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Review

Intravenous immunoglobulins for refractory status epilepticus, part I: A scoping systematic review of the adult literature

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ABSTRACT

Purpose: Our goal was to perform a scoping systematic review of the literature on the use of intravenous immunoglobulins (IVIG) for refractory status epilepticus (RSE) in adults.
Method: Articles from MEDLINE, BIOSIS, EMBASE, Global Health, Healthstar, Scopus, Cochrane Library, the International Clinical Trials Registry Platform, clinicaltrials.gov (inception to May 2016), reference lists of relevant articles, and gray literature were searched. The strength of evidence was adjudicated using both the Oxford and GRADE methodology by two independent reviewers.
Results: Twenty-four original articles were identified. A total of 33 adult patients were described as receiving IVIG for RSE. Seizure reduction/control with IVIG occurred in 15 of the 33 patients (45.4%), with 1 (3.0%) and 14 (42.4%) displaying partial and complete responses respectively. No adverse events were recorded.
Conclusion: Oxford level 4, GRADE D evidence exists to suggest an unclear impact of IVIG therapy in adult RSE. Routine use of IVIG in adult RSE cannot be recommended at this time.

1. Introduction

The use of intravenous immunoglobulin (IVIG) therapy within neurology has been primarily limited to autoimmune disorders, with the goal of reversing or halting progressive neurological deterioration related to the underlying immune mediated attack on the nervous system.

Occasionally, patients with autoimmune encephalitis, either formally diagnosed or suspected, will develop seizures. Such seizures can lead to refractory status epilepticus (RSE) and super refractory status epilepticus (SRSE) [1,2]. In these circumstances a variety of immunotherapies are applied as a means of both seizure control, and treatment for the underlying immune dysfunction.

Immunotherapies employed in RSE/SRSE include, but are not limited to: IVIG, plasmapheresis or plasma exchange (PE), corticosteroids, and monoclonal antibodies [1–5]. Administration of IVIG is thought to flood the system with non-reactive antibodies leading to a downregulation of inflammatory response via direct leukocyte interactions and catabolism of pathologic antibodies [6].

To date the literature on the administration of IVIG for RSE in adults is limited and widely dispersed [7–32]. Our goal was to perform a scoping systematic review of the literature on the use of IVIG for RSE in adults, in order to gain a better understanding of its current use and reported efficacy. This manuscript is part I in a two-part series of IVIG for RSE. Part II focuses on IVIG in pediatric RSE.

2. Materials and methods

A scoping systematic review using the methodology outlined in the Cochrane Handbook for Systematic Reviewers [33] was conducted. The data was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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(PRISMA) [34]. The review questions and search strategy were decided upon by the primary author (FZ) and senior author (LG). The process undertaken was identical to that seen in the companion paper on the pediatric response to IVIG, hence almost identical methods sections are seen in this manuscript and the pediatric companion piece.

2.1. Search question, population, inclusion and exclusion criteria

The question posed for scoping systematic review was: what is the effectiveness of IVIG in adult RSE? Similar to our other review papers on therapies in RSE, the definition of SE, and RSE was as per the Neurocritical Care Society guidelines on the management of SE [35]. The term generalized refractory status epilepticus (GRSE) was used to refer to generalized tonic–clonic RSE. The term focal refractory status epilepticus (FRSE) was used to refer focal tonic–clonic RSE. The term multi-focal refractory status epilepticus (MFRSE) was used to refer to RSE that had a mutli-focal tonic–clonic nature. The term non-convulsive refractory status epilepticus (NCRSE) was used for non-convulsive seizures that fulfilled the criteria for RSE.

All studies, prospective and retrospective of any size based on adult human subjects were included. The reason for an all-inclusive search was based on the small number of studies of any type identified by the primary author during a preliminary search of MEDLINE.

The primary outcome measure was electrographic seizure control, defined as: complete resolution, partial seizure reduction, and failure. This qualitative seizure response grading was used given the lack of detail around the electroencephalographic response reported within the studies found. Secondary outcome measures were patient outcome (if reported), and adverse effects of the administration of IVIG.

Inclusion criteria were: All studies including human subjects whether prospective or retrospective, all study sizes, the age category adults only (i.e. age 18 years or older), the documented use of IVIG for the purpose of seizure control in the setting of RSE, and documentation of some response to IVIG administration. Exclusion criteria were: pediatric studies, animal and non-English studies, and any studies failing to describe the use of IVIG or a response to IVIG administration.

2.3. Search strategy

MEDLINE, BIOSIS, EMBASE, Global Health, Healthstar, SCOPUS, and Cochrane Library from inception to May 2016 were searched using individualized search strategies for each database. The search strategy for MEDLINE can be seen in Appendix A of the Supplementary material, with a similar search strategy utilized for the other databases. In addition, the World Health Organizations International Clinical Trials Registry Platform and ClinicalTrials.gov were searched looking for studies planned or underway, with none identified.

