# Hemolytic disease of the fetus and newborn: awareness precedes change

Winter, D.P. de


CHAPTER
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# Hemolytic Disease Of The Fetus And Newborn: Rapid Review Of Postnatal Care And Outcomes

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## ABSTRACT

**Background***:* Advances in postnatal care for hemolytic disease of the fetus and newborn (HDFN) have occurred over the past decades, but little is known regarding the frequency of postnatal treatment and the clinical outcomes of affected neonates. Most studies reporting on HDFN originate from high-income countries or relatively large centers, but important differences between centers and countries may exist due to differences in prevalence and available treatment options. We therefore aimed to evaluate the postnatal treatment landscape and clinical outcomes in neonates with Rhesus factor D (Rh(D))- and/or K-mediated HDFN and to provide recommendations for future research.

**Methods***:* We conducted a rapid literature review of case reports and series, observational retrospective and prospective cohort studies, and trials describing pregnancies or children affected by Rh(D)- or K-mediated HDFN published between 2005 and 2021. Information relevant to the treatment of HDFN and clinical outcomes was extracted. Medline, ClinicalTrials.gov and EMBASE were searched for relevant studies by two independent reviewers through title/abstract and full-text screening. Two independent reviewers extracted data and assessed methodological quality of included studies.

**Results***:* Forty-three studies reporting postnatal data were included. The median frequency of exchange transfusions was 6.0% [interquartile range (IQR): 0.0-20.0] in K-mediated HDFN and 26.5% [IQR: 18.0-42.9] in Rh(D)-mediated HDFN. The median use of simple red blood cell transfusions in K-mediated HDFN was 50.0% [IQR: 25.0-56.0] and 60.0% [IQR: 20.0-72.0] in Rh(D)-mediated HDFN. Large differences in transfusion rates were found between centers. Neonatal mortality amongst cases treated with intrauterine transfusion(s) was 1.2% [IQR: 0-4.4]. Guidelines and thresholds for exchange transfusions and simple RBC transfusions were reported in 50% of studies.

**Conclusion***:* Most included studies were from middle- to high-income countries. No studies with a higher level of evidence from centers in low-income countries were available. We noted a shortage and inconsistency in the reporting of relevant data and provide recommendations for future reports. Although large variations between studies was found and information was often missing, analysis showed that the postnatal burden of HDFN, including need for neonatal interventions, remains high.

## BACKGROUND

In neonates affected by hemolytic disease of the fetus and newborn (HDFN), maternally formed immunoglobulin G (IgG) antibodies directed against the child's erythrocytes invoke a persistent hemolysis. In recent decades, advances in the identification, care, and management of these affected infants have been developed and improved. The prevalence of Rhesus D (Rh(D))-mediated HDFN has significantly decreased due to the introduction of Rh(D) immunoprophylaxis (RhIG).[1-4] Also, cases at risk of mild to severe hemolysis can now be detected and monitored antenatally with serological parameters[5-8] and ultrasound[9-11], and treated with intrauterine transfusions in cases of severe fetal anemia. However, the prevalence of Rh(D)-mediated HDFN, the availability of RhIG and prenatal and postnatal treatment options may vary across countries due to sociodemographic, political, economic and geographical differences.[12]



Postnatal treatment of HDFN focuses on preventing and minimizing the potential complications of anemia and hyperbilirubinemia.[13] Potential permanent consequences of severe hyperbilirubinemia, such as bilirubin encephalopathy, are prevented by intensive phototherapy and exchange transfusions. Hemoglobulin levels and reticulocyte counts may be monitored throughout the first 3 months of life, and anemia may treated with simple red blood cell (RBC) transfusions if needed. Currently, there are no approved therapies for HDFN.

Even though advances have been made, much is still unknown on the exact frequency of the need for postnatal treatment and the clinical outcomes of these affected neonates. Previous studies have reported on the rate of thrombocytopenia[14], iron overload[15], cholestasis[16-19], necrotizing enterocolitis[20] and sepsis[21] in HDFN-affected neonates, although many of these studies originate from the national referral center for fetal therapy in the Netherlands and other centers from high-income countries and may therefore not be directly translatable to other centers and countries. Large differences between centers and countries in, for instance, the rate of exchange transfusions, RBC transfusions and associated morbidities may exist, but have not been addressed before. Therefore, this rapid review aims to gain an insight into the postnatal treatment landscape, clinical outcomes, and burden of the disease in neonates affected by Rh(D)- and/or Kell (K)-mediated HDFN and to identify gaps in the currently available literature and subsequently provide recommendations for future research.

# METHODS

## Literature searches

Research questions were devised using a PICO structure (Supplemental Table 1).The protocol for this study was developed according to Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines[22] and MOOSE Reporting Guidelines for Meta-Analysis of Observational Studies[23] and registered prospectively on PROSPERO (CRD42021234940). Medline, ClinicalTrials.gov and EMBASE were searched for journal articles and congress abstracts (EMBASE only) published between January 1, 2005 and March 10, 2021. A restriction on publication date was set due to improvements in intensive phototherapy and its application throughout the decades, possibly resulting in a decreased role for exchange transfusions in the management of hyperbilirubinemia. The search was conducted using ProQuest (Supplemental Appendix 1). The search strategy and used search terms are also defined in the prenatal companion manuscript.[24] Studies reporting on postnatal treatment and clinical outcomes were included in this manuscript. No restrictions were set on studies reporting on cases before January 1, 2005. Duplicate articles were removed automatically. Additionally, reference lists from relevant systematic literature reviews of cohort studies were hand-searched, together with the authors' personal libraries.

## Study selection

Two independent reviewers (D.P.d.W. and A.K.) reviewed citations, firstly the titles/abstracts in Rayyan (https://rayyan.ai/cite) and then the full texts, which were extracted into Microsoft Excel. Both reviewers hold a Masters degree relevant to the topic. Project director (D.O.) and the project team adjudicated decisions. Observational studies, trials, modeling studies, systematic reviews of cohort studies (to identify primary studies only), and case reports and case series of infants or children experiencing or having experienced Rh(D)- or K-mediated HDFN were included (Supplemental Appendix 2). Non–English-language articles were excluded, as were notes, editorials, and commentaries; nonsystematic reviews; reports of populations, interventions, outcomes, or study designs not of interest; publication types not of interest; indexed conference abstracts; and reports of animal or preclinical studies.

Two reviewers (D.P.d.W. and A.K.) extracted data independently for each study (presented in Supplemental Table 2), including study characteristics (i.e., citation information, study design, and data source), patient characteristics (i.e., population description, sample size, antigen status), treatment patterns (i.e., use of phototherapy, exchange transfusion, simple RBC transfusion, or other treatments), and clinical

outcomes (i.e., mortality, anemia, hyperbilirubinemia). Additionally, reporting of guidelines and thresholds used for exchange transfusions and simple RBC transfusions were collected. Discrepancies in data extraction between reviewers were resolved and the project director (D.O) adjudicated decisions in data extraction. Extracted variables were predefined by the authors. The Population, Intervention, Comparison, Outcomes, and Study (PICOS) design was used as a framework to formulate the study eligibility criteria.[25] Abstracted data underwent quality control by the project director (D.O.) who screened 10% of included/excluded articles. Methodological quality of the selected studies was independently assessed (D.P.d.W. and A.K.) using the JBI Critical Appraisal Checklist for Case Reports and Case Series, Newcastle–Ottawa Scale for observational studies, Checklist for Reporting Results of Internet E-Surveys (CHERRIES) for questionnaires and the NICE-checklist for randomized controlled trials.



