r = 0.48, p < 0.01 *Accuracy of test in detecting TSB > 205 micromol/L (N = Not reported)* Sensitivity: 75% Specificity: 72%	
Riskin A; Year: 2003 Country: Israel [56]	Study Type: Diagnostic study Evidence Level: II	Full term babies (37-42 weeks) with clinical jaundice in the nursery of a tertiary care hospital. Includes babies with ABO incompatibility and G-6PD deficiency. N = 283 mean age at assessment 63.8 $\pm$ 21.6 hours mean GA: 39.5 $\pm$ 1.5 weeks mean BW: 3223 $\pm$ 484 grams Gender: Males = 51.2% Ethnicity Majority reported as Jews (76%) or Arabs (24%) Exclusion: not defined	Visual observation by one of four attending neonatologists before discharge of baby from the nursery regarding a) Assessment of clinical jaundice severe enough to draw blood sample b) Estimated TSB levels <u>Reference standard:</u> Laboratory TSB levels within 30 mins	<u>Correlation of estimated TSB levels with lab TSB (Pearson correlation coefficient)</u> All physicians (N = 283): r = 0.68, p<0.001 Physician 1 (N = 74) r = 0.79, p < 0.001 Physician 2 (N = 62) r = 0.64, p < 0.001 Physician 3 (N = 69) r = 0.70, p < 0.001 Physician 4 (N = 78) r = 0.62, p < 0.001	Selected population with no exclusion criterion Test & Reference test described in detail Test and reference test carried out within one hour Blinding – yes Data not extractable for calculating TP, FP, TN & FN values

Madlon-Kay DJ; Year: 1997 Country: USA [57]	Study Type: Diagnostic study Evidence Level: II	Babies with age >2 days in a normal newborn nursery.in a teaching hospital (N = 171 mean GA 39 weeks) mean BW: Not reported Gender: Not reported Maternal ethnicity white = 50% black = 24% Asian = 13% Hispanic = 9% Other = 4% Exclusion: babies who received phototherapy, and whose parents were unable to read and understand the instruction form	1) Clinical estimation of degree of jaundice and cephalo-caudal progression by nurses and physicians by blanching the skin. (36 nurses, 20 family physicians and 4 paediatricians) 2) Clinical assessment of jaundice by the parents after receiving written and verbal instructions about the process (147 parents with 81% having English as the primary language and 46% having completed high school) 3) Ingram Icterometer readings from nose (N = 132 readings) <u>Reference standard:</u> Laboratory TSB levels within 1 hr Correlation between the estimated and the observed TSB values determined before and after adjusting for various factors	<u>Prevalence of hyperbilirubinaemia (TSB = 205</u> micromol/L 11/89 (12.3%) <u>Correlation of estimated TSB levels with lab TSB values after adjusting for various confounding factors like level of training, race, etc (Pearson correlation coefficient)</u> *Nurse estimate of TSB* r = 0.52, p < 0.001 *Nurse assessment of cephalo-caudal progress* r = 0.48. p < 0.05 *Physician estimate of TSB* r = 0.55, p < 0.05 *Physician assessment of cephalo-caudal progress* r = 0.35. p > 0.05 *Parent assessment of cephalo-caudal progress* r = 0.71, p < 0.01 *Icterometer* r = 0.57, p = 0.002	Study population selected by convenience sampling Test & Reference test described in detail Test and reference test carried out within one hour, but reference test (laboratory TSB) not conducted in all babies (89/171) Blinding – yes Data not extractable for calculating exact values of TP, FP, TN & FN
Szabo P; Year: 2004 Country: Switzerland [59]	Study Type: Diagnostic study Evidence Level: II	Healthy preterm babies 34-37 weeks with BW > 2000 grams and no older than 6 days in maternity ward and intermediate care neonatal unit. N = 69, median GA: 35.7 weeks – range 34 to 36.9 weeks median BW 2530 grams – range 2050 to 3630 grams	1) Clinical assessment by nurses and primary investigator using Kramer criterion 2) TcB using Minolta JM-102 at the sternum (mean of two readings used for analysis) 3) TcB using BiliChek at the	<u>Comparison 1:</u> *Correlation of estimated TSB levels with lab TSB (Pearson correlation coefficient, N = 107 observations)* By nurses $R^2 = 0.22$, p < 0.01 By primary investigator $R^2 = 0.20$, p < 0.01	Unselected population Test & Reference test described in detail Test and reference test carried out within one hour Blinding – not specified Data not extractable for calculating values for TP, FP, TN & FN

		Gender: Not reported Ethnicity white = 87% black = 4% Asian = 7% Other = 2% Exclusion: jaundice above zone 3 of Kramer scale within 48 hours, positive DCT, BW < 10th centile for GA, any sign or symptom of illness, phototherapy already started	forehead and sternum (mean of 5 readings used for analysis) <u>Reference standard:</u> Laboratory TSB levels within 30 min. Mean of two samples used for analysis. For diagnostic accuracy: Area under ROC curve calculated for detecting TSB > 190	*Diagnostic accuracy for detecting TSB > 190 micromol/L (Area under ROC curve, N = Not reported)* By nurses Area = 0.73 By primary investigator Area = 0.70 Kappa = 0.48 <u>Comparison 2:</u> *Correlation of JM-102 with lab TSB levels (Pearson correlation coefficient, N = 107 observations)* R^2 = 0.76, p < 0.01 Difference to TSB: 56 ± 28 micromol/L *Diagnostic accuracy for detecting TSB > 190 micromol/L (Area underROC curve, N = Not reported)* Area = 0.96 <u>Comparison 3:</u> **At forehead** *Correlation of BiliChek with lab TSB levels (Pearson correlation coefficient, N = 107 observations)* R^2 = 0.45, p < 0.01 Difference to TSB: -8 ± 33 micromol/L *Diagnostic accuracy for detecting TSB > 190 micromol/L (Area underROC curve, N = Not reported)* Area = 0.88 **At sternum** *Correlation of BiliChek with lab TSB levels (Pearson correlation coefficient, N = 107 observations)*	

				R^2 = 0.59, p < 0.01 Difference to TSB: 10 ± 31 micromol/L *Diagnostic accuracy for detecting TSB > 190 micromol/L (Area underROC curve, N = Not reported)* Area = 0.89	
Szabo P; Year: 2004 Country: Switzerland [58]	Study Type: Diagnostic study Evidence Level: II	Healthy full-term babies (37-41 weeks) with BW > 2000 grams and no older than 6 days. (N = 140, 92 white and 48 non-white babies, median BW 3320 grams) range 2050 to 4400 grams median GA: 39 weeks – range 37 to 41.9 weeks Gender: Not reported Ethnicity white = 66% Asian = 13% Other = 21% Exclusion: Haemolysis jaundice within first 36 hours phototherapy	1) Clinical assessment by nurses and primary investigator using Kramer criterion 2) TcB using Minolta JM-102 at the sternum (higher of two readings used for analysis) 3) TcB using BiliChek at the forehead and sternum (mean of 5 readings used for analysis) Reference standard: Laboratory TSB levels within 30 min For diagnostic accuracy: Area under ROC curve calculated for detecting TSB > 250 micromol/L	Comparison 1: *Correlation of estimated TSB levels with lab TSB (Pearson correlation coefficient, N = not reported)* For white babies R^2 = 0.74 (by nurse) R^2 = 0.70 (by investigator) For non-white babies R^2 = 0.71 (by nurse) R^2 = 0.65 (by investigator) *Diagnostic accuracy for detecting TSB > 250 micromol/L (Area underROC curve, N = Not reported)* Area = 0.84 Comparison 2: *Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient, N = Not reported)* R^2 = 0.82, p < 0.01 *Diagnostic accuracy for detecting TSB > 250 micromol/L (Area under ROC curve, N = Not reported)* Area = 0.98 Comparison 3 (at forehead):	Unselected population Test & Reference test described in detail Test and reference test carried out within one hour Blinding – not specified Data not extractable for calculating values of TP, FP, TN & FN

				Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient, N = Not reported) $R^2 = 0.79$, $p < 0.01$ *Diagnostic accuracy for detecting TSB > 250 micromol/L (Area under ROC curve, N = Not reported)* Area = 0.92	
Crofts DJ; Year: 1999 Country: UK [60]	Study Type: Non-diagnostic study (Project report) Evidence Level: III	Mothers and their newborn babies born and resident of Sheffield and who were routinely visited by the health visitor at 28 days of age. Phase 1: (N = 109 parent-baby pairs, total stool observations = 5053) Mean BW: Not reported Mean GA: Not reported Gender: Males = 56.9% Ethnicity: Not reported Phase 3: (N = 3629 mother-baby pairs)	Phase 1: Inspection of stools, by parents, from healthy babies and babies with cholestatic liver disease during the first 28 days of age to devise a stool colour chart using 20 colours Phase 2: development of stool chart – six most commonly selected stool colours from each of main colour groups together with three pale colours used to develop a stool chart. Phase 3: Assess specificity of colour chart – charts given to all mothers at first health visitor visit (at 10-14 days), and information collected at second visit of health visitor (at 28 days). Babies with suspicion of jaundice or history of passing pale stools referred for further investigation	Incidence of jaundice *Related to breastfeeding* 3.4% (95%CI 2.9%, 4.1%) *At 28 days in breast-fed babies* 9.2% (95%CI 7.8%, 11.0%) % with abnormal LFT (N = 60) *Abnormal GGT and ALT* 38.3% (23/60) *Abnormal Alk. phosphate* 70% (42/60) Reasons for non-referral of babies with prolonged jaundice (N = 14) 9 = babies well and thriving 2 = confusion between midwife and health visitor 2 = family moving out 1 = refusal	Report of a community programme (non-diagnostic study) Unselected population No demographic details reported
Bilgen H; Year: 1998 Country: Turkey	Study Type: Diagnostic study Evidence Level: II	Healthy term babies with jaundice aged more than 1 day but less than 5 days in a hospital. N = 96 mean BW 3380 ± 419 grams	1) Ingram Icterometer on the nose Threshold: reading ≥ 33 for best accuracy results	Prevalence of TSB > 220 micromol/L = 18% (17/96) Comparison 1: *Correlation of JM-102 with lab TSB*	Selected population Test & Reference test not described in detail Test and reference test carried out within one hour Blinding – yes

[61]		mean GA: 39.6 ± 1.4 weeks age at presentation: range 1 to 5 days Gender: Males = 58% Ethnicity: Not reported Exclusion: not received phototherapy	2) TcB using Minolta JM-102 on the forehead Threshold: reading > 13 for best accuracy results Reference standard: Laboratory TSB levels within 30 min	*levels (Pearson correlation coefficient, N = 96)* r = 0.83, p < 0.01 *Diagnostic accuracy for detecting TSB > 220 micromol/L* Sensitivity: 100% (17/17) Specificity: 55.7% (35/79) PPV: 32.7% (17/52) NPV: 100% (44/44) Comparison 2: *Correlation of Icterometer with lab TSB levels (Pearson correlation coefficient, N = 96)* r = 0.78, p < 0.01 *Diagnostic accuracy for detecting TSB > 220 micromol/L* Sensitivity: 100% (17/17) Specificity: 48.1% (38/79) PPV: 29.3% (17/58) NPV: 100% (38/38)	
Merritt KA; Year: 1994 Country: USA [62]	Study Type: Diagnostic study Evidence Level: II	Preterm babies with jaundice in a hospital. N = 90 mean BW 1676 grams, mean GA 31.7 weeks age at presentation: Not reported Gender: Not reported Ethnicity White = 95% Other = 5% Exclusion: not defined	1) Gosset Icterometer on the nose by two experienced and one inexperienced observer Reference standard: Laboratory TSB levels within 30 min	Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient, N = number of observations) All infants (N = 296) r = 0.72, p < 0.01 Experienced observer 1 (N = 239) r = 0.71, p < 0.01 Experienced observer 2 (N = 166) r = 0.75, p < 0.01 Inexperienced observer r = 0.63, p < 0.01	Selected population Test & Reference test described in detail Test and reference test carried out within one hour Blinding – yes Data not extractable for calculating values of TP, FP, TN & FN
Hamel BCJ;	Study Type:	Newborn babies with clinical jaundice	Gosset Icterometer reading by	Correlation of Icterometer readings with	Unselected population

Year: 1982 Country: Tanzania 63	Diagnostic study Evidence Level: III	admitted for various reasons to neonatal unit of a medical centre N = 70 Mean BW: Not reported GA: Range 30 to 42 weeks Postnatal age: Range 2 to 14 days Gender: Not reported Ethnicity: Black = 100% Exclusion: not defined	blanching the gum Reference standard: Blood drawn for laboratory TSB levels at the same time	lab TSB levels (Pearson correlation coefficient) r = 0.91, p < 0.01	Test & Reference test not described in detail Test and reference test carried out simultaneously (exact timing not specified) Blinding – not specified Data not extractable for calculating values of TP, FP, TN & FN
Chaibva NTRM; Year: 1974 Country: Rhodesia 64	Study Type: Diagnostic study Evidence Level: III	Newborn babies with clinical jaundice N = 55 infants and 125 readings BW: Range 1050 to 3925 grams GA: Not reported Postnatal age: Range 2 to 24 days Gender: Not reported Ethnicity: Black = 100% Exclusion: not defined	Gosset Icterometer reading (site not specified) Reference standard: Laboratory TSB levels (timing not specified)	Correlation of Icterometer readings with lab TSB levels (Pearson correlation coefficient) r = 0.96, p < 0.001	Unselected population Test & Reference test not described in detail Test and reference test carried out at same time (exact timing not specified) Blinding – yes Data not extractable for calculating values of TP, FP, TN & FN
Briscoe L; Year: 2002 Country: UK 47	Study Type: Diagnostic study Evidence Level: II	Babies > 34 weeks who were having blood taken for any reason, mostly done for clinical jaundice. N = 303 median BW 3267 grams - range 1800-5008 median GA 39 weeks - range 34-42 median age at presentation: 3 – range 0 to 13 days Gender: Not reported Ethnicity White: 94.7% Prevalence of TSB > 300 micromol/L	TcB reading using Minolta JM-102 at the forehead (mean of 3 readings used for analysis) Reference standard: Laboratory TSB levels measured concurrently For diagnostic accuracy: Area under ROC curve calculated for detecting TSB > 249 micromol/L	Correlation of JM-102 with lab TSB levels (Pearson correlation coefficient, N = 303) r = 0.76, p < 0.0001 Diagnostic accuracy of JM-102 for detecting TSB > 249 micromol/L (N = 303) Area under ROC = 0.89 *Predictive accuracy of JM-102 value 19.9 (highest accuracy from ROC curve)* Sensitivity: 86% (81-89%) Specificity: 78% (73-83%)	Unselected population Test & Reference test described in detail Test and reference test carried out within one hour Blinding – not specified Data not extractable for calculating values of TP, FP, TN & FN

		= 3.3% (10/303) Exclusion: babies who had previously received phototherapy		PPV: Not reported NPV: Not reported	
Carbonell X; Year: 2001 Country: Spain [29]	Study Type: Diagnostic study Evidence Level: II	Healthy term babies N = 2004 – 610 in phase one + 1394 in phase 2 mean BW 3230 ± 491 grams mean GA 39 weeks Gender: Males = 50.7% Ethnicity Not reported In first phase (N = 610), cord bilirubin (UCB) at birth and TcB with Minolta JM-102 measured at 24 hours, 48 hours & 60-96 hours of life. Additionally TSB was done for all at 60-96 hours. On 169 babies TSB also measured at 24 & 48hours In second phase (N = 1,394), TcB and lab TSB values obtained to find accuracy of TSB and TcB at 24hours and 48 hours to predict hyperbilirubinaemia. Prevalence of TSB > 290 micromol/L = 2.9% in phase 1 (18/610) and 3.25% in phase 2 (46/1324) Exclusion: not defined	Test: 1. Umbilical cord bilirubin (UCB) measured at birth (threshold value: ≥ 37 micromol/L) ROC curve used to find the best cut-off value of UCB. 2. TSB (in phase 1 & 2) and TcB (phase 1 only) measured at 24 hours (threshold value for TSB = 102 micromol/L and for TcB > 11) 3. TSB and TcB (in phase 1 & 2) measured at 48 hours (threshold value for TSB = 154 micromol/L and for TcB > 13) TcB reading using Minolta JM-102 at the forehead and the sternum (mean of 3 measurements recorded at each site used for analysis) Reference standard: Laboratory TSB measured on Day 3 - 4 TSB = 290 micromol/L taken as indicative of hyperbilirubinaemia	Correlation of TcB levels with lab TSB levels for Sternal vs. Forehead site (Pearson correlation coefficient) At < 24 hours (N = 120) *Sternum Forehead* 0.81 0.77 At 24-48 hours (N = 126) *Sternum Forehead* 0.89 0.83 At > 48 hours (N = 412) *Sternum Forehead* 0.94 0.83 Diagnostic accuracy of TcB for detecting TSB > 222 micromol/L Sensitivity: 98% Specificity: 72% Diagnostic accuracy for predicting TSB = 290 micromol/L *Prevalence of TSB = 290 micromol/L* 2.9% in phase 1 (18/610) and 3.25% in phase 2 (46/1324) **1. For UCB (threshold = 37 micromol/L)** Sensitivity: 4/18 (22.2%) Specificity: 537/567 (94.7%) PPV: 4/34 (11.7%) NPV: 537/551 (97.4%) **2. At 24 hours** *For TcB in phase 1 (threshold > 11 Reflectance Units)*	Unselected population but no exclusion criterion Test & Reference test described in detail Reference test a standard one Test and reference test carried out within one hour Blinding – not specified

				Sensitivity: 15/18 (83.3%) Specificity: 368/556 (66.2%) PPV: 15/203 (7.4%) NPV: 368/371 (99.2%) *For TSB in phase 1 (threshold = 102 micromol/L)* Sensitivity: 7/7 (100%) Specificity: 74/162 (45.7%) PPV: 7/95 (7.4%) NPV:74/74 (100%) *For TSB in phase 2 (threshold = 102 micromol/L)* Sensitivity: 25/25 (100%) Specificity: 239/398 (60%) PPV: 25/95 (26.3%) NPV: 239/239 (100%) **2. At 48 hours** *For TcB in phase 1 (threshold > 13 reflectance units)* Sensitivity: 17/18 (94.4%) Specificity: 288/556 (51.7%) PPV: NPV: *For TcB in phase 2 (threshold > 13 reflectance units)* Sensitivity: 45/46 (97.8%) Specificity: 262/819 (32.0%) PPV: 45/602 (7.5%) NPV: 262/263 (99.6%) *For TSB in phase 1 (threshold = 154 micromol/L)* Sensitivity: 11/11 (100%) Specificity: 102/158 (64.6%) PPV: 11/67 (16.4%) NPV: 101/102 (100%) *For TSB in phase 2 (threshold = 154 micromol/L)* Sensitivity: 45/46 (97.8%) Specificity: 348/774 (45%)	

				PPV: 45/471 (9.5%) NPV: 348/349 (99.7%)	
Knudsen A; Year: 1989 Country: Denmark 65	Study Type: Diagnostic study Evidence Level:III	Babies in a newborn nursery were eligible if a visible jaundice was noted in first 5 days of life N = 76, Mean BW: Not reported Median GA: Not reported Gender: Not reported Ethnicity: Not reported Exclusion: None	Test: TcB reading from the forehead using JM-102 Reference standard: Laboratory TSB method measured on blood collected at the same time as TcB.	Correlation of TcB levels with TSB levels (Pearson correlation coefficient, N = 76) *Forehead* r = 0.83; p < 0.0001	Unselected population Test & Reference test not described in detail Test and reference test carried out within one hour Blinding – not specified No demographic details reported
Karrar Z; Year: 1989 Country: Saudi Arabia 66	Study Type: Diagnostic study Evidence Level: III	Healthy term babies with visible jaundice aged between 4 and 10 days. N = 155 Mean BW: Not reported Mean GA: Not reported Gender: Not reported Ethnicity Saudi 100% Prevalence of TSB > 214 micromol/L = 31.6% (49/155) Exclusion: preterm infants, ill newborns, those requiring phototherapy or exchange transfusion	TcB using Minolta JM-101 on the forehead – single measurement made Reference standard: Laboratory TSB levels at the same time as TcB measured	Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient, N = 155) r = 0.82, p < 0.01 Diagnostic accuracy of TcB (threshold value > 21 reflectance units) for detecting TSB > 214 micromol/L Sensitivity: 36/49 (73.5%) Specificity: 95/106 (89.6%) PPV: 36/47 (76.6%) NPV: 95/108 (88.0%)	Unselected population Test & Reference test not described in detail Test and reference test carried out within one hour Blinding – not specified
Maisels MJ; Year: 1982	Study Type: Diagnostic study	Randomly selected full term White babies in a well baby nursery N = 157	TcB using Minolta JM-102 from the forehead and the sternum Measurements routinely made on	Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient) *At forehead (157 observations)*	No exclusion criterion Test & Reference test described adequately Test and reference test carried

Country: USA 67	Evidence Level: II	Mean BW: Not reported Mean GA: Not reported Gender: Not reported Ethnicity Not reported Exclusion: not defined <u>Prevalence of TSB > 221 micromol/L</u> = 7/157 (4.5%)	the 3rd day except in 11 infants where earlier sampling done <u>Reference standard:</u> Laboratory TSB levels at the same time as TcB measured	r = 0.93, p < 0.0001 *At mid-sternum (135 observations)* r = 0.93, p < 0.0001 <u>Diagnostic accuracy of TcB (Sternum threshold value > 23 reflectance units) for detecting TSB > 221 micromol/L</u> Sensitivity: 4/4 (100%) Specificity: 126/131 (96.2%) PPV: 4/9 (44.4%) NPV: 126/126 (100%) <u>Diagnostic accuracy of TcB (Forehead threshold value > 24 reflectance units) for detecting TSB > 221 micromol/L</u> Sensitivity: 7/7 (100%) Specificity: 145/150 (96.7%) PPV: 7/12 (58.3%) NPV: 145/145 (100%)	out within one hour Blinding – not specified
Tsai LT; Year: 1988 Country: China 68	Study Type: Diagnostic study Evidence Level: III	Term healthy babies > 37 weeks and less than 7 days old who had jaundice or TSB measurement N = 98 paired observations from each of the 8 sites = 178 mean BW: Not reported mean GA: Not reported Gender: Not reported Ethnicity Chinese (100%) Exclusion: not defined <u>Prevalence of TSB > 222 micromol/L</u> = 19.6% (35/178 – site forehead)	TcB using Minolta JM-102 Measurements made at the time of sampling from 8 sites – forehead, cheek, sternum, abdomen, upper back, lower back, palm and sole. <u>Reference standard:</u> Laboratory TSB levels at the same time as TcB measured	<u>Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient, N = 178)</u> *Forehead* r = 0.87, p < 0.001 *Cheek* r = 0.76, p < 0.001 *Sternum* r = 0.78, p < 0.001 *For all other sites* r from 0.47 to 0.76 <u>Diagnostic accuracy of TcB (threshold value > 16 relectance units) for detecting TSB > 222 micromol/L</u>	No exclusion criterion Test & Reference test described adequately Test and reference test carried out within one hour Blinding – not specified

				Sensitivity: 19/21 (90.5%) Specificity: 141/157 (89.8%) PPV: 19/35 (54.3%) NPV: 141/143 (98.6%)	
Maisels MJ; Year: 2004 Country: USA [69]	Study Type: Diagnostic study Evidence Level: II	Convenience sample of newborn babies ≥ 35 weeks in the well-baby nursery of 3 hospitals. N = 849 Mean BW: Not reported Mean GA: Not reported Gender: Not reported Ethnicity white = 59.2% black = 29.8% other = 10.9% Prevalence of TSB > 257 micromol/L = 3.3% (28/849) Exclusion: babies who had received phototherapy	TcB using Minolta JM-103 from the mid-sternum Triplicate measurements made in two hospitals while only single made in the third, but single TcB measurement taken for each baby for data analysis. Reference standard: Laboratory TSB levels within 1 hour of TcB measurement Area under ROC curve (AROC) calculated for detecting TSB > 170, 222 and 255 micromol/L	Correlation of TcB levels with lab TSB levels and area under ROC curve (Pearson correlation coefficient, AROC for TSB > 222 micromol/L) *All infants (N = 849)* r = 0.91, p < 0.001 AROC = 0.96 *White infants (N = 503)* r = 0.95, p < 0.001 AROC = 0.96 *Black infants (N = 253)* r = 0.82, p < 0.001 AROC = 0.97 *Other infants (N = 93)* r = 0.92, p < 0.001 AROC = 0.96 % of infants with difference between TSB & TcB levels of > 34 micromol/L (overestimation by TcB) *Difference 34 to 50 micromol/L* White – 4.0% Black – 24.1% Others – 5.4% *Difference 51 to 67 micromol/L* White – 2.0% Black – 10.7% Others – 2.2% *Difference > 68 micromol/L* White – 0% Black – 6.7% Others – 1.1%	No exclusion criterion Test & Reference test described adequately Test and reference test carried out within one hour Blinding – not specified Data not extractable for calculating values of TP, FP, TN & FN for different thresholds

