METHODOLOGICAL APPENDIX

Guideline for Management of Indirect Neonatal Hyperbilirubinemia 2017 Literature Review Methods and Results

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Section 1. Overview

This document details the methods and results of the systematic literature review performed for the 2017 UMHS clinical guideline for Management of Indirect Neonatal Hyperbilirubinemia.

A systematic search for best evidence was provided by the informationists at the Taubman Health Sciences Library, University of Michigan, which reviewed evidence from January 1, 2004-June 4, 2015. The search included publications:

- Indexed in the Medline (Ovid) database and the Cochrane Database of Systematic Reviews
- Addressing humans, all ages, pediatric (separate) and in the English language
- Categorized as clinical guidelines, controlled trials or meta-analyses, and cohort studies
- From January 1, 2004-June 4, 2015

The searched addressed 19 topics. The topics are listed in Section II. The detailed search specifications are listed in Section III. This search was supplemented by the literature review results included in the Clinical Practice Guideline: Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. *Pediatrics* 2004; 114, 297-316.

Section IV lists the number of publications identified by topic and type of publication. The search identified a total of 462 potentially relevant publications.

Members of the guideline team reviewed these publications, excluding those found not to be relevant to our population or topic (eg, study population, measures/outcomes) or not to be the best evidence (eg, studies with better methodology already available). This process is summarized in Section V.

Additional articles were identified by searching references in retrieved publications. Very recent publications known to expert members of the guideline team were also considered.

The review process resulted in 91 studies identified as presenting best evidence on a topic. For each topic for which "best evidence" was identified, the evidence was synthesized in an evidence table that describes for each article the key aspects of methods, results, and issues (eg, benefits and harms). The 16 evidence tables are presented in Section VI.

Section II. Search Framework and Topics

Presented below is the outline for a systematic search on specific topics relevant to the Management of Indirect Neonatal Hyperbilirubinemia in the inpatient care setting. For each topic, searches were performed for (a) guidelines, (b) controlled trials and meta-analyses, and (c) cohort studies. The topic searches are not mutually exclusive. This approach assumes that each topic will be reviewed independently and that the search on a topic must include all references relevant to it.

Recent Systematic Search and Review

We performed a systematic search and review of literature concerning indirect neonatal hyperbilirubinemia in an inpatient setting in preparing the Clinical Practice Guideline for the Management of Indirect Neonatal Hyperbilirubinemia. Inclusion/exclusion criteria are listed below.

Inclusion and Exclusion Criteria for Systematic Search of More Recent Literature

To search perform a search of relevant literature published we developed the following framework of inclusion and exclusion criteria.

Domain	**Inclusion**	**Exclusion**
Language:	English	Not written in English
Time frame	Literature search included articles published from January 1, 2004-June 4, 2015.	Studies published previous to or following these dates unless within categories noted in section (2) below
Study type/design	Meta-analyses, controlled trials, cohort studies, guidelines	Opinion, letter, commentary
Study population	Neonate, infant	Non-human, adult
Medical condition	Hyperbilirubinemia, jaundice, kernicterus	
Setting	Inpatient	Ambulatory care, population health
Interventions/ indicators	<u>A. Clinical presentation/complications</u> 1. Incidence 2. Etiology 3. Complications <u>B. Diagnosis</u> 1. History, etc 2. Evaluation a. Transcutaneous bilirubin b. Serum bilirubin c. Infant jaundice studies 3. Etiology a. When to broaden diff diagnosis b. Additional lab studies 4. Withholding breast milk 5. Diagnosis, not in 4-7 <u>C. Risk Stratification</u> 1. Interpretation of risk stratification <u>D. Treatment</u> 1. Supplementation of breast milk 2. Phototherapy	Interventions/indications that are out of scope for guideline.

	3. Intravenous hydration 4. Exchange transfusion, albumin, IVIG 5. Monitoring: technique and frequency 6. Triage/disposition planning a. Indications for admission - light level (nomograms from AAP guideline) - rate of rise of bilirubin - risk factors b. Need for escalation of care (NICU) c. Outpatient management and follow-up - Timing of first follow-up after discharge - Frequency of monitoring after discharge - Role of the Children's Emergency Services in outpatient monitoring/evaluation (institution specific) 7. Treatment, not in 10-15 <u>E. Prevention</u> 1. Newborn nursery discharge instruction/outpatient educations a. Frequency and duration of nursing b. Guidelines for formula fed infants 2. All neonatal hyperbilirubinemia not in 1-17 <u>F. Other</u> 1. Other articles not included in A-E	
Outcomes	• For diagnosis test, studies that report sensitivity / specificity of diagnostic test or procedure • For treatment, studies that report cure rate, infection rate, or time to improvement • For other studies: Any quantitative outcomes reported in studies meeting our other inclusion criteria	
Relative quality of evidence available		Articles are excluded if other articles within retrieved literature are deemed methodologically superior, e.g. have more representative relevant population; larger sample size; stronger methodological design, superior execution of study.

Additional sources considered to supplement our search were:

- References cited in articles identified by the literature search from January 1, 2004 to June 4, 2015 (section 1, described above).
- Publications (meta-analyses, controlled trials, cohort studies, and guidelines) published since the literature search was completed, though June 4, 2015, known to members to the guideline team.

Search of Literature from January 1, 2004-June 4, 2015

An initial search was performed for the time period January 1, 2004 to June 4, 2015, performed by informationists at the Taubman Health Science Library carried out from May 20 - June 4, 2015.

The general specifications for the search are outlined below. The detailed search terms and specifications are reproduced in Section III.

Within the Medline (Ovid) database, hyperbilirubinemia, neonatal, jaundice, kernicterus (for pediatric only) were searched as major topics. The MEDLINE In-Process database was also searched, using a keyword search. The strategy is available in Section III.

The Cochrane Database of Systematic Reviews was searched using the terms listed in Section III.

Overall specification terms

- Major topic area: hyperbilirubinemia, neonatal, jaundice, kernicterus, infant, newborn
- Time frame: January 1, 2004-June 4, 2015
- Population: human, birth to 23 months, pediatric
- Language: English

Specific searches

A. Clinical presentation/complications
1. Incidence
2. Etiology
3. Complications

B. Diagnosis
1. History, etc
2. Evaluation
   a. Transcutaneous bilirubin
   b. Serum bilirubin
   c. Infant jaundice studies
3. Etiology
   a. When to broaden diff diagnosis
   b. Additional lab studies
4. Withholding breast milk
5. Diagnosis, not in 4-7

C. Risk Stratification
1. Interpretation of risk stratification

D. Treatment
1. Supplementation of breast milk
2. Phototherapy
3. Intravenous hydration
4. Exchange transfusion, albumin, IVIG
5. Monitoring: technique and frequency
6. Triage/disposition planning
   a. Indications for admission
      - light level (nomograms from AAP guideline)
      - rate of rise of bilirubin
      - risk factors
   b. Need for escalation of care (NICU)
   c. Outpatient management and follow-up
      - Timing of first follow-up after discharge
      - Frequency of monitoring after discharge
      - Role of the Children's Emergency Services in outpatient monitoring/evaluation (institution specific)
7. Treatment, not in 10-15

E. Prevention
1. Newborn nursery discharge instruction/outpatient educations
   a. Frequency and duration of nursing
   b. Guidelines for formula fed infants
2. All neonatal hyperbilirubinemia not in 1-17

Section III. Detailed Search Terms and Strategy

The searches were performed by informationists at the Taubman Health Sciences Library, University of Michigan.

Overall searches were performed on the date June 4, 2015 for the period from January 1, 2004 - June 4, 2015.

The search strategies are listed below.

Neonatal Hyperbilirubinemia Main Search (NOTE: Referred to throughout strategies as Main)

1. exp *hyperbilirubinemia, neonatal
2. *hyperbilirubinemia/ or *jaundice or *kernicterus
3. limit 2 to "all infant (birth to 23 months)"
4. (neonatal or neonate* or infant* or newborn*).ti.
5. 2 and 4
6. exp animals not (exp animals and humans)
7. 5 not 6
8. 1 or 3 or 7
9. limit 8 to (English language and yr = "2004 -Current")
10. remove duplicates from 9

Clinical Trials Search Hedge

1. randomized controlled trial or controlled clinical trial or multicenter study or meta-analysis or clinical trial, phase iv
2. clinical trial
3. limit 2 to humans
4. 1 or 3

Cohort Studies Search Hedge

1. randomized controlled trial or controlled clinical trial or multicenter study or meta-analysis or clinical trial, phase iv
2. clinical trial
3. limit 2 to humans
4. 1 or 3
5. exp cohort studies not 4

Guideline Search Hedge

1. clinical protocols or physician's practice patterns or algorithms or "Outcome and Process Assessment (Health Care)" or consensus development conference, nih or consensus development conference or practice guideline or guideline
2. randomized controlled trial or controlled clinical trial or multicenter study or meta-analysis or clinical trial, phase iv
3. clinical trial
4. limit 3 to humans
5. 2 or 4 or exp cohort studies
6. 1 not 5

Clinical presentation/complications

1. Incidence

a. incidence and Main

2. Etiology

a. et.xs. and Main

3. Complications: kernicterus

a. co.xs. and Main

Diagnosis

4. History, maternal history/risk factors/prior infant with hyperbilirubinemia, physical exam, signs, symptoms

a. exp *medical history taking or exp *physical examination
b. ((patient or maternal) adj history).ti,ab.
c. exp "signs and symptoms" or exp *Disease Susceptibility or risk factors
d. or 1-3
e. 4 and Main

5. Evaluation

a. Transcutaneous bilirubin
b. Serum bilirubin (total vs fractionated)
c. Infant jaundice studies/Direct antibody testing (DAT)

1. ((transcutaneous or serum) adj3 bilirubin).ti.
2. exp *Bilirubin/an, bl or exp *Antibodies/bl
3. 1 or 2
4. 3 and Main

6. Etiology of hyperbilirubinemia:

a. When to broaden the differential diagnosis (i.e. G6PD)
b. Additional laboratory studies (i.e. reticulocyte count) for consideration

1. et.xs.
2. exp Diagnosis, Differential or exp *Clinical Laboratory Techniques or Reticulocytes
3. Glucosephosphate Dehydrogenase or ("glucose-6-phosphate dehydrogenase" or g6pd).ti.
4. or 1-3
5. 4 and Main

7. Withholding breast milk

a. exp Milk, Human or exp Breast Feeding
b. 1 and Main

8. Diagnosis, not in 4-7

a. exp *medical history taking or exp *physical examination/
b. ((patient or maternal) adj history).ti,ab.
c. exp "signs and symptoms" or exp *Disease Susceptibility or risk factors/
d. ((transcutaneous or serum) adj3 bilirubin).ti.
e. exp *Bilirubin/an, bl or exp *Antibodies/bl
f. et.xs.
g. exp Diagnosis, Differential or exp *Clinical Laboratory Techniques or Reticulocytes
h. Glucosephosphate Dehydrogenase or ("glucose-6-phosphate dehydrogenase" or g6pd).ti.
i. exp Milk, Human or exp Breast Feeding
j. or 1-9
k. false negative reactions or false positive reactions or likelihood functions or exp "sensitivity and specificity"
l. exp diagnosis or di.xs. or du.fs. or (sensitivity or specificity or predictive value).af.
m. 11 or 12
n. 13 not 10
o. 14 and Main

<u>Risk Stratification</u>

9. Interpretation of risk stratification into low, medium, high risk groups

a. Infant jaundice studies
b. Rate of rise of bilirubin
c. Direct antibody testing (DAT)
d. Hemolysis
e. Weight loss/percent below birth weight
f. Poor feeding
g. Maternal chorioaminitis (note: misspelled on search outline; should be chorioamnionitis)

1. exp *antibodies/bl, du or exp *deglutition disorders or *eating disorders or *failure to thrive or *feeding behavior or *Chorioamnionitis/
2. *Neonatal Screening or exp risk or *Hemolysis or exp *Jaundice, Neonatal or *bilirubin/bl
3. 1 or 2

4. 3 and Main

Treatment

10. Supplementation of breast milk

a. Dietary Supplements and (Milk, Human or exp Breast Feeding)
b. 1 and Main

11. Phototherapy:

a. When to initiate/discontinue (bili-tools/nomograms/etc.)
b. Phototherapy technique
   i. Fiberoptic phototherapy blankets (bili blanket, fiberoptic mattress, etc.)
   ii. Conventional neonatal phototherapy units (overhead fluorescent bulbs, halogen quartz lamps, light-emitting diodes, etc.)
c. Inpatient or outpatient phototherapy
d. Neonate protection (eye protection)

1. exp *Phototherapy
2. 1 and Main

12. Intravenous hydration

a. exp fluid therapy
b. 1 and Main

13. Exchange transfusion, albumin, IVIG

a. exp Exchange Transfusion, Whole Blood or Immunoglobulins, Intravenous or albumins
b. 1 and Main

14. Monitoring: technique and frequency

a. Intervals for monitoring bilirubin levels when an inpatient
b. Intervals for monitoring bilirubin levels when an outpatient
c. Intervals for monitoring bilirubin levels when near exchange transfusion levels
d. Transcutaneous measurement for monitoring: appropriate, or not?

