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REVIEW

TRANSFUSION

Incidence and risk factors for intravenous immunoglobulin-related hemolysis: A systematic review of clinical trial and real-world populations

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Abstract

Background: Severe hemolysis rarely occurs in patients receiving intravenous immunoglobulin (IVIG) therapy. A systematic review was performed to assess the incidence of IVIG-related hemolysis and the impact of patient and product risk factors.

Study Design and Methods: A systematic literature search for terms related to "IVIG products", "hemolysis," and "adverse events" was conducted in Embase for articles published between January 1, 2015, and May 31, 2021. Studies with no clinical datasets, no IVIG treatment, or where IVIG was used to treat hemolytic conditions were excluded. Of the 430 articles retrieved, 383 were excluded based on titles/abstracts and 14 were excluded after in-depth review.

Results: In total, 33 articles were analyzed and separated into observational studies ($n = 16$), clinical trials ($n = 8$), and case reports ($n = 9$). The incidence proportion for IVIG-related hemolysis ranged from 0% to 19% in observational studies and 0%–21% in clinical trials. A higher incidence of IVIG-related hemolysis was consistently reported in patients with blood groups A and AB. Hemolysis occurred more frequently in patients treated with IVIG for some conditions such as Kawasaki disease; however, this may be confounded by the high dose of IVIG therapy. IVIG-related hemolysis incidence was lower in studies using IVIG products citing manufacturing processes to reduce isoagglutinin levels than products that did not.

Conclusion: This analysis identified patient and product risk factors including blood group, IVIG dose, and IVIG manufacturing processes associated with elevated IVIG-related hemolysis incidence.

Abbreviations: CBC, complete blood count; CIDP, chronic inflammatory demyelinating polyneuropathy; EtOH, ethanol; GBS, Guillain-Barré syndrome; Hb, hemoglobin; IAC, immunoaffinity chromatography; Ig, immunoglobulin; ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; MG, myasthenia gravis; MMN, multifocal motor neuropathy; MS, multiple sclerosis; N.R., not reported; OA, ethanol-octanoic acid; PEG, polyethylene glycol; PI, primary immunodeficiency; SID, secondary immunodeficiency.

KEYWORDS
ABO blood group, hemolysis, intravenous immunoglobulin, isoagglutinins

1 | INTRODUCTION

Intravenous immunoglobulin (IVIG) products consist of immunoglobulin (Ig) G purified from the plasma of healthy donors. Initially, IVIG products were used as replacement therapy in patients with immunodeficiency syndromes but are now also used as immunomodulatory treatment in autoimmune diseases such as chronic inflammatory demyelinating polyneuropathy (CIDP), immune thrombocytopenia (ITP), Guillain-Barré syndrome (GBS), and Kawasaki disease (KD).[1] Although rare, the use of Ig is sometimes associated with hemolysis, with studies suggesting that isoagglutinins in products are a probable cause.[2] Plasma for IVIG production is obtained from donors of all ABO blood groups, the majority being groups O and A; therefore, plasma for IVIG contains IgG anti-A and anti-B antibodies, as postulated by Landsteiner's Law.[3] Common consequences of hemolysis include anemia and jaundice.[4] However, if not appropriately managed, hemolysis can lead to more severe complications, such as renal failure, shock with multiorgan failure, and even death.[4]

The aim of this review is to assess the incidence of IVIG-related hemolysis and the impact of patient and product risk factors by means of a systematic review of published literature.

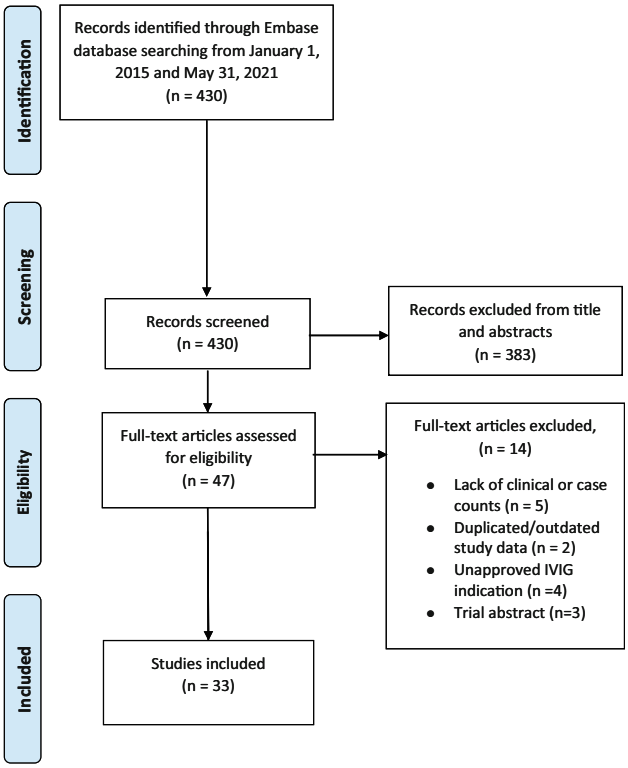

FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram for the selection of related articles identified through Embase[5] [Color figure can be viewed at wileyonlinelibrary.com]

