EL USO DE INMUNOGLOBULINA INTRAVENOSA EN NEONATOS EN UN HOSPITAL UNIVERSITARIO TERCIARIO: UN ESTUDIO RETROSPECTIVO DE 11 AÑOS.

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Fundamento: La inmunoglobulina intravenosa (IVIG) se utiliza para tratar una variedad de enfermedades en la unidad de cuidados intensivos neonatales (UCIN). Aunque las auditorías han informado sobre el espectro del uso de IVIG en adultos, las indicaciones y la utilización en neonatos no han sido investigadas.

OBJETIVOS.

Los objetivos de este estudio fueron describir el patrón de uso y las indicaciones para IVIG en una UTI terciaria.

METODO

Se realizó una revisión retrospectiva de todos los recién nacidos que recibieron IgIV en la UCIN de enero de 2003 a diciembre de 2013. Los datos recogidos incluyeron características demográficas del paciente, detalles maternos prenatales, resultados de laboratorio neonatales, detalles de tratamiento, eventos adversos y resultados en pacientes.

RESULTADOS: Treinta y siete recién nacidos recibieron IVIG durante el período de 11 años. Veintitrés (67%) fueron tratados por enfermedad hemolítica del recién nacido (EH); 13 tratamientos estaban relacionados con ABO, seis estaban relacionados con anti-D y cuatro con anticuerpos clínicamente significativos. Catorce (33%) fueron tratados por causas no relacionadas con HE, incluyendo ocho para neonatos sépticos, dos para neonatos con enterocolitis necrotizante, dos para neonatos con un anticuerpo clínicamente significativo pero sin evidencia de hemólisis y dos para neonatos con glucosa 6-fosfato deshidrogenasa deficiencia. No se realizó una evaluación hemolítica consistente antes de la recepción de IVIG.

Conclusiones: Esta nueva evaluación del uso de IgIV en la UCIN reveló el espectro de la enfermedad para la cual se ordenó la IVIG. Este estudio también encontró que las pruebas diagnósticas clave necesarias para confirmar la etiología inmunológica de la ictericia idiopática no se realizan rutinariamente antes de la recepción de la IVIG. Se necesitan bases de datos relacionadas con transfusiones neonatales para llevar a cabo ensayos clínicos pragmáticos para establecer mejores guías basadas en la evidencia para la terapia IVIG en la UCIN.

CME/SAM Use of intravenous immunoglobulin in neonates at a tertiary academic hospital: a retrospective 11-year study

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BACKGROUND: Intravenous immunoglobulin (IVIG) is used to treat a variety of diseases in the neonatal intensive care unit (NICU). Although audits have reported on the spectrum of IVIG use in adults, the indications and utilization in neonates has not been investigated. The objectives of this study were to describe the usage pattern of and indications for IVIG in a tertiary care NICU.

STUDY DESIGN AND METHODS: A retrospective chart review was performed of all neonates who received IVIG in the NICU from January 2003 to December 2013. Data collected included patient demographic features, antenatal maternal details, neonatal laboratory results, treatment details, adverse events, and patient outcome.

RESULTS: Thirty-seven neonates received IVIG over the 11-year period. Twenty-three (67%) were treated for hemolytic disease of the newborn (HDN); 13 treatments were ABO related, six were anti-D related, and four were for clinically significant antibodies. Fourteen (33%) were treated for non-HDN causes, including eight for septic neonates, two for neonates with necrotizing enterocolitis, two for neonates with a clinically significant antibody but without evidence of hemolysis, and two for neonates with glucose 6-phosphate dehydrogenase deficiency. A complete hemolytic workup was not performed consistently before the receipt of IVIG.

CONCLUSIONS: This novel assessment of IVIG use in the NICU revealed the spectrum of disease for which IVIG is ordered. This study also found that key diagnostic tests needed to confirm an immune etiology for idiopathic jaundice are not performed routinely before IVIG receipt. Neonatal transfusion-related databases are needed to carry out pragmatic clinical trials to establish better evidence-based guidelines for IVIG therapy in the NICU.