### Analyses

Data from eligible studies were characterized as representative, which included data from studies that accurately reflected the characteristics of the larger group (e.g., larger case series, retrospective or prospective studies, randomized controlled trials [RCTs]), or nonrepresentative, which included data from studies that reflected a small proportion of the characteristics of the larger group (e.g., case reports or small case series, or studies in a subset of the larger group, such as cases treated with intrauterine transfusion, or cases with hydrops fetalis). When possible, we aggregated information reported in a similar manner. For unique outcomes, we highlighted information from generalizable studies. Where appropriate, data were summarized as percentage (mean±standard deviation [SD] or range) or median (interquartile range [IQR]) for patient groups or patient populations.

Assessment of available findings was conducted to identify evidence gaps, and recommendations to fill unmet needs were formulated. Results pertinent to neonates are reported here; maternal and fetal outcomes and methods as described above have been reported in a companion publication by de Winter et al.[24]

Methodological quality was assessed by two independent reviewers (D.P.d.W. and A.K) until consensus was reached, using the JBI Critical Appraisal Checklist for Case Reports, JBI Critical Appraisal Checklist for Case Series, Newcastle–Ottawa Scale for retrospective and prospective cohort studies, Checklist for Reporting Results of Internet E-Surveys (CHERRIES) for questionnaires and the NICE Checklist for randomized controlled trials. The overall methodological quality scores are reported in Supplemental Table 6. Detailed methodological analyses are available in the prenatal companion publication.[24]

# RESULTS

## Study selection and characteristics

A total of 2538 articles were identified through searches on Medline, ClinicalTrials.gov and EMBASE, and an additional 3 articles were identified from personal libraries (Figure 1). Initially, 2363 articles were excluded based on the title and abstract screening and 136 articles were excluded based on full-text review. An additional article was identified through a reference search from eligible systematic reviews and cohort studies, resulting in a total of 60 included studies. Finally, 43 out of 60 studies reported postnatal data. Characteristics of the 43 included studies are reported in Supplemental Table 2.[16, 20, 26-66]

The included studies were comprised of 12 (28%) case reports, 6 (14%) case series, 1 (2%) questionnaire, 19 (44%) retrospective cohort studies, 4 (9%) prospective cohort studies, and 1 (2%) RCT. Studies were performed in 22 countries, most originated from Turkey (n=6 [14%]), followed by The Netherlands (n=5 [12%]) and the United States (n=5 [12%]).

The 43 studies comprised 113 groups of neonates/infants, of which 12 (11%) were from single case reports and 14 (12%) were from case series (Table (Table1).1). The selected studies reported on cases managed between 1985 and 2019. Mean (range) group size was 36.5 (1–235). Mean (SD) gestational age was 35.0 (32.3–40.2) weeks, and mean birth weight was 2.67 (2.22–3.19) kg.

**Table 1.** Patient Characteristics Among Neonates and Infants From 43 Eligible Studies

| Characteristic | Mean (range) | Patient groups (n) | No. of studies |
|---|---|---|---|
| Patient group size, n | 36.5 (1-235) | 113 | 43 |
| Gestational age at birth, weeks | | | |
| Mean | 35.0 (32.3-40.2) | 11 | 7 |
| Median | 35.8 (32.0-37.0) | 19 | 9 |
| Exact | 34.2 (28.1-38.1) | 16 | 12 |
| Birth weight, grams | | | |
| Mean | 2670 (2220-3190) | 11 | 7 |
| Exact | 2346 (1385-3750) | 20 | 13 |

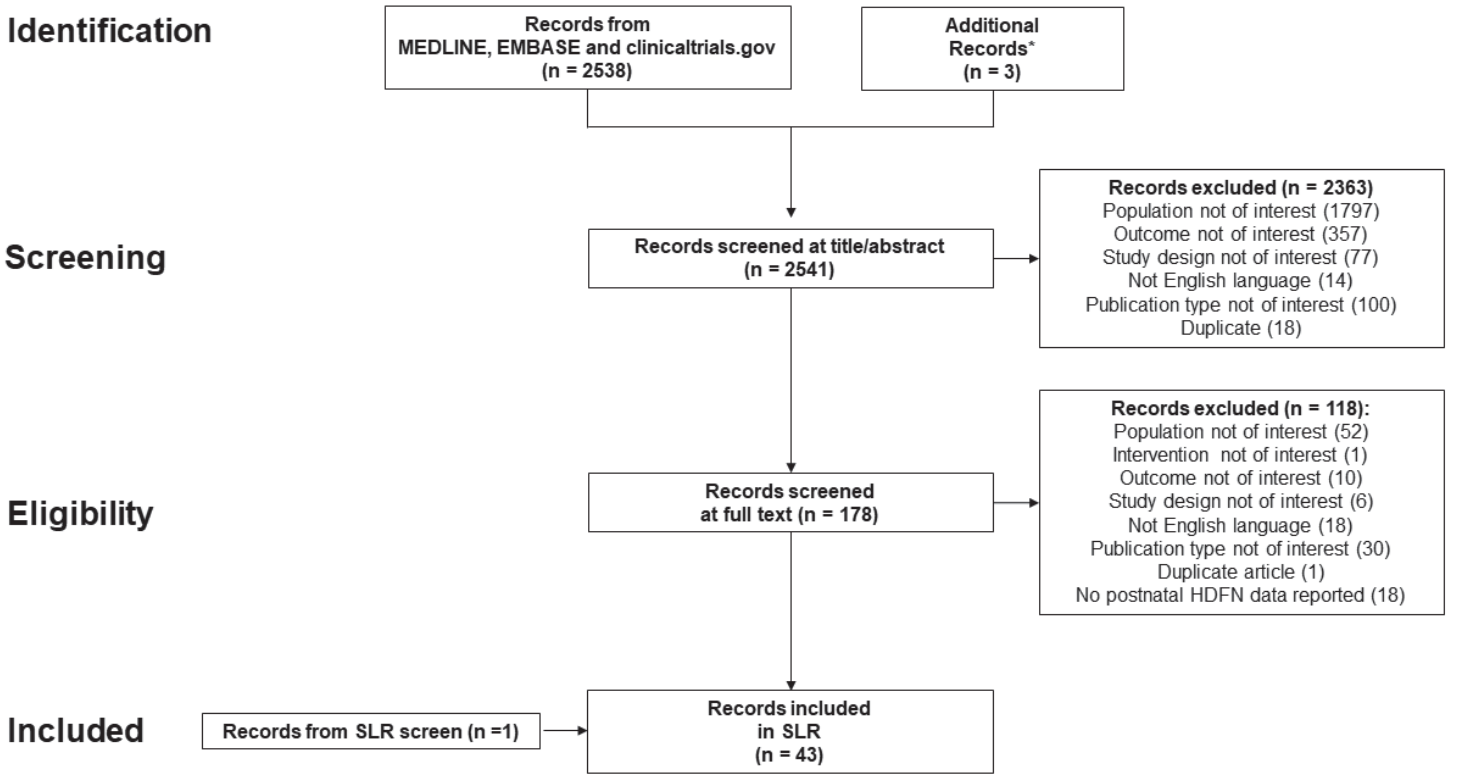


**Figure 1:** PRISMA flow diagram of study selection. SLR, systematic literature review. *From authors' personal libraries

## Methodological quality of the studies

Six of 12 included case reports received a perfect score, whereas the remaining six studies lacked in accurately reporting the patients previous history, current condition or post-intervention condition (Supplemental Table 6). Only one case series received a perfect score, the remaining six case series lacked in accurately reporting the inclusion process and the clinical outcomes and follow-up. Of the 20 retrospective studies, 18 were of good quality and 2 of fair quality. All prospective studies were of good quality. The methodological quality of these studies were also described in more detail in the prenatal study of the same literature search.[24]