1. exp Monitoring, Physiologic or bilirubinometr*.ti,ab. or *bilirubins/bl
2. 1 and Main

15. Triage/Disposition planning

a. Indications for admission
   i. Light level (nomograms from AAP guideline)
   ii. Rate of rise of bilirubin
   iii. Risk factors

1. Triage or Patient Admission or exp Hospitalization or admission criteria.mp. or Child, Hospitalized
2. 1 and Main

b. Need for escalation of care (neonatal intensive care unit)

1. Intensive Care Units, Neonatal
2. 1 and Main

c. Outpatient management and follow-up
   i. Timing of first follow-up after discharge
   ii. Frequency of monitoring after discharge
   iii. Role of the Children's Emergency Services in outpatient monitoring/evaluation (institution specific)

1. Ambulatory Care or outpatients or follow-up studies or exp Emergency Medical Services or patient discharge or patient readmission or "follow up".ti,ab.
2. 1 and Main

16. Treatment, not in 10-15

a. Dietary Supplements and (Milk, Human or exp Breast Feeding)
b. exp *phototherapy or exp fluid therapy
c. exp Exchange Transfusion, Whole Blood or Immunoglobulins, Intravenous or albumins
d. exp Monitoring, Physiologic or bilirubinometr*.ti,ab. or *bilirubins/bl

e. Triage or Patient Admission or exp Hospitalization or admission criteria.mp. or Child, Hospitalized
f. Triage or Patient Admission or exp Hospitalization or admission criteria.mp. or Child, Hospitalized or Intensive Care Units, Neonatal
g. Ambulatory Care or outpatients or follow-up studies or exp Emergency Medical Services or patient discharge or patient readmission or "follow up".ti,ab.
h. or 1-7
i. (tu or th).xs. or exp therapeutics
j. 9 not 8
k. 10 and Main

Prevention

17. Newborn nursery discharge instructions/outpatient educations:

a. Frequency and duration of nursing
b. Guidelines for formula fed infants

1. breast feeding or bottle feeding or exp patient education as topic or discharg*.ti.
2. 1 and Main

Section IV. Number of Search Results by Topic and Type of Publication

The search (literature published January 1, 2004-June 4, 2015) identified 462 unique indexed publications in Medline, listed as the "Base Search" and 1 Cochrane review.

The results by topic and type of publication are drawn from this base search, and summarized below. Note that a publication may be relevant to more than one topic, so the sum of entries by topic is greater than the number of unique publications overall.

Results for Search, January 1, 2004-June 4, 2015

	Guidelines (-GDL)	Clinical Trials (-Trials)	Cohort Studies (-Cohort)
Base Numbers:	35	125	262
A. Clinical presentation/complications			
A1. Incidence	0	7	37
A2. Etiology	12	28	134
A3. Complications	6	11	70
B. Diagnosis			
B4. History, etc.	7	27	108
B5. Evaluation a. Transcutaneous bilirubin (ML/MS) b. Serum bilirubin (ML) c. Infant jaundice studies/DAT (ML)	4	36	81
B6. Etiology a. When to broaden diff diagnosis b. Additional lab studies	16	45	166
B7. Withholding breast milk	6	3	21
B8. Diagnosis, not in 4-7	8	26	27
C. Risk Stratification			
C9. Interpretation of risk stratification	15	76	186
D. Treatment			
D10. Supplementation of breast milk	0	0	0
D11. Phototherapy	4	54	22
D12. Intravenous hydration	3	0	1

D13. Exchange transfusion, albumin, IVIG	5	10	28
D14. Monitoring: technique and frequency	1	6	5
D15. Triage/Disposition planning			
a. Indications for admission i. Light level (nomograms from AAP guideline) ii. rate of rise of bilirubin iii. Risk factors	3	11	26
b. Need for escalation of care (NICU)	1	6	9
c. Outpatient management and follow-up i. Timing of first follow-up after discharge ii. Frequency of monitoring after discharge iii. Role of the Children's Emergency Services in outpatient monitoring/evaluation (institution specific)	7	19	105
D16. Treatment, not in 10-15	18	30	39
E. <u>Prevention</u>			
E17. Newborn nursery discharge instruction/outpatient educations a. Frequency and duration of nursing b. Guidelines for formula fed infants	6	7	23
E18. All neonatal hyperbilirubinemia not in 1-17	0	1	0
F. Medline In-Process	2	11	21
G. Cochrane	6		

Section V. Evidence Review and Identification of Best Evidence

Criteria for Best Evidence

In order to identify best evidence, team members were assigned topics, then team members reviewed publications to identify studies that had the overall best methods ("best evidence") taking into consideration:

Study setting: reflects care and care settings that are similar to inpatient care in the U.S.

Study population and sample(s): represents neonate patients typically seen related to hyperbilirubinemia management seen inpatient in the U.S.

Study design: strength of design in the ability to identify causal relationships using the following categories.

A = systematic reviews of randomized controlled trials with or without meta-analysis,
B = randomized controlled trials,
C = systematic review of non-randomized controlled trials or observational studies, non-randomized controlled trials, group observation studies (cohort, cross-sectional, case-control),
D = individual observation studies (case study/case series),
E = expert opinion regarding benefits and harm

Size of study sample: larger size generally reflecting more stable results

Variables: Extent to which the variables studied matched topics of interest in the inclusion criteria

Measures: Extent to which the measures likely reflected the conceptual variables

Data collection: Extent to which data collection procedures were likely to collect data appropriate for the measures

Intervention appropriateness: Extent to which an intervention was likely to produce the desired condition

Intervention execution: Extent to which interventions were carried out as planned

Analysis appropriateness: Appropriateness of analyses to address the questions of interest

Clarity of description: Extent to which the above information was communicated to readers

Best Evidence Identified and Organized into Evidence Tables

The best evidence for the current guideline is synthesized into 16 evidence tables reflecting the primary questions posed in the literature review. These tables include a total of 91 publications. The tables themselves are contained in Section VI, and present the synthesis of the best evidence identified.

Section VI. Evidence Synthesis: Tables Describing Best Evidence

The best evidence for the current guideline is synthesized into 16 evidence tables reflecting the primary questions posed in the literature review. These tables include a total of 91 publications.

*For all evidence tables, level of evidence rating is noted as follows:

A = systematic reviews of randomized controlled trials with or without meta-analysis,
B = randomized controlled trials,
C = systematic review of non-randomized controlled trials or observational studies, non-randomized controlled trials, group observation studies (cohort, cross-sectional, case-control),
D = individual observation studies (case study/case series),
E = expert opinion regarding benefits and harm

Topic A. History for Management of Indirect Neonatal Hyperbilirubinemia

Reference Citation	Study Design	Patient Population (n)	Main variables or predictors [e.g. study group (n) & comparison group (n)]	Main relevant outcomes, results, and significance	Reviewer notes (include (a) methodological issues, (b) noteworthy harms)
AAP 2004. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2004 Oct;114(4):1138.	Guideline	NA	NA	Major risk factors: predischarge TB n high risk zone, jaundince in first 24 hours, +DAT or other hemolytic disease, GA 35-36 wk, previous sibling received phototherapy, cephalohematoma or sig bruising, exclusive BF, east Asian race. Minor risk factors: Predischarge TB in high-intermeidate risk zone, GA 37-38 weeks, jaundice observed before discharge, previous sibling with jaundice, macrosomic IDM, maternal age >25y, male gender.	Systematic review/Guideline, see evidence tables in source.
Keren R1, Bhutani VK, Luan X, Nihtianova S, Cnaan A, Schwartz JS. Identifying newborns at risk of significant hyperbilirubinaemia: a comparison of two recommended approaches. Arch Dis Child. 2005 Apr;90(4):415-21.	C	n = 996 term or near term infants	Odds of developing serum bilirubin >95th% centile with and without presence of clinical factors.	GA <38 weeks (OR 2.6), oxytocin (OR 2.0), vacuum delivery (OR 2.2), exclusive breastfeeding (OR 2.6).	Predischarge level more predictive than clinical score.
Thomas B. Newman, MD, MPH; Blong Xiong, MPH; Veronica M. Gonzales, BS; et al. Prediction and Prevention of Extreme Neonatal Hyperbilirubinemia in a Mature Health Maintenance Organization. Arch Pediatr Adolesc Med. 2000;154(11):1140-1147.	C	n = 73 cases, 423 controls, from population of 51,387	Odds of developing TSB >25, multiple logistic regression.	Exclusive BF (OR 5.7), Bruising (OR4.0), Asian race (OR 3.5), maternal age >25y (OR 3.1), cephalohematoma (OR3.3), family history of jaundice in newborn (OR 6.0), lower GA (OR 0.6 per week), maternal age >25y (OR 3.1).	Caution with applying data to other populations.

Topic B. Hyperbilirubinemia Inpatient Guideline Evidence. Clinical Incidence

Reference Citation	Study Design	Patient Population (n)	Main variables or predictors [e.g. study group (n) & comparison group (n)]	Main relevant outcomes, results, and significance	Reviewer notes (include (a) methodological issues, (b) noteworthy harms)
AAP Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation Pediatrics 2004; 114(1): 297-316.	Guideline	n = newborn infants of >35 weeks gestation	NA	Rec performing at risk stratified threshold values. TSB is at or higher at any time, it is a medical emergency and the infant should be admitted immediately and directly to a hospital pediatric service for intensive phototherapy. These infants should not be referred to the emergency department, because it delays the initiation of treatment. Exchange if signs of acute bili encephalopathy.	Noted to be consensus and based on limited evidence. Not made of implied trial of intensive phototherapy.
National Collaborating Centre for Women's and Children's Health. Neonatal jaundice Clinical Guideline May 2010. NHS / NICE	Guideline Systematic review	Various but targeted to > older nml newborn Many isoimmune	EXT v: none EXT v Simple tx EXT with alb v EXT w/o EXT with Ca2+ v EXT w/o EXT whole blood v frozen recon. EXT central v brachial art	No difference in mortality. No different kernicterus Rec performing ET at "Threshold" values. Charts available by GA From ~12mg/dl at 12 hrs to ~26mg/dl hrs= >42 Charts available Exchange if signs of acute bili encephalopathy.	Thresholds age dependent bili values and gest age. Some mentions of isoimmunization but not risk adjusted. (e.g. rate of rise underlying issues??) Evidence very old and sketchy. Only RCT of ext v no was 50 years ago. Note made of morbidity usually seen only in "sick babies". RT probably lacked power. EXT regarded as fairly safe.
Srinivas M., Kumar, P. Blood Exchange Transfusion for Infants with Severe Neonatal Hyperbilirubinemia Seminars in Perinatology 35(3):175-184 © 2011	Review	n = 6 studies size 68 to 232 infants all observational one prospective. Mixed birth weight	Adverse events (AE) attributed to EXT.	AE seen more often in sick babies. Mortality seen in sick babies (only 2 in "nml infants". "Serious" AE seen in NEC (2cases), A&B, Bleeding associated with low Plts., hypocalcemia, seizures (n-1) When given AE rate listed as 6%,12%,21%,38%,68%. Clearly heterogeneity the rule. Most common/shared thrombocytopenia, hypocalcemia w/o clinical signs.	Very hard to find correct / representative AE rate. Older care practices, serious comorbidity big issues. Many AEs biochemical only.
Smits-Wintjens V, E, H, J, Rath M, E, A, van Zwet E, W, Oepkes D, Brand A, Walther F, J, Lopriore E. Neonatal	C	Term and preterm Maternal isoimmunization	Outcome = rate of complications. ET V no ET Univariate analysis to ID variable in multi log regression model.	No difference in number of deaths (0) ET associated with proven sepsis [8 vs. 1%, odds ratio (OR) 8.3, 95% confidence interval (CI) 1.7–40.3; p = 0.009], leukocytopenia (88 vs. 23%,	Sepsis outcome seems high, authors cite similar lit but also admit no clear reason why?