Engle WD; Year: 2005 Country: USA [70]	Study Type: Diagnostic study Evidence Level: II	Term and near term neonates who had been discharged from the hospital and evaluated during first week postnatally in a follow-up centre. N = 121 median BW: 3280 grams – range 2265 to 4590 median GA: 40 weeks – range 35 to 41 median age at TSB: 91 hours – range 51 to 166 Gender: Males = 56.2%) Ethnicity Hispanic = 92% Black = 3% Asian = 3% White = 2% Prevalence of TSB > 255 micromol/L = 47% (57/121) Exclusion: not defined	TcB using Minolta JM-103 from the sternum – single measurements taken. Reference standard: Laboratory TSB levels within 30 minutes of TcB measurement Diagnostic accuracy of TcB (various thresholds) calculated for detecting TSB > 255, > 272, > 290 and > 306 micromol/L	Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient, N = 121) r = 0.77, p < 0.001 Bland Altman analysis for difference between TSB and TcB MD = 27 micromol/L Diagnostic accuracy of TcB (threshold value > 205 micromol/L for detecting TSB > 255 micromol/L Sensitivity: 52/57 (91.2%) Specificity: 34/64 (53.1%) PPV: 52/82 (63.4%) NPV: 34/39 (87.2%)	Exclusion criterion not defined Test & Reference test described adequately Test and reference test carried out within one hour Blinding – not specified
Sanpavat S; Year: 2004 Country: Thailand [71]	Study Type: Diagnostic study Evidence Level: II	Term and near term clinically healthy neonates ≥ 36 weeks with visible jaundice which necessitated TSB determination. N = 388 mean BW 3117 ± 425 grams mean GA: Not reported Postnatal age: range 11 to 216 hours Gender: Males = 57.5% Ethnicity Not reported Prevalence of TSB > 255 micromol/L = 2.8% (13/460) Exclusion: babies receiving	TcB using Minolta JM-103 from the forehead Mean of three measurements taken for data analysis. Reference standard: Laboratory TSB levels within 10-15 minutes of TcB measurement Diagnostic accuracy of TcB (various thresholds) calculated for detecting TSB > 170, > 204, > 222 and > 255 micromol/L	Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient, N = 460 observations) r = 0.80, p < 0.001 Bland Altman analysis for difference between TSB and TcB MD = 12 micromol/L (95%CI 9.4 to 14.5) SD = 27.4micromol/L Diagnostic accuracy of TcB (threshold value > 205 micromol/L) for detecting TSB > 255 micromol/L Sensitivity: 13/14 (92.9%)	Unselected population Test & Reference test described adequately Test and reference test carried out within one hour Blinding – not specified

		phototherapy or already received exchange transfusion		Specificity: 373/446 (83.6$) PPV: 13/86 (15.1%) NPV: 373/374 (99.7%)	
Sanpavat S; Year: 2007 Country: Thailand [72]	Study Type: Diagnostic study Evidence Level: II	Clinically healthy preterm babies with BW > 1000 grams and GA < 36 weeks with visible jaundice which necessitated TSB determination. N = 196 mean BW 1887 ± 344.4 grams mean GA 33.2 ± 1.7 weeks, postnatal age: 108 ± 77 hours Gender: Males = 55% Ethnicity Not reported Total paired (TcB-TSB) observations = 249 Exclusion: babies receiving phototherapy or already received exchange transfusion	TcB using Minolta JM-103 from the forehead Mean of three measurements taken for data analysis. Reference standard: Laboratory TSB levels within 1 hour of TcB measurement Percentage of TcB readings which overestimated (TcB > 10% of TSB) or underestimated (TcB < 10% of TSB)	Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient, N = 249 observations) r = 0.79, p < 0.0001 Bland Altman analysis for difference between TSB and TcB MD = -5.0 micromol/L (95%CI -1.7 to -8.5) SD = 25.5 micromol/L Comparison of TcB readings with TSB levels at different postnatal ages (N = 249) *Day 1-2 (N = 67)* Overestimate = 47.8% Underestimate = 14.9% *Day 3-4 (N = 103)* Overestimate = 34.0% Underestimate = 13.6% *Day 5-7 (N = 45)* Overestimate = 20.0% Underestimate = 28.9% *> 7 day (N = 34)* Overestimate = 17.6% Underestimate = 35.3%	Unselected population Test & Reference test described adequately Test and reference test carried out within one hour Blinding – not specified
Chang YH; Year: 2006 Country:	Study Type: Diagnostic study Evidence Level:	Healthy term and near term babies born in a tertiary hospital. N = 447 mean BW 3185 ± 399.9 grams	TcB using Minolta JM-103 Three measurements made from the forehead, right and left side of the anterior chest wall, and	Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient, N = 447) r = 0.83, p < 0.0001	No exclusion criterion Test & Reference test described adequately Test and reference test carried out within one hour

China [73]	II	mean GA 38.6 ± 1.3 weeks Postnatal age: Not reported Gender: Males = 51.2% Prevalence of TSB > 255 micromol/L = 15% (67/447) Exclusion: not defined	their mean taken for data analysis. Reference standard: Laboratory TSB levels within 1 hour of TcB measurement Diagnostic accuracy calculated for detecting TSB > 255 micromol/L	Bland Altman analysis for difference between TSB and TcB MD = -17 micromol/L (95%CI 15.3 to 20.4) SD = 27.2micromol/L Diagnostic accuracy of TcB (threshold value > 200 micromol/L) for detecting TSB > 255 micromol/L Sensitivity: 53/67 (79.1%) Specificity: 301/380 (79.2%) PPV: 53/132 (40.1%) NPV: 301/315 (95.6%)	Blinding – not specified
Rubaltelli FF; Year: 2001 Country: Europe (multi-centre study in UK, Germany, France, Italy, Switzerland) [74]	Study Type: Diagnostic study Evidence Level: 1b	Term and pre-term neonates who underwent TSB tests as part of normal care at 6 European Hospitals. N = 210 with 35 babies from each hospital BW: <2500 grams = 16.3% GA: >36 week = 80.2% Postnatal age: <48 hours = 16.3% Gender: Not reported Ethnicity White = 66.7% Asian = 14.8% Hispanic = 6.7% Other = 11.9% Exclusion: not defined	TcB using BiliChek from the forehead and sternum – single measurement taken from each site. Reference standard: Laboratory TSB levels within 30 minutes of TcB measurement Blood sample also collected for TSB estimation using HPLC-B technique at the same time Diagnostic accuracy of TcB (various thresholds) estimated at various thresholds and plotted on ROC curve.	Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient, N = 210) *Forehead* r = 0.87, p < 0.001 *Sternum* r = 0.85, p < 0.001 Correlation of lab TSB levels with TSB levels using HPLC-B (Pearson correlation coefficient, N = 210) r = 0.93, p < 0.001 Bland Altman analysis for difference between lab TSB and TcB *Forehead* MD = +2.4 micromol/L (95%CI -2.4 to +7.1) SD = 35.4 micromol/L *Sternum* MD = -14.8 micromol/L (95%CI -19.9 to	Unselected population but exclusion criterion not defined Test & Reference test described adequately Test and reference test carried out within one hour Blinding – yes

				+9.5) SD = 38.4 micromol/L <u>Diagnostic accuracy of TcB on forehead (threshold 187 micromol/L) for detecting TSB > 222 micromol/L by HLPC-B</u> Sensitivity: 93% Specificity: 73% <u>Diagnostic accuracy of TcB (threshold 238 micromol/L) for detecting TSB > 290 micromol/L by HLPC-B</u> Sensitivity: 90% Specificity: 87%	
Boo NY; Year: 2007 Country: Malaysia [75]	Study Type: Diagnostic study Evidence Level: 1b	Healthy term Malaysian babies with hyperbilirubinaemia N = 345 mean BW: 3056 <u>+</u> 487 grams, median GA 38 weeks postnatal age: range 9 – 388 Gender: Males = 60% Ethnicity Malays = 63.8% Chinese = 30.7% Indians = 5.5%, <u>Prevalence of TSB > 300 micromol/L</u> = 27.5% (95/345) Exclusion: infants who had received phototherapy or exchange transfusion, congenital anomalies, severely ill, foreigners, those with conjugated hyperbilirubinaemia.	TcB using BiliChek from the forehead and midpoint of sternum – number of measurements from each site not specified <u>Reference standard:</u> Laboratory TSB levels within 30 minutes of TcB measurement Diagnostic accuracy of TcB (various thresholds) calculated for detecting TSB > 250, > 280, and > 300 micromol/L	<u>Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient, N = 345)</u> *Forehead* All babies r = 0.80, p < 0.0001 Malays: r = 0.79, p < 0.0001 Chinese: r = 0.84, p < 0.0001 Indians: r = 0.83, p < 0.0001 *Sternum* All babies r = 0.86, p < 0.0001 Malays: r = 0.86, p < 0.0001 Chinese: r = 0.86, p < 0.0001 Indians: r = 0.94, p < 0.0001 <u>Correlation of TcB levels with lab TSB levels depending on the time of measurement</u> <u>(Pearson correlation coefficient, 79% of infants with TSB > 300 had measurement at > 80 hours)</u> *<u>At ≤</u> 80 hours*	Unselected population Test & Reference test described adequately Test and reference test carried out within one hour Blinding – yes Data not given for the mean difference and SD from Bland Altman analysis for TSB – TcB

				r = 0.85, p < 0.001 *At > 80 hours* r = 0.71, p < 0.001 <u>Diagnostic accuracy of TcB for detecting TSB > 300 micromol/L</u> *Forehead (threshold 250 micromol/L)* Sensitivity: 100% Specificity: 39.2% *Forehead (threshold 260 micromol/L)* Sensitivity: 75.8% Specificity: 84.8% *Sternum (threshold 200 micromol/L)* Sensitivity: 100% Specificity: 33.6% *Sternum (threshold 280 micromol/L)* Sensitivity: 92.6% Specificity: 84%	
Ebbesen F; Year: 2002 Country: Denmark [45]	Study Type: Diagnostic study Evidence Level: III	All newborns more than 24 hours old who for clinical reasons had their plasma bilirubin determination during the day, except at weekends. <u>Group 1:</u> Both preterm infants < 35 weeks and sick term and near-term infants in the NICU N = 261 mean BW 2521 grams - range 680 to 4645 grams, mean GA 34.6 weeks - range 25 to 43 weeks postnatal age at 1st TcB: 98.4 - range 48 – 840 Gender: Males = 60.1% Ethnicity: Non-northern European descent = 9%	TcB measurement using BiliChek from forehead, sternum, knee and the foot – mean of 5 measurements from each site taken for data analysis. <u>Reference standard:</u> Laboratory TSB levels taken concurrently with TcB measurement Diagnostic accuracy of TcB from forehead (threshold <u>></u> 0.70 of phototherapy limit) estimated for predicting TSB levels <u>></u> phototherapy limits as suggested by the Danish Pediatric Society	<u>Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient, N = 210)</u> **Group 1:** *Forehead* r = 0.88, p > 0.05 *Sternum* r = 0.82, p < 0.001 *Knee* r = 0.77, p < 0.001 *Foot* r = 0.51, p < 0.001 On comparing correlation coefficient of forehead with that for sternum, knee and foot, p < 0.001 for each of the comparison **Group 2:**	Unselected population Test & Reference test described adequately Test and reference test carried out within one hour Blinding – not specified Data not given for the mean difference and SD from Bland Altman analysis for TSB - TcB

		Group 2: Healthy term and near-term infants with GA ≥ 35 weeks in the maternity ward N = 227 mean BW 3362 grams - ange 2170 to 5000 grams mean GA 38.6 weeks - range 35 to 43 weeks postnatal age at 1st TcB: 74.4 - range 48 – 360 Gender: Males = 55.5% Ethnicity: Non-northern European descent = 7% Exclusion: babies already receiving phototherapy or who received phototherapy 6 hours before TSB measurement, with skin infection, purpura, bruising		*Forehead* r = 0.87, p > 0.05 *Sternum* r = 0.90, p < 0.05 *Knee* r = 0.83, p < 0.05 *Foot* r = 0.67, p < 0.001 On comparing correlation coefficient of forehead with that for sternum, knee and foot, p < 0.05 for comparison with knee and foot only Diagnostic accuracy of TcB (threshold value > 0.70 times the phototherapy limit) from forehead in detecting TSB > phototherapy limit **Group 1 (N = 504 observations):** Sensitivity: 108/109 (99.1%) Specificity: 177/395 (44.8%) PPV: 108/326 (33.1%) NPV: 177/178 (99.4%) **Group 2 (N = 317 observations):** Sensitivity: 3/3 (100%) Specificity: 254/314 (80.9%) PPV: 3/63 (4.8%) NPV: 254/254 (100%)	
Samanta S; Year: 2004 Country: UK 46	Study Type: Diagnostic study Evidence Level: II	All babies > 33 weeks in the postnatal ward of a regional teaching hospital who were due to have blood taken for TSB estimation N = 300 median BW 3295 grams – range 1972 to 4720 median GA 39 weeks – range 33 to 42 median postnatal age: 72 hours – range 24 to 264 Gender: Males = 50%	TcB using BiliChek (site not specified) – single measurement taken. Reference standard: Laboratory TSB levels taken concurrently with TcB measurement Diagnostic accuracy of TcB (various thresholds) estimated by plotting ROC curve.	Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient, N = 300) r = 0.77, p < 0.0001 Bland Altman analysis for difference between lab TSB and TcB MD = -10.6 micromol/L (95%CI -80.0 to +60.0) SD = Not reported	Unselected population Test & Reference test described adequately Test and reference test carried out within one hour Blinding – not specified

		Prevalence of TSB > 250 micromol/L = 55/300 (18.3%) Exclusion: babies who had previously received phototherapy		Diagnostic accuracy of TcB (threshold value > 195 micromol/L) for detecting TSB > 250 micromol/L Sensitivity: 50/55 (90.9%) Specificity: 162/245 (66.1%) PPV: 50/133 (37.6%) NPV: 162/167 (97%)	
De Luca D; Year: 2007 Country: Italy [76]	Study Type: Diagnostic study Evidence Level: 1b	Preterm babies with GA between 30-36 weeks admitted in the neonatal sub-intensive unit of tertiary hospital. N = 340 mean BW 2145 ± 518 grams mean GA 33.5 ± 1.9 weeks mean postnatal age: Not reported Gender: Males = 48.2% Exclusion: babies receiving phototherapy or exchange transfusion, asphyxia (Apgar score < 7 at 5 min), Rh or major ABO incompatibility, conjugated bilirubin > 17.1 micromol/L, congenital malformation, liver disease.	TcB using BiliChek from the forehead – mean of 5 measurements taken for data analysis. Reference standard: Laboratory TSB levels within 10 minutes of TcB measurement Diagnostic accuracy of TcB estimated by plotting ROC curve and results given for best thresholds	Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient, N = 210) r = 0.79, p < 0.001 Bland Altman analysis for difference between mean lab TSB and mean TcB % with difference > 8.55 micromol/L = 61.5% (209/340) MD = -18.8 micromol/L SD = 34.2 micromol/L Diagnostic accuracy of TcB (threshold value > 111 micromol/L) for detecting TSB > 171 micromol/L Sensitivity: 100% Specificity: 40% Diagnostic accuracy of TcB (threshold value > 171 micromol/L) for detecting TSB > 205 micromol/L Sensitivity: 100% Specificity: 72%	Unselected population Test & Reference test described adequately Test and reference test carried out within one hour Blinding – yes but only investigator Data not extractable for calculating values of TP, FP, TN & FN for detecting hyperbilirubinaemia
Karon B; Year: 2008 Country: USA [78]	Study Type: Diagnostic study Evidence Level: III	Babies in a well-infant nursery were eligible if a serum bilirubin was ordered to assess risk of hyperbilirubinaemia. N = 177 Mean BW: Not reported Median GA: 39.9 weeks (32.7 to 41.4)	Test: TcB reading from the forehead using BiliChek – mean of 5 measurements taken for data analysis Reference standard: 1.Laboratory TSB diazo method	Correlation of TcB levels with TSB levels (Pearson correlation coefficient, N = 177) *Forehead* Diazo: $r^2 = 0.65$ Vitros: $r^2 = 0.66$	Unselected population Test & Reference test described adequately Test and reference test carried out within one hour Blinding – No

		Gender: Not reported Ethnicity: White = 82.5% Black = 1.7% Hispanic = 5.1% Asian = 10.7% Exclusion: None	measured on blood collected within 30 minutes as TcB. 2. Laboratory TSB vitros method measured on blood collected within 30 minutes as TcB.	Diagnostic accuracy of TcB (threshold value >75 centile on Bhutani nomogram **Diazo:** Sensitivity: 56/57 (98.2%) Specificity: 48/120 (40%) PPV: 56/127 (43.7%) NPV: 48/49 (98%) **Vitros:** Sensitivity: 63/67 (94%) Specificity: 35/64 (54.7%) PPV: 63/92 (68.5%) NPV: 35/39 (89.7%)	
Slusher TM; Year: 2004 Country: Nigeria [77]	Study Type: Diagnostic study Evidence Level: II	Clinically jaundiced term and preterm babies with age < 14 days admitted in two hospitals N = 127 mean BW: 2.72 ± 0.62 kg mean GA: Not reported Gender: Males = 60%, Pigmentation – dark pigmentation 10% medium pigmentation = 36% light pigmentation = 54% Hospital A: 500-bed tertiary teaching hospital (N = 98) Hospital B: 168-bed hospital located in a rural village (N = 29) Exclusion: not defined	TcB using BiliChek from the forehead and before starting phototherapy Skin pigmentation determined through visual observation Reference standard: Laboratory TSB levels obtained simultaneously with TcB measurement	Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient) *Both hospital together* r = 0.92 *Babies with TSB ≥ 205 micromol/L* r = 0.84 *Babies with TSB < 205 micromol/L* r = 0.67 *Based on pigmentation* Light: r = 0.91 Medium: r = 0.94 Dark: r = 0.87 Bland Altman analysis for difference between mean TcB and mean lab TSB values *Both hospitals together* MD = 8.5 micromol/L (95%CI -3.4 to 21.4 micromol/L SD = 129.2 micromol/L *Babies with TSB ≥ 205 micromol/L* MD = --21.4 micromol/L (95%CI -40.8 to 0.0 micromol/L)	Unselected population Test & Reference test described adequately Test and reference test carried out within one hour Blinding – yes but only investigator Data not extractable for calculating values of TP, FP, TN & FN for detecting hyperbil

				SD = 146.2 micromol/L *Babies with TSB < 205 micromol/L* MD = 35.7 micromol/L (95%CI 25.5 to 45.9 micromol/L) SD = 129.2 micromol/L *Based on pigmentation* **Light:** MD = 18.4 micromol/L, SD = 91.8 micromol/L **Medium:** MD = 13.6 micromol/L, SD = 132.6 micromol/L **Dark:** MD = -3.4 micromol/L, SD = 197.2 micromol/L	

Q4. What should be included in a formal assessment of a baby with neonatal hyperbilirubinaemia?

Evidence Table – Assessment Tests
TSB < 255micromol/L

Bibliographic details	Study type & Evidence level	Patient characteristics	Results	Reviewers Comments
Author: Werblinska B Year: 1981 Country: Nigeria Ref ID: [89]	Study type: Case-control study Evidence level: 2-	Diagnosis: Jaundice Criteria: TSB ≥ 171 micromol/L Setting: Hospital Sample Size: 40 GA: Not reported Mean BW: Not reported. Gender M/F: 19/21 Ethnicity: Not reported Exclusion: None	Mean bilirubin levels TSB: 253 micromol/L ABO incompatibility: 8/40 (20%) Rh incompatibility: 3/40 (7.5%) G6PD deficiency: 13/40 (32.5%) P value < 0.001 Infection: 34/40 (85%) P value < 0.001 Idiopathic: 3/40 (7.5)	Small study, Incomplete data from three subject so not included in analysis All 38controls (14 M & 24 F) were delivered by Caesarean Section due to maternal complication
Author: Azubuike J Year: 1979 Country: Nigeria Ref ID: [88]	Study type: Case series Evidence level: 3	Diagnosis: Jaundice Criteria: TSB ≥ 170 micromol/L Setting: Hospital Sample Size: 424 GA: Not reported Mean BW: Not reported Gender M/F: Not reported Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Days 0 – 10 Exclusion: None	Mean bilirubin levels TSB: Not reported ABO incompatibility: 178/424 (41.2%) Rh incompatibility:2/424 (0.5%) G6PD deficiency: 229/424 (54%) Infection: 60/424 (14.1%) Idiopathic: 39/424 (9.2%)	
Author: Guaran R Year: 1992 Country: Australia	Study type: Retrospective chart review Evidence level: 3	Diagnosis: Jaundice Criteria: TSB ≥ 154 micromol/L Setting: Hospital Sample Size: 10944 GA: Not reported.	Mean bilirubin levels TSB: Not reported ABO incompatibility: 601/6129 (9.8%) Rh incompatibility:193/6129 (3.1%)	4815 cases had no investigations Prematurity is reported to be the most common cause 2,226/61290 (36.3%)

Ref ID: [95]		Mean BW: Not reported Gender M/F: Not reported Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Not reported Exclusion: None (4,815 Not investigated)	G6PD deficiency: 51/6129 (0.8%) Infection: 198/6129 (3.2%) **Exchange Transfusion (N = 248)** ABO incompatibility: 58/248 (23.4%) Rh incompatibility: 108/248 (43.5%) G6PD deficiency: 2/248 (0.8%) Infection: 2/248 (0.8%)	
Author: Sodeinde O Year: 1995 Country: Nigeria Ref ID: [90]	Study type: Case control study Evidence level: 2-	Diagnosis: Jaundice Criteria: TSB ≥ 205 micromol/L Setting: Hospital Sample Size: 327 Mean GA: Not reported. 87 (26.5%) were premature < 37 weeks Mean BW: 2.73 ± 0.74 kgs Gender M/F: Not reported Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Not reported Exclusion: None	Mean bilirubin levels TSB: Not reported ABO incompatibility: 40/150 (26.7%) Rh incompatibility: 3/150 (2.0%) G6PD deficiency: 109/327 (33.3%) (P value < 0.0087) Infection: 38/217 (17.5%) Idiopathic: Not reported	Not all subjects tested for ABO incompatibility or infection
Author: Yeung C Year: 1973 Country: China Ref ID: [96]	Study type: Case series Evidence level: 3	Diagnosis: Jaundice Criteria: TSB ≥ 171 micromol/L Setting: Hospital Sample Size: 1811 Mean GA: Not reported Mean BW: Not reported. 65 (3.6%) were premature <38 weeks Gender M/F: 1054/755 Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Day 0 - 10 Exclusion: None	Mean bilirubin levels TSB: Not reported ABO incompatibility: 414/1811(22.8%) Rh incompatibility: Not reported G6PD deficiency: 241/1811 (13.3) Infection: Not reported Idiopathic: Not reported	

			Exchange transfusion (N = 581) ABO incompatibility: 157/581 (27.0%) G6PD deficiency: 13/581 (22.4%) Infection: Not reported Idiopathic: Not reported **Kernicterus (N = 156)** ABO incompatibility: 51/156 (32.7%) G6PD deficiency: 58/156 (37.2%) Infection: Not reported Idiopathic: Not reported	
Author: Bhandari A Year: 1982 Country: India Ref ID: [91]	Study type: Case control study Evidence level: 2-	Diagnosis: Jaundice Criteria: TSB ≥ 171 micromol/L Setting: Hospital Sample Size: 100 Mean GA: Not reported Mean BW: Not reported Gender M/F: 58/42 Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Day 0 - 5 Exclusion: None	Mean bilirubin levels TSB: Not reported ABO incompatibility: 10/100 (10.0%) Rh incompatibility: 20/100 (20.0%) G6PD deficiency: 4/100 (4.0%) Infection: Not reported Idiopathic: Not reported	
Author: Bajpai P Year: 1971 Country: India Ref ID: [92]	Study type: Case control study Evidence level: 2-	Diagnosis: Jaundice Criteria: TSB ≥205 micromol/L Setting: Hospital Sample Size: 50 Mean GA: Not reported Mean BW: Not reported Gender M/F: Not reported Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Not reported Exclusion: None	Mean bilirubin levels TSB: Not reported ABO incompatibility: 8/50 (16.0%) Rh incompatibility: 1/50 (2.0%) G6PD deficiency: 2/50 (4.0%) Infection: 7/50 (14.0%) Idiopathic: 19/50 (38%)	