2 | METHODS

We performed a systematic literature search in Embase using a search algorithm to identify articles on IVIG-related hemolysis. The search algorithm contained terms related to IVIG products, including product brand names, hemolysis, and adverse events (full search string provided in Appendix S1). We searched for articles published between January 1, 2015, and May 31, 2021. Titles and abstracts from the search results were screened independently by two authors to identify any articles describing hemolysis in patients receiving IVIG, which were selected for subsequent in-depth review. Studies with no IVIG treatment, articles on unrelated topics, studies reporting IVIG used to treat hemolytic conditions (autoimmune hemolytic anemia, hemolytic disease of the newborn, etc.), review articles, clinical guidelines, and other articles that did not present clinical data or case counts were excluded. Relevant full-text articles were screened in-depth to extract information such as the definition of hemolysis used, the incidence of hemolysis in the population, indication, IVIG dose, and blood group. At this stage, any duplicates, congress abstracts, and studies among hemolysis cases only (thus lacking a denominator to calculate the incidence of hemolysis) were excluded. We included both observational real-world studies, and clinical trials in our review, however, due to differences in methodology and follow-up between these two types of studies, we report these incidence proportions separately. Two reviewers screened titles/abstracts independently, rated each independently, and met to resolve any discrepancies in ratings. This process was then repeated for full-text article review. The review was not registered, and a protocol was not prepared.

3 | RESULTS

Following the screening of titles and abstracts, 430 total search results were selected for detailed data extraction.

TABLE 1 Clinical and observational real-world studies of patients treated with IVIG that reported hemolysis incidence

	Study information					Hemolysis case information			
Reference	**Study type**	**Number of patients receiving IVIG**	**IVIG product and manufacturing process (where reported)**	**Primary patient population and indication(s)/ IVIG dose**	**Blood group details of the study population**	**Number of hemolysis cases**	**IVIG dose of patients with hemolysis**	**Hemolysis incidence estimate**	**Blood group details of patients with hemolysis**
Observational real-world studies									
Keh et al. 2020[6]	Retrospective cohort	90	N.R.	Adult patients with CIDP or MMN/Mean dose: 1.57 g/kg/month	N.R.	0	N.R.; no hemolysis observed in IVIG-treated patients	Clinically significant hemolysis: 0% (0–3.3) per patient; 0% (0–0.16) per infusion	N.R.
Nolan et al. 2018[7]	Retrospective cohort	419 (123 with CBC data to evaluate hemolysis)	N.R.	Pediatric patients with KD/Dose: 2 or 4 g/kg	N.R.	18	2/18 (11%): 2 g/kg 16/18 (89%): 4 g/kg	15%; risk factors were Non–African-American race, higher IVIG dose and higher pre-IVIG Hb	A: 8/18 (44%) B: 5/18 (28%) AB: 4/18 (22%) O: 1/18 (6%)
Cicha et al. 2018[8]	Retrospective cohort	16	N.R.	Adult patients with dermatological conditions/Dose: 1–3 g/kg	A: 4/16 (25%) B: 4/16 (25%) AB: 1/16 (6%) O: 3/16 (19%) N.R.: 4/16 (25%)	1	2 g/kg	6.25%	A+: 1/1 (100%)
Sridhar et al. 2018[9]	Retrospective cohort	20,440	Multiple manufacturing methods	N.R. (multiple indications)/Dose: N.R.	N.R.	211	N.R.	Hemolysis occurring same day: 1%	N.R.
Liu et al. 2018[10]	Retrospective cohort	55	N.R.	Adult and pediatric patients with small-fiber polyneuropathy/ Dose: ≥1 g/kg/4 weeks	N.R.	1	N.R.	1.8%	N.R.
Donga et al. 2017[11]	Database (claims/ EMR study)	1061	N.R.	Adult patients with ITP/Dose: N.R.	N.R.	12 cases of HA (used as proxy for intravascular hemolysis)	N.R.	Hemolytic anemia occurring within 3 days: 1.1%	N.R.
Akman et al. 2017[12]	Prospective cohort	31	N.R.	Multiple indications/ Dose: 2 g/kg	A: 14/31 (45%) B: 3/31 (10%) AB: 1/31 (3%) O: 13/31 (42%)	6	N.R.	Hemolysis occurring within 3–10 days: 19%	A+: 4 (66.6%) AB+: 1 (16.7%) O+: 1 (16.7%)

TABLE 1 (Continued)