Morbidity after Exchange Transfusion for Red Cell Alloimmune Hemolytic Disease. Neonatology 2013;103:141-147		n = 348 ET = 134.		respectively; OR 36.0, 95% CI 17.5–73.8; p < 0.001). Severe thrombocytopenia (platelet count < 50k; 63 vs. 8%, respectively; OR 31.4, 95% CI 14.0–70.4; p < 0.001). Hypocalcemia (22 vs. 1%, respectively; OR 27.4, 95% CI 5.9–126.8; p < 0.001). Hypernatremia (8 vs. 0%, respectively; p < 0.001).	
K.K. Locham Kiranjeet Kaur*Rajeev Tandon Manpreet Kaur Rajinder Garg Indian Pediatrics 2002; 39:657-659	C	Hyperbili requiring ET n = 30 Term	ET with calcium sup q 100 ml v ET with no sup. Outcome of interest = bradycardia, hypocalcemia, change in blood Ca (1ml of 10% calcium gluconate IV for every 100 ml of CPD blood exchanged)	No hypocalcemia seen. RX group did have rise in ionized CA (p<005). Control did have fall but no hypocalcemia noted. No change in HR	NA

Topic C. Hyperbilirubinemia Inpatient Guideline Evidence. Bili Incidence

Reference Citation	Study Design	Patient Population (n)	Main variables or predictors [e.g. study group (n) & comparison group (n)]	Main relevant outcomes, results, and significance	Reviewer notes (include (a) methodological issues, (b) noteworthy harms)
Donald Manning, Peter Todd, Melanie Maxwell, Mary Jane Platt Prospective surveillance study of severe hyperbilirubinaemia in the newborn in the UK and Ireland Arch Dis Child Fetal Neonatal Ed 2007;92:342–346	C	n = 1,500,052 Live Births	Primary objective of this study was to determine the incidence of severe hyperbilirubinemia in the UK and Ireland. "Secondary objectives were to document clinical and demographic variables associated with severe jaundice, and the associated consequences, including the need for exchange transfusion, bilirubin encephalopathy and death." Severe hyperbilirubinemia = unconjugated serum bilirubin concentration of >510 mmol/l (30 mg/dl) in the first month of life.	108 Cases. 7.1/100 000 live births (95% CI 5.8 to 8.6/100 000 live births) 88 presented as outpatients. 48 treated with exchange tx 13 infants had Bilirubin encephalopathy, an incidence of 0.9/100 000 live births (95% CI 0.46 to 1.5). Four of these infants did not have ET. Predictors: Boys (12 (85%), p=0.037) black/ British black (6 (43%), p,0.001); significantly higher peak Serum bilirubin concentrations (mean 627 mmol/l v 573 mmol/l Coexistent infection (3 (21%), p=0.007); Multiple logistic regression Model group (black) and glucose 6-phosphate dehydrogenase deficiency independently increased the risk of encephalopathy in infants with hyperbilirubinemia.	Raye of 0.9/100,000 lb similar to other populations
Finn Ebbesen (fe@rn.dk)1, Jesper V Bjerre2, Pernille K Vandborg Relation between serum bilirubin levels ‡450 lmol⁄L and bilirubin encephalopathy; a Danish population-based study Acta Pædiatrica 2012 101, pp. 384–389	C	n = 502 766 infants born at gestational age ≥ 35 weeks Denmark January 2, 2000 December 31, 2007. Reviewed national laboratory information system Chart review of all identified cases	Describe the relationship between the levels of total serum bilirubin concentration (TsB) and acute intermediate, acute advanced and chronic bilirubin encephalopathy in late preterm and term infants with a TsB ‡450 lmol⁄L. (26mg/dl) Estimated the incidence of acute advanced and chronic bilirubin encephalopathy.	TsB ‡450 lmol⁄L -annual incidence of 45 per 100 000 birthsPeak TsB 450–499 lmol⁄L 149 29.6 (25.1;34.8) Encephalopathy 0 (0, 0–2). Peak TsB 500–599 lmol⁄L 64 12.7 (9.8;16.3) Encephalopathy 0 (0, 0-6). Peak TsB 600–1000 lmol⁄L 11 2.2 (1.1;3.9) enceph-3 (27, 6–61) Etiology of enceph / extreme hyperbilirubinaemia: ABO blood group isoimmunisation in 3 infants. Glucose-6-phosphate dehydrogenase deficiency in one infant. Two infants had a weight loss of 15–20%. Incidence acute advanced and chronic bilirubin encephalopathy were 0.6 (95% CI 0.1; 1.7) per 100 000.	

				Two infants with acute intermediate bilirubin encephalopathy suffered no sequelae.	
S Zoubir,1 R Arlettaz Mieth,2 S Berrut,3 M Roth-Kleiner1; Incidence of severe hyperbilirubinaemia Switzerland: a nationwide population-based prospective study Arch Dis Child Fetal Neonatal Ed July 2011 Vol 96 No 4	C	n = 151,185 births >=35 wks, 2007-08	(TSB) exceeding the upper limit of exchange transfusion (ET) were included. ET limits: 430 μmol/l for healthy term infants; 370 μmol/l for sick term infants or term infants with haemolysis 320 μmol/l for preterm infants.	Incidence of 41/100 000 live births 3 patients had a TSB value > 510 μmol/l (30 mg/dl) "Etiology": Blood group incompatibility, hematoma, infection, spherocytosis, feto-fetal transfusion.	
Michael W. Kuzniewicz, MD, MPH,a,b Andrea Wickremasinghe, MD,c,d Yvonne W. Wu, MD, MPH,b,e Charles E. McCulloch, PhD,d Eileen M. Walsh, RN, MPH,a Soora Wi, MPH,a Thomas B. Newman, MD, MPHa Incidence, Etiology, and Outcomes of Hazardous Hyperbilirubinemia in Newborns PEDIATRICS Volume 134, Number 3, September	Review	n = 525 409 infants born ≥35 weeks' gestational age from 1995 through 2011	Maximum TSB >30 mg/dL. Acute / Chronic encephalopathy ID'd.	8.6 per 100 000 live births (47 cases) 40% were <38 weeks' gestational age. Most were in the AAP low risk group (54%), 44% were medium risk, and only 2% were high risk. 4/47 had chronic encephalopathy. 3<37 wks. 2 with only sensorineural hearing loss (peak bili>35mg/dl) 2 had CP peak .45 mg/dl. All infants with CBE had an additional factor (prematurity, decreased G6PD activity, sepsis) and a TSB level>15 mg/dL above AAP exchange levels. Statistically significant reduction in the incidence of TSB>30 mg/dL after universal bilirubin screening. Three cases of CBE occurred at facilities before universal bilirubin screening (0.88 per 100 000 infants), and 1 case occurred after universal bilirubin screening (0.54 per 100 000 infants), P = .70.	Among children with a maximum TSB>30 mg/dL, chronic, bilirubin-induced neurotoxicity was uncommon (8.5%, 4 of 47)
Andrea C. Wickremasinghe, MDa,b, Robert J. Risley, AudDc, Michael W. Kuzniewicz, MD, MPHd,e, Yvonne W. Wu, MD, MPHe,f, Eileen M. Walsh, RN, MPHd, Soora Wi, MPHd, Charles E. McCulloch, PhDb, Thomas B. Newman, MD, MPHb	C	n = 525 409 subjects born at >=35 wks All sensorineural hearing loss (SNHL) confirmed by review (blinded audiologist)	Primary predictor variable was having a TSB level at or above AAP ETT. Outcome variable was confirmed SNHL. Exposed cohort any TSB levels at or above 2004 AAP ETT (n = 1834). Unexposed cohort 3.6% random sample from whose TSB levels were all below AAP ETT. 10:1	Crude risk of confirmed SNHL was 11 of 1834 (6.0 per 1000) in the exposed cohort and 43 of 19 004 (2.3 of 1000) in the unexposed cohort (risk ratio: 2.65; exact P = .007). Unadjusted Cox proportional hazards models, subjects with TSB levels at or above AAP ETT (as a dichotomous variable) did not have a statistically significant increased risk of having	Some BAER responses known to be acutely altered by high bili but usually reversible. This suggests rate of true SNHL very rare.

Risk of Sensorineural Hearing Loss and Bilirubin Exchange Transfusion Thresholds PEDIATRICS Volume 136, number 3, September 2015			ratio of unexposed: exposed subjects (n = 19 004). Determine whether the peak difference between TSB level and ETT vs peak TSB level itself better predicts SNHL, --compared areas under ROC curves.	SNHL (HR: 1.6 [95% CI: 0.8 to 3.1]; P = .18). Only levels >10 mg/dL above ETT or >35mg/dl = sig. increase in risk of SNHL. Hazard Ratio 36 (13 to 101) RD 15 (3.4 to 32).	
Michael Sgro, MD, Douglas M. Campbell, MD, Sharmilaa Kandasamy, Vibhuti Shah, Incidence of Chronic Bilirubin Encephalopathy in Canada, 2007–2008 PEDIATRICS Volume 130, Number 4, October 2012	C	n = 20 infants born with symptoms of CBE and a history of hyperbilirubinemia and an abnormal MRI	CBE defined 2 ways: Neonatal TSB (highest recorded bilirubin >425 mmol/L [24.8 mg/L] or exchange transfusion) and 2 or more chronic neurologic symptoms: (a) extrapyramidal disorders (b) other movement disorders (spasticity or hypotonia); (c) gaze abnormalities; (d) sensorineural hearing loss; (e) intellectual deficits; and/or (f) enamel dysplasia of the deciduous teeth. History of significant neonatal hyperbilirubinemia (bilirubin .425 mmol/L or 24.8 mg/L), and an abnormal MRI finding.	20 confirmed cases of CBE. In follow-up 17 were abnormal neuro. Incidence 2.5 per 100,000. Etiologies: 8 – Hemolysis blood group incompatibilities. 5-G6PD 2- sepsis	Much higher than others reported.