Intravenous immunoglobulin (IVIG) is a fractionated blood product used to treat a wide range of diseases in neonatal intensive care units (NICUs). Its use has been associated with significant morbidity,[1] including severe hemolysis[2] and necrotizing enterocolitis (NEC).[3,4] Although experts recommend using this product to prevent severe cases of hemolytic disease of the newborn (HDN)[5-7] and neonatal alloimmune thrombocytopenia,[8] its value in other scenarios, such as sepsis, appears to be limited.[9-11] Another challenge with the use of IVIG has been the changing evidence supporting its use over time. Neonatologists need to consider both the benefits and the risks of IVIG given the limited number of research trials in neonates.

Canada is currently one of the leaders in IVIG utilization per capita around the world.[12,13] Several audits have reported high rates of inappropriate IVIG usage in adults.[14,15] Although audits related to appropriate use

ABBREVIATIONS: DAT = direct antiglobulin test; ET = exchange transfusion; G6PD = glucose 6-phosphate dehydrogenase; HDN = hemolytic disease of the newborn; IVIG = intravenous immunoglobulin; MBR = microbilirubin; NEC = necrotizing enterocolitis.

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have been performed in adults, few studies have assessed rates of appropriate utilization in neonatal patients.

The primary objective of this study was to describe the usage pattern of IVIG in a tertiary care NICU over an 11-year period, including indications for use, associated laboratory investigations, dosing, patient outcomes, and adverse events. The secondary objective was to assess the indications for IVIG use in light of the current evidence base.

MATERIALS AND METHODS

This retrospective chart review was conducted at a large tertiary NICU in Toronto, Canada. Infants who were admitted to the NICU between January 2003 and December 2013 and received at least one dose of IVIG were identified through the transfusion laboratory database and were eligible for the study. This hospital delivers approximately 4200 infants/year and supports neonates $\geq$23 weeks of age. The hospital research ethics board reviewed and approved the study.

Data collected included patient demographics, antenatal maternal details, neonatal clinical and laboratory results, treatment details, adverse events, and patient outcomes. Maternal details recorded included blood group, antenatal antibody results, serologic titers performed during pregnancy (if available), details regarding treatment at a high-risk pregnancy unit, and history of a previous pregnancy with HDN. The neonatal laboratory results collected included a complete blood count (CBC), blood group, direct antiglobulin test (DAT) results, hemolytic indices (bilirubin, reticulocyte count, lactate dehydrogenase, haptoglobin, and blood film), glucose 6-phosphate dehydrogenase (G6PD) assay, pyruvate kinase, and osmotic fragility testing results if ordered. A standard bilirubin assay for neonates at our institution reports microbilirubin (MBR) levels, which measure both direct and indirect bilirubin. The prefix "micro" bilirubin indicates that the blood sample was taken from a capillary source versus a venous source. "Bilirubin" and "MBR" are used interchangeably throughout this report.

Data regarding treatment for jaundice, including phototherapy duration, IVIG dose, and exchange transfusion (ET), were collected. Information regarding acute and delayed adverse events as well as final outcome at discharge was recorded. An acute transfusion reaction was defined as a record of a significant, unexplained change in vital signs reported by the nurse within 24 hours of a blood product administration. A delayed reaction was defined as a record of aseptic meningitis, hemolysis, or a thromboembolic event within 28 days after IVIG.

To assess whether the IVIG was ordered to avoid ET or because phototherapy was failing, surrogate markers were used. If two MBR results preceding IVIG were increasing, then it was assumed that the MBR level was rising despite phototherapy, leading to IVIG administration. If the MBR immediately before IVIG had reached the ET level, then it was assumed that IVIG was ordered to avoid an ET.

An IVIG order was assessed as being prescribed for a patient with a diagnosis of HDN, with HDN being defined by the following criteria: presence of an antibody, hyperbilirubinemia, a positive DAT, and evidence of hemolysis. Patient HDN diagnoses included the following: (1) ABO HDN—mother group O and infant group A, B, or AB; (2) anti-D HDN—mother Rh positive (D positive) and infant Rh negative (D negative); or (3) clinically significant, antibody-related HDN—mother with clinically significant red blood cell antibody and infant positive for the corresponding antigen. Evidence of hemolysis was defined by at least one of the following four criteria: (1) anemia, (2) elevated reticulocyte count, (3) spherocytosis on the blood film, or (4) elevated lactate dehydrogenase (LDH) or abnormal haptoglobin immediately before IVIG administration. See Table 1 for a complete definition of patients considered to have HDN.[16] If IVIG was not ordered for hemolysis, then the indications for IVIG use were determined by chart review. If an indication for IVIG was not explicitly stated in the medical chart, any diagnosis or clinical finding (using the discretion of a reviewer to exclude diagnoses or findings overtly unrelated to IVIG) recorded by the ordering physician immediately before an IVIG order was considered to be the primary indication for IVIG. If neither of the aforementioned were observed during review of the chart, then the indication for IVIG was considered unknown.

