Received: 10 February 2022 | Accepted: 16 March 2022

DOI: 10.1111/bjh.18170

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

ORIGINAL PAPER

International guidelines regarding the role of IVIG in the management of Rh- and ABO-mediated haemolytic disease of the newborn

Lani Lieberman[1,2,3] | Enrico Lopriore[4] | Jillian M. Baker[5,6] | Rachel S. Bercovitz[7] | Robert D. Christensen[8,9] | Gemma Crighton[10] | Meghan Delaney[11,12] | Ruchika Goel[13,14] | Jeanne E. Hendrickson[15] | Amy Keir[16,17] | Denise Landry[18] | Ursula La Rocca[19,20] | Brigitte Lemyre[21] | Rolf F. Maier[22] | Eduardo Muniz-Diaz[23] | Susan Nahirniak[24] | Helen V. New[25,26] | Katerina Pavenski[27] | Maria Cristina Pessoa dos Santos[28] | Glenn Ramsey[29] | Nadine Shehata[30] | for the International Collaboration for Transfusion Medicine Guidelines (ICTMG)

[1]Department of Clinical Pathology, University Health Network, Toronto, Ontario, Canada

[2]Department of Laboratory Medicine & Pathobiology, University of Toronto, Toronto, Ontario, Canada

[3]Department of Laboratory Medicine and Molecular Diagnostics, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

[4]Division of Neonatology, Department of Pediatrics, Leiden University Medical Center, Leiden, The Netherlands

[5]Department of Pediatrics, Unity Health Toronto (St. Michael's Hospital), Toronto, Ontario, Canada

[6]Division of Haematology-Oncology, The Hospital for Sick Children, Toronto, Ontario, Canada

[7]Division of Hematology, Oncology, and Stem Cell Transplant, Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

[8]Divisions of Neonatology and Hematology/Oncology, University of Utah Health, Salt Lake City, UT, USA

[9]Department of Women and Newborn's Research, Intermountain Healthcare, Salt Lake City, Utah, USA

[10]Department of Haematology, Royal Children's Hospital, Melbourne, Australia

[11]Division of Pathology & Laboratory Medicine, Children's National Hospital, Washington, District of Columbia, USA

[12]Department of Pathology & Pediatrics, The George Washington University Health Sciences, Washington, District of Columbia, USA

[13]Division of Transfusion Medicine, Department of Pathology, School of Medicine, Johns Hopkins University, Baltimore, Maryland, USA

[14]Simmons Cancer Institute at SIU School of Medicine, Springfield, Illinois, USA

[15]Departments of Laboratory Medicine and Pediatrics, Yale University, New Haven, Connecticut, USA

[16]SAHMRI Women and Kids, South Australian Health and Medical Institute, North Adelaide, South Australia, Australia

[17]Adelaide Medical School and the Robinson Research Institute, the University of Adelaide, North Adelaide, South Australia, Australia

[18]Canadian Blood Services, Ottawa, Ontario, Canada

[19]Department of Translational and Precision Medicine, Sapienza University, Rome, Italy

[20]Italian National Blood Centre, National Institute of Health, Rome, Italy

[21]Department of Pediatrics, University of Ottawa, Ottawa, Ontario, Canada

[22]Children's Hospital, University Hospital, Philipps University, Marburg, Germany

[23]Department of Immunohematology, Blood and Tissue Bank of Catalonia, Barcelona, Spain

[24]Alberta Precision Laboratories and Department of Laboratory Medicine and Pathology, University of Alberta, Edmonton, Alberta, Canada

[25]Clinical Directorate, NHS Blood and Transplant, London, UK

[26]Centre for Haematology, Imperial College London, London, UK

[27]Department of Laboratory Medicine and Pathology, Unity Health Toronto (St. Michael's Hospital), Toronto, Ontario, Canada

[28]IFF/Fundação Oswaldo Cruz, Rio de Janeiro, Brazil

Abbreviations: AAP, American Academy of Paediatrics; CI, confidence interval; ET, exchange transfusion; GA, gestational age; HDN, haemolytic disease of the newborn; ICTMG, International Collaboration for Transfusion Medicine Guidelines; IVIG, intravenous immunoglobulin; MD, mean difference; PT, phototherapy; RBC, red blood cell; RCT, randomized controlled trial; RR, relative risk; SR, systematic review.

[29]Department of Pathology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA

[30]Departments of Medicine, Laboratory Medicine and Pathobiology, Institute of Health, Policy Management and Evaluation, University of Toronto, Mount Sinai Hospital, Toronto, Ontario, Canada

Correspondence
Lani Lieberman, Transfusion Medicine Specialist, University Health Network, 200 Elizabeth Street Room 306, Toronto, ON M5G 2C4, Canada.
Email: lani.lieberman@uhn.ca

Funding information
This guideline was prepared on behalf of the ICTMG (www.ICTMG.org). The ICTMG receives funding from Canadian Blood Services [funded by the federal government (Health Canada) and the provincial and territorial ministries of health]. The views herein do not necessarily reflect the views of Canadian Blood Services or the federal, provincial, or territorial governments of Canada. Canadian Blood Services did not have any role in the design, analysis and interpretation of the data or preparation, review, and approval of the manuscript.

Abstract

Haemolytic disease of the newborn (HDN) can be associated with significant morbidity. Prompt treatment with intensive phototherapy (PT) and exchange transfusions (ETs) can dramatically improve outcomes. ET is invasive and associated with risks. Intravenous immunoglobulin (IVIG) may be an alternative therapy to prevent use of ET. An international panel of experts was convened to develop evidence-based recommendations regarding the effectiveness and safety of IVIG to reduce the need for ETs, improve neurocognitive outcomes, reduce bilirubin level, reduce the frequency of red blood cell (RBC) transfusions and severity of anaemia, and/or reduce duration of hospitalization for neonates with Rh or ABO-mediated HDN. We used a systematic approach to search and review the literature and then develop recommendations from published data. These recommendations conclude that IVIG should not be routinely used to treat Rh or ABO antibody-mediated HDN. In situations where hyperbilirubinaemia is severe (and ET is imminent), or when ET is not readily available, the role of IVIG is unclear. High-quality studies are urgently needed to assess the optimal use of IVIG in patients with HDN.