Topic D. Hyperbilirubinemia Inpatient Guideline Evidence. Evaluation – Tc Bili

Reference Citation	Study Design	Patient Population (n)	Main variables or predictors [e.g. study group (n) & comparison group (n)]	Main relevant outcomes, results, and significance	Reviewer notes (include (a) methodological issues, (b) noteworthy harms)
Zabetta, Coda; Iskander, IF; Greco, C; Bellarosa, C; Demarini, S; Tiribelli, C; Wennberg, RP. Bilistick: A Low-Cost Point of Care System to Measure Total Plasma Bilirubin. Neonatology 2013; 103:177-181.	A	n = 118 neonates involved in a multicenter comparable study	Compare bilicheck (POC low cost) and serum bilirubin. 118 neonates, non-US.	The mean bilirubin concentration (+/-SD) was 215.6 +/- 85.5 micromol/l for Bilistick and 226.1 +/- 86.4 micromol/l by laboratory determination. Pearson's correlation coefficient between all paired results was 0.961, and the Bland-Altman analysis showed a mean difference of 10.3 micromol/l with a 95% interval of agreement of -38.0 to 58.7 micromol/l.	100 micro mol = 5.86 mg/dl.
Mandelbrot, L; Mazy, F; Floch-Tudal, C; Meier, F; Azria, E; Crenn-Hebert, C; Treluyer, JM; Herinomenzanahary, E; Ferreira, C; Peytavin, G. Atazanavir in Pregnancy: Impact on Neonatal Hyperbilirubinemia. European Journal of Obstetrics & Gynecology and Reproductive Biology, 2011; V: 157(1) 18-21	C	n = 22 HIV-infected women receiving atanazavir (ATV300)	23 term infants from 22 HIV-infected women receiving atanazavir (ATV300).	Bilirubin concentrations at birth were significantly higher than maternal concentrations, with a median of 44 mum/L [range 24-129]; values on days 2-3 were 63 [8-212]. Five neonates had jaundice requiring phototherapy, without liver damage, and recovered without sequelae.	These babies should be monitored differently (exclusion from the "healthy term" guideline?)
Hulzebos et al. The Bilirubin Albumin Ratio in the Management of Hyperbilirubinemia in Preterm Infants to Improve Neurodevelopmental Outcome: A Randomized Controlled Trial—BARTrial. PLoS One, 2014; 9(6).	A	n = 615 preterm infants of 32 weeks' gestation or less	RCT assigned to treatment based on either B/A ratio and TSB thresholds.	Motor and cognitive function at 24 and 48 months – no difference. Composite motor (100 ± 13 vs. 101 ± 12) and cognitive (101 ± 12 vs. 101 ± 11) scores did not differ between the B/A ratio and TSB groups. Demographic characteristics, maximal TSB levels, B/A ratios, and other secondary outcomes were similar. The rates of death and/or severe neurodevelopmental impairment for the B/A ratio versus TSB groups were 15.4% versus 15.5% (P = 1.0) and 2.8% versus 1.4% (P = 0.62) for birth weights ≤ 1000 g and 1.8% versus 5.8% (P = 0.03) and 4.1% versus 2.0% (P = 0.26) for birth weights of >1000 g.	NA

Topic E. Hyperbilirubinemia Inpatient Guideline Evidence. Risk

Reference Citation	Study Design	Patient Population (n)	Main variables or predictors [e.g. study group (n) & comparison group (n)]	Main relevant outcomes, results, and significance	Reviewer notes (include (a) methodological issues, (b) noteworthy harms)
Gamaleldin et al. Risk Factors for Neurotoxicity in Newborns with Severe Neonatal Hyperbilirubinemia. Pediatrics, October 2011; 128, 4.	C	n = 249 newborns with TSB level of ≥ 25 mg/dL	44 mod-severe ABE, 55 subtle ABE, 150 no ABE 35 had BE at discharge/death	Odds ratio (OR) of ABE or BE: Rh incompatible/anemia OR=48.6 Sepsis OR=20.6. ABO incompatible OR 1.8 (not sig).	BW/GA not assessed, no G6PD testing.
Weng et al. Risk Assessment for Adverse Outcome in Term and Late Preterm Neonates with Bilirubin Values of 20 mg/dL or More. Amer J Perinatol 2011; 28(5); 4405-412.	C	n = 288 infants with a TSB ≥ 20 mg/dL from 1995 to 2007	18 infants with bili >20 and neurologic sequelae 270 infants with bili >20 and no sequelae	Sepsis odds ratio (OR) =161, GI obstruction OR=39.2, Rh incompatibility OR=31.0, H.S. OR=19.6, ABO incompatibility OR=5.1, G6PD OR=4.7.	Only enrolled 67% of cases, small number of affected infants.
Maisels et al. Hyperbilirubinemia in the Newborn Infant ≥ 35 Weeks' Gestation: An Update with Clarifications. Pediatrics 2009; 124(4).	Guideline	NA	NA	Same risk factors as 2004 guideline. "Might increase the risk of brain damage."	Systematic review/guideline, see evidence tables in source.
Watchko, J.F. Identification of Neonates at Risk for Hazardous Hyperbilirubinemia: Emerging Clinical Insights. Pediatric Clinics of North America 2009; 56(3), 671-687.	Guideline	NA	NA	Late preterm, G6PD disproportionally present in US Pilot Kernicterus registry. ABO incompatibility in 15%, but small percentage develop bili >12.8. Often clinical jaundice in first 12-24 hours.	Systematic review/guideline, see evidence tables in source.
AAP, Management of Hyperbilirubinemia in the Newborn Infant 35 or more Weeks of Gestation. Pediatrics 2004; Jul; 114(1):297-316.	Guideline	NA	NA	Original definition of neurotoxicity risk factors by consensus. IJS not required for O+ if adequate risk assessment and follow up. IJS: on lights, rising rapidly (crossing percentiles).	Systematic review/guideline, see evidence tables in source.
Madan et al. Readmission for Newborn Jaundice: The Value of the Coombs' Test in Predicting the Need for Phototherapy. Sage Journals 2004; 43(1); 63-68.	C	n = 2443 infants with maternal blood type) or Rh Negative (Cord blood DAT performed)	n = 193 infants DAT positive n = 2250 infants DAT negative	DAT positive readmissions 2.6% DAT negative readmissions 0.9% (p=-.07)	DAT may have benefitted 3 infants, 2 who got early photo and 1 who had late-onset jaundice.
Judd et al. Practice Guidelines for Prenatal and Perinatal Immunohematology, revisited. TOC 2001; 41(11); 1445—1452.	Guideline	NA	NA	All women should be tested for ABO, D, and antibody screen Routine cord blood tests not necessary. If mom Rh neg, send baby Rh. If mom has potentially significant antibodies, send ABO/Rh/DAT.	Systematic review/guideline, see evidence tables in source.

Topic F. Hyperbilirubinemia Inpatient Guideline Evidence. Etiology and Diagnostics

Reference Citation	Study Design	Patient Population (n)	Main variables or predictors [e.g. study group (n) & comparison group (n)]	Main relevant outcomes, results, and significance	Reviewer notes (include (a) methodological issues, (b) noteworthy harms)
American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. Pediatrics 2004; 114(1).	Guideline	NA	NA	Infants who have an elevation of direct reacting bilirubin should have UA and urine culture, and sepsis work-up. (if TSH >5, direct>20% is abnormal) (level C) Sick infants and prolonged jaundice >3w should have split bili to identify cholestasis (B/H exceptional) If direct bili is elevated, additional eval for cholestasis should be done (level C) G6PD level is recommended for infants with phototherapy + family h/o G6PD or ethnically suggestive of G6PD, or poor response to phototherapy. (Level C) It is option to measure albumin to lower threashold of phototherapy Albumin should be measured if exchange transfusion is being considered.	Systematic review/Guideline, see evidence tables in source.
NICE Neonatal Jaundice. May 2010	Guideline	n = 12 studies with 2333 participants	Causes of jaundice	Blood incompatibility G6PD Infection No known causes	Systematic review/Guideline, see evidence tables in source.
		3 case series (N 42-381)	Prolonged (>14d) jaundice	Guidance suggests to: 1. look for pale chalky stools and/or dark urine that stains the nappy 2. Measure split 3. CBC 4. blood type and DAT 5. urine culture Consult specialist if DB> 1.46	Systematic review/Guideline, see evidence tables in source.
Tizzard, S; Davenport, M. Early Identification and Referral of Liver Disease. Community Practitioner; London, 2007; 80(9).	Guideline	NA	NA	Causes of jaundice	Prolong jaundice over 2 weeks in term, 3 weeks in preterm, need to get split. Additional tests: LFT (albumin, AST, ALT, ALP, GGT), coagulation (PT, PTT), glucose.

Rodie, MD; Barclay, A; Harry, C; Simpson, J. NICE Recommendations for the Formal Aassessment of Babies with Prolonged Jaundice: Too Much for Well Infants? BMJ Journals, 2012; 96(1).	D	n = 197 babies, 1.5% of live births, were referred with PJ	197 of 12 986 live births referred to prolonged jaundice.	PJ: 2–15% of all neonates and up to 40% of breastfed infants 1. Group 1 (NICE recommended algorithm) vs Group 2 (split bili + G6PD if ethnically appropriate). G2 reduced visits.	NA
Fattah, MA; Ghany, EA; Mosallam, D; Kamal, S. Glucose-6-Phosphate Dehydrogenase and Red Cell Pyruvate Kinase Deficiency in Neonatal Jaundice Cases in Egypt. Pediatric Hematology and Oncology, 2010; 27(4), 262-271.	D	n = 69 newborns with indirect hyperbilirubinemia	Sixty-nine newborns with unconjugated hyperbilirubinemia that required admission for treatment. Age = less than 28 days	G6PD deficiency among Egyptian neonates with hyperbilirubinemia (10 cases) is 14.4% (21.2% of males). Two cases with PK deficiency were detected, making the prevalence of its deficiency 2.8%.	Small sample.
Bhutani, VK et al. Predischarge Screening for Severe Neonatal Hyperbilirubinemia Identifies Infants Who Need Phototherapy. Journal of Pediatrics, 2013; 162(3), 477-482.e1	D	n = healthy infants of ≥ 35 weeks' gestation	1157 infants (2005-2007). multiple logistic regression analysis to evaluate the predictive value of bilirubin measurements. Measurements before discharge, 3-5 days, and 7-14 days.	Predictors for phototherapy use highest with combination model: clinical risk factors and age-adjusted (for hours) TSB/TcB, which is same as Age-adjusted (for hours) TSB/TcB and GA (weeks). (Risk factors: GA < 39 weeks, bruising, cephalohematoma, blood type incompatibility, East Asian ancestry, and positive DAT test.)	When bilirubin effects are included in the model, jaundice zone and positive DAT no longer add significant information. The statistical significance of predischarge exclusive breastfeeding and cephalohematoma was also reduced. Agreeing 2009 AAP update on the guideline on risk factors. Babies treated with phototherapy < 60 hours were excluded. NICU babies were excluded.
Poddar, U; Bhattacharya, A; Thapa, BR; Mittal, BR; Singh, K. Ursodeoxycholic Acid-Augmented Hepatobiliary Scintigraphy in the Evaluation of Neonatal Jaundice.	4	n = 51 Jaundice babies (0.3 mo-5.5 mo, median 2.9 mo)	51 infants with jaundice underwent 99 mTc-mebrofenin hepatobiliary scintigraphy, followed by UDCA if not excreted in 24 hour.	19 showed biliary excretion in the first study, ruling out extrahepatic biliary atresia. Neonatal hepatitis was the final diagnosis in these. Of the remaining 32 patients, 12 nonexcretors converted to excretors after UDCA treatment, whereas 20 still showed no biliary drainage. Four nonexcretors on scintigraphy had a final diagnosis of neonatal hepatitis with galactosemia; the remaining 16 had extrahepatic biliary atresia. The specificity of hepatobiliary scintigraphy in ruling out extrahepatic biliary atresia improved from 54.3% to 88.6% (P < 0.001) after UDCA treatment. None of the patients experienced any ill effects from UDCA administration.	Author's conclusion: Pretreatment with UDCA significantly improves the specificity of hepatobiliary scintigraphy in ruling out extrahepatic biliary atresia as a cause of prolonged neonatal jaundice. Prolonged jaundice- needs further tests (what defines "prolonged"?).

