



Technical Report: Diagnosis and Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation

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CONTEXT: Severe hyperbilirubinemia is associated with kernicterus. Informed guidance on hyperbilirubinemia management, including preventive treatment thresholds, is essential to safely minimize neurodevelopmental risk.

OBJECTIVE: To update the evidence base necessary to develop the 2022 American Academy of Pediatrics clinical practice guideline for management of hyperbilirubinemia in the newborn infant ≥ 35 weeks' gestation.

DATA SOURCE: PubMed.

STUDY SELECTION: English language randomized controlled trials and observational studies. Excluded: case reports or series, nonsystematic reviews, and investigations focused on < 35 -weeks' gestation infants.

DATA EXTRACTION: Topics addressed in the previous clinical practice guideline (2004) and follow-up commentary (2009) were updated with new evidence published through March 2022. Evidence reviews were conducted for previously unaddressed topics (phototherapy-associated adverse effects and effectiveness of intravenous immune globulin [IVIG] to prevent exchange transfusion).

RESULTS: New evidence indicates that neurotoxicity does not occur until bilirubin concentrations are well above the 2004 exchange transfusion thresholds. Systematic review of phototherapy-associated adverse effects found limited and/or inconsistent evidence of late adverse effects, including cancer and epilepsy. IVIG has unclear benefit for preventing exchange transfusion in infants with isoimmune hemolytic disease, with a possible risk of harm due to necrotizing enterocolitis.

LIMITATIONS: The search was limited to 1 database and English language studies.

CONCLUSIONS: Accumulated evidence justified narrowly raising phototherapy treatment thresholds in the updated clinical practice guideline. Limited evidence for effectiveness with some evidence of risk of harm support the revised recommendations to limit IVIG use.

abstract

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Dr Slaughter oversaw the search strategy and drafted the technical report; Dr Kemper and Dr Newman participated in the evidence review and revised the report; and all authors approved the final report and agree to be accountable for all aspects of the work.

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The 2022 American Academy of Pediatrics publication, “Clinical Practice Guideline Revision: Diagnosis and Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation,”¹ builds on the previous 2004 guideline, “Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation,”² and a 2009 follow-up commentary, “Hyperbilirubinemia in the Newborn Infant ≥ 35 Weeks’ Gestation: An Update With Clarifications.”³ The gestational age cutoff of ≥ 35 weeks was chosen because it includes most newborn infants cared for by general pediatricians and other primary care clinicians in mother-baby units and well-baby nurseries. This guideline does not apply to preterm newborns born < 35 weeks’ gestation, who generally receive care in neonatal intensive care units (NICUs).

Hyperbilirubinemia management presents a unique challenge for clinicians. Although rare in high-resource settings, kernicterus is deadly and leads to severe, lifelong neurodevelopmental impairment in survivors.^{2,4} At some patient-specific threshold, severe bilirubinemia can lead to bilirubin encephalopathy and kernicterus. However, the current evidence base is insufficient to quantitatively derive the exact treatment threshold at which hyperbilirubinemia should be treated in a given infant to prevent kernicterus. Thus, expert opinion remains crucial to the development of hyperbilirubinemia treatment guidance. The committee’s approach was to improve on the expert-driven 2004 American Academy of Pediatrics (AAP) guideline² and 2009 follow-up commentary³ through the incorporation of new evidence. Recent, large cohort investigations have provided reassurance that there are certain total serum bilirubin concentrations

below which kernicterus or adverse effects are not observed.^{5–11} In addition, large cohort studies have suggested that phototherapy itself may carry some risk for patient harm.^{12,13} The committee incorporated this new evidence including each infant’s birth gestation and the presence or absence of neurotoxicity risk factors to develop new phototherapy and exchange transfusion thresholds that aim to continue to safely reduce the risk of kernicterus while reducing the risk of unnecessary treatment.¹

APPROACH TO DEVELOPING THE UPDATED CLINICAL PRACTICE GUIDELINE

In January of 2014, Dr Alex Kemper was approved by the AAP Board of Directors as the Chair of the Clinical Practice Guideline Subcommittee on Hyperbilirubinemia. Dr Kemper was charged with leading the update of the hyperbilirubinemia clinical practice guideline (CPG) focused on the diagnosis and management of hyperbilirubinemia in newborn infants born at ≥ 35 weeks’ gestation. The rationale for development of an updated guideline included the following:

1. New evidence that bilirubin neurotoxicity does not occur until concentrations well above the 2004 exchange transfusion thresholds justified raising the phototherapy treatment thresholds by a narrow range; and
2. Increasing evidence that phototherapy may have rare but serious late adverse effects.

In April 2014, the AAP Executive Committee approved the final subcommittee members for the formation of the Clinical Practice Guideline Subcommittee on Hyperbilirubinemia.

COMPOSITION OF THE SUBCOMMITTEE MEMBERS AND MEETINGS

The subcommittee consisted of individuals with expertise in neonatal hyperbilirubinemia and late-preterm and term newborn care, including members of multiple relevant AAP committees. The subcommittee was chaired by Alex R. Kemper, MD, MPH, MS, FAAP, who appointed Thomas B. Newman, MD, MPH, FAAP, as vice chair in 2017. Jonathan L. Slaughter, MD, MPH, FAAP, a neonatologist, served as epidemiologist and methodologist. He developed the initial evidence-review questions and evidence tables for the potential use of intravenous immune globulin (IVIG) and/or exchange transfusion. Three librarians—Susi Miller, Teri Ballard, and Allison Erlinger—assisted with the primary literature search. Kymika Okechukwu, MPA, was the AAP staff representative for the project. All conflicts of interest were disclosed at the beginning of the process and updated throughout.

The subcommittee met face-to-face in August of 2014, May of 2017, and virtually in August of 2018. Conference call and E-mail correspondence were frequent and used to assess the quality of evidence, reach consensus, and develop the final clinical practice guideline.

FORMULATION AND ARTICULATION OF THE QUESTIONS ADDRESSED BY THE CLINICAL PRACTICE GUIDELINE SUBCOMMITTEE

The AAP *Evidence-Based Clinical Practice Guidelines Development and Implementation Manual*¹⁴ recommends that clinical practice guidelines be reviewed periodically and updated if “literature surveillance suggests that significant changes in clinical practice would be supported by strong evidence or monitoring of implementations suggests that the current guideline

results in care that would be unnecessarily harmful to patients.” Since the original 2004 clinical practice guideline² and the 2009 update with clarifications,³ new data have emerged regarding potential phototherapy-related harms (Table 1),^{12,13,15–17} along with evidence that the phototherapy and exchange transfusion treatment thresholds from the previous 2004 clinical practice guideline could be raised to safely reduce overtreatment.^{5–11}

In addition, neonatal hyperbilirubinemia experts have noted the need for additional guidance to separate routine phototherapy from “escalation of care,” including more aggressive phototherapy, intravenous hydration for dehydrated infants, and the potential use of IVIG and/or exchange transfusion. In recent years, multiple randomized controlled trials evaluated the effectiveness of IVIG to prevent exchange transfusion in infants with indirect hyperbilirubinemia from hemolysis precipitated by maternal-infant blood group incompatibility. Most of the subject areas within the 2022 guideline update were previously included in the 2004 clinical practice guideline² and/or 2009 commentary.³ Accordingly, for most subjects, the committee reviewed the peer-reviewed literature for new, subsequent evidence since 2009. Complete systematic reviews were conducted and new evidence-tables created for two topics: phototherapy-related harm and the effectiveness of IVIG to prevent exchange transfusion in infants with indirect hyperbilirubinemia. For phototherapy-related harm, an emerging subject that was not previously covered, the committee reviewed all relevant literature without a date restriction. In addition, the committee reviewed all randomized

controlled trials on the effectiveness of IVIG to prevent exchange transfusion in infants with indirect hyperbilirubinemia, to develop an evidence-table comparing recent placebo-controlled trials of infants with Rhesus (Rh) incompatibility to previous literature on IVIG treatment of infants with maternal-infant blood group incompatibility-mediated hemolysis.

SYSTEMATIC REVIEW PROCESS

The two systematic reviews were conducted in accordance with the “Preferred Reporting Items for Systematic Reviews and Meta-Analysis Guideline.”¹⁸ The epidemiologist developed questions to guide the literature search, evidence abstraction, and construction of the tables. The primary literature search was assisted by librarians Susi Miller, Teri Ballard, and Allison Erlinger.

SEARCH STRATEGY

The epidemiologist and librarians created a list of search terms and strategies.

Question 1: What are the adverse clinically detectable effects of phototherapy in newborns?

Population: Neonates born at ≥ 35 weeks’ gestation with indirect hyperbilirubinemia who are candidates for phototherapy.

Intervention: Treatment with phototherapy.

Comparator: Nontreatment.

Outcome: Increased risk of any adverse clinical outcome that is important to neonatal patients, their families, and/or the clinicians treating them.

The first search (conducted May 24, 2018; repeated March 5, 2021 and April 7, 2022) focused on medical

diagnoses and adverse effects associated with phototherapy and was age-limited to newborn infants from birth to one month of age with the Medline limiter “newborn infant (birth to one month).” It was further limited using the Medical Subject Headings (MeSH) term: Phototherapy with subheading Adverse Effects. The search strategy was expanded to include phototherapy (keyword) AND – any of the following MeSH terms or keywords (newborn*; neonat*; adverse; asthma; Asthma[MeSH]; epilepsy; Epilepsy[MeSH]; cancer; Neoplasms[MeSH]; neuro*; seizure*; Seizure[MeSH]).

A second search (October 1, 2018; repeated March 5, 2021 and April 7, 2022) focused on the effects of phototherapy on family bonding and breastfeeding. The search strategy included searching Medline for articles indexed with either Phototherapy[MeSH term] OR Neonatal Jaundice[MeSH term with subheading Therapy] AND ALSO one of the following MeSH terms: Mothers/subheading psychology; Maternal Behavior; Parent-Child-Relations; Breast Feeding; breastmilk; Family Relations OR one of the following key word/phrases: “maternal-infant bond” or “mother-infant separation.” Our search strategy also including searching for keyword “phototherapy” AND one or more of the following keywords or phrases: “breastfeeding,” “bonding,” “separation,” “family dynamics,” or “family relationships.” A final search strategy including searching for articles indexed with both of the following: Object attachment[MeSH term] AND Phototherapy[MeSH term]. Case reports or series, nonsystematic review articles, and manuscripts focused on preterm infants born at < 35 weeks’ gestation were excluded.

TABLE 1 Adverse Effects of Phototherapy in Newborn Infants

Citation Country	Methods	Participants or Inclusion Criteria	Exclusion Criteria	Interventions	Outcomes	Results	Risk of Bias	Notes or Conclusions
Asthma and Allergies Aspberg 2007 Sweden	Retrospective population-based registry study	14 805 children born between 1987 and 1999 and recorded in the Swedish Hospital Discharge Register as hospitalized with asthma between 2 y of age and 2001 were compared to all children in the Swedish Medical Birth Registry ($n = 1\,386\,029$) for those same years.	Children younger than 2 y of age at the time of hospital admission for asthma were excluded because of uncertainty of asthma diagnosis at <2 y.	Multiple maternal and infant characteristics including phototherapy exposure were studied.	Hospitalization for childhood asthma after age 2 y.	Phototherapy-associated odds ratio (Mantel-Haenszel) for asthma requiring hospitalization (OR: 1.27, 95% CI: 1.08–1.5) after excluding infants with risk factors (except for icterus or jaundice) associated with both asthma and phototherapy (measured confounders).	Unable to adjust for bilirubin levels when estimating associations between phototherapy and asthma. Evaluated multiple risk factors (multiple comparisons). However, it was impossible to distinguish the phototherapy-associated effect on asthma from that of jaundice.	Hyperbilirubinemia and phototherapy were both associated with increased odds of a childhood asthma hospitalization after age 2 y. However, it was impossible to distinguish the phototherapy-associated effect on asthma from that of jaundice.
Aspberg 2010 Sweden		Perinatal data for singleton children prescribed antiasthmatic medication ($n = 61\,256$) were compared to corresponding data for all singleton children born in Sweden from January 1990 to June 2003 and surviving through June 2005 ($n = 1\,338\,319$). Data from 3 large Swedish health registers: Swedish Medical Birth Register, Swedish Prescribed Drug Register, and Swedish Hospital Discharge Register.		Numerous antenatal and Asthma as defined by neonatal variables including icterus and phototherapy.	Association of phototherapy with: All childhood asthma (OR 1.35; 95% CI: 1.3–1.4). Asthma stated in prescription (OR 1.42; 95% CI: 1.3–1.5). Asthma on systemic corticosteroids (OR 1.47; 95% CI: 1.2–1.8). A diagnosis of icterus (jaundice) was also associated with asthma (OR 1.45, 95% CI: 1.4–1.5).	Adjusted for birth year, maternal age, parity, smoking during pregnancy, and years of involuntary childlessness. Evaluated multiple risk factors (multiple comparisons). There was no adjustment for degree of hyperbilirubinemia. Phototherapy duration and intensity could not be evaluated.	Phototherapy and jaundice were both associated with a diagnosis of asthma. However, it was impossible to distinguish the phototherapy-associated effect on asthma from that of jaundice.	