Author: Arif K Year: 1999 Country: Pakistan Ref ID: [94]	Study type: Case series Evidence level: 3	Diagnosis: Jaundice *Criteria:* None Setting: Hospital Sample Size: 869 Mean GA: 37.2 ± 2.8 weeks Mean BW: 27574 ± 735 grams Gender M/F: 484/385 Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Not reported Exclusion: None	Mean bilirubin levels TSB: 221 ± 42 micromol/L ABO incompatibility: 56/869 (6.4%) Rh incompatibility: 57/869 (6.6%) G6PD deficiency: 20/869 (2.3%) Infection: 165/869 (19.0%) **Exchange transfusion** ABO incompatibility: 4/27 (14.8%) Rh incompatibility: 7/27 (25.9%) G6PD deficiency: 2/27 (7.4%) Infection: 6/27 (22.2%)	Retrospective study
Author: Singhal P Year: 1992 Country: India Ref ID: [93]	Study type: Case series Evidence level: 3	Diagnosis: Hyperbilirubinaemia Criteria: TsB >205 micromol/L Setting: Hospital Sample Size: 454 Mean GA: Not reported Mean BW: Not reported Gender M/F: 258/196 Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Not reported Exclusion: None	Mean bilirubin levels TSB: Not reported ABO incompatibility: 65/454 (14.3%) Rh incompatibility: 37/454 (8.1%) G6PD deficiency: 23/454 (5.1%) **Exchange transfusion** ABO incompatibility: 18/66 (27.4%) Rh incompatibility: 21/66 (31.8%) G6PD deficiency: 11/66 (16.7%)	From 7680 live births 454 (5.9%) has TsB >205 micromol/L

Evidence Table – Assessment Tests
TSB 255 – 399 micromol/L

Bibliographic details	Study type & Evidence level	Patient characteristics	Results	Reviewers Comments
Author: Biddulph J Year: 1974 Country: Papua New Guinea Ref ID: [101]	Study type: Consecutive case-series Evidence level: 3	Diagnosis: Jaundice Criteria: TSB ≥ 256 micromol/L Setting: *Hospital* Sample Size: 50 Mean GA: Not reported Mean BW: Not reported Gender M/F:29/21 Ethnicity: Not reported Breastfeeding: 50 (100%) Onset of Jaundice: Day 1 - 17 Duration of jaundice: 26 (52%) < 1 week Exclusion: None	Mean bilirubin levels TSB: Not reported Incidence of ABO incompatibility: 12/50 (24%) Rh incompatibility: Not reported Incidence of G6PD deficiency: 11/50 (22%) Incidence of sepsis: 8/50 (16%) Idiopathic: 19/50 (38%) **Exchange transfusion (N = 11)** Incidence of ABO incompatibility: 4/11 (36.4%) Incidence of G6PD deficiency: 3/11 (27.3%) Incidence of sepsis: 2/11 (18.2%) Idiopathic: 2/11 (18.2%)	Small study
Author: Seidman D Year: 1995 Country: Israel Ref ID: [99]	Study type: Case series Evidence level: 3	Diagnosis: Jaundice Criteria: TSB ≥ 308 micromol/L Setting: Hospital Sample Size: 21 Mean GA: 39.3 ± 1.2 weeks Mean BW: 3206 ± 340 gms Gender M/F: 15/6 Ethnicity: 9 Jew Askenazi, 3 Kurdish, 2 Iraqi and others. Breastfeeding: 20/21 Onset of Jaundice: Day 0 - 10 Exclusion: None	Mean bilirubin levels TSB: 335 ± 43 micromol/L ABO incompatibility: 0/21 (0%) Rh incompatibility: 0/21 (0%) G6PD deficiency: 2/21 (9.5%) Infection: 0/21 (0%) Idiopathic: Not reported	Small study Subjects had received phototherapy and were discharged with TSB > 171 micromol/L so could qualify as persistent jaundice
Author: Effiong C	Study type:	Diagnosis: Jaundice	Mean bilirubin levels	

Year: 1975 Country: Nigeria Ref ID: [100]	Case series Evidence level: 3	Criteria: TSB ≥ 256 micromol/L Setting: Hospital Sample Size: 125 Mean GA: Not reported Mean BW: Not reported Gender M/F: 70/55 Ethnicity: Not reported Breastfeeding: Onset of Jaundice: Days 0 – 7 Duration of jaundice: Exclusion: None	TSB: Not reported ABO incompatibility: 26/125 (20.6%) Rh incompatibility: 2/125 (1.6%) G6PD deficiency: 49/125 (39.2%) Infection: 1/125 (0.8%) Idiopathic: 35/125 (28%) **Exchange Transfusion (N = 53)** ABO incompatibility: 15/53 (20.6%) Rh incompatibility:1/53 (1.9%) G6PD deficiency: 21/53 (39.6%) Infection: 0/53 (0%) Idiopathic: 11/53 (20.7%)	
Author: Ho K Year: 1991 Country: Singapore Ref ID: [102]	Study type: Retrospective chart review Evidence level: 3	Diagnosis: Jaundice Criteria: TSB ≥256 micromol/L Setting: Hospital Sample Size: 270 Mean GA: Not reported Mean BW: Not reported Gender M/F: Not reported Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Not reported Exclusion: None	Mean bilirubin levels TSB: Not reported ABO incompatibility: 73/270 (27.0%) Rh incompatibility:1/270 (0.4%) G6PD deficiency: 18/270 (6.7%) Infection: Not reported Idiopathic: Not reported **Exchange Transfusion (N = 46)** ABO incompatibility: 17/46 (37.0%) Rh incompatibility: 1/46 (2.2%) G6PD deficiency: 2/46 (4.3%)	Authors report a drop in number of G-6-PD cases requiring exchange transfusion on new guidelines that specified that G-G-PD be screened for at birth and deficient babies be kept in hospital for a minimum of 2 weeks

			Infection: 8/46 (17.4%) Idiopathic: 6/46(13.0%)	
Author: Ahmed H Year: 1995 Country: Nigeria Ref ID: [98]	Study type: Case control study Evidence level: 2-	Diagnosis: Jaundice Criteria: TSB ≥171 micromol/L Setting: Hospital Sample Size: 102 Mean GA: Not reported Mean BW: Not reported Gender M/F: 65/37 Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Not reported Exclusion: None	Mean bilirubin levels TSB: 312 micromol/L ABO incompatibility: 24/102 (23.5%) Rh incompatibility: 0/102 (0%) G6PD deficiency: 41/102 (41.2%) Infection: 57/102 (55.9%) Idiopathic: Not reported	Incidence of infection higher in babies re-admitted from home
Author: Mamtani M Year: 2007 Country: India Ref ID: [97]	Study type: Cohort Evidence level: 2-	Diagnosis: Jaundice Criteria: TSB ≥ 256 micromol/L if the age of the baby is ≤15 days Setting: Tertiary care Hospital Sample Size: 92 Mean GA: Not reported. 17 were Preterm Mean BW: Not reported: 35 were small for GA Gender M/F: 57/35 Ethnicity: Not reported Breastfeeding: 58 (63%) Onset of Jaundice: Day 0 - 15 Exclusion: None	Mean bilirubin levels TSB: 376 ± 85 micromol/L ABO incompatibility: 14/92 (15.3%) Rh incompatibility:10/92 (10.9%) G6PD deficiency: 4/92 (4.3%) Infection: 18/92 (19.6%) Idiopathic: Not reported	
Author: Tay J Year: 1984 Country: Singapore Ref ID: [103]	Study type: Cohort Evidence level: 2-	Diagnosis: Jaundice Criteria: TSB ≥ 222 micromol/L Setting: Hospital Sample Size: 181 Mean GA: Not reported. 15 were preterm Mean BW: Not reported. 25 were less than 2500gms Gender M/F: Not reported Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Not reported Exclusion: None	Mean bilirubin levels TSB: 330 ± 51micromol/L ABO incompatibility: 42/181 (23.2%) Rh incompatibility: 1/181 (0.6%) G6PD deficiency: 4/181 (2.2%) Infection: Not reported Idiopathic: Not reported	Those with G-6-PD deficiency kept in hospital for 21 days

			Kernicterus (N = 8) ABO incompatibility: 4/8 (50.0%) Rh incompatibility: 1/8 (12,5) G6PD deficiency: 0/8 (0%) Infection: Not reported Idiopathic: Not reported	
Author: Chen W Year: 1981 Country: Taiwan Ref ID: [104]	Study type: Case series Evidence level: 3	Diagnosis: Jaundice Criteria: TSB ≥ 25 micromol/L Setting: Hospital Sample Size: 196 Mean GA: Not reported. Mean BW: Not reported: 25 had low birth weight Gender M/F: Not reported Ethnicity: Chinese Breastfeeding: Not reported Onset of Jaundice: Day 0 - 15 Exclusion: None	Mean bilirubin levels TSB: 327 ± 72 micromol/L ABO incompatibility: 61/196(31.1%) Rh incompatibility:1/196 (0.5%) G6PD deficiency: 43/196(21.9%) Infection: 10/196 (5.1%) Idiopathic: 53/196 (17.0%)	
Author: Atay E Year: 2006 Country: Turkey Ref ID: [105]	Study type: Case series Evidence level: 3	Diagnosis: Indirect hyperbilirubinaemia Criteria: None Setting: Hospital Sample Size: 624 Mean GA: Not reported. Mean BW: 3082 ± 530 grams Gender M/F: 330/294 Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: 6.57 ± 4.04 days Exclusion: None	Mean bilirubin levels TSB: 359 + 70 micromol/L ABO incompatibility: 171/624 (27.4%) Rh incompatibility:52/624 (8.3%) G6PD deficiency: 24/624 (3.8%) Infection: 36/624 (5.8%) Idiopathic: 312/624 (50.0%) **Kernicterus** ABO incompatibility: 2/6 (33.3%) Rh incompatibility: 1/6 (16.6%) G6PD deficiency: 1/6 (16.6%)	

			Infection: 0/6 (0%) Idiopathic: 0/6 (0%)	
Author: Al-Omran A Year: 1999 Country: Saudi Arabia Ref ID: [108]	Study type: Case series Evidence level: 3	Diagnosis: Jaundice Criteria: TsB >256 micromol/L Setting: Hospital Sample Size: 211 Mean GA: Not reported. Mean BW: Not reported Gender M/F: Not reported Ethnicity: Saudis (97%) Breastfeeding: Not reported Onset of Jaundice: Not reported Exclusion: None	Mean bilirubin levels TSB: Not reported ABO incompatibility: 21/211 (9.9%) Rh incompatibility: 2/211 (0.9%) G6PD deficiency: 64/211 (30.3%) Infection: 4/211 (1.9%) Idiopathic: 108/211 (51.2%)	
Author: Dawodu A Year: 1998 Country: UAE Ref ID: [107]	Study type: Case series Evidence level: 3	Diagnosis: Jaundice Criteria: Cockington Setting: Hospital Sample Size: 85 Mean GA: Not reported. Mean BW: Not reported Gender M/F: Not reported Ethnicity: 57 (67%) Arab 26 (30%) Asian Breastfeeding: Not reported Onset of Jaundice: Not reported Exclusion: None	Mean bilirubin levels TSB: Not reported ABO incompatibility: 22/85 (25.9%) Rh incompatibility: 1/85 (1.2%) G6PD deficiency: 8/85 (9.4%)	
Author: Koosha A Year: 2007 Country: Iran Ref ID: [106]	Study type: Case series Evidence level: 3	Diagnosis: Hyperbilirubinaemia Criteria: ICD Setting: Hospital Sample Size: 376 Mean GA: Not reported. Mean BW: Not reported Gender M/F: 159/217 Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Not reported	Mean bilirubin levels TSB: Not reported ABO incompatibility: 14/376 (3.7%) Rh incompatibility: 8/376 (2.1%) G6PD deficiency: 8/376 (2.1%) Infection: 59/376 (15.7%)	

		Exclusion: None		

Evidence Table – Assessment Tests
TSB >400 micromol/L / or Exchange Transfusion

Bibliographic details	Study type & Evidence level	Patient characteristics	Results	Reviewers Comments
Author: Nkrumah F Year: 1973 Country: Ghana Ref ID: [110]	Study type: Case series Evidence level: 3	Diagnosis: Jaundice Criteria: TSB ≥ 342 micromol/L Setting: Hospital / Paediatric outpatient Sample Size: 35 Mean GA: Not reported Mean BW: Not reported Gender M/F: 26/9 Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Day 0 - 8 Duration of jaundice: Not reported Exclusion: None	Mean bilirubin levels TSB: 551 ± 182 micromol/L Incidence of ABO incompatibility: 14/35 (40%) Rh incompatibility: 1/35 (2.9%) Incidence of G6PD deficiency: 13/35 (37.1%) Incidence of sepsis: Not reported Idiopathic: 10/35 (28.6%) **Kernicterus** Incidence of ABO incompatibility: 6/17 (35.3%) Rh incompatibility: 1/17 (5.9%) Incidence of G6PD deficiency: 8/17 (47.0%) Incidence of sepsis: Not reported Idiopathic: 3/17 (17.6%)	Small study
Author: Manning D Year: 2007 Country: UK & Republic of Ireland Ref ID: [18]	Study type: Survey Evidence level: 3	Diagnosis: Jaundice Criteria: TSB ≥ 513 micromol/L Setting: Not reported Sample Size: 106 Mean GA: 38.2 ± 1.7 weeks Mean BW: 3170 ± 480 gms Gender M/F: 64/42 Ethnicity: White 52 (48.1%), Asian 18 (16.7%), Black 11 (10.1%), Mixed 11 (10.1%) Breastfeeding: 87 (80.5%) Onset of Jaundice: Not reported	Mean bilirubin levels TSB: 581 micromol/L (510-802) ABO incompatibility: 33/106 (31.1%) Rh incompatibility:6/106 (5.7%) G6PD deficiency: 5/106 (4.7%) Infection: 4/106 (3.8%) Idiopathic: 29/106 (27.3%)	

		Exclusion: None	**Kernicterus Cases (N = 14)** ABO incompatibility: 3/14 (21.4%) Rh incompatibility: 1/14 (7.1%) G6PD deficiency: 3/14 (21.4%) Infection: 2/14 (14.3%) Idiopathic: 1/14 (7.1%)	
Author: Katar S Year: 2008 Country: Turkey Ref ID: [112]	Study type: Case series Evidence level: 3	Diagnosis: Jaundice Criteria: TSB > 342 micromol/L at 24-48 hours or ≥ 427 micromol/L) at >48 hours after birth Setting: Neonatal clinic Sample Size: 21 Mean GA: Not reported. All were term babies Mean BW: 2943 ± 533 gms Gender M/F: 15/6 Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Not reported Exclusion: None	Mean bilirubin levels TSB: 598 ± 185 micromol/L ABO incompatibility: 4/21 (19.5) Rh incompatibility: 4/21 (19.5%) G6PD deficiency: 4/21 (19.5%) Infection: Not reported Idiopathic: 10/21 (47.5%)	Small study
Author: Dawodu A Year: 1984 Country: Nigeria Ref ID: [111]	Study type: Case series Evidence level: 3	Diagnosis: Jaundice Criteria: TSB ≥ 205 micromol/L Setting: Hospital Sample Size: 109 Mean GA: Not reported Mean BW: Not reported Gender M/F: 77/32 Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Not reported Exclusion: None	Mean bilirubin levels TSB: 616 ± 197 micromol/L : ABO incompatibility: 15/109 (13.8%) Rh incompatibility: Not reported G6PD deficiency: 67/109 (61.5%) Infection: 24/109 (22.0%) Idiopathic: 13/109 (11.9%)	Only subjects with indication for infection were tested
Author: Tiker F Year: 2006 Country: Turkey	Study type: Case series Evidence level: 3	Diagnosis: Jaundice Criteria: TSB ≥ 428 micromol/L Setting: Neonatal Intensive Care Unit Sample Size: 93 Mean GA: 38.57 weeks	Mean bilirubin levels TSB: 515 ± 97 micromol/L ABO incompatibility: 7/93 (7.5%) Rh incompatibility: 7/93 (7.5%)	Not all babies tested for G-6-PD levels

Ref ID: [113]		Mean BW: Not reported Gender M/F: 51/42 Ethnicity: Not reported Breastfeeding: 93/93 Onset of Jaundice: Day 0 - 30 Exclusion: None	G6PD deficiency: 2/39 (5.1%) Infection: 7/93 (7.5%) Idiopathic: 61/93 (615.6%) **Kernicterus (N = 6)** ABO incompatibility: 1/6 (16.7%) Rh incompatibility: 0/6 (0%) G6PD deficiency: 1/6 (16.7%) Infection: 3/6 (50.0%) Idiopathic: 1/6 (16.7%)	
Author: Sgro M Year: 2006 Country: Canada Ref ID: [116]	Study type: Case series Evidence level: 3	Diagnosis: Jaundice Criteria: TSB ≥ 427 micromol/L) Setting: Hospital Sample Size: 258 Mean GA: 38.5 ± 1.4 weeks Mean BW: 3360 ± 489 gms Gender M/F: 162/96 Ethnicity: White 55.4%, Asian 24.3%, Aboriginal 7.6%, black 5.2%, Middle Eastern 4.0%, Latin American 2.8% Breastfeeding: Not reported Onset of Jaundice: Day 0 - 60 Exclusion: None	Mean bilirubin levels TSB: 464 ± 75 micromol/L ABO incompatibility: 49/258 (18.9%) Rh incompatibility: Not reported Incidence of G6PD deficiency: 20/258 (7.7%) Infection: 3/258 (1.2%) Idiopathic: Unclear	
Author: Bjerre J Year: 2008 Country: Denmark Ref ID: [115]	Study type: Case series Evidence level: 3	Diagnosis: Jaundice Criteria: TSB ≥ 445 micromol/L Setting: Hospital Sample Size: 113 GA (range): 35 – 42 weeks BW (range): 2380 - 4870gms Gender M/F: 69/44 Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Day 0 - 28	Mean bilirubin levels TSB: Not reported ABO incompatibility: 52/113 (46.0%) Rh incompatibility: 2/113 (0.2%) Incidence of G6PD deficiency: 1/113 (0.9%) Infection: Not reported	

		Exclusion: None	Idiopathic: Unclear	
Author: Necheles T Year: 1976 Countries: United States & Greece Ref ID: [114]	Study type: *Case series* Evidence level: 3	Diagnosis: Severe jaundice requiring exchange transfusions Criteria: Not reported Setting: Hospital Sample Size: 75 GA: Not reported BW: Not reported Gender M/F: 69/44 Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Not reported Exclusion: None	Mean bilirubin levels TSB: Not reported ABO incompatibility: 29/75 (38.7%) Rh incompatibility: 6/75 (8.0%) Incidence of G6PD deficiency: 14/75 (18.7%) **Kernicterus** ABO incompatibility: 1/6 (16.7%) Rh incompatibility: 0/6 (0%) Incidence of G6PD deficiency: 3/6 (50.0%)	66 babies were in Greece and 9 were in the USA
Author: Narang A Year: 1997 Country: India Ref ID: [109]	Study type: Case series Evidence level: 3	Diagnosis: Hyperbilirubinaemia Criteria: Exchange transfusion Setting: Hospital Sample Size: 141 Mean GA: Not reported. Mean BW: Not reported Gender M/F: Not reported Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Not reported Exclusion: None	Mean bilirubin levels TSB: Not reported ABO incompatibility: 8/141 (5.7%) Rh incompatibility: 13/141 (9.2%) G6PD deficiency: 24/141 (17.2%) Infection: 34/141 (24.1%) Idiopathic: 50/141 (35.4%)	Demographic data reported for all babies who received PT/ET (Cockington charts) and data Not reported for those with serum bilirubin > 256 micromol/L

Evidence Table – Assessment Tests
Kernicterus

Author: Maisels J Year: 1995 Country: USA Ref ID: [118]	Study type: Case series Evidence level: 3	Diagnosis: Kernicterus Criteria: Not reported Setting: Not reported Sample Size: 14 GA (range): 37 – 42 weeks BW (range): Not reported) Gender M/F: Not reported Ethnicity: Not reported Breastfeeding: All Onset of Jaundice: Not reported Exclusion: None	Mean bilirubin levels TSB: (Not reported) ABO incompatibility: 1/14 (7.1%) Rh incompatibility: 0/14 (0 %) Incidence of G6PD deficiency: 3/14 (21.4%) Infection: 2/14 (14.3%) Idiopathic: 6/14 (42.8%)	
Author: Bhutani V Year: 2006 Country: USA Ref ID: [21]	Study type: Case series Evidence level: 3	Diagnosis: Kernicterus Criteria: Not reported Setting: Hospital Sample Size: 125 GA (range): 35 – 42 weeks BW (range): 2015 – 4730 gms Gender M/F: Not reported Ethnicity: White (58.4%), Black (26.4%), Hispanic (8.8%) and Asian (6.4%) Breastfeeding: Not reported Onset of Jaundice: Not reported Exclusion: None	Mean bilirubin levels TSB: Not reported ABO incompatibility: Not reported Rh incompatibility: Not reported Incidence of G6PD deficiency: 26/125 (20.8%) Infection: Not reported Idiopathic: 44/125 (35.2%)	Demographc data reported for all cases on Kernicterus Register not just the sample used here
Author: Ogunlesi T Year: 2007 Country: Nigeria Ref ID: [117]	Study type: Case series Evidence level: 3	Diagnosis: Bilirubin Encephalopathy Criteria: severe jaundice and tone abnormalities, abnormal cry and abnormal movements Setting: Hospital Sample Size: 115 GA: 97 (84,3%) were term BW:> 77 (69.9%) >500 grams Gender M/F: 88/27 Ethnicity: Not reported Breastfeeding: Not reported Onset of Jaundice: Not reported Exclusion: None	Mean bilirubin levels (unconjugated) TSB: 348 ± 113 micromol/L ABO incompatibility: 22/115 (19.2%) Rh incompatibility: 7/115 (6.1%) Incidence of G6PD deficiency: 40/115 (34.8%) Infection: 12/115 (10.4%)	Also 2 had mixed ABO/Rh incompatibilities 4 had mixed ABO incompatibility and septicaemia

Evidence Table – Additional Tests

Author: Hulzebos C Year: 2008 Country: USA Ref ID: [79]	Study type: Systematic review Evidence level: 1^{++}	Inclusion criteria Studies of Premature babies with hyperbilirubinaemia that used the Bilirubin/Albumin ratio to predict BIND	6 studies included. Higher B/A ratio was associated with abnormal ABR in 2 studies, lower IQ at 6 years in one study and with Kernicterus in one study One study found no difference One study found that binding capacities (expressed a B/A molar ratio) were lower in babies with kernicterus	
Author: Malik G Year: 1986 Country: India Ref ID: [80]	Study type: Case-series Evidence level: 3	Diagnosis: Jaundice Criteria: Not reported Exclusion: Respiratory distress, Sepsis, Hypothermia, Hypoglycaemia, Postasphysial seizure, bleeding diathesis Setting: Special baby care unit Sample Size: 53 Gender M/F: Not reported Mean GA: 37.9 ± 2.2 weeks Mean BW: 2780 ± 620 grams Ethnicity: Not reported	Mean TsB levels 227 ± 80 micromol/L Mean free bilirubin 8.7 ± 5.6 nmol/l Mean Albumin levels 3.6. ± 0. g/dl Mean Bilirubin/Albumin ratio 3.7 Mean Molar B/A ratio 0.41 correlation between free bilirubin and B-A ratio 0.74 ($p<0.001$)	
Author: Chan G Year: 1980 Country: Canada Ref ID: [81]	Study type: Case series Evidence level: 3	Diagnosis: Jaundice Criteria: Jaundice Exclusion: Not reported Setting:	Mean TsB levels Not reported Mean free bilirubin Not reported Mean Albumin levels Not reported Mean B/A ratio	

		Neonatal Intensive Care Unit Sample Size: 46 (55 samples used) Gender M/F: Not reported Mean GA: 36 ± 4 weeks Mean BW: 2453 ± 813 grams Ethnicity: Not reported	Not reported correlation between free bilirubin and Bilirubin/Albumin molar ratio r = 0.75, p < 0.001	
Author: De Carvalho W Year: 1992 Country: Brazil Ref ID: [82]	Study type: Case series Evidence level: 3	Diagnosis: Non-haemolytic jaundice Criteria: Mothers who received prenatal care and no previous history of lues and with negative serologic test for syphilis, Birthweight ≥ 2500 grams, Negative direct Coombs test, Gestational age between 37 and 41 weeks, < 7 days old, no history of neonatal anoxia and Apgar ≥ 8 at 1 and 5 minutes, normal infants no administration of substances competing for albumin binding site, no phototherapy, exchange transfusion or human albumin Exclusion: Not reported Setting: Neonatal service Sample Size: Not reported Gender M/F: 25/18 Mean GA: Not reported Mean BW: Not reported Ethnicity: Not reported	Mean TsB levels Not reported Mean free bilirubin 11.5 ± 6.0 nmol/L 0.0115 ± 0.006 micromol/L Mean Albumin levels 3.33 + 0.3 g/dl correlation between free bilirubin and indirect bilirubin 0.69 (p<0.01)	Serum albumin levels not taken in 6 babies
Author: Newman T Year: 1991 Country: USA Ref ID: [83]	Study type: Retrospective case series Evidence level: 3	Diagnosis: Jaundice Criteria: Not reported Exclusion: None Setting: Hospital	Mean TsB levels Not reported Mean free bilirubin Not reported Mean Albumin levels Not reported Mean B/A ratio Not reported	Abnormal direct bilirubin = direct bilirubin above 95th percentile in each centre (UCSF = ≥39micromol/L, Stanford = ≥17 micromol/L)