Cartledge, P. Prolonged Jaundice in Infants. Community Practitioner, 2009; 82(5), 36-7.	Guideline	Guideline on prolonged jaundice	NA	Term- over 2w, preterm=over 3w. Direct bili 20% of total bili – indicative of liver disease	Recommendation is for "practitioner" to to refer to pediatritian if total bili is over 11.7 mg/DL even if split is less than 20%.

Topic G. Hyperbilirubinemia Inpatient Guideline Evidence. Nursing Discharge

Reference Citation	Study Design	Patient Population (n)	Main variables or predictors [e.g. study group (n) & comparison group (n)]	Main relevant outcomes, results, and significance	Reviewer notes (include (a) methodological issues, (b) noteworthy harms)
Maisels, MJ; Bhutani, VK; Bogen, D; Newman, TB; Stark, AR; Watchko, JF. Hyperbilirubinemia in the Newborn Infant > or = 35 Weeks' Gestation: An Update with Clarifications. Pediatrics, 2009; 124(4): 1193-1198.	Guideline	AAP guideline 2009	NA	Most infants discharged < 72 hours should be seen within 2 days of DC (recommendation- no data). Algorithm after discharge TcB *2. TSB should always be measured if therapeutic intervention is considered. TcB underestimate particularly at higher levels. To avoid missing high TSB, measure TcB is 70% of recommended treatment value, or 75%ile. Or, at follow up outpatient, TcB 13 or higher.	Systematic review/Guideline, see evidence tables in source.
Romagnoli et al. Italian Guidelines for Management and Treatment of Hyperbilirubinaemia of Newborn Infants ≥ 35 Weeks' Gestational Age. Ital J Pediatr 2014; 40(11).	Guideline	N/A	NA	If TcB > 75%, TSB is done. TSB < 50% before48 hours or < 75% after 48 hours, no further evaluation is needed. TSB > 50% before 48 hours or 75% after 48 hours, TSB should be repeated in 24-48 hours.	Systematic review/Guideline, see evidence tables in source. Analysis of 3 Italian studies to norm literature findings to the Italian population.
Romagnoli et al. Development and Validation of Serum Bilirubin Nomogram to Predict the Absence of Risk for Severe Hyperbilirubinaemia Before Discharge: A Prospective, Multicenter Study. Italian Journal of Pediatrics 2012; 38(6).	C	n = 1708 healthy full term neonates	A percentile-based hour-specific nomogram for TSB values was performed using TSB data of 1708 healthy full term neonates.	If TcB > 75%ile, serum B. If < 50% during first 48 hours, no evaluations. If 50-75 during first 48 hours, test again.	NA
Darling, KE; Ramsay, T; Sprague, AI; Walker, MC; Guttmann, A. Universal Bilirubin Screening and Health Care Utilization. Pediatrics 2014; 134(4): 1017-24.	C	n = newborns 2003-2011 from 42 hospitals in Ontario, Canada	2003-2011 from 42 hospitals that implemented universal bilirubin screening between July 2007 and June 2010 to compare costs and LOS.	Screening was associated with an increase in phototherapy during hospitalization at birth (relative risk, 1.32; 95% confidence interval, 1.09-1.59) and a decrease in jaundice-related emergency department visits (relative risk, 0.79; 95% confidence interval, 0.64-0.96) but no statistically significant difference in phototherapy after discharge, LOS, or jaundice-related readmissions after accounting for preexisting temporal trends in health care service use and other patient sociodemographic and hospital characteristics.	NA

Eggert, LD; Wiedmeier, SE; Wilson, J; Christensen, RD. The Effect of Instituting a Prehospital-discharge Newborn Bilirubin Screening Program in an 18 Hospital Health System. Pediatrics, 2006; 117(5): 855-62.	C	n = 101,272 neonates delivered at > or = 35 weeks' gestation	Before and after universal screening of TSB/TcB. March 1, 2001, to December 31, 2002, versus January 1, 2003, to December 31, 2004. A bilirubin screening program, instituted in December 2002.	The study involved 101,272 neonates: 48,789 in period 1 and 52,483 in period 2. Before the program, 1 in every 77 neonates born had 1 or more serum bilirubin levels > 20 mg/dL. After initiating the program, the incidence fell to 1 in 142 and the number of neonates with a level > 25 mg/dL fell from 1 in 1,522 before to 1 in 4,037 after. The rate of hospital readmission with a primary diagnosis of jaundice fell from 0.55% in period 1 to 0.43% in period 2.	NA
Engle, WD; Jackson, GL; Stehel, EK; Sendelbach, DM; Manning, MD. Evaluation of a Transcutaneous Jaundice Meter Following Hospital Discharge in Term and Near-term Neonates. Journal of Perinatology, 2005; 25(7): 486-490.	C	n = 121 neonates median gestational age of 40 either exclusively or partially breastfed	Minolta JM-103 Jaundice Meter (JM) were compared with serum bilirubin.	Overall correlation between JM and TSB was 0.77 (p17 mg/dl, a cutoff value for JM of 13 mg/dl had a sensitivity of 1.0, and 50% of TSB determinations would be avoided. JM may facilitate outpatient management of hyperbilirubinemia by reducing the number of TSB determinations required; however, it does not provide a reliable substitute for laboratory measurement of TSB.	NA
Ho, Ey; Lee, Sy; Chow, CB; Chung, JW. BiliCheck Transcutaneous Bilirubinometer: A Screening Tool for Neonatal Jaundice in the Chinese Population. Hong Kong Medical Journal, 2006; 12(2): 99-102.	C	n = 83 neonates with gestation above 32 weeks with neonatal jaundice	Neonates with gestation above 32 weeks with neonatal jaundice who were admitted between April 2001 and February 2002. 77 term and six near-term babies, sternum and forehead Tc Bili (JM and bilicheck) compared with serum bili.	The correlations between serum bilirubin and transcutaneous bilirubin measurements of the two devices at the two sites were high, with a coefficient of 0.718 (95% confidence interval, 0.610-0.800; n=100) for forehead measurements, and 0.814 (95% confidence interval, 0.740-0.870; n=99) for sternum using the Minolta Airshields JM 102; and a coefficient of 0.757 (95% confidence interval, 0.657-0.827; n=98) for forehead measurements, and 0.794 (95% confidence interval, 0.700-0.862; n=92) for sternum using the BiliCheck. For BiliCheck, a cut-off point of 250 micromol/L at the forehead and 260 micromol/L at the sternum had a specificity of 61.9% and 70.0%, respectively with a sensitivity of 100% for the detection of serum bilirubin concentrations of 250 micromol/L or higher. This level is commonly used as the level for initiation of treatment such as phototherapy.	BiliCheck is a useful screening tool for neonatal jaundice in the Chinese population and is comparable with the Minolta Airshields JM 102.

Ip, S; Chung, M; Kulig, J; O'Brien, R; Sege, R; Glicken, S; Maisels, MJ; Lau, J; American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. An Evidence-based Review of Important Issues Concerning Neonatal Hyperbilirubinemia. Pediatrics, 2004; 114(1): 130-53.	A	n = 35 articles in the correlation section (questions 1 and 2) 28 articles of kernicterus case reports, 21 articles in the treatment section (question 3), and 54 articles in the diagnosis section (questions 4 and 5).	Target population of this review was healthy, term infants. This review included articles concerning infants who were at least 34 weeks' EGA at the time of birth. From studies that reported birth weight rather than age, infants whose birth weight was greater than or equal to 2500 g were included.	Transcutaneous measurements of bilirubin have a linear correlation to total serum bilirubin and may be useful as screening devices to detect clinically significant jaundice and decrease the need for serum bilirubin determinations.	NA
Raimondi, F; Lama, S; Landolfo, F; Sellitto, M; Maffucci, R; Milite, P; Capasso, L. Measuring Transcutaneous Bilirubin: A Comparative Analysis of Three Devices on a Multiracial Population. BMC Pediatrics, 2012: 12(70).	C	San Francisco n = 289 neonates, 35 – 41w, BW 1800 - 4350 g, 4h to 424h	Examine Tc bilirubin and TSB.	Pearson coefficients showed good results for Bilicheck (r = 0.86) and JM-103 (r = 0.85) but poor for BiliMed (r = 0.70). Similar results were found for the non-Caucasian neonates subgroup. Bilicheck and JM-103 had a greater area under the curve than BiliMed when TSB = 14 mg/dl was chosen as a threshold value both for the total study population and the non-Caucasian subgroup.	NA

Rodriguez-Capote, K; Kim, K; Paes, B; turner, D; Grey, V. Clinical Implication of the Difference Between Transcutaneous Bilirubinometry and Total Serum Bilirubin for the Classification of Newborns at Risk of Hyperbilirubinemia. Clin Biochem, 2009, 42(3): 176-179.	C	Ontario, Canada n = 154 term infants	Examine Tc bilirubin and TSB.	TC bili correlated (BiliCheck-Vitros, R2=0.86; Minolta Air-Shields JM-103-Vitros, R2=0.85), but underestimated the serum bilirubin. Applying the risk classification using the 40th, 75th, and 95th percentile of the Bhutani nomogram a 6%, 0%, and 1% false negative rate was found for BiliCheck and 62%, 74% and 81% for the Minolta Air-Shields JM-103 device. After correcting for the differences using either the bias or the 95% CI the false negative rate was reduced to zero in all cases.	TcB measurements cannot be directly applied to a TSB nomogram but must be adjusted for any observed biases in order to avoid misclassifying newborns at risk for hyperbilirubinemia.
Romagnoli, C; Tiberi, E; Barone, G; DeCurtis, M; Regoli, D; Paolillo, P; Picone, S; Anania, S; Finocchi, M; Cardiello, V; Zecca, E. Validation of Transcutaneous Bilirubin Nomogram in Identifying Neonates not at Risk of Hyperbilirubinemia: A Prospective, Observational, Multicenter Study. Early Hum Dev., 2012; 88(1): 51-55.	C	Italy, prospective multicenter n = 2167 term and late preterm infants born in 5 neonatal units	All neonates had simultaneous TcB and total serum bilirubin (TSB) measurements, when jaundice appeared and/or before hospital discharge. TcB and TSB values were plotted on a percentile-based hour-specific transcutaneous nomogram previously developed, to identify the safe percentile able to predict subsequent significant hyperbilirubinemia defined as serum bilirubin >17 mg/dL or need for phototherapy.	Fifty-five babies (2.5%) developed significant hyperbilirubinemia. The 50th percentile of our nomogram was able to identify all babies who were at risk of significant hyperbilirubinemia, but with a high false positive rate. Using the 75th percentile, two false negatives reduced sensitivity in the first 48 hours but we were able to detect all babies at risk after the 48th hour of age.	75th percentile of our TcB nomogram is able to exclude any subsequent severe hyperbilirubinemia from 48 hour of life ahead.
Wickremasinghe, AC; Karon, BS; Cook, WJ. Acuracy of Neonatal Transcutaneous Bilirubin Measurement in the Outpatient Setting. Clin Pediatr., 2011; 50(12): 1144-1149.	C	n = 79 infants discharged with high-risk or high-intermediate risk total serum bilirubin	Tc bili and TSB were measured at outpatient at 3-7 days, and plotted.	Mean bias and standard deviation between TcB and TsB was 1.5 +/- 2.1 mg/dL for outpatients, compared with 2.7 +/- 1.3 mg/dL for inpatients. The sensitivity and specificity of HR or HIR TcB for predicting an HR or HIR TSB were 87% and 58%, respectively. Of 9 infants readmitted for phototherapy, 1 had a low-risk TcB and high-risk TSB.	NA

Keren R, Luan X, Friedman S, Saddlemire S, Cnaan A, Bhutani VK. A Comparison of Alternative Risk-Assessment Strategies for Predicting Significant Neonatal Hyperbilirubinemia in Term and Near-term Infants. Pediatrics, 2008; 121(1): e170.	C	n = 823 infant > 35w in Pennsylvania	Compare discharge TcB only vs TcB plus risk factors (GA, black race, intended breast feeding, extent of jaundice and gender).	Risk of development of significant jaundice is higher only with low GA (< 38w).	An infant's risk of developing significant hyperbilirubinemia can be simply and accurately assessed by using just the infant's predischarge bilirubin level and gestational age.
Maisels MJ, Deridder JM, Kring EA, Balasubramaniam M. Routine Transcutaneous Bilirubin Measurements Combined with Clinical Risk Factors Improve the Prediction of Subsequent Hyperbilirubinemia. J Perinatol., 2009; 29(9): 512.	C	n = 11,456 discharged infants in Michigan from a well-baby nursery	75 infants admitted for hyperbili TSB>17. Compared factors.	Combining discharge TcB plus GA and exclusive breastfeeding improved prediction.	Adding breast feeding does not show significant difference from GA plus TcB only.

