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Off-Label Use of Intravenous Immunoglobulin for Hematological Conditions: A Review of Clinical Effectiveness

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Context and Policy Issues

Hemolytic disease of the fetus and neonate (HDFN) and fetal and neonatal alloimmune thrombocytopenia (FNAIT) are examples of hematological conditions related to complications of pregnancy.[1] HDFN is diagnosed when a pregnant person's antibodies attack fetal erythrocytes causing hemolysis, severe jaundice, anemia, hyperbilirubinemia, or hepatosplenomegaly in their fetus or neonate.[1] Severe HDFN has been linked to rhesus incompatibility between a pregnant person and their fetus.[2] Rhesus incompatibility or sensitization occurs when Rh(D)-positive fetal cells induce an antibody response from a pregnant person whose blood type is Rh(D)-antigen negative.[1] Similarly, FNAIT occurs when a pregnant person becomes alloimmunized to their fetal platelets.[3] There remains some uncertainty around the mechanism of maternal-fetal alloimmunization.[4] It has been suggested that the immunizing antigen enters the maternal blood stream from the fetus through the placenta.[4] Maternal antibodies then cross the placenta into the fetus' blood stream, binding to fetal platelets which are then removed from circulation by the reticuloendothelial system, causing severe fetal thrombocytopenia.[1,4] Alloimmunization leads to a reduction in platelets which, in turn, puts fetuses and neonates at risk of intracranial hemorrhage, neurologic impairment and death.[3,4] Although some cases are identified antenatally, FNAIT is typically diagnosed after birth.[3,4] Prevalence of FNAIT in Caucasian populations is reported between 1 in 1000 and 1 in 1500 live births.[4]

The conventional treatment for HDFN consists mainly of treating neonates with intensive phototherapy or exchange transfusions (ETs).[5] Phototherapy reduces bilirubin levels and transfusions work by removing bilirubin and hemolytic antibodies.[6] Severe cases are treated with top-up red blood cell transfusion.[5] Treatment for FNAIT includes intrauterine platelet transfusion (IUPT) for fetuses or direct platelet transfusions for neonates; both counteract the decrease in platelets caused by alloimmunization of the pregnant person.[1] Corticosteroid therapy may also be used to decrease hemolysis, however there is uncertainty regarding dosage and severity of side effects.[1] Intravenous immunoglobulin (IVIG) has increasingly been considered for or used off-label for HDFN and FNAIT.

Immunoglobulin (also referred to as immune globulin or gamma globulin) is a purified blood product pooled from the plasma of healthy blood donors.[7] Immunoglobulin may be administered as IVIG or as subcutaneous immunoglobulin (SCIG). In Canada, various preparations of immunoglobulin are approved specifically for use in patients with one or more of the following six conditions: primary immune deficiency, immune thrombocytopenic purpura, secondary immune deficiency states, chronic inflammatory demyelinating polyneuropathy, Guillain-Barré Syndrome, and multifocal motor neuropathy.[8] The products approved for use are ANTHRASIL, Flebogamma, Octagam, Cutaquig (subcutaneous), and WinRho SDF.[8,9] Others approved for marketing are Atgam, Cytogam, Gammagard, Gamunex, Hepagam B, Igivnex, Panzyga, Privigen, and Varizig.[9]

Although IVIG has the potential to reduce the need for ETs, timing, dose, and effectiveness of IVIG infusions for various hematological conditions (including HDFN and FNAIT) is under debate.[2] The purpose of this report is to provide a synthesis of the available evidence on the clinical effectiveness of off-label use of IVIG for hematological conditions. This report is complementary to a 2017 CADTH Rapid Response, Summary of Abstracts report: "Off-Label Use of Intravenous Immunoglobulin for Hematological Conditions: Clinical Effectiveness."[10]

Research Question

What is the clinical effectiveness of off-label use of intravenous or subcutaneous immunoglobulin for the treatment of hematological conditions?

Key Findings

Four studies met the inclusion criteria for this report. One systematic review reported on patients with fetal and neonatal alloimmune thrombocytopenia (FNAIT) and one systematic review, one randomized controlled study (RCT) and one non-randomized study included patients with hemolytic disease of the fetus and neonate (HDFN). The studies compared intravenous immunoglobulin (IVIG) with or without corticosteroids to no treatment, placebo, or a combination of corticosteroids, phototherapy, exchange transfusion (ET), fetal blood sampling, and intrauterine platelet transfusion (IUPT). The results of this report must be interpreted with caution given the heterogeneity observed among the included studies, as well as some limitations in study quality.

Overall, the evidence on the effectiveness of off-label use of IVIG for hematological conditions was mixed. Compared with FNAIT patients who were treated with corticosteroids or IUPT, a smaller proportion of patients on IVIG had low platelet counts (i.e., $< 50 \times 10^9$ L). However, the statistical significance of the difference was not reported in each case. For patients with HDFN, IVIG reduced the need for ET relative to placebo or no treatment and the number of days with an umbilical venous catheter relative to IVIG and phototherapy with or without ET. On the other hand, IVIG alone resulted in an increase in the number of days on phototherapy, top-up red blood cell transfusions, and length of stay in hospital relative to IVIG and phototherapy with or without ET. One systematic review reported that headache and rash were the most common side effects of IVIG treatment leading to treatment being discontinued in one out of 497 patients.

No study involving subcutaneous immunoglobulin met the inclusion criteria for this report. Furthermore, this report lacks evidence on the use of IVIG for other off-label hematological conditions such as aplastic anemia, autoimmune neutropenia, hyperhemolysis after transfusion, and acquired hemophilia.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases , Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval health technology assessments, systematic reviews, and meta-analyses, randomized controlled trials, and non-randomized studies. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents published between January 1, 2012 and October 11, 2017.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed

for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients any age with hematological conditions that are not approved indications for IVIG, including but not limited to : • Acquired hemophilia • Acquired von Willebrand Disease • Alloimmune thrombocytopenia • Aplastic anemia • Autoimmune hemolytic anemia • Autoimmune neutropenia • Erythroid aplasia • Evans syndrome • Hemolytic disease of the fetus and newborn • Hemolytic uremic syndrome • Hyperhemolysis after transfusion • Low platelet counts in adult patients with HIV • Post-transfusion purpura • POEMS syndrome[a]
Intervention	Human IVIG or SCIG products, including but not limited to those available in Canada, alone or in combination with corticosteroids or other immunomodulation therapy
Comparator	Treatment as usual, placebo, no treatment
Outcomes	Clinical benefits and harms
Study Designs	Health technology assessments, systematic reviews, meta-analyses, and randomized controlled trials, non-randomized studies

IVIG = intravenous immunoglobulin; SCIG = subcutaneous immunoglobulin.