TABLE 1 Continued

Citation Country	Methods	Participants or Inclusion Criteria	Exclusion Criteria	Interventions	Outcomes	Results	Risk of Bias	Notes or Conclusions
Ku 2012 Taiwan	Retrospective cohort	11 321 children born 1997–2000 and randomly selected from the Taiwanese National Health Insurance Research Database (NHIRD).	Subjects with questionable basic data (not precisely defined) were excluded.	Those with neonatal jaundice (exposed) were classified as the study group or icteric children. Those without (nonexposed) were classified as the control group or nonicteric children.	Asthma defined as: at least 4 outpatient or emergency department diagnoses of asthma between ages 1–10 y, or 1 asthma diagnosis during a hospital admission between ages 1–10 y.	Phototherapy-associated odds ratio (Mantel-Haenszel) after excluding children with 5 risk factors associated with asthma and phototherapy (confounders) (preterm or low birth wt, neonatal infections, other respiratory conditions, other birth conditions, and sex). (OR: 1.03; 95% CI 0.72–1.4; <i>P</i> = .958.) Jaundice ICD-9 diagnosis-associated odds of asthma after exclusion of children with the above risk factors (OR: 1.64; 95% CI 1.36–1.98; <i>P</i> < .001).	Unable to adjust for bilirubin concentrations when estimating associations between phototherapy and asthma.	Hyperbilirubinemia but not phototherapy was associated with increased odds of a childhood asthma diagnosis after age 1 y.
Sun 2013 Taiwan	Retrospective cohort	11 328 children randomly selected from the Taiwanese National Health Insurance Research Database (NHIRD) and born between 1997 and 2000.	Incomplete basic data, such as conflicting sex and uncertain birth date.	Main exposure of interest was neonatal jaundice as measured by ICD code. Phototherapy was also recorded as a proxy for bilirubin concentration >15 mg/dL, at which phototherapy charges were reimbursed.	Childhood allergic rhinitis between birth and 10-y of age. Diagnostic criteria for allergic rhinitis were at least 3 outpatient allergic rhinitis diagnoses, 1 during a hospitalization, or 1 in an emergency department.	Association between allergic rhinitis and Phototherapy (RR 1.06; 95% CI: 0.89–1.27) (Risk difference 2.7; 95% CI: -4.8 to 10.1) Neonatal jaundice (aOR 1.46; 95% CI: 1.2–1.7).	Adjusted for the following confounders: preterm/low birth wt, neonatal infection, other respiratory conditions, other birth conditions, and sex. Unable to adjust for bilirubin concentration and intensity could not be evaluated.	There was no association between phototherapy and childhood allergic rhinitis. Neonatal jaundice was associated with a childhood allergic rhinitis diagnosis before age 10 y.

TABLE 1 Continued

Citation Country	Methods	Participants or Inclusion Criteria	Exclusion Criteria	Interventions	Outcomes	Results	Risk of Bias	Notes or Conclusions
Das 2015	Systematic review and meta-analysis	7 observational studies (n = 101 499 total participants) that included infants with hyperbilirubinemia and/or those receiving phototherapy in the neonatal period and who were followed up to 12 y.		(hyperbilirubinemia OR icterus OR jaundice) AND (phototherapy OR therapy OR treatment) AND (allergy OR atopy OR asthma OR allergic rhinitis OR rhinoconjunctivitis OR hay fever OR atopic dermatitis OR allergic eczema)].	Children with outcome assessment at <1 y of age or those with chronic illness, congenital malformation, or kernicterus.	Neonatal hyperbilirubinemia (cutoff level not defined). Neonatal phototherapy.	Allergic rhinitis or conjunctivitis. Asthma. Eczema.	Hyperbilirubinemia: Asthma (OR: 4.26; 95% CI: 4.05–4.5). Allergic rhinitis (OR: 5.37; 95% CI: 4.16–6.92). Phototherapy: Asthma (OR: 3.81; 95% CI: 3.53–4.11). Allergic rhinitis (OR: 3.04; 95% CI: 2.13–4.32).
Fixed-effects logistic regression model was used for meta-analysis of the individual study results. Did not identify whether studies adjusted for bilirubin levels when estimating associations between phototherapy and allergy or asthma outcomes. Did not evaluate duration of phototherapy exposure. Only 2 of the 7 included		Search terms: [(newborn OR infant OR neonate*) AND Hyperbilirubinemia and phototherapy were both associated with increased odds of asthma and allergic rhinitis. However, it was impossible to separate the		hyperbilirubinemia-associated effect from that of phototherapy. Risk differences and number needed to harm were not calculated.				

TABLE 1 Continued

Citation Country	Methods	Participants or Inclusion Criteria	Exclusion Criteria	Interventions	Outcomes	Results	Risk of Bias	Notes or Conclusions
Wei 2015 Taiwan	Nested case-control	27 693 patients within the Taiwanese National Health Insurance Research database (NHIRD) with a new diagnosis of neonatal jaundice from 2000 to 2007. For each child with neonatal jaundice, 2 children without neonatal jaundice from the same period were randomly selected and included in the nonneonatal jaundice cohort ($n = 55\,367$)	Children >1 mo of age, diagnosed with allergic disease before the index date of neonatal jaundice diagnosis, and those missing information on sex or age.	The main exposure of interest was neonatal jaundice as diagnosed by ICD code. Other diagnoses including phototherapy were examined within the cohort of infants with neonatal jaundice.	Allergic conjunctivitis, allergic rhinitis, atopic dermatitis, asthma, and urticaria as diagnosed by ICD code by the end of 2008	Association between phototherapy in infants with neonatal jaundice and Allergic conjunctivitis (aHR 1.38; 95% CI: 1.3–1.5). Allergic rhinitis (aHR 1.37; 95% CI: 1.3–1.4). Asthma (aHR 1.21; 95% CI: 1.2–1.3). Atopic dermatitis (aHR 1.22; 95% CI: 1.1–1.3). Urticaria (aHR 1.12; 95% CI: 1.03–1.2). All 5 allergic disease were increased in the neonatal jaundice cases as compared to the group of matched nonjaundiced patients).	Analyses were adjusted for age, sex, comorbidities of fetal and newborn respiratory conditions, infections, prematurity, low birth wt, other birth conditions, and glucose-6-phosphate dehydrogenase deficiency. There was no adjustment for degree of hyperbilirubinemia and effects of phototherapy duration and intensity could not be evaluated.	Phototherapy and a diagnosis of neonatal jaundice were both associated with 5 childhood allergic diseases (allergic conjunctivitis, allergic rhinitis, asthma, allergic dermatitis, and urticaria). It was not possible to differentiate the effects of hyperbilirubinemia and effects of phototherapy on these allergic outcomes.
Egeberg 2016 Denmark	Retrospective cohort	All children ($n = 673\,614$) born in the 10-y period between	As per inclusion criteria.	Neonatal blue light phototherapy, neonatal jaundice, birth gestation, birth	Primary end-point was the first occurrence of atopic dermatitis	Association between atopic dermatitis and: Phototherapy at first birthday	Adjusted IRRs were mutually adjusted for age, sex, neonatal phototherapy, neonatal	Although neonatal jaundice was linked to an increased rate of childhood atopic

TABLE 1 Continued

Citation Country	Methods	Participants or Inclusion Criteria	Exclusion Criteria	Interventions	Outcomes	Results	Risk of Bias	Notes or Conclusions
Kuzniewicz 2018 Northern California, USA	Retrospective cohort	1997-2006 and recorded in the Danish National Patient Register.	Infants who did not remain in the same hospital system during their birth admission, infants who did not remain in the KP health plan for at least 25 mo, and infants without TSB levels.	wt as recorded in the Danish National Patient Register.	measured at first, second, and fifth birthdays as recorded in the Danish National Patient Register.	(aIRR 1.11; 95% CI: 0.92-1.35). Phototherapy at second birthday (aIRR 1.01; 95% CI: 0.88-1.15). Phototherapy at fifth birthday (aIRR 0.97; 95% CI: 0.88-1.08). Neonatal jaundice at first birthday (aIRR 1.13; 95% CI: 1.06-1.21). Neonatal jaundice at second birthday (aIRR 1.13; 95% CI: 1.08-1.18). Neonatal jaundice at fifth birthday (aIRR 1.12; 95% CI: 1.08-1.16).	jaundice, birth wt, gestation, and season of birth. <i>P</i> values corrected by the Bonferroni method with corrected 2-tailed <i>P</i> value <0.008 considered significant. Children were followed from birth until either first occurrence of atopic dermatitis, migration, death, or (in 3 separate analyses) their first, second, or fifth birthday.	dermatitis, neonatal phototherapy was not associated with an atopic dermatitis diagnosis.
		109212 newborns born during 2010-2014 at ≥35 wk' gestation.	Infants who did not remain in the same hospital system during their birth admission, infants who did not remain in the KP health plan for at least 25 mo, and infants without TSB levels.	Phototherapy (defined as Asthma (diagnosed after 2 y of age: defined as 1) at least 2 asthma diagnoses from any outpatient encounter separated by ≥30 d; and 2) at least 2 asthma medication prescriptions in a 12-mo period separated by ≥30 d).	Association of phototherapy with asthma: (multivariable Cox-model adjusted hazard ratio [aHR]: 1.01; 95% CI: 0.92-1.11). (Propensity-score aHR: 1.07; 95% CI: 0.96-1.20) Relative to TSB levels of 3-5.9 mg/dL, infants with maximum TSB levels between 9-17 mg/dL were at a significantly	Cox proportional hazard models used for primary multivariable analysis to account for differing follow-up times by infant. Among infants within 3 mg/dL of 2009 AAP phototherapy threshold, propensity scores for receiving phototherapy were associated with an increased risk of asthma, but this association was not observed at higher bilirubin levels.	Phototherapy use was not associated with asthma, and phototherapy is unlikely to increase or decrease asthma risk. Modest levels of hyperbilirubinemia were associated with an increased risk of asthma, but this association was not observed at higher bilirubin levels.	

TABLE 1 Continued

Citation Country	Methods	Participants or Inclusion Criteria	Exclusion Criteria	Interventions	Outcomes	Results	Risk of Bias	Notes or Conclusions
Tham 2018 Singapore	Prospective cohort	Growing Up in Singapore Toward Healthy Outcomes (GUSTO) study	Per inclusion criteria.	Neonatal phototherapy for hyperbilirubinemia during the birth hospitalization as recorded for the GUSTO study	Diagnosis of eczema, wheezing or use of nebulizer or inhaler, and rhinitis by parental survey Atopic sensitization was assessed through skin prick testing.	increased hazard for asthma. However, there was not a significant increase in asthma associated with maximum TSB \geq 18 mg/dL (no TSB dose-effect) (aHR: 1.04; 95% CI: 0.90–1.20). Association of phototherapy with: Allergen sensitization by month 60 (aOR 1.1; 95% CI: 0.6–2.0) Eczema by month 60 (aOR 1.3; 95% CI: 0.7–2.3). Rhinitis by month 60 (aOR 1.0; 95% CI: 0.6–1.9). Early onset of wheeze and use of nebulizer or inhaler by month 60 (aOR 0.6; 95% CI: 0.3–1.2). No associations were found between bilirubin levels and these measured outcomes.	Adjusted for sex, ethnicity, breastfeeding levels, family history of allergy, gestational age, maternal education levels and mode of delivery. Parental surveys at risk for recall bias.	No association was found between either phototherapy or bilirubin level and allergic sensitization, eczema, rhinitis, wheezing or nebulizer or inhaler use.
Kuniyoshi 2021	Systematic review and meta-analysis	The systematic review included 19 observational studies (cohort, case-control, cross-sectional) that evaluated the association of neonatal jaundice and neonatal phototherapy with childhood allergic	Case-reports, case-series, systematic reviews, and meta-analyses were excluded. 5 studies were excluded from meta-analysis because no effect-estimate was reported.	Neonatal jaundice and phototherapy. For studies that stratified bilirubin levels, results with TSB > 15 mg/dL were used.	Childhood-onset (\leq 19-y) allergic diseases (asthma, atopic dermatitis, or allergic rhinitis, or food allergies).	Association of phototherapy with: Asthma (OR 1.24; 95% CI: 1.1–1.4). Atopic dermatitis (OR 1.31; 95% CI: 1.2–1.4). Allergic rhinitis (OR 1.38; 95% CI: 0.9–2.0). Association of jaundice with:	Random-effects models weighted by inverse variance estimates were used for meta-analysis. Did not evaluate intensity or duration of phototherapy exposure.	Jaundice and phototherapy were both associated with increased odds of asthma and atopic dermatitis. Jaundice, but not phototherapy, was associated with allergic rhinitis. No studies were found that quantitatively assessed the