As well, meeting proceedings for the last 5 years looking for ongoing and unpublished work based on IVIG for RSE were examined. The meeting proceedings of the following professional societies were searched: Canadian Neurological Sciences Federation (CNSF), American Association of Neurological Surgeons (AANS), Congress of Neurological Surgeons (CNS), European Neurosurgical Society (ENSS), World Federation of Neurological Surgeons (WFNS), American Neurology Association (ANA), American Academy of Neurology (AAN), European Federation of Neurological Science (EFNS), World Congress of Neurology (WCN), American Epilepsy Society (AES), International League Against Epilepsy (ILAE), Society of Critical Care Medicine (SCCM), Neurocritical Care Society (NCS), World Federation of Societies of Intensive and Critical Care Medicine (WFSICCM), American Society for Anesthesiologists (ASA), World Federation of Societies of Anesthesiologist (WFSA), Australian Society of Anesthesiologists, International Anesthesia Research Society (IARS), Society of Neurosurgical Anesthesiology and Critical Care (SNACC), Society for Neuroscience in Anesthesiology and Critical Care, and the Japanese Society of Neuroanesthesia and Critical Care (JSNCC).

Finally, reference lists of any review articles or systematic reviews on seizure management were reviewed for relevant studies on immunotherapy usage for RSE that were missed during the database and meeting proceeding search.

2.3. Study selection

This process was identical to other systematic reviews we have performed. Utilizing two reviewers (FZ and MM), a two-step review of all articles returned by our search strategies was performed. First, the reviewers independently screened all titles and abstracts of the returned articles to decide if they met the inclusion criteria. Second, full text of the chosen articles was then assessed to confirm if they met the inclusion criteria and that the primary outcome of seizure control was reported in the study. Any discrepancies between the two reviewers were resolved by a third party (LG).

2.4. Data collection

Data was extracted from the selected articles and stored in an electronic database. Data fields included: patient demographics, type of study (prospective or retrospective), number of patients, dose of IVIG used, timing to administration of IVIG, other immunotherapies administered, how many other AED were utilized prior to implementation of IVIG therapy, degree of seizure control (as described previously), adverse effects, and patient outcome.

2.5. Quality of evidence assessment

Assessment of the level of evidence for each included study was conducted by a panel of two independent reviewers, utilizing the Oxford criteria [36] and the Grading of Recommendation Assessment Development and Education (GRADE) criteria [37–41] for level of evidence. We elected on utilizing two different systems to grade level of evidence given that these two systems are amongst the most commonly used. We believe this would allow a larger audience to follow our systematic approach in the setting of unfamiliarity with a particular grading system.

The Oxford criteria consists of a 5 level grading system for literature. Level 1 is split into subcategories 1a, 1b, and 1c which represent a systematic review of randomized control trials (RCT) with homogeneity, individual RCT with narrow confidence interval, and all or none studies respectively. Oxford level 2 is split into 2a, 2b, and 2c representing systematic review of cohort studies with homogeneity of data, individual cohort study or low quality RCT, and outcomes research respectively. Oxford level 3 is split into 3a and 3b representing systematic review of case-control studies with homogeneity of data and individual case-control study respectively. Oxford level 4 represents case-series and poor cohort studies. Finally, Oxford level 5 represents expert opinion.

The GRADE level of evidence is split into 4 levels: A–D. GRADE level A represents high evidence with multiple high quality studies having consistent results. GRADE level B represents moderate evidence with one high quality study, or multiple low quality studies. GRADE level C evidence represents low evidence with one or more studies with severe limitations. Finally, GRADE level D

represents very low evidence based on either expert opinion or few studies with severe limitations.

Any discrepancies between the grading of the two reviewers (FZ and LG) were resolved via a third party (CK) if needed.

2.6. Statistical analysis

The goal of this study was to provide a scoping systematic review of the literature on IVIG administration for RSE in adults, only. A meta-analysis was not performed in this study due to the heterogeneity of data within the articles and the presence of low quality retrospective studies.

3. Results

The results of the search strategy across all databases and other sources are summarized in Fig. 1. A total of 452 articles were identified, with 434 from the database search and 18 from the search of published meeting proceedings. After removing duplicates, there were 320 articles. Through the first filtering process, we identified 46 articles that fit these criteria. Ten articles were added from the reference sections of relevant review articles and those articles identified in the first filtering process. Applying the inclusion/exclusion criteria to the full text documents, only 26 articles were eligible for inclusion in the systematic review, with 6 from database and 20 from meeting proceeding sources. Reference sections from these review articles were searched for any other articles missed in the database search, none were identified.

Of the 26 articles included in the review [7–32], 24 were original studies [7–30] and 2 were companion publications [31,32] with duplicate patient data. Madisi et al. [32] and Madisi and Berkeley [21] were meeting proceedings describing the same patient. Similarly, Alam et al. [31] and Alam et al. [9] both described the same patient. These 2 articles [31,32] were not included in the final data summary in order to prevent duplication of patient data.

All 24 original studies were retrospective studies [7–30], with 3 retrospective case series [13,18,29] and 21 retrospective case reports [7–12,14–17,19–28,30]. All were single center reports.

A total of 33 adult patients were documented as having received IVIG for RSE (mean 1.4 patients/study; range: 1–7 patients/study). The mean age was 31.8 years (median = 31; age range: 18–69 years). Three patients had no specific documented age [29], but were noted to be adults within the text of the manuscript.

Seizures were classified as GRSE in 14 patients [13,18,19,21,22,29], FRSE in 7 patients [7,10–12,15,28], MFRSE in 3 patients [8,13,16], NCRSE in 5 patients [17,20,25,26,27], and non-defined RSE in 4 patients [9,14,24,30].

The etiology of RSE varied significantly between studies and were as follows: new onset resistant status epilepticus (NORSE)