Statistical analysis

Categorical data were reported as frequencies and proportions, and continuous variables were reported as means with standard deviations (SDs) or medians with interquartile ranges (IQRs) if data were skewed.

RESULTS

Demographic and baseline features

Over the 11-year period, 37 infants received IVIG. Baseline demographics of these neonates and their mothers are shown in Table 2. The median gestational age of the neonates was 36 weeks (range, 23-41 weeks). Of the 37 neonates who received IVIG, the indication listed in the chart was suspected HDN in 25, sepsis in eight, and NEC in two; and two others received IVIG for reasons that could not be determined by chart review. Of the 25 patients with suspected HDN, 23 met our definition of HDN. Thirteen of those with HDN had ABO incompatibility between mother and infant, six had maternal anti-D antibodies, and four had other non-ABO antibodies (C, E, Kell, and Wr^a). The two patients who received IVIG for an "unknown reason" were later diagnosed with G6PD

TABLE 1. Patients were considered to have HDN if they met the requirements of one of the following three categories[16]

(1) ABO HDN
- Mother: Group O
- Infant: Group A, B, or AB
- Direct antiglobulin test (DAT) positive
- Elevated microbilirubin (MBR) (according to local hospital guidelines)

AND
- Evidence of hemolysis (one of the following):
  (a) Elevated reticulocyte count (>300 × 10^9/L)
  (b) Presence of spherocytes on blood film as noted by pathologist
  (c) Elevated lactate dehydrogenase (LDH) (>1200 IU/L) or depressed haptoglobin (<0.2 g/L)
  (d) Anemia[17]

(2) Anti-D HDN
- Mother: Rh negative
- Infant: Rh positive
- Presence of anti-D antibodies in maternal plasma
- DAT positive
- Elevated MBR

AND
- Evidence of hemolysis (one of the following):
  (a) Elevated reticulocyte count (> 300 × 10^9/L)
  (b) Presence of spherocytes on blood film as noted by pathologist
  (c) Elevated LDH (>1200 IU/L) or depressed haptoglobin (<0.2 g/L)
  (d) Anemia

(3) Other clinically significant antibody-related HDN
- Mother: Presence of any clinically significant RBC antibody
- Infant: Antigen positive
- Presence of antibodies in maternal plasma
- DAT positive
- Elevated MBR

AND
- Evidence of hemolysis (one of the following):
  (a) Elevated reticulocyte count (>300 × 10^9/L)
  (b) Presence of spherocytes on blood film as noted by pathologist
  (c) Elevated LDH (>1200 IU/L) or depressed haptoglobin (<0.2 g/L)
  (d) Anemia

TABLE 2. Infant and maternal demographics (n = 37)

Demographics	No. (%)
Maternal details (n = 37)	
Blood group*	
A	6 (17)
B	6 (17)
AB	0
O	24 (67)
Rh positive	28 (78)
Rh negative	8 (22)
Presence of maternal antibodies	12 (33)
Previous pregnancies with jaundiced infant	6 (17)
Infant details (n = 37)	
Male	25 (68)
Female	12 (32)
Blood group	
A	19 (51)
B	9 (24)
AB	0
O	9 (24)
Rh positive	35 (95)
Rh negative	2 (5)
Direct anti-globulin test positive	24 (83)
Gestational age, weeks	36 [23-41]†

*In one mother, the maternal blood group was unknown; thus, maternal blood group percentages were calculated using a denominator of 36.
†Data are presented as median [range].

deficiency. The median age upon IVIG receipt was 1 day (range, 0.25-5 days) for HDN patients, 8 days for enzymopathy patients, and 6 days (range, 1-20 days) for the infants who received IVIG for sepsis or NEC (Table 3).