TABLE 1 Continued

Citation Country	Methods	Participants or Inclusion Criteria	Exclusion Criteria	Interventions	Outcomes	Results	Risk of Bias	Notes or Conclusions
Autism Spectrum Disorder Wu 2016 Northern California, USA	Retrospective Cohort Study	457 855 infants born at ≥ 35 wk' gestation who were recorded in the Kaiser Permanente of Northern California (KPNC) Database (1995–2011).	Infants who died during the birth hospitalization, were transferred out of the KPNC system, or were followed < 60 d. Infants with at least 2 inpatient or outpatient physician ICD diagnoses of: Trisomy 21, other genetic disorders, or congenital anomalies diagnosed at < 15 d.	In-hospital or home phototherapy.	ASD diagnosis either by ASD evaluation center, a clinical ASD specialist outside the ASD center (ie, psychiatrist, psychologist, or developmental pediatrician), or by a general pediatrician. Hyperbilirubinemia was also not associated with ASD after adjustment for confounders.	Asthma (OR 1.46; 95% CI: 1.4–1.5). Atopic dermatitis (OR 1.3; 95% CI: 1.1–1.6). Allergic rhinitis (OR 3.01; 95% CI: 0.9–10.3).	Propensity-adjusted sensitivity analyses also revealed no association between phototherapy and ASD (aHR: 1.09; 95% CI: 0.95–1.24). This model examined the effect of phototherapy among only infants who had a TSB level within 3 mg/dL of the 2004 AAP phototherapy threshold. TSB ≥ 20 (aHR: 1.09; 95% CI: 0.89–1.35) was also not associated with ASD.	association between either jaundice or phototherapy and food allergies. It was impossible to separate the jaundice-associated effect from that of phototherapy.
Breastfeeding and Familial Bonding Kemper 1989 Yale-New Haven Hospital, New Haven, Connecticut, USA	Prospective observational study with matched controls	101 jaundiced infants born in 1987–1988 with a total serum bilirubin > 11.99 mg/dL measured before discharge. 155 comparison	Birth wt < 2500 g or if infant spent > 6 h in the ICU. Comparison group infants were excluded if a bilirubin level was	Diagnosis of jaundice (mean peak bilirubin in jaundiced infants was 16.2 mg/dL, and 55% received phototherapy).	Mothers were surveyed at 1 mo postnatal to assess (1) concerns about jaundice and phototherapy. (2)	Of mothers whose infants received phototherapy, 70% thought its use implied that their child was moderately to seriously ill and	Risk of recall bias (survey). Difficult to determine effect sizes for phototherapy since the main focus of the study was a jaundice	Mothers of infants who had a jaundice diagnosis were more concerned about their infant's overall health at 1-mo postnatal. Maternal concerns

TABLE 1 Continued

Citation Country	Methods	Participants or Inclusion Criteria	Exclusion Criteria	Interventions	Outcomes	Results	Risk of Bias	Notes or Conclusions
Schedle 1990 County Hospital		subjects who were not visually jaundiced and who were seen by the same pediatrician as the matched, jaundiced infant.	obtained anytime up to 1 mo postnatal.	107 healthy, term infants, 1986-1987.	<p>termination of breastfeeding within 1 mo postnatal, and (3) maternal behaviors consistent with the vulnerable child syndrome.</p> <p>74% found its use upsetting. 53% of mothers whose infants received phototherapy vs 31% of those with jaundiced, non-phototherapy-treated infants had ever left their child with someone else for >1 h at 1 mo postnatal. 64% of those with breastfeeding interrupted in the hospital vs 36% without interruption had completely stopped breastfeeding at 1 mo ($P < .05$). 84% of mothers of jaundiced infants completed the 1-mo survey, as did 80% of mothers of comparison group infants.</p>	<p>diagnosis versus no jaundice diagnosis. Phototherapy specific data are presented as proportions for some outcomes. Although some baseline variables (potential confounders) were collected, these were not used to adjust estimates between jaundiced infants receiving phototherapy and jaundiced nontreated infants.</p> <p>There were no differences in Denver scores for social contact ($\chi^2 = 0.1$; $P = .93$), gross motor behavior ($\chi^2 = 0.5$; $P = .77$), and fine motor and adaptive performance ($\chi^2 = 4.5$; $P = .10$) at 1 y of age.</p> <p>No significant difference in the three study groups was found for mother-child attachment at 1 y</p>		
					<p>Pregnancy complication, >10th percentile wt for gestation, congenital malformation, or neonatal illness.</p>	<p>(1) 29 jaundiced infants with mean peak TSB of 15.85 mg/dL who received 2-3 d of phototherapy and partial mother-child separation, (2) 40 mildly jaundiced infants with mean peak TSB of 12.22 mg/dL who received neither phototherapy nor separation, and (3) a control group of</p>	<p>Denver Developmental Screening Test and Ainsworth Attachment Scores at 1 y of age.</p> <p>contact ($\chi^2 = 0.1$; $P = .93$), gross motor behavior ($\chi^2 = 0.5$; $P = .77$), and fine motor and adaptive performance ($\chi^2 = 4.5$; $P = .10$) at 1 y of age.</p> <p>There were no differences in Denver scores for social contact ($\chi^2 = 0.1$; $P = .93$), gross motor behavior ($\chi^2 = 0.5$; $P = .77$), and fine motor and adaptive performance ($\chi^2 = 4.5$; $P = .10$) at 1 y of age.</p>	

TABLE 1 Continued

Citation Country	Methods	Participants or Inclusion Criteria	Exclusion Criteria	Interventions	Outcomes	Results	Risk of Bias	Notes or Conclusions
Were unable to completely differentiate effect of bilirubin and phototherapy since mean TSB was lower in the jaundiced	Retrospective cohort	non-phototherapy-treated group. Small-sample size.	Treatment with phototherapy as a newborn did not appear to affect	neurodevelopment, as measured by the Denver Developmental Screening Test at 1-y of age and by maternal-infant attachment at 1 y of age.	Primary outcome variables: Total outpatient visits during postnatal days 15–364 and total numbers of various types of outpatient visits at ages (in days): 15–59, 60–119, 120–179, 180–364.	38 infants with no apparent jaundice. Measured baseline variables were similar in all groups except the phototherapy group had significantly more boys relative to the other 2 groups ($\chi^2 = 0.48$; $P = .009$).		of age ($\chi^2 = 1.5$; $P = .83$).
Usatin 2010 Northern California, USA	Retrospective cohort	Infants born between 1995 and 2004 at gestation ≥ 36 wk with birth wt ≥ 2 kg. Patients were eligible if they (1) never had a TSB ≥ 12 mg/dL ($n = 128417$) or (2) when they had a TSB ≥ 17 to < 23 mg/dL (a range where phototherapy might be discretionary) as outpatients at 2 to 7 d postnatal and did ($n = 1765$) or did not	Newborns that received phototherapy during their initial birth admission, those with birth admission > 48 h, or a conjugated or direct bilirubin ≥ 2 mg/dL in the first 30 postnatal days. Those that were readmitted to the hospital for any reason with a length of stay ≥ 96 h within the first 14 postnatal days. Those with < 4 outpatient visits in the first year and/	The 3 study comparison groups: 1) never had a TSB ≥ 12 mg/dL, 2) TSB ≥ 17 to < 23 mg/dL without phototherapy, and 3) TSB ≥ 17 to < 23 mg/dL with phototherapy.	There were small increases in total year-1 visits for jaundiced infants without phototherapy (group 2) (adjusted incident rate ratio [aIRR]: 1.04; 95% CI: 1.02–1.05) compared to infants with bilirubin < 12 mg/dL (group 1). There were also slightly more total year-1 visits for jaundiced infants with phototherapy (group 3) (aIRR: 1.03; 95% CI: 1.01–1.06) relative to those with jaundice and phototherapy (group 2).	Poisson regression was used to account for potentially confounding variables including mother's age, infant's year, month, and hospital of birth, gestational age, sex, and race. TSB level that qualified for groups 2 or 3 were dichotomized at 17–19.9 and 20–22.9 mg/dL and used to adjust comparisons between group 2 and group 3 (phototherapy exposure). The authors noted that estimates should be interpreted in light of	Small increases in outpatient visits before age 1 were seen with both neonatal jaundice phototherapy (+0.73) and that most often occurred in the first 2 postnatal months. Phototherapy treatment and jaundice diagnoses were associated with only small increases in first-year outpatient visit rates, consistent with mild or infrequent contribution to the vulnerable child syndrome.	

TABLE 1 Continued

Citation Country	Methods	Participants or Inclusion Criteria	Exclusion Criteria	Interventions	Outcomes	Results	Risk of Bias	Notes or Conclusions
Waite 2016 United States of America	Retrospective cohort	4441 ever-breastfed infants born >35 wk gestation at ≥200 g between May-December 2005 and recorded in the Centers for Disease Control and Prevention Infant Feeding Practices Study II (IFPS II). Infants who received	Breastfeeds were never initiated or if mothers answered via survey that their infants received “other treatment for jaundice,” which included switching completely to formula feeds.	Phototherapy for the treatment of jaundice as indicated by parental report via survey at ~3 wk postnatal. Parents first indicated that their child was ever jaundice and if so, they were asked whether treatment was required with phototherapy being 1	Primary outcome variables: Any breastfeeding at 1, 2, 4, 6, 9, and 12 mo postnatal based on maternal survey response. Secondary outcome variables: Exclusive breastfeeding at 1, 2, and 4 mo postnatal based on phototherapy being 1	For both phototherapy and untreated groups of infants with bilirubin ≥17 to <23 mg/dL, increases in visits were greatest during days 15–59, appeared related to follow-up for the diagnosis of jaundice itself, and were not statistically significant in any other measured year-1 time periods. The adjusted increase in visits over group 1 (bilirubin <12 mg/dL) were 0.36 visits in year-1 by group 2 (jaundice and no phototherapy) and 0.73 visits by group 3 (jaundice and phototherapy). The average number of outpatient visits for the 8 most common sick-visit diagnostic codes did not vary by phototherapy use.	Potential for recall bias due to determination of phototherapy exposure and breastfeeding history via postnatal maternal survey. The first postnatal survey at ~3 wk asked the respondent whether the infant had jaundice at any time since birth. Mothers that	Phototherapy treatment of hyperbilirubinemia may be associated with a decreased odds of exclusive breastfeeding during months 1–4 postnatal. Phototherapy was not associated with a change in the odds of any breastfeeding. Although there was a decrease in the odds

TABLE 1 Continued

Citation Country	Methods	Participants or Inclusion Criteria	Exclusion Criteria	Interventions	Outcomes	Results	Risk of Bias	Notes or Conclusions
Digitale Northern California, USA	Retrospective cohort	25 853 infants born at ≥ 35 -wk' gestation with TSB levels from 3 mg/dL below to 2.9 mg/dL above 2004 AAP phototherapy thresholds. Medical records at 16 Northern California Hospitals (Kaiser Permanente [KPI]) from 2013-2017.	Infants with missing data on length of birth hospital stay, TSB < 3 mg/dL, or TSB not measured were excluded. Infants whose first TSB higher than 3 mg/dL below phototherapy threshold was ≥ 5 mg/dL above threshold excluded from primary analysis because phototherapy is no longer optional at those higher TSB concentrations.	Inpatient phototherapy during birth hospitalization defined as presence of phototherapy flow sheet in chart or both ICD procedure code and phototherapy order.	maternal survey response. Exclusive breast milk feeding via caregiver self-report at 2-mo well-child visit. Reporting feeding infant any breast milk at 2-mo well-child visit.	phototherapy exposure was associated with a reduced odds of any breastfeeding (aOR: 0.58; 95% CI: 0.37–0.91). There was a reduced odds of exclusive breastfeeding in phototherapy-exposed infants (aOR: 0.69; 95% CI: 0.49–0.95) at 1-mo postnatal. The reduced odds of breastfeeding in phototherapy-exposed infants persisted at 2 and 4 mo postnatal.	answered that their baby had jaundice were then asked about phototherapy treatment. It is possible that some mothers may not have understood that jaundice and high bilirubin are synonymous terms. jaundiced infants receiving treatment phototherapy has a more adverse effect on breastfeeding than other interventions.	of any breastfeeding at 12 mo postnatal, it seems unlikely that phototherapy was the cause given the one-year duration between phototherapy-exposure and change in breastfeeding habits. Unclear whether among jaundiced infants receiving treatment phototherapy has a more adverse effect on breastfeeding than other interventions.

TABLE 1 Continued

Citation	Methods	Participants or Inclusion Criteria	Exclusion Criteria	Interventions	Outcomes	Results	Risk of Bias	Notes or Conclusions
Infant Behavior Telzrow 1980 Boston Hospital for Women, Boston, Massachusetts, USA	Observational study with matched controls	10 low-risk term, nursery infants who subsequently received phototherapy for high bilirubin were compared to 10 similar infants who did not receive phototherapy. Sex, maternal breastfeeding intent, and rooming-in proportions were similar between groups.	Infants with intrapartum or postnatal abnormalities, including infants of Rh-positive mothers, were excluded.	Phototherapy at clinician discretion (high bilirubin was defined as >9 mg/dL before 48 h postnatal and >11 mg/dL before 72 h).	Brazelton Scale scoring at 3, 6, and 10 d postnatal. (Phototherapy was started at an average age of 76.5 h).	Visual orientation scores were lower in the phototherapy-treated group relative to the nontreated comparison group on postnatal days 3 ($P <$.01), 6 ($P <$.01), and 10 (P < .05). Motor scores were lower on day 6 ($P <$.05).	The authors were unable to separate phototherapy-specific effects from bilirubin- attributable or separation-attributable effects. It was not possible for the examiners to be blinded to treatment group Separate components (26 separate components and 6 cluster-group scores) were assessed within the Brazelton tests (multiple comparisons). Difficult to determine an estimate of effect-size. Decision to initiate phototherapy was at clinician discretion. Mothers were discharged at 3 d. Examinations at 6 d were performed for the phototherapy group within the hospital and for the comparison group at home.	Infants that received phototherapy may have had short-term changes in visual orientation. Results may not apply to infants whose eyes are not covered during phototherapy or who are not separated from their parents.