[a] POEMS syndrome refers to a rare blood disorder with signs and symptoms that include polyneuropathy, organomegaly, endocrinopathy, monoclonal plasmaproliferative disorder, and skin changes.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, or they were duplicate publications.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using the AMSTAR 2 checklist.[11] The Downs and Black checklist[12] was used for quality assessment of the randomized controlled and non-randomized studies. Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 227 citations were identified in the literature search. Following screening of titles and abstracts, 219 citations were excluded and eight potentially relevant reports from the electronic search were retrieved for full-text review. No publication was retrieved from the grey literature search. Of the eight potentially relevant articles, four publications were excluded for various reasons, while four publications, including two systematic reviews,[13,14] one randomized controlled trial (RCT),[5] and one non-randomized study[15] met the inclusion criteria for this report. Appendix 1 presents the PRISMA flowchart of the study selection.

Summary of Study Characteristics

The body of evidence identified for this report includes two systematic reviews,[13,14] one RCT,[5] and one non-randomized study.[15] The studies addressed the effectiveness of IVIG in patients at risk of or diagnosed with FNAIT,[13] and patients diagnosed with HDFN secondary to rhesus or ABO incompatibility.[5,14,15] ABO incompatibility refers to immunization of individuals with blood types, A, B, or O, to a different blood type. Study characteristics are summarized below. Details are available in Table 2 and

Table **3** of Appendix 2.

Study Design

The systematic reviews[13,14] performed comprehensive searches of two or more electronic bibliographic databases. In addition, they specified the eligibility criteria for participants, interventions, comparators, and outcomes, and assessed the quality of the included studies. One review performed searches between 1946 and December 2015,[13] while the other searched databases from 1948 to May 2018. One of the systematic reviews included 12 RCTs[14] while the other included five prospective and 17 retrospective studies along with four RCTs.[13] All included studies were relevant to the current review. The quality of the included studies was assessed using the Cochrane Collaboration's tool for assessing risk of bias in randomized studies[13,14] and the Newcastle-Ottawa Scale for nonrandomized studies.[13] One systematic review conducted a meta-analysis to synthesize data from its included studies.[14] The other review used descriptive synthesis citing considerable methodological heterogeneity of its included studies.[13] The RCT was placebo-controlled.[5] The non-randomized study involved retrospective chart reviews.[15]

Year of Publication and Country of Origin

The systematic reviews were published in 2014 by authors based in Canada[14] and in 2017 by authors in Australia, Canada, France, Germany, The Netherlands, Norway, Sweden, United Kingdom, and United States.[13] The RCT was published in 2010 and enrolled patients in The Netherlands,[5] while the non-randomized study was published in 2012 and enrolled patients in Italy.[15]

Patient Population

One systematic review included studies that enrolled at least five pregnant women with pregnancies at risk of FNAIT or fetuses/neonates at risk of or diagnosed with FNAIT.[13] The second review included studies that enrolled neonates with the diagnosis of isoimmune HDFN secondary to rhesus or ABO incompatibility, if results were presented separately.[14] The remaining studies included patients (neonates) diagnosed with isoimmune HDFN

secondary to rhesus or ABO incompatibility.[5,15] The RCT enrolled 80 neonates with HDFN and their parents and followed 66 of them for a median of four years.[5] The remaining patients were lost to follow-up due to loss of contact or parents declining to participate.[5] The authors of the non-randomized study conducted retrospective chart reviews of a historical cohort of 34 infants who received phototherapy with or without ET and an intervention cohort of 54 infants who had IVIG added to phototherapy with or without ET.[15]

Interventions and Comparators

One systematic review included studies in which the intervention was IVIG with or without corticosteroids or intrauterine platelet transfusion (IUPT)[13] and the comparators were IVIG with corticosteroids, IUPT and/or fetal blood sampling (FBS), corticosteroids alone, IUPT alone, or no treatment.[13] The second systematic review included studies in which the intervention was IVIG alone as prophylaxis or treatment for HDFN while the comparators were placebo or no treatment.[14]

The RCT compared IVIG with placebo.[5] The IVIG product and dose were not reported.[5] In the non-randomized study, patients in the intervention group received one infusion of 0.5 g/kg of Intratect IVIG in the first four hours of life.[15] A second infusion was delivered 12 hours after the first infusion if bilirubin values had not decreased. If bilirubin values did not decrease 12 hours after the second infusion, a third infusion was delivered 72 hours after the first infusion. Patients in both the intervention and comparator groups were treated with phototherapy and ETs as needed. Adjunct treatment included the use of an umbilical venous catheter, and top-up red blood cell infusions.[15]

Outcomes

The primary outcomes of interest were incidence of intracranial hemorrhage (ICH),[13] fetal/neonatal platelet count,[13] incidence of fetal/neonatal platelet count < 50 x 10^9L,[13] rate of ET,[14,15] incidence of neurodevelopmental impairment,[5] number of days of adjunct treatment,[15] and length of stay in hospital.[15] Secondary outcomes included incidence of allergies, parent-reported recurrent ear, nose and throat infections,[5] hospitalization,[5] death,[13] and other adverse events.[13,15] Adverse events included but were not limited to, necrotizing enterocolitis,[15] headache,[13] rash,[13] oligohydramnios,[13] persisting bradycardia,[15] and fetal decelerations.[13]

Determination of ICH was done using cranial ultrasound,[13] and incidence of neurodevelopmental impairment was assessed in children aged 3 to 7 with the Bayley Scales of Infant and Toddler Development (BSID-II) and the Dutch version of the Wechsler Preschool and Primary Scale of Intelligence, 3rd edition WPPSI-III.[5] Children with BSID and WPPSI scores less than 70 (i.e., less than 2 SD lower than the mean score of 100) were diagnosed with severe delay while those with test scores of 70 to 84 (i.e., less than 1 SD lower than the mean score of 100) were diagnosed with mild delay. Neurodevelopmental impairment was diagnosed in the presence of at least one of the following: cerebral palsy, severe cognitive delay, severe motor delay, bilateral deafness requiring hearing amplification, and/or bilateral blindness.[5]

Outcomes that were reported in the studies but not relevant to the research question were not included in this report.