Fourteen patients received IVIG for indications other than HDN: eight orders were for septic neonates, and two were for neonates who had NEC; the four remaining orders were for neonates who were without evidence of immune-mediated hemolysis (two had antibodies without hemolysis, and two were diagnosed later with G6PD deficiency) (Fig. 1). Further details are provided below regarding the four nonseptic patients without NEC who received IVIG. One patient was a 27-week premature infant with an Rh antibody, positive DAT, normal hemoglobin and bilirubin levels, and no evidence of spherocytosis on the blood smear. The second patient was an infant with ABO incompatibility; a negative DAT; normal hemoglobin, reticulocyte, and bilirubin levels; and a normal blood smear without spherocytosis. The third patient was not at risk for an ABO incompatibility and was not an infant of an alloimmunized mother. MBR was elevated at birth, he was not anemic, there was no evidence of reticulocytosis, and the blood film did not show significant spherocytosis. The patient was later diagnosed with G6PD deficiency. The fourth patient was an infant with ABO incompatibility, a negative DAT, elevated bilirubin, anemia, and rare spherocytes present on the blood film. The patient was diagnosed with G6PD deficiency before receiving IVIG.

Laboratory investigations

Table 4 highlights the tests performed in the NICU during the stay before IVIG administration. Hemolytic tests performed before IVIG receipt included a CBC (100%), DAT (29 of 37 patients; 78%), blood film (28 of 37 patients; 76%), reticulocyte count (11 of 37 patients; 30%), and LDH (1 of 37 patients; 3%). Table 5 compares the proportion of HDN neonates who had abnormal laboratory results before IVIG receipt with the number of non-HDN neonates who had abnormal results. Abnormal results were observed more often among HDN neonates consistently across all hemolytic tests. For the non-HDN neonates, one in six (17%) had positive DATs, and 25% displayed hyperbilirubinemia. By definition, all HDN neonates had positive DATs and displayed hyperbilirubinemia. Increased spherocytes were reported on the blood smear

TABLE 3. NICU treatment details (n = 37)

Treatment	Patients with HDN, n = 23*	Patients with ABO incompatibility or RBC antibody with no hemolysis, n = 2	Patients with G6PD deficiency, n = 2†	Septic and NEC patients, n = 10‡	All patients, n = 37
IVIG alone: no. (%)	0	0	0	5 (50)	5 (14)
Phototherapy + IVIG: no. (%)	19 (83)	2 (100)	1 (50)	5 (50)	27 (73)
Phototherapy + IVIG + ET: no. (%)	4 (17)	0	1 (50)	0	5 (14)
Age upon IVIG receipt: median [range], days	1 [0.25-2]	3 [1-5]	8 [8-8]	6 [1-20]	2 [0.25-20]
Length of stay: median [range], days	8 [2-43]	52 [10-94]	5 [2-8]	8 [2-54]	8 [2-94]
Mortality: no. (%)	0 (0)	0 (0)	0 (0)	6 (60)	6 (16)

*For a definition of HDN, see Table 1.
†G6PD-deficient infants were defined as those who had a G6PD enzyme test that showed a deficiency.
‡Septic and NEC infants were defined as those who had "sepsis" or "NEC" recorded as the indication for IVIG in their medical chart or if a diagnosis of sepsis or NEC was recorded by the ordering physician immediately prior to IVIG order in absence of other diagnoses that may overtly explain IVIG administration.
HDN = hemolytic disease of the newborn; G6PD = glucose-6 phosphate dehydrogenase; NEC = necrotizing enterocolitis; IVIG = intravenous immunoglobulin G; ET = exchange transfusion.