TABLE 1 Continued

Citation Country	Methods	Participants or Inclusion Criteria	Exclusion Criteria	Interventions	Outcomes	Results	Risk of Bias	Notes or Conclusions
Paludetto 1983 Newborn Nursery of Second School of Medicine; Naples, Italy	Prospective observational study with matched controls	30 term infants undergoing phototherapy for 6 h or more for jaundice (mean bilirubin, 13.3 mg/dL) and 30 comparison subjects matched for sex, gestation, Apgar score, obstetric history, and father's profession. Enrolled on postnatal day 3.	Infants transferred to special care nursery or with any neonatal illness including Rh and ABO mismatch.	Phototherapy for 6 h or more for jaundice. (Treated with phototherapy in the nursery and the mothers fed them every 3 h versus rooming-in in the non-phototherapy-treated comparison group.)	Brazelton Scale scores at (1) postnatal day 3 (day of enrollment) (treated infants were under phototherapy an average of 24 h at first examination), (2) 24 h postenrollment, and 3) at 1 mo of age.	Visual orientation scores were lower in the phototherapy-treated group relative to the nontreated comparison group on postnatal days 3 ($P < .005$) and 4 ($P < .01$) and at 1 mo of age ($P < .05$).	Interrater reliability coefficient was >0.85 . The mean total bilirubin levels were lower in the comparison group (9.6 [range, 3.5–14.3]) relative to the phototherapy group (13.3 [range, 8.4–17.5]). The authors were unable to separate phototherapy-specific effects from bilirubin-attributable or separation-attributable effects. 26 separate components were assessed within the Brazelton tests (multiple comparisons). Difficult to determine an estimate of effect-size. Although there were general newborn unit phototherapy guidelines, clinicians were free to decide whether to start phototherapy. Only 12 matched pairs were available for 12-mo scoring follow-up. Brazelton scorers were unaware of treatment assignment, but might have noted different levels of visible skin jaundice in subjects.	Infants that received phototherapy may have had short-term changes in visual orientation. Results may not apply to infants whose eyes are not covered during phototherapy or who are not separated from their parents.
Cancer Grattingius 1995 (June) Sweden	Nested case-control study	613 cases of lymphatic leukemia were identified in	93 total antenatal and perinatal exposures were examined	Lymphatic (ie, acute, chronic, or unspecified)	Association of childhood lymphatic leukemia with:	Given number of studied exposures, the authors estimated 4 or 5 neonatal jaundice was	Neither the use of phototherapy or neonatal jaundice was	

TABLE 1 Continued

Citation Country	Methods	Participants or Inclusion Criteria	Exclusion Criteria	Interventions	Outcomes	Results	Risk of Bias	Notes or Conclusions
Gnattingius 1995 (July) Sweden	Nested case-control study	the Swedish National Cancer Register and the Medical Birth Register between 1973-1989. 5 controls were matched to every case by sex and birth month and year.		including phototherapy and neonatal jaundice. Diagnoses and procedures determined by ICD codes.	lymphocytic) leukemia.	Phototherapy (OR 1.0; 95% CI: 0.5-1.8). Physiologic jaundice (OR 1.2; 95% CI: 0.8-1.7).	significant associations would be detected by chance alone.	found to increase the odds of childhood lymphatic leukemia. The authors were unable to adjust for degree of hyperbilirubinemia or phototherapy intensity or duration.
		98 cases of myeloid leukemia were identified in the Swedish National Cancer Register and the Medical Birth Register between 1973 and 1989. 5 controls were matched to every case by sex and birth month and year.		Numerous antenatal and perinatal exposures were examined including phototherapy and neonatal jaundice. Diagnoses and procedures determined by ICD codes.	Myeloid (acute, chronic, or unspecified) leukemia.	Association of childhood myeloid leukemia with: Phototherapy (OR 7.5; 95% CI: 1.8-31.9). Physiologic jaundice (OR 2.5; 95% CI: 1.2-5.0). Reanalysis excluding cases with Trisomy 21: Phototherapy (OR 4.3; 95% CI: 0.9-21.9). Physiologic jaundice (OR 1.7; 95% CI: 0.8-4.0).	Given number of studied exposures, significant associations might be detected by chance alone.	Phototherapy and neonatal jaundice were associated with an increased odds of childhood myeloid leukemia. However, these associations were no longer statistically significant after excluding children with Trisomy 21 diagnoses. The authors were unable to adjust for degree of hyperbilirubinemia or phototherapy intensity or duration.
Olsen 1996 Denmark	Retrospective cohort	66 430 neonates discharged with a history of neonatal hyperbilirubinemia between 1977 and 1989 and recorded in the Danish Central Hospital Discharge Register.	Supplementary diagnoses of neonatal immaturity or hemolytic disease.	Diagnosis of hyperbilirubinemia by ICD code.	Diagnosis of cancer within the Danish Cancer Registry.	Among infants with hyperbilirubinemia diagnoses, 87 cancers were observed compared to 85 expected yielding standardized incidence [SIR] ratio = 1.0; 95% CI: 0.8-1.3. Leukemia (SIR = 1.2; 95% CI: 0.8-1.7)	Phototherapy diagnoses were not recorded. It was estimated that 85% to 50% of infants in the study received phototherapy based on a random sample of 150 neonates with hyperbilirubinemia in Copenhagen in 1981. Average follow-up of 9.1 y (range 0-15 y) (= 499 502 person-years).	Hyperbilirubinemia was not associated with childhood cancer. The authors were not able to directly estimate the effect of phototherapy on cancer.
	Case-control		Per inclusion criteria.					

TABLE 1 Continued

Citation Country	Methods	Participants or Inclusion Criteria	Exclusion Criteria	Interventions	Outcomes	Results	Risk of Bias	Notes or Conclusions
Berg 1997 Sweden		30 cases of childhood malignant melanoma between 1973 and 1992 and 120 controls matched by same date of birth, same hospital, and same sex.	Neonatal phototherapy as determined by Swedish Medical Birth Registry.	Childhood malignant melanoma as determined by Swedish Cancer Registry.	None of the infants diagnosed with malignant melanoma had received phototherapy compared to 11 of 120 controls (one-tailed <i>P</i> value as calculated in study = 0.08) (Odds ratio = 0; 95% CI: 0–1.2). Calculated 2-tailed <i>P</i> value = 0.156).	Association between any leukemia and: Phototherapy (OR 0.5; 95% CI: 0.1–2.3). Jaundice (OR 0.8; 95% CI: 0.5–1.5). Additionally, no associations were detected between jaundice or phototherapy and acute lymphocytic leukemia, acute myeloid leukemia, or non-Hodgkin's lymphoma).	The average follow-up time was 18 y (range: 10–19). Phototherapy estimates were not adjusted for degree of hyperbilirubinemia or phototherapy intensity or duration.	No association was detected between phototherapy and childhood malignant melanoma.
Roman 1997 Southern England, UK	Case-control	177 cases with leukemia or non-Hodgkin's lymphoma and 354 age and sex-matched controls identified from the medical records of 3 hospitals.	Infants from multiple gestation pregnancies who died before birth hospital discharge, or with identified chromosomal anomalies or malformations.	Multiple antenatal and perinatal risk factors including phototherapy and neonatal jaundice, as extracted from hospital medical records.	Leukemia or non-Hodgkin's lymphoma diagnosed between the age of 3 mo–30 y. Cases for children (0–14 y) extracted from the Childhood Cancer Research Group (1962–1992). Cases for young adults (15–29 y) extracted from Office of National Statistics (ONS) (1972–1987).	Phototherapy estimates were not adjusted for degree of hyperbilirubinemia.	Phototherapy and jaundice were not associated with leukemia or non-Hodgkin's lymphoma in young adults.	
Podvin 2006 Washington, USA	Case-control	595 cases born between 1980–2002 were identified from the Washington State Cancer Registry or Cancer Surveillance System of Western Washington. Controls (<i>n</i> = 5950) were randomly	Per inclusion criteria. Multiple antenatal and perinatal risk factors including phototherapy and neonatal jaundice. Jaundice diagnoses were documented on birth certificates before 1992. After 1987, ICD code-based phototherapy and neonatal jaundice	Childhood leukemia diagnosis (age < 20).	Phototherapy (aOR 2.2; 95% CI: 1.0–4.9). Neonatal jaundice as documented by ICD code (aOR 1.4; 95% CI: 1.0–1.9). Neonatal jaundice as documented on birth certificate (aOR 2.1; 95% CI: 1.2–3.8).	Estimates were adjusted for maternal age, gestation, birth wt and race. A secondary analysis that excluded infants with Trisomy 21 found similar results. Phototherapy estimates were not adjusted for degree of hyperbilirubinemia.	Phototherapy and neonatal jaundice were associated with childhood leukemia. The authors were unable to adjust for degree of hyperbilirubinemia or intensity or duration of phototherapy.	

TABLE 1 Continued

Citation Country	Methods	Participants or Inclusion Criteria	Exclusion Criteria	Interventions	Outcomes	Results	Risk of Bias	Notes or Conclusions
Brewster 2010 Grampian Region, Scotland, UK	Retrospective cohort	selected from birth certificate records of infants without leukemia and frequency of controls were matched to cases by year. 77518 singleton newborn infants born 1976–1990 that survived the neonatal period.	Neonatal deaths.	Received neonatal phototherapy versus no phototherapy.	Standardized incidence ratios for melanoma, basal cell, and squamous cell skin cancer.	Two cases of melanoma occurred in phototherapy-exposed versus 16 cases in unexposed. Standardized incidence ratio of 1.40 (95% CI, 0.17–5.04; $P = .834$) for melanoma. No cases of squamous cell or basal cell carcinoma of skin were observed in exposed persons.	Limited confounder control for age, sex, calendar period, and socioeconomic measure within a postal code. Bilirubin level unmeasured. Duration of phototherapy unmeasured. Median follow-up of 24 y.	No difference in skin cancer risk was detected in infants exposed to neonatal phototherapy.
Newman 2016 Northern California, USA	Retrospective cohort	449 621 newborn infants born 1995–2011 at ≥ 35 wk' gestation who survived to discharge and were followed ≥ 60 d. Database from 15 Northern California Hospitals (Kaiser Permanente). 1995–2011.	Death or transferred to another hospital before initial hospital diagnosis. Cancer diagnosis before 60 postnatal days. Infants born at < 35 wk' gestation.	Received any neonatal phototherapy (in hospital, at home, or both) vs no phototherapy. Dose-response phototherapy variable (0- none, 1-home phototherapy only, 2-single admission, 3-phototherapy in multiple admits).	Cancer diagnoses between postnatal day 60 and the end of the follow-up period. Examined multiple categories of leukemia and other forms/sites of cancer.	Propensity-score adjusted hazard ratio for any cancer after phototherapy: (aHR: 1.0; 95% CI: 0.7–1.6). Lower limit of 95% CI for number needed to harm (NNH) for 10-y cancer risk ~ 1100 . For children with Down syndrome, lower limit of 95% CI for estimated NNH for leukemia = 23. Propensity-score adjusted hazard ratios mutually consistent for: Any leukemia: (aHR: 1.6; 95% CI: 0.8–3.5). Nonlymphocytic leukemia: (aHR: 1.9;	Cox regression models including both traditional multivariable models and propensity-score adjustment were used to adjust for potential measured confounders, and duration of follow-up. Multivariable and propensity-score estimates were mutually consistent. Unable to measure total duration of phototherapy exposure. Used a directed acyclic	In adjusted analyses, there was no statistically significant elevation in the risk for cancer. Unadjusted analyses did show an elevated risk. Given their elevated baseline risk for leukemia, children with trisomy 21 may be at an even higher risk for leukemia after phototherapy.