Summary of Critical Appraisal

Detailed summaries of the critical appraisal of the included systematic reviews and other studies are provided in Appendix 3: Table 4 and

Table **5** respectively.

The systematic review on patients with FNAIT was sponsored by the Canadian Blood Society and was written by authors who owned a manufacturing company pursuing active development of a prophylaxis for FNAIT, consulted for producers of blood products and biologics, or received research funding for a study that involved screening pregnant patients.[13] The sponsorship and author affiliations may have influenced the quality of the systematic review. The organization that sponsored the report was a distributor of blood products and two of the authors were founders and owners of a company that was coordinating a consortium that was developing a prophylaxis against FNAIT at the time the study was published.[13] One author was a consultant of the sponsor.[13] One author had previously received research funding for the project "Towards Routine HPA-Screening in Pregnancy", suggesting support for screening.[13] One author was a consultant of Baxalta, Superior Biologics.[13] The organizations and some of the authors were potential beneficiaries of findings that supported additional screening for hematological conditions and the use of blood products.

The systematic review on patients with isoimmune HDFN had more strengths than limitations.[14] A comprehensive literature search was conducted and study selection and data extraction were done in triplicate. Data extraction done in triplicate should increase the reader's confidence that the authors did not miss a pivotal study and that there were no errors in data extraction. The characteristics and a quality assessment of the included studies were documented. With respect to limitations, it was unclear whether an *a priori* design was used and the likelihood of publication bias was not assessed due to the number of studies included in each outcome category. An *a priori* study design implies that the authors determined the patient population, interventions, comparators, and outcomes before embarking on the study, thereby minimizing opportunities for patient selection bias, and bias due to selective outcomes reporting. A study with an *a priori* design is expected to be more trustworthy than one whose design is not pre-determined.

The RCT involving patients with isoimmune HDFN clearly described its study objectives, eligibility criteria, intervention, comparator, and the main outcome measures.[5] The reader should have confidence in the results. Patients in both groups were recruited from the same population and appropriate statistical tests were used to assess the outcomes. Recruiting patients from the same population minimizes (but does not eliminate) the potential for pre-existing differences between the groups. With respect to limitations, the authors stated that there was no difference between the baseline characteristics and socioeconomic status of enrolled patients and patients lost to follow-up; however, they did not provide details of the similarities. This means the distribution of potential confounders such as treatment dose and duration of treatment could not be evaluated. It is also possible that patients that may have done better or worse may have dropped out at differential rates. The authors reported that 18% of patients were lost to follow-up due to loss of contact or parents declining to participate. Further detail on reasons for withdrawing from the study and whether there was differential drop out between study groups was warranted but not provided. The study did not provide sufficient information to determine whether the baseline characteristics of the patients who withdrew from the study were similar to those who remained in the study. Patients were blinded to treatment allocation suggesting that outcome evaluators may have been influenced by their knowledge of treatment allocation.

Furthermore, it is unclear whether the study was powered to detect differences between the study groups. If the study was underpowered, observed differences in outcomes may not be statistically significant.

Finally, the non-randomized study adequately described its objectives, eligibility criteria, intervention, comparator, and main outcome measures.[15] The identifiable limitations were that the patients in the comparator group were from a historical cohort and it was unclear whether all patients were representative of the source population. Patients from a historical cohort may have had characteristics that may have amplified or moderated their outcomes.

Summary of Findings

The overall findings of the review are summarized below by clinical outcome. Additional details are available in Appendix 4:

Table **6** and

Table **7**.

What is the clinical effectiveness of off-label use of intravenous or subcutaneous immunoglobulin for the treatment of hematological conditions?

Two systematic reviews,[13,14] one RCT,[5] and one non-randomized study[15] provided evidence on the off-label use of IVIG for patients with FNAIT[13] and HDFN.[5,14,15] No studies on subcutaneous immunoglobulin met the inclusion criteria. Clinical effectiveness outcome measures included incidence of intracranial hemorrhage (ICH),[13] fetal or neonatal platelet count,[13] incidence of fetal/neonatal platelet count < 50 x 10^9L,[13] rate of ET,[14,15] incidence of neurodevelopmental impairment,[5] number of days of adjunct treatment (such as phototherapy),[15] and length of stay in hospital.[15] Secondary outcomes included incidence of allergies, parent-reported recurrent ear, nose and throat infections,[5] hospitalization,[5] death,[13] and other adverse events.[13,15] Adverse events included but were not limited to, necrotizing enterocolitis,[15] headache,[13] rash,[13] oligohydramnios,[13] persisting bradycardia,[15] and fetal decelerations.[13]

Intracranial hemorrhage

Of 26 studies included in the systematic review on FNAIT, six reported on incidence of ICH after the start of treatment.[13] The impact of IVIG was unclear from these studies.

In a study of 37 high-risk pregnancies treated with either 1 or 2 g/kg IVIG with or without corticosteroids, five fetal ICHs were discovered.[13] The pregnancies were considered high risk because the patients had previously delivered babies with ICH.[13] Two grade III to IV hemorrhages (resulting in fetal death) and one grade I hemorrhage were found in a group of 19 patients who received 1 g/kg per week of IVIG and 1 mg/kg per day of prednisone.[13] There was a grade II to III perinatal hemorrhage after delivery at 24 weeks of gestation and one patient in a group of nine who received 2 g/kg per week of IVIG with 1 mg/kg per day of prednisone had a grade I hemorrhage.[13] No ICHs were found in a group of four patients who received 2 g/kg per week of IVIG only and in a group of five patients who were treated with 1 g/kg per week of IVIG only.

In a cohort of 27 pregnancies treated with 1 g/kg per week of IVIG, one fetal ICH ended in death and one resulted in neurological sequela.[13] Treatment did not have an impact on low platelet count.[13] Incidence of ICH was not reported for a group of 10 patients treated with corticosteroids only.