KEYWORDS
alloimmunization, evidence-based guidelines, haemolytic disease of the newborn, intravenous immunoglobulin, pregnancy

INTRODUCTION

Despite preventative strategies, haemolytic disease of newborn (HDN) continues to occur in 3–80/10 000 neonates/year.[1,2] HDN occurs when maternal IgG antibodies reactive to paternal blood group antigens traverse the placenta and cause immune-mediated haemolysis of fetal red blood cells (RBCs). Alloimmunization can be triggered by more than 50 blood group antigens; the most severe disease involves RhD, Rhc and K antigens. When severe, HDN can be associated with significant morbidity, particularly neurocognitive deficits and mortality.[3]

First-line treatment for neonates with severe jaundice includes intensive phototherapy (PT). Intensive PT is defined by the American Academy of Paediatrics (AAP) as a spectral irradiance of at least 30 mW/cm^2/nm delivered to as much of the infant's surface area as possible.[4] For intensive PT, the intensity of each PT light should be >30 mW/cm^2/nm. For severe, non-responsive hyperbilirubinaemia, exchange transfusion (ET) is recommended to remove bilirubin, the implicated maternal alloantibodies and antibody-coated RBCs.[4–6] Despite its therapeutic benefits, ETs can be associated with catheter-related infections, hypocalcaemia, thrombosis, haemorrhage, cardio-respiratory instability and necrotizing enterocolitis; ETs have a mortality rate up to 5%.[7–10]

Intravenous immunoglobulin (IVIG) is used to delay or avoid ET.[4,5,11] IVIG blocks Fc receptors on macrophages which reduces destruction of antibody-coated RBCs, enhancing the clearance of maternal antibodies and lowering the circulating unconjugated bilirubin levels.[12] Although a number of randomized, controlled trials (RCTs) have shown that IVIG is effective in decreasing the need for ET, these RCTs had moderate to high risk of bias and the majority were conducted prior to use of high-intensity PT. Several international guidelines recommend IVIG, particularly if the total serum bilirubin is rising despite intensive therapy or the bilirubin level is within 2–3 mg/dl (34–51 mmol/l) of the threshold level when ET is used.[4,5,13] IVIG use is not without risks and has been associated with haemolysis,[14] and necrotizing enterocolitis.[15] As there is uncertainty about the optimal strategy for HDN, we embarked on a guideline development initiative to address whether the use of IVIG in neonates with RhD or ABO-mediated HDN in addition to intensive PT was associated with the following outcomes: mortality, neurocognitive outcomes (encephalopathy, acute impairment, chronic impairment), need for or frequency of ET, bilirubin level, frequency of RBC transfusions

(number or volume), severity of anaemia or duration of hospitalization?[16,17]

METHODS

An international panel of haematologists, neonatologists and transfusion specialists was convened. A systematic search for articles published (1946–2021) in MEDLINE, EMBASE, NHS Economic Evaluation Database, HTA and Cochrane Central Register of Controlled Trials and SR was completed (Appendix S1) and the systematic review was registered in Prospero (CRD42019142072). Study inclusion criteria were: (1) original peer-reviewed; (2) at least five neonates with diagnosis or at risk of HDN; (3) comparing either of the following interventions: PT or ET, with IVIG; (4) reporting one of the following outcomes: bilirubin level, anaemia, frequency of RBC transfusions, neurocognitive outcome or mortality; (5) RCT or comparative trial; (6) English. A secondary search with a focus on ABO-mediated HDN was performed. Two reviewers (LL, NS) screened publications for eligibility, independently extracted data and assessed risk of bias using criteria established for the reporting of randomized and non-randomized studies.[18–20] Meta-analyses were conducted if not available from previously published systematic reviews.

Recommendations were formulated on the basis of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) and the level of evidence was graded as high, moderate, low or very low.[21,22] Recommendation strength was evaluated as strong or conditional. The panel ranked clinical outcomes relevant for the development of recommendations according to GRADE. (Appendix S2) Web conferences and electronic correspondence were used to discuss the clinical questions and formulate recommendations. Electronic surveys were sent to members to assess agreement with recommendations. Disagreements were resolved by group discussions. If disagreements could not be resolved, a recommendation was accepted if the majority (≥50%) agreed. Members recorded their disclosures but none were excluded from voting. The final guidance document was sent to numerous societies for feedback (Appendix S3).

The recommendations will be reviewed every two years from publication. If a study is published that may impact patients prior to that time, a comment will be added on the International Collaboration for Transfusion Medicine Guidelines (ICTMG) website (ictmg.org) along with the guideline and additional resources for physicians and patients.

RESULTS

Study inclusion

In all, 1242 abstracts were reviewed and 25 full-text articles were retrieved. Two systematic reviews (SRs),[23,24] and two non-randomized studies[25,26] met inclusion criteria (Figure 1). One Cochrane systematic review (SR)[24] included nine RCTs (n = 658); Rh-mediated HDN (N = 5), ABO-mediated HDN (N = 1) and three studies included neonates with both ABO- and Rh-mediated HDN. The second SR included 12 RCTs (n = 426); Rh incompatibility alone in seven studies, ABO incompatibility in two studies, while three enrolled neonates with both Rh and ABO incompatibility.[23] The second SR[23] included four studies not included in the Cochrane SR.[24] The Cochrane SR included one study not included in the SR conducted by Lois and colleagues. The two retrospective studies focused on ABO incompatibility.[25,26] For Rh-mediated HDN, data and analysis from both SRs were utilized to make recommendations regarding the benefit of IVIG for Rh-mediated HDN. For ABO-mediated HDN, data and analysis from one of the SRs[23] were used to make recommendations for use of IVIG for ABO-mediated HDN as separate data were available for ABO incompatibility. The studies were conducted in diverse countries including Turkey, Egypt, Saudi Arabia, Iran, Germany, Brazil and the Netherlands.

Mortality, kernicterus, acute neurological impairment, chronic neurologic impairment and need for ET were ranked by the panel as critical for decision making, and the need for RBC transfusion, bilirubin level, anaemia and length of hospital stay were ranked as important (Appendix S2). Most of the included studies did not report on critical clinical outcomes; only two studies reported on one-[27] and two-year[28] outcomes.

Study characteristics

Details regarding study characteristics and risk of bias are summarized (Table 1, Appendices S4–S7). A number of the studies issued IVIG early or close to the time of delivery, before neonates developed significant hyperbilirubinaemia[27-31] with the goal to prevent the need for ET. The majority of studies enrolled term neonates of 37 weeks gestational age (GA) or greater,[29,32–37] two included neonates of all GAs,[27,28] one enrolled only preterm neonates,[38] and two studies did not describe details of GA.[30,39]

Summary of results

The Cochrane SR[24] combined the outcomes for neonates with Rh-mediated HDN and ABO-mediated HDN who received PT alone to those who received PT and IVIG. The IVIG group had a reduced need for an ET [relative risk (RR) 0.35; 95% confidence interval (CI) −0.25, 0.49], had a significantly lower maximum total serum bilirubin level [mean difference (MD) 25.4 mmol lower; 95% CI −34 to −16.7] and a shorter duration of PT (MD 0.98 days less with IVIG, 95% CI −1.31 to 0.66). Use of top-up RBC transfusion in the first week or after the first week was not significantly different between the two groups (first week: RR 1.05; 95% CI −0.65 to 1.69; following first week: RR 1.16; 95% CI −0.97 to 1.38).