		Sample Size: 149 (9 from Stanford) Gender M/F: Not reported Mean GA: Not reported Mean BW: Not reported Ethnicity: Not reported	Direct Bilirubin Not reported Direct bilirubin levels were unexplained in 52% of cases while 24% were laboratory errors. The remainder were as follows; Isoimmunisation = 19 (12.7%) Sepsis or pneumonia = 5 (3.6%) Congestive Heart failure = 5 (3.6%) Multiple anomalies = 2 (1.3%) Pyloric Stenosis = 2 (1.3%) Extreme SGA (possible Rubella) = 1(0.7%) Hypothyroid = 1(0.7%) Choledochal cyst = 1(0.7%) Slightly high aminotransferase levels (100 U/L) = 3(2.0%) Sludge in gallbladder = 1(0.7%)	
Author: Newman T Year: 1990 Country: USA Ref ID: [84]	Study type: Retrospective chart review Evidence level: 3	Diagnosis: Hyperbilirubinaemia Criteria: Birthweight > 2500 grams, Hyperbilirubinaemia Exclusion: Low birthweight Setting: Hospital Sample Size: 447 Gender M/F: Not reported Mean GA: Not reported Mean BW: 3440 ± 485 grams Ethnicity: Not reported	Routine hyperbilirubinaemia tests Direct Bilirubin Blood type, Complete blood count, Differential cell count, Reticulocyte count, Platelet count, Morph, Urinalysis Usefulness of tests Possible cause of hyperbilirubinaemia identified from history, physical exam or routine haematocrit done at 4 hours 145/447 (32.4%) Other diagnosis related to hyperbilirubinaemia no made due to routine hyperbil. investigations 13/447 (2.9%) No specific diagnosis related to hyperbilirubinaemia: 214/447 (47.8%) Diagnoses possibly from routine hyperbil investigations not accompanied by other diagnoses	

			58/447 (12.9%) Diagnoses possibly from routine hyperbil investigations accompanied by other diagnoses 17/447 (3.8%)	
Author: Tiker F Year: 2006 Country: Turkey Ref ID: [87]	Study type: Retrospective chart review Evidence level: 3	Diagnosis: Conjugated Hyperbilirubinaemia Criteria: Direct bilirubin >15% of total TsB Elevation in biliary enzymes (gamma glutamyl transpeptidase (GGT), alkaline pjosphatse (ALP), asparttate transaminase (AST) or alanine transaminase (ALT) Exclusion: Not reported Setting: Neonatal Intensive Care Unit Sample Size: 42 Gender M/F: Not reported Mean GA: 37 weeks Mean BW: Not reported Ethnicity: Not reported	Mean age at presentation 240 hours Mean peak TsB levels 292 ± 193 micromol/L Mean peak conjugated bilirubin 130 ± 130 micromol/L Diagnoses in conjugated jaundice Culture-proven sepsis: 14/42 (35.7%) Perinatal hypoxia-ischemia: 7/42 (16.7%) Blood group incompatibility: 5/42 (11.9%) Trisomy 21: 3/42 (7.1%) TPN-associated cholestasis (3/42 (7.1%) Neonatal hepatitis: 2/42 (4.8%) Metabolic liver disease: 1/42 (2.4%) Biliary atresia: 1/42 (2.4%) Portal venous thrombosis: 1/42 (2.4%) Unknown: 4/42 (9.5%)	
Author: Sarlik Y Year: 2003 Country: Turkey Ref ID: [86]	Study type: Case series Evidence level: 3	Diagnosis: Prolonged Jaundice Criteria: Jaundiced at day 14 Setting: Neonatal Intensive Care Unit Sample Size: 26 Mean GA: 38 weeks Mean BW: 3164 grams Gender M/F: 15/11 Ethnicity: Not reported Breastfeeding: 96% Mean age jaundice recognised: 19 days: Exclusion: Pre-term babies	Prevalence of prolonged jaundice/hyperbilirubinaemia 31/381 (8.1%) Median bilirubin levels TSB: 246 micromol/L Blood group incompatibility: 7/26 (26.9%) Breastmilk jaundice: 14/26 (53.8%) Possible Biliary Atresia : 1/26 (3.8%) referred to pediatric gastroenterology due to direct bilirubin Inadequate caloric intake: 4/26 (15.4%)	

Author: Hannam S Year: 2000 Country: UK Ref ID: [85]	Study type: Case series Evidence level: 3	Diagnosis: Prolonged Jaundice Criteria: jaundiced at day 14 Setting: Outpatient Sample Size: 154 GA (range): 39(37 – 43) weeks BW (range): 3.2 (1.98 – 4.8 kgs Gender M/F: 96/58 Ethnicity: 89 (57%) Caucasian, 36 (23%) Black, 20 (13%) Asian, 9 (6%) Mediterranean Breastfeeding: 96% Jaundice recognised: Older than 14 days: Exclusion: Not reported	Median bilirubin levels TSB: 179 micromol/L ABO incompatibility: 0/154 (0%) Incidence of G6PD deficiency: 3/59 (5.1%) Infection (UTI): 2/154 (1.3%) Idiopathic: Not reported	G-6-PD testing done where indicated by ethnic background of baby Clinical Examination by a Paediatrician is vital Recommended Investigations in prolonged jaundice • Total & unconugated bilirubin • PCV & G6PD level (where appropriate) • Urine microscopy & culture • Inspection of recent stool sample for bile pigmentation

Q6. Phototherapy

Bibliographic Information	Study Type & Evidence Level	Number of Patients/ Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)
Author: NICHHD Year:1985 Country: USA ID: [119]	Methodology: RCT Blinding: Not reported Randomisation: Random numbers table, Sealed envelopes Evidence level: 1++	N: 1339 Inclusion: BW <2000gms or BW between 2000 gms and 2500 gms and TSB >171 micromol/L in 96 hours or BW > 2500 and TSB > 222 micromol/L in 96 hours Exclusion: Rh hemolysis TSB > 171 micromol/L in 24 hours Babies with severe conditions / anomalies who care would be compromised by protocol Demographics: **BW less than 2000 gms** Gender (M/F) :Not reported Mean GA: Not reported Mean BW: Not reported Mean age at entry to study: 24.2 ± 8.0 hours Mean TSB: 97 ± 33 micromol/L **BW between 2000 gms and 2500 gms** Gender (M/F): 73/66 Mean GA: Not reported Mean BW: Not reported Age at entry to study: 62.6 ± 17.1 hours Mean TSB: 212 ± 37 micromol/L	Group 1: Usual care Group 2: Conventional phototherapy Conventional Phototherapy (Air Shields) consisted of 96 hours (with 30 min breaks every 4 hours for feeding etc) Daylight fluorescent bulbs 35 – 55cm above the baby. Baby naked and with eye pads (changed every 8 hours) Irradiance measured with a light monitoring badge Babies received 25ml/kg of body weight extra fluids	ET: **BW less than 2000 grams** Group 1: 22/462 Group 2: 110/460 **BW between 2000 gms and 2500 gms** Group 1: 3/70 Group 2: 18/71 **BW above 2500 gms** Group 1: 14/140 Group 2: 23/136 :	

		BW > 2500 Gender (M/F): 157/119 Mean GA: Not reported Mean BW: Not reported Age at entry to study: 64.8 ± 18.4 hours Mean TSB: 15.6 ± 2.49 MG/DL			
Author: Martinez J Year: 1993 Country: USA ID: [123]	Methodology: RCT Blinding: Not reported Randomisation: Computer-generated Evidence level: 1^+	N: 125 Inclusion: TSB > 291 micromol/L Exclusion: Congenital anomalies Neonatal complications Birthweight below 10^{th} percentile or above 90^{th} percentile Venous hematocrit >65% Significant bruising Large cephalhematoma Haemolytic disease Demographics: Gender (M/F):70/55 Mean GA: 39.2 ± 0.9 weeks Mean BW: 3404 ± 361gms Age at entry to study: Not reported Mean TSB: 306 ± 12 micromol/L	Group 1: Continue breastfeeding Group 2: Discontinue breastfeeding, substitute formula feeds Group 3: Discontinue breastfeeding, substitute formula feeds, add Conventional phototherapy Group 4: Continue breastfeeding, add phototherapy Conventional phototherapy Conventional Phototherapy consisted of Quartz halide spot unit Irradiance = 10microW/cm^2 Light band = 400 – 480 nm Babies were naked in a bassinette with their eyes patched Phototherapy discontinued at TSB < 231 micromol/L	ET: Group 1: 0/25 Group 2: 0/26 Group 3: 0/38 Group 4: 0/36 Treatment failure: Group 1: 6/25 Group 2: 5/26 Group 3: 1/38 Group 4: 5/36	TSB levels – change **Groups 1 + 2** 48 hours: -27 ± 43 micromol/L **Groups 3 + 4** 48 hours: -72 ± 380 micromol/L

Author: Sisson T Year: 1971 Country: USA ID: [120]	Methodology: RCT Blinding: Not reported Randomisation: Coin toss Evidence level: 1^-	N: 35 Inclusion: TSB > 162 micromol/L Exclusion: Sepsis, Cephalhaematoma Massive ecchymosis Demographics: Gender (M/F) :16/19 Mean GA: Not reported Mean BW: 2567 $\pm$ 709 gms Age at entry to study: Not reported Mean TSB: 193 micromol/L	Group 1: No treatment Group 2: Conventional phototherapy Conventional Phototherapy consisted of 10 (20 watt) fluorescent lamps Units were 45 cm above the baby and had a Plexiglas shields to block ultraviolet radiation. Canopies were vented so lamp heat was dissipated Babies removed for no more than 20 minutes a time for feeding etc Babies were naked except for eye shields and diapers Light band = 410 – 490 Phototherapy discontinued at TSB < 145 micromol/L	ET: Group 1: 2/14 Group 2: 3/21 Treatment failure: Group 1: 9/16 Group 2: 2/19	TSB levels – change Incomplete data Mean change in TSB: Incomplete data Time to max TSB (hours): Incomplete data
Author: Meloni T Year: 1974 Country: Italy ID: [122]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1^-	N: 24 Inclusion: TSB > 188 micromol/L Exclusion: Unclear Demographics: Gender (M/F): Not reported Mean GA: Not reported Mean BW: Not reported Age at entry to study: Not reported Mean TSB: 209 $\pm$ 24 micromol/L	Group 1:No treatment Group 2: Conventional phototherapy Conventional Phototherapy consisted of continuous phototherapy for 96 - 120 hours 8 cool white fluorescent tubes which deliver (at mattress level) 13.5 $\pm$ 3.5 watts/m^2	ET: Group 1: 6/12 Group 2: 2/12 Treatment failure: Group 1: 6/12 Group 2: 2/12	

Author: Ju S Year: 1991 Country: Taiwan ID: [124]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1^-	N: 29 Inclusion: TSB between 205 and 256 micromol/L Full term singletons Normal pregnancy Normal birth/caesarean Birthweight between 10^{th} and 90^{th} percentile Apgar scores $\geq$ 7 at 1 and 5 minutes Exclusion: Perinatal complication Congenital anomalies Possible haemolysis Demographics: Gender (M/F): 12/14 Mean GA: 39.0 $\pm$ 0.8 weeks Mean BW: 3364 $\pm$ 334 gms Age at entry to study: 97.2 $\pm$ 22.4 hours Mean TSB: 221 $\pm$ 13 micromol/L	Group 1: No treatment Group 2: Conventional phototherapy : Conventional Phototherapy consisted of a portable unit of 4 blue and 4 white 20-watt fluorescent lamps Irradiance at baby skin levels was 5-6microW/cm^2/nm Babies moved every 4 hours for feeding Phototherapy discontinued at TSB < 205 micromol/L	ET: Group 1: 0/13 Group 2: 0/13 Treatment failure: Group 1: 4/17 Group 2: 0/13	
Author: Lewis H Year: 1982 Country: UK ID: [121]	Methodology: RCT Blinding: Not reported Randomisation: Random numbers table Evidence level: 1^+	N: 40 Inclusion: Birthweight > 2500gms, Gestational Age > 37 weeks, TSB $\geq$ 250 micromol/L Exclusion: Perinatal asphyxia, Apgar score <5 at 4 minutes, Positive DAT test Demographics: Gender (M/F): 27/13	Group 1: Conventional Phototherapy Group 2: Conventional Phototherapy - Delayed (initiated if TSB rose to $\geq$ 320 micromol/L : Conventional Phototherapy consisted of a Vickers 80 white light phototherapy unit mounted 50 cm above the baby. Babies were blindfolded, naked except for a	ET: Group 1: 0/20 Group 2: 0/20 Treatment failure: Group 1: 0/20 Group 2: 3/20	

		Mean GA: Not reported Mean BW: 3200 ± 260 gms Age at entry to study: 84 hours Mean TSB: 263 micromol/L	napkin while nursing and were turned every 3 hours. Phototherapy discontinued at TSB < 250 micromol/L		
Author: Holtrop P Year: 1992 Country: USA ID: [141]	Methodology: RCT Blinding: Not reported Randomisation: Computer generated Evidence level: 1^+	N: 70 Inclusion: Birthweight <2500, Birthweight between 10^{th} and 90^{th} percentile, >24 1 day old, no congenital anomalies, no Rh incompatibility TSB >85 micromol/L at BW <1000gms TSB >103 micromol/L at BW 1000 - 1200gms TSB >120 micromol/L at BW 1200 - 1400gms TSB >137 micromol/L at BW 1400 - 1600gms TSB >1071 micromol/L at BW 1600 - 1800gms TSB >12 at BW 1800 - 2200gms TSB 12 - 15 at BW 2200 - 2500gms Exclusion: Not reported Demographics:	Group 1: Conventional phototherapy Group 2: Double phototherapy (Conventional phototherapy + Fiberoptic phototherapy) Single Conventional phototherapy consisted of either 1/ if baby was in an incubator, a standard unit (Olympic Bili-lite) with 4 white and 4 blue fluorescent lamps 35 cm above the baby. Irradiance at skin level was 9.2microW/cm^2/nm Light range was 425 – 475 Or 2/ if baby was on a radiant warmer, 3 halogen lights on each side(Air Shields7850) with an irradiance of 7microW/cm^2/nm Double phototherapy consisted of single Conventional phototherapy as above combined with a 'Wallaby' fiberoptic blanket measuring 10 X 35 cm. Mean irradiance on the blanket's surface was 8.2microW/cm^2/nm Babies wore eye patches and wore disposable diapers cut to allow maximum skin exposure Fluids were administered on clinician advice	ET: Group 1: 0/37 Group 2: 0/33 Kernicterus: Group 1: 0/37 Group 2: 0/33 Mortality: Group 1: 0/37 Group 2: 0/33 Rebound jaundice: Group 1: 14/37 Group 2: 12/33	Mean duration Group 1: Not reported Group 2: Not reported Mean change in TSB: Group 1:- 45 ± 18 micromol/L Group 2: - 28 ± 20 micromol/L
Author: Nuntnarumit P Year: 2002 Country: Thailand ID: [126]	Methodology: RCT Blinding: Not reported Randomisation:	N: 51 Inclusion: BW > 2500gms GA > 37 weeks TSB≥ 205 micromol/L at 24-48 hours TSB≥ 256 micromol/L at 49-72 hours	Group 1: Single Conventional phototherapy Group 2: Double Conventional phototherapy Single Conventional phototherapy consisted of	ET: Group 1: 0/27 Group 2: 0/24 Rebound jaundice: Group 1: 1/27 Group 2: 0/24	Mean duration Group 1: 43.7 ± 17.5 hours Group 2: 34.9 ± 12.6 hours Mean change in TSB: Group 1: -98 ± 46 micromol/L Group 2: - 156± 67 micromol/L

	Not reported Evidence level: 1-	TSB≥ 291 micromol/L at ≥72 hours Exclusion: Babies who had been on ventilator support or incubator, Babies who had been on phototherapy, Direct hyperbilirubinaemia Demographics: Gender (M/F) : 34/17 Mean GA: 38.7 ± 1.29 weeks Mean BW: 3104 ± 284 Age at entry to study 74.6 ± 27.4 Mean TSB: 316 ± 47 micromol/L	3 daylights and 2 blue lights 38 cm above the baby. Double Conventional phototherapy consisted of single phototherapy plus an additional bank of 8 20watt daylight fluorescents lamps 32 cm below the baby. A ventilated fan was used to prevent overheating Target irradiance was 9-10microW/cm^2/nm Phototherapy was discontinued when TSB <205 micromol/L at <96 hours of age or TSB <256 micromol/L at > 96 hours of age		Stools/day: Group 1: 2.8 ± 1.7 Group 2: 2.2 ± 1.4
Author: Boonyarittipong P Year: 2008 Country: Thailand ID: [127]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1-	N: 60 Inclusion: Full term (37–42 weeks), Birthweight >2500gms, Apgar > 6 T 1 and 5 minutes TSB between 222 -340 micromol/L, Nonhemolytic hyperbilirubinaemia Exclusively breastfed, Exclusion: Not reported Demographics: Gender (M/F): 32/28 Mean GA: 38.6 ± 1.15 weeks Mean BW: 3130 ± 311 gms Age at entry to study Not reported Mean TSB: 260 ± 30 micromol/L	Group 1: Single Conventional phototherapy Group 2: Double Conventional phototherapy Single Conventional phototherapy consisted of 4 blue and 2 daylight fluorescent lamps at least 30 cm above the baby Mean irradiance was 32.7 ± 2.6microW/cm^2/nm Baby wore eye patches and cotton diapers Double Conventional phototherapy (Neonatal Jaundice phototherapy apparatus/XHZ) was single phototherapy and an additional bank of 4 blue fluorescent lamps 25 cm beneath the bassinette. A fan was used to prevent overheating Mean irradiance of overhead unit was 33.7 ± 1.6microW/cm^2/nm and not reported for the unit underneath the baby	ET: Group 1: 0/30 Group 2: 0/30 Treatment failure: Group 1: 0/30 Group 2: 0/30	Mean change in TSB: Group 1: -111 ± 39 micromol/L Group 2: -144 ± 36 micromol/L Stools/day: Group 1: 2.8 ± 1.7 Group 2: 2.2 ± 1.4

			Phototherapy was discontinued at TSB < 222 micromol/L or phototherapy >48 hours		
Author: Sarici S Year: 2001 Country: Turkey ID: [129]	Methodology: RCT Blinding: Blind allocation Randomisation: Sequential Evidence level: 1^+	N: 100 Inclusion: Birthweight > 2500 gms, Nonhemolytic indirect hyperbilirubinaemia, Normal Reticulocyte count, Negative DAT, No evidence of blood group isoimmunization TSB ≥ 256 micromol/L Exclusion: Direct hyperbilirubinaemia, Enclosed haemorrhage, Infection, congenital malformations Demographics: Gender (M/F): 54/46 Mean GA: 39.0 + 0.7 weeks Mean BW: 3380 + 359 gms Age at entry to study 105.4 + 42.8 hours Mean TSB: 308 ± 47 micromol/L	Group 1: Conventional phototherapy Group 2: Fiberoptic phototherapy Conventional Phototherapy (Ohio Medical Products) consisted of a bank of 5 daylight fluorescent lamps 30cm above the baby Fiberoptic phototherapy (Walley II Phototherapy System) consisted of a single pad (7.6 X 35.5 cm) Babies in both groups were placed in a prone position and all babies wore disposable diapers. Babies in the phototherapy group wore eye patches Irradiance and light range were not reported Phototherapy considered to have failure if two consecutive measures showed an increase in TSB	ET: Group 1: 0/50 Group 2: 0/50 : Erythema: Group 1: 1/50 Group 2: 1/50 Watery stools: Group 1: 3/50 Group 2: 3/50 Rebound jaundice: Group 1: 3/50 Group 2: 2/50 Treatment failure: Group 1: 0/50 Group 2: 4/50	Mean duration: Group 1: 49.4 ± 14.4 hours Group 2: 61.0 ± 13.1 hours Mean change in TSB: Group 1: 125 ± 39 micromol/L Group 2: 111 ± 42 micromol/L
Author: Gale R Year: 1990 Country: USA ID: [130]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1^-	N: 42 Inclusion: Full-term (>37 weeks), No haemolytic jaundice TSB > 200 micromol/L but if babies had rapidly increasing TSB levels they could be entered into the study before they reached 200 micromol/L Exclusion: Evidence of hemolysis Demographics: Gender (M/F): Not reported Mean GA: 39.6 ± 1.6 weeks	Group 1: Conventional phototherapy Group 2: Fiberoptic phototherapy Conventional Phototherapy (Air Shields PT 53-3) consisted of a standard phototherapy unit (both daylight and blue lamps) positioned above the baby. Babies were naked, with eyes covered, and were alternate between prone and supine position every 6 hours. Irradiance at blanket level was 7.0 ± 0.5microW/cm^2/nm.	ET: Group 1: 0/22 Group 2: 0/20	Mean duration of phototherapy Group 1: Not reported Group 2: Not reported

		Mean BW: 3197 ± 475 Age at entry to study Not reported Mean TSB: 186 ± 86 micromol/L	Fiberoptic phototherapy (Wallaby Phototherapy System) consisted of a single fiberoptic pad linked to a lightbox with 150-watt halogen lamp and a fan with 150.ft^2/minute air volume. Irradiance spectrum was between 425 and 475 nm. Irradiance at blanket level was 7.0 ± 0.5microW/cm^2/nm. Babies were placed naked on the blanked. While nursing the mother could hold the baby wrapped in the blanket In both group babies were kept on phototherapy for 48 hours but could be withdrawn at any stage.		
Author: Dani C Year: 2004 Country: Italy ID: [143]	Methodology: RCT Blinding: Not reported Randomisation: Allocation method not reported but sealed envelopes used Evidence level: 1$^-$	N: 23 Inclusion: Preterm (GA < 34 weeks), No haemolytic jaundice, not on respiratory support, Clinically stable. Exclusion: Major congenital malformations, patent ductus arteriosus, intracranial haemorrhage, Perinatal asphyxia, receiving cardiovascular drugs Demographics: Gender (M/F): Not reported Mean GA: 31.0 ± 1.8 weeks Mean BW: 1468 ± 400 gms Age at entry to study 63.2 ± 15.0 hours Mean TSB: 241 ± 9 micromol/L	Group 1: Conventional phototherapy Group 2: Fiberoptic phototherapy Conventional Phototherapy consisted of a Photo-Therapie 800 system. Baby was naked except for eye patches and in a supine position. Irradiance and light range not reported Fiberoptic phototherapy (BiliBlanket) consisted of a mat that covered the baby up to the upper abdomen. Irradiance and light range not reported To avoid trans-epidermal water loss the babies were placed in incubators with a thermo-monitoring system to maintain normal body temperature (46.5^{o}C) at a relative humidity of 60%.	ET: Group 1: 0/12 Group 2: 0/11	Mean duration of phototherapy Group 1: 43.0 ± 3.1 hours Group 2: 38.7 ± 4.5 hours Mean change in TSB: Group 1: -69 ± 13 micromol/L Group 2: -62 ± 17 micromol/L
Author: Al-Alaiyan S Year: 1996 Country:	Methodology: RCT Blinding: Not reported	N: 46 Inclusion: GA > 36 weeks, Nonhemolytic jaundice Age > 1 day,	Group 1: Conventional phototherapy Group 2: Fiberoptic phototherapy	ET: Group 1: 0/15 Group 2: 0/16 Group 3: 0/15 Rebound jaundice:	Mean duration of phototherapy Group 1: 52.8 ± 24.8 hours Group 2: 47.5 ± 24.8 hours Group 3: 50.7 ± 24.8 hours Mean change in TSB:

Saudi Arabia ID: [125]	Randomisation: Allocation method not reported but shuffled, sealed envelopes used Evidence level: 1^-	Normal hemoglobin, No evidence of blood group incompatibility, Exclusion: Not reported Demographics: Gender (M/F): 23/23 Mean GA: 37.9 ± 2.08 weeks Mean BW: 2921 ± 696 gms Age at entry to study 37.9 ± 24.1 hours Mean TSB: 185 ± 56 micromol/L	Group 3: Combined phototherapy and fiberoptic phototherapy Conventional Phototherapy (Air Shields Fluoro-Lite) consisted of a standard unit of blue and white fluorescent bulbs 50 cm from the baby. Mean irradiance was 11.6 ± 2.2microW/cm^2/nm Light range = 425 – 475 nm Phototherapy was interrupted for feeding etc for an average of 115 minutes per day. Babies were naked except for eye patches. Fiberoptic phototherapy (BiliBlanket) consisted of a halogen lamp linked to a fiberoptic blanket. Mean irradiance was 22.3 ± 2.2microW/cm^2/nm Light range = 400 – 500 nm Fiberoptic phototherapy was continuous. Combined therapy consisted of both conventional and fiberoptic phototherapy as above.	Group 1: 0/15 Group 2: 0/16 Group 3: 0/15	Group 1: -14 ± 28 micromol/L Group 2: 19 ± 35 micromol/L Group 3: -23 ± 39 micromol/L :
Author: Pezzati M Year: 2000 Country: Italy ID: [147]	Methodology: RCT Blinding: Clinician blinded Randomisation: Allocation method not reported but shuffled, sealed envelopes used Evidence level: 1^+	N: 39 Inclusion: Pre-term babies with hyperbilirubinaemia > 171 micromol/L Exclusion: Malformations, Perinatal asphyxia, Respiratory distress, renal or gastrointestinal abnormalities, Patent ductus arteriosus, hypotension, Hypertension, Infection, Anaemia, polycythemia Demographics: Gender (M/F): 21/18	Group 1: Conventional phototherapy Group 2: Fiberoptic phototherapy Conventional Phototherapy (Photo grph – Therapie 800) consisted of a standard unit of blue lamp with two filters (infrared and uiltraviolet) . Babies were naked except for eye patches. Fiberoptic phototherapy (BiliBlanket)	ET: Group 1: 0/19 Group 2: 0/20	