In a study of 73 low-risk pregnancies (i.e., none of the siblings had an ICH), two grade I subependymal hemorrhages were found in two neonates who had normal neonatal platelet counts at birth.[13] One incident followed treatment with 2 g/kg per week of IVIG and the other occurred after 1 g/kg per week of IVIG with 1 mg/kg per day of prednisone.[13]

In a cohort of 40 pregnancies, two grade I hemorrhages and one grade III hemorrhage were found in one neonate who was delivered at 28 weeks of gestation because of persisting fetal bradycardia after FBS.[13] No ICHs were discovered in 19 patients treated with IVIG and corticosteroids or with corticosteroids alone.[13]

Finally, four ICHs were found in a cohort of 40 pregnancies treated with intrauterine platelet transfusion (IUPT) with or without IVIG or corticosteroids, while none were found in seven patients treated with IVIG and/or steroids and eight patients given no treatment.[13] This study was part of a large retrospective analysis of patients with suspected FNAIT.[13]

Platelet count

The evidence provided by the systematic review on the impact of IVIG on platelet count in patients with FNAIT was mixed.[13] Comparator arms included different doses of IVIG, corticosteroids alone, IUPT alone, no treatment, IVIG and corticosteroids, IVIG and IUPT, IVIG and FBS, and IUPT and FBS.[13] The proportion of patients with low platelet count (i.e., $< 50 \times 10^9$ L) was lower in cohorts treated with IVIG compared with cohorts treated with corticosteroids or IUPT alone.[13] However, there was insufficient data to perform meta-analysis and statistical significance of the differences in platelet count were not reported.[13]

Exchange transfusion

Relative to placebo or no treatment, IVIG treatment of patients with rhesus or ABO HDNF appears to have reduced the rate of exchange transfusion (ET) in studies that were at high risk of bias.[14] Nine of twelve studies included in this systematic review were reported to be at high risk of bias due to lack of blinding of outcome evaluators.[14] A meta-analysis of nine studies suggested that there was a reduction in the rate of ET in patients with rhesus incompatibility who were treated with IVIG compared to patients who were either on placebo or not treated.[14] Sub-group analysis that excluded six studies that were at high risk of bias suggested that the difference between IVIG and placebo was not statistically significant.[14] When patients with rhesus incompatibility were given prophylactic IVIG in three high-risk studies, there was a reduction in the incidence of ET relative to no treatment.[14] Similarly, no statistically significant difference was found relative to placebo prophylaxis in three low-risk studies.[14] For patients with ABO incompatibility, IVIG treatment led to fewer ETs relative to no treatment in five studies at high risk of bias.[14] IVIG had no statistically significant impact on preterm neonates with rhesus incompatibility.[14]

The non-randomized study reported that the addition of IVIG to phototherapy and/or ET caused a statistically significant reduction in the incidence of ET (11% versus 82.3%) in newborns with rhesus hemolytic disease relative to a historical cohort of patients treated with phototherapy and ET as needed.[15]

Neurodevelopment impairment

Relative to placebo, IVIG had no statistically significant impact on the incidence of overall neurodevelopment impairment, median cognitive score, or incidence of mild cognitive delay, as reported in an RCT.[5]

Number of days of adjunct treatment and length of stay in hospital

Relative to phototherapy and ET treatment, adding IVIG increased the median number of days on phototherapy, the median number of top-up red blood cells transfusions, and the median length of stay in hospital, but reduced the median number of days with an umbilical venous catheter.[15]

Adverse events (including mortality)

One systematic review reported that headache and rash led to treatment discontinuation in one out of 497 patients who were treated with IVIG.[13] In comparison, 11% (i.e., 54) of 497 patients treated with fetal blood sampling or IUPT experienced adverse events, including but not limited to emergency caesarean section, mainly due to fetal distress (persisting bradycardia or fetal decelerations).[13] One patient who was treated with dexamethasone experienced oligohydramnios.[13]

Relative to placebo, IVIG did not have a statistically significant impact on the incidence of allergies or recurrent ear, nose, and throat infections in neonates.[5] Two necrotizing enterocolitis cases were reported in a group of 54 neonates with rhesus hemolytic disease who had IVIG added to their treatment of phototherapy with or without ET.[15] None were reported in the comparator group of 34 neonates who were treated with phototherapy with or without ET.[15]

Across 821 pregnancies in 24 studies, the overall fetal or neonatal mortality rate was 4% with 17 mortalities resulting from fetal blood sampling or intrauterine platelet transfusion, seven from ICHs, and six from unknown causes.[13] Two other fetal or neonatal deaths unrelated to treatment were reported in this systematic review.[13]

Limitations

The evidence on the use of IVIG for hematological conditions has some limitations stemming primarily from the heterogeneity in study designs. First, patients were enrolled between 1988 and 2015 covering periods with different treatment standards and with different risk profiles. Second, comparators ranged from phototherapy and exchange transfusion,[15] corticosteroids, intrauterine platelet transfusion, fetal blood sampling,[13] through to placebo or no treatment.[14] The variety of comparators makes it difficult to quantitatively synthesize results across the studies. Third, the outcomes of interest varied widely from incidence of exchange transfusion to neurodevelopmental impairment. These outcomes require diverse measures and methods of assessments, such as quantitative laboratory tests on one end of the spectrum to qualitative evaluations of cognitive skills. Fourth, the follow up times for observing the outcomes of interest were not specified in three of the four included studies.[13-15] The heterogeneity in the risk profiles of the included populations, comparators, and outcomes makes it challenging to draw firm conclusions on the effectiveness of the off-label use of IVIG for hematological conditions. As such, the results of this report must be interpreted with caution.

Specific to the systematic review on FNAIT, some patients were at a high risk of developing ICH given that they had at least one sibling with a history of ICH while others were at low risk.[13] The number of comparators (corticosteroids, IUPT, and FBS, alone or in combination) that were spread across 26 studies meant the authors had to perform a narrative review rather than a meta-analysis.[13] For neonates with HDFN, there were fewer comparators but each study reported on a unique set of outcomes (other than ET). One systematic review,[14] one RCT,[5] and one non-randomized study[15] compared outcomes in

patients treated with IVIG to patients treated with phototherapy and ET,[15] or patients who were given placebo or no treatment.[5,14]

Conclusions and Implications for Decision or Policy Making

The current review summarized the results of two systematic reviews (including one meta-analysis),[13,14] one RCT,[5] and one non-randomized study.[15]