## Treatment landscape

Data on intensive phototherapy was available in 23 studies (Supplemental Table 3,) of which 15 studies provided representative data with a median use of 99% [IQR: 75.7–100.0] for Rh(D)-mediated HDFN and 95.5% [IQR: 88.3–100.0] for K-mediated HDFN (Table 2). No adverse events related to intensive phototherapy were described. Use of exchange transfusions was reported in 27 studies. Eighteen studies reported representative data on the frequency of exchange transfusions. In these studies, the frequency of exchange transfusions was found to be lower in K-mediated HDFN (median use of 6.0% [IQR: 0.0–20.0]) in comparison to Rh(D)-mediated HDFN (median use of 26.5% [IQR: 18.0–42.9]). The frequency of simple RBC transfusions was reported in 19 studies, of which 11 provided representative data. Median use of simple RBC transfusions in Rh(D)-mediated HDFN was 60.0% [IQR: 20.0–72.0] and 50.0% [IQR: 25.0–56.0] in K-mediated HDFN. We were unable to accurately extract adverse events related to exchange transfusions or simple RBC transfusions from the included articles. Two studies reported on the use of intravenous immunoglobulin (IVIG) in Rh(D) or K-mediated HDFN.[32, 40] One retrospective study reported on the employment of delayed cord clamping.[52] A single case report reported on the use of recombinant erythropoietin in K-mediated HDFN.[45]

**Table 2.** Frequencies of treatments employed in Rh(D)- and K-mediated HDFN

| Treatment type* | Rh(D) | Kell |
|---|---|---|
| Intensive phototherapy | 99 [75.7-100] | 95.5 [88.3-100] |
| Exchange transfusion | 26.5 [18-42.9] | 6.0 [0-20] |
| Simple RBC transfusion | 60 [20-72] | 50 [25-56] |

*Data presented as median % [IQR].

## Neonatal outcomes

Various adverse events were reported in 7 studies, of which 4 studies provided representative data (Supplemental Table 4). We were unable to aggregate the data due to a large heterogeneity in patient characteristics and employed treatment types. No studies reported representative data on cardiac dysfunction, necrotizing enterocolitis, the use of (non-)mechanical ventilation, or the use of umbilical venous catheters. Neurodevelopmental outcome was reported by 3 studies, where 25% (2/8) of patients presented with neurodevelopmental abnormalities. The case series by Harper 2006 reported on the neurodevelopmental outcome in a cohort of 16 post-hydropic children who were treated with an intrauterine transfusion for HDFN. Five cases, 3 with Rh(D)-mediated HDFN and 2 with K-mediated HDFN were reported upon and included in this review (Supplemental Table 4). Twelve studies reported on neonatal mortality rates (Supplemental Table 5). The median neonatal mortality rate among neonates treated with intrauterine transfusion(s), reported in 5 studies, was 1.2% [IQR: 0–4.4]. Aggregation of neonatal mortality rates for other included cohorts was not possible due to large variations in employed treatment options.



## Reporting of guidelines and thresholds

To better understand the implementation of guidelines in the care of HDFN-affected neonates, an additional analysis was performed to assess which publications specified guideline thresholds for exchange transfusions and simple RBC transfusions. Nine out of 18 (50%) studies reporting representative data on the frequency of exchange transfusions reported the guidelines and thresholds used. Among these, only 1 study reported on the method of exchange transfusions. The Turkish Neonatal Society guidelines to the approach, follow-up, and treatment of neonatal jaundice[67] was used in 2 studies, the American Academy of Pediatrics (AAP) guidelines[68] in 5 studies, and the remaining 2 studies provided details on the thresholds used without reference to a previously published guideline. Five out of 12 (42%) studies reporting representative data on the use of simple RBC transfusions reported the thresholds used. None of these studies provided a reference to a previously published guideline. None of the nonrepresentative studies reported the guidelines or thresholds for exchange transfusions (n=9) or simple RBC transfusions (n=8).

# DISCUSSION

## Main findings

We found that the current clinical burden of HDFN, based on the use of exchange transfusions and simple RBC transfusions in neonates affected by Rh(D)- and/or K-mediated HDFN, is relatively high with a median exchange transfusion use of 27% in Rh(D)-mediated HDFN and 6% in K-mediated HDFN. We also found that the need for at least 1 simple RBC transfusion was required in 60% of Rh(D)-mediated HDFN and in 50% of K-mediated HDFN. In addition, a large variance in the rate of exchange transfusions and RBC transfusions in both Rh(D)-mediated HDFN and K-mediated HDFN was found, indicating that the rate of these procedures may vary widely between centers and countries and that a consensus on the management may be lacking. We were unable to determine the frequency of adverse events related to exchange transfusions and RBC transfusions. However, it was reported that delayed onset anemia occurred in 72% of infants with K-mediated HDFN, indicative that the effects of antenatal maternal alloimmunization can carry over into infancy and that clinicians should be aware of anti-K mediated inhibition of erythroid progenitors. We were unable to extract representative data on the occurrence of delayed onset anemia in Rh(D)-mediated HDFN, demonstrating that it may not be well recognized or reported in literature due to a false sense of security despite the persistence of maternal IgG in neonatal blood after birth. It should also be taken into consideration that most of the neonates with Rh(D)- and/or K-mediated HDFN in the included studies were born late preterm, thereby disrupting the intrauterine development. This was previously described elsewhere in more detail in the prenatal study from the same literature search.[24]

## Strengths and limitations

There are several limitations to this study. Firstly, mostly studies from middle- to high-income countries and relatively large centers were included. No studies with a higher level of evidence (e.g., observational cohort studies or trials) from centers in low-income countries were available, which is a natural consequence of rare diseases and a general absence of centralization of prenatal care that is currently not feasible in many countries. More insight into performed treatments and clinical outcomes from centers with fewer cases and low-to-middle income countries is needed to more accurately determine the current postnatal treatment landscape and clinical outcomes of HDFN. Also the performed search and selection of studies may have been limited as the search was not performed on Scientific Electronic Library Online (Scielo) or African Index Medicus and only English language studies were selected. However, through including case series and case reports we were able to retrieve the currently available

data from centers with fewer cases. Moreover, we were unable to identify the number of records found stratified per database and the number of duplicate records that were automatically removed. Additionally, we performed the search using ProQuest and were consequently unable to retrieve the specific search strategies for Medline, clinicaltrials.gov and EMBASE limiting the preferred transparency and repeatability of the study. Lastly, through selecting cases with Rh(D)-mediated HDFN or K-mediated HDFN, we were unable to determine the treatment landscape and clinical outcomes of other alloantibodies that may induce disease, such as anti-Rh(c) or anti-Rh(E).



Even though we employed minimal limits on study design, we were unable to accurately determine the frequency of alternative postnatal treatment options. Due to a lack of representative studies, a generally low methodological quality, and a limited number of cases in the included studies, we were unable to determine frequencies of neonatal IVIG, recombinant erythropoietin, or plasma exchange and plasmapheresis. Mostly case reports and case series reported on the use of these less frequently used treatment types, indicative of a potential low frequency. Also, we were unable to extract data on neonatal comorbidities (e.g., cardiac dysfunction, sepsis, necrotizing enterocolitis and bilirubin encephalopathy) or standard-of-care neonatal treatments (e.g., the need for (non-)mechanical ventilation or the use of umbilical venous catheters) that might have an effect on the clinical outcome of these sometimes severely ill patients. Thus, the evidence does reveal a significant lack of available information on both the employment of less frequently used treatments for HDFN, the use of other neonatal standard-of-care treatments, and the occurrence of comorbidities that may be due to premature delivery of HDFN-affected neonates. Also, using these inclusion and exclusion criteria, no studies on long-term neurodevelopmental outcome were included in this review. Lastly, due to the descriptive nature of this rapid review and the consequent lack of interventions, we were unable to assess the level of heterogeneity between studies using the Chi2- and I2-statistic. However, a certain level of heterogeneity between studies may be expected, due to a large variety in included cases, transfusion rates and employed guidelines. Additionally, sociodemographic and geographical differences, that are commonly not reported on, may add to the level of heterogeneity.