		Mean GA: 34.3 weeks Mean BW: 2101 grams Age at entry to study Not reported Mean TSB: Not reported			
Author: Holtrop P Year: 1992 Country: USA ID: [131]	Methodology: RCT Blinding: Not reported Randomisation: Computer generated Evidence level: 1^+	N: 26 Inclusion: Birthweight >2500 gms, Age > 1 day, No Rh incompatibility, Clinical need for phototherapy Exclusion: Not reported Demographics: Gender (M/F): 17/9 Mean GA: 38.1 ± 2.5 weeks Mean BW: 3377 ± 541 gms Age at entry to study 66.3 ± 19.4 hours Mean TSB: 231 ± 24 µmol/L	Group 1: Conventional phototherapy Group 2: Fiberoptic phototherapy Conventional phototherapy (Olympic Bili-lite) consisted of an overhead bank of 4 white and 4 blue 35 cm above the baby. Babies were naked except for diapers and eye patches. Babies were removed for feeding. Mean irradiance was 9.2 ± 0.9microW/cm^2/nm Fiberoptic phototherapy (Wallaby Phototherapy System) consisted of a cummerbund which was wrapped around the torso. Babies wore eye patches. Mean irradiance was 8.2 ± 1.2microW/cm^2/nm Babies were removed form the study if the TSB rose by more than 9 micromol/L/h	ET: Group 1: 0/14 Group 2: 0/12 Treatment failure: Group 1: 1/14 Group 2: 3/12	Mean duration of phototherapy Group 1: Not reported Group 2: Not reported :
Author: Pezzati M Year: 2002 Country: Italy ID: [132]	Methodology: RCT Blinding: Not reported Randomisation: Not report but sealed envelopes used Evidence level: 1^+	N: 41 Inclusion: Exclusion: Demographics: Gender (M/F) : Not reported Mean GA: 39.6 ± 1.2 weeks Mean BW: 3236 ± 425 gms Age at entry to study Not reported Mean TSB: 296 ± 32 µmol/L	Group 1: Conventional Phototherapy Group 2: Fiberoptic Phototherapy Conventional phototherapy ("Photo-Therapie 800") consisted of a unit incorporating a metal vapour discharge blue lamp with 2 filters (an infrared filter and a Plexiglas ultraviolet filter). A fan was fitted to remove heat generated by lamp. Fiberoptic phototherapy (BiliBlanket PT) consisted of a 140W quartz halogen lamp with a	ET: Group 1: 0/21 Group 2: 0/20	Mean duration of phototherapy Group 1: Not reported Group 2: Not reported Mean change in TSB: Group 1: -55 ± 16 micromol/L Group 2: -51 ± 23 micromol/L

			built-in dichroic reflector with low infrared and ultraviolet radiation reflectivity. Light range was restricted to 400 – 550 nm. All babies were naked in a supine position at a stabilized room temperature.		
Author: Romagnoli C Year: 2006 Country: Italy ID: [142]	Methodology: RCT Blinding: No reported Randomisation: Not reported but sealed envelopes used Evidence level: 1^+	N: 136 Inclusion: TSB> 103 micromol/L GA < 30 weeks Exclusion: Not reported Demographics: Gender (M/F): 72/64 Mean GA: 27.9 ± 1.4 weeks Mean BW: 1019 ± 283 gms Age at entry to study 38.3 ± 7.1 hours Mean TSB: 109 ± 5 micromol/L	Group 1: Conventional phototherapy Group 2: Fiberoptic (Wallaby) phototherapy Group 3: Fiberoptic (BiliBlanket) phototherapy Group 4: Combined conventional and Fiberoptic (Wallaby) phototherapy Conventional phototherapy consisted of standard phototherapy composed of 4 fluorescent lamps and 4 blue lamps 40cm above the baby. Irradiance at skin level was 22 – 24 microW/cm^2/nm. Babies were naked except for eye patches and disposable diapers. Baby position was changed from prone to supine and vice versa every 6 hours. Fiberoptic Wallaby phototherapy consisted of a 10.1 X 15.2 cm pad linked to a 150W quartz halogen lamp. A light filter is placed between the lamp and the fiberoptic bundle to allow only 400 – 550 nm range through. Irradiance at skin level was 8 – 10 microW/cm^2/nm. Baby position was changed from prone to supine and vice versa every 6 hours. Fiberoptic BiliBlanket phototherapy consisted of an 11 X 13 cm pad linked to a 150W tungsten halogen lamp. A light filter is placed between the lamp and the fiberoptic bundle to allow only 400 – 550 nm range through.	ET: Group 1: 2/33 Group 2: 2/35 Group 3: 1/35 Group 4: 0/33 Erythema: Group 1: 10/33 Group 2: 9/35 Group 3: 8/35 Group 4: 12/33 Treatment failure: Group 1: 2/33 Group 2: 4/35 Group 3: 1/35 Group 4: 0/33	Mean duration of phototherapy Group 1: 90.2 ± 24.3 hours Group 2: 92.1 ± 43.3 hours Group 3: 94.4 ± 43.3 hours Group 4: 75.1 ± 23.6 hours Max TSB: Group 1: 157 ± 43 micromol/L Group 2: 169 ± 56 micromol/L Group 3: 161 ± 44 micromol/L Group 4: 130 ± 22 micromol/L

			Irradiance at skin level was 35microW/cm^2/nm. Baby position was changed from prone to supine and vice versa every 6 hours. Combined phototherapy consisted of conventional phototherapy as above and the fiberoptic Wallaby system as above.		
Author: Tan K Year: 1997 Country: Singapore ID: [128]	Methodology: RCT Blinding: Not reported Randomisation: Lottery method Evidence level: 1$^+$	N: 171 Inclusion: Nonhemolytic jaundice, TSB > 256 micromol/L or >222 micromol/L before 48 hours, Exclusion: Not reported Demographics: Gender (M/F): 96/75 Mean GA: 38.5 ± 1.5 weeks Mean BW: 3114 ± 415 gms Age at entry to study 96.9 ± 30.9 days Mean TSB: 262 ± 17 micromol/L	Group 1: Conventional Phototherapy Group 2: Fiberoptic phototherapy - Standard Group 3: Fiberoptic phototherapy – Large Group 4: Fiberoptic phototherapy - Double Conventional phototherapy consisted of seven overhead daylight fluorescent lamps arrange din an arc 35cm above the baby. The baby was kept unclothed except for eye coverings. Irradiance was 6.73 microW/cm^2/nm The standard fiberoptic (BiliBlanket) phototherapy consisted of a pad, 11 X 20 cm (illuminated part was 11 X 13cm) which was used without its sheath and at maximal power. Irradiance was an average of 19.01 microW/cm^2/nm when measured at the centre and at the four corners. The standard fiberoptic phototherapy consisted of a pad, 11 X 24 cm (illuminated part was 11 X 16cm) which was used without its sheath and at maximal power. The irradiance was calculated to be 23% more than that of the standard fiberoptic pad. The double fiberoptic phototherapy consisted of two standard pads one on the back and one the	ET: Group 1: 0/44 Group 2: 0/42 Group 3: 0/43 Group 4: 0/42 Rebound jaundice: Group 1: 1/44 Group 2: 0/42 Group 3: 0/43 Group 4: 1/42 Treatment failure: Group 1: 0/44 Group 2: 4/42 Group 3: 3/43 Group 4: 0/42	Mean duration of phototherapy Group 1: 62.6 ± 24.8 hours Group 2: 87.0 ± 39.5 hours Group 3: 82.6 ± 38.3 hours Group 4: 64.8 ± 35.2 hours :

			front of the baby. Phototherapy was terminated when TSB <188 micromol/L on at least two occasions Phototherapy was deemed to have failed when TSB values exceeded start level on at least two occasions and when direct bilirubin was minimal < 0.6 MG/DL		
Author: Van Kamm A Year: 1998 Country: Netherlands ID: [144]	Methodology: RCT Blinding: Not reported Randomisation: Not reported but sealed envelopes used Evidence level: 1^+	N: 124 Inclusion: Preterm babies with birthweight <2000gms, Nonhaemolytic jaundice Exclusion: Prior phototherapy, Met criteria for exchange transfusion Demographics: Gender (M/F) : 72/52 Mean GA: 29.7 ± 2.4 weeks Mean BW: 1250 ± 353 gms Age at entry to study 26.5 ± 17.5 Mean TSB: 94 ± 36 micromol/L	Group 1: Conventional phototherapy Group 2: Fiberoptic phototherapy Conventional phototherapy consisted of 4 overhead fluorescent lamps arranged in an arc 40 cm above the baby. Baby was naked except for eye patches. The light range is in the 380 – 480 nm range. Irradiance level was 16 microW/cm^2/nm Fiberoptic phototherapy (Ohmeda BiliBlanket) consisted of a halogen lamp illuminating a flat mat using a fiberoptic attachment containing 2400 optic givers woven into the mat. Baby was naked. The illuminating part of the mat is 11 X 13 cm. The light range is in the 400 – 550 nm range. Irradiance level was 35 microW/cm^2/nm If TSB levels increased above predetermined cut-offs double phototherapy was started using conventional phototherapy as above.	ET: Group 1: 3/68 Group 2: 4/56 Treatment failure: Group 1: 27/68 Group 2: 29/56	Mean duration of phototherapy Group 1: Not reported Group 2: Not reported: Mean change in TSB: Group 1: -2 ± 25 micromol/L Group 2: -2 ± 20 micromol/L :
Author: Dani C Year: 2001 Country: Italy	Methodology: RCT Blinding: Not reported Randomisation: Not reported but sealed envelopes used	N: 20 Inclusion: Aged ≤ 3 days, Gestational age between 31 and 36 weeks, Clinically stable, No major congenital malformations	Group 1: Conventional phototherapy Group 2: Fiberoptic phototherapy Conventional phototherapy consisted of a Photo-Therapie 800	ET: Group 1: 0/10 Group 2: 0/10	Mean duration of phototherapy Group 1: 25.8 ± 3.4 hours Group 2: 24.0 ± 2.5 hours Mean change in TSB: Group 1: Incomplete data Group 2: Incomplete data

ID: [145]	Evidence level: 1+	Exclusion: Non-haemolytic jaundice Demographics: Gender (M/F): Not reported Mean GA: 34.4 ± 1.2 weeks Mean BW: 2600 ± 382 Age at entry to study 49.5 ± 2.9 hours Mean TSB: 227 ± 10 micromol/L	Fiberoptic phototherapy was an Ohmeda BiliBlanket which was wrapped around the baby's torso. Babies were naked except for eye patches and were in a supine position. Phototherapy was initiated when TSB > 220micromol/L and discontinued when TSB ≤ 170 micromol/L.		
Author: Morris B Year: 2008 Country: USA ID: [135]	Methodology: RCT Blinding: Single-blind – outcome assessors were unaware of allocation Randomisation: Computer-generated Evidence level: 1++	N: 1974 Inclusion: Birthweight between 5001 and 1000 grams Between 12 and 36 hurs of age Exclusion: Terminal condition (Ph <6.8 or persistent bradycardia with hypoxaemia for >2 hours), Previous phototherapy, Major congenital anomaly, Hydrops fetalis, Severe haemolytic disease, Congenital nonbacterial infection, Judgement at parents may be able to return for final assessment at 18 – 22 months Demographics: Gender (M/F) : 1013/961 Mean GA: 26.0 ± 2.0 weeks Mean BW: 777 ± 134 grams Mean age at entry to study: Not reported Mean TSB: Not reported for all babies	Group 1: Early Phototherapy – begun when Day 1 – 7 TSB > 85 micromol/L Day 8 – 14 TSB > 120 micromol/L Group 2: Phototherapy at TSB ≥ 137 micromol/L for BW 501 – 750 grams Or 171 micromol/L for BW 751 – 1000 grams TSB was measured daily. Irradiance was 15 – 40 µw/cm^2/nm and was increased if TSB > 222 micromol/L in BW 501 – 750 grams or TSB > 256 in BW 751 – 1000 grams Exchange transfusion was indicated TSB exceeded threshold after 8 hours of intensive phototherapy	ET: Group 1: 2/990 Group 2: 3/984 Intensive phototherapy: Group 1: 3/990 Group 2: 13/984 Mortality: Group 1: 209/990 Group 2: 201/984 **18 – 22 months** Mortality Group 1: 230/946 Group 2: 218/944 RR = 1.05 (95%CI: 0.90, 1.22) Neurodevelopmental impairment Group 1: 235/902 Group 2: 275/902 RR = 0.86 (95%CI: 0.74, 0.99)	Max TSB: Group 1: 120 ± 31 micromol/L Group 2: 168 ± 36 micromol/L
Author: Valdes O Year: 1971	Methodology: RCT Blinding: Not reported	N: 75 Inclusion: Birthweight < 2500 grams	Group 1: Phenobarbital Group 2: Phototherapy		Max TSB: Group 1: 96 ± 57 micromol/L Group 2: 58 ± 52 micromol/L Group 3: 63 ± 58 micromol/L Group 4: 140 ± 53 micromol/L

Country: USA ID: [136]	Randomisation: Not reported Evidence level: 1^-	Exclusion: Positive Coombs test, ABO incompatibility, Sepsis Demographics: Gender (M/F): Not reported Mean GA: Not reported Mean BW: 1766 grams Age at entry to study: Not reported Mean TSB: Not reported	Group 3: Phenobarbital + Phototherapy Group 4: No treatment		
Author: Costello S Year: 1994 Country: Australia ID: [146]	Methodology: RCT Blinding: Not reported Randomisation: Lottery method Evidence level: 1^+	N: 44 Inclusion: Gestational age between 27 and 36 weeks TSB > 125 micromol/L) (increased with age (hours) and birthweight Exclusion: Not reported Demographics: Gender (M/F): Not reported Mean GA: 32.0 $\pm$ 0.54 weeks Mean BW: 1614 $\pm$ 140 gms Age at entry to study 56.6 $\pm$ 37.0 hours Mean TSB: Not reported	Group 1: Conventional Phototherapy Group 2: Fiberoptic phototherapy Conventional phototherapy consisted of a standard system of four white and 4 blue fluorescent lamps 50cm above the baby with an intensity of 8 microW/cm^2/nm Fiberoptic phototherapy (BiliBlanket) with a constant setting of 35microW/cm^2/nm. Baby was nursed in an open cot or isolette and turned at regular intervals from prone to supine positions. Eyes pads were used for babies <1500gms.	ET: Group 1: 0/24 Group 2: 0/20 Treatment failure: Group 1: 3/24 Group 2: 1/20	Mean duration of phototherapy Group 1: 44.0 $\pm$ 42.8 hours Group 2: 42.0 $\pm$ 39.1 hours Max TSB: Group 1: 210 $\pm$ 58 micromol/L Group 2: 198 $\pm$ 53 micromol/L
Author: Bertini G Year: 2008 Country: Italy ID: [149]	Methodology: RCT Blinding: Not reported Randomisation: Not reported but sealed envelopes used Evidence level: $1+^-$	N: 31 Inclusion: TSB $\geq$ 171 micromol/L, Gestational ages < 34 weeks, Age $\leq$ 7days, Did not require respiratory support, Clinically stable Exclusion: Malformations, Perinatal asphyxia, Patent ductus arteriosus, intracranial	Group 1: Conventional phototherapy Group 2: LED Phototherapy Conventional phototherapy (Photo-Therapie 800) incorporating a metal vapour discharge blue lamp with two filters (an infrared cut-off filter and a Plexiglas ultraviolet cut-off filter). 20 cm above the baby. LED phototherapy (Natus NeoBlue system).	ET: Group 1: 0/14 Group 2: 0/17	Mean duration of phototherapy Group 1: 38.7 $\pm$ 5.0 hours Group 2: 34.0 $\pm$ 12.0 hours TSB levels – change Group 1: -62 $\pm$ 24 micromol/L Group 2: -55 + 5 micromol/L :

		haemorrhage, hypotension, Hypertension, Infection, Anemia (venous Hb<10g/dl), Polycythemia (venous Hb>22 g/dl), Infants receiving cardiovascular drugs. Demographics: Gender (M/F): Not reported Mean GA: 30.7 ± 2.0 weeks Mean BW: 1192 ± 238 gms Age at entry to study 64.4 ± 15.2 hours Mean TSB: 200 ± 16 micromol/L	Light range 450-470nm spectrum. Irradiance was at the intensive setting at 30-35 microW/cm^2/nm. Unit was placed 30cm above the baby. All babies were placed in incubators with a thermo-monitoring system to maintain a normal body temperature (36.5^{o}C) at a relative humidity of 60%. Babies received full enteral feeding with human milk. Babies were naked except for eye patches and were in a supine position. Phototherapy discontinued at <145 micromol/L		
Author: Seidman D Year: 2000 Country: Israel ID: [133]	Methodology: RCT Blinding: Open label study Randomisation: Computer generated Evidence level: 1+	N: 69 Inclusion: Full-term (Gestational age > 37 weeks), Jaundice according to AAP criteria for phototherapy Exclusion: None reported Demographics: Gender (M/F): Not reported Mean GA: Not reported Mean BW: Not reported Age at entry to study Not reported Mean TSB: 251 ± 77 micromol/L	Group 1: Conventional phototherapy Group 2: LED phototherapy Conventional phototherapy (Micro-lites PTL 68-1) units equipped with 3 halogen quartz bulbs. Irradiance was 5-6 microW/cm^2/nm. LED phototherapy consisted of 6 focussed arrays each with 100 3-mm blue LED's. Unit was placed 50cm above the baby, to achieve an irradiance of 5-6microW/cm^2/nm. All babies were placed in a crib and were naked except for diapers and eye coverings.	ET: Group 1: 0/35 Group 2: 0/34	Mean duration of phototherapy Group 1: 32.0 ± 17.0 hours Group 2: 31.0 ± 17.0 hours Mean change in TSB: Group 1: -44 ± 58 micromol/L Group 2: -44 ± 46 micromol/L
Author: Seidman D Year: 2003 Country: Israel ID: [134]	Methodology: RCT Blinding: Not reported Randomisation: Computer generated Evidence level: 1+	N: 114 Inclusion: AAP criteria for phototherapy, Exclusion: Not reported Demographics: Gender (M/F): Not reported Mean GA: 39.5 ± 1.5 weeks	Group 1: Conventional phototherapy Group 2: LED phototherapy - Blue Group 3: LED Phototherapy - Blue-Green Conventional phototherapy (Air Shields Micro-lites PTL 68-1) units equipped with 3 halogen	ET: Group 1: 0/57 Group 2: 0/25 Group 3: 0/22 Erythema: Group 1: 0/57 Group 2: 0/25 Group 3: 0/22	Mean duration of phototherapy Group 1: 35.4 ± 20.2 hours Group 2: 31.6 ± 19.6 hours Group 3: 39.2 ± 25.5 hours Mean change in TSB: Group 1: -44 ± 33 micromol/L Group 2: -39 ± 46 micromol/L Group 3: -41 ± 48 micromol/L

		Mean BW: Not reported Age at entry to study 53.9 ± 37.8 hours Mean TSB: 251 ± 73 micromol/L	quartz bulbs. Irradiance was 5-6 microW/cm^2/nm. Blue LED phototherapy consisted of 6 focussed arrays each with 100 3-mm blue LED's. Peak wavelength was 459nm with a half spectral width of 22nm. Unit was placed 50cm above the baby, to achieve an irradiance of 5-6microW/cm^2/nm. Blue-Green LED phototherapy consisted of 6 focussed arrays each with 100 3-mm blue-green LED's. Peak wavelength was 505nm with a half spectral width of 38nm. Unit was placed 50cm above the baby, to achieve an irradiance of 5-6microW/cm^2/nm. All babies were placed in open cribs and were naked except for diapers and eye coverings.		
Author: Martins B Year: 2007 Country: Brazil ID: [148]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1-	N: 88 Inclusion: Need for phototherapy according to birthweight Exclusion: Direct bilirubin >34 micromol/L Haemolytic jaundice, Ecchymosis, Malformations, Congenital infection Demographics: Gender (M/F):58/30 Mean GA: 33.6 ± 1.9 weeks Mean BW: 1998 ± 541 gms Age at entry to study 68.1 ± 25.5 hours Mean TSB: 179 ± 38 micromol/L	Group 1: Conventional Phototherapy Group 2: LED phototherapy Conventional phototherapy consisted of a single quartz-halogen lamp, with a dichroic reflector, positioned 50cm from the baby and illuminating a circle of 18cm diameter. Mean irradiance was 21 ± 6microW/cm^2/nm LED phototherapy consisted of the Super LED system positioned 30cm from the patient and illuminating an elliptical area of 38cm x 27cm diameter. Mean irradiance was 37 ± 9microW/cm^2/nm Phototherapy discontinued when TSB levels decreased 30% from original levels Treatment was considered to have failed if TSB	ET: Group 1: 0/44 Group 2: 0/44 Erythema: Group 1: 0/44 Group 2: 0/44 Treatment failure: Group 1: 0/44 Group 2: 0/44	Mean duration of phototherapy Group 1: 63.8 ± 37 hours Group 2: 36.8 ± 21 hours TSB levels – change 24 hours Group 1: -22 ± 25 micromol/L Group 2: -50 ± 26 micromol/L

			continued to rise and reached a level 30% below TSB levels required for exchange transfusion.		
Author: Ebbesen F Year: 2007 Country: Denmark ID: [150]	Methodology: RCT Blinding: Not reported Randomisation: Not stated but sealed envelopes used Evidence level: 1^+	N: 141 Inclusion: Preterm infants (28 – 36.6 weeks), Age > 24 hours, No previous phototherapy, Non-haemolytic hyperbilirubinaemia Exclusion: Not reported Demographics: Gender (M/F): 80/61 Mean GA: 33.8 ± 2.49 weeks Mean BW: 2078 ± 605 gms Age at entry to study 74.0 ± 31.9 hours Mean TSB: 221 ± 60 micromol/L	Group 1: Blue phototherapy Group 2: Turquoise phototherapy Treatment duration was fixed (24 hours) Phototherapy consisted of either 8 blue fluorescent lamps (20 W, 60 x 3.7cm) 41 cm above the baby or 8 turquoise fluorescent lamps (18 W, 60 x 2.6cm) 41 cm above the baby. Distance from baby was different to ensure irradiance was identical in both groups Phototherapy was continuous with breaks for feeding etc Babies were naked except for eye patches and diapers	ET: Group 1: 0/69 Group 2: 0/72	Mean change in TSB: Group 1: -78 ± 31 micromol/L Group 2: -92 ± 31 micromol/L
Author: Ebbesen F Year: 2003 Country: Denmark ID: [151]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1^-	N: 85 Inclusion: Preterm infants (28 – 36.8 weeks), Age > 24 hours, Non-haemolytic hyperbilirubinaemia Exclusion: Not reported Demographics: Gender (M/F): 49/36 Mean GA: Not reported Mean BW: Not reported Age at entry to study Not reported Mean TSB: Not reported	Group 1: Blue phototherapy Group 2: Turquoise phototherapy Treatment duration was fixed (48 hours) Phototherapy consisted of either 6 blue + 2 daylight fluorescent lamps 32 cm above the baby or 6 turquoise + 2 daylight fluorescent lamps 32 cm above the baby. Irradiance for turquoise lamps was 2.72 ± 0.25 mW/cm^2 Irradiance for blue lamps was 3.52 ± 0.33 mW/cm^2 Irradiance for white lamps was 0.56 ± 0.07 mW/cm^2		:

			Phototherapy was continuous with breaks for feeding etc Babies were naked except for eye patches and diapers		
Author: Ayyash H Year: 1987 Country: Greece ID: [152]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1-	Study 1: Full-term N: 200 Inclusion: Idiopathic jaundice Exclusion: Haemolytic jaundice Demographics: Gender (M/F): Not reported Mean GA: 38.9 ± 0.14 weeks Mean BW: 3394 ± 43 gms Age at entry to study 101.8 ± 4.32 hours Mean TSB: 286 ± 60 micromol/L Study 2: Pre-term N: 62 Inclusion: Idiopathic jaundice Exclusion: Haemolytic jaundice Demographics: Gender (M/F): Not reported Mean GA: 34.6 ± 0.36 weeks Mean BW: 2361 ± 102 gms Age at entry to study 85.6 ± 5.52 hours Mean TSB: 239 ± 16 micromol/L	Group 1: Blue Phototherapy Group 2: Green Phototherapy Phototherapy consisted of 5, either green or blue, fluorescent tubes mounted on a conventional phototherapy unit.		**Study 1 – Full-term** Mean duration of phototherapy Group 1: 49.88 ± 3.02 hours Group 2: 42.68 ± 2.74 hours Mean change in TSB: Group 1: -39 ± 2 micromol/L Group 2: -43± 2 micromol/L **Study 2 – Pre-term** Mean duration of phototherapy Group 1: 53.29 ± 5.9 hours Group 2: 53.26 ± 5.52 hours Mean change in TSB: Group 1: -34 ± 6 micromol/L Group 2: -38 ± 8 micromol/L