	Study information					Hemolysis case information			
Reference	**Study type**	**Number of patients receiving IVIG**	**IVIG product and manufacturing process (where reported)**	**Primary patient population and indication(s)/ IVIG dose**	**Blood group details of the study population**	**Number of hemolysis cases**	**IVIG dose of patients with hemolysis**	**Hemolysis incidence estimate**	**Blood group details of patients with hemolysis**
Levine et al. 2017[13]	Retrospective cohort	166	Multiple manufacturing methods	Patients with CIDP, MMN, polymyositis, dermatomyositis, MG and MS/Mean dose: 1.2/kg/ month	N.R.	0; no patients with clinically significant hemolysis	N.R.; no hemolysis observed in IVIG-treated patients	N.R.; no hemolysis observed in IVIG-treated patients	N.R.
Winiecki et al. 2015[14]	Database (FAERS)	236 suspected hemolysis	N.R.	Patients with CIDP, GBS, ITP, KD, MG and PI/Dose: 0.8–4 g/kg	N.R.	109	Dosing information available for 80 patients; 83% (66/80) had ≥2 g/ kg	N.R. Risk factors were high dose and non-O blood group	52 cases with known blood groups. A: 35 (67.3%) AB: 11 (21.2%) B: 5 (9.6%) O: 1 (1.9%)
	Database (Mini-Sentinel)[†]	313,045 treatment episodes	N.R.	Patients with CIDP, GBS, ITP, KD, MG and PI	N.R.	337	N.R.	Hemolysis occurring within 14 days: 337 episodes of hemolysis in 313,045 episodes of Ig treatment (0.1%)	N.R.
Quinti et al. 2015[15]	Prospective cohort	162 *(142 regularly received IVIG in hospital at intervals of 2/3 weeks; 20 patients self-administered SCIG)*	N.R.	Patients with primary antibody deficiency/Mean dose: 0.3 g/kg/ month	A: 66/162 (41%) B: 16/162 (10%) AB: 13/162 (8%) O: 57/162 (35%) N.R.: 10/162 (6%)	6	Monthly dose of 0.37–0.46 g/kg	Hemolysis occurring within 10 days: 3.7%	A: 4 (60%) O: 2 (40%)
Ghiasi et al. 2017[16]	Retrospective cohort	67	N.R.	Adult and pediatric patients with dermatologic conditions/Mean dose: 2.01 ± 1.38 g/kg	N.R.	1	N.R.	1.5%	N.R.

(Continues)

TABLE 1 (Continued)

	Study information					Hemolysis case information			
Reference	**Study type**	**Number of patients receiving IVIG**	**IVIG product and manufacturing process (where reported)**	**Primary patient population and indication(s)/ IVIG dose**	**Blood group details of the study population**	**Number of hemolysis cases**	**IVIG dose of patients with hemolysis**	**Hemolysis incidence estimate**	**Blood group details of patients with hemolysis**
Wallenhorst et al. 2020[17]	Database (claims/ EMR study)	Study period 1: 9439	Ethanol octanoic acid	Adult and pediatric patients with any indication, including PI, SID, GBS, KD, CIDP, MG and ITP/Mean dose: 0.76 (Period 1) to 0.85 (Period 2/3) g/kg	N.R.	38	<1 g/kg: 18; 1–1.5: 5; >1.5: 13; Unknown: 2	N.R.	N.R.
		Study period 2: 7710	Ethanol octanoic acid donor screening			20	<1 g/kg: 9; 1–1.5: 0; >1.5: 10; Unknown: 1		
		Study period 3: 7759	Ethanol octanoic acid with IAC			3	<1 g/kg: 1; 1–1.5: 0; >1.5: 2		
Van Anh et al. 2020[18]	Cohort study	562	Ethanol fractionation followed by ion exchange chromatography	Patients with acute KD/Dose: 2 g/kg (additional dose if refractory)	N.R.	4 (2 IVIG-responsive; 2 IVIG-resistant)	2/4 (50%): 2 g/kg 2/4 (50%): 4 g/kg	Total: 0.71% IVIG responsive: 0.4% IVIG-resistant: 6.7%	A: 1 (25%) A+: 1 (25%) Unknown: 2 (50%)
Bruggeman et al. 2020[19]	Retrospective cohort	581 (cohort 1: 440; cohort 2: 141)	Various brands	Pediatric patients with KD/Dose: 2 g/kg (max 70 g)	N.R.	Cohort 1: 20 Cohort 2: 13	N.R., but IVIG dose was a risk factor	Cohort 1: 4.5% Cohort 2: 9.2%	Cohort 1;2: A: 12/46 (26%); 7/35 (20%) B: 0/17 (0%); 1/21 (5%) AB: 5/12 (42%); 4/12 (33%) O: 0/33 (0%); 0/45 (0%)
Tong et al. 2020[20]	Prospective cohort	42 patients (50 samples)	Various brands	Patients with autoimmune disorders/Dose: ≥2 g/kg	non–blood group O; A: 27/42 (64%) B: 9/42 (21%) AB: 6/42 (14%)	20	N.R.	40%	A: 8/20 (40%) B: 5/20 (25%) AB: 7/20 (35%)
Pendergrast et al. 2021[21]	Prospective observational study	78 patients; 99 infusions	Multiple manufacturing methods	Adult and pediatric patients with neurologic Conditions: CIDP, GBS, MG or MMN (63%), ITP (13%), other conditions: dermatologic, rheumatologic and miscellaneous conditions (24%) Dose: ≥2 g/kg	Non-blood group O patients; A: 43/78 (55%) B: 25/78 (32%) AB: 9/78 (12%) Other: 1/78 (1%)	31	Average dose: 2.0 ± 0.1 g/kg	40%	A: 14/31 (45%) B: 9/31(29%) AB: 8/31 (26%)

TABLE 1 (Continued)