## Implication of the findings

Great advances in the postnatal management of HDFN have been made since the very first exchange transfusion for neonatal icterus in 1924.[69] As a consequence, the neonatal mortality rate among infants treated with exchange transfusions decreased from approximately 12% in the late 1940s and early 1950s[70, 71] to 0–6% in the twenty-first century[72-74]. In addition, the recently published 2022 AAP guidelines for the management

of hyperbilirubinemia recommends to increase the total bilirubin threshold for exchange transfusions, potentially leading to another decrease in the rate of exchange transfusions and underlining the importance of intensive phototherapy.[75] Intensive phototherapy was found to be employed in nearly all of the reported cases in the included studies. The serious risk of complications associated with exchange transfusions, inherent to its invasive nature, should not be taken lightly. As previously stated, we were unable to extract data on adverse events associated with exchange transfusions in this literature search. But, in a recent retrospective study—a study that was excluded from this rapid review—of exchange transfusions performed over a 20-year period in the national referral center for HDFN in the Netherlands, thrombocytopenia (<100×109/L) occurred in>90% of cases, of which 20% with a thrombocyte count<25×109/L, and leukopenia (<5×109/L) occurred in 71% of cases. Importantly, proven sepsis related to exchange transfusions occurred in 11% of neonates.[73]

As previously mentioned, a large variance was found in the rate of exchange transfusions and simple RBC transfusions, suggestive of a lack of consensus on transfusions thresholds. Future studies ought to more accurately identify differences and similarities in the postnatal management strategies, as well as the available therapy options, and the clinical outcomes of those affected between centers in an international perspective. This information may be used to open a discussion, encourage international cooperation and, importantly, improve the care and outcomes of those affected. Lastly, we noted a shortage and inconsistency in the reporting of relevant data. For instance, approximately 50% of the studies did not report essential information on guidelines and thresholds used for exchange transfusions and simple RBC transfusions. Therefore, we have developed a list of parameters that are recommended to be reported in future studies, if available, as these parameters could nuance and provide a better framework for the studies' findings (Figure 2).

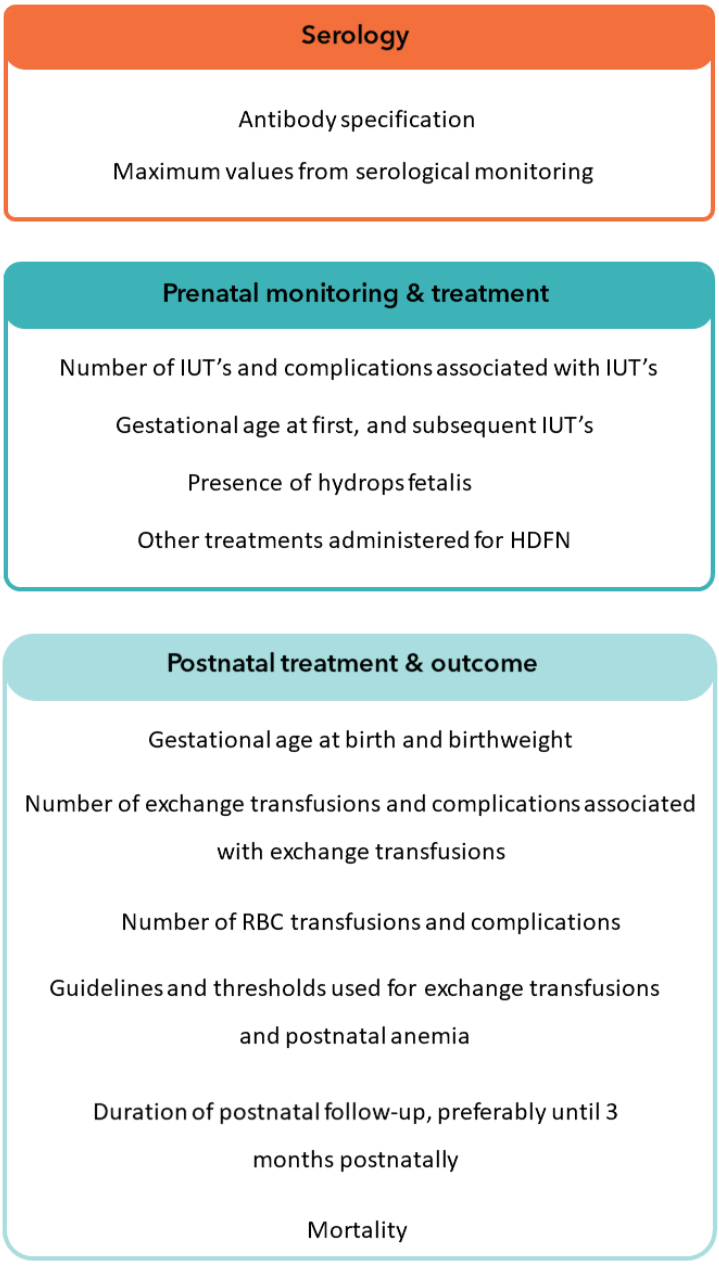


**Figure 2:** Recommended parameters for future studies. HDFN, hemolytic disease of the fetus and newborn; IUT, intrauterine transfusion; RBC, red blood cell

## CONCLUSION

In summary, we found that, although the neonatal mortality rate is nowadays low, the postnatal clinical burden of Rh(D)- and/or K-mediated HDFN remains relatively high, with a high need for exchange transfusions and simple RBC transfusions. Large differences between centers and countries may exist in the rate of exchange transfusions and simple RBC transfusions. We have identified several evidence gaps that should be addressed and provide an opportunity for future studies in an international perspective. Future studies should also report several vital parameters on guidelines and thresholds, methodology, and results to ensure an increase in the quality, validity, and replicability of the study.

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# SUPPLEMENTAL FILES

**Supplementary Table** 1. Research Questions

| PICO categories | Research question 1 | Research question 2 |
|---|---|---|
| **P**atient | In neonates | In neonates |
| **I**ntervention | Affected by Rh(D)-mediated and/or K-mediated HDFN | Affected by Rh(D)-mediated and/or K-mediated HDFN |
| **C**omparison | Not applicable | Not applicable |
| **O**utcome | What is the: Mortality rate, gestational age at birth, complication rate and rate of comorbidities (cardiac dysfunction, respiratory distress syndrome, necrotizing enterocolitis, sepsis, bilirubin encephalopathy) | What is the: Rate of exchange transfusions, phototherapy, RBC transfusions, standard-of-care neonatal treatments ((non-) mechanical ventilation and use of umbilical venous catheters) |