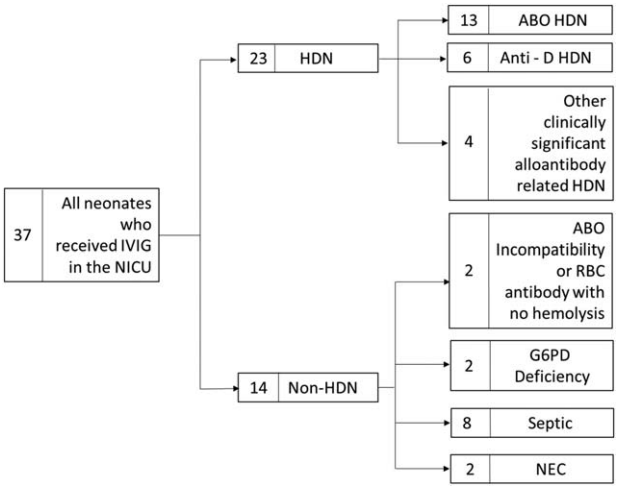

Fig. 1. Distribution of patients who received intravenous immunoglobulin (IVIG) in the neonatal intensive care unit (NICU). HDN = hemolytic disease of the newborn; RBC = red blood cells; G6PD = glucose-6 phosphate dehydrogenase; NEC = necrotizing enterocolitis.

of over half of the HDN neonates (eight of 15 patients) but only for one of the 13 non-HDN neonates who had a smear performed.

Order details, treatment, and outcome

The median dose ordered was 1 g/kg (range, 0.5-1 g/kg) for IVIG. Seven patients received more than one dose of IVIG. For HDN patients, IVIG was ordered because phototherapy was failing in three of 23 patients (13%) and to avoid ET in nine of 23 (41%). The average length of time from birth to treatment with phototherapy, IVIG, and ET was 16 hours (median, 15 hours; IQR, 5-28 hours), 63 hours (median, 24 hours; IQR, 13-61 hours), and 6 hours (median, 7 hours; IQR, 1-10 hours), respectively (Table 3).

Table 3 highlights details related to therapy for jaundice. None of the HDN patients received IVIG alone. Four of the 23 HDN neonates (17%) underwent an ET in addition to the IVIG. The HDN neonates were younger compared with the septic and NEC group and the enzymopathy group (mean age ± SD: 1.4 ± 1.0 days vs. 7.5 ± days; $p < 0.0001$). The average length of stay was 12 days (median, 8 days; range, 2-94 days). Six patients died (five were septic and one had NEC), and the median time between IVIG receipt and death was 22 hours (range, 7-97 hours). There were no chart-documented acute or long-term adverse events attributed to the IVIG, including hemolysis.

DISCUSSION

This study highlights the patient demographics, physician ordering patterns, laboratory results, treatment details, and adverse events in a cohort of neonates who received treatment with IVIG. IVIG was ordered mostly for

TABLE 4. Investigations performed in the NICU before IVIG (n = 37)

Laboratory test	No. of neonates (%)
Complete blood count	37 (100)
Microbilirubin	35 (95)
Blood film	28 (76)
Reticulocyte	11 (30)
Lactate dehydrogenase	1 (3)
Haptoglobin	0 (0)
Direct antiglobulin test	29 (78)
Eluate	0 (0)
Glucose-6 phosphate dehydrogenase	5 (14)
Pyruvate kinase	1 (3)
Osmotic fragility	0 (0)

TABLE 5. Proportion of neonates with HDN versus non-HDN neonates with abnormal laboratory results within 24 hours of receiving IVIG (n = 37)*

Patient type	No.†	Positive DAT, no. (%)	No.	Elevated MBR, no. (%)	No.	Spherocytes on blood film, no. (%)	No.	Elevated reticulocyte count, no. (%)	No.	Anemia, no. (%)
HDN patients (n = 23)	23	23 (100)	23	23 (100)	15	8 (53)	9	7 (78)	23	21 (91)
Non-HDN patients (n = 14)	6	1 (17)	12	3 (25)	13	1 (8)	2	1 (50)	14	11 (79)

*For a definition of HDN, see Table 1.
†Columns headed "No." indicate the number of neonates who received testing.
DAT = direct antiglobulin test; MBR = microbilirubin (mmol/L).