Available evidence from one systematic review suggested that compared with patients who were treated with corticosteroids or IUPT, a smaller proportion of patients on IVIG had low platelet count (i.e., < 50 x 10^9 L).[13] This review also reported that headache and rash were the most common side effects of IVIG treatment leading to treatment being discontinued in one patient out of 497. The most common side effect of dexamethasone (corticosteroid) was oligohydramnios.[13] A second systematic review reported that, relative to placebo or no treatment, IVIG appears to have decreased the need for ET in patients with rhesus or ABO HDFN.[14] However, the effect was not considered statistically significant when studies with high risk of bias were excluded from analysis.[14] Relative to placebo alone, IVIG prophylaxis had no statistically significant impact on the incidence of overall neurodevelopment impairment, median cognitive score, incidence of mild cognitive delay, incidence of allergies, or incidence of recurrent ear, nose, and throat infections in HDFN patients at ages two through seven years in one RCT.[5] According to results from a non-randomized study, a statistically significant reduction in the need for ET and the median number of days with an umbilical venous catheter was observed in neonates with rhesus HDFN who had IVIG added to their treatment relative to neonates on phototherapy with or without ET.[15] This study also suggested that adding IVIG to a regimen of phototherapy and ET increased the median number of days on phototherapy, the median number of top-up red blood cells transfusions, and the median length of stay in hospital, but reduced the median number of days with an umbilical venous catheter.[15] Two necrotizing enterocolitis cases were reported in a group of 54 that had IVIG added to their treatment.[15] None of the patients in the comparator group of 34 treated with phototherapy with or without ET had necrotizing enterocolitis.[15]

There are some limitations to the body of evidence worth highlighting. It is unclear to what extent author affiliations may have influenced the quality of the systematic review on patients with FNAIT. The systematic review on patients with HDFN was comprehensive and included a quality assessment of its included studies. However, it was unclear whether an *a priori* design was used and the likelihood of publication bias was not assessed due to the number of studies included in each outcome category. Critical details regarding characteristics of patients who were lost to follow up were missing from the RCT. This means the distribution of potential confounders such as treatment dose and duration of treatment could not be evaluated. The comparator group of patients in the non-randomized study was from a historical cohort and it was unclear whether all patients were representative of the source population.

No evidence on the use of subcutaneous immunoglobulin and on the use of IVIG for other hematological conditions such as aplastic anemia, autoimmune neutropenia, hyperhemolysis after transfusion, and acquired hemophilia was identified and thus no conclusions regarding efficacy or adverse events can be made. Further high quality randomized trials are required to produce evidence to support the use of IVIG in treating Canadian patients with hematological conditions.

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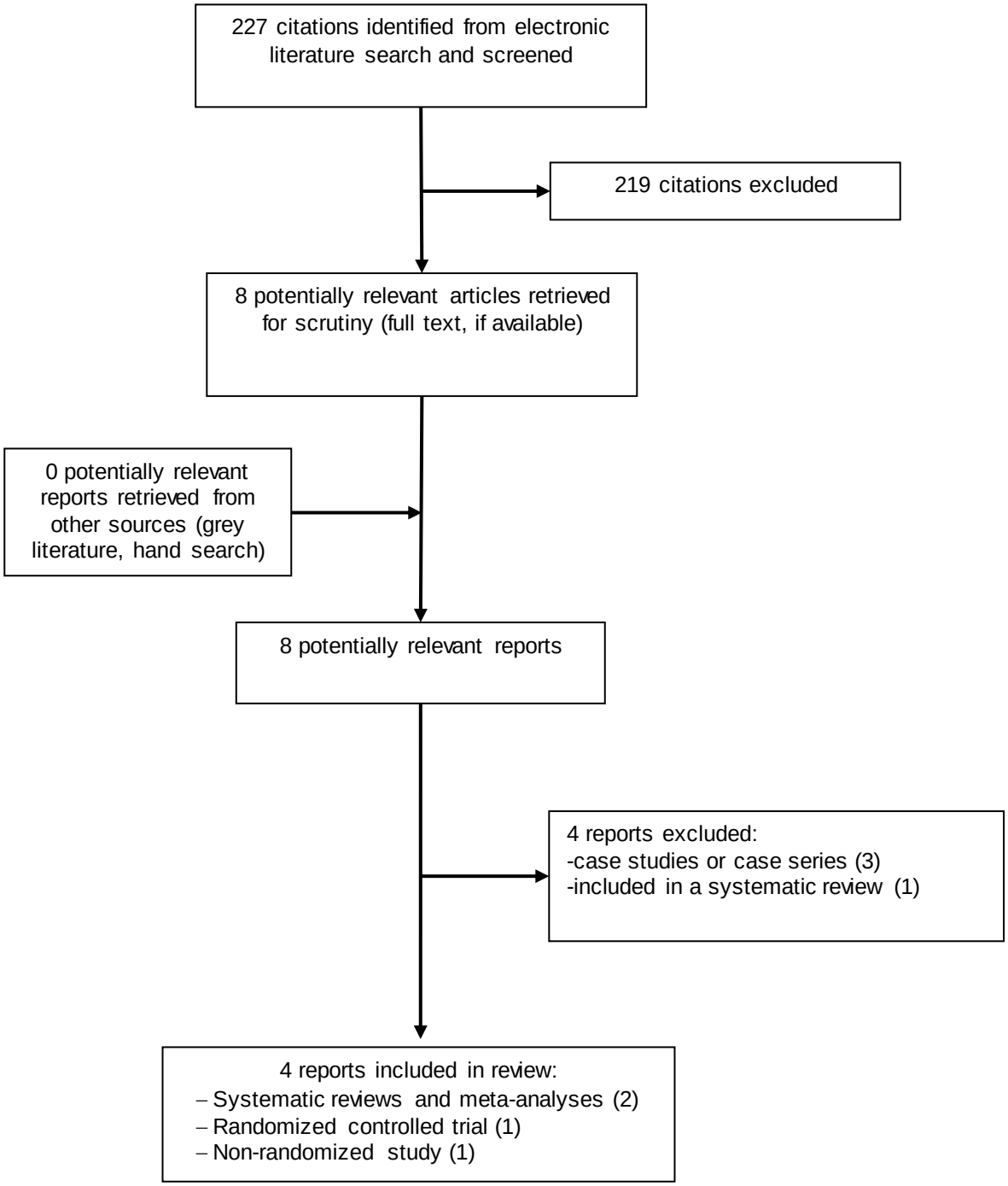
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-analyses