HDFN, hemolytic disease of the fetus and newborn. RBC, red blood cell

**Supplementary Table 2.** General Characteristics of Included Studies

| Study | Study type | Data source | Sample size | Groups | Group size | Data collection period | Country | Funding source |
|---|---|---|---|---|---|---|---|---|
| Akdag 2012 (27) | Case report | Medical record | 1 | Neonate, K-mediated HDFN | 1 | NR | Turkey | Not funded |
| Azavkli 2020 (61) | Retrospective cohort | Medical records | 110 | Neonate, Rh(D)-mediated HDFN | 42 | January 2015-July 2018 | Turkey | Not reported |
| Bek 2019 (28) | Case report | Medical record | 1 | Neonate, Rh(D)-mediated HDFN | 1 | NR | Turkey | Not reported |
| Bennardello 2013 (29) | Questionnaire | Questionnaire | 1661 | Neonates, Rh(D)-mediated HDFN | 111 | NR | Italy | Not reported |
| Bi 2019 (30) | Prospective cohort | Prospective registry | 18 | Rh(D)-mediated HDFN | 5 | January 2017-June 2019 | People's Republic of China | Not reported |
| Brumbaugh 2011 (31) | Case report | Medical record | 1 | Neonate, K-mediated HDFN | 1 | NR | USA | Not funded |
| Chatziantoniou 2017 (32) | Retrospective cohort | Medical records | 130 | Neonates, Rh(D)-mediated HDFN | 22 | June 2006-June 2013 | UK | Not reported |
| | | | | Neonate, K-mediated HDFN | 1 | | | |
| Colpo 2017 (33) | Case report | Medical record | 1 | Neonate, Rh(D)-mediated HDFN | 1 | NR | Italy | Not funded |
| De Assuncão 2016 (34) | Prospective cohort | Prospective registry | 13 | Neonates, Rh(D)-mediated HDFN | 13 | NR | Brazil | Not reported |
| Gottvall 2008 (35) | Retrospective cohort | Medical records | 78,145 | Neonates, Rh(D)-mediated HDFN | 71 | January 1992-December 2005 | Sweden | Not reported |
| Gudlaugsson 2020 (36) | Retrospective cohort | Medical records | 132 | Neonates, Rh(D)-mediated HDFN | 85 | 1996-2015 | Iceland | Not reported |

| Study | Study type | Data source | Sample size | Groups | Group size | Data collection period | Country | Funding source |
|---|---|---|---|---|---|---|---|---|
| Haider 2020 (37) | Case report | Medical record | 1 | Neonate, Rh(D)-mediated HDFN | 1 | NA | Pakistan | Not funded |
| Harper 2006 (38) | Prospective cohort | Prospective registry | 18 | Neonates, Rh(D)-mediated HDFN<br>Neonates, K-mediated HDFN | 3<br>2 | July 1985-October 1995 | USA | Supported by the General Clinical Research Centers Program, grant NCRR RR00059; the National Institutes of Health, grant P01 HL46925; and the Children's Miracle Network Telethon of Iowa. |
| Hassan 2019 (39) | Case report | Medical record | 1 | Neonate, Rh(D)-mediated HDFN | 1 | NA | Malaysia | Not funded |
| Karagol 2012 (40) | Retrospective cohort | Medical records | 106 | Neonates, K-mediated HDFN | 5 | January 2005-December 2010 | Turkey | Not reported |
| Kriplani 2007 (41) | Case series | Medical records | 4 | Neonates, Rh(D)-mediated HDFN | 4 | NR | India | Not reported |
| Lakhwani 2011 (42) | Case report | Medical record | 1 | Neonate, K-mediated HDFN | 1 | NR | Spain | Not reported |
| Levy-Zauberman 2011 (43) | Case report | Medical record | 1 | Neonate, Rh(D)-mediated HDFN | 1 | NR | France | Not funded |
| Lieberman 2020 (44) | Retrospective cohort | Medical records | 128 | Neonates, Rh(D)-mediated HDFN<br>Neonates, K-mediated HDFN | 18<br>2 | November 2020-June 2017 | Canada | Laboratory Medicine and Pathology Summer Student Research Grant, University of Toronto; Canadian Blood Services, Transfusion Medicine Research Program Support Award |
| Manoura 2007 (45) | Case report | Medical record | 1 | Neonate, K-mediated HDFN | 1 | NR | Greece | Not reported |

| Study | Study type | Data source | Sample size | Groups | Group size | Data collection period | Country | Funding source |
|---|---|---|---|---|---|---|---|---|
| Matijevic 2005 (46) | Retrospective cohort | Medical records | 23 | Neonates, Rh(D)-mediated HDFN | 15 | January 1997-January 2003 | | Not reported |
| | | | | Neonate, K-mediated HDFN | 1 | | | |
| Mayer 2018 (47) | Case series | Medical records | 3 | Neonate, Rh(D)-mediated HDFN | 1 | NR | Germany | Not reported |
| | | | | Neonate, K-mediated HDFN | 1 | | | |
| Meraj 2015 (48) | Retrospective cohort | Medical records | 8 | Neonates, Rh(D)-mediated HDFN | 5 | January 2001-December 2001 | Pakistan | Not reported |
| Navarro 2009 (49) | Case series | Medical records | 3 | Neonate, Rh(D)-mediated HDFN | 1 | NR | USA | Not reported |
| Nwogu 2018 (50) | Case series | Medical records | 5 | Neonates, Rh(D)-mediated HDFN | 3 | November 2011-December 2015 | USA | Not reported |
| | | | | Neonate, K-mediated HDFN | 1 | | | |
| | | | | Neonate, Rh(D)- and K-mediated HDFN | 1 | | | |
| Palfi 2006 (51) | Case report | Medical record | 1 | Neonate, Rh(D)-mediated HDFN | 1 | NA | Sweden | Not reported |
| Phung 2018 (52) | Retrospective cohort | Medical records | 106 | Neonates, isolated Rh(D)-mediated HDFN | 27 | 1999-2015 | France | Not reported |

| Study | Study type | Data source | Sample size | Groups | Group size | Data collection period | Country | Funding source |
|---|---|---|---|---|---|---|---|---|
| Raguz 2020 (26) | Retrospective | Medical records | 29,663 pregnancies | Infants, Rh(D)-mediated HDFN | 59 | 2000-2019 | Bosnia and Herzegovina | Not reported |
| | | | | Infants, K-mediated HDFN | 5 | | | |
| Rahimi-Sharbaf 2007 (53) | Case report | Medical record | 1 | Neonate, Rh(D)-mediated HDFN | 1 | NA | Iran | Not reported |
| Rath 2011 (54) | Retrospective | Medical records | 191 | (Near)-term neonates, Rh(D)-mediated HDFN | 157 | January 2000-December 2008 | The Netherlands | Not reported |
| | | | | (Near)-term neonates, K-mediated HDFN | 34 | | | |
| Rath 2013 (55) | Retrospective cohort | Medical records | 125 | Neonates, Rh(D)-mediated HDFN | 103 | January 2000-October 2011 | The Netherlands | Not reported |
| Ree 2019 (56) | Retrospective cohort | Medical records | 298 | Infants, Rh(D)-mediated HDFN | 224 | January 2006-Jaunary 2018 | The Netherlands | Not reported |
| | | | | Infants, K-mediated HDFN | 39 | | | |
| Ree 2020a (20) | Retrospective cohort | Medical records | 317 | Infants, Rh(D)-mediated HDFN | 2 | January 2000-December 2016 | The Netherlands | Not reported |
| | | | | Infant, K-mediated HDFN | 1 | | | |