Topic H. Hyperbilirubinemia Inpatient Guideline Evidence. Prevention

Reference Citation	Study Design	Patient Population (n)	Main variables or predictors [e.g. study group (n) & comparison group (n)]	Main relevant outcomes, results, and significance	Reviewer notes (include (a) methodological issues, (b) noteworthy harms)
McDonald, S; Middleton, P; Dowswell, T; Morris, P. Effect of Timing of Umbilical Cord Clamping of Term Infants on Maternal and Neonatal Outcomes. Cochrane Database of Systemic Reviews, July 2013,	A	n = 15 studies involving 3,911 women and infant pairs	Early versus late cord cramp	Fewer infants in the early cord clamping group required phototherapy for jaundice than in the late cord clamping group (RR 0.62, 95% CI 0.41 to 0.96, data from seven trials, 2324 infants with a LCER of 4.36%, I2 0%). Haemoglobin concentration in infants at 24 to 48 hours was significantly lower in the early cord clamping group (MD -1.49 g/dL, 95% CI -1.78 to -1.21; 884 infants, I2 59%). This difference in haemoglobin concentration was not seen at subsequent assessments. Improvement in iron stores appeared to persist, with infants in the early cord clamping over twice as likely to be iron deficient at three to six months compared with infants whose cord clamping was delayed (RR 2.65 95% CI 1.04 to 6.73, five trials, 1152 infants, I2 82%). In the only trial to report longer-term neurodevelopmental outcomes so far, no overall differences between early and late clamping were seen for Ages and Stages Questionnaire scores.	A more liberal approach to delaying clamping of the umbilical cord in healthy term infants appears to be warranted, particularly in light of growing evidence that delayed cord clamping increases early haemoglobin concentrations and iron stores in infants. Delayed cord clamping is likely to be beneficial as long as access to treatment for jaundice requiring phototherapy is available.
American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. Journal of neurosurgery. Pediatrics, 2004.	Guideline	NA	NA	Recommends 8-10 feeds during first 24 hours, but no data.	Systematic review/Guideline, see evidence tables in source.
Martin TC; Shea M; Alexander D; Bradbury L; Lovell-Roberts L; Francis. Did exclusive Breast-feeding and Early Discharge Lead to Excessive Bilirubin Levels in Newborns in Antigua and Barbuda? West Indian Med Journal, 2002; V51 (2) 84.	E	n = 3,721 infants born in Antigua and Barbuda with hyperbilirubinemia	Review of Special Care Nursery and Maternity Ward records was undertaken to determine the incidence and etiology of hyperbilirubinemia from 1992 to 1994.	Higher incidence of hyperbilirubinemia (total bilirubin > 15 mg/dl 7.1% compared to 5.9% in India and 2% of breast-fed infants in USA. Total bilirubin > 20 mg/dl 2.5% exceeding reported prevalence in the USA for both African-American and Caucasian infants (1%) and equal to the reported prevalence in Asian infants (2%). Following the appointment of a dietitian to supervise breast-feeding, admissions for hyperbilirubinemia fell by 50% by 1998.	These data suggest that exclusive breast-feeding and early discharge led to an epidemic of neonatal hyperbilirubinemia in Antigua and Barbuda.

Demiraran, Y. Effect of Anesthesiological Strategies on Neonatal Bilirubin Levels During Cesarean Section: A Prospective and Randomized Trial. Archives of Gynecology & Obstetrics, 2011; V: 284 (5) 1059.	B	n = 167 ASA I–II status uncomplicated pregnant women who delivered by caesarean section	167 women who had CS were randomized based on anesthesiological strategy: inhalation (IA), spinal (SA), total intravenous (TIVA), and epidural anesthesia (EA) groups.	Direct bilirubin levels at 24th hour of SA group and EA group were higher compared to IA group ($p = 0.008$). When DB levels at fifth day were compared, levels in group TIVA were significantly higher than group SA ($p = 0.019$). TB levels at fifth day in group TIVA were higher than SA and EA groups ($p = 0.05$). The percentage of newborns needing phototherapy did not differ significantly among groups, but was highest in the TIVA group (25%), followed by the IA (15%), EA (10%) and SA (7%) groups ($p = 0.08$).	EA and SA are the standard of care in U.S.
Yaseen, H. Does Prophylactic Phototherapy Prevent Hyperbilirubinemia in Neonates with ABO Incompatibility and Positive Coombs' Test? Journal of Perinatology, 2005; V: 25 (9) 590.	B	n = 242 United Arab Emeritus newborns with positive DCT	242 babies with ABO incompatibility with positive DAT enrolled to phototherapy for 24 hours or no treatment by 4 hours of life.	A total of 102 infants were allocated to the prophylactic phototherapy arm and 140 as controls. Prophylactic phototherapy was associated with a significant decrease in the TSB at 24 hours ($p=0.002$) and at 48 hours ($p=0.003$) but not later on.	Prophylactic phototherapy was associated with a significant reduction of TSB in the first 48 hours of life but not later on. Clinical benefits of this strategy could not be proven.
Gourley, GR. A Controlled, Randomized, Double-blind Trial of Prophylaxis Against Jaundice Among Breastfed Newborns. Pediatrics, 2005; V: 116 (2) 385.	B	n = 64 Oregon breastfed newborns were randomized into 4 groups	Control or receiving 6 doses per day (5 mL per dose) of L-aspartic acid, enzymatically hydrolyzed casein (EHC), or whey/casein (W/C) for the first week.	L-aspartic acid, EHC, and W/C groups had significantly lower transcutaneous bilirubin levels than did the control group (75.8%, 69.6%, and 69.2%, respectively, of the control mean, 8.53 mg/dL at the bilirubin peak on day 4). The L-aspartic acid, EHC, and W/C groups had significantly lower transcutaneous bilirubin levels on days 3 to 7. Fecal bile pigment excretion was greatest in the L-aspartic acid group, significantly greater than control values.	Small study and small difference to recommend them to all newborn (SL).

Topic I. Hyperbilirubinemia Inpatient Guideline Evidence. Evaluation

Reference Citation	Study Design	Patient Population (n)	Main variables or predictors [e.g. study group (n) & comparison group (n)]	Main relevant outcomes, results, and significance	Reviewer notes (include (a) methodological issues, (b) noteworthy harms)
Taylor, JA; Burgos, AE; Flaherman, V; Chung, EK; Simpson, EA; Goyal, NK; Von Kohorn, I; Dhepyasuwan, N. Discrepancies Between Transcutaneous and Serum Bilirubin Measurements. Pediatrics, 2015; 135(2).	C	n = 925 linked transcutaneous and serum measurements	TcB measurements were collected during two 2-week periods on neonates admitted to participating newborn nurseries.	TcB underestimates in first 48 hours (OR 3.31), overestimates in African-Americans (OR 3.09) TcB average 1.4 lower when TsB>15 2.2% of measurements underestimated by 3 or more.	NA
Bhat, RY; Kumar, PC. Sixth Hour Transcutaneous Bilirubin Predicting Significant Hyperbilirubinemia in ABO incompatible Neonates. World Journal of Pediatrics, 2014; 10(2): 182-185.	C	n = 144 ABO incompatible newborns had TcB measured	Cases – 41 required phototherapy. Controls – 103 did not require phototherapy.	6^{th} hour levels without significant hyperbili = 3.65+/-0.96, with hyperbili = 5.83+/-1.35 ($p<0.001$).	
Wickremasinghe, AC; Karon, BS; Saenger, AK; Cook, WJ. Effect of Universal neonatal Transcutaneous Bilirubin Screening on Blood Draws for Bilirubin Analysis and Phototherapy Usage. Journal of Perinatology, 2012; 32: 851-855.	C	n = 3381 infants ⩾36 weeks gestation	Period 1: serum bilirubin ordered at clinicians' discretion Period 2: Universal TcB	Total blood draws the same Increase in outpatient blood draws ($p<0.0001$) Decrease in phototherapy rate ($p<0.0001$) Increase in readmissions for phototherapy ($p=0.04$)	
Schutzman, DL; Sekhon, R; Hundalani, S. Hour-specific Bilirubin Nomogram in Infants with ABO Incompatibility and Direct Coombs-positive Results. Arch Pediatr Adolesc Med., 2010; 164(12): 1158-1164.	C	n = 240 coombs positive, 460 coombs negative	Subsequent need for phototherapy	Sensitivity and specificity in zone 4 (74%, 97%) and zones 3/4 combined (97%, 84%). Compared with Bhutani zone 4 (54%, 96%) and zone 3/4 combined (90%, 85%). LR Zone 4 = 25.8, compared with Bhutani 14.1 in coombs-negative.	Zones 2 and 3 actually had lower LR than Bhutani.

Topic J. Hyperbilirubinemia Inpatient Guideline Evidence. Admission Triage

Reference Citation	Study Design	Patient Population (n)	Main variables or predictors [e.g. study group (n) & comparison group (n)]	Main relevant outcomes, results, and significance	Reviewer notes (include (a) methodological issues, (b) noteworthy harms)
American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. Pediatrics 2004; 114(1).	Guideline	AAP 2004	Follow up	All infants should be examined in first few days after discharge. Discharge before 24h, should be seen by 72h. DC 24h-48h, by 96h but may need 2 visits. DC 48-72h should be seen by 120h. Follow up assessment should include the infants' weight, percent change from BW, adequacy of feeding, pattern of voiding and stooling, and presence of jaundice. Bilirubin measurement is determined by clinical judgement, with low threshold.	No data. There is comment on evaluation of adequacy of breast fed infants (went diaper, meconium change, weight loss over 10%).
Mishra, S; Chawla, D; Agarwal, R; Deorari, AK; Paul, VK; Bhutani, VK. Transcutaneous Bilirubinometry Reduces the Need for Blood Sampling in Neonates with Visible Jaundice. Paediatrica 2009.	A	India, Neonate, n = 314 vs 303	Visual assessment versus TcB to measure serum bilirubin check.	TcB reduced the need for Serum TB measurement.	Only one pediatrician for visual assessment.
Madlon-Kay, DJ. Home Health Nurse Clinical Assessment of Neonatal Jaundice. Arch Pediatr Adolesc Med. 2001;155(5): 583-586.	A	US, home health (2-14 days old) n = 164	Compare nurses' assessment, caudal progression, icterometer, with serum bilirubin.	Most correlated with nurse's assessment.	Small samples.
Bhutani, VK; Johnson, LH; Schwoebel, A; Gennaro, S. A Systems Approach for Neonatal Hyperbilirubinemia in Term and Near-term Newborns. J. Obstet Gynecol Neonatal Nurs, 2006; 35(4): 444-55.	C	n = 31,059 well babies discharged from the hospital	System based approach, algorithm based on nomogram. 99^{th} %ile, intensive treatment, 95-99, TSB in 6-12 h, 75-95%, TSB/TcB and MD FU in 24h, 40-75%, TcB in 48h. Check for jaundice every 8-12 hours until 48h.	Readmission rate is less with system-approach, compared to AAP guidelines +universal screen.	NA

American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. Pediatrics 2004; 114(1).	Guideline	AAP 2004	Follow up	All infants should be examined in first few days after discharge. Discharge before 24h, should be seen by 72h. DC 24h-48h, by 96h but may need 2 visits. DC 48-72h should be seen by 120h. Follow up assessment should include the infants' weight, percent change from BW, adequacy of feeding, pattern of voiding and stooling, and presence of jaundice. Bilirubin measurement is determined by clinical judgement, with low threshold.	No data There is comment on evaluation of adequacy of breast fed infants (went diaper, meconium change, weight loss over 10%).