	Study information					Hemolysis case information			
Reference	**Study type**	**Number of patients receiving IVIG**	**IVIG product and manufacturing process (where reported)**	**Primary patient population and indication(s)/ IVIG dose**	**Blood group details of the study population**	**Number of hemolysis cases**	**IVIG dose of patients with hemolysis**	**Hemolysis incidence estimate**	**Blood group details of patients with hemolysis**
Clinical trials									
Leger et al. 2019[22]	Interventional trial	22	Ethanol octanoic acid with IAC	Adult patients with MMN/Dose: 1–2 g/kg every 4–8 weeks	N.R.	0	N.R.; no hemolysis observed in IVIG-treated patients	N.R.; no hemolysis observed in IVIG-treated patients	N.R.
Koochakzadeh et al. 2018[23]	Interventional trial	49	N.R.	Pediatric patients with acute ITP/Dose: 1 g/kg	N.R.	0	N.R.; no hemolysis observed in IVIG-treated patients	N.R.; no hemolysis observed in IVIG-treated patients	N.R.
Mielke et al. 2017[24]	Single-arm trial	57	Ethanol octanoic acid	Adult patients with ITP/Dose: 1–2 g/kg	A: 30/57 (53%) B: 11/57 (19%) O:16/57 (28%)	12	12/12 (100%): 2 g/kg	Mild hemolysis evaluated at day 9: 21.1%	A: 10/12 (83%) B: 2/12 (17%)
Viallard et al. 2017[25]	Single-arm trial	22	Cohn fractionation	Adult patients with PI/Dose: 0.2–0.8 g/kg every 3–4 weeks	N.R.	0	N.R.; no hemolysis observed in IVIG-treated patients	N.R. (0 cases in 9 months)	N.R.
Lakkaraja et al. 2016[26]	Interventional trial	102; Arm A $n = 51$, Arm B $n = 51$ Data from 69 women (Arm A = 36 and Arm B = 33) were analyzed	N.R.	Pregnant women with fetal and neonatal alloimmune thrombocytopenia/ Dose: 2 g/kg (Arm A) or 1 g/kg (Arm B)	A: 40% B: 11% AB: 4% O: 45%	30 (Arm A, $n = 21$; Arm B $n = 9$)	Arm A: 21/36 (58%) Arm B: 9/33 (27%)	N.R.	A: 61.9% B: 17.5% AB: 12.7% O: 4.8%
Melamed et al. 2016[27]	Single-arm trial	25	Ethanol fractionation followed by ion exchange chromatography	Pediatric patients with PI/Dose: 0.3–0.8 g/kg per infusion	N.R.	0	N.R.; no hemolysis observed in IVIG-treated patients	Hemolysis occurring within 3 days of infusion: 0%	N.R.
Karelis et al. 2019[28]	Single-arm trial	49	Ethanol octanoic acid followed by chromatography	MG exacerbations/ Dose: 2 g/kg	N.R.	5	N.R.	10.2%	N.R.

(Continues)

TABLE 1 (Continued)

Reference	Study information: Study type	Study information: Number of patients receiving IVIG	Study information: IVIG product and manufacturing process (where reported)	Study information: Primary patient population and indication(s)/IVIG dose	Study information: Blood group details of the study population	Hemolysis case information: Number of hemolysis cases	Hemolysis case information: IVIG dose of patients with hemolysis	Hemolysis case information: Hemolysis incidence estimate	Hemolysis case information: Blood group details of patients with hemolysis
Nobile-Orazio et al. 2020[29]	Single-arm trial	43 patients	Ethanol octanoic acid with IAC	Adult patients with CIDP Dose: an initial dose of 2 g/kg over 2–5 days during the first course; maintenance doses of 1 g/kg over 1–2 days every 3 weeks	N.R.	0	N.R.; no hemolysis observed	N.R.; no hemolysis observed	N.R.

Abbreviations: CBC, complete blood count; CIDP, chronic inflammatory demyelinating polyneuropathy; GBS, Guillain-Barré syndrome; Hb, hemoglobin; IAC, immunoaffinity chromatography; ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; MMN, multifocal motor neuropathy; MG, myasthenia gravis; MS, multiple sclerosis; N.R., not reported; PI, primary immunodeficiency; SID, secondary immunodeficiency.
[a]Number of patients was not specified.

Out of the 430 articles, 383 records were excluded based on the title and abstract and a further 14 articles were excluded based on the defined exclusion criteria (Figure 1). This left a total of 33 relevant articles, of which 16 were observational real-world studies, eight were clinical trials (both summarized in Table 1; with hemolysis definitions/assessments described in Table S1), and an additional nine were case reports (summarized in Table 2).