| Study | Study type | Data source | Sample size | Groups | Group size | Data collection period | Country | Funding source |
|---|---|---|---|---|---|---|---|---|
| Ree 2020b (57) | Retrospective cohort | Medical records | 235 | Neonates, Rh(D)-mediated HDFN | 189 | January 2005-December 2018 | The Netherlands | Not reported |
| | | | | Neonates, K-mediated HDFN | 46 | | | |
| Ruma 2007 (58) | Multicenter case series | Medical records | 9 | Infants, Rh(D)-mediated HDFN | 5 | 1996-2005 | USA | Not reported |
| | | | | Infants, K-mediated HDFN | 4 | | | |
| Sainio 2015 (59) | Retrospective cohort | Finnish Red Cross Blood Service Database and questionnaires | 104 | Neonates, Rh(D)-mediated HDFN | 86 | 2003-2012 | Finland | Not funded |
| | | | | Neonates, K-mediated HDFN | 6 | | | |
| Santos 2013 (60) | RCT | Prospective registry | 92 | Infants, Rh(D)-mediated HDFN | 92 | April 2006-June 2009 | Brazil | Not reported |
| Simonazzi 2016 (62) | Case series | Medical records | 4 | Neonates, Rh(D)-mediated HDFN | 3 | NR | Italy | Not reported |
| Takci 2013 (16) | Retrospective cohort | Medical records | 30 | Hydropic infants, Rh(D)-mediated HDFN | 30 | January 2001-June 2012 | Turkey | Not reported |
| Temel Yuksel 2019 (63) | Prospective cohort | Prospective registry | 17 | Neonates, Rh(D)-mediated HDFN | 17 | January 2018-June 2019 | Turkey | Not reported |

| Study | Study type | Data source | Sample size | Groups | Group size | Data collection period | Country | Funding source |
|---|---|---|---|---|---|---|---|---|
| Tiblad 2011 (64) | Retrospective cohort | Medical records, local databases and the Swedish Quality Register on Neonatal Intensive Care | 84 | Neonates, Rh(D)-mediated HDFN<br>Neonates, K-mediated HDFN | 67<br>9 | June 1990-June 2010 | Sweden | Not reported |
| Walsh 2013 (65) | Retrospective cohort | Medical records | 102 | Neonates, Rh(D)-mediated HDFN<br>Neonates, K-mediated HDFN | 26<br>11 | January 1, 1996-December 31, 2011 | Republic of Ireland | Not funded |
| Xu 2013 (66) | Case report | Medical record | 1 | Neonate | 1 | NA | People's Republic of China | Not reported |

HDFN, hemolytic disease of the fetus and newborn; NA, not applicable; NR, not reported; RCT, randomized controlled trial; Rh(D), Rhesus factor D.

**Supplementary Table 3.** Postnatal Treatments Reported in Studies With Representative Data

| Citation | Study design | Population | Rh(D) or K | Treatment type | Treatment (%) |
|---|---|---|---|---|---|
| **Phototherapy** | | | | | |
| Azavkli 2020 (61) | Retrospective cohort | 42 | Rh(D) | IUT, phototherapy, RBC transfusion | 100 |
| Gottvall 2008 (35) | Retrospective cohort | 71 | Rh(D) | Maternal plasma exchange and/or high-dose IVIG, neonatal exchange transfusion, phototherapy | 15.5 |
| Karagol 2012 (40) | Retrospective cohort | 5 | K | IVIG, neonatal exchange transfusion, phototherapy | 80 |
| Kriplani 2007 (41) | Case series | 4 | Rh(D) | Maternal IVIG, IUT, phototherapy | 50 |
| Lieberman 2020 (44) | Retrospective cohort | 18 | Rh(D) | Neonatal IVIG, neonatal exchange transfusion, phototherapy, RBC transfusion | 67 |
| | | 2 | K | Neonatal IVIG, phototherapy, RBC transfusion | 100 |
| Matijevic 2005 (46) | Retrospective cohort | 16 | Rh(D) & K | IUT, neonatal exchange transfusion, phototherapy | 75 |
| Meraj 2015 (48) | Retrospective cohort | 5 | Rh(D) | Exchange transfusion, phototherapy, RBC transfusion | 100 |
| Phung 2018 (52) | Retrospective cohort | 27 | Rh(D) | IUT, neonatal exchange transfusion, phototherapy, RBC transfusion, delayed cord clamping | 78.6 |
| Raguz 2020 (26) | Retrospective cohort | 59 | Rh(D) | Exchange transfusion, phototherapy | 100 |
| | | 5 | K | Exchange transfusion, phototherapy | 100 |
| Rath 2011 (54) | Retrospective cohort | 157 | Rh(D) | IUT, neonatal exchange transfusion, RBC transfusion, phototherapy | 98 |
| | | 34 | K | IUT, neonatal exchange transfusion, RBC transfusion, phototherapy | 91 |
| Rath 2013 (55)b | Retrospective cohort | 103 | Rh(D) | Maternal IVIG, IUT, neonatal exchange transfusion, phototherapy, RBC transfusion | 98 |
| Ree 2020b (57) | Retrospective cohort | 189 | Rh(D) | Maternal IVIG, IUT, neonatal exchange transfusion, phototherapy, RBC transfusion | 100 |
| | | 46 | K | Maternal IVIG, IUT, phototherapy, RBC transfusion | 100 |
| Ruma 2007 (58) | Case series | 9 | Rh(D) & K | IVIG, IUT, phototherapy, RBC transfusion | 22 |

| Citation | Study design | Population | Rh(D) or K | Treatment type | Treatment (%) |
|---|---|---|---|---|---|
| Santos 2013 (60) | RCT | 46 | Rh(D) | IUT, neonatal IVIG, neonatal exchange transfusion, phototherapy | 100 |
| | | 46 | Rh(D) | IUT, neonatal exchange transfusion, phototherapy | 100 |
| Temel Yuksel 2019 (63) | Prospective cohort | 17 | Rh(D) | IUT, phototherapy | 100 |
| **Exchange transfusion** | | | | | |
| Azavkli 2020 (61) | Retrospective cohort | 42 | Rh(D) | IUT, phototherapy, RBC transfusion | 58.8 |
| Bennardello 2013 (29) | Questionnaire | 111 | Rh(D) | Maternal IVIG, IUT | 28.8 |
| Bi 2019 (30) | Prospective cohort | 5 | Rh(D) | Neonatal exchange transfusion only | 100 |
| Gottvall 2008 (35) | Retrospective cohort | 71 | Rh(D) | Maternal plasma exchange and/or high-dose IVIG, neonatal exchange transfusion, phototherapy | 19.6 |
| Gudlaugson 2020 | Retrospective cohort | 85 | Rh(D) | Exchange transfusion only | 100 |
| Karagol 2012 (40) | Retrospective cohort | 5 | K | IVIG, exchange transfusion, phototherapy | 80 |
| Lieberman 2020 (44) | Retrospective cohort | 18 | Rh(D) | Neonatal IVIG, neonatal exchange transfusion, phototherapy, RBC transfusion | 6 |
| | | 2 | K | Neonatal IVIG, phototherapy, RBC transfusion | 0 |
| Matijevic 2005 (46) | Retrospective cohort | 16 | Rh(D) & Kell | IUT, exchange transfusion, phototherapy | 62.5 |
| Meraj 2015 (48) | Retrospective cohort | 5 | Rh(D) | Exchange transfusion, phototherapy, RBC transfusion | 20 |
| Phung 2018 (52) | Retrospective cohort | 27 | Rh(D) | IUT, neonatal exchange transfusion, phototherapy, RBC transfusion, delayed cord clamping | 42.9 |
| Raguz 2020 (26) | Retrospective cohort | 59 | Rh(D) | Exchange transfusion, phototherapy | 26 |
| | | 5 | K | Exchange transfusion, phototherapy | 20 |
| Rath 2011 (54) | Retrospective cohort | 157 | Rh(D) | IUT, neonatal exchange transfusion, RBC transfusion, phototherapy | 6 |
| | | 34 | K | IUT, neonatal exchange transfusion, RBC transfusion, phototherapy | 62 |