Topic K. Hyperbilirubinemia Inpatient Guideline Evidence. Albumin Prime

Reference Citation	Study Design	Patient Population (n)	Main variables or predictors [e.g. study group (n) & comparison group (n)]	Main relevant outcomes, results, and significance	Reviewer notes (include (a) methodological issues, (b) noteworthy harms)
Shahian et al. Effect of albumin administration prior to exchange transfusion in term neonates with hyperbilirubinemia – A randomized controlled trial. Indian Pediatrics 2010; 47: 241–4. https://doi.org/10.1007/s13312-010-0046-x	B	n = 50 out-born term neonates (gestational age > 37 weeks) with non-haemolytic hyperbilirubinaemia (TSB ≥ 25 mg/dl [427.5 micromol/l]) who had not responded to 'intensive' phototherapy Iranian pts	25 infants received an albumin infusion of 20%- 1 /kg, 1 hour before exchange transfusion. Control group (n=25), exchange transfusion was done without prior albumin infusion.	TSB lower in the albumin group at 6 hours (mean ± SD = 14.4 ± 1.7 mg/dl [246.2 ± 29.1 micromol/l] vs 21.7 ± 3.2 mg/dl [371.1 ± 54.7 micromol/l] respectively, p < 0.001), and at 12 hours (8 ± 1.5 mg/dl [136.8 ± 25.7 micromol/l] vs 16.1 ± 2.1 mg/dl [275.3 ± 35.9 micromol/l] respectively, p < 0.001). Duration of phototherapy was shorter in the albumin group (8.6 ± 2.4 hours' vs 25 ± 8.2 hours, p < 0.001). No infant in the albumin group needed a second exchange transfusion but four infants in the control group did.	The only RCT in term infants found. Control – no extra volume (20% 1g/kg = 5ml/kg?) IV hydration may lower TSB. No harm seen.
Souvik Mitra, Moumita Samanta, Mihir Sarkar, Arun Kumar De, and Sukanta Chatterjee Pre-exchange 5% Albumin Infusion in Low Birth Weight Neonates with Intensive Phototherapy Failure—A Randomized Controlled Trial Journal of Tropical Pediatrics, Vol. 57, No. 3, 2011	B	n = 42 Healthy Low birth Weight (gest age >32 weeks) infants with phototherapy failure	Treatment = 5% albumin 1g/kg IV over 2hrs. prior to ET. Control = 20ml kg maintenance IV fluid over 2 hrs.	TSB lower in the RX group at 6 and 12 hr. Fewer repeat ETs in treatment group (p=0.05) A shorter hospital stay in RX group.	No harm seen. Not the patient of interest (premies) to us, but pts are bigger premies (>32 weeks) and finding mimic the only RCT in bigger babies.

Topic L. Bilirubinemia Inpatient Guideline Evidence. Phototx

Reference Citation	Study Design	Patient Population (n)	Main variables or predictors [e.g. study group (n) & comparison group (n)]	Main relevant outcomes, results, and significance	Reviewer notes (include (a) methodological issues, (b) noteworthy harms)
NICE. Neonatal Jaundice. May 2010.	B	Term near term n = 7 studies RCT, 667 pts	Phototx versus usual care.	Fewer ET needed with phototx. RR 0.36 (CI 0.22-0.59). Fewer treatment failures. (ET or 2 successive increases in bili values or > bili considered failure. RR 0.37 (CI 0.24-0,58)).	Older studies used lower irradiance values underestimating effectiveness of Phototx. Various thresholds to start phototx.
Maurer, HM; Kirkpatrick, BV; McWilliams, NB; Draper, DA; Bryla, DA. Phototherapy for hyperbilirubinemia of Hemolytic Disease of the Newborn. Pediatrics, 1985; 75(2): 407-412.	A	n = 64 infants with positive Coombs test Mixed race BW mean > 2500gms Phototx initiated when bili > 13mg/dl	Phototx n=34 vs usual care n=30	6 Rh infant's Rh disease, 58 ABO. 7/34 Phototx, 6/30 control required ET p>0.05.	Phototx initiated at mean bili > 15 mg/dl. Late start of phototx and lower irradiance may have prevented effectiveness of phototx.
Kuzniewicz, MW; Escobar, GJ; Wi, S; Liljestrand, P; McCulloch, C; Newman, TB. Risk Factors for Severe Hyperbilirubinemia Among Infants with Borderline Bilirubin Levels: A Nested Case-Control Study. J. Pediatr, 2008; 153(2): 234-240.	C	n = 285,295 infants > = 34 wks > 2000gms 17,986 with bili 17 - 22.9 mg selected Case = bili > = 25 mg/dl n = 64 101 controls matched for initial bili Phototx of different types	ANOVA with Multiple predictor variables included phototx.	Phototx associated with fewer bili values > 25. OR 0.15 (0.06-0.40). Family hx jaundice, bruising, TSB rise > 6mg/dl /day, exclusive breast feeding all associated with ET. GA > 37wks associated with decreased TSB > 25. DAT = + not associated with bili > 25. No evidence of decreased effectiveness of phototx with DAT+.	Study in 2008, AAP guidelines in effect.
Newman, TB; Kuzniewicz, MW; Liljestrand, P; Wi, S; McCulloch, C; Escobar, GJ. Numbers Needed to Treat with Phototherapy According to American Academy of Pediatrics Guidelines. Pediatrics 2009; 123:1352–1359.	C	n = 281,898 infants n = 2.0 kg, > = 35 wks GA Qualifying TSB within 3 mg/dl of AAP rec phototx values. n = 22,547 5251 had phototx within 8 hrs 354 exceeded exchange TSB value	Outcome: AAP exchange value TSB. Phototx within 8 hrs of qualifying value. Multiple log reg to predict effectiveness of phototx to prevent TSB exceeding ET values. Gest age, age at initiation of phototx, TSB at initiation, DAT positive.	Gest age, age at initiation of phototx, TSB at initiation, DAT positive all OR sig. Sex GA, age at qualifying phototx all effect NNT, which ranged from 10 (male, 36 weeks, quali TSB at < 24 hrs) to 3041 (girls >41 weeks, > 72 hrs at qualifying bili). DAT+ phototx interaction noted. OR of 3.46 for the interaction term means the estimated OR for phototherapy when the DAT is positive is 3.46 times higher than when the DAT is negative, that is, 0.547 (95% CI: 0.21–1.45).	DAT positive diff results than above: 1. n = larger cohort. 2. TSB ET value = AAP vs 25mg/dl. Relied on procedure codes for data values.

Topic M. Hyperbilirubinemia Inpatient Guideline Evidence. Ivig

Reference Citation	Study Design	Patient Population (n)	Main variables or predictors [e.g. study group (n) & comparison group (n)]	Main relevant outcomes, results, and significance	Reviewer notes (include (a) methodological issues, (b) noteworthy harms)
Louis, D; More, K; Oberoi, S; Shah, PS. Intravenous Immunoglobulin in Isoimmune Haemolytic Disease of Newborn: An Updated Systematic Review and Meta-analysis. Arch Dis Child Fetal Neonatal ED, 2014; 99(4): F325-31.	A	n = 12 RCT studies (from 2200 citations) comparing IVIG with placebo/controls in neonates	Term and preterm (> 32 weeks) infants with hemolytic disease (criteria for isoimmune disease, Rh or ABO). All with phototherapy. IVIG in varying doses (most common 0.5 g/kg (up to 1 g/kg) various dosing intervals vs placebo or albumin or no rx. Risk of study bias assigned (high/low). Secondary analysis according to bias status. Prophylaxis (upon dx of hemolysis) versus with significant hyperbili).	Primary outcome = exchange tx (ET). Multiple secondary outcomes. Significant heterogeneity in bias noted precluding meta of group. 9 studies high risk of bias RH disease. RR 0.23 (CI 0.13 -0.40, NNT 3). 3 studies with low risk of bias RH disease RR 0.82 (CI 0.53-1.26). All ABO studies at high risk of bias. RR 0.31 (CI 0.18-0.55). RH prophylaxis (biased showed significant reduction in ET). No bias- no reduction.	No harm seen. Relatively small n for ABO disease. Heterogeneity in dosing amount and schedule compromises statistical power.
Keir AK, Dunn M, Callum J. Should intravenous immunoglobulin be used in infants with isoimmune haemolytic disease due to ABO incompatibility? J Paediatr Child Health. 2013 Dec;49(12):1072-8. doi: 10.1111/jpc.12440. Review. PubMed. PMID: 24325716.	A	n = 9 RCT	Infants with hemolysis, no search for G6PD (some studies in areas of high prevalence. IVIG vs Control. IVIG doses varying, schedule varying, phototx at various levels of bilirubin.	All studies biased or missing important data that could affect outcome. 3 studies showed decreased bili values, 6 reduced need for exchange tx.	No harm seen, but notes IVIG has risk, allergic, vol overload, tx associated lung disease, aseptic meningitis, thrombosis, and association with NEC. G6PD a concern for bias.
American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. Pediatrics, 2004; 114(4): 1138.	Guideline	NA	NA	ABO Recommends 0.5 g/kg over 2 hours with repeat dosing q 12 hours if necessary	Old Studies. Systematic review/Guideline, see evidence tables in source.
NICE guidelines, 2010. Jaundice in Newborn Babies Under 28 Days.	Guideline	NA	NA	ABO or Rh dz recommends 0.5 g/kg over 4 hours when serum bili rising rapidly (> 8.5 micro ml/ hour).	Systematic review/Guideline, see evidence tables in source.
Miqdad, AM; Abdelbasit, OB; Shaheed, MM; Seidahmed, MZ; Arcala, OP. IntravenousImmunoglobulin G (IVIG) Therapy for Significant Hyperbilirubinemia in ABO Hemolytic Disease of the Newborn. J Matern Fetal Neonatal Med, 2004; 16(3): 163-6.	A	n = 112 healthy term babies with ABO hemolytic disease	112 infants with Rh or ABO and hemolysis and rapidly rising bilirubin or at bili levels at risk. IVIG and Photo vs Photo alone.	IVIG reduced need for exchange tx.	Per Keil best study in their SR.