TABLE 6. Current uses of IVIG in the NICU and related evidence for use in the literature*

Medical condition	Recommendation	Dose/frequency of administration	Evidence
Hemolytic disease of the newborn (HDN)[5,6]	IVIG should be offered to patients for treatment of hyperbilirubinemia with proven immune hemolytic etiology who are failing phototherapy and are at clear risk of exchange transfusion; immune-mediated hemolysis should be confirmed using a CBC, blood film, reticulocyte count, and DAT test	0.5-1.0 g/kg over 2 hours; if necessary, dose can be repeated in 12 hours	Randomized controlled trial, meta-analysis, expert opinion
Neonatal alloimmune thrombocytopenia (NAIT)[8,36-38]	IVIG is recommended as an adjunct to platelet transfusion; IVIG is not indicated as the sole therapy for NAIT	1 g/kg daily for 2 days	Retrospective literature, expert opinion
Neonates of mothers with immune thrombocytopenia purpura (ITP)[37,39]	IVIG is recommended for neonates with no evidence of intracranial hemorrhage (ICH) and a platelet count $<20 \times 10^9$/L; combined glucocorticoid and IVIG therapy is recommended for neonates with imaging evidence of ICH and a platelet count $<20 \times 10^9$/L	1 g/kg with the second 1 g/kg dose to be given only if the platelet count is $<30 \times 10^9$/L or in the presence of clinically significant bleeding, associated significant coagulopathy or platelet dysfunction, or documented severe internal hemorrhage (e.g., ICH)	Retrospective literature, expert opinion

*There is no established benefit supporting the use of IVIG in the following conditions in the NICU: neonatal sepsis.[10,11]

neonates who had suspected HDN but also for septic neonates (eight of 37 patients), neonates with NEC (two of 37 patients), neonates with nonimmune-mediated hemolysis (two of 37 patients), and neonates who had antibodies without hemolysis (two of 37 patients). IVIG was ordered infrequently in the NICU over the 11-year study period.

One-third of all IVIG was ordered for the management of septic infants or infants with NEC. Interestingly, these neonates tended to be older; 60% died, and half died within 48 hours of IVIG receipt. This may reflect what occurs anecdotally in these patients. IVIG is used as the last hope in an attempt to "save" the patient. A Cochrane review from 2010 stated that, although there was scientific rationale for administering IVIG in the face of sepsis, there were insufficient data to support the routine use of IVIG to prevent death in infants with suspected sepsis.[18] A follow-up Cochrane review from 2013, which focused on the treatment of sepsis in neonates, found that there was no significant reduction in mortality for standard IVIG (relative risk [RR], 1.00; 95% confidence interval [CI], 0.92-1.08) or IgM-enriched polyclonal IVIG (RR, 0.57; 95% CI, 0.31-1.04).[10] Interestingly, in this study, the majority of IVIG administrations for septic infants occurred in the first half of the study (between 2004 and 2007). IVIG may have been used for sepsis during that earlier period, when the evidence for use was less clear. Publication of the more recent Cochrane review showing uncertain benefit may have decreased IVIG ordering practices for sepsis thereafter.[10,11] The neonates with NEC were very unwell and likely were treated as septic infants. There is no existing literature investigating IVIG administration for neonates with NEC. However, several studies have reported an association between IVIG administration and the development of NEC in neonates. Similar to septic infants, IVIG administration for NEC occurred in the first half of the study, before other studies reporting NEC as an adverse reaction to IVIG were published.[4,19,20] Earlier publication of those findings may have influenced practice.

In neonates with HDN, early studies concluded that IVIG reduced the need for an ET; however, more recent randomized trials as well as a meta-analysis have questioned these results in all HDN cases.[5,7,21] Studies with a high risk of bias reported that, for neonates with anti-D alloimmunization, IVIG reduced the need for ET, the duration of phototherapy, and the duration of hospitalization. In contrast, studies with a low risk of bias focusing on neonates with anti-D alloimmunization did not report a benefit in any of these outcomes. In infants with ABO HDN, IVIG reduced the number of ETs, peak serum bilirubin levels, and the duration of phototherapy.[5] Current guidelines from the United States, Australia, the United Kingdom, and Canada[22-24] reflect these study results and recommend IVIG administration only for neonates with severe hyperbilirubinemia who are unresponsive to intensive phototherapy and have a proven immunological etiology to their jaundice. In the current study, less than half of the neonates with HDN (seven of 23 patients; 30%) met these criteria for IVIG administration. This may reflect the common challenge related to knowledge translation into clinical practice or the fact that during the earlier phase of the study, these recommendations had not yet been published.