First Author Year Country	Search Dates and Sources	Number and Types of Included Studies	Eligibility Criteria	Intervention/ Comparison groups	Reported Clinical Outcomes	Evidence Synthesis and Analytical Methods
Winkelhorst, 2017[13] Authors were from multiple countries	Medline, EMBASE, and Cochrane Library databases from 1946 to December 2015). Reference lists were cross-checked for relevant citations	4 RCTs, 5 prospective, and 17 retrospective studies n = 839	Inclusion criteria: Original studies included ≥ 5 pregnant women with pregnancies at risk of FNAIT or fetuses/neonates diagnosed with FNAIT Exclusion criteria: None reported.	Intervention: IVIG alone, IVIG with corticosteroids or IUPT Comparator(s): IVIG alone, IVIG with corticosteroids, IUPT and/or FBS, corticosteroids alone, IUPT alone, no tx	ICH, fetal/neonatal platelet count, adverse events, fetal or neonatal mortality rate	Descriptive analysis
Louis, 2014[14] Canada	Medline (1948–May 2013), EMBASE (1980–May 2013), and Cochrane Central Register of Controlled Trials (May 2013 Issue of the Cochrane Library)	12 RCTs n = 426	Inclusion criteria: Neonates with the diagnosis of isoimmune HDFN secondary to rhesus or ABO incompatibility, if results were presented separately Exclusion criteria: Neonates who had isolated minor group incompatibility	Intervention: IVIG as prophylaxis or tx in any dose Comparator(s): Placebo or no tx	Incidence of ET following prophylaxis or tx Excluded secondary outcomes that were not relevant to this report	Meta-analysis, risk of publication bias

ET = exchange transfusion; FBS = fetal blood sampling; FNAIT = Fetal and neonatal alloimmune thrombocytopenia; HDFN = hemolytic disease of fetus and newborn; ICH = intracranial hemorrhage; IUPT = intrauterine platelet transfusion; IVIG = intravenous immunoglobulin; RCT(s) = randomized controlled trial(s); tx = treat/treatment.

Table 3: Characteristics of Included Randomized Controlled Trials and Non-randomized Studies

First Author Year Country	Study Design (follow up)	Study Population [enrollment period]	Intervention (sample size)	Comparator (sample size)	Reported Outcomes
van Klink, 2016[5] The Netherlands	RCT (4 years, range 2 to 7)	Inclusion criteria: Neonates with rhesus HDFN and their parents Exclusion criteria: NR [2006- 2010]	IVIG (prophylaxis, n = 41) Lost to f/u = 7 due to declined consent or loss of contact information	Placebo (n = 39) Lost to f/u = 7 due to declined consent or loss of contact information	Primary: Incidence of NDI using the BSID (for children aged 2-3 years) and the Dutch version of the WPPSI-III Secondary: Presence of allergies; parent-reported presence of recurrent ear, nose and throat infections; hospitalization and required surgery
Corvaglia, 2012[15] Italy	Non-randomized study. Retrospective chart reviews of historical cohort born between 1999 and 2002 and IVIG cohort born between 2005 and 2009 (Rollow-up NR)	Inclusion criteria: Infants admitted for rhesus HDFN between 1999 and 2002 (historical cohort) and between 2005 and 2009; presence of rhesus isoimmunisation identified with positive direct antiglobulin test and/or one or more intrauterine transfusions. Exclusion criteria: NR [1999-2002, 2005-2009]	IVIG (0.5 g/kg of Intratect, n = 54) plus phototherapy and ET (as needed) Lost to f/u = 0	Phototherapy and ET (as needed) (n = 34) Lost to f/u = 0	Primary: Incidence of ET; number of days on: phototherapy, with an umbilical venous catheter; number of top-up red blood cells infusions; length of hospital stay Secondary: Adverse events

BSID = Bayley Scales of Infant and Toddler Development; ET = exchange transfusion; f/u = follow-up; HDFN = hemolytic disease of the fetus and neonate; IgG = immunoglobulin-G; IVIG = intravenous immunoglobulin; NDI = neurodevelopmental impairment; NR = not reported; RCT(s) = randomized controlled trial(s); WPPSI = Wechsler Preschool and Primary Scale of Intelligence, 3rd edition.

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Included Systematic Reviews and Meta-Analyses using the AMSTAR Checklist[11]

Strengths	Limitations
Winkelhorst, 2017[13]	
– A comprehensive literature search was performed – A list of the included studies was provided – The characteristics of the included studies were provided – The quality of the included study was assessed and documented. The results of quality appraisal were reported – A conflict of interest declaration was included – The sources of funding for the systematic review were disclosed	– It was unclear whether an "a priori" design was used – A list of the excluded studies was not provided – Study selection and data extraction were done by a single researcher – Likelihood of publication bias was not assessed – Two of the authors were founders and owners of Prophylix Pharma AS, a Norwegian biotech company coordinating the European Union–funded PROFNAIT Consortium, which was developing a prophylaxis against FNAIT at the time the study was published. One author was a consultant for Canadian Blood Services. One author had previously received research funding for the project "Towards Routine HPA-Screening in Pregnancy." One author was a consultant of Baxalta, Superior Biologics. – The review was funded by Canadian Blood Services
Louis, 2014[14]	
– A comprehensive literature search was performed – Study selection and data extraction were completed by three authors – A list of the included and excluded studies was provided – The characteristics of the included studies were provided – The quality of the included study was assessed and documented. The results of quality appraisal were reported – The authors declared that they had no conflicts of interest	– It was unclear whether an "a priori" design was used although this was an update to a previous study – Likelihood of publication bias was not assessed

Table 5: Strengths and Limitations of Included Randomized Controlled Trials and Non-randomized studies using the Downs and Black Checklist[12]

Strengths	Limitations
van Klink, 2016[5]	
– Objectives of the study were described – The eligibility criteria, intervention, and comparator were described – All study participants were recruited from the same population, using the same inclusion criteria, and over the same period – Study participants were randomized to intervention groups – Although they were not described, there was no difference between the baseline characteristics and socioeconomic status of enrolled patients and patients lost to follow-up – Participants (i.e. parents of patients) were blinded to treatment allocations – The main findings, adverse events, and their probability values were clearly described	– It is unclear whether the participants were representative of the source population – Researchers were not blind to treatment allocations – 18% of the study participants were lost to follow-up – Characteristics of the study participants who were lost to follow-up were not described separately – The distributions of principal confounders in each comparison group were not described – Sample size for statistical power was not calculated – Estimates of random variability were not provided
Corvaglia, 2012[15]	
– Objectives of the study were described – The eligibility criteria, intervention, and comparator were described – The distribution of one principal confounder (i.e., high-risk bilirubin) was described – The main findings, adverse events, and their probability values were clearly described – Estimates of random variability were provided	– It is unclear whether the participants were representative of the source population – Patients in the comparator group were from a historical cohort who were treated at least two years before patients in the intervention group