4 | PATIENT CHARACTERISTICS

4.1 | Observational real-world studies

Among the 16 observational, real-world studies included in this review, the patient sample size ranged from 16 to over 20,000 patients (Table 1). Patients treated with IVIG were aged between 2 and 85 years old and 52% were male (sex breakdown detailed in 12 studies[6–12,14–17,21]). The most commonly reported conditions treated by IVIG included KD (three studies[7,18,19]) and dermatologic conditions (two studies[8,16]). Other conditions included CIDP or multifocal motor neuropathy (MMN), immune thrombocytopenia (ITP), and small-fiber polyneuropathy.[6,10,11] In total, eight studies included patients with multiple diseases treated with IVIG.[9,12–15,17,20,21] Of the 16 studies, five reported the blood group details from the whole study population. The most common blood group was group A (range 25%–64%) and group O (range 19%–42%), followed by group B and AB (ranges 10%–32% and 3%–14%, respectively).[8,12,15,20,21] Two studies included only patients with non-O blood group.[20,21] Where patient populations were stated, there was a total of 514 reported hemolysis cases observed across real-world studies from a combined population of 49,836 patients (Table 1).

4.2 | Clinical trials

From the eight clinical trials included, patient sample size ranged from 22 to 102 patients (Table 1). Patients treated with IVIG were between 3 and 82 years old and 64% were male (sex breakdown detailed in seven of the eight clinical trials[22–25,27–29]). Reported conditions being treated by IVIG in these clinical trials included ITP (three studies[23,24,26]), with other studies including patients with CIDP,[29] MMN,[22] or myasthenia gravis (MG).[28] Two studies included patients with primary immunodeficiencies treated with IVIG.[25,27] From all studies combined there was a total of 47 reported hemolysis cases among 419 patients treated with IVIG included in the trials.

TABLE 2 Hemolysis case reports

Reference	Patient details	IVIG dose	First dose of IVIG	Indication	Blood group	Drop in Hb
Shimomura et al. 2020[30]	3-year-old Asian male	2 g/kg followed by an additional 2 g/kg 4 days later	Yes	KD	A+	Nadir: 57 g/L; Baseline: 110 g/L; Drop: 53 g/L
Chadha et al. 2019[31]	Case 1: 75-year-old male Case 2: 59-year-old female Case 3: 20-year-old female	N.R.	N.R.	Patient 1: MG Patient 2: MG Patient 3: GBS	Case 1: AB+ Case 2: AB+ Case 3: A+	Case 1: Drop: 3 g/dL Case 2: Drop: 5 g/dL Case 3: Drop: 6 g/dL
Lasica and Zantomio 2016[32]	63-year-old male	1.4 g/kg over 3 days	N.R.	CIDP	O	Nadir: 120 g/L; Baseline: 140 g/L; Drop: 20 g/L
Sharma and Aryal 2018[33]	56-year-old Asian male	2 mg/kg over 5 days	Yes	GBS	A+	Nadir: 8.3 g/dL; Baseline: 15.3 g/dL; Drop: 7 g/dL
Tocan et al. 2017[39]	10-month-old male	2 g/kg	Yes	KD	A-	Nadir: 3.4 g/dL; Baseline: 9.0 g/dL; Drop: 5.6 g/dL
Welsh and Bai 2015[34]	Patient 1: 57-year-old male Patient 2: 35-year-old female Patient 3: 56-year-old female	Patient 1: 100 g for 5 days Patient 2: Unspecified dosage for 8 days Patient 3: 180 g over 3 days	N.R.	Patient 1: GBS Patient 2: ITP Patient 3: nonischemic cardiomyopathy	Patient 1: A+ Patient 2: O+ Patient 3: A+	Patient 1: Nadir: 4.6 g/dL; Baseline: 14.4 g/dL; Drop: 9.8 g/L Patient 2: Nadir: 1.5 g/dL; Baseline: 14.6 g/dL: Drop: 13.1 g/L Patient 3: hemoglobin levels remained stable
Luban et al. 2015[35]	Patient 1: 16-year-old female Patient 2: 4-year-old female Patient 3: 7-year-old female Patient 4: 3-month-old female Patient 5: 10-month-old male	Patient 1: 3 doses over 8 days, with a cumulative dose of 3 g/kg Patient 2: 2 doses over 2 days, with a cumulative dose of 1.2 g/kg Patient 3: 2 doses 2 days apart, with a cumulative dose of 2 g/kg Patient 4: 2 doses over 24 hours with a cumulative dose of 4 g/kg Patient 5: 2 doses 2 days apart, with a cumulative dose of 4 g/kg	N.R.	Patient 1: atypical KD Patient 2: KD Patient 3: atypical KD Patient 4: KD Patient 5: KD	Patient 1: AB D+ Patient 2: A D+ Patient 3: A D+ Patient 4: A+ Patient 5: AB D+	Patient 1: Drop: 4 g/dL Patient 2: N.R. Patient 3: Drop: 2.3 g/dL Patient 4: Drop: 2.6 g/dL Patient 5: Drop: 5 g/dL

(Continues)

TABLE 2 (Continued)

Reference	Patient details	IVIG dose	First dose of IVIG	Indication	Blood group	Drop in Hb
Jacobs et al.[36]	59-year-old female	2 g/kg over 2 days	N.R.	ITP	AB-	Nadir: 8.8 g/dL; Baseline: 14.7 g/dL: Drop: 5.9 g/dL
Nguyen et al.[37]	Patient 1: 32 years old Patient 2: 57 years old Patient 3: 61 years old	Patient 1: 4 g/kg over 10 days Patient 2: 5 g/kg over 5 days Patient 3: 4 g/kg over 10 days	N.R.	Patient 1: GBS and acute motor axonal neuropathy Patient 2: Miller Fisher syndrome Patient 3: GBS	Patient 1: A+ Patient 2: A+ Patient 3: B+	N.R.