| Citation | Study design | Population | Rh(D) or K | Treatment type | Treatment (%) |
|---|---|---|---|---|---|
| Rath 2013 (55)b | Retrospective cohort | 103 | Rh(D) | Maternal IVIG, IUT, neonatal exchange transfusion, phototherapy, RBC transfusion | 53.4 |
| Ree 2019 (56) | Retrospective cohort | 148 | Rh(D) | IUT, RBC transfusion | 20 |
| | | 76 | Rh(D) | RBC transfusion | 18 |
| Ree 2020b (57) | Retrospective cohort | 189 | Rh(D) | Maternal IVIG, IUT, neonatal exchange transfusion, phototherapy, RBC transfusion | 26.5 |
| | | 46 | K | Maternal IVIG, IUT, phototherapy | 0 |
| Santos 2013 (60) | RCT | 46 | Rh(D) | IUT, neonatal IVIG, neonatal exchange transfusion, phototherapy | 13 |
| | | 46 | Rh(D) | IUT, neonatal exchange transfusion, phototherapy | 15.2 |
| Takci 2013 (16) | Retrospective cohort | 30 | Rh(D) and K | IUT, neonatal exchange transfusion, RBC transfusion, parenteral nutrition, oral ursodeoxycholic acid (phenobarbital), oral erythromycin | 90 |
| Temel Yuksel 2019 (63) | Prospective cohort | 17 | Rh(D) | IUT, phototherapy | 41.1 |
| **RBC transfusion** | | | | | |
| Azavkli 2020 (61) | Retrospective cohort | 42 | Rh(D) | IUT, phototherapy, RBC transfusion | 73.5 |
| Lieberman 2020 (44) | Retrospective cohort | 18 | Rh(D) | Neonatal IVIG, exchange transfusion, phototherapy, RBC transfusion | 17 |
| | | 2 | K | Neonatal IVIG, phototherapy, RBC transfusion | 50 |
| Meraj 2015 (48) | Retrospective cohort | 5 | Rh(D) | Exchange transfusion, phototherapy, RBC transfusion | 60 |
| Phung 2018 (52) | Retrospective cohort | 27 | Rh(D) | IUT, neonatal exchange transfusion, phototherapy, RBC transfusion, delayed cord clamping | 67.9 |
| Rath 2011 (54) | Retrospective cohort | 157 | Rh(D) | IUT, neonatal exchange transfusion, RBC transfusion, phototherapy | 62 |
| | | 34 | K | IUT, neonatal exchange transfusion, RBC transfusion, phototherapy | 72 |
| Rath 2013 (55)b | Retrospective cohort | 103 | Rh(D) | Maternal IVIG, IUT, neonatal exchange transfusion, phototherapy, RBC transfusion | 78 |
| Ree 2019 (56) | Retrospective cohort | 148 | Rh(D) | IUT, RBC transfusion | 20 |
| | | 76 | Rh(D) | RBC transfusion | 18 |

| Citation | Study design | Population | Rh(D) or K | Treatment type | Treatment (%) |
|---|---|---|---|---|---|
| Ree 2020b (57) | Retrospective cohort | 189 | Rh(D) | Maternal IVIG, IUT, neonatal exchange transfusion, phototherapy, RBC transfusion | 26.5 |
| | | 46 | K | Maternal IVIG, IUT, phototherapy, RBC transfusion | 71.7 |
| Ruma 2007 (58) | Case series | 9 | Rh(D) & K | IVIG + IUT, phototherapy, RBC transfusion | 56 |
| Takci 2013 (16) | Retrospective cohort | 30 | Rh(D) & K | IUT, neonatal exchange transfusion, RBC transfusion, parenteral nutrition, oral ursodeoxycholic acid (phenobarbital), oral erythromycin | 73.3 |
| **Neonatal IVIG** | | | | | |
| Lieberman 2020 (44) | Retrospective cohort | 18 | Rh(D) | Neonatal IVIG, exchange transfusion, phototherapy, RBC transfusion | 28 |
| | | 2 | K | Neonatal IVIG, phototherapy, RBC transfusion | 50 |
| | | 46 | Rh(D) | IUT, neonatal exchange transfusion, phototherapy | 0 |
| **Other treatments** | | | | | |
| Brumbaugh 2011 (31) | Case report | 1 | K | Neonatal IVIG, platelet, plasma, and cryoprecipitate transfusion, chelation therapy | 100 |
| Chatziantoniou 2017 (32) | Retrospective cohort | 22 | Rh(D) | IUT + exchange transfusion + phototherapy + IVIG | 4.5 |
| | | | | Exchange transfusion + phototherapy + IVIG | 13.6 |
| | | | | Phototherapy + IVIG | 31.8 |
| Karagol 2012 (40) | Retrospective cohort | 5 | K | IVIG, exchange transfusion, phototherapy | 20 |
| Levy-Zauberman 2011 (43) | Case report | 1 | Rh(D) | IUT, phototherapy, platelets, frozen plasma transfusion | 100 |
| Manoura 2007 (45) | Case report | 1 | K | Recombinant erythropoietin and oral iron supplement | 100 |
| Takci 2013 (16) | Retrospective cohort | 30 | Rh(D) & K | IUT, neonatal exchange transfusion, RBC transfusion, parenteral nutrition, oral ursodeoxycholic acid (phenobarbital), oral erythromycin | 40 |

HDFN, hemolytic disease of the fetus and newborn; IQR, interquartile range; IUT, intrauterine transfusion; IVIG, intravenous immunoglobulin; RBC, red blood cell; RCT, randomized controlled trial; Rh(D), Rhesus factor D; SD, standard deviation.

**Supplementary Table 4.** Delayed-onset Anemia, Hyperbilirubinemia, Neurodevelopmental Outcomes, and Adverse Events Reported in Studies With Representative Data

| Citation | Study design | Patient group | N | Treatment (%) | Events (%) |
|---|---|---|---|---|---|
| **Delayed onset anemia** | | | | | |
| Ree 2019 (56) | Retrospective cohort | Infants, K-mediated HDFN | 39 | IUT (90), exchange transfusion (72) | 72 |
| **Hyperbilirubinemia** | | | | | |
| Meraj 2015 (48) | Retrospective cohort | Neonates, Rh(D)-mediated HDFN | 5 | Neonatal exchange transfusion (20), phototherapy (100), RBC transfusion (60) | 100 |
| **Adverse events** | | | | | |
| Bi 2019 (30) | Prospective cohort | Neonates, Rh(D)-mediated HDFN | 5 | Exchange therapy (100) | No adverse events reported |
| de Assunção 2016 (33) | Prospective cohort | Neonates, Rh(D)-mediated HDFN | 13 | IUT (100) | Kernicterus (7.7)<br>Pulmonary hypertension (7.7)<br>RDS (7.7)<br>BPD (7.7)<br>Sepsis (15.4) |
| Takci 2013 (16) | Retrospective cohort | Neonates, Rh(D)-mediated HDFN | 30 | IUT (76.7), exchange therapy (90), RBC transfusion (73.3), parenteral nutrition (40) | Sepsis (13.3) |
| Temel Yuksel 2019 (63) | Prospective cohort | Neonates, Rh(D)-mediated HDFN | 17 | IUT (100), exchange therapy (41.1), phototherapy (100) | Respiratory distress (17.6)<br>Cord pH <7.2 (11.7)<br>NICU admission (70.5) |