Author: Amato M Year: 1991 Country: Switzerland ID: [153]	Methodology: RCT Blinding: Not reported Randomisation: Random-numbers table Evidence level: 1^+	N: 30 Inclusion: Idiopathic hyperbilirubinaemia TSB ≥ 250 micromol/L Exclusion: Perinatal asphyxia, Apgar < 4 at 1 minute and <6 at 5 minutes, Signs of haemolytic disease, secondary hyperbilirubinaemia Demographics: Gender (M/F): 13/17 Mean GA: 39.0 ± 1.03 weeks Mean BW: 3395 ± 547 gms Age at entry to study 70.5 ± 23,1 hours Mean TSB: 291± 35 micromol/L	Group 1: Blue Phototherapy Group 2: Green Phototherapy Phototherapy consisted of either blue or green fluorescent tubes 30cm above the mattress. The baby was placed naked, except for eye patches and gonadal protection, on a Plexiglas surface. Light spectral range of green tubes was 350-650 nm and 300-600 for the blue tubes Babies were supplemented with 5% glucose (15mg/kg per day) Phototherapy discontinued at TSB < 200 micromol/L Rebound jaundice was a rise of 17 micromol/L after phototherapy discontinuation	ET: Group 1: 0/15 Group 2: 0/15 Rebound jaundice: Group 1: 12/15 Group 2: 3/15	Mean duration of phototherapy Group 1: 34 ± 10 hours Group 2: 70 ± 23 hours Mean change in TSB: Group 1: -157 ± 22 micromol/L Group 2: -154 ± 31 micromol/L
Author: Vecchi C Year: 1986 Country: Italy ID: [154]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1^-	N: 84 Inclusion: Hyperbilirubinaemia Exclusion: Blood group incompatibility, Haemolytic disease, Respiratory distress, Sepsis Demographics: Gender (M/F): Not reported Mean GA: 35 weeks Mean BW: 1930 gms Age at entry to study Not reported Mean TSB: 227 ± 40 micromol/L	Group 1: Blue Phototherapy Group 2: Green Phototherapy Phototherapy units consisted of 8 (blue or green) fluorescent tubes positioned 46 cm above the mattress. The total power irradiance reaching the baby through two plastic shields was 2.3 mW/cm^2 for green phototherapy and 3.2 mW/cm^2 for blue phototherapy Phototherapy was continuous except for feeding etc Babies were placed in an incubator		TSB levels – change 24 hours: Group 1: -50 ± 23 micromol/L Group 2: -48 ± 26 micromol/L
Author: Sisson T Year: 1972	Methodology: RCT Blinding:	N: 72 Inclusion: TSB ≥ 150 micromol/L	Group 1: Blue Phototherapy Group 2:	Incomplete data for all outcomes	Mean duration of phototherapy Group 1: 46 ± 15.7 hours Group 2: 40 ± 18.3 hours Group 3: 75 ± 29.4 hours

Country: USA ID: [155]	Not reported Randomisation: Random numbers Evidence level: 1^-	Exclusion: Sepsis, Respiratory distress, Blood group incompatibility, Haemolytic disease Demographics: Gender (M/F): Not reported Mean GA: Not reported Mean BW: 2097 gms Age at entry to study Not reported Mean TSB: 190 micromol/L	Special Blue phototherapy Group 3: White phototherapy Each phototherapy unit consisted of 10 fluorescent tubes. Irradiance for blue lamps was 0.91 mW/cm^2 Irradiance for special blue lamps was 2.9 mW/cm^2 Irradiance for white lamps was 0.32 mW/cm^2 Babies wore eye patches Phototherapy was continuous except for breaks for feeding etc Phototherapy discontinued at a steady rate and reached TSB ≤ 137 micromol/L		
Author: Shinwell E Year: 2002 Country: Israel ID: [156]	Methodology: RCT Blinding: Not reported Randomisation: Not reported but sealed, opaque envelopes used Evidence level: 1^+	N: 32 Inclusion: Full-term, Birthweight > 2500gms, TSB > 308 micromol/L Exclusion: Congenital malformation Demographics: Gender (M/F): 8/22 Mean GA: 38 ± 1 weeks Mean BW: 3500 ± 478 gms Age at entry to study 104.2 ± 33.7 hours Mean TSB: 320 ± 17 micromol/L	Group 1: Supine position Group 2: Changing positions All babies received identical phototherapy for periods of 150 minutes followed by 30 minute breaks for feeding and routine nursing care. Babies in changing position group were alternated between supine and prone Phototherapy discontinued after two consecutive measurements TSB < 239 micromol/L	ET: Group 1: 0/16 Group 2: 1/16 Rebound jaundice: Not reported Treatment failure: Group 1: 0/16 Group 2: 1/16	Mean duration of phototherapy Group 1: 28 ± 9 hours Group 2: 40 ± 15 hours Mean change in TSB: Group 1: -114 ± 23 micromol/L Group 2: -108 ± 11 micromol/L
Author: Chen C Year: 2002 Country:	Methodology: RCT Blinding: Not reported Randomisation:	N: 51 Inclusion: TSB > 256 micromol/L, Absence of blood group incompatibility, Normal G-6-PD status,	Group 1: Supine position Group 2: Changing position		Mean duration of phototherapy Group 1: 53.3 ± 17.9 hours Group 2: 52.8 ± 20.2 hours Mean change in TSB: Group 1: -128 ± 54 micromol/L Group 2: -126 ± 45 micromol/L

Taiwan ID: [157]	Not reported but sealed envelopes used. Evidence level: 1+	Haemoglobin > 14g/dl Exclusion: Congenital anomalies, Significant bruising, Large cephalhematoma Demographics: Gender (M/F): 19/32 Mean GA: 38.2 ± 1.14 weeks Mean BW:3137 ± 384 gms Age at entry to study 143.4 ± 48.5 hours Mean TSB: Not reported	Phototherapy initiated at TSB ≥ 256 micromol/L and discontinued at TSB ≤ 171 micromol/L Babies in changing position group were alternated between supine and prone every 120 minutes		
Author: Mohammadzadeh A Year: 2004 Country: Iran ID: [158]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1-	N: 50 Inclusion: TSB ≥ 256 micromol/L (49-72 hours) TSB ≥ 291 micromol/L (>72 hours) Exclusion: Haemolytic disease, Congenital anomalies, Cephalhaematoma, Metabolic disease Demographics: Gender (M/F) : Not reported Mean GA: Not reported Mean BW: Not reported Age at entry to study Not reported Mean TSB: 321 ± 39 micromol/L	Group 1: Supine position Group 2: Changing position All babies received identical phototherapy for periods of 150 minutes followed by 30 minute breaks for feeding and routine nursing care. Babies in changing position group were alternated between supine and prone Phototherapy discontinued after two consecutive measurements TSB < 239 micromol/L		Mean change in TSB: Group 1: -68 ± 27 micromol/L Group 2: -62 ± 21 micromol/L
Author: Lau S Year: 1984 Country: Hong Kong ID: [159]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1-	N: 34 Inclusion: Full-term, Birthweight > 2500gms, TSB between 190 – 205 micromol/L Exclusion: Jaundice with known causes	Group 1: Continuous Phototherapy Group 2: Intermittent Phototherapy – 4 hours on - 4 hours off Group 3: Intermittent Phototherapy – 1 hour on - 3 hours off		Mean duration of phototherapy Group 1: 89.9 ± 54.2 hours Group 2: 86.7 ± 28.9 hours Group 3: 100.0 ± 61.0 hours

		Demographics: Gender (M/F): Not reported Mean GA: 39.9 ± 1.5 weeks Mean BW: 3229 ± 394 gms Age at entry to study Not reported Mean TSB: 198 ± 25 micromol/L	Phototherapy was discontinued when TSB < 171 micromol/L		
Author: Vogl T Year: 1978 Country: USA ID: [160]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1^-	N: 76 Inclusion: Birthweight between 1200 and 2400gms, TSB > 137 micromol/L Exclusion: Haemolytic anaemia, Positive Coombs tests, Respiratory distress syndrome Demographics: Gender (M/F) : Mean GA: 34.7 ± 2.0 weeks Mean BW: 1836 ± 299 gms Age at entry to study 56.8 ± 10.8 hours Mean TSB: 150 ± 19 micromol/L	Group 1: Continuous Phototherapy Group 2: Intermittent Phototherapy – 15 minutes on – 15 minutes off Group 3: Intermittent Phototherapy – 15 minutes on – 30 minutes off Group 4: Intermittent Phototherapy – 15 minutes on – 60 minutes off Therapy was discontinued when TSB < 137 micromol/L on two successive occasions		Mean duration of phototherapy Group 1: 64 ± 50 hours Group 2: 57 ± 45 hours Group 3: 79 ± 40 hours Group 4: 80 ± 50 hours
Author: Fok T Year: 1995 Country: Hong Kong ID: [161]	Methodology: RCT Blinding: Not reported Randomisation: Computer generated random numbers Evidence level: 1^+	N: 203 Inclusion: Gestational age > 35 weeks, Birthweight > 2300 gms, Exclusion: Other systemic illness, Eye infection, Haemolysis, Treatment with antibiotics, History of infection, Demographics: Gender (M/F): 106/97 Mean GA: 38.6 ± 2.56 weeks	Group 1: Eye patches Group 2: Head box Eye patches were obtained commercially, were removed during feeding and were replaced daily Head box consisted of an opaque plastic box (20 x 20 x 16cm). Holes were used for ventilation.	Prurient eye discharge Group 1: 23/102 Group 2: 9/101 Features of Conjunctivitis Group 1: 13/102 Group 2: 2/101	Mean duration of phototherapy Group 1: 67.2 ± 33.6 hours Group 2: 64.5 ± 26.6 hours HC Professional satisfaction: 76 (70.4%) of nurse preferred the head box while 17 (15.7%) preferred the eye patches.

		Mean BW: 3087 ± 611 gms Age at entry to study 89.5 ± 27.6 hours Mean TSB: 258 ± 27 micromol/L			
Author: Paludetto R Year: 1985 Country: Italy ID: [163]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1-	N: 38 Inclusion: Healthy normal labour and delivery, Single birth, No congenital malformation, Apgar > 7 at 5 minutes, Birthweight > 2500 gms, Full-term, Breast –feeding, No perinatal complications Exclusion: Babies in Special Care Unit, Haemolytic disease, Hypocalcaemia, Polycythemia Demographics: Gender (M/F): 24/14 Mean GA: 39 weeks Mean BW: 3395 gms Age at entry to study 66.5 hours Mean TSB 232 micromol/L	Group 1: Eye patches Group 2: Screen Screen consisted of an opaque fabric suspended from the head end of the bassinet with ribbons attached to both upper sides of the crib so that the head is covered and the fabric falls freely upon the shoulders and neck of the baby. Two other ribbons tied to the lower part of the fabric are attached with adhesive tape behind the neck in a way that the bay is free to move and the fabric does not create any tension in the neck.		Mean duration of phototherapy Group 1: 23.9 hours Group 2: 22.6 hours
Author: Wu P Year: 1974 Country: USA ID: [138]	Methodology: RCT Blinding: Not reported Randomisation: Randomised cards Evidence level: 1-	N: 120 Inclusion: Pre-term babies with birthweight between 1250 and 2000 grams Exclusion: Gross congenital anomalies, Haemolytic anaemias, Severe respiratory distress syndrome Demographics: Gender (M/F): 59/61	Group 1: No treatment Group 2: Phototherapy - continuous Group 3: Phototherapy – Intermittent Babies in phototherapy group received 5 days of phototherapy while in incubators Phototherapy consisted of 10 20w cool-white fluorescent lamps suspended 45cm above the	ET: Group 1: 0/40 Group 2: 0/40 Group 3: 0/40 Mortality: Group 1: 2/40 Group 2: 2/40 Group 3: 0/40	Max TSB: Group 1: 161 ± 51 micromol/L Group 2: 115 ± 34 micromol/L Group 3: 134 ± 32 micromol/L

		Mean GA: 34.0 ± 2.5 weeks Mean BW: 1736 ± 199 grams Mean age at entry to study: Not reported Mean TSB: Not reported	baby. Average irradiance during day was 0.05microW/cm^2/nm and at night was 0.01microW/cm^2/nm in the 400 – 500 nm wave band.		
Author: Curtis-Cohen M Year: 1985 Country: USA ID: [139]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1$^-$	N: 22 Inclusion: Pre-term babies Exclusion: Haemolytic disease, Direct hyperbilirubinaemia, sepsis Demographics: Gender (M/F) : Not reported Mean GA: 27.4 ± 1.4 weeks Mean BW: 858 ± 214 grams Mean age at entry to study: Not reported Mean TSB: Not reported	Group 1: Early Phototherapy Group 2: Delayed start of treatment – Phototherapy started at TsB >85.5micromol/L Phototherapy consisted of a broad spectrum white light from a tungsten-halogen lamp in a Model 1400 phototherapy unit. Irradiance was maintained at 12microW/cm^2/nm at 450nm	ET: Group 1: 0/11 Group 2: 0/11 Mortality: Group 1: 0/11 Group 2: 0/11	Max TSB: Group 1: 112 ± 27 micromol/L Group 2: 123 ± 20 micromol/L
Author: Leite M Year: 2004 Country: Brazil ID: [140]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1$^-$	N: 81 Inclusion: Birthweight <2000 grams Exclusion: Haemolysis, G-6-PD deficiency, Malformations, Intestinal obstructions, Cholestasis, congenital infections, Maternal or neonatal use of Phenobarbital, TCB > 256.5micromol/L Demographics: Gender (M/F) : 37/33 Mean GA: Not reported	Group 1: Early Phototherapy Group 2: Phototherapy at TsB ≥ 136.8micromol/L Phototherapy discontinued at TsB ≤ 85.5micromol/L Phototherapy consisted of fanem Mod 007 units equipped with 7 Philips fluorescent lamps (special blue), 400 – 540 nm Average irradiance was 14.4microW/cm^2/nm	ET: Group 1: 0/35 Group 2: 0/35	Max TSB: Group 1: 113 ± 49 micromol/L Group 2: 147 + 36 micromol/L

		Mean BW: Not reported Mean age at entry to study: Not reported Mean TSB: Not reported			
Author: Maurer H Year: 1973 Country: USA ID: [137]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1-	N: 69 Inclusion: Birthweight <2500 grams Exclusion: Positive Coombs test, Potential ABO incompatibility, sepsis Demographics: Gender (M/F) : 39/30 Mean GA: 34.2 ± 3.8 weeks Mean BW: 1860 ± 344 grams Age at entry to study: <24 hours Mean TSB: Not reported	Group 1: Agar – 125mg in first 4ml of formula beginning at 18 hours and continued at 3 hourly intervals for 4 days Group 2: Early phototherapy – Intermittent – 12 hours daily for 4 days Group 3: Early phototherapy – Continuous – 24 hours daily for 4 days Group 4: No treatment Phototherapy consisted of 8 blue fluorescent lamps (200 – 300 foot candles) 40 cm above the baby		Max TSB: Group 1: 118 ± 40 micromol/L Group 2: 108 + 36 micromol/L Group 3: 60 ± 42 micromol/L Group 4: 147 ± 57 micromol/L
Author: Wananukul S Year: 2002 Country: Thailand ID: [177]	Methodology: RCT Blinding: Not reported Randomisation: Nor reported Evidence level: 1-	N: 40 Inclusion: Preterm babies requiring phototherapy for hyperbilirubinaemia Exclusion: Skin disease, Respiratory distress Demographics: Gender (M/F) : 22/18 Mean GA: 33.1 ± 2.6 weeks Mean BW: 1444 ± 196 grams Mean age at entry to study: Not reported Mean TSB: 171 ± 39 micromol/L	Group 1: Clear topical ointment 3.0 ml (Vaseline:liquid paraffin = 1:1) Group 2: No ointment All babies were placed in incubators. Ointment was applied to the whole body, measurements taken from upper arms, back and legs. Evaporation rate was measured by a method based on the determination of the water vapour pressure gradient in the air layer closed to the skin surface. (Tewameter TM 210)		TEWL – at 5 hours Group 1: 7.5 ± 1.5 g/m^2/h Group 2: 8.9 ± 1.6 g/m^2/h
Author: Eggert P	Methodology: RCT	N: 101	Group 1: Conventional Phototherapy		Mean change in TsB (24 hours) Group 1: -56 ± 26 micromol/L

Year: 1988 Country: Germany ID: [165]	Blinding: Not reported Randomisation: Not reported Evidence level: 1^-	Inclusion: Uncomplicated hyperbilirubinaemia Exclusion: Age < 40 hours with ABO or Rh incompatibility, Babies who received antibiotics Demographics: Gender (M/F): 62/39 Median GA: 40 weeks Mean BW: Not reported Mean age at entry to study: Not reported Mean TSB: 243 ± 28 micromol/L	Group 2: Conventional Phototherapy + white curtains Group 3: Halide Phototherapy All babies were treated in intensive care incubators. Conventional phototherapy consisted of a Drager 76 unit equipped with 6 blue standard fluorescent lights (light range 410 – 520 nm) In the second group the four outer walls of the incubator were draped in white cloth The halide phototherapy consisted of a Drager 8000 halide lamp (light range 400 – 580 nm) All phototherapy units were 34cm above the mattress. Babies were naked except for a bikini diaper and blindfolds and were their position was changed every 4 hours. Phototherapy could be interrupted for nursing care and feedings. Babies received oral feedings of either mother's milk or adapted formula and dextrose solution.		Group 2: -80 ± 27 micromol/L Group 3: -55 ± 22 micromol/L
Author: Djokomuljanto S Year: 2006 Country: Malaysia ID: [164]	Methodology: RCT Blinding: Investigators blinded to allocation Randomisation: Block randomisation Evidence level: 1^+	N: 100 Inclusion: Term babies with uncomplicated jaundice requiring phototherapy Exclusion: TsB approaching criteria for exchange transfusion Demographics: Gender (M/F): 56/44 Mean GA: Not reported	Group 1: Conventional phototherapy Group 2: Conventional phototherapy + white curtains Conventional phototherapy consisted of Phoenix Medical Systems unit of 6 compact blue fluorescent lamps 45 cm above the baby. Curtains were hung on both sides if the phototherapy unit.		Mean change in TsB (4 hours) Group 1: -4 ± 24 micromol/L Group 2: -28 ± 25 micromol/L

		Mean BW: Not reported Mean age at entry to study: 105 ± 35 hours Mean TSB: 264 ± 59 micromol/L			
Author: Sivanandan S Year: 2009 Country: India ID: [166]	Methodology: RCT Blinding: Not reported Randomisation: Not reported but sealed opaque envelopes use Evidence level: 1^+	N: 84 Inclusion: Term babies with non-haemolytic jaundice on a postnatal ward of a tertiary level neonatal unit Age ≥ 24 hours and ≤ 20 days, 5 minute Apgar > 6, TSB < 359 micromol/L Exclusion: Hyperbilirubinaemia requiring exchange transfusion, Rh haemolysis, G-6-PD deficiency, Evidence of haemolysis, Positive Coombs' test, Major congenital malformation, Culture-positive sepsis, Need of intensive care Demographics: Gender (M/F): 47/35 Mean GA: 37.5 ± 1.3 weeks Mean BW: 2856 ± 345 grams Mean age at entry to study: 69 ± 36 hours Mean TSB: 280 ± 39 micromol/L	Group 1: Conventional phototherapy Group 2: Conventional phototherapy + white curtains Conventional phototherapy consisted of Phoenix Medical Systems unit of 4 blue and 2 white compact fluorescent lamps 45 cm above the baby. Light range was425 – 475 nm White plastic sheets could be attached to the sides of the unit Treatment failure was defined as TSB > 342 micromol/L Phototherapy was discontinued if If started after 72 hours of age after two consecutive TSB < 256 micromol/L If started before 72 hours of age after two consecutive were less than age-specific threshold for phototherapy TSB was measured for rebound after 8 hours	Phototherapy failure Group 1: 52 Group 2: 4/42 ET: Group 1: 0/10 Group 2: 0/10 Mortality: Group 1: 0/10 Group 2: 0/10	Mean change in TsB (24 hours) Group 1: -34 ± 63 micromol/L Group 2: -39 ± 56 micromol/L Mean duration of phototherapy Group 1: 24.9 ± 15.4 hours Group 2: 23.3 ± 12.9 hours
Author: Grunhagen D Year: 2002 Country: Netherlands ID: [176]	Methodology: Case series Blinding: None Randomisation: None Evidence level:	N: 18 Inclusion: Pre-term with non-haemolytic hyperbilirubinaemia Exclusion: None	All babies received phototherapy which consisted of a single quartz spotlight (Bililight Ohmeda) 55 cm above the baby. The irradiance was 12.5microW/cm^2/nm. Light range was 420 – 480 nm. TEWL was measured with a Tewameter TM210 (YSI Inc) and measurements taken on chest or back of the baby.		Mean change in TEWL 2.9 ± 3.9 g/m^2/h TEWL retuned to pre-phototherapy levels within 1 hour of discontinuation of phototherapy

	3	Demographics: Gender (M/F): / Mean GA: 30.6 ± 1.6 weeks Mean BW: 1412 ± 256 grams Mean age at entry to study: 120 ± 72 hours Mean TSB: Not reported	TEWL was measured when hyperbilirubinaemia was diagnosed and 60 minutes after initiation of phototherapy.		
Author: Wananukul S Year: 2001 Country: Thailand ID: [174]	Methodology: Comparative study Blinding: None Randomisation: None Evidence level: 2^-	N: 80 (40 with hyperbilirubinaemia who received phototherapy and 40 healthy controls) Inclusion: Term babies Exclusion: None Demographics: Gender (M/F): 44/36 Mean GA: 39.0 ± 1.2 weeks Mean BW: 3166 ± 435 grams Mean age at entry to study: Not reported Mean TSB: Not reported	Babies with hyperbilirubinaemia received conventional phototherapy in open cribs. Phototherapy consisted of 6 white and 2 blue fluorescent bulbs in a plexiglass-bottomed box 30cm above the baby. Irradiance was 10microW/cm^2/nm. TEWL was measured with a Tewameter TM 2/0 (Courage & Khazama) and measurements were taken at chest, interscapular and buttocks of the baby. Measurements were taken before phototherapy and repeated at 30 minutes and 6 hours during phototherapy.	ET: Group 1: Group 2: Mortality: Group 1: Group 2:	Mean change in TEWL PT: 1.2 ± 3.9 g/m^2/h Control: 0.2 ± 0.9 g/m^2/h TEWL retuned to pre-phototherapy levels within 1 hour of discontinuation of phototherapy
Author: Maayan-Metzeger A Year: 2001 Country: Israel ID: [175]	Methodology: Case series Blinding: None Randomisation: None Evidence level: 3	N: 31 Inclusion: Preterm with hyperbilirubinaemia Exclusion: Respiratory distress, Sepsis, Need for ventilatory support Demographics: Gender (M/F): 15/16 Mean GA: 31.2 weeks Mean BW: 1447 grams Mean age at entry to study: 106 hours Mean TSB: Not reported	All babies were nursed naked, except for eye pads, in incubators and received phototherapy.. Conventional phototherapy consisted of (Air Shields Micro-Lite) Light range was 400 – 500 nm. TEWL was measured usinga combined Tewameter and corneometer (Courage and Khazka) TEWL was measure in seven body areas; forehead, upper back, cubital fossa, palms, abdomen, soles, and inguinal region. Measurement were taken before start of phototherapy and repeated during phototherapy (at least 4 and up to 24 hours)		Mean change in TEWL PT: 4.3 ± 4.7 g/m^2/h
Author:	Methodology:	N:	Group 1:	Patent Ductus Arteriosus	

Rosenfeld W Year: 1986 Country: USA ID: [180]	RCT Blinding: Not reported Randomisation: Randomisation chart Evidence level: 1^+	74 Inclusion: Pre-term babies with gestational age between 26 and 32 weeks Exclusion: None Demographics: Gender (M/F):Not reported Mean GA: 29.4 weeks Mean BW: 2034 grams Mean age at entry to study: Not reported Mean TSB: micromol/L	Phototherapy Group 2: Phototherapy with Chest shields All babies were receiving early phototherapy to prevent hyperbilirubinaemia and were nursed under radiant warmers, receive mechanical ventilation for respiratory distress syndrome. Standard phototherapy units (Air Shields) were used Mean light intensity was 4.77microW/nm Chest shields were folded (doubled) piece of aluminium foil covered in a gauze pad and taped over the left chest.	Group 1: 23/38 Group 2: 11/36 Late mortality Group 1: 4/38 Group 2: 10/36	
Author: Tatli M Year: 2008 Country: Turkey ID: [169]	Methodology: Comparative study with healthy controls Blinding: None Randomisation: None Evidence level: 2^-	N: 47 (14 were healthy controls) Inclusion: Term babies with non-haemolytic hyperbilirubinaemia Exclusion: None Demographics: Gender (M/F):29/18 Mean GA: 39.3 $\pm$ 0.9 weeks Mean BW: 3021 $\pm$ 450 grams Mean age at entry to study: 113 $\pm$ 46 hours Mean TSB: Not reported	Phototherapy consisted of standard unit of 4 blue and 2 white fluorescent tubes (Air Shields) with a light range of 480 – 520 nm and an irradiance of 12microW/cm^2/nm. Phototherapy lasted 72 hours, babies whose TsB declined to normal levels before 72 hours were excluded.		Mean change in Lymphocyte-DNA damage PT: 29.1 $\pm$ 1.9 Control: 2.7 $\pm$ 2.9
Author: Berg P Year: 1997 Country: Sweden ID: [171]	Methodology: Retrospective matched case-control study Blinding: None Randomisation: None Evidence level:	N: 150 Inclusion: 30 cases of childhood cancer before 20 years of age and 120 controls Exclusion: None Demographics:		PT Cases: 0/30 Controls: 11/120	No increased risk of developing childhood malignant melanoma in skin of babies who received phototherapy