Abbreviations: CIDP, chronic inflammatory demyelinating polyneuropathy; GBS, Guillain-Barré syndrome; Hb, hemoglobin; IAC, immunoaffinity chromatography; ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; MG, myasthenia gravis; N.R., not reported.

5 | PATIENT-ASSOCIATED RISK FACTORS FOR IVIG HEMOLYSIS

5.1 | Observational real-world studies

When examining hemolysis cases, nine of the 16 real-world studies included blood group details of patients; with the majority of hemolysis cases observed in patients with blood group A (range 20%–100%), followed by blood group AB or B (ranges 17%–42% and 0%–29% respectively).[7,8,12,14,15,18–21] This highlights the high incidence of hemolysis in non-blood group O patients, particularly in blood group AB, which has one of the highest incidence rates despite a low population prevalence. In regards to gender breakdown, in one study, IVIG-related hemolysis incidence was lower in female versus male patients (28% vs. 72%,[7] respectively), and in four articles it was greater in female versus male patients (83% vs. 17%,[12] 50% vs. 45%,[14] 83% vs. 17%,[15] and 58% vs. 42%,[21] respectively). The reported incidence proportions of hemolysis ranged from 0% to 40% across all real-world studies (Table 1).[6–8,10,12,14,15,17,19,20] However, the studies by Tong et al. and Pendergrast et al. assessed incidence in non-O blood group patients only.[20,21] When these studies were removed to ensure hemolysis incidence was reported as a percentage of all blood groups, the estimated incidence proportions of hemolysis ranged from 0% to 19% in the remaining real-world studies (Table 1).[6–8,10,12,14,15,17,19]

5.2 | Clinical trials

The estimated incidence of hemolysis ranged from 0% to 21% in clinical trials (Table 1).[23,24,27,28]Two studies reported the blood group details of the whole study population and blood group details of patients with hemolysis.[24,26] A higher proportion of hemolysis cases were experienced in patients with blood group A or AB than in blood groups B or O.[38] In the study by Lakkaraja et al., 12.7% of hemolysis cases were observed in patients with blood group AB from a study population where only 4% of patients were blood group AB.[26] In the study by Mielke et al., 83% of hemolysis cases were observed in patients with blood group A from a study population where 53% were blood group A.[24] In both studies, the lowest rates of hemolysis cases were observed in patients with blood group O.[24,26] In the Lakkaraja et al. study, 4.8% of hemolysis cases were observed in patients with blood group O from a study population of 45% blood group O patients.[26] In the Mielke et al. study, no hemolysis cases were observed within the 28% of the study population having blood group O.[24] In the Lakkaraja et al. study, hemolysis

was observed in a cohort of pregnant women.[26] No other clinical studies detailed gender breakdown.

5.3 | Case studies

A further 19 cases of hemolysis were identified in case reports and case series (Table 2). The number of hemolysis cases was slightly greater in females (nine cases out of 16 cases where sex was reported (56%), and patients were aged between 3 months to 75 years old). Of the 19 cases, seven were in pediatric patients (<18 years old),[30,35,39] three patients were aged between 18 and 50 years old, and nine were in patients over 50 years of age.[31–34,36,37] The most common indication was KD (seven cases[30,35,39]) followed by GBS (six cases; including one patient with Miller Fisher syndrome, a subtype of GBS[31,33,34,37]), ITP (two cases[34,36]) or MG (two cases[31]). Other cases reported CIDP[34] or nonischemic cardiomyopathy.[34] Of the 19 cases, 11 patients were blood group A, five were blood group AB, two were blood group O, and one was blood group B.

5.4 | Product-associated risk factors for IVIG hemolysis

IVIG-related hemolysis incidence was greatest in patients who received high doses (≥2 g/kg) of IVIG, with up to 89% and 11% of patients experiencing hemolysis with doses of ≥4 g/kg and 2 g/kg, respectively.[7] In the study by Quinti et al., only six out of 162 patients (3.7%) receiving low doses of immunoglobulin (between 0.37 and 0.46 g/kg a month) had signs and symptoms of immunoglobulin-induced hemolysis.[15] Taken together, these studies demonstrate that higher doses of IVIG are associated with higher rates of hemolysis.[7,15] In one study which used the FAERS database, 83% of hemolysis cases were in patients who had ≥2 g/kg IVIG.[14] This relationship was further observed across a number of additional studies using different IVIG products (Table 1).[7,14,17,23,24,26,39]

Preparations of IVIG products were also shown to affect the incidence of hemolysis in some studies. In one study, incidence rates dropped from 1.49 to 0.1 per 100,000 when the manufacturing process of the IVIG product replaced the exclusion of high-anti-A-titer donors by specific immunoaffinity chromatography (IAC); reducing median anti-A and anti-B titers to 8 and 4, respectively.[17] Incidence of hemolysis was also low in one study of patients treated with IVIG manufactured using an ethanol-octanoic acid (OA) process with additional cation and anion exchange chromatography, where only four IVIG-related hemolysis cases were recorded out of 562 patients.[18] Furthermore, no hemolysis cases were observed in clinical trials that used IVIG products produced by Cohn fractionation or ethanol-OA fractionation followed by IAC isoagglutinin reduction. However, cases were observed in IVIG products that used ethanol-OA-purified products.[22,25,29]