| Citation | Study design | Patient group | N | Treatment (%) | Events (%) |
|---|---|---|---|---|---|
| **Neurodevelopmental outcomes** | | | | | |
| Harper 2006 (38) | Gestational age at first IUT (weeks) | Hemoglobin at first IUT (g/dL) | Total no. IUTs | Age at neurodevelopmental assessment (years) | Result of neurodevelopmental assessment |
| Case #3: Rh(D) | 22.0 | 3.3 | 5 | 12.4 | Static encephalopathy and cerebral palsy. Bilateral lower extremity paresis and atrophy, dystonic posturing of the right hand, and monocular esotropia |
| Case #7: K | 22.0 | 1.8 | 7 | 9.5 | No reported abnormalities |
| Case #10: Rh(D) | 23.5 | 2.7 | 6 | 6.2 | No reported abnormalities |
| Case #13: K | 23.5 | 2.7 | 6 | 6.2 | No reported abnormalities |
| Case #15: Rh(D) | 23.4 | 4.0 | 5 | 4.7 | No reported abnormalities |
| Levy-Zauberman 2011 (43) | | | | | |
| Rh(D) | 21.7 | 2.5 | 4 | 1.5 | No clinically detectable motor or cognitive impairment |
| Simonazzi 2016 (62) | | | | | |
| Case 2: Rh(D) | 23 | 1.6 | 6 | 12.0 | No reported abnormalities |
| Case 3: Rh(D) | 16 (intraperitoneal)<br>21 (intravascular) | 2.6 | 4 intraperitoneal<br>5 intravascular | 2.0 | Neurodevelopment delay, in particular truncal ataxia |

BPD, bronchopulmonary dysplasia; HDFN, hemolytic disease of the fetus and newborn; IUT, intrauterine transfusion; IVIG, intravenous immunoglobulin; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; RBC, red blood cell; RDS, respiratory distress syndrome; Rh(D), Rhesus factor D.

**Supplementary Table 5**. Overall Neonatal Mortality Associated With HDFN

| Citation | Study design | Patient group | N | Treatment (%) | Mortality rate (%) |
|---|---|---|---|---|---|
| Azavkli 2020 (61) | Retrospective cohort | Neonates, Rh(D)-mediated HDFN | 42 | IUT (100), phototherapy (100), exchange transfusion (58.8) | 4.8 |
| Chatziantoniou 2017 (32) | Retrospective cohort | Neonate, Rh(D)-mediated HDFN | 1 | No treatment | 0 |
| | | Neonates, Rh(D)-mediated HDFN | 22 | IUT + exchange transfusion + phototherapy + IVIG (4.5) Exchange transfusion + phototherapy + IVIG (3.6) Phototherapy + IVIG (31.8) | 0 |
| Gotvall 2008 (35) | Retrospective cohort | Neonates, Rh(D)-mediated HDFN | 71 | Exchange transfusion (29.5), phototherapy (15.5) | 0 |
| Gudlaugsson 2020 (36) | Retrospective cohort | Neonates, Rh(D)-mediated HDFN | 135 | Exchange transfusion (96), no treatment (4) | 2.2 |
| Lieberman 2020 (44) | Retrospective cohort | Neonates, Rh(D)-mediated HDFN | 18 | Neonatal IVIG (28), neonatal exchange transfusion (6), phototherapy (67), RBC transfusion (17) | 0 |
| | | Neonates, K-mediated HDFN | 2 | Neonatal IVIG (50), phototherapy (50), RBC transfusion (50) | 0 |
| Ree 2020a (20) | Retrospective cohort | Neonate, Rh(D)-mediated HDFN | 1 | IUT, neonatal exchange transfusion, RBC transfusion | 0 |
| | | Neonate, Rh(D)-mediated HDFN | 1 | IUT, RBC transfusion | 0 |
| | | Neonate, K-mediated HDFN | 1 | IUT, neonatal IVIG | 100 |
| Sainio 2015 (59) | Retrospective cohort | Neonates, Rh(D)-mediated HDFN | 86 | IUT (100) | 1.2 |
| Takci 2013 (16) | Retrospective cohort | Hydropic infants, Rh(D)-mediated HDFN | 30 | IUT (76.7), neonatal exchange transfusion (90%), RBC transfusion (73.3), parenteral nutrition (40), oral ursodeoxycholic acid (± phenobarbital) (10), oral erythromycin (3.3) | 50 |
| Temel Yuksel 2019 (63) | Prospective cohort | Neonates, Rh(D)-mediated HDFN | 17 | IUT (100), neonatal exchange transfusion (41.1), phototherapy (100) | 5.8 |
| Walsh 2013 (65) | Retrospective cohort | Neonates, K-mediated HDFN | 11 | IUT (100) | 0 |
| Hassan 2019 (39) | Case report | Neonate, Rh(D)-mediated HDFN | 1 | Neonatal IVIG, RBC transfusion | 100 |

HDFN, hemolytic disease of the fetus and newborn; IUT, intrauterine transfusion; IVIG, intravenous immunoglobulin; RBC, red blood cell; Rh(D), Rhesus factor D

**Supplementary Table 6.** Overall methodological quality score, defined per study

| Citation | Overall methodological quality score |
|---|---|
| **Case reports assessed with JBI Critical Appraisal Checklist for Case Reports** | |
| Akdag 2012 (27) | 7/8 |
| Bek 2019 (28) | 7/8 |
| Brumbaugh 2011 (31) | 8/8 |
| Colpo 2017 (33) | 8/8 |
| Haider 2020 (37) | 6/8 |
| Hassan 2019 (39) | 5/8 |
| Lakhwani 2011 (42) | 8/8 |
| Levy-Zauberman 2011 (43) | 8/8 |
| Manoura 2007 (45) | 3/8 |
| Palfi 2006 (51) | 8/8 |
| Rahimi-Sharbaf 2007 (53) | 4/8 |
| Xu 2013 (66) | 8/8 |
| **Case series assessed with JBI Critical Appraisal Checklist for Case Series** | |
| Kriplani 2007 (41) | 5/9 |
| Mayer 2018 (47) | 4/9 |
| Navarro 2009 (49) | 5/9 |
| Nwogu 2018 (50) | 8/9 |
| Ruma 2007 (58) | 10/10 |
| Simonazzi 2016 (62) | 5/9 |
| **Retrospective Cohort Studies assessed using the Newcastle-Ottawa Scale** | |
| Åžavkli 2020 (61) | Good (8) |
| Chatziantoniou 2017 (32) | Good (8) |
| Gottvall 2008 (35) | Good (8) |
| Gudlaugsson 2020 (36) | Good (8) |
| Karagol 2012 (40) | Good (8) |
| Lieberman 2020 (44) | Good (8) |
| Matijevic 2005 (46) | Fair (6) |
| Meraj 2015 (48) | Fair (6) |
| Phung 2018 (52) | Fair (7) |
| Raguz 2020 (26) | Fair (7) |
| Rath 2013 (55)b | Good (8) |
| Ree 2019 (56) | Good (8) |
| Ree 2020a (20) | Good (8) |
| Ree 2020b (57) | Good (8) |

| Citation | Overall methodological quality score |
|---|---|
| Sainio 2015 (59) | Good (8) |
| Takci 2013 (16) | Fair (7) |
| Tiblad 2011 (64) | Good (8) |
| Walsh 2013 (65) | Good (8) |
| Rath 2011 (54) | Good (8) |
| **Prospective Cohort Studies assessed using the Newcastle-Ottawa Scale** | |
| Bi 2019 (30) | Good (7) |
| de Assunção 2016 (33) | Good (8) |
| Temel 2019 | Good (8) |
| Harper 2006 (38) | Good (8) |
| **Questionnaire study assessed using the CHERRIES-checklist** | |
| Bennardello 2013 (29) | Good |