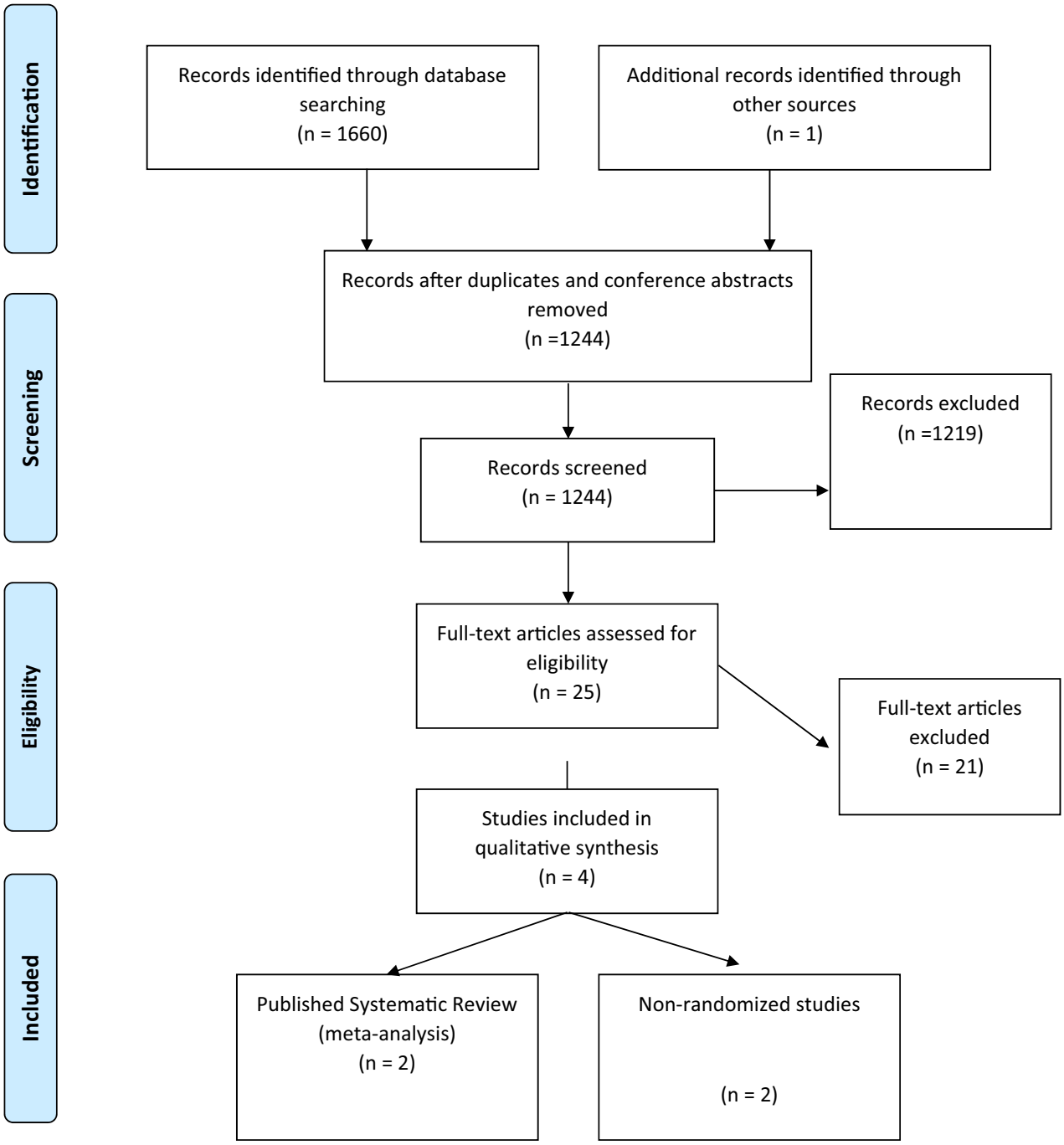

FIGURE 1 Article inclusion to assess use of IVIG for haemolytic diseases of the newborn [Colour figure can be viewed at wileyonlinelibrary.com]

Shorter duration of hospitalization was reported for the IVIG group (MD −1.34 days, 95% CI −1.6 to −1.09). Mortality, kernicterus as well as acute and chronic neurologic impairment were not reported.

For neonates with Rh-mediated HDN, the Cochrane SR included seven studies with 371 neonates and compared PT alone and PT with IVIG.[24] IVIG resulted in a reduction in use of ET (RR 0.38, 95% CI 0.25–0.58), similar need for RBC transfusions during the first week and thereafter (first week; RR 1.08, 95% CI 0.65–1.77; after first week: RR 1.09, 95% CI 0.92–1.28), lowered maximum bilirubin levels (MD −21.77 mmol/l; 95% CI −30.86 to −12.67) and shortened duration of PT (MD −1.23 days; 95% CI −1.43 to −1.02). Review of the quality of these studies confirmed a high risk of bias.

Louis' analysis described significant reduction in the need for ET (RR 0.23, 95% CI 0.13–0.4), duration of PT (MD −1.1, 95% CI −1.7 to −0.6) and duration of hospitalization (MD −1.1, 95% CI −2.4 to −0.2) but studies had a high risk of bias (six studies, 236 neonates with Rh incompatibility). IVIG did not affect the peak serum bilirubin level (MD −24.9; 95% CI −68.4 to 18.6) or the need for top-up transfusions (RR 1.2; 95% CI 0.4–3.9). Studies with low risk of bias (three studies,

190 Rh-incompatible neonates) revealed no difference in the need for ET (RR 0.82, 95% CI 0.53–1.26) or any secondary outcomes.[23]

For neonates with ABO-mediated HDN, data from five RCTs (N = 350) were included.[23] IVIG reduced the number of ETs (RR 0.31; 95% CI 0.18–0.55), peak serum bilirubin levels (MD −60.6; 95% CI −83.2 to −37.9), duration of PT (MD −0.7; 95% CI −1.1 to −0.4) and duration of hospitalization (MD −1.2; 95% CI −1.8 to −0.5), but it did not reduce the need for top-up transfusion (RR = 1.7; 95% CI 0.6–5.3). These studies displayed a high risk of bias, with significant heterogeneity and small sample sizes. The two retrospective studies did not find a difference in bilirubin, haemoglobin or duration of PT.[25,26]

Subgroup analysis was performed by Louis to compare outcomes between Rh-incompatible neonates who received IVIG prophylaxis (six studies, n = 300). Studies with a high risk of bias (three studies, 110 neonates) described a reduction in ET with IVIG (RR 0.21; 95% CI 0.1–0.45), whereas studies with low risk of bias did not (three studies, 190 neonates, RR 0.82; 95% CI 0.53–1.26).[23]

Rationale for recommendation regarding use of IVIG for Rh-mediated HDN

The majority of the studies included were considered to have a high risk of bias due to heterogeneity and small sample sizes. When the moderate quality randomized, placebo-controlled blinded trials with low risk of bias were analysed separately,[27,28] IVIG did not decrease the need for ET (0.98, 95% CI 0.48–1.98), the need for a RBC transfusion within the first week of life (RR 1.18; 95% CI 0.7–2) or following the first week (RR 1.01; 95% CI 0.8–1.27) and did not decrease the mean serum bilirubin level (MD 0.93 mol/l; 95% CI 23.94–25.79).These two studies included 172 neonates (either >32 weeks GA[27] or 35 weeks GA[28]) with RhD- and Rhc-mediated HDN, who received IVIG within the first 4–6 h of life. Eighty-seven patients received IVIG and 85 received a placebo. The GRADE certainty of evidence was considered moderate (Tables 2 and 3). The results of these higher-quality trials were utilized to make recommendations regarding prophylactic use of IVIG for Rh-mediated HDN.