5.5 | Complications

Anemia severe enough to require transfusion of RBCs was a common complication that was reported in a number of studies.[7,40,41] Case reports provided additional examples of complications, including dark urine and jaundice (one patient had chronic renal failure),[32,36] hyperbilirubinemia in patients with KD,[35] and acute kidney injury in a patient with ITP.[36] However, it is worth noting that complications were not described in all studies, and as a result, the data may not provide a complete view of potential complications associated with IVIG-related hemolysis.

6 | DISCUSSION

In this review, we show the incidence of IVIG-related hemolysis as a percentage of all patients regardless of blood group, ranging from 0% to 19% in observational real-world studies and 0%–21% in clinical trials.

This large variance in IVIG-related hemolysis may be explained by variations in the definition of hemolysis (Table S1) and study design (including the timing of hemolysis assessment) and patient and product factors. For the definition of hemolysis, hemoglobin levels or drops in hemoglobin levels were used in conjunction with parameters such as (i) a positive direct antiglobulin test, (ii) elevated levels of lactate dehydrogenase or (iii) low haptoglobin[8]; one study by Lakkaraja M et al. considered a hemoglobin level of less than 10 g/L anemia, presumably due to hemolysis.[26] Moreover, some studies only included patients with hemolysis (assessing clinically significant or severe hemolytic anemia),[6] whereas others made a distinction between clinically significant hemolysis (recorded adverse event) and laboratory signs of hemolysis (blood sampling),[42] and some studies did not specify the definition used.[13,25]

The assessment time point of hemolysis also differed across studies. In clinical trials, the cut-off period for hemolysis to be considered IVIG-treatment-related in clinical trials is commonly 10 days,[8,15] with limited differences observed between utilizing a 10-day or 30-day risk period.[17] Some studies in this review used a shorter cut-off period for example, 1 or 3 days,[9,11] which may lead to cases being missed.

Patient factors such as blood group and co-morbidities influence the differences in hemolysis proportions reported across studies. Blood groups A and AB are associated with the greatest risk of hemolysis risk

followed by blood group B and blood group O. This observation is supported in this review, as in studies when blood group distribution was reported, greater hemolysis risk was observed in patients with blood group A and AB.[7,12,14,19,20,26] This is effectively demonstrated in the prospective observational study by Pendergrast et al., which assessed the incidence of IVIG-mediated hemolysis in non-blood group O patients that were administered a high dose of IVIG (2 g/kg).[21] This study concluded that patients with blood group AB were at a significantly increased risk of hemolysis compared to patients with blood group A or B (89% vs. 33% vs. 36%, respectively).[21] Furthermore, the study by Bruggeman et al. reported that IVIG-related hemolysis was greatest in patients with blood group AB, with no IVIG-related hemolysis cases observed in patients with blood group O.[19] In addition, Pendergrast et al. showed that hemolysis risk is associated with ABO zygosity, but not secretor status or Fc receptor polymorphisms suggesting patients with heterozygous A or B may be protected.[21]

Differences in patient co-morbidities and underlying health conditions may also affect hemolysis risk.[6–8,10,11,15,18,19,35,39,43] A high incidence of hemolysis has been observed among studies and case reports in patients with KD: a rare disease where hemolysis risk appears much greater than in most other conditions for which IVIG is indicated.[35,39,43] This increased risk could be related to patients' underlying inflammatory state.[7,43] In addition, high-dose immunomodulatory therapy (typically 2 g/kg) is standard in this indication and is sometimes increased to a cumulative dose of 4 g/kg.[7]

Additionally, the IVIG product itself can influence the incidence of hemolysis, with higher IVIG doses associated with a higher risk of hemolysis.[7,14,15] Data from the FAERS database showed that the majority of patients (n = 66/80) who experienced IVIG-related hemolysis were treated with IVIG doses of ≥2 g/kg IVIG.[14]

The production of IVIG can also impact the incidence of hemolysis. In studies where the specific IVIG product was named, different hemolysis incidence proportions were observed and were associated with isoagglutinins levels in the final manufactured product.[2] Previous studies have shown that the anti-A and anti-B content of IVIGs correlate with the risk of Ig-related hemolysis.[2] Anti-A donor screening and exclusion has been attempted but were found to produce only a moderate reduction in isoagglutinins, following exclusion of about 5% of donors with high anti-A.[44] Alterations to the manufacturing process have also been attempted to further reduce isoagglutinins in the final IVIG product.