TABLE 1 Continued

Citation Country	Methods	Participants or Inclusion Criteria	Exclusion Criteria	Interventions	Outcomes	Results	Risk of Bias	Notes or Conclusions
						95% CI: 0.6–6.9). Liver cancer: (aHR 1.4; 95% CI: 0.2–12). In infants with ≥ 2 phototherapy admissions there was an association between phototherapy and acute myelogenous leukemia (AML) (aHR 8.5; 95% CI 1.9–38) (note: based on only 2 cases of AML with ≥ 2 readmissions for phototherapy).	graph (DAG) to illustrate modeling assumptions. Cancer diagnoses were confirmed by a medical record review.	
		Wickremasinghe 2016 California, USA	Retrospective cohort	5 144 849 infants born at ≥ 35 wk' gestation who survived >60 d. California Vital Statistics/Patient Discharge Dataset 1998-2007.	Death within 60-d of birth. Cancer diagnosis before 60 postnatal days. Infants born at <35 wk' gestation.	Receipt of phototherapy during a hospitalization that began within the first 2 postnatal weeks as recorded by ICD-9 code for phototherapy (99.83, 99.83).	Hospital discharge diagnosis of cancer via ICD-9 code between 60-d postnatal and 1 y of age.	Propensity-score adjusted odds ratio for: 60-All cancer: (aOR: 1.4; 95% CI: 1.1-1.9). Myeloid leukemia: (aOR: 2.6; 95% CI: 1.3–5.0). Renal cancer: (aOR: 2.5; 95% CI: 1.2–5.1). Found NNH of 10 638 in the general population and 1285 in children with trisomy 21.
	Adjusted for the presence of a jaundice diagnosis, but unable to control for bilirubin concentration, which is also associated with a cancer diagnosis. Phototherapy duration was not measurable.	phototherapy may slightly increase the risk of cancer in the first postnatal year.						

TABLE 1 Continued

Citation	Participants or Inclusion Criteria	Exclusion Criteria	Interventions	Outcomes	Results	Risk of Bias	Notes or Conclusions
Auger 2019 Quebec, Canada	Retrospective cohort 786 998 infants born between 2006 and 2016. Dataset of discharge abstracts from all Quebec hospitals: "Maintenance and Use of Data for the Study of Hospital Clientele Registry of Quebec."	Cancer diagnosis before age 2 mo or less than 2 mo of follow-up. Infants with missing gestational age or birth wt.	The exposure was defined as a 3-category variable: phototherapy, untreated jaundice, or no exposure Phototherapy at birth or during admissions in the first 28 postnatal days, as recorded by Canadian Health interventions procedure codes (1.YZ.12.JA-DQ). Jaundice diagnosis recorded via ICD-10 codes (P58, P59).	Hospitalization for solid or hematopoietic childhood tumors between 2 mo and 11 y of age.	Propensity-score adjusted hazard ratios for: Any cancer: Phototherapy versus no exposure: aHR, 1.16; 95% CI: 0.9–1.6). (Phototherapy versus untreated jaundice: aHR: 1.07; 95% CI: 0.8–1.5). (Untreated jaundice versus no exposure: aHR: 1.09; 95% CI: 0.9–1.3). Any cancer at 4–11 y: (Phototherapy versus no exposure: aHR 2.21; 95% CI 1.5–3.3) (Phototherapy versus untreated jaundice: aHR 2.21; 95% CI 1.3–3.7). Late onset solid tumors, between age 4 and 11 y: (Phototherapy versus no exposure: aHR: 2.26; 95% CI: 1.3–3.8) (Phototherapy versus untreated jaundice: aHR: 2.21; 95% CI: 1.2–4.3). The cumulative incidence of childhood cancer	Unable to adjust for bilirubin concentration, which is also associated with a cancer diagnosis. Phototherapy duration was not measurable. Propensity-score adjustment to adjust for potential, measured confounders. Fine-Gray subdistribution hazard model to allow for estimation of probability of cancer over time (cumulative incidence function [CIF]), while accounting for death as a competing risk. Adjusted hazard ratios for any cancer and for solid tumor cancers, but not for hematopoietic cancers, significantly increased with age for infants exposed to phototherapy.	Neonatal phototherapy may be associated with a slightly increased risk of solid tumors in childhood. It was not possible to rule out increasing bilirubin concentration as a potential confounder, since a jaundice diagnosis was also associated with cancer, bilirubin concentrations were not available, and phototherapy would likely be initiated at higher bilirubin levels compared to untreated jaundice. Adjusted hazard ratios for any cancer and for solid tumor cancers, but not for hematopoietic cancers, significantly increased with age for infants exposed to phototherapy.

TABLE 1 Continued

Citation Country	Methods	Participants or Inclusion Criteria	Exclusion Criteria	Interventions	Outcomes	Results	Risk of Bias	Notes or Conclusions
Seppala 2020 Finland	Case-control	2037 cases with childhood cancer diagnosed from Finnish Cancer Registry between 1996-2014. 5 sex and year-matched controls (n = 10 185) for each case from Finnish Medical Birth Registry.	8 cases and 82 controls due to missing birth wt or gestation data.	Multiple antenatal and perinatal risk factors. Prematurity associated variables were the main exposure variables of interest. Perinatal conditions and procedures, including phototherapy, were secondary exposures of interest.	Childhood cancer (age <20 y) as diagnosed from the Finnish Cancer Registry.	Association between childhood cancer and phototherapy: All newborns (aOR 1.11; 95% CI: 0.91-1.35). Term newborns (aOR 1.17; 95% CI: 0.91-1.49).	Analyses were adjusted for maternal age, maternal smoking, and number of pregnancies. Phototherapy estimates were not adjusted for degree of hyperbilirubinemia or phototherapy intensity or duration.	Phototherapy was not associated with childhood cancer.
Digitale 2021 Northern California, USA	Retrospective cohort	139 100 infants born at >35 wk' gestation from 1995-2017 with qualifying bilirubin concentration 3 mg/dL below to 4.9 mg/dL above the 2004 AAP phototherapy threshold. Database from Northern California Hospitals (Kaiser Permanente). *Note: This is an extension of the Newman 2016 cohort with an additional 453 786 person-years of follow-up	Patients who died or were transferred to another hospital before initial hospital discharge Cancer diagnosis before 60 postnatal days or only had a secondary cancer diagnosis. <60 d of follow-up. Northern California infants born at <35 wk' gestation.	Received any neonatal phototherapy during birth hospitalization or readmission versus no inpatient phototherapy.	Cancer diagnoses between postnatal day 60 and the end of the follow-up period. Required 2 total cancer diagnoses at different departments to reduce false-positive diagnoses. Time of cancer diagnosis defined as date of initial ICD cancer diagnosis. Examined multiple categories of hematopoietic cancers, solid tumors, and other cancers.	Propensity-score adjusted hazard ratio for any cancer after phototherapy: (aHR: 1.13; 95% CI: 0.8-1.5). Propensity-score adjusted hazard ratios for: Any hematopoietic cancer: (aHR: 1.17; 95% CI: 0.7-1.8). Solid tumors: (aHR: 1.01; 95% CI: 0.7-1.6). Analyses specifically looking for an increase in cancer risk after age 4 y were also negative.	Cox regression models incorporated propensity-score adjustment to adjust for potential, measured confounders, (including bilirubin concentration) and duration of follow-up. Unable to measure total duration or intensity of phototherapy exposure.	Adjusted analyses, detected no significant elevation in the baseline risk for cancer.

TABLE 1 Continued

Citation Country	Methods	Participants or Inclusion Criteria	Exclusion Criteria	Interventions	Outcomes	Results	Risk of Bias	Notes or Conclusions
Bugaiski-Shaked 2022	Retrospective cohort	342 172 infants born at ≥ 32 wk' gestation born 1998-2018.	Neonates who died or were diagnosed with any malignancy before 30-d postnatal.	Phototherapy performed during the first 2 wk postnatal as defined by ICD-9 code for phototherapy diagnosis (Z9983).	First pediatric hospitalization with any diagnosis of neoplasm (malignant or benign).	Preterm birth and maternal age adjusted hazard ratios for: Childhood malignancies (aHR 1.89; 95% CI: 1.4–2.7)	Unable to adjust for bilirubin concentration when estimating associations between phototherapy and neoplasms.	Adjusted analyses indicated that phototherapy may slightly increase the risk of childhood malignancies and benign tumors cancer in the first postnatal year.
Soroka University Medical Center, Be'er-Sheva, Israel	Perinatal database of obstetric and neonatal discharge summary data merged with hospitalization records from Soroka University Medical Center.					Benign tumors: (aHR: 1.27; 95% CI: 1.02–1.6) Childhood malignancies in term-infants: (aHR: 1.84; 95% CI: 1.2–2.7)	Phototherapy intensity and duration were not measurable. Used Israeli Ministry of Health national cancer registry to cross-reference and verify child malignancy diagnoses that were in database. Median follow-up of 9.5 y (range 0–18 y).	It was not possible to rule out increasing bilirubin concentration as a potential confounder or to evaluate the impact of phototherapy intensity or duration on outcomes.
Insulin-Dependent Diabetes Mellitus Dahlquist 2003	Case-control	6487 cases born 1973–1997 who were recorded in the Swedish Childhood Diabetes Registry and also linked with the Swedish Medical Birth Registry.	Twins, infants born of diabetic mothers, and infants whose county of birth was unknown,	Phototherapy as recorded in database. Jaundice was also evaluated as an exposure.	A diagnosis of childhood diabetes as recorded in the Swedish Childhood Diabetes Registry.	Adjusted odds of type 1 diabetes in infants who had received phototherapy in 2 high-risk counties with high type 1 diabetes prevalence: (aOR 1.95; 95% CI: 1.2–3.2).	Multivariable logistic regression analyses adjusted for birth year, preterm birth, newborn respiratory symptoms, and blood group immunization. Unable to adjust for bilirubin concentration or phototherapy duration or intensity.	Phototherapy was associated with type 1 diabetes in 2 Swedish counties with high diabetes prevalence, following adjustment for measured confounding variables. This association was not observed in all other Swedish counties in adjusted analyses.
Sweden	2.8 million births for comparison.					Association between phototherapy and diabetes in all other counties: (aOR 1.06; 95% CI 0.8–1.4). Unadjusted association between therapy and diabetes, irrespective of diagnosis: (OR 3.79; 95% CI: 3.1–4.6). Unadjusted association between jaundice diagnosis and		The analysis did not attempt to separate the jaundice-associated effect from that of phototherapy.

TABLE 1 Continued

Citation Country	Methods	Participants or Inclusion Criteria	Exclusion Criteria	Interventions	Outcomes	Results	Risk of Bias	Notes or Conclusions
Newman 2016 Northern California, USA	Retrospective cohort	499 642 infants born at ≥ 35 wk' gestation who were recorded in the Kaiser Permanente of Northern California (KPNC) Database (1995–2011).	Infants who died during birth hospitalization, who were transferred, and who were followed <60 d after birth.	In-hospital or home phototherapy.	Type-1 diabetes diagnosis defined as either ≥ 2 (inpatient or outpatient) with a diagnosis of type 1 diabetes or 1 encounter and either ≥ 2 hemoglobin A1c levels $\geq 6.5\%$ or a pharmacy record indicating insulin prescribing. Diagnoses obtained from KPNC virtual data warehouse and diabetes registry.	diabetes: (OR 1.13; 95% CI 1.01–1.3). Association between any phototherapy and type 1 diabetes: (aHR 1.06; 95% CI: 0.8 to 1.5). Adjusted incidence rate ratio (aIRR) for phototherapy: 1.03 (95% CI: 0.8–1.4) corresponding to an estimated excess risk of 0.58 (95% CI, –4.7 to 5.9) per 100 000 person-years. Propensity-adjusted Cox model-derived association between phototherapy and type 1 diabetes: Restricted model that included only those with ≥ 1 TSB between –3 and +4.9 mg/dL from 2004 AAP phototherapy threshold (aHR 0.95; 95% CI, 0.60–1.5) Inclusive model of all subjects with dichotomous variable for any TSB level exceeding 2004 AAP (aHR 0.91; 95% CI: 0.7–1.3).	Propensity-analyses adjusted for bilirubin level before phototherapy. Unable to measure phototherapy duration or intensity.	There was no evidence of increased type 1 diabetes risk in children who had received phototherapy.
Melanocytic Nevi Bauer 2004 Germany	Cross-sectional study	1812 white children aged 2–7 y attending day care centers in 2 German cities in 1998. Note: this very brief report describes a	Per inclusion criteria. Neonatal phototherapy as determined by parent survey.	Neonatal phototherapy as determined by parent survey.	Total body nevus counts and pigmentation characteristics were assessed in all participating children (52.9% boys).	Multiple linear regression analysis did not identify an association between neonatal phototherapy and the number of melanocytic nevi in children ($P = .21$).	Limited data are presented in this brief report. Thus, we are unable to calculate measures of effect size. A standardized interview of parents included	No association was found between phototherapy as reported via parent survey and childhood melanocytic nevus count at ages 2–7 y. Limitations include the potential for recall