Overall indications for PT and criteria for ET were not detailed. Intensity of PT treatments has advanced over the past decade,[41] and neonates in the more recent high-quality studies may have received more intensive treatments than neonates treated in the earlier studies. Only three of the included studies,[27,28,32] provided intensive PT as per AAP guidelines.[4] One study used three overhead lights from a single angle,[36] and a second study did not use a PT blanket.[35] The rest of the studies did not describe the intensity of the PT in detail. Allocation concealment was generally not used (Table 4).

Additionally, definitions of anaemia and pre-transfusion haemoglobin thresholds were not provided[32,36] or differed among studies, which may have led to different transfusion decisions and outcomes. Finally, only two studies used predefined criteria for hospital discharge. Due to the variability between studies in the definitions used for the outcome measures, the results of the two studies with moderate certainty of evidence of effects, and the potential risks of IVIG, routine prophylactic use of IVIG for Rh HDN was not recommended.

All of the studies included in this analysis reported that there were no definitive short-term adverse reactions specifically related to IVIG. Two of the nine studies did report adverse events, but it was unclear if these were secondary to IVIG or ET. The first study reported that 10 neonates who received ET were treated for sepsis.[35] The second study described an infant who received IVIG and developed sepsis and brain abscesses secondary to *Bacillus cereus* a few days after ET; IVIG and cultures of blood products used for ET were sterile. It was hypothesized that the sepsis may have been related to the umbilical catheterization and ET.[28]

Recommendation for management of Rh-mediated HDN

In neonates with Rh-mediated HDN, routine IVIG is not recommended to reduce the need for ET (low certainty of evidence of effects, conditional recommendation).

Studies that focus on HDN secondary to other non-ABO antibodies (e.g. Rhc, K, Jk[a]) have not been performed, but the same recommendations would apply.

Rationale for recommendation for IVIG for ABO-mediated HDN

ABO incompatibility between mother and fetus occurs in approximately 20% of all pregnancies; HDN only occurs in 1% of these pregnancies.[42] ABO-mediated HDN occurs almost exclusively in group O mothers with non-O neonates and unlike Rh-mediated HDN, can occur during the first pregnancy. Compared to Rh-mediated incompatibilities, ABO-mediated incompatibility is associated with a lower risk of significant hyperbilirubinaemia and readmission for jaundice. Most neonates are asymptomatic or experience mild jaundice and neonatal anaemia is rare.[43–45] At times, non-immune causes of jaundice including physiologic jaundice, poor feeding/dehydration and decreased milk production may exacerbate the hyperbilirubinaemia. ETs are infrequently performed, but may be needed due to delayed access to PT (e.g. remote areas) or lack of a universal bilirubin screening strategy.

ABO incompatibility is associated with less severe HDN as A and B antigens are expressed on fetal tissues lowering the titre of maternal anti-A or anti-B in the fetal circulation, leaving less to bind to fetal RBCs. Secondly, soluble A and B substances in fetal/neonatal plasma can bind maternal anti-A or anti-B, leaving less antibody available to bind to fetal/neonatal RBCs. In addition, allo-antibodies reacting with A and B antigens have a weaker affinity than those binding with

TABLE 1 Characteristics of included studies

Author, year	Criteria for study inclusion	Dose of IVIG	Prophylactic IVIG?[a] Y/N	Details about use of IUT recorded Y/N
Alpay, 1999[37]	(1) ABO/Rh incompatibility (2) Positive DAT (3) Hyperbilirubinaemia (>204 mmol/l) (4) Elevated reticulocyte count (≥10%)	1 g/kg	N	NR
Beken, 2014[25]	(1) ABO incompatibility (2) DAT Positive	1 g/kg	NR	NR
Dagoglu, 1995[29]	(1) Rh incompatibility (2) Positive DAT	500 mg/kg	Y	NR
Demirel, 2011[26]	(1) ABO incompatibility and (2) Positive DAT (3) Reticulocytosis	1 g/kg or 2 g/kg	N	NR
Elalfy, 2011[32]	(1) Rh incompatibility (2) Positive DAT (3) Elevated indirect hyperbilirubinaemia requiring PT in the first 12 h of life and/or rising by 0.5 mg/dl/h (4) Term newborn >38 wks GA (5) High reticulocyte count	500 mg/kg and 1 g/kg	N	Y
Garcia, 2004[38d]	(1) Rh incompatibility	0.75 g/kg daily × 3 days	Y[c]	Y
Huang, 2006[34d]	(1) ABO incompatibility (2) Positive DAT (3) Term (4) Titre >1:128	1 g/kg	N	NA
Miqdad, 2004[35]	(1) ABO incompatibility (2) DAT positive (3) Hyperbilirubinaemia Bilirubin >8.5 mmol/l/h or if bilirubin >170 mmol/l/h, 204 mmol/h or 238 mmol/h at <12, <18 or <24 h, respectively IVIG if bilirubin rising by ≥8.5 mmol/l/h	500 mg/kg	N	NR
Nasseri, 2006[33]	(1) ABO/Rh incompatibility (2) Positive DAT (3) Hyperbilirubinaemia (>0.5 mg/dl/h) (4) Bilirubin levels below ET criterion on admission (5) GA >37 weeks	500 mg/kg every 12 hs, total 3 doses	N Within 2–4 h of admission Median 18–22 h	N
Pishva N, 2000[40]	(1) Rh/ABO incompatibility (2) Positive DAT (3) History Rh-positive sibling	400–600 mg/kg	Y[c]	Y
Rubo, 1992[30]	(1) Rh incompatibility (2) Positive DAT Excluded (1) Unconjugated bilirubin >4 mg/dl	500 mg/kg	Y[c]	
Santos, 2013[27]	(1) Rh incompatibility (2) Positive DAT (3) Elevated bilirubin >4 mg/dl (4) >32 weeks GA	500 mg/kg	Y	NR
Smits-Wintjens, 2011[28]	(1) Rh(D) or Rh(c) incompatibility (2) Positive DAT with eluate (3) Maternal antibody-dependent cell cytotoxity test >50% predicting severe haemolysis (4) Antibody titre >1:64 (5) GA >35 weeks	750 g/kg	Y	Y