If clinicians do decide to order IVIG, whether within or outside of clinical guidelines, then the benefits and risks must be considered and discussed with the patient's family. IVIG is a blood product, and adverse events, including NEC[4,19,20] and severe hemolysis,[2,25] have been reported after its use. IVIG also potentially may cause hemolysis in nongroup O neonates, because IVIG contains anti-A and anti-B.

For neonates with hyperbilirubinemia, hemolytic tests are key to determining the etiology of hyperbilirubinemia and ensuring that IVIG is used in the appropriate clinical setting. Reviewing the blood film for spherocytes is a practical, inexpensive screening tool with which to evaluate neonates who have severe hyperbilirubinemia.[26,27] In the current study, blood films were ordered before the receipt of IVIG only 76% of the time. Spherocytes were detected on 53% of the blood smears performed on HDN neonates and on 8% of non-HDN neonates, supporting the value of the test. The DAT detects the presence of immunoglobulin, complement, or both bound to the red blood cell membrane. A DAT is required when considering the diagnosis of HDN and should be ordered only if the neonate has clinical evidence of jaundice and laboratory evidence of hemolysis.[28,29] Thus, a DAT should always be ordered when considering the use of IVIG for HDN. However, because this test has a poor positive predictive value for identifying neonates who will require phototherapy for HDN, it should not be ordered when hemolysis is not present. In addition, a negative DAT does not exclude a nonimmune hemolytic etiology to explain the clinically significant hyperbilirubinemia.[28] DATs were performed 78% (29 of 37 neonates) of the time and were negative for all tested patients who had sepsis and NEC and for half of those (one of two neonates) who had enzymopathy (Table 5). Tests to diagnose G6PD deficiency, pyruvate kinase deficiency, and hereditary spherocytosis as well as haptoglobin were ordered infrequently; this is not surprising given the limitations of these tests during the newborn period.[27,30-33] Our research mirrors the results reported by Christensen and colleagues,[34] who reported that, 66% of the time, no specific cause for severe jaundice is identified and that hemolytic tests are rarely performed. Commonly, the physician treats the potentially kernicteric infant and classifies the jaundice as idiopathic (or incorrectly assumes it is immune mediated) without identifying the root cause of the problem.

The current study is unique, because it makes a novel contribution to the literature on the ordering of IVIG in the NICU. This study included patients who had diverse diagnoses and were treated over 11 years at a tertiary care academic center, and the results may be similar to those from other tertiary care neonatal centers. The major limitations of the study are its small sample, its retrospective nature, and the frequent incomplete work-up of the jaundiced neonate. Finally, there may have been additional infants with HDN who met the criteria to receive IVIG but were not treated. Detailed information regarding this group of patients was not explored.

Current guidelines recommend the use of IVIG in specific neonatal conditions, particularly for the jaundiced neonate, with immune-mediated hemolysis to avoid ET.[22-24] The 2004 American Academy of Pediatrics recommendations suggest using IVIG at a dose from 0.5 to 1.0 g/kg to treat HDN when phototherapy is failing to avoid ET.[22] The risks related to ET are likely to be more severe than those associated with IVIG. A recent editorial calls into question the safety and effectiveness of IVIG treatment of neonates with severe hyperbilirubinemia. Some neonatology experts are reluctant to administer IVIG to neonates with HDN, because they judge that the risk-to-benefit ratio is unfavorable. This emphasizes that the use of IVIG in HDN remains a moving target.[35] Revised local or national guidelines need to include suggestions regarding the appropriate diagnostic tests to be ordered when assessing neonates with hyperbilirubinemia to determine whether an immune etiology is present. Neonates with severe jaundice requiring urgent phototherapy should be investigated with a CBC, blood film, reticulocyte count to confirm hemolysis, and a DAT to confirm an immune-mediated process.

Finally, the use of IVIG should be reconsidered in the setting of sepsis with current, updated evidence. Table 6 highlights the current clinical indications for use of IVIG in the NICU and the level of evidence to support this.[36-39] The results from our single-center study call attention to the need for larger neonatal/infant databases to collect essential information for gathering critical, representative,

demographic transfusion-related data on neonates and carrying out pragmatic clinical trials to establish better evidence-based guidelines for IVIG therapy.

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CONFLICT OF INTEREST

The authors disclosed no conflicts of interest.

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