TABLE 1 Continued

Citation Country	Methods	Participants or Inclusion Criteria	Exclusion Criteria	Interventions	Outcomes	Results	Risk of Bias	Notes or Conclusions
Matichard 2006 Necker Hospital, Paris, France	Case-control	Eighteen 8- to 9-y-old children who were born from 1994 to 1995 and treated with phototherapy for jaundice at birth and 40 age-matched schoolchildren who had not received neonatal phototherapy.	Per inclusion criteria.	Neonatal phototherapy for jaundice.	Total nevus count and nevus count by size in millimeters (mm) at ages 8–9 y.	Multivariate analysis using a variance model demonstrated an associated increase in nevi of size 2–5 mm ($P < .001$), but not an increase in total nevus count. Reported solar exposure was associated with an increase in the total nevus count ($P = .02$) and age ($P = .02$) and freckles ($P = .03$) were associated with an increase in 2–5 mm nevi.	A variance model was used to adjust for age, skin/eye/hair classifications, and survey-reported solar exposure. Effect sizes for multivariate analysis are not reported. Multiple comparisons. The evaluations were performed by the same dermatologist but at different locations: at the hospital for those receiving phototherapy and at a school for the nonexposed comparator group. Thus, the evaluation was not blinded.	An association was found at ages 8–9 between neonatal phototherapy exposure and an increased 2–5 mm nevus count. There was no association between phototherapy and total nevus count. Limitations include a nonblinded examination and the inability to control for confounders and bilirubin concentration in both groups at the time of potential phototherapy exposure shortly after birth.
Mahé 2008 France	Retrospective cohort	828 9-y-old children at 52 French primary schools in May–June 2007.	Children absent from school on the day of the skin examination.	Neonatal phototherapy for neonatal jaundice as determined by a standardized survey	Melanocytic nevus count as performed by 2	No difference in the melanocytic nevus count was detected between students that	Statistical analysis was done by χ^2 test. A standardized interview	No association was found between phototherapy as reported via parent/child survey

TABLE 1 Continued

Citation Country	Methods	Participants or Inclusion Criteria	Exclusion Criteria	Interventions	Outcomes	Results	Risk of Bias	Notes or Conclusions			
Csoma The University of Szeged, Hungary	Cross-sectional twin study	58 pairs of twins (15 monozygotic pairs, 43 dizygotic) and one set of dizygotic triplets aged 3–30 y between January–April 2008 at The University of Szeged, Hungary. In each pair, one twin had received phototherapy for neonatal jaundice and the other had not.	Per inclusion criteria.	Neonatal blue light phototherapy as recorded in the neonatal medical chart. Icterus/jaundice, and prematurity as recorded in neonatal charts.	Melanocytic lesions as determined by skin examination. Uveal melanocytic lesions as determined by detailed ophthalmic examination.	In the multivariable linear regression analysis, neonatal blue light phototherapy was significantly associated with increased melanocytic nevi prevalence: (standardized coefficient: 0.158; 95% CI: 0.003–0.352; $P = .47$) (unstandardized β coefficient: 0.076). Age (standardized coefficient: 0.503; 95% CI: 0.051–0.101; $P < .0001$) and number of subtropical/tropical holidays (0.178; 95% CI: 0.012–0.332; $P = .035$) were also	of parents and children.	dermatologist-trained nurses.	reported phototherapy exposure versus unexposed students (mean \pm SD nevus count of 16.8 \pm 9.8 in exposed vs 16.7 \pm 10.5 in unexposed). Skin phototype, skin color, eye color, and number of sunburn episodes were associated with nevus count.	of parents included questions of sun exposure history, sun protection, and history of neonatal phototherapy. Risk of recall bias from the use of survey to determine phototherapy. Limited control for potential confounders at the time of phototherapy attributable to survey design. Unable to adjust for specific bilirubin concentrations in phototherapy-treated infants versus unexposed infants. Evaluation was not blinded.	and melanocytic nevus count at age 9 y. Limitations include the potential for recall bias because of the survey design, an unblinded analysis, and an inability to adequately control for potential confounders at the time of phototherapy.

TABLE 1 Continued

Citation Country	Methods	Participants or Inclusion Criteria	Exclusion Criteria	Interventions	Outcomes	Results	Risk of Bias	Notes or Conclusions
Wintermeier 2014 Ludwig-Maximilian Hospital in Munich, Germany	Case-control	52 white, 5- to 6-y-old children who were previously exposed to neonatal blue light phototherapy after birth at Ludwig-Maximilian Hospital in Munich, Germany and 52 nonexposed children who were matched on age, gender, gestational age at birth, and skin phototype.	Per inclusion criteria.	Neonatal blue light phototherapy exposure.	Melanocytic nevus count at age 5–6 y by a single investigator. Café-au-lait macules, congenital nevi, and freckles were assessed separately.	<p>associated with increased skin lesion prevalence.</p> <p>Neonatal blue light phototherapy was associated with an increased odds of benign pigmented ocular lesions (aOR: 3.778; 95% CI: 1.694–8.423; $P = .001$).</p> <p>The median nevus count in children with phototherapy was 17 compared to 18.5 in the matched nonexposed comparator group ($P = .18$) (Mann-Whitney U test).</p> <p>A higher count of café-au-lait macules (mean 0.5) were noted in the phototherapy exposed children relative to the nonexposed (mean 0.2) ($P = .001$).</p> <p>Skin phototype ($P = .05$), duration of sunny vacations ($P = .02$), and vacations in sunny areas ($P = .03$) were associated with increased melanocytic nevi.</p>	<p>along with age and pigmentary traits were adjusted for in the multivariable analyses.</p> <p>Multivariable linear regression for skin lesions (natural log of skin lesions was normally distributed) and multivariable logistic regression for uveal lesions (not normally distributed).</p> <p>Limited control for potential confounders at the time of phototherapy. Unable to adjust for specific bilirubin concentrations in phototherapy-treated infants versus unexposed infants.</p> <p>A history of family history of skin cancer, sun exposure, and sun protection was obtained by parental survey.</p> <p>Blinding of the examining dermatologist to phototherapy exposure was not noted.</p>	<p>No association was found at ages 5–6 between neonatal phototherapy exposure and melanocytic nevus count. Limitations include a nonblinded outcome examination and the inability to adjust for confounders and bilirubin concentration in both groups shortly after birth, the time of potential phototherapy exposure.</p>
Lai 2016	Systematic review and meta-analysis	5 observational studies ($n = 2921$ total subjects) that evaluated the association of	Studies were excluded if they were not cohort, case-control, or cross-sectional	Neonatal phototherapy for hyperbilirubinemia.	Melanocytic nevus count.	<p>Those with previous phototherapy were not found to have a significantly higher mean melanocytic nevus.</p>	<p>DerSimonian and Laird random-effects models were used to calculate a weighted mean difference.</p>	<p>This meta-analysis of published studies did not demonstrate a significantly higher mean number of</p>

TABLE 1 Continued

Citation Country	Methods	Participants or Inclusion Criteria	Exclusion Criteria	Interventions	Outcomes	Results	Risk of Bias	Notes or Conclusions
Neurologic Maimburg 2016 Denmark	Retrospective cohort	neonatal phototherapy with melanocytic nevi development. (Bauer 2004, Csoma 2011, Mahé 2008, Matichard 2006, Wintermeier 2014.) Search terms: ("photo-therapy"[Mesh] AND blue light*) AND ("nevus, pigmented"[Mesh] OR moles OR melanocytic nevi).	designs or if mean values and standard deviations of nevi counts were not included or calculable from the presented data. (4 reviews excluded and 1 excluded for insufficient information.)	Information on exposure to phototherapy for hyperbilirubinemia was obtained from a maternal questionnaire at 6 months postnatal. When estimating the risk of epilepsy, children were followed from postnatal day 29 until onset of epilepsy, death, or end of the follow-up in August 2010. In the analyses for the risk of febrile seizure, children were followed from postnatal day 90 until onset of febrile seizure, death, or 5 y, whichever came first.	Information on epilepsy and febrile seizures were obtained from ICD-10 diagnoses within the Danish National Hospital Registry (DNHR).	nevus count: (Weighted mean difference: 0.32; 95% CI: -0.67 to 1.31; $P = .53$).	There was both clinical heterogeneity and significant statistical heterogeneity between the 5 studies ($I^2 = 69.1\%$; $P = .01$). Visual inspection of the funnel plot could not exclude publication bias. Formal Egger's test failed to provide strong evidence of a small-study effect ($P = .09$).	melanocytic nevi after exposure to neonatal phototherapy. However, there was a great degree of heterogeneity between the included studies.
				Information on exposure to phototherapy for hyperbilirubinemia was obtained from a maternal questionnaire at 6 months postnatal. When estimating the risk of epilepsy, children were followed from postnatal day 29 until onset of epilepsy, death, or end of the follow-up in August 2010. In the analyses for the risk of febrile seizure, children were followed from postnatal day 90 until onset of febrile seizure, death, or 5 y, whichever came first.	Information on epilepsy and febrile seizures were obtained from ICD-10 diagnoses within the Danish National Hospital Registry (DNHR).	Treatment with phototherapy for hyperbilirubinemia was associated with an increased hazard for developing epilepsy in early childhood (aHR: 1.66; 95% CI: 1.23–2.24). Phototherapy treatment was not associated with febrile seizures (aHR: 1.04; 95% CI: 0.86–1.27). The increased hazard of epilepsy was present for boys (aHR: 1.98; 95% CI: 1.40–2.78) but not for girls (aHR: 1.14; 95% CI: 0.64–2.02).	Cox proportional hazard regression models accounted for observed follow-up time of each subject and adjusted for potential, measured confounders (gender, birth gestation, socioeconomic status, maternal risk factors during pregnancy, and maternal age, parity, infertility treatment). Were unable to adjust for bilirubin concentrations at the time of potential phototherapy exposure. Maternal survey response for phototherapy was validated via a medical record review of a random 100-patient sample of infants born at Aarhus University	Phototherapy for hyperbilirubinemia in newborn infants was associated with an increased risk of epilepsy for males in early childhood. No excess risk for febrile seizures was seen. A limitation was the inability to adjust for bilirubin concentration in both groups at the time of potential phototherapy exposure.

TABLE 1 Continued

Citation Country	Methods	Participants or Inclusion Criteria	Exclusion Criteria	Interventions	Outcomes	Results	Risk of Bias	Notes or Conclusions
Newman 2018 Northern California, USA	Retrospective cohort	496 632 infants born at ≥ 35 wk' gestation in 1995–2011 and followed ≥ 60 d. Kaiser Permanente of Northern California Database of 15 hospitals.	Exceeded 2009 AAP exchange transfusion thresholds ($n = 1773$) and those with seizure diagnoses at < 60 d postnatal ($n = 1237$). Died during birth admission.	Dichotomous variable for any phototherapy within the hospital or at home.	Primary outcome: ≥ 1 seizure diagnosis plus ≥ 1 AED prescription. Secondary outcomes: other combinations of ≥ 1 or ≥ 2 encounters with seizure or epilepsy diagnoses and ≥ 1 AED prescriptions.	Phototherapy-associated hazard ratio for Seizure (aHR: 1.22, 95% CI: 1.05–1.42; $P = .009$). Use of phototherapy increased during the study period from 2.4% in 1995% to 15.9% in 2011. More boys experienced both phototherapy and also seizures, but there was no effect modification (interaction) between sex and phototherapy exposure. Adjusted 10-y excess risks per 1000 infants associated with phototherapy were 2.4 (95% CI: 0.6–4.1) overall, 3.7 (95% CI: 1.2–6.1) for boys, and 0.8 (95% CI: -1.7 to 3.2) for girls.	Hospital, which revealed 96% agreement. and Poisson regression models were used to adjust for TSB concentrations and other measured, potential confounders. Cox models accounted for observed follow-up time of each subject. Propensity-score adjusted model estimates were similar to Cox model estimates. Additional analyses showed that bilirubin concentrations of 20–24.9 mg/dL only became significantly associated with seizure-diagnoses in adjusted models when the phototherapy-exposure variable was removed. Did not have data on the duration or intensity of phototherapy.	Neonatal phototherapy treatment is associated with a slight risk in childhood seizures diagnosed after ≥ 60 d postnatal following adjustment for bilirubin measurements. Boys are more likely than girls to both receive phototherapy and to be diagnosed with childhood seizure.

aHR, adjusted hazard ratio; aRR, adjusted relative risk; AED, antiepileptic drug; ICD, International Classification of Diseases; IRR, incidence rate ratio; TSB, total serum bilirubin; ASD, autism spectrum disorder; AET, average treatment effect on the treated.

Question: What are the adverse clinically detectable effects of phototherapy in newborns?