Details regarding phototherapy provided Y/N	Indication for ET	Haemoglobin threshold/ trigger for transfusion (g/l)	Definition of anaemia
Y Conventional PT Five special blue lamps	Serum bilirubin >290 mmol and increased >17 mmol/h despite treatment	NR[b]	NR
Y LED PT 30 μW/cm^2/nm spectrum 450–750 nm	NR	NR	14 g/l
Y Blue light (420–460 nm)	Term neonates: total bilirubin >1 mg/dl/h or total bilirubin level >20 mg/dl during first 72 h. neonates >2000 g: 18 mg/dl	NR	NR
Yes LED PT 30 μW/cm^2/nm spectrum 450–750 nm	Bilirubin level exceeded the limits defined by AAP	NR	NR
Y Fibre-optic blanket 30–40 cm from special blue lights 4 lights	Bilirubin increased by 1 mg/dl/h as per AAP guidelines	NR	NR
NA	NA	NA	NA
NA	NA	NA	NA
NR	Bilirubin ≥340 mmol/l (20 mg/dl) or if rising by 8.5 mmol/l/h (0.5 mg/dl/h) in neonates not receiving IVIG	<70 g/l	Hgb < 120 g/l anaemia at postnatal 6–12 weeks
Y Double surface blue light PT	Bilirubin ≥20 mg/dl or rise by 1 mg/dl/h	<70 g/l	Hgb < 120 g/l at 2, 4, 6 weeks
NR	NR	NR	NR
Y Quartz lamps or blue light	If unconjugated biliruinb exceeded modified curves by Site specific ET criteria by >34 mmol/l (2 mg/dl)	NR	NR
Y Prophylactic high intensity PT (spectral irradiance >30 l W/cm^2/nm) Stopping criteria provided	Total serum bilirubin level ≥340 mmol/l (20 mg/dl) or increased by 8.5 mmol/l/h (0.5 mg/dl/h) despite PT	NR	NR
Y Intensive PT using white light with intensity of 12–20 μW/cm/nm Bilirubin blanket providing blue light 30 W/cm/nm	ET criteria as per AAP guidelines	<80 or <96 g/l with clinical symptoms of anaemia e.g. lethargy, feeding problems, need for O_2 or failure to thrive	NR

TABLE 1 (Continued)

Author, year	Criteria for study inclusion	Dose of IVIG	Prophylactic IVIG?[a] Y/N	Details about use of IUT recorded Y/N
Tanyer, 2001[36]	(1) ABO or Rh incompatibility, (2) Positive DAT (3) no risk factors (e.g. sepsis), (4) no prematurity (define?) (5) Bilirubin <ET level at birth	IVIG 500 mg/kg or 500 mg/kg daily for 3 days	Y	NR
Voto, 1995[39]	(1) Rh incompatibility (2) Positive DAT	800 g/kg/d × 3 days	N	Y

Abbreviations: AAP, American Academy of Paediatrics; DAT, direct antiglobulin test; ET, exchange transfusion; FTT, failure to thrive; GA, gestational age; Hgb, haemoglobin; h, hour; IVIG, intravenous immune globulin; IUT, intrauterine transfusion; LED, light-emitting diodes; N, No; NA, not available (full manuscript); NR, not recorded; PT, phototherapy; Y, yes.

[a]Prophylactic IVIG defined as preventative or routine IVIG administered shortly after birth prior to the development of significant jaundice.

[b]Five patients transfused as haemoglobin dropped <87 g/l.

[c]Prophylactic IVIG ordered but did not provide exact time of administration.

[d]Data obtained from Louis systematic review (article not available or published in Chinese).

TABLE 2 Grading of Recommendations, Assessment, Development and Evaluation (GRADE) for Rh incompatibility (data from Zwiers et al.)[24]

Certainty assessment						
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Use of exchange transfusion (studies without a placebo control)						
5	Randomized trials	Very serious[a]	Not serious	Serious[b]	Not serious	None
Use of exchange transfusion (placebo-controlled trials)						
2	Randomized trials	Not serious	Not serious	Not serious	Not serious	None
Number of exchange transfusions per infant (studies without a placebo control)						
5	Randomized trials	Very serious[a]	Not serious	Serious[b]	Not serious	None
Number of exchange transfusions per infant (placebo-controlled trials)						
2	Randomized trials	Not serious	Not serious	Serious[b]	Not serious	None
Maximum total serum bilirubin level μmol/l (studies without a placebo control)						
4	Randomized trials	Very serious[a]	Serious	Serious[c]	Not serious	None
Maximum total serum bilirubin level μmol/l (placebo-controlled trials)						
2	Randomized trials	Not serious	Not serious	Serious[c]	Not serious	None
Duration of phototherapy (studies without a placebo control)						
3	Randomized trials	Very serious[a]	Not serious	Not serious	Not serious	None
Duration of phototherapy (placebo-controlled trials)						
2	Randomized trials	Not serious	Not serious	Not serious	Not serious	None
Use of top up transfusion (studies without a placebo control)						
2	Randomized trials	Very serious[a,d]	Serious[e]	Serious[e]	Serious[e]	None
Use of top up transfusion (placebo-controlled trials)						
2	Randomized trials	Not serious	Not serious	Very serious[f]	Serious	None

[a]Studies were not blinded generally and a few were limited by lack of random sequence generation, selective reporting and incomplete reporting.

[b]Indications for exchange were not consistent.

[c]Serum bilirubin is dependent on other factors in addition to haemolysis such as postnatal age.

[d]Haemoglobin concentrations for transfusion not reported.

[e]Only one study had outcomes. The second had 0 events.

[f]One study did not report haemoglobin concentrations for transfusion.

protein antigens. Moreover, there are relatively few group A or B antigenic sites on neonatal RBC as AB antigens are not well developed in the fetus.[41] Some suggest that neonates with severe jaundice and ABO incompatibility may not have been assessed for other non-immune haemolytic aetiologies (e.g. glucose 6-phosphate dehydrogenase deficiency).[46] The recommendation to not provide IVIG routinely for HDN assumed to be secondary to ABO incompatibility between

Details regarding phototherapy provided Y/N	Indication for ET	Haemoglobin threshold/ trigger for transfusion (g/l)	Definition of anaemia
Y White quartz halogen lamp with distance between neonate and light of 41 cm	Site specific ET criteria	NR	NR
NR	Site specific ET criteria	NR	NR

mother and neonate took into account not only the aspects above but also the lack of high-quality studies for ABO-mediated HDN, along with the low likelihood of significant jaundice and morbidity related to ABO-mediated HDN.

Recommendation for management of ABO-mediated HDN

In neonates at risk of ABO-mediated HDN, routine IVIG is not recommended to reduce the need for ET (very low certainty of evidence of effects, conditional recommendation).

The recommendations developed refer to routine use of IVIG for any neonates with Rh- or ABO-mediated HDN and hyperbilirubinaemia requiring PT, but not yet at the level requiring an ET. Routine use refers to prophylactic IVIG use to prevent progression to severe consequences of hyperbilirubinaemia. Recommendations could not be made for or against use of IVIG for neonates with rapidly rising bilirubin and emergent need for ET, as no studies have addressed this specific indication.