Appendix 4: Main Study Findings and Author's Conclusions

Table 6: Summary of Findings of Included Systematic reviews and Meta-analyses

Main Study Findings	Author's Conclusion
Winkelhorst, 2017[13]	
A subset of results from 26 studies pertaining to outcomes relevant to this review are presented in this table **ICH (25 studies, n = 839)** Overall: 2.9% (24/839). The differences in occurrence of ICHs between various study arms were not significant Fetal ICH In a high-risk population (all siblings suffered from an ICH) of 37 pregnancies IVIG (1 g/kg/week) and corticosteroids (n = 19): 2 grade III-IV hemorrhages resulting in fetal demise and 1 grade I hemorrhage IVIG (2 g/kg/week) and corticosteroids (n = 9) or IVIG (1 g/kg/week) (n = 5): 1 grade I hemorrhage and 1 grade II-III perinatal hemorrhage after delivery at 24 weeks' gestation IVIG (2 g/kg/week) (n = 4): None In a study of 27 pregnancies IVIG (1 g/kg/week) (n = 27): 1 ICH resulted in death and 1 ICH resulted in neurological sequela. Both patients had persistently low platelets throughout tx Corticosteroids (n = 10): NR Neonatal ICH In a low-risk population (none of the siblings had suffered an ICH) of 73 pregnancies IVIG (2 g/kg/week) (n = 37): 1 grade I subependymal hemorrhage, detected postnatally with normal neonatal platelet counts at birth (133 x 10^9 L) IVIG (1 g/kg/week) and corticosteroids (treatment started at 20 weeks) (n = 36): 1 grade I subependymal hemorrhage, detected postnatally with normal neonatal platelet counts at birth (197 x 10^9 L) In a study of 79 pregnancies IVIG (1 g/kg/week) (n = 40): 2 grade I hemorrhages and 1 grade III hemorrhage in 1 neonate delivered at 28 weeks' gestation because of persisting fetal bradycardia after FBS. IVIG and corticosteroids (n = 19): None Corticosteroids (n = 20): None Fetal or neonatal ICH (retrospective analysis) IUPT with or without IVIG or corticosteroids (n = 40): 4 IVIG and/or steroids (n = 7): None No treatment (n = 8): None	The authors suggested that *"the optimal approach is a noninvasive approach, involving weekly administration of IVIG, with or without the addition [of] corticosteroids. Regarding the optimal dose and start of the treatment, there are insufficient data to recommend a specific gestational age or a specific dose. However, the data support the treatment of high-risk pregnancies (ie, sibling suffered from an ICH) with a dose of 1 g/kg per week of IVIG, started between 12 and 20 weeks' gestation. For standard risk pregnancies (ie, no sibling suffered from an ICH), the data support starting treatment between 20 and 24 weeks' gestation and the use of IVIG at a dose of 1 g/kg per week with or without steroids."*[13] page 1546.

Table 6: Summary of Findings of Included Systematic reviews and Meta-analyses

Main Study Findings	Author's Conclusion
Proportion of patients with platelet count < 50 x 10^9 L (20 studies, n = NR) IVIG alone vs. corticosteroids alone *Study 1:* 44% vs.. 73% *Study 2:* 48% vs.. 60% IVIG alone vs. IUPT 44% vs. 100% (56% in IVIG group were high risk vs. 0% in the IUPT group) **Platelet count (20 studies, n = NR)** IVIG (0.5 g/kg/week) vs. IVIG (1 g/kg/week) 81 x 10^9L vs. 110 x 10^9 L IVIG (0.5 g/kg/week) vs. IVIG (1 g/kg/week) 104 x 10^9L vs. 63 x 10^9 L IVIG alone vs. corticosteroids alone 57 x 10^9 L vs. 64 x 10^9 L IVIG alone vs. IVIG and corticosteroids 169 x 10^9 L vs. 134 x 10^9 L 96 x 10^9 L vs. 110 x 10^9 L 68 x 10^9 L vs. 78 x 10^9 L 60 x 10^9 L vs. 146 x 10^9 L IVIG alone vs. corticosteroids alone vs. IVIG and corticosteroids 104 x 10^9 L vs. 108 x 10^9 L vs. 99 x 10^9 L (mean) 89 x 10^9 L vs. 46 x 10^9 L vs. 135 x 10^9 L (mean) IVIG alone vs. IVIG and IUPT 98 x 10^9 L vs. 182 x 10^9 L; IVIG alone improved platelet count in 4 out of 6 patients (1 high-risk pregnancy) IVIG alone vs. IUPT vs. no treatment 90 x 10^9 L vs. 47 x 10^9 L vs. 9 x 10^9 L (median) in neonates IVIG alone vs. IVIG and FBS vs. IUPT and FBS 125 x 10^9 L vs. 175 x 10^9 L vs. 145 x 10^9 L **Tx-related adverse events rate (26 studies, n = 839)** IVIG (n = NR): Headache and rash leading to discontinuing of the treatment in 1 patient FBS or IUPT: 11% (54/497) including emergency caesarean section, mainly due to fetal distress Dexamethasone (n = NR): oligohydramnios **Tx-related mortality (24 studies, n = 821)**	