Population: Neonates born at ≥ 35 weeks' gestation with hyperbilirubinemia who are candidates for phototherapy

Intervention: Treatment with phototherapy

Comparator: Nontreatment

Outcome: Increased risk of any adverse clinical outcome that is important to neonatal patients, their families, and/or the clinicians treating them

Excluded: case reports/series, nonsystematic review articles, manuscripts focused on preterm infants born at < 35 weeks' gestation

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TABLE 2 IVIG to Prevent Exchange Transfusion in Infants With Indirect Hyperbilirubinemia

Citation and Setting	Methods	Participants or Inclusion Criteria	Exclusion Criteria	Interventions	Outcomes	Results	Risk of Bias	Notes or Conclusions
ABO Isoimmunization Miqdad 2004 Riyadh, Saudi Arabia	Randomized controlled trial	112 newborn infants born in a single-center between 2000-2002 at ≥ 36 wk' gestation with ABO incompatibility and a positive direct antiglobulin test (DAT) with serum bilirubin rate of increase ≥ 0.5 mg/dL/hour.	As per inclusion criteria.	Randomized to phototherapy plus 500 mg/kg IVIG or phototherapy alone.	Exchange transfusion (conducted in both groups if the serum bilirubin was ≥ 20 mg/dL). (Exchange transfusion was also conducted in the phototherapy-only control group [not the IVIG group] if the serum bilirubin rate of increase was ≥ 0.5 mg/dL/hour).	Exchange transfusion risk in IVIG exposed: 7.1%. Risk in placebo group: 28.6%. Risk ratio: 0.25 (95% CI: 0.09–0.7). Risk difference: –21.4 (95% CI: –35.1 to –7.8). No adverse events noted.	The investigators and clinicians were not blinded to treatment. The control group had an additional trigger for exchange transfusion based on bilirubin rate of increase. This increased the likelihood that infants in the control group might qualify for exchange transfusion.	IVIG treated infants with ABO incompatibility were less likely to receive an exchange transfusion than those in the control group. It should be noted that by design, the control group had an increased opportunity to qualify for an exchange transfusion (bilirubin rate of rise ≥ 0.5 mg/dL/hour or serum bilirubin ≥ 20 mg/dL), relative to the IVIG treated group (exchange transfusion only for serum bilirubin ≥ 20 mg/dL). The number of infants in the control group that were exchanged

TABLE 2 Continued

Citation and Setting	Methods	Participants or Inclusion Criteria	Exclusion Criteria	Interventions	Outcomes	Results	Risk of Bias	Notes or Conclusions
Rhesus (Rh) isoimmunization Rübo 1992 Germany	Randomized controlled trial	32 term and preterm newborn infants with positive direct antiglobulin tests born at 11 German children's hospitals between 1989-1990. Treatment began as soon as Rh-isoimmunization was established and consent was obtained.	As per inclusion criteria.	Randomized to phototherapy plus 500 mg/kg IVIG, as soon as Rh-isoimmunization was established and informed consent obtained, or to phototherapy alone.	Exchange transfusion (conducted if bilirubin concentrations exceeded the modified curves of Poláček ^a by more than 2 mg/dL).	Exchange transfusion risk in IVIG exposed: 12.5%. Risk in placebo group: 68.8%. Risk ratio: 0.18 (95% CI: 0.05-0.69). Risk difference: -56.3% (95% CI: -84.2 to -28.4). No adverse events noted.	The investigators and clinicians were not blinded to treatment. Randomization concealment and allocation process not described. Noted that 1 child in each group was excluded for unnamed protocol violations. The study was originally planned for 34 infants.	because of bilirubin rate of increase (≥ 0.5 mg/dL/hr) rather than a serum bilirubin ≥ 20 mg/dL was not reported. IVIG treated infants with Rh-isoimmunization were less likely to receive an exchange transfusion than those in the control group. The authors reported that the difference in birth wt or age between groups was not statistically significant. However, there was no report of the number of infants by specific gestational age. Of the 13 infants that received exchange transfusion, 8 were >2.5 kg birth wt term

TABLE 2 Continued

Citation and Setting	Methods	Participants or Inclusion Criteria	Exclusion Criteria	Interventions	Outcomes	Results	Risk of Bias	Notes or Conclusions
Dağoğlu 1995 Istanbul, Turkey	Randomized controlled trial	41 newborn infants (mean gestational age: 36.1 wk) with Rh- incompatibility and a positive DAT who were admitted to a single-center between August 1992- and June 1994. Mean gestation of treated group: 36.1 wk; SD: 2.3. Mean gestation of untreated group: 36.1 wk; SD: 1.7.	As per inclusion criteria.	Randomized to phototherapy plus 500 mg/kg IVIG as soon as possible after birth (usually within 2 h) or to phototherapy alone. Phototherapy was initiated when bilirubin concentrations exceeded the relevant curves of Oski and Naiman, ^b IVIG treatment was usually administered within 2 h postnatal.	Exchange transfusion (conducted if the increase of total bilirubin exceeded 1 mg/dL/hour or when, during the first 72 h, the total concentration exceeded 20 mg/dL in term infants or 18 mg/dL in infants weighing more than 2000 g).	Exchange transfusion risk in IVIG exposed: 20%. Risk in placebo group: 75%. Risk ratio: 0.27 (95% CI: 0.11–0.66). Risk difference: –55% (95% CI: –80.8 to –29.17). No adverse events noted.	The investigators and clinicians were not blinded to treatment.	IVIG treated infants with Rh- isoimmunization were less likely to receive an exchange transfusion than those in the control group Mothers of enrolled infants received 2–3 in-utero transfusions on average, before delivery for treatment of Rh-mediated hemolysis. IVIG-treated infants with Rh- incompatibility were less likely to receive an exchange transfusion than those in the control group. It should be noted that the original randomization assignment was not followed for
Elalfy 2011 Cairo, Egypt	Randomized controlled trial	90 newborns with Rh- isoimmunization who were born at >38weeks' gestation with serum bilirubin increasing by 0.5 mg/dL/hour and/or required phototherapy in the first 12 h postnatal, who were not yet eligible for exchange transfusion and who were admitted to a single center between March	Perinatal asphyxia, neonatal sepsis, or presence of hematomas.	Randomized at 12 h to 500 mg/kg IVIG plus phototherapy (n = 23 assigned; n = 25 treated), 1 g/kg IVIG plus phototherapy (n = 22 assigned; n = 15 treated) or phototherapy only (n = 45 assigned; n = 50 treated). Parents of 5	Exchange transfusion (conducted per the 2004 AAP exchange transfusion thresholds if the bilirubin was increasing by ≥1 mg/dL/hour).	Exchange transfusion risk in IVIG exposed (inclusive of low- and high-dose treatment groups): 5%. Risk in placebo group: 22%. Risk ratio: 0.23 (95% CI: 0.05–0.97). Risk difference: –17% (95% CI: –30.3 to –3.7). The 2 IVIG-treated infants who	The investigators and clinicians were not blinded to treatment. Parents were able to refuse assigned treatment after study enrollment and receive treatment in a different group. Small sample sizes in the high- and low-dose treatment groups reduced	

TABLE 2 Continued

Citation and Setting	Methods	Participants or Inclusion Criteria	Exclusion Criteria	Interventions	Outcomes	Results	Risk of Bias	Notes or Conclusions
Smits-Wintjens 2011 Leiden, Netherlands	Randomized, double-blinded, placebo-controlled trial	80 newborn infants born at ≥ 35 wk' gestation and admitted to a single center between 2006 and 2010 with maternal and neonatal testing consistent with Rhesus D- or anti C-mediated hemolytic disease of the newborn (HDN). Rhesus HDN defined as (1) a maternal antibody-dependent	Infants with perinatal asphyxia (5-min Apgar < 3 or cord pH < 7.0), hemolytic disease other than Rhesus D or c, and Rhesus hemolytic disease presenting > 4 h after birth.	infants assigned to the intervention group were reassigned to the control group when their parents refused IVIG and 5 babies assigned to the high-dose IVIG group were assigned to the low-dose IVIG group per parental wishes. Parental reasoning for refusing treatment or switching dosage groups was not provided.	Primary: need for exchange transfusion (per the 2004 AAP recommended exchange transfusion levels) and the number of exchange transfusions per infant. Secondary: duration of phototherapy and hospital stay, maximum intensity of	received an exchange transfusion were both in the low-dose (500 mg/kg) group. Risk difference between high- versus low-dose treatment of preventing an exchange transfusion: -8% (95% CI: -18.6 to 2.63) Note: risk ratio not calculable because of no events in high-dose group. No adverse events noted.	the power for comparison of the effect of low- vs high-dose IVIG dosing for preventing exchange transfusion. Double-blinded. Adequate allocation concealment. Inadequate power: confidence interval includes clinically meaningful absolute risk reduction -14%).	all enrolled infants. An intention to treat analysis was not provided and authors did not respond to emailed queries requesting one. No data on outcomes according to original treatment assignment were provided. None of the mothers of enrolled infants had a history of antenatal IVIG treatment or in utero transfusion. No difference in exchange transfusion risk or in measured secondary outcomes were detected between groups randomized to IVIG treatment versus placebo.

TABLE 2 Continued

Citation and Setting	Methods	Participants or Inclusion Criteria	Exclusion Criteria	Interventions	Outcomes	Results	Risk of Bias	Notes or Conclusions
Santos 2013 Rio de Janeiro, Brazil	Randomized, double-blinded, placebo-controlled trial	cellular cytotoxicity test with a >50% result (comparable with an antibody titer of >1:64) ^c and (2) a direct antiglobulin test with positive results caused by anti-rhesus D or c antibodies in the fetus/neonate of a rhesus D or c-negative mother. 92 newborn infants born at ≥ 32 wk' gestation admitted to a single-center between April 2006 and June 2009 with a positive DAT whose mothers where Rh-alloimmunized. Mean gestation of treated group: 36.5 wk; SD: 1.5. Mean gestation of placebo group: 36.1 wk; SD: 1.6.	Hydrops fetalis, cardiac instability, severe asphyxia, other non-Rh red blood cell antibodies, initial bilirubin >4 mg/dL and/or cord hematocrit <30%.	12 to 20 $\mu\text{W}/\text{cm}^2$ per nm given by air shield and Ohmeda lamps in combination with blue-light bilirubin blanket phototherapy (30 $\mu\text{W}/\text{cm}^2$ per nm).	serum bilirubin concentrations, and need for red-cell transfusion in the first 3 mo postnatal.	No adverse events noted.	Double-blinded. Adequate allocation concealment. Inadequate power: confidence interval includes clinically meaningful absolute risk reduction -16%.	No difference in exchange transfusion risk or in measured secondary outcomes were detected between groups randomized to IVIG treatment versus placebo.
Rh- and ABO isoimmunization Alpay 1999 Ankara, Turkey	Randomized controlled trial (RCT)	116 term newborn infants with ABO and/or Rh incompatibility with bilirubin >11.9 mg/dL, and positive DAT, and	As per inclusion criteria.	Randomized to conventional phototherapy plus a single 1 g/kg dose of IVIG or to conventional phototherapy.	Primary: need for exchange transfusion (at a serum bilirubin concentration of 20 mg/dL or increase ≥ 0.5 mg/dL/hour). Secondary: peak bilirubin, phototherapy duration, length of stay, drug, or drug administration related adverse effects or events.	Exchange transfusion risk in IVIG-exposed infants: 13%. Risk in placebo group: 15.2%. Risk ratio: 0.857 (95% CI: 0.32-2.36). Risk difference: -2.17% (95% CI: -16.4% to 12.1%). No differences between groups in secondary outcomes. No adverse events noted.	The investigators and clinicians were not blinded to treatment. Randomization assignment was	IVIG treated infants with ABO or Rh-incompatibility were less likely to receive an

TABLE 2 Continued

Citation and Setting	Methods	Participants or Inclusion Criteria	Exclusion Criteria	Interventions	Outcomes	Results	Risk of Bias	Notes or Conclusions
Tanyer 2001 Ankara, Turkey	Quasi-randomized trial	61 full-term newborn infants admitted to a single center between January 1996 and November 1998 with Rh-, ABO-, or subgroup-incompatibility, bilirubin concentrations below the exchange transfusion criteria at admission, and a positive DAT.	Contributing risk factors (such as sepsis, drug use by mothers) that could raise bilirubin concentrations.	Assigned by order of admission to phototherapy plus 500 mg/kg multiple-dose IVIG treatment (daily on 3- consecutive days), phototherapy plus single-dose 500 mg/kg IVIG treatment, or phototherapy alone. Initial IVIG doses were administered between 2-4 h of admission.	Exchange transfusion (conducted if bilirubin exceeded limits on included table 120 mg/dL for low-risk infants at >2500 g; 18 mg/dL for low-risk infants at 2000-2499 g).	0.36 (95% CI: 0.18-0.75). Risk difference: -24.1% (95% CI: -39.5% to -8.82%). Duration of phototherapy and duration of hospitalization were shorter in the IVIG-treated group ($P < .05$). No adverse events were reported.	done by a neonatologist different from those conducting the study. Randomization concealment and allocation process not otherwise described. The investigators and clinicians were not blinded to treatment. Treatment assignment was per order of admission rather than by a randomization process. Small sample sizes in the multiple- and single-dose treatment groups reduced the power for comparison of multiple- versus single-dose dosing for preventing exchange transfusion.	exchange transfusion than those in the control group. The majority of study subjects had ABO incompatibility (80%), 14% had Rh incompatibility, and 6% had ABO and Rh incompatibility. IVIG treated infants with Rh-, ABO-, or subgroup incompatibility were less likely to receive an exchange transfusion than those in the control group. The majority of study subjects had ABO incompatibility (55.7%), 29.5% had Rh incompatibility, 3.3% had subgroup incompatibility, and 11.5% had more than 1 incompatibility type.