Severe hyperbilirubinaemia unresponsive to phototherapy

In neonates where hyperbilirubinaemia is severe (unresponsive to intensive PT) and requirement for ET is emergent, but not available on site within a timely manner, no evidence-based recommendations regarding the use of IVIG can be made. While awaiting transport to a facility where ET is available, first-line treatment is intensive PT.[4] Various non-evidence-based treatment suggestions have been described, but none can be endorsed at this time.

DISCUSSION

For jaundiced neonates with antibody-mediated HDN and severe hyperbilirubinaemia who do not respond to intensive PT, IVIG is sometimes administered with the goal of avoiding ET and decreasing neonatal morbidity. Studies with moderate certainty of evidence of effects suggest that early administration of IVIG (within a few hours of birth) as a preventative measure is not effective in reducing the need for ET, RBC transfusions or hyperbilirubinaemia in neonates with Rh isoimmunization.[27,28] In these studies, intensive PT may have treated the bilirubin rise early, and the use of IVIG may not have led to additional benefits. Currently, no studies with high certainty of evidence of effects have assessed the value of IVIG to avoid ET for ABO-mediated HDN; fortunately, ABO HDN rarely leads to severe HDN or the need for an ET, RBC transfusions or severe jaundice. Studies assessing treatment strategies for antibody-mediated HDN when hyperbilirubinaemia is severe and ET requirement is emergent were not available for recommendation development. If the diagnosis of severe jaundice is delayed or HDN occurs in remote hospitals or low-resource countries where intensive PT is not immediately available, IVIG may be considered, if ET is not readily available.

The benefit of using IVIG needs to balance risks. IVIG is a fractionated blood product manufactured from multiple donors. Previous literature has reported immediate (10%) and delayed (41%) adverse events following IVIG infusion in children,[47] including headaches, haemolysis[48] and aseptic meningitis.[49] For neonates, published reports of adverse events are limited and include apnoea,[50] haemolysis[14] and a higher incidence of necrotizing enterocolitis.[15] In addition, although fractionation leads to a virally inactivated product, the risk of viral transmission is not completely negligible.

CONCLUSION

The intent of this guidance document was to develop recommendations regarding the use of IVIG for Rh- and ABO-mediated HDN. We were unable to find studies that support the routine use of IVIG. Reducing the morbidity

TABLE 3 Grading of Recommendations, Assessment, Development and Evaluation (GRADE) for ABO incompatibility (data from Louis et al.)[23]

Certainty assessment						
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**
Need for exchange transfusion						
5	Randomized trials	Very serious[a,b]	Not serious	Serious	Serious[a]	None
Number of exchange transfusions per infant						
3	Randomized trials	Very serious[b]	Not serious	Serious[a]	Serious	None
Peak serum bilirubin (μmol/l)						
1	Randomized trials	Very serious[b,c,d]	Very serious[c]	Very serious[c]	Serious	None
Duration of phototherapy						
3	Randomized trials	Very serious[b]	Not serious	Serious	Not serious	None
Duration of hospitalization						
2	Randomized trials	Very serious[b]	Not serious	Serious	Serious	None
Need for top up transfusion						
3	Randomized trials	Very serious[e]	Not serious	Serious	Serious	None

Abbreviations: CI, confidence interval; IVIG, intravenous immune globulin; MD, mean difference; RR, risk ratio.

[a]Definitions for need were not consistent.

[b]None of the trials used allocation concealment, had blinded participants, or used blinded outcome assessment. Selective reporting could not be determined.

[c]Only one study.

[d]Only one study.

[e]Variable reporting for haemoglobin concentrations for transfusion.

TABLE 4 International recommendations for use of intravenous immunoglobulin to manage haemolytic disease of the newborn

Recommendations	
1	In neonates with Rh-mediated HDN, *routine*[a] IVIG is not recommended to reduce the need for exchange transfusion (low certainty of evidence of effects, conditional recommendation)
2	In neonates at risk of ABO-mediated HDN, *routine*[a] IVIG is not recommended to reduce the need of exchange transfusion (very low certainty of evidence of effects, conditional recommendation)

Abbreviations: HDN, haemolytic disease of the newborn; IVIG, intravenous immune globulin.

[a]*Routine* use refers to prophylactic IVIG use to prevent progression to severe consequences of hyperbilirubinaemia.

and mortality of HDN and its treatments remains a priority and there continues to be a pressing need for additional collaborative research. Future, prospective multicentred studies with clearly defined inclusion criteria, detailed algorithms regarding use of PT and need for ETs, as well as standardized follow-up frequency and transfusion threshold guidelines would enable the question to be addressed properly. Due to the relative rarity of HDN, well-powered trials will be a challenge to execute. If small studies remain the most pragmatic approach, the only strategy for meaningful conclusions in future meta-analyses on HDN management is standardization of criteria for commencement and termination of intensive PT as well as criteria for ET and top-up RBC transfusions.

ACKNOWLEDGEMENTS

International Collaboration for Transfusion Medicine Guidelines (ICTMG) members: Arwa Al Riyami MD, FRCPC, Sultan Qaboos University Hospital, Oman; Shubha Allard, MD, FRCP, FRCPath, National Health Service Blood & Transplant, United Kingdom; Melissa Brouwers, PhD, University of Ottawa, Canada; Jeannie Callum, MD, FRCPC, Sunnybrooke Health Sciences Centre and University of Toronto, Canada; James Daly, MBBS, FRACP, FRCPA, Australian Red Cross Lifeblood, Australia; Gregory A. Denomme, PhD, FCSMLS(D), Versiti Blood Center of Wisconsin, United States; Lise Estcourt, MB BChir, MA(Cantab), MA(MEL), MSc, DLSHTM, DPhil, MRCP, FRCPath, National Health Services Blood & Transplant, United Kingdom; Dean Fergusson, PhD, MHA, Ottawa Hospital Research Institute, Canada; Mark Fung, MD, PhD, University of Vermont Medical Center, United States; Laura Green, MBBS, MD (Res), FRCP, FRCPath, National Health Service Blood & Transplant, United Kingdom; Andreas

No. of patients		Effect			
IVIG	Control	Relative (95% CI)	Absolute (95% CI)	Certainty[abcd]	Importance
13/174 (7.5%)	46/176 (26.1%)	RR 0.31 (0.18 to 0.55)	180 fewer per 1000 (from 214 fewer to 118 fewer)	⨁◯◯◯ Very low	Critical
112	114	—	MD 0–0.2 (0.3 lower to 0.09 lower)	⨁◯◯◯ Very low	Critical
45	48	—	MD 60.6 µmol/l lower (83.2 lower to 38 lower)	⨁◯◯◯ Very low	Critical
112	114	—	MD 0.74 days lower (1.1 lower to 0.4 lower)	⨁◯◯◯ Very low	Important
56	58	—	MD 1.2 days lower (1.8 lower to 0.51 lower)	⨁◯◯◯ Very low	Important
7/112 (6.3%)	4/114 (3.5%)	RR 1.7 (0.6 to 5.0)	25 more per 1000 (from 14 fewer to 140 more)	⨁◯◯◯ Very low	Important