Table 6: Summary of Findings of Included Systematic reviews and Meta-analyses

Main Study Findings	Author's Conclusion
Overall: 4% (30/821) following FBS or IUPT (n = 17), ICH (n = 7), and an unknown cause (n = 6)	
Louis, 2014[14]	
Rate of ET in patients with Rh incompatibility IVIG vs. no tx (6 studies, n = 236, high risk of bias) 9.5% (11/116) vs. 40.8% (49/120); RR = 0.23 (CI 0.13, 0.40); RD = −0.40 (CI −0.69, −0.11); I^2 = 0%; *P* <0.0001 These values suggest that fewer ETs were needed in patients treated with IVIG IVIG vs. placebo (3 studies, n = 190, low risk of bias) 20.4% (20/98) vs. 20.7% (19/92); RR = 0.82 (CI 0.53,1.26); RD = −0.02 (CI −0.12, 0.08); I^2 = 0%; NNT = 3 (CI 1,9) ; *P* = 0.37 These values suggest that there was no statistically significant difference in the incidence of ET Post-hoc sensitivity analysis IVIG vs. placebo or no tx (9 studies, n = 426) 14.5% (31/214) vs. 32.1% (68/212); RR = 0.43 (CI 0.25, 0.74); RD = −0.27 (CI −0.45, −0.10); I^2 = 86%; NNT = 4 (CI 2, 10); *P* = NR These values suggest that studies with high risk of bias are driving the combined estimate **Incidence of ET in patients with Rh incompatibility (prophylaxis)** IVIG prophylaxis vs. no tx (3 studies, n = 110, high risk of bias) 10.5% (6/57) vs. 49.1% (26/53); RR = 0.21 (CI 0.10, 0.45); I^2 = 0%; *P*<0.0001 These values suggest that fewer ETs were needed in patients treated with IVIG prophylaxis IVIG prophylaxis vs. placebo (3 studies, n = 190, low risk of bias) 20.4% (20/98) vs. 20.7% (19/92); RR = 0.82 (CI 0.53,1.26); I^2 = 0%; *P* = 0.73 These values suggest that there was no statistically significant difference in the incidence of ET **Incidence of ET in patients with Rh incompatibility (preterm neonates)** IVIG vs. placebo (2 studies, n = 64, low risk of bias) RR = 0.73 (CI 0.44, 1.19); I^2 = 0%; *P*<NR These values suggest that there was no statistically significant difference in the incidence of ET **Incidence of ET in patients with ABO incompatibility** IVIG vs. placebo or no tx (5 studies, n = 350, high risk of bias) 7.5% (13/174) vs. 26.1% (46/176); RR = 0.31 (CI 0.18, 0.55); RD = −0.17 (CI −0.24, −0.10); I^2 = 0%, NNT = 6 (CI 4, 10); *P*<0.0001 These values suggest that fewer ETs were needed in patients treated with IVIG	*"…among studies that had low risk of bias, IVIG was not effective in reducing the need for ET in neonates with Rh isoimmunisation. However, studies with high risk of bias identified benefit of IVIG in reducing the ET in Rh and ABO haemolytic disease."*[14] page F329.

CI = 95% confidence interval; ET = exchange transfusion; FBS = fetal blood sampling; g = gram; f/u = follow up; ICH = intracranial hemorrhage; IUPT = intrauterine platelet transfusion; IVIG = intravenous immunoglobulin; kg = kilogram; L = litre; NNT = number needed to treat; NR = not reported; RD = risk difference; Rh = rhesus; RR = risk ratio; tx = treatment; vs. = versus.

Table 7: Summary of Findings of the Included Randomized Controlled Trial

Main Study Findings	Author's Conclusion
van Klink, 2016[5]	
Lost to f/u = 18% (14/80) IVIG vs. placebo **Incidence of NDI** 3% (1/34) vs. 3% (1/32); *P* = 1.00; indicating that there was no statistically significant difference NDI in the 2 children was due to severe cognitive delay (with cognitive scores of 66 and 68). **Median cognitive score** 96 (range 68-118) vs. 97 (range 66-118); *P* = 0.79; indicating that there was no statistically significant difference **Incidence of mild cognitive delay (< -1 SD)** 18% (6/34) vs. 16% (5/32); *P* = 0.83; indicating that there was no statistically significant difference **Incidence of allergies** 12% (4/34) vs. 19% (6/32); *P* = 0.51; indicating that there was no statistically significant difference **Incidence of recurrent ear, nose and throat infections** 21% (7/34) vs. 28% (9/32); *P* = 0.48; indicating that there was no statistically significant difference None of the children had cerebral palsy, bilateral blindness or deafness. Similar results were observed in the subgroups of children after stratification for tx with or without IUT.	*"We found no differences in long-term NDI in children with rhesus HDFN treated with IVIG compared to placebo".*[5] page 212.

f/u = follow-up; IUT = intrauterine transfusion; IVIG = intravenous immunoglobulin; NDI = neurodevelopmental impairment; SD = standard deviation; tx = treatment; vs. = versus.

Table 8: Summary of Findings of the Included Non-Randomized Study

Main Study Findings	Author's Conclusion
Corvaglia, 2012[15]	
Lost to f/u = 0 IVIG plus phototherapy and ET as needed (n = 54)[a] vs. phototherapy and ET as needed (without IVIG) (n = 34) **Incidence of ET** 11% (6/54) vs. 82.3% (28/34); *P* = 0.0001; indicating a statistically significant reduction in the need for ET in patients treated with IVIG **Median (range) # days on phototherapy** 7 (2-18) vs. 4 (1-11); *P* = 0.000; indicating a statistically significant increase in the need for phototherapy in patients treated with IVIG **Median (range) # days with an umbilical venous catheter** 2 (0-12) vs. 5 (0-8); *P* = 0.001; indicating a statistically significant reduction in the need for an umbilical venous catheter in patients treated with IVIG **Median (range) length of stay in hospital** 10 (3-29) vs. 6 (3-25) *P* = 0.000; indicating a statistically significant increase in the length of stay in hospital for patients treated with IVIG **Median (range) # top-up red blood cells transfusions** 1 (0-4) vs. 0 (0-3) *P* = 0.005; indicating a statistically significant increase in the need for top-up red blood cells transfusions in patients treated with IVIG **Incidence of NEC (stage II according to Bell's criteria)** 1 at gestational age 34 weeks after 1 IVIG infusion and 1 at gestational age 37 weeks after 2 IVIG infusions **ET-related adverse events** Mild to severe thrombocytopenia: 18 (43.9%) Hypocalcaemia 8 (21.9%) (2 required IV calcium supplement) Hypomagnesaemia in 2 (4.9%) Procedure-related events (apnoeas, bradycardia, tachycardia, seizure requiring phenobarbital): 4 (9.8%) Complications related to the umbilical venous catheter: 8 (19.5%)	*"…our data support the use of IVIG as an effective alternative to ET for the treatment of rhesus haemolytic disease of the newborn."[15] page 2785.*

ET = exchange transfusion; f/u = follow-up; IV = intravenous; IVIG = intravenous immunoglobulin; NEC = necrotizing enterocolitis

[a] 2 out of 54 patients did not receive IVIG transfusions