	2-	Gender (M/F):Not reported Mean GA: Not reported Mean BW: Not reported Mean age at entry to study: Not reported Mean TSB: Not reported			
Author: Matichard E Year: 2006 Country: France ID: [173]	Methodology: Case control study Blinding: Not reported Randomisation: Not reported Evidence level: 2-	N: 58 Inclusion: Primary school children (age 8 – 9) Exclusion: Not reported Demographics: Gender (M/F) 30/28 Mean GA: N/A Mean BW: NA Mean age at entry to study: N/A Mean TSB: N/A	Collected information included, Phototype (Fitzpatrick's classification), Behaviour in the sun, Sun protection policy, History of phototherapy for neonatal jaundice A melanocytic nevus count was conducted by a dermatologistpy The size of nevi was recorded <2mm, 2-5mm, >5mm	Received phototherapy = 18 Controls = 40	Mean melanocytic coun (nevus > 2mm): Phototherapy 3.5 ± 3.03 Controls:1.45 ± 1.99
Author: Turan O Year: 2004 Country: Turkey ID: [179]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1-	N: 98 Inclusion: Term and pre-term babies receiving phototherapy for hyperbilirubinaemia Exclusion: Congenital malformations, Sepsis, babies receiving positive inotropic drugs Demographics: Gender (M/F):Not reported Mean GA: 36.7 ± 3.2 weeks Mean BW: 2880 ± 803 grams Mean age at entry to study: Not reported Mean TSB: Not reported			No significant correlation found between heart rate, systolic blood pressure, diastolic blood pressure and mean blood pressure and serum nitric oxide and vascular endothelial growth factor.
Author: Speck W Year:	Methodology: Review Blinding:	Review of in vivo studies of effects of phototherapy on cell DNA			

1979 Country: USA ID: [168]	Not reported Randomisation: Not reported Evidence level: 1-				
Author: Weissman A Year: 2009 Country: Israel ID: [178]	Methodology: Before-after study Blinding: None Randomisation: None Evidence level: 3	N: 30 Inclusion: Jaundice GA = 37 – 42 weeks Apgar (1 min) > 7 Apgar (5 min) > 8 Exclusion: Haemolysis, G-6-PD, Fever, Maternal use of narcotic analgesic drugs during labour, Ruptured membranes > 18ours Demographics: Gender (M/F)16/14 Mean GA: 39.1 ± 1.5 weeks Mean BW: 3116 ± 392 grams Mean age at entry to study: 53 ± 31 hours Mean TSB: 238 ± 43 micromol/L	Phototherapy consisted of an overhead LED unit (neoBLUE) Irradiance was 34microW/cm^2/nm.		Heart Rate variability – SD1 Before: 12 ± 8 ms After : 8 ± 4ms P < 0.02 Heart Rate variability – SD2 Before: 33 ± 16 ms After : 22 ± 10 ms P < 0.01 Heart Rate variability – SDDN Before: 30 ± 14 ms After : 18 ± 7 ms P < 0.01 Heart Rate variability – RMSSD Before: 18 ± 12 ms After : 11 ± 6 ms P < 0.02
Author: Mahe E Year: 2009 Country: France ID: [172]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 2-	N: 828 Inclusion: Primary school children (age 8 – 9) Exclusion: Not reported Demographics: Gender (M/F) 415/413 Mean GA: N/A	Collected information included, Phototype (Fitzpatrick's classification), Behaviour in the sun, Sun protection policy, History of phototherapy for neonatal jaundice A melanocytic nevus count was conducted by trained nurses who was blind to whether the child had received phototherapy The size of exposed body parts (arm and back)was record <2mm, 2-5mm, >5mm	Received phototherapy = 180 Controls = 648	There was no difference in nevus counts as a function of exposure to neonatal phototherapy. Mean melanocytic count: Phototherapy 16.8 ± 9.8 Controls:16.7 ± 10.5

		Mean BW: NA Mean age at entry to study: N/A Mean TSB: N/A			
Author: Ayclcek A Year: 2008 Country: Turkey ID: [170]	Methodology: Case control study Blinding: Not reported Randomisation: Not reported Evidence level: 2^-	N: 65 Inclusion: Indirect hyperbilirubinaemia TSB > 222 micromol/L Exclusion: Severe congenital malformation, Prematurity or postmaturity, Maternal diabetes, Birth asphyxia, Sepsis, Haemolysis due to ABO/Rh incompatibility, Phototherapy before blood was collected, Bilirubin rising by more than 85 micromol./L day in first 24 hour, Tsb > 410 micromol/L Demographics: Gender (M/F) 35/28 Mean GA: Not reported Mean BW: Not reported Mean age at entry to study: Not reported Mean TSB: Not reported	Group 1: Intensive phototherapy Group 2: Conventional phototherapy Group 3: No phototherapy Phototherapy consisted of six white fluorescent tubes 40cm above the baby. 12-16 microW/cm^2/nm. Intensive phototehrpay consisted of 12 white fluorescent tubes 20cm above and below the baby. 30-34 microW/cm^2/nm. DNA damage was measured in blood samples taken after phototherapy. The images of 100 randomly selected nuclei (50 from each of two replicate slides) were analysed visually.		Mean duration of phototherapy: Group 1: 54 $\pm$ 6 hours Group 2: 61 $\pm$ 10 hours Group 3: N/A DNA damage (arbitrary units): Group 1: 32 $\pm$ 9 Group 2: 28 $\pm$ 9 Group 3: 21 $\pm$ 10 P < 0.001

Q7. Is it beneficial to give additional fluids (cup feeds, fluids) during treatment with phototherapy?

Bibliographic Information	Study Type & Evidence Level	Number of Patients/ Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)	Comments
Author: Tontisirin K Year: 1989 Country: Thailand ID: [187]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1^-	N: 25 Inclusion: Hyperbilirubinaemia TSB ≥ 256.5 micromol/L Exclusion: Not reported Demographics: Gender (M/F): Not reported Mean GA: Not reported Mean BW: 3185 ± 288 gms Age at entry to study: 95 ± 17.7 hours Mean TSB: Not reported	Group 1: Formula feed – *Enfamil (Energy = 20 kcal/oz, contains 1.5 g/dl protein, 3.7 g/dl fat, 7 g/dl carbohydrate, mineral 0.34 g/dl, water 87.4 g/dl)* Group 2: Lactose-free Formula feed - *Prosobee(Energy = 20 kcal/oz, contains 2 g/dl protein, 3.6 g/dl fat, 6.6 g/dl carbohydrate, mineral 0.3 g/dl, water 87.4 g/dl)* Babies were fed ad libitum with formula (3 ounces) 8 times/day.		Mean decrease in TsB: Group 1: -97 ± 41 micromol/L Group 2: -92 ± 46 micromol/L Weight gain/loss: Group 1: 33 ± 65 gms Group 2: -7 ± 55 gms	
Author: Mehta S Year: 2005 Country: India ID: [185]	Methodology: RCT Blinding: Not reported Randomisation: Stratified block randomisation (based on TsB levels) using sealed opaque envelopes Evidence level: 1^{++}	N: 74 Inclusion: Hyperbilirubinaemia TsB > 308 micromol/L Exclusion: TsB > 427 micromol/L, Kernicterus, Evidence of hemolysis, Signs of dehydration, Major congenital malformations, Babies on IV fluids Demographics: Gender (M/F): 52/22 Mean GA: 37.6 ± 0.9 weeks Mean BW: 2936 ± 473 gms Age at entry to study 130 ± 31 hours	Group 1: Phototherapy + Usual feeds Group 2: Phototherapy + Usual Feeds + Extra fluids Extra fluids consisted of IV fluid supplementation with N/5 saline in 5% dextrose for a period of 8 hours before phototherapy. After babies were offered 30mL/kg/day of extra oral feeds (expressed breast milk or formula) until phototherapy discontinued Phototherapy was discontinued when two TsB values obtain 12 hours apart were < 256 micromol/L Exchange transfusion was done if at 4 hours into the study TsB increased by > 34 micromol/L or if at 8 hours TsB remained > 342 micromol/L	Exchange Transfusions Group 1: 20/37 Group 2: 6/37	Mean decrease in TsB (24 hours): Group 1: -69 ± 28 micromol/L N = 17 Group 2: -95 ± 22 micromol/L N = 31 Mean duration of treatment: Group 1: 73 ± 31 hours Group 2: 52 ± 18 hours	

		Mean TSB: 350 ± 31micromol/L				
Author: Boo N Year: 2002 Country: Malaysia ID: [186]	Methodology: RCT Blinding: Not reported Randomisation: Stratified randomisation (type of feed, hydration status, and TsB levels) using sealed envelopes Evidence level: 1+	N: 54 Inclusion: TsB > 300 micromol/L with conjugated bilirubin ≤15% of TsB Exclusion: Sick babies, Major congenital malformations, Conjugated hyperbilirubinaemia, prolonged jaundice Demographics: Gender (M/F): 28/26 Mean GA: 39.4 ± 0.9 weeks Mean BW: 3075 ± 429 gms Age at entry to study: 139 ± 47 hours Mean TSB: 377 ± 66 micromol/L	Group 1: Phototherapy + Enteral feeds alone Group 2: Phototherapy + 50 % Enteral feeds + 50 % Intravenous feeds All babies received a daily maintenance fluid level of 90 mL/kg on day 2, 1290 mL/kg on day 3 and 150 mL/kg from day 4 onwards. They were also given an additional 10% of their respective total daily fluid requirement to compensate for the fluid loss. Enteral feeds group Formula-fed babies were given 8 divided feeds at 3 hour intervals. Breast-fed babies were breast-fed on demand. In addition they were given half of the calculated volume of formula feeds given to the formula fed babies. Enteral + Intravenous group Formula fed babies were given half of their 24hour fluid requirement at eight divided feeds at 3hour intervals. The remaining half of their daily fluid requirement was given as continuous intravenous1/5 normal saline and 5% dextrose infusion via a peripheral vein over 24 hours. Breastfed babies were breast-fed on demand. Half of their daily fluid requirement was given as continuous intravenous1/5 normal saline and 5% dextrose infusion via a peripheral vein over 24 hours.	Exchange Transfusions Group 1: 5/27 Group 2: 8/27 Mortality Group 1: 0/27 Group 2: 0/27	Mean decrease in TsB (4 hours): Group 1: -37 ± 44 micromol/L Group 2: -43 ± 37 micromol/L	
Author: Martinez J Year: 1993 Country: Argentina ID: [123]	Methodology: RCT Blinding: Not reported Randomisation: Computer-generated	N: 125 Inclusion: TSB >291micromol/L Exclusion: Congenital anomalies Neonatal complications Birthweight below 10th	Group 1: Continue breastfeeding Group 2: Discontinue breastfeeding, substitute formula feeds Group 3: Discontinue breastfeeding, substitute formula	ET: Group 1: 0/25 Group 2: 0/26 Group 3: 0/38 Group 4: 0/36 Treatment failure: Group 1: 6/25 Group 2: 5/26	Mean decrease in TsB (48 hours): Group 3: -77 ± 41 micromol/L Group 4: -65 ± 34 micromol/L	Only data from groups 3 and 4 used

	Evidence level: 1^{+}	percentile or above 90th percentile Venous hematocrit >65% Significant bruising Large cephalhematoma Haemolytic disease Demographics: Gender (M/F):70/55 Mean GA: 39.2 $\pm$ 0.9 weeks Mean BW: 3404 $\pm$ 361gms Age at entry to study: Not reported Mean TSB: 306 $\pm$ 12 micromol/L	feeds, add Conventional phototherapy Group 4: Continue breastfeeding, add Conventional Phototherapy Conventional Phototherapy consisted of Quartz halide spot unit Irradiance = 10µW/cm^2 Light band = 400 – 480 nm Babies were naked with eyes patched in a bassinette Phototherapy discontinued at TSB < 231 micromol/L	Group 3: 1/38 Group 4: 5/36		

Q10. How to monitor a baby with jaundice?

Q11. When to discharge a baby treated for hyperbilirubinaemia? What follow-up is required?

Author: Kaplan M Year: 2005 Country: Israel ID: [182]	Study Type: Clinical study Evidence Level: 3	Diagnosis Hyperbilirubinaemia Criteria: Need for phototherapy: according to AAP 1997 Setting Medical Center Demographics: Sample size: 226 Gender (M/F): 134/92 Mean GA: 39 ± 2 weeks Mean BW: 3204 ± 445 grams	Phototherapy criteria <24 hours 170 micromol/L 24-38 hours 205 micromol/L 48-72 hours 256 micromol/L >72 hours 291-308 micromol/L Babies with risk factors at 17 – 34 micromol/L below these levels For readmitted babies TsB ≥308 – 342 micromol/L Bilirubin routinely measured every 12 hours (checked more if clinical need) Phototherapy discontinued at 205 micromol/L or if TsB did not reach 205 once TsB stabilized and became lower than 75th centile on the hour specific nomogram Rebound Jaundice criteria TsB measured between 2 and 36 hours after discontinuation of phototherapy If TsB was ≥ 120% of post-phototherapy or ≥ 239 micromol/L were followed at 12-24 hour intervals Phototherapy was r-continued at clinician discretion but usually not below 256 micromol/L	**Primary phototherapy** Mean TsB at onset: 251 ± 53 micromol/L Age at onset 53 ± 29 hours Mean duration 43 ± 23 hours Mean TsB at discontinuation 182 ± 20 micromol/L Rebound Jaundice 30/196 (15.3%) **Phototherapy after readmission** Mean TsB at onset: 318 ± 22 micromol/L Age at onset 122 ± 38 hours Mean duration 30 ± 9 hours Mean TsB at discontinuation 182 ± 18 micromol/L Rebound Jaundice 0/30 (0.0%)	
Author: Barak M Year:	Study Type: RCT Evidence Level:	Diagnosis Hyperbilirubinaemia Criteria:	Once TsB reached criteria for phototherapy (AAP 2004) the baby was given phototherapy to two group for when phototherapy should be discontinued	Duration of phototherapy: Group 1: 22 ± 13 hours Group 2: 27 ± 12 hours	

2009 Country: Israel ID: [181]	1++	GA > 36 weeks BW > 2500 grams Setting Medical Center Randomisation method: Computer-generated block randomisation. Sequence was concealed until allocation was completed Blinding: Parents Demographics: Sample size: 52 Gender (M/F): 27/25 Mean GA: 38.7 ± 1.6 weeks Mean BW: 3302 ± 453 grams Mean TsB: 252 + 36 micromol/L	Group 1 TsB ≥ 17 micromol/L below threshold Group 2 TsB ≥ 51 micromol/L below threshold	Rebound level – 10 hours: Group 1: 1.8 ± 25.6 micromol/L Group 2: 4.8 ± 22.2 micromol/L Rebound level – 28 hours: Group 1: 19.1 ± 29.1 micromol/L Group 2: 11.6 ± 36.4 micromol/L Number requiring PT Group 1: 5/25 (20.0%) Group 2: 5/27 (18.5%)	

Q8. Exchange transfusion

Bibliographic Information	Study Type & Evidence Level	Number of Patients/ Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)	Comments
Author: Tan K Year: 1975 Country: Singapore ID: [193]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1^-	N: 52 Inclusion: Non-hemolytic jaundice Exclusion: Not reported Demographics: Gender (M/F): 28/24 Mean GA: 37.0 ± 2.78 weeks Mean BW: 2501 ± 576 gms Age at entry to study 84 ± 12 hrs Mean TSB: 297 ± 25 micromol/L	Group 1: Double Volume Exchange transfusion Group 2: Phototherapy Both treatments initiated at 256.micromol/L in pre-term babies and at 308 micromol/L in term babies Exchange transfusion was performed in the morning using the umbilical vein. Acid Citrate Dextrose blood (warmed to 37^oC) less than 5 days old was used. Volume was 170ml/kg body weight Daily TSB values from capillary blood were determined until stabilization at a safe level or an obviously decreasing trend were observed. Phototherapy consisted of seven fluorescent lamps Light spectral range = 400 – 500 nm Energy output range = 250 –330 $\mu W/cm^2$ Phototherapy discontinued at TSB < 188 micromol/L	Mortality: Group 1: 0/26 Group 2: 0/26 Treatment failure (repeated treatment) Group 1: 8/26 Group 2: 0/26 TSB < 188 micromol/L Group 1: 3/26 Group 2: 25/26	Mean decrease in TSB (24 hours): Group 1: -26 ± 24 micromol/L Group 2: -77 ± 17 micromol/L	
Author: Amato M Year: 1988 Country: Switzerland ID: [191]	Methodology: RCT Blinding: Not reported Randomisation: Random numbers table Evidence level:	N: 20 Inclusion: ABO incompatibility, Hyperbilirubinaemia Exclusion: Perinatal asphyxia, Congenital anomalies, Documented congenital	Group 1: Double Volume Exchange Transfusion Group 2: Single Volume Exchange Transfusion Blood preparation A unit of packed red cells was used. Mean blood volume of each unit was 280 + 40 ml (2/3 red cell volume and 1/3 plasma volume)	Mortality: Group 1: 0/10 Group 2: 0/10	Mean decrease in TSB: Group 1: -73 ± 33 micromol/L Group 2: -69 ± 20 micromol/L Duration of phototherapy (hours): Group 1: 38.1 ± 16.4 hours Group 2: 45.4 ± 17.7 hours Rebound level: Group 1: 74 ± 41 micromol/L Group 2: 65 ± 17 micromol/L	

	1-	infection, Suspected or proven bacterial infection, Respiratory distress, Secondary hyperbilirubinaemia (due to medications, polycythemia, skin hematomas or cephalhematoma) Demographics: Gender (M/F): 15/5 Mean GA: 39.5 ± 1.0 weeks Mean BW: 3305 ± 392 gms Age at entry to study 17.9 ± 6.13 hrs Mean TSB: 207 ± 45 micromol/L	Mean sodium was 168 ± 43 micromol/L Mean potassium 6.8 ± 1.4 micromol/L No immunoglobulin or clotting factors were present. Hemoglobin and hematocrit values were equally distributed between the two samples. Exchange transfusion was performed through the umbilical vein in 1 hour using a disposable exchange transfusion set in 10 ml portions. No additional calcium or human albumin given All babies received double phototherapy after exchange transfusion. Phototherapy consisted of a double blue light united (2 x 30μW/cm^2) mounted 30 cm above and under the mattress. Babies were nursed with 10%(120ml/kg) glucose Phototherapy discontinued at TSB < 205 micromol/L on two successive occasions. Rebound jaundice was defined as a rise of 17 micromol/L or more after treatment was discontinued.			
Author: Chan G Year: 1976 Country: Canada ID: [194]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1-	N: 42 Inclusion: Need for exchange transfusion Exclusion: Not reported Demographics: Gender (M/F): 25/17 Mean GA: 36.0 ± 0.7 weeks Mean BW: 2455 ± 153 gms Age at entry to study Not reported Mean TSB: 263 ± 82	Group 1: Double Volume Exchange Transfusion Group 2: Double Volume Exchange Transfusion + Albumin priming Double Volume Exchange Transfusion consisted of Acid Citrate Dextrose blood less than 48 hours old Albumin priming consisted 1 gm/kg of salt-poor human albumin given intravenously 1 hour prior to the exchange transfusion	Mortality: Group 1: 0/27 Group 2: 0/15	Mean decrease in TSB: Group 1: -193 ± 56 micromol/L Group 2: -168 ± 63 micromol/L Rebound level: Group 1: 74 ± 32 micromol/L Group 2: 92 ± 56 micromol/L	

		micromol/L				
Author: Grajwer L Year: 1976 Country: USA ID: [195]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1-	N: 43 Inclusion: Need for exchange transfusion Exclusion: Not reported Demographics: **>2500gms** Gender (M/F): Not reported Mean GA: 39.1 ± 1.8 weeks Mean BW:3234 ± 494 gms Age at entry to study Not reported Mean TSB: 328 ± 25 micromol/L **<2500gms** Gender (M/F): Not reported Mean GA: 32.6 ± 3.2 weeks Mean BW:1670 ± 434 gms Age at entry to study Not reported Mean TSB: 304 ± 48 micromol/L	**>2500gms** Group 1: Double Volume Exchange Transfusion of whole blood less than 5 days old Group 2: Frozen erythrocytes diluted in plasma **<2500gms** Group 1: Exchange transfusion of whole blood less than 5 days old Group 2: Frozen erythrocytes diluted in plasma Exchange transfusion criteria were 1/ Cord bilirubin >85.5 micromol/L and rapidly increasing by more than 8.5 micromol/L an hour) 2/ Increase of TSB >17.1 micromol/L per hour during first 24 hours if cord bilirubin is unknown 3/ Two repeated values of 342 micromol/L indirect bilirubin for babies > 2500 gms or 273.6 micromol/L in babies < 2500gms 4/ In sick premature babies with asphyxia or acidosis or receiving ventilatory assistance ET was performed at two repeated values of 356.5 micromol/L Exchange transfusion was repeated after two repeated values of 342 micromol/L indirect bilirubin for babies > 2500gms and 273.6 micromol/L for babies < 2500gms	**>2500gms** Mortality: Group 1: 0/5 Group 2: 1/8 **<2500gms** Mortality: Group 1: 1/14 Group 2: 3/16 **>2500gms** Repeat ET: Group 1: 1/5 Group 2: 1/8 **<2500gms** Repeat ET: Group 1: 4/14 Group 2: 7/16	**>2500gms** Mean decrease in TSB: Group 1: -144 ± 17 micromol/L Group 2: -149 ± 22 micromol/L **<2500gms** Mean decrease in TSB: Group 1: -156 ± 51 micromol/L Group 2: -177 ± 24 micromol/L	Sample was divided into 2 groups <2500gms and > 2500gms before randomisation
Author: Locham K Year: 2002 Country:	Methodology: CCT Blinding: None Randomisation:	N: 30 Inclusion: Jaundice requiring exchange transfusion	Group 1: Double Volume Exchange Transfusion Group 2: Double Volume Exchange Transfusion + Supplementary calcium		No jaundice related outcomes	Noted increased instances of bradycardia and fluctuations in heart rate after calcium injections. One baby had cardiac arrest.