Greinacher, MD, University of Greifswald, Germany; Heather Hume, MD, FRCPC, MSc, University of Montreal, Canada; Rachel Jug, MB, BCh, BAO, Canadian Blood Services, Canada; Richard Kaufman, MD, Brigham & Woman's Hospital Adult Transfusion Service, United States; Hyungsuk Kim, MD, Seoul National University Hospital, Korea; Vernon Louw, MBChB (Stell), MMed(Int Med)(Stell), PhD(HPE)(UFS), Groote Schuur Hospital, University of Cape Town, South Africa; Tadashi Matsushita, Nagoya University Hospital, Japan; Michael Murphy, MD FRCP, FRCPath, FFPath, University of Oxford and National Health Service Blood & Transplant, United Kingdom; Joanne Pink, MBBS, FRACP, FRCPA, GAICD, Australian Red Cross Lifeblood, Australia; Susan Robinson, MBBS, FRACP, FRCPA, GAID, Guy's and St. Thomas' NHS Foundation Trust, United Kingdom; Cynthia So-Osman, MD, PhD, Sanquin and Erasmus Medical Center, The Netherlands; Simon Stanworth, MA, FRCP (Peads, UK), PhD, FRCPath, NHS Blood and Transplant and Oxford University, United Kingdom; Zbigniew M. Szczepiorski, MD, PhD, Dartmouth-Hitchcock Medical Center, United States; Aaron Tobian, MD, PhD, Johns Hopkins University, United States; Erica Wood, MBBS, FRACP, FRCPA, Monash University, Australia. The authors thank Ms Kimberly Figures for administrative support, Ms Melanie Anderson for assistance with the library searches, and Dr Prakesh Shah for sharing forest plots.

CONFLICT OF INTEREST

The authors have no financial or intellectual conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Dr Lieberman designed the study, identified and selected studies, extracted data, assessed methodologic quality and bias, and drafted the guideline manuscript; Dr Lopriore designed the study, and edited and approved the final manuscript; Dr Shehata identified and selected studies, extracted data, assessed methodologic quality and bias, and edited the guideline manuscript; Dr Landry identified and selected studies. All authors contributed to the development of recommendations, revision of recommendations, response to external reviewers, critically reviewing the manuscript, approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DISCLAIMER

The purpose of this document is to provide guidance on the use of IVIG in the management of HDN based on published evidence. The recommendations are not intended to replace either the physicians' clinical judgement of the specific case or the physicians' personal experience. The final decision should be made by the treating physician in light of the current clinical details.

ORCID

Lani Lieberman https://orcid.org/0000-0002-3633-0728
Jeanne E. Hendrickson https://orcid.org/0000-0002-7928-3132
Helen V. New https://orcid.org/0000-0001-6290-8004