Most modern, large-scale Ig manufacturing processes are based on combinations of cold ethanol precipitation, to separate IgG from albumin, followed by precipitation and chromatographic steps to increase IgG purity. In the Cohn fractionation process, isoagglutinins are reduced with the elimination of FrIII, which beyond IgM contains most IgG

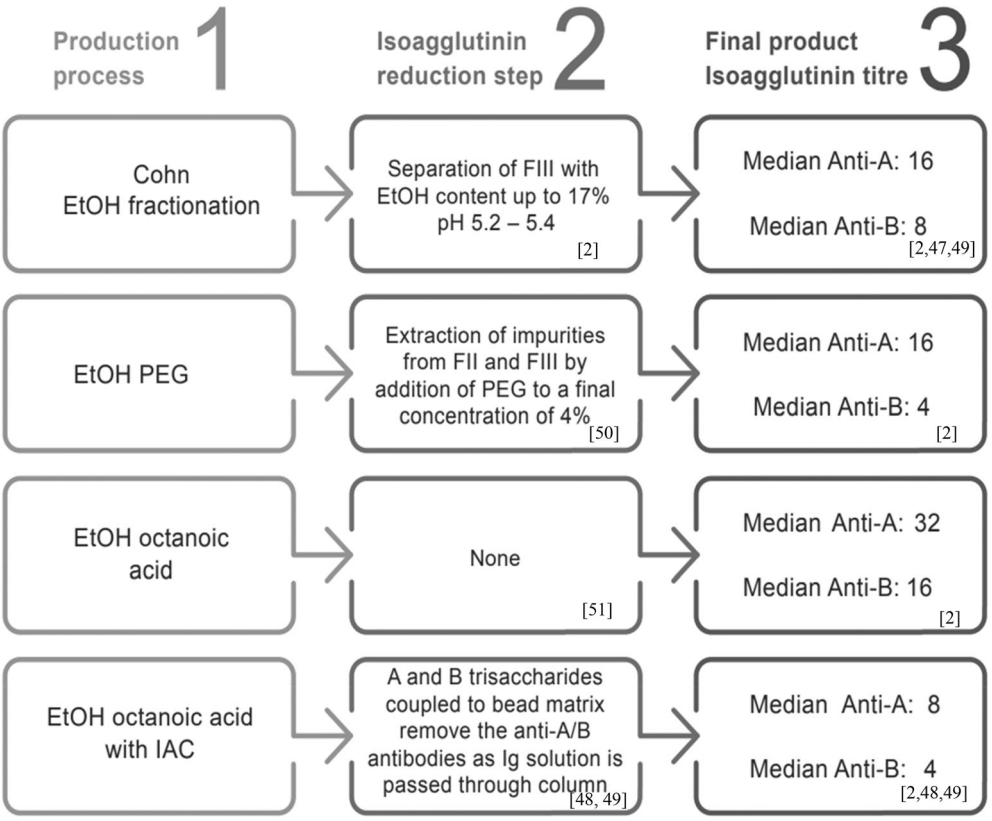

FIGURE 2 Production processes and isoagglutinin content.[2,47–51] EtOH, ethanol; IAC, immunoaffinity chromatography; Ig, immunoglobulin; PEG, polyethylene glycol.

isoagglutinins.[45] Other processes that have replaced the elimination of FrIII still remove IgM and with it most isoagglutinins; however, they may or may not reduce IgG isoagglutinin, for example, polyethylene glycol (PEG) precipitation reduces isoagglutinins whereas OA precipitation does not. Modern IVIG purification processes include anion exchange chromatography steps that increase the purity of IgG but do not reduce levels of isoagglutinins. Some IVIG purification processes include a specific immunoaffinity isoagglutinin reduction step, with a recent study showing that hemolytic events are significantly reduced from around 4.05 cases at baseline (per 1000 kg) to 0.50 cases when immunoaffinity chromatography (IAC) is utilized.[46] An overview of the main production processes and resulting isoagglutinin content is shown in Figure 2.

In studies that reported IVIG dose and product, the majority of hemolytic events occur with IVIG products produced by ethanol-OA fractionation given at a high dose (≥2 g/kg), with incidence rates of 0.7%–21.1% observed.[18,24] Only a few hemolytic events have been reported when products produced by Cohn fractionation, ethanol-PEG, and ethanol-OA plus IAC were given.[22,27] This suggests an association between an increased risk of hemolysis with increased amounts of isoagglutinins administered to the patient. However, further analyses to investigate this relationship and the impact of patient risk factors, like blood group, are required.

Limitations of this study include: first, studies had diverse patient inclusion criteria and definitions of hemolysis; second, many of the studies were not of high quality, with most being retrospective, some prospective observational, and none randomized controlled; and finally, this review only selected studies available on Embase written in English.

7 | CONCLUSION

In conclusion, the incidence of IVIG-related hemolysis differed across study types, ranging from 0% to 19% in observational studies and from 0% to 21% in clinical trials. Several factors appear to influence the risk of IVIG-related hemolysis, including blood groups AB, A, and B, high dose IVIG therapy, and products with anti-A/B. Therefore, monitoring patients for hemolysis is warranted particularly in these patient groups. IVIG production technique and the resulting isoagglutinin content may play a major role as well.

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CONFLICT OF INTEREST

Hillary Cuesta was a CSL employee at the time of development; Ibrahim El Menyawi, Alphonse Hubsch, Liane Hoefferer, Orell Mielke, Susie Gabriel, and Amgad Shebl are employees of CSL Behring.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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