Topic N. Hyperbilirubinemia Inpatient Guideline Evidence. Treatment

Reference Citation	Study Design	Patient Population (n)	Main variables or predictors [e.g. study group (n) & comparison group (n)]	Main relevant outcomes, results, and significance	Reviewer notes (include (a) methodological issues, (b) noteworthy harms)
Neonatal Jaundice. May 2010.	Guideline	NA	NA	NA	Systematic review/Guideline, see evidence tables in source.
Mehta, S; Kumar, P; Narang, A. A Randomized Controlled Trial of Fluid Supplementation in Term Neonates with Severe Hyperbilirubinemia. The Journal of Pediatrics 2005; 147(6): 781-785.	A	Northern India. n = 74 term neonates with severe nonhemolytic hyperbilirubinemia (TSB > 18 mg/dL	Randomized to an "extra fluids" group (intravenous fluid supplementation for 8 hours and oral supplementation for the duration of phototherapy; n = 37) or a control group (n = 37).	At inclusion, 54 infants (73%) had high serum osmolality, including 28 (75%) in the extra fluids group and 26 (70%) in the control group. The proportion of infants who underwent exchange transfusion was lower in the extra fluids group than in the control group: 6 (16%) versus 20 (54%) (P = .001; relative risk = 0.30; 95% confidence interval = 0.14 to 0.66). The duration of phototherapy was also shorter in the extra fluids group: 52 +/- 18 hours versus 73 +/- 31 hours (P = .004).	Supplement is probably beneficial in “severe” hyperbilirubinemia (SL, what defines severe?)

Topic O. Hyperbilirubinemia Inpatient Guideline Evidence. Hydration

Reference Citation	Study Design	Patient Population (n)	Main variables or predictors [e.g. study group (n) & comparison group (n)]	Main relevant outcomes, results, and significance	Reviewer notes (include (a) methodological issues, (b) noteworthy harms)
Mehta, S., Kumar, P., Narang, A. A Randomized Controlled Trial of Fluid Supplementation in Term Neonates with Severe Hyperbilirubinemia. J Pediatrics 2005;147(6):781-785).	A	n = 74 term neonates (total serum bilirubin > 18 mg/dL [308 lmol/L] to < 25 mg/dL[427 lmol/L])	The subjects were randomized to an ‘‘extra fluids’’ group (intravenous fluid supplementation for 8 hours and oral supplementation for the duration of phototherapy; n = 37) or a control group (n = 37).	The proportion of infants who underwent exchange transfusion was lower in the extra fluids group than in the control group: 6 (16%) versus 20 (54%) (P = .001; relative risk = 0.30; 95% confidence interval = 0.14 to 0.66). The duration of phototherapy was shorter in the extra fluids group: 52 ± 18 hours versus 73 ± 31 hours (P = .004).	NICU in India Frequency and Volume of breast feeding not changed. Urine and stool frequency higher in supplemented group.
Iranpour R, Nohekhan R, Haghshenas, I. Effect of Intravenous Fluid Supplementation on Serum Bilirubin Level in Jaundiced Healthy Neonates during Conventional Phototherapy Journal of Research in Medical Sciences 2004;9(4): 186-190	A	n = 60 healthy breast-fed neonates with non-hemolytic hyperbilirubinemia. Dehydrated infants excluded. (Clinical signs and weight loss of more than 8% of birth weight)	Assigned randomly to receive either breast milk exclusively (non-supplemented group; n=30) or intravenous fluid in addition to breast milk (supplemented group; n=30) during conventional phototherapy. Neonates in the fluid-supplemented group received an additional 25% of their maintenance fluid requirement.	TSB levels at the time of enrollment and within 84 hours after phototherapy were not statistically different between two groups. Similarly, the mean rate of decrease in TSB levels during the first 12 h of phototherapy were 0.13 ± 0.06 and 0.10 ± 0.1 mg/dL/h in supplemented and non-supplemented groups respectively (P=0.13). Duration of phototherapy was not different.	Makes sense that excluding dehydration may account for findings.
Boo, NY, Lee, HT. Randomized Controlled trial of Oral Versus Intravenous Fluid Supplementation on Serum Bilirubin Level During Phototherapy of Term Infants with Severe Hyperbilirubinemia. J. Paediatrics and Child Health 2002, 38(2), 151–155.	A	n = 54 healthy term infants with severe hyperbilirubinemia	Randomized to receive either solely enteral feeds or both enteral and IV (n = 27) fluid during phototx. Hydration status assessed independently by at least two doctors. Fluid administered included deficit estimated by hydration status.	The mean rates of decrease in iSB during the first 4 hours of phototherapy were also not significantly different. There was no significant difference in the proportion of infants requiring exchange transfusion (P = 0.3) nor in the median duration of hospitalization (P = 0.7) between the two groups.	Either they work equally well or neither works…. ☺ Au note oral hydration avoids IVs!
Saeidi, R., Heydarian, F., Fakehi, V.	A	n = 100 Iranian neonates.	RCT to receive IV fluids at rate appropriate to provide age	Mean decrease in TCB at 24 hours of RX was greater with IV fluids.	All appeared well hydrated.

Role of Intravenous Extra Fluid Therapy in Icteric Neonates Receiving Phototherapy. Saudi Medical Journal 2009; 30(9); 1176-1179		Healthy hemolysis excluded	(days) appropriate fluids versus breast feeding.	IV fluid patients had lower TSB values starting at 12hrs after No change LOS No diff ET (p=0.09)	
Shailender Mehta, MD, Praveen Kumar, MD, Anil Narang, MD. A Randomized Controlled Trial of Fluid Supplementation in Term Neonates with Severe Hyperbilirubinemia. The Journal of Pediatrics, 2005; 147 (6); 781-785.	A	N=74, N India Term >=37wks TSB >=18 =<25mg/dl No hemolysis No obvious dehydration	Intervention: N/5 saline in 5% dextrose for 8 hours 70ML/kg/ hour over 8 hours. Continued breast feeding as before entry into study.	Outcome: need for ET. Fewer infants in IV group received exchange transfusion RR 0.3 (CI.14-.66) Secondary: TSB @predefined target times, duration of photo therapy. Duration of photo therapy shorter. At initiation serum osmol values high > 300 Sec analysis found benefit of treatment only realized in pts with high serum osmoles.	Dehydration excluded as could not deny IV to control group if dehydrated. Bias results in favor of control – underestimates effect of IV.

Topic P. Hyperbilirubinemia Inpatient Guideline Evidence. Monitoring

Reference Citation	Study Design	Patient Population (n)	Main variables or predictors [e.g. study group (n) & comparison group (n)]	Main relevant outcomes, results, and significance	Reviewer notes (include (a) methodological issues, (b) noteworthy harms)
Berkwitt, A, Osborn, R, Grossman, M. The Utility of Inpatient Rebound Bilirubin Levels in Infants Readmitted After Birth Hospitalization for Hyperbilirubinemia. Hospital Pediatrics 2015; 5(2).	C	n = 226 infants readmitted after their birth hospitalization for indirect hyperbilirubinemia	n = 130 had rebounds at 6.1+/-2.4 hours n = 96 had no rebound	5/130 readmitted vs 4/96 readmitted (p=0.98). Length of stay longer for rebound. 2/129 repeat photo when <14, vs 12/97 when >14 (p=0.001).	Excluded those treated in first 24 hours.
Grabenhenrich, J, Grabenhenrich, L, Buhrer, C, Berns, M. Transcutaneous Bilirubin After Phototherapy in Term and Preterm Infants. Pediatrics 2014; 134(5).	C	n = 86 (62 >35 weeks) newborn infants underwent a total of 189 parallel measurements	Paired measurements of TcB and TsB before and after phototherapy.	Before treatment, difference was -0.6mg/dL. In first 8 hours after phototherapy, TcB -2.4mg/dL. Safety margin of -7.3mg/dL to get <1% false-negative. (Can be used to reduce post-treatment blood draws).	Included preterm. Used different phototherapy thresholds than U.S., intermittent phototherapy strategy.
Fonseca, R.; Kyralessa, R.; Malloy, M.; Richardons, J.; Jain, SK. Covered skin transcutaneous bilirubin estimation is comparable with serum bilirubin during and after phototherapy. Journal of Perinatology (2012) 32, 129–131(2012)	C	39	Simultaneous measurements of serum, transcutaneous of covered skin, and transcutaneous of exposed skin.	Before starting phototherapy, all three measurements not statistically different. TcB-exposed skin significantly lower (p<0.05) than TsB and TcB-covered skin at all-time points. (12, 24, 36, 48 hours and 6 hours after discontinuing).	80% Hispanic population
Barak, M.; Berger, I.; Dollberg, S.; Mimouni, F.; Mandel, D. When should phototherapy be stopped? A pilot study comparing two targets of serum bilirubin concentration. Acta Paediatrica. Sept. 2008.	A	n = 52 infants	25 infants: high-threshold to stop phototherapy (>1 below light level). 27 infants: low-threshold (>3 below light level).	High threshold had shorter phototherapy (P=0.03), shorter length of stay (p=0.05). Repeat phototherapy in 20% of high- vs 18% of low-threshold (p=0.58).	Rebounds measured at 6-12 hours. Significant rise = above light level. Repeat photo required for 28% with hemolysis, 8% without.
Kaplan, M.; Kaplan, E.; Hammerman, C.; Algur, N.;	C	n = 226 term and near-term	Rebound levels tested 12-36 hours after stopping phototherapy.	13.3% developed rebound.	Different phototherapy criteria, using a more

Bromiker, R.; Schimmel, MS.; Eidelman, AI. Post-phototherapy neonatal bilirubin rebound: a potential cause of significant hyperbilirubinaemia. Archives of Disease in Childhood. Volume91, Issue1.		neonates treated with phototherapy >=35weeks	Significant rebound defined as level >15mg/dL.	Risk factors: DAT+ (OR=2.44), GA<37 weeks (OR=3.21), phototherapy started <72 hours (OR=3.61).	strict version of 1994 guideline.
American Academy of Pediatrics. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2004 Oct;114(4):1138.	Guideline	NA	NA	Stop phototherapy when <13-14mg/dL (applies to readmitted patients). Intensive phototherapy can decrease 30-40% by 24 hours, most in first 4-6.	No guidance for stopping at earlier age, i.e. when treated during birth hospitalization.
Maisels, M.; Dring, E. Rebound in Serum Bilirubin Level Following Intensive Phototherapy. Arch Pediatr Adolesc Med. 2002;156(7):669-672	C	n = 303 term treated with phototherapy	Requirement of repeat phototherapy and degrees of rebound.	13/158 required repeat photo if initially treated during birth hospitalization. Photo stopped at 10.4+/-1.8. Rebounded by 1.3+/-2.0. 1/144 required repeat photo if first treatment was a readmission. Photo stopped at 12.3+/-1.3. Rebounded by 0.27+/-1.46.	Rebound obtained at 4-48 hours and not obtained in all patients.
Romagnoli et al. Italian Guidelines for Management and Treatmetn of Hyperbilirubinaemia of Newborn Infants ≥ 35 Weeks' Gestational Age. Italian Journal of pediatrics 2014; 40(11).	Guideline	NA	NA	TSB should be tested 4-8h after beginning of phototherapy, or earlier if TSB<3 mg/dL less than threshold of exchange transfusion. Subsequently, TSB q12-24h. If treatment failure, multiple light should be started Phototherapy to be DCd if TSB is less than treatment threshold on 2 consecutive measurements, 6-12h apart. TSB should be checked 12-24h after DC treatment for rebound (by consensus)	Systematic review/Guideline, see evidence tables in source.
Bhutani, V; The Committee on Fetus and Newborn. Phototherapy to Prevent Severe Neonatal Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. Pediatrics 2011; 128(4)	Guideline	NA	NA	Clinical impact of phototherapy should be evident within 4-6 hours (2 mg/dL reduction) No recommendation how often, what methods. Rebound measurement?	Systematic review/Guideline, see evidence tables in source.
NICE 2010 Jaundice in Newborn Babies under 28 Days.	Guideline	NA	NA	Use TSB to monitor during phototherapy TSB 4–6 hours after initiating phototherapy Repeat TSB q 6-12h when Bilirubin is stable or falling Stop phototherapy once serum bilirubin has fallen to a level at least 3 mg/dL below the phototherapy threshold Check TSB 12–18 hours after stopping phototherapy (can be outpatient)	NA