REFERENCES

1. Webb J, Delaney M. Red blood cell alloimmunization in the pregnant patient. Transfus Med Rev. 2018;32(4):213–9.
2. Lieberman L, Callum J, Cohen R, Cserti-Gazdewich C, Ladhani N, Pendergrast J & Buckstein J Impact of red blood cell alloimmunization on fetal and neonatal outcomes: a single center cohort study transfusion. Transfusion. 2020;60(11):2537–46.
3. Rath MEA, Smits-Wintjens VEHJ, Lindenburg ITM, Folman CC, Brand A, van Kamp IL, et al. Postnatal outcome in neonates with severe rhesus c compared to rhesus D hemolytic disease. Transfusion. 2013;53(7):1580–5.
4. American Academy of Pediatrics Subcommittee on H. management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2004;114(1):297–316.
5. Barrington KJSKCPS. Guidelines for detection, management and prevention of hyperbilirubinemia in term and late preterm newborn infants. Paediatr Child Health. 2007;12(Suppl B):1B–12B.
6. Maisels MJ, Bhutani VK, Bogen D, Newman TB, Stark AR, Watchko JF. Hyperbilirubinemia in the newborn infant > or =35 weeks' gestation: an update with clarifications. Pediatrics. 2009;124(4):1193–8.
7. Smits-Wintjens VE, Walther FJ, Lopriore E. Rhesus haemolytic disease of the newborn: postnatal management, associated morbidity and long-term outcome. Semin Fetal Neonatal Med. 2008;13(4):265–71.
8. Murki S, Kumar P. Blood exchange transfusion for infants with severe neonatal hyperbilirubinemia. Semin Perinatol. 2011;35(3):175–84.
9. Jackson JC. Adverse events associated with exchange transfusion in healthy and ill newborns. Pediatrics. 1997;99(5):E7.
10. Diamond LK, Allen FH Jr, Thomas WO Jr. Erythroblastosis fetalis. VII. Treatment with exchange transfusion. N Engl J Med. 1951;244(2):39–49.
11. Kubo S, Ariga T, Tsuneta H, Ishii T. Can high-dose immunoglobulin therapy be indicated in neonatal rhesus haemolysis? A successful case of haemolytic disease due to rhesus (c + E) incompatibility. Eur J Pediatr. 1991;150(7):507–8.
12. Ballow M. The IgG molecule as a biological immune response modifier: mechanisms of action of intravenous immune serum globulin in autoimmune and inflammatory disorders. J Allergy Clin Immunol 2011;127(2):315–23; quiz 24–5.
13. Amos RC, Jacob H, Leith W. Jaundice in newborn babies under 28 days: NICE guideline 2016 (CG98). Arch Dis Child Educ Prac. 2017;102(4):207–9.
14. Christensen RD, Ilstrup SJ, Baer VL, Lambert DK. Increased hemolysis after administering intravenous immunoglobulin to a neonate with erythroblastosis fetalis due to Rh hemolytic disease. Transfusion. 2015;55(6):1365–6.
15. Figueras-Aloy J, Rodriguez-Miguelez JM, Iriondo-Sanz M, Salvia-Roiges M-D, Botet-Mussons F, Carbonell-Estrany X. Intravenous immunoglobulin and necrotizing enterocolitis in newborns with hemolytic disease. Pediatrics. 2010;125(1):139–44.
16. Gottstein R, Cooke RW. Systematic review of intravenous immunoglobulin in haemolytic disease of the newborn. Arch Dis Child Fetal Neonatal Ed. 2003;88(1):F6–10.
17. Keir AK, Dunn M, Callum J. Should intravenous immunoglobulin be used in infants with isoimmune haemolytic disease due to ABO incompatibility? J Paediatr Child Health. 2013;49(12):1072–8.
18. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. bmj. 2017;358.
19. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;366:l4898.
20. Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
21. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383–94.
22. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004;328(7454):1490.
23. Louis D, More K, Oberoi S, Shah PS. Intravenous immunoglobulin in isoimmune haemolytic disease of newborn: an updated systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed. 2014;99(4):F325–31.
24. Zwiers C, Scheffer-Rath EAM, Lopriore E, de Haas M, Liley HG. Immunoglobulin for alloimmune hemolytic disease in neonates. Cochrane Database Syst Rev. 2018;3:1–64.
25. Beken S, Hirfanoglu I, Turkyilmaz C, Altuntas N, Unal S, Turan O, et al. Intravenous immunoglobulin G treatment in ABO hemolytic disease of the newborn, is it myth or real? Indian Journal of Hematology and Blood Transfusion. 2014;30(1):12–5.
26. Demirel G, Akar M, Celik IH, Erdeve O, Uras N, Oguz SS, et al. Single versus multiple dose intravenous immunoglobulin in combination with LED phototherapy in the treatment of ABO hemolytic disease in neonates. Int J Hematol. 2011;93(6):700–3.
27. Santos MC, Sa C, Gomes SC Jr, Camacho LA, Moreira ME. The efficacy of the use of intravenous human immunoglobulin in Brazilian newborns with rhesus hemolytic disease: a randomized double-blind trial. Transfusion. 2013;53(4):777–82.
28. Smits-Wintjens VE, Walther FJ, Rath ME, Lindenburg IT, te Pas AB, Kramer CM, et al. Intravenous immunoglobulin in neonates with rhesus hemolytic disease: a randomized controlled trial. Pediatrics. 2011;127(4):680–6.
29. Dagoglu T, Ovali F, Samanci N, Bengisu E. High-dose intravenous immunoglobulin therapy for rhesus haemolytic disease. J Int Med Res. 1995;23(4):264–71.
30. Rubo J, Albrecht K, Lasch P, Laufkotter E, Leititis J, Marsan D, et al. High-dose intravenous immune globulin therapy for hyperbilirubinemia caused by Rh hemolytic disease. J Pediatr. 1992;121(1):93–7.
31. Mishra S, Cheema A, Agarwal R, Deorari A, Paul V. Oral zinc for the prevention of hyperbilirubinaemia in neonates. Cochrane Database Syst Rev. 2015;7:1–12.
32. Elalfy MS, Elbarbary NS, Abaza HW. Early intravenous immunoglobin (two-dose regimen) in the management of severe Rh hemolytic disease of newborn – a prospective randomized controlled trial. Eur J Pediatr. 2011;170(4):461–7.
33. Nasseri F, Mamouri GA, Babaei H. Intravenous immunoglobulin in ABO and Rh hemolytic diseases of newborn. Saudi Med J. 2006;27(12):1827–30.
34. Huang W-m, Chen H-w, Li N, Yang M, Jiao P-y. Clinical study of early interventions for ABO hemolytic disease of the newborn. Nan fang yi ke da xue xue bao = J South Med Univ. 2006;26(9):1350–5.
35. Miqdad AM, Abdelbasit OB, Shaheed MM, Seidahmed MZ, Abomelha AM, Arcala OP. Intravenous immunoglobulin G (IVIG) therapy for significant hyperbilirubinemia in ABO hemolytic disease of the newborn. J Matern Fetal Neonatal Med. 2004;16(3):163–6.
36. Tanyer G, Siklar Z, Dallar Y, Yildirmak Y, Tiras U. Multiple dose IVIG treatment in neonatal immune hemolytic jaundice. J Trop Pediatr. 2001;47(1):50–3.
37. Alpay F, Sarici SU, Okutan V, Erdem G, Ozcan O, Gokcay E. High-dose intravenous immunoglobulin therapy in neonatal immune haemolytic jaundice. Acta Paediatr. 1999;88(2):216–9.
38. Garcia M, Cordero G, Mucino P, Salinas V, Fernandez L, Christensen R (Eds). Intravenous Immunoglobulin (IVIG) Administration as a Treatment for Rh Hemolytic Jaundice in Mexico City. Pediatric Research; 2004: INT Pediatric Research Foundation, Inc.
39. Voto LS, Sexer H, Ferreiro G, Tavosnanska J, Orti J, Mathet ER, et al. Neonatal administration of high-dose intravenous immunoglobulin in rhesus hemolytic disease. J Perinat Med. 1995;23(6):443–51.

40. Pishva N, Madani A, Homayoon K. Prophylactic intravenous immunoglobulin in neonatal immune hemolytic jaundice. Irn J Med Sci. 2000;25:129–33.
41. Murray NA, Roberts IA. Haemolytic disease of the newborn. Arch Dis Child Fetal Neonatal Ed. 2007;92(2):F83–8.
42. Desjardins L, Blajchman M, Chintu C, Gent M, Zipursky A. The spectrum of ABO hemolytic disease of the newborn infant. J Pediatr. 1979;95(3):447–9.
43. Christensen RD, Baer VL, MacQueen BC, O'Brien EA, Ilstrup SJ. ABO hemolytic disease of the fetus and newborn: thirteen years of data after implementing a universal bilirubin screening and management program. J Perinatol. 2018;38(5):517–25.
44. Delaney M, Matthews DC. Hemolytic disease of the fetus and newborn: managing the mother, fetus, and newborn. Hematology Am Soc Hematol Educ Program. 2015;2015:146–51.
45. Geaghan SM. Diagnostic Laboratory Technologies for the Fetus and Neonate with isoimmunization. Semin Perinatol. 2011;35(3):148–54.
46. Christensen RD, Lambert DK, Henry E, Eggert LD, Yaish HM, Reading NS, et al. Unexplained extreme hyperbilirubinemia among neonates in a multihospital healthcare system. Blood Cells Mol Dis. 2013;50(2):105–9.
47. Singh-Grewal D, Kemp A, Wong M. A prospective study of the immediate and delayed adverse events following intravenous immunoglobulin infusions. Arch Dis Child. 2006;91(8):651–4.
48. Akman AO, Kara FK, Koksal T, Cakir BC, Karagol C, Sayli T. Association of hemolysis with high dose intravenous immunoglobulin therapy in pediatric patients: an open-label prospective trial. Transfus Apher Sci. 2017;56(4):531–4.
49. Bharath V, Eckert K, Kang M, Chin-Yee IH, Hsia CC. Incidence and natural history of intravenous immunoglobulin-induced aseptic meningitis: a retrospective review at a single tertiary care center. Transfusion. 2015;55(11):2597–605.
50. Kumar A, Kapoor R, Basu S. Apnea as a complication of intravenous immunoglobulin therapy in a neonate. Indian J Pediatr. 2014;81(12):1415.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Lieberman L, Lopriore E, Baker JM, Bercovitz RS, Christensen RD, Crighton G, et al. International guidelines regarding the role of IVIG in the management of Rh- and ABO-mediated haemolytic disease of the newborn. Br J Haematol. 2022;198:183–195. https://doi.org/10.1111/bjh.18170