India ID: [196]	None Evidence level: 1-	Exclusion: Not reported Demographics: Gender (M/F): Not reported Mean GA: Not reported Mean BW: Not reported Age at entry to study Hrs: Not reported Mean TSB: Not reported				
Author: Ahmed S Year: 2005 Country: India ID: [197]	Methodology: Case series Blinding: None Randomisation: None Evidence level: 1-	N: 198 Inclusion: Need for exchange transfusion Exclusion: None Demographics: Gender (M/F): 65/3 Mean GA: 34.5 weeks Mean BW: Not reported Age at entry to study Not reported Mean TSB: Not reported	Peripheral exchange transfusion Brachial or radial artery was cannulated with a 24G cannula under all aseptic conditions. A good peripheral or antecubital vein on the other side was cannulated with a 22G or a 24G angiocath. Citrate phosphate dextrose fresh blood was used for the procedure & and phototherapy was used pre & post exchange. Two operators carried out the procedure using aliquots of 5-10 ml on withdrawal; and infusion. Three way stop-cocks were used on either side and arterial catheter flushed with 0.5ml of heparin solution (5units/ml) after every 50ml. Procedure was performed under radiant warmer with monitoring of heart rate, respiratory rate, body temperature and oxygen saturation.	Reported decreased chances of sepsis, complete exchange and more safety in peripheral exchange transfusion/ It is also cost effective as only two angiocaths, two stop-cocks and two 10ml syringes are needed compared to a complete exchange set used in umbilical route.	:	
Author: Keenan W Year: 1985 Country: USA ID: [119]	Methodology: Cohort study Blinding: None Randomisation: None Evidence level: 2-	N: 190 Inclusion: Received an exchange transfusion Exclusion: None Demographics: Gender (M/F): Not reported Mean GA: Not reported Mean BW:		Adverse effects: :Transient bradycardia: 8 (4.2%) - 6 with calcium Transient cyanosis: 3 (1.6%) Transient vasospasm: 2 (1.0%) Vasospasm with thrombosis: 2 (1.0%) Apnea and/or bradycardia	Mean decrease in TSB after ET: 139 ± 30 micromol/L	NICCHD study

		Not reported Age at entry to study Not reported Mean TSB: Not reported		requiring treatment: 7 (3.7%) Mortality: One baby died with 6 hours of ET Three died with 24 hours of ET		
Author: Mollison P Year: 1952 Country: UK ID: [189]	Methodology: RCT Blinding: Not reported Randomisation: Random numbers, Sealed envelopes used Evidence level: 1^+	N: 137 Inclusion: Haemolytic disease of the newborn, Term babies Exclusion: Not reported Demographics: Gender (M/F): Not reported Mean GA: Not reported Mean BW: Not reported Age at entry to study Not reported Mean TSB: Not reported	Group 1: Exchange transfusion Group 2: Simple transfusion All exchange transfusion were carried out with 9 hours of birth, using a concentrated suspension of Rh-negative red cells (60ml/lb)	Mortality: Group 1: 8/62 Group 2: 21/57 Deaths due to kernicterus Group 1: 6/62 Group 2: 18/57 Kernicterus Group 1: 12/62 Group 2: 22/57		Data from one centre "N" used
Author: Armitage P Year: 1953 Country: UK ID: [190]	Methodology: RCT Blinding: Not reported Randomisation: Random numbers, Sealed envelopes used Evidence level: 1^+					Secondary publication of [189]
Author: Patra K Year: 2004	Methodology: Retrospective chart review Blinding: Not reported	N: 55 Inclusion: Babies who had an exchange transfusion,		Adverse Effects/ET Mortality: 1/66 Hypotension: 5/66 Seizures: 1/66 Platelets <50,000 µl/L : 29/66		

Country: USA ID: [198]	Randomisation: Not reported Evidence level: 3-	Hyperbilirubinaemia Exclusion: Poplycythemia, anaemia Demographics: Gender (M/F): 30/25 Mean GA: 35 ± 4 weeks Mean BW:2388 ± 973 grams Age at entry to study: Not reported Mean TSB: 307.8 ± 136.8 micromol/L		Calcium <8mg/dl: 19/66 Catheter malfunction: 6/66 Hypoglycemia: 2/66 Respiratory distress: 2/66 Bradycardia: 1/66 Hypokalemia: 1/66 Acute renal failure: 1/66 Omphalitis: 1/66		
Author: Wishingrad L Year: 1965 Country: USA ID: [188]	Methodology: RCT Blinding: Not reported Randomisation: Stratified randomisation And sealed envelopes used Evidence level: 1+	N: 100 Inclusion: Indirect serum Bilirubin > 307.8 micromol/L No anomalies, Less than 7 days old Exclusion: Not reported Demographics: Gender (M/F): Unclear Mean GA: Not reported Mean BW: Not reported Age at entry to study: Not reported Mean TSB: Not reported	Group 1: Double volume exchange transfusion Group 2: No treatment The double volume exchange transfusion (based on an estimated blood volume of 75ml/kg) was carried out with type specific blood, less than 72 hours old, and warmed to room temperature. The umbilical vein was cannulated with a plastic catheter and plastic disposable equipment used. 10ml aliquots were used. Small amounts (0.5ml) of 10% calcium gluconate were given after each 100ml of donor blood with continuous auscultation of the heart. All babies in exchange transfusion group received penicillin and streptomycin.	Mortality: Group 1: 3/50 Group 2: 3/50 Abnormal neurological examination (1 – 2 years) Group 1: 7/50 Group 2: 6/50		
Author: Jackson J Year: 1997	Methodology: Retrospective chart review Blinding: None	N: 106 Inclusion: Babies who had an exchange transfusion	Group 1: Exchange transfusion	Mortality:due to ET 2/106 (1.9 %) Permament serious sequelae due to ET 4/106 (3.8%)		

Country: USA ID: [199]	Randomisation: None Evidence level: 3-	Exclusion: None Demographics: Gender (M/F): Not reported Mean GA: 36.6 ± 3.6 weeks Mean BW: 2846 ± 806 grams Age at entry to study Not reported Mean TSB: Not reported		Serious prolonged sequelae due to ET 5/106 (4.7%) Serious transient sequelae due to ET 18/106 (17.0%) Asymptomatic treated complications 27/106 (25.5%) Asymptomatic laboratory complications 11/106 (10.4%)		

Q9. What are the other ways of treating hyperbilirubinaemia? Are they effective?

Bibliographic Information	Study Type & Evidence Level	Number of Patients/ Characteristics	Intervention & Comparison	Dichotomous outcomes (E:C)	Continuous Outcomes (Mean:SD: N)	Comments
Author: Pascale J Year: 1976 Country: USA ID: [212]	Methodology: RCT Blinding: Not reported Randomisation: Random numerical selection Evidence level: 1^+	N: 24 Inclusion: Hyperbilirubinaemia Exclusion: Not reported Demographics: Gender (M/F): 12/12 Mean GA: Not reported Mean BW: Not reported Age at entry to study: 71.3 + 24.1 hours Mean TSB: Not reported	Group 1: Phototherapy Group 2: Low-irradiance Phototherapy + Riboflavin Group 3: Phototherapy + Riboflavin Riboflavin was given for 6 hours prior to phototherapy and was discontinued after 24 hours of phototherapy. Riboflavin consisted of sodium phosphate 1.5mg/kg every 12 hours Phototherapy irradiance was 8 – 10 $\mu W/cm^2$ Low irradiance was Phototherapy irradiance was 6 – 7 $\mu W/cm^2$	:	Mean decrease in TSB (24 hours): Group 1: -53 ± 13.5 micromol/L Group 2: -52 ± 10.2 micromol/L Group 3: -89 ± 18.8 micromol/L	
Author: Pataki L Year: 1985 Country: Hungary ID: [213]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1^-	N: 28 Inclusion: ABO – Incompatible jaundice Exclusion: Not reported Demographics: Gender (M/F): Not reported Mean GA: Not reported Mean BW: 3338 ± 425 grams Age at entry to study: 50.2 ± 27.2 hours Mean TSB: 358 ± 71micromol/L	Group 1: Phototherapy Group 2: Phototherapy + Riboflavin Riboflavin (Vitamin B_2) was diluted by a three-fold volume of physiological saline and a single intravenous dose of 10mg/kg was given slowly.		Mean decrease in TSB (3 hours) Group 1: 32 ± 55 micromol/L Group 2: -87 ± 40 micromol/L	Subjects were awaiting exchange transfusion
Author: Yurdakok M	Methodology: RCT	N: 124	Group 1: Phototherapy		Mean decrease in TSB: Group 1: -55 ± 67.2 micromol/L	

Year: 1988 Country: Turkey ID: [214]	Blinding: Not reported Randomisation: Not reported Evidence level: 1-	Inclusion: Indirect hyperbilirubinaemia Exclusion: Those who received exchange transfusions Demographics: Gender (M/F): Not reported Mean GA: Not reported Mean BW: 3230 ± 502 grams Age at entry to study: 61.9 ± 11.0 hours Mean TSB: Not reported	Group 2: Phototherapy + Riboflavin Riboflavin (Vitamin B_2) was given as a single oral dose of 3mg/kg within 30 minutes of start of phototherapy.		Group 2: -85 ± 42.1 micromol/L Mean duration of treatment: Group 1: 45.7 ± 27.5 hours Group 2: 55.0 ± 31.1 hours	
Author: Ashkan M Year: 2007 Country: Iran ID: [200]	Methodology: RCT Blinding: Not reported Randomisation: Computerized using sealed opaque envelopes Evidence level: 1++	N: 90 Inclusion: Term babies, Birthweight between 2500 and 3500 grams, TsB between 292 and 425 micromol/L Exclusion: Congenital anomaly, Haemolytic disease, Infection, Dehydration, G-6-PD deficiency, Conjugated hyperbilirubinaemia Demographics: Gender (M/F): 47/43 Mean GA: 38.8 ± 1.6 weeks Mean BW: 2542 ± 547 grams Age at entry to study: 125 + 45.6 hours Mean TSB: 301 ± 23.4 micromol/L	Group 1: Phototherapy Group 2: Phototherapy + Low-dose clofibrate Group 2: Phototherapy + Moderate-dose clofibrate Clofibrate was administered in a single dose (either low-dose = 25mg/kg or moderate dose = 50mg/kg) orally in a mixture of corn oil 30 minutes before breastfeeding.	No side-effects were noted	Mean decrease in TSB (24 hours) : Group 1: -104 ± 14 micromol/L Group 2: -186 ± 13 micromol/L Group 3: -186 ± 16 micromol/L Mean duration of treatment: Group 1: 25.3 ± 4.4 hours Group 2: 14.2 ± 1.2 hours Group 3: 14.7 ± 1.5 hours	Clofibrate groups were combined
Author: Mohammadzadeh A	Methodology: RCT	N: 60	Group 1: Phototherapy	No adverse effects noted	Mean decrease in TSB: Group 1: -210 ± 44 micromol/L Group 2: -184 ± 37 micromol/L	

Year: 2005 Country: Iran ID: [201]	Blinding: Not reported Randomisation: Random numbers table Evidence level: 1+	Inclusion: Term, breastfed babies, TsB between 291 and 512micromol/L Exclusion: Congenital anomaly, Haemolytic disease, Dehydration, G-6-PD deficiency, Conjugated hyperbilirubinaemia Demographics: Gender (M/F):34/26 Mean GA: 38.7 ± 0.9 weeks Mean BW: 3259 ± 481 grams Age at entry to study: 216 ± 94.8 hours Mean TSB: 395 ± 58 micromol/L	Group 2: Phototherapy + Clofibrate Clofibrate was administered in a single oral dose (100mg/kg birthweight)		Mean duration of treatment: Group 1: 54 ± 18.8 hours Group 2: 30 ± 12.9 hours	
Author: Zahedpasha Y Year: 2007 Country: Iran ID: [203]	Methodology: RCT Blinding: No reported Randomisation: Not reported Evidence level: 1-	N: 60 Inclusion: Gestational age between 38 and 41 weeks, TsB between 256 and 427micromol/L Exclusion: Haemolytic disease, Rh or ABO incompatibility, G-6-PD deficiency, dehydration, Infection, Conjugated hyperbilirubinaemia, History of Phenobarbital intake by mother or infant Demographics: Gender (M/F): 28/32 Mean GA: Not reported Mean BW: Not reported	Group 1: Phototherapy + Placebo Group 2: Phototherapy + Clofibrate Subject in the clofibrate group received a single oral dose of clofibrate (100mg/kg) while the control group received distilled water in the same amount and colour.	No adverse effects were noted	Mean decrease in TSB: Group 1: -108 ± 24 micromol/L Group 2: -148 ± 20 micromol/L	

		Age at entry to study: 144 ± 71 hours Mean TSB: 305 ± 36micromol/L				
Author: Zahedpasha Y Year: 2008 Country: Iran ID: [204]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1^-	N: 40 Inclusion: G-6-PD deficiency, Gestation age between 38 and 41 weeks, Birthweight > 2500 grams TsB between 256 and 342 micromol/L Exclusion: Haemolytic disease, conjugated hyperbilirubinaemia, dehydration, infection, history of Phenobarbital intake by mother or infant Demographics: Gender (M/F): Not reported Mean GA: Not reported Mean BW: 3257 ± 479 grams Age at entry to study: 123 ± 55 hours Mean TSB: 307 ± 33micromol/L	Group 1: Phototherapy Group 2: Phototherapy + Clofibrate Subject in the clofibrate group received a single oral dose of clofibrate (100mg/kg)	No adverse effects were noted	Mean decrease in TSB: Group 1: -104 ± 29 micromol/L Group 2: -142 ± 26 micromol/L	
Author: Eghbalian F Year: 2007 Country: Iran ID: [202]	Methodology: RCT Blinding: Not reported Randomisation: Random numbers table Evidence level: 1^+	N: 60 Inclusion: Term, breastfed babies, Birthweight > 2500 grams, TsB between 256 and 427micromol/L Exclusion: Congenital anomalies, Haemolytic disease, Sepsis, Dehydration,	Group 1: Phototherapy Group 2: Phototherapy + Clofibrate Subject in the clofibrate group received a single dose of clofibrate (100mg/kg)	No adverse effects were noted	Mean decrease in TSB: Group 1: -137 ± 45 micromol/L Group 2: -171 ± 30 micromol/L Mean duration of treatment: Group 1: 68.8 + 21.6 hours Group 2: 53.6 + 15 hours	

		Exchange transfusion Demographics:				
Author: Miqdad A Year: 2004 Country: Saudi Arabia ID: [206]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1-	N: 112 Inclusion: Hyperbilirubinaemia due to ABO incompatibility Exclusion: Low birthweight, Rh haemolytic disease,, Perinatal asphyxia, severe congenital malformations Demographics: Gender (M/F): 70/42 Mean GA: 38 weeks Mean BW: Not reported Age at entry to study: Not reported Mean TSB: Not reported	Group 1: Phototherapy Group 2: Phototherapy + IVIG 500mg/kg over 4 hours	Mortality: Group 1: 4/56 Group 2: 16/56	Mean duration of treatment: Group 1: 106 ± 29 hours Group 2: 92 ± 29 hours	
Author: Voto L Year: 1997 Country: Argentina ID: [205]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1-	N: 40 Inclusion: Rh positive blood type and Positive Coombs' test Exclusion: Rh positive blood and negative Coombs' test, Histroy of prenatal therapy (Imaternal IVIG/IUT) ABO incompatibility, Other causes of haemolyisis Demographics: Gender (M/F): Not reported Mean GA: 37.2 ± 2.7 Mean BW: 2834 ± 569 grams Age at entry to study: Not	Group 1: Phototherapy Group 2: Phototherapy + IVIG 800mg/kg/day for 3 days	Exchange transfusion: Group 1: 8/19 Group 2: 12/18 No adverse effects were noted		

		reported Mean TSB: Not reported				
Author: Rubo J Year: 1992 Country: Germany ID: [207]	Methodology: RCT Blinding: Not reported Randomisation: Not reported Evidence level: 1^-	N: 32 Inclusion: Babies with Rh antigens born to mothers lacking Rh antigens, Positive Coombs' test Exclusion: Not reported Demographics: Gender (M/F): Not reported Mean GA: Not reported Mean BW: Not reported Age at entry to study: Not reported Mean TSB: Not reported	Group 1: Phototherapy Group 2: Phototherapy + IVIG 500mg/kg over 2 hours	Exchange transfusion: Group 1: 11/16 Group 2: 2/16 No adverse effects were noted	Max TsB: Group 1: 240 $\pm$ 78 micromol/L Group 2: 254 $\pm$ 86 micromol/L:	Prevention study One baby in each group excluded for protocol violations
Author: Dagoglu T Year: 1995 Country: Turkey ID: [208]	Methodology: RCT Blinding: None Randomisation: Random numbers table with sealed envelopes Evidence level: 1^{++}	N: 41 Inclusion: Babies with Rh antigens born to mothers lacking Rh antigens, Positive Coombs' test Exclusion: Not reported Demographics: Gender (M/F): 25/16 Mean GA: 36.1 $\pm$ 2.0 weeks Mean BW: 2776 $\pm$ 419 grams Age at entry to study: Not reported Mean TSB: Not reported	Group 1: Phototherapy Group 2: Phototherapy + IVIG 500mg/kg as soon as possible after birth	Exchange transfusion: Group 1: 15/19 Group 2: 4/22	Max TSB: Group 1: 224 + 99 micromol/L Group 2: 198 + 106 micromol/L	
Author: Nasseri F Year: 2006	Methodology: RCT Blinding: Not reported	N: 34 Inclusion: Gestation age > 37 weeks, Positive Coombs' test,	Group 1: Phototherapy Group 2: Phototherapy + IVIG	Exchange transfusion: Group 1: 11/17 Group 2: 3/17 No adverse effects were noted	Mean duration of treatment: Group 1: 154 $\pm$ 48 hours Group 2: 119 $\pm$ 23 hours	

Country: Iran ID: [209]	Randomisation: Not reported Evidence level: 1-	Significant hyperbilirubinaemia rising at 8.5micromol/L per hour, TsB below exchange transfusion levels, Exclusion: Risk factors for hyperbilirubinaemia i.e. sepsis, G-6-PD deficiency Demographics: Gender (M/F): 14/20 Mean GA: Not reported Mean BW: 2683 ± 292 grams Age at entry to study: 20.2 ± 9.5 hours Mean TSB: 254 ± 57micromol/L	IVIG (500mg/kg) was given with 2-4 hours of admission for 3 consecutive doses each 12 hours			
Author: Farhat A Year: 2006 Country: Iran ID: [220]	Methodology: RCT Blinding: Double-blind Randomisation: Not reported Evidence level: 1-	N: 104 Inclusion: TsB between 308 and 496micromol/L Exclusion: Birthweight < 2500 grams, Renal failure, Systemic infections, Already taken Shirkhest Demographics: Gender (M/F): Not reported Mean GA: Not reported Mean BW: Not reported Age at entry to study: Not reported Mean TSB: 401 ± 53 micromol/L	Group 1: Phototherapy + Placebo Group 2: Phototherapy + Shirkhest Shirkhest (6 grams) was diluted in 8mL of distilled water while the control group were given a starch solution (0.1%, 8mL) coloured with 1 drop of caramel solution to appear identical to Shirkhest solution. Phototherapy was discontinued at 256micromol/L	No adverse effects were noted	Mean decrease in TsB: Group 1: -164 Group 2: -154	
Author: Nicolopoulos D Year:	Methodology: CCT Blinding:	N: 40 Inclusion:	Group 1: Phototherapy Group 2:	No adverse effects were noted	Mean duration of treatment: **Term babies** Group 1: 84.4 ± 12 hours Group 2: 41.8 ± 5.5 hours	

1978 Country: Greece ID: [215]	Not reported Randomisation: Alternation Evidence level: 2-	Jaundice Exclusion: Babies of diabetic mothers, Rh incompatibility, Perinatal asphyxia, Large cephalhaematoma Demographics: **Term babies** Gender (M/F): 6/14 Mean GA: 39.1 ± 0.3 weeks Mean BW: 3286 ± 39 grams Age at entry to study: 90 ± 1.5 hours Mean TSB: 298 ± 5 micromol/L **Pre-term babies** Gender (M/F): 9/11 Mean GA: 33.4 ± 0.3 weeks Mean BW: 2077 ± 88 grams Age at entry to study: 76 ± 2.9 hours Mean TSB:198 + 5micromol/L	Phototherapy + Cholestyramine Babies received 1.5gm/kg/day of cholestyramine powder mixed in milk No Phenobarbital, other medications, or parenteral fluids were administered.		**Pre-term babies** Group 1: 73.3 ± 9 hours Group 2: 47.0 ± 6 hours	
Author: Tan K Year: 1984 Country: Singapore ID: [216]	Methodology: CCT Blinding: Not reported Randomisation: Alternation Evidence level: 2-	N: 84 Inclusion: Term babies with non-haemolytic hyperbilirubinaemia (TsB ≥ 256.5micromol/L) Normal G-6-PD status, No isoimmunization, no cephalhaematoma Exclusion: Not reported Demographics: Gender (M/F): Not reported Mean GA: 38.9 ± 0.2 weeks Mean BW: 3154 ± 139 grams Age at entry to study: 84 ± 2.9 hours	Group 1: Phototherapy Group 2: Phototherapy + Cholestyramine Babies received 1.5gm/kg/day of cholestyramine powder mixed in milk		Mean decrease in TSB: Group 1: -168 ± 24 micromol/L Group 2: -150 ± 20 micromol/L	

		Mean TSB: 298 ± 5micromol/L				
Author: Martin J Year: 1974 Country: New Zealand ID: [219]	Methodology: CCT Blinding: Not reported Randomisation: "allocated in rotation" Evidence level: 1-	N: 100 Inclusion: physiological jaundice Exclusion: Not reported Demographics: Gender (M/F) : 49/51 Mean GA: 34.8 ± 2.7 weeks Mean BW: 2155 ± 632 gms Age at entry to study 48.1 ± 14.7 hrs Mean TSB: 174 ± 40 micromol/L	Group 1: Usual nursery care Group 2: Usual nursery care + Conventional phototherapy Group 3: Usual nursery care + phototherapy + phenobarbital (dosage not reported) Conventional Phototherapy consisted of a single bank of eight 30 watt fluorescent tubes behind a Perspex screen 50cm above the baby in a bassinet Light intensity = 2500 lux Light band = 441 nm Baby naked and with eyes covered No deliberate attempt to sequentially rotate the baby	ET: Group 1: 3/35 Group 2: 0/34 Group 3: 1/31 Mortality: Group 1: 2/35 Group 2: 0/34 Group 3: 1/31	Mean duration of phototherapy Group 1: NA Group 2: 67 ± 33 hours Group 3: 72 ± 31 hours Mean rise to max TSB: Group 1: 80.4 ± 49.6 micromol/L Group 2: 22.2 ± 29.1 micromol/L Group 3: 18.8 ± 29.1 micromol/L Time to max TSB (hours): Group 1: 51 ± 23 hours Group 2: 14 ± 19 hours Group 3: 13 ± 18 hours	No significant differences between groups No reason given for mortality
Author: Odell G Year: 1983 Country: USA ID: [217]	Methodology: CCT Blinding: Not reported Randomisation: By patient number Evidence level: 2-	N: 52 Inclusion: Hyperbilirubinaemia requiring phototherapy Exclusion: Not reported Demographics: Gender (M/F): 31/21 GA: Not reported BW:2767 ± 69 grams Mean age at entry to study: 80.6 ± 28.7 hours Mean TSB: 234 ± 46.8 micromol/L	Group 1: Phototherapy Group 2: Phototherapy + Agar 250mg orally every 8 hours during phototherapy Phototherapy initiated at 239.4 micromol/L for term babies and 171 micromol/L for pre-term babies Phototherapy discontinued 188.1 micromol/L for term babies and 171 micromol/L for pre-term babies		Mean duration of Phototherapy Group 1: 48.1 + 23.0 hours Group 2: 37.6 + 18.0 hours	15 babies excluded retrospectively
Author: Ebbesen F Year:	Methodology: CCT Blinding:	N: 49 Inclusion:	Group 1: Phototherapy Group 2:		Mean decrease in TsB Group 1: 87 ± 39 micromol/L Group 2: 85 ± 40 micromol/L	

1977 Country: Denmark ID: [218]	Not reported Randomisation: By patient number Evidence level: 2-	Hyperbilirubinaemia requiring phototherapy Exclusion: Not reported Demographics: Gender (M/F): 26/23 GA: 36.8 ± 2.5 weeks BW:2729 ± 538 grams Mean age at entry to study: 87 ± 26 hours Mean TSB: 274 ± 51 micromol/L	Phototherapy + Agar 250mg orally at feedings every three hours Phototherapy initiated at 274 micromol/L Phototherapy discontinued when TsB fell continuously for 24 hours		Mean duration of Phototherapy Group 1: 60 ± 30 hours Group 2: 61 ± 28 hours	

Q13. What information and support should be given to parents/carers of babies with neonatal hyperbilirubinaemia?

Author: Salem-Schatz S Year: 2004 Country: USA ID: [222]	Study Type: Focus group study Evidence Level: III	Four focus groups 1 for physicians (N = 9) 1 for nurses (N = 9) 2 for parents/carers (N = 14) Aim: To identify barriers to timely follow-up of hyperbilirubinaemia in 1st 7 days Focus had between 7 and 9 participants and lasted for between 90 and 120 minutes Content was the importance of 1st week newborn follow-up and key questions relating to physican and parent/carer experiences	Barriers - communication Conflicting advice from HCP's on readiness for discharge - MD Communication gaps between handover from hospital to community - MD, RN Key information missing MD, RN Barriers – systems and process Delays in outpatient bilirubin testing and reporting - MD, RN Barrier to home visits – MD, RN, P Barriers to office visits in week 1 – MD, RN, P Barriers – systems and process Shorter hospital stays leave less time for parent education –RN Clinicians may be reluctant to educate about hyperbilirubinaemia prenatally – MD, RN Poor understanding by clinicians of risks of near-terms – MD Lack of clinician awareness of the recommendations of early follow-up visits – MD HCP recommendations forgotten once parent is home – P	Solutions - communication Improve communication between HCP - MD Notify community HCP by email when baby born – MD, RN Provide easy-access (on-line or form parent) for community HCP for lab results – MD, RN Give parents/carers 'early warning signs' to report – MD, P Continued contact from birth hospital to parent/carer – P Solutions – systems and process Home visit by a physician – P Encourage home visits, RN, P Choose paediatrician before discharge/book appointment before discharge – MD Separate visiting toom for well children – P More flexible visiting time – P Community HCP to visit pre-discharge – RN, P Ensure quick easy access to labs – MD, RN Solutions – systems and process Increase professional awareness – MD, RN Parental education through continuum of care – MD, RN, P Support groups for new and expectant parents – MD, RN	MD = physician RN = Nurse P = Parent

Author: Willis S Year: 2002 Country: USA ID: [224]	Study Type: Qualitative study Evidence Level: III	Population Mother of newborn babies with jaundice Criteria: Breastfeeding babies with TsB > 170 micromol/L Setting Hospital Demographics: Sample size: 45 Mean age: 27 years More than half of multiparous mother had a previous baby with jaundice and ¾ had breastfed a previous child. Mothers interview between 2.5 and 14.5 weeks postpartum	Half of the mothers described how jaundice had influenced, positive or negatively their breastfeeding patterns.		