Note: risk ratio not calculable due

TABLE 2 Continued

Citation and Setting	Methods	Participants or Inclusion Criteria	Exclusion Criteria	Interventions	Outcomes	Results	Risk of Bias	Notes or Conclusions
Nasseri 2006 Mashhad, Iran	Randomized controlled trial	34 newborn infants at a single center between October 2003 and October 2004 who were Born at ≥ 37 wk gestation with Rh-incompatibility and had a positive DAT and a serum bilirubin rate of increase > 0.5 mg/dL/hour.	Sepsis, glucose-6-phosphate dehydrogenase (G6PD) deficiency, or other illnesses that could result in increased bilirubin concentrations.	Randomized to phototherapy plus 500 mg/kg IVIG within 2 h of admission and then every 12 h for 3 total doses or to phototherapy alone.	Exchange transfusion (conducted if serum bilirubin was ≥ 20 mg/dL or for a rate of rise > 1 mg/dL/hour).	to no events in multidose group. No adverse events noted. Exchange transfusion risk in IVIG exposed: 17.7%. Risk in placebo group: 64.7%. Risk ratio: 0.27 (95% CI: 0.09–0.8). Risk difference: -47.1 (95% CI: -76.1 to -18.0). No adverse events noted.	The investigators and clinicians were not blinded to treatment. Manuscript describes randomization in multiple places, but also describes the study as a prospective, case-control study in the Methods section. Randomization concealment and allocation process not described.	IVIG treated infants with ABO or Rh-incompatibility were less likely to receive an exchange transfusion than those in the control group. The majority of study subjects had ABO incompatibility (62%). The remaining 38% had Rh-incompatibility. IVIG is relatively safe and effective means of reducing the need for exchange transfusion. There is a large degree of heterogeneity between the included studies. Note: This review
Systematic Reviews Walsh 2009	Systematic review	Manuscripts on neonatal hyperbilirubinemia and immunoglobulin. Restricted to humans, newborn infants, and English. Included 7 randomized controlled trials and 3 prospective observational studies, 2	As per inclusion criteria.	IVIG administration to patients with isoimmune hemolytic jaundice.	Effective reduction of serum bilirubin concentrations. Avoidance of exchange transfusion.	The authors noted a large degree of heterogeneity between studies. Overall, they concluded that IVIG is a relatively safe and effective means of reducing the need for exchange transfusion.	Search terms specified. Loose inclusion criteria based on broad search.	IVIG is relatively safe and effective means of reducing the need for exchange transfusion. There is a large degree of heterogeneity between the included studies. Note: This review

TABLE 2 Continued

Citation and Setting	Methods	Participants or Inclusion Criteria	Exclusion Criteria	Interventions	Outcomes	Results	Risk of Bias	Notes or Conclusions
Zwiers 2018	Systematic review	Randomized trials of IVIG for treatment of alloimmune hyperbilirubinemia of the newborn infant. Trials must have used predefined criteria for IVIG use and exchange transfusion. (included 9 RCTs published between 1992 and 2013; 658 total participants).		IVIG treatment of alloimmune thrombocytopenia. Infants in all arms of the included studies received intensive phototherapy.	Primary: need for exchange transfusion.	Overall, found that IVIG reduced exchange transfusion. Risk ratio: 0.35 (95% CI: 0.25–0.49). Risk difference: –0.22 (95% CI: –0.27 to –0.16). Two placebo-controlled RCTs of infants with Rh-incompatibility Risk ratio: 0.98 (95% CI: 0.48–1.98).	Reported that overall RCT evidence was of low quality. Only two RCTs (Santos 2013 and Smits-Wintjens 2011), both on Rh-alloimmunization, used a placebo.	was conducted before the placebo-controlled RCTs by Santos and Smit-Wintjens. There was a great deal of heterogeneity between studies. Five studies were restricted to Rh-disease, one study was restricted to ABO disease, and three enrolled patients with both ABO and Rh incompatibility. The systematic review conclusions were based primarily on the 2 placebo-controlled trials of infants with Rh-disease (Santos 2013; Smits-Wintjens 2011). The most recent, placebo-controlled trials did not demonstrate a reduced risk for exchange

TABLE 2 Continued

Citation and Setting	Methods	Participants or Inclusion Criteria	Exclusion Criteria	Interventions	Outcomes	Results	Risk of Bias	Notes or Conclusions
								transfusion in Rh-positive infants after IVIG treatment. Overall, there is weak evidence that IVIG may reduce the need for exchange transfusion. Non-Rh mediated forms of hyperbilirubinemia including ABO incompatibility are not well studied.

Question: What is the effectiveness of IVIG for prevention of exchange transfusion in infants with indirect hyperbilirubinemia?

Population: Neonates born at ≥ 35 weeks' gestation with isoimmunization and hyperbilirubinemia who are at risk of exchange transfusion

Intervention: Treatment with IVIG

Comparator: Nontreatment with IVIG

Outcome: Need for exchange transfusion

Included: randomized controlled trials, quasi-randomized trials, and systematic reviews that include randomized trials

^aPolacek K. Die frühzeitige Indikationstellung zur Austausch-transfusion bei hämolytischen Neugeborenenkrankungen. *Monatsschr Kinderheilkd.* 1963;111:6-10; and Polacek K. Das universale Diagramm zur Behandlung der Hyperbilirubinämie der Neugeborenen. *Pediatrische Praxis.* 1984;29:1-3.

^bOski FA, Naiman JL: Erythroblastosis fetalis. In: Oski FA, Naiman JL, eds. *Hematologic Problems in the Newborn*. Philadelphia: WB Saunders Company; 1982:283-346.

^cOepkes D, van Kamp IL, Simon MJ, Mesman J, Overbeek MA, Kanhai HH. Clinical value of an antibody-dependent cell-mediated cytotoxicity assay in the management of Rh D alloimmunization. *Am J Obstet Gynecol.* 2001;184(5):1015-1020.

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AGGREGATE EVIDENCE QUALITY	BENEFIT OR HARM PREDOMINATES	BENEFIT AND HARM BALANCED
LEVEL A Intervention: Well-designed and conducted trials, meta-analyses on applicable populations Diagnosis: Independent gold standard studies of applicable populations	STRONG RECOMMENDATION	WEAK RECOMMENDATION (based on balance of benefit and harm)
LEVEL B Trials or diagnostic studies with minor limitations; consistent findings from multiple observational studies	MODERATE RECOMMENDATION	
LEVEL C Single or few observational studies or multiple studies with inconsistent findings or major limitations	WEAK RECOMMENDATION (based on low quality evidence)	No recommendation may be made.
LEVEL D Expert opinion, case reports, reasoning from first principles		
LEVEL X Exceptional situations in which validating studies cannot be performed and benefit or harm clearly predominates	STRONG RECOMMENDATION	

FIGURE 1
Evidence grading.

Question 2: How effective is IVIG for preventing exchange transfusion in infants with indirect hyperbilirubinemia?

Population: Neonates born at ≥ 35 weeks' gestation with isoimmunization and hyperbilirubinemia who are at risk for exchange transfusion.

Intervention: Treatment with IVIG.

Comparator: Nontreatment with IVIG.

Outcome: Need for exchange transfusion.

The search, initially performed on May 24, 2018 and repeated March 5, 2021 and April 7, 2022, included MeSH term Hyperbilirubinemia or keyword hyperbilirubinemia AND – any of the following MeSH terms or keywords (Immunoglobulins, Intravenous[MeSH]; IVIG; intravenous immunoglobulin*;

immunoglobulin*). Commentaries, editorials, and letters were excluded.

After the initial search produced multiple randomized trials, the article inclusion criteria were subsequently limited to randomized controlled trials, quasi-randomized trials, and systematic reviews that included randomized trials.

SELECTION OF INCLUDED EVIDENCE

References obtained from Medline via the search process were initially selected on the basis of the article title and abstract and the prewritten inclusion criteria for each question. Each reference was reviewed by 2 reviewers (JLS and ARK), and a third reviewer (TBN) was the deciding vote in instances of disagreement. The first 2 reviewers subsequently reviewed the full texts of the included articles.

Question 1: What are the adverse clinically detectable effects of phototherapy in newborns?

The search produced 45 manuscripts. Eighteen were excluded: 12 did not report clinically relevant phototherapy-related outcomes, 2 compared phototherapy modalities rather than outcomes, 1 focused on preterm infants born at < 35 weeks' gestation, 1 was a case report, 1 a case series, and 1 a nonsystematic review article. A review of the selected manuscripts yielded 14 additional publications which were included. An evidence table (Table 1) details the study design of and evidence derived from each of the 38 included manuscripts for question 1.

Summary: Phototherapy is associated with a significant yet low overall risk of potential harm. Childhood seizures are one of the most serious, but infrequent, conditions (adjusted 10-year excess risk of 2.4; 95% confidence interval [CI]: 0.6, 4.1 per 1000 phototherapy-treated infants) associated with phototherapy.¹² Although the topic is understudied, there is some evidence that phototherapy may limit familial bonding with the infant. Therefore, treatment thresholds must attempt to balance the risk of adverse effects of phototherapy with its possible benefit at reducing the risk of total serum bilirubin concentrations at which exchange transfusion is recommended and/or neurotoxicity has been found.

Question 2: How effective is IVIG for preventing exchange transfusion in infants with indirect hyperbilirubinemia?

The search produced 13 manuscripts. Two were excluded because they were not randomized trials, quasi-randomized trials, or systematic reviews inclusive of randomized trials. An evidence table (Table 2)

details the study design of and evidence derived from each of the 11 included manuscripts for question 2.

Summary: IVIG may not be effective in preventing exchange transfusion for infants with severe Rh disease. Larger, randomized, placebo-controlled trials are needed to confirm this finding. The effect of IVIG for non-Rh-mediated hemolysis including ABO incompatibility is understudied. There is a large degree of heterogeneity between available trials, which are all of low to moderate quality. Thus, there is a need for well-designed placebo-controlled trials. There were no IVIG-related safety concerns reported in the included randomized trials. However, observational investigations have reported associations between IVIG and necrotizing enterocolitis (NEC). Figueras-Aloy et al conducted a retrospective cohort investigation in Barcelona, Spain, and found an association between IVIG and risk of NEC (odds ratio [OR]: 31.66; 95% CI: 3.25–308.57) but no increase in mortality.¹⁹ The authors attempted to adjust for severity of illness using propensity scoring PS, but it does not appear that all of the included variables (eg, peak bilirubin concentration or exchange transfusion) were measured before the receipt of IVIG, as should be done when using propensity scoring to mimic a randomized trial. Although care practices mostly seemed similar to the United States, they did administer phenobarbital to infants receiving phototherapy. A meta-analysis that included the Figueras-Aloy et al investigation specifically evaluated the association between IVIG and NEC and reported a higher incidence of NEC after IVIG infusion for hyperbilirubinemia (OR: 4.53; 95% CI, 2.34–8.79) with no increase in mortality.²⁰ However, the study was limited by inclusion of multiple nonrandomized studies,

an unclear definition of NEC grade, a large degree of heterogeneity (eg, proportion of small for gestational age infants) between available studies, and an incomplete description of the evaluated studies including the baseline severity of illness in infants who were treated with IVIG, as compared to untreated infants with hyperbilirubinemia.¹⁹ Despite these limitations, the signal for IVIG-related harm from increased NEC must be considered, because observational studies are often better powered than randomized trials to pick up rare, serious adverse drug events. Given an unclear but potential benefit from IVIG in preventing exchange transfusion and limited evidence of an increased NEC risk, the risks and benefits of IVIG must be carefully considered. The 2022 guideline notes that clinicians may consider the administration of IVIG to infants with isoimmune hemolytic disease (ie, positive direct antiglobulin test [DAT]) who have not initially responded to phototherapy with a reduction in total bilirubin only in circumstances when the TSB is rising despite intensive phototherapy or within 2 to 3 mg/dL of the exchange level and there is concern that a timely exchange transfusion will be difficult.¹

GENERATION OF RECOMMENDATIONS

All first drafts of recommendations were created by members of the subcommittee that were assigned as content experts and authors for each subsection of the guideline. In many instances, these recommendations were closely adapted from similar recommendation statements in the 2004 guideline and/or the 2009 commentary by reviewing and incorporating any new evidence on each previous recommendation topic, when available. The original drafts of recommendations for the 2 questions, as derived from the systematic reviews and evidence

tables, were written by the epidemiologist.

All members of the subcommittee then reviewed all recommendation drafts and offered amendments before a final acceptance of all recommendations by vote of the entire subcommittee. The derived language for each recommendation reflected the strength of graded evidence.

GRADING OF THE EVIDENCE

The identified evidence for each recommendation within the clinical practice guideline was appraised and summarized per AAP policy.¹⁴ Then a level of evidence, from strongest to weakest, was assigned (Fig 1).¹⁴ This information is provided in Supplemental Appendix B of the clinical practice guideline.¹

CONCLUSIONS

A systematic approach combining the best available evidence and expert opinion, when necessary, was used to generate an updated guideline for the diagnosis and management of hyperbilirubinemia in neonates ≥ 35 weeks' gestation. The committee's approach was to improve on the expert-driven 2004 AAP guideline² and 2009 follow-up commentary³ through the incorporation of new evidence. The committee has developed new phototherapy and exchange transfusion treatment recommendations that should reduce the numbers of infants unnecessarily treated with phototherapy while at the same time ensuring that infants at higher risk for bilirubin-associated neurotoxicity, on the basis of serum bilirubin concentrations, gestational age, and neurotoxicity risk factors, will receive proper treatment to prevent hyperbilirubinemia-associated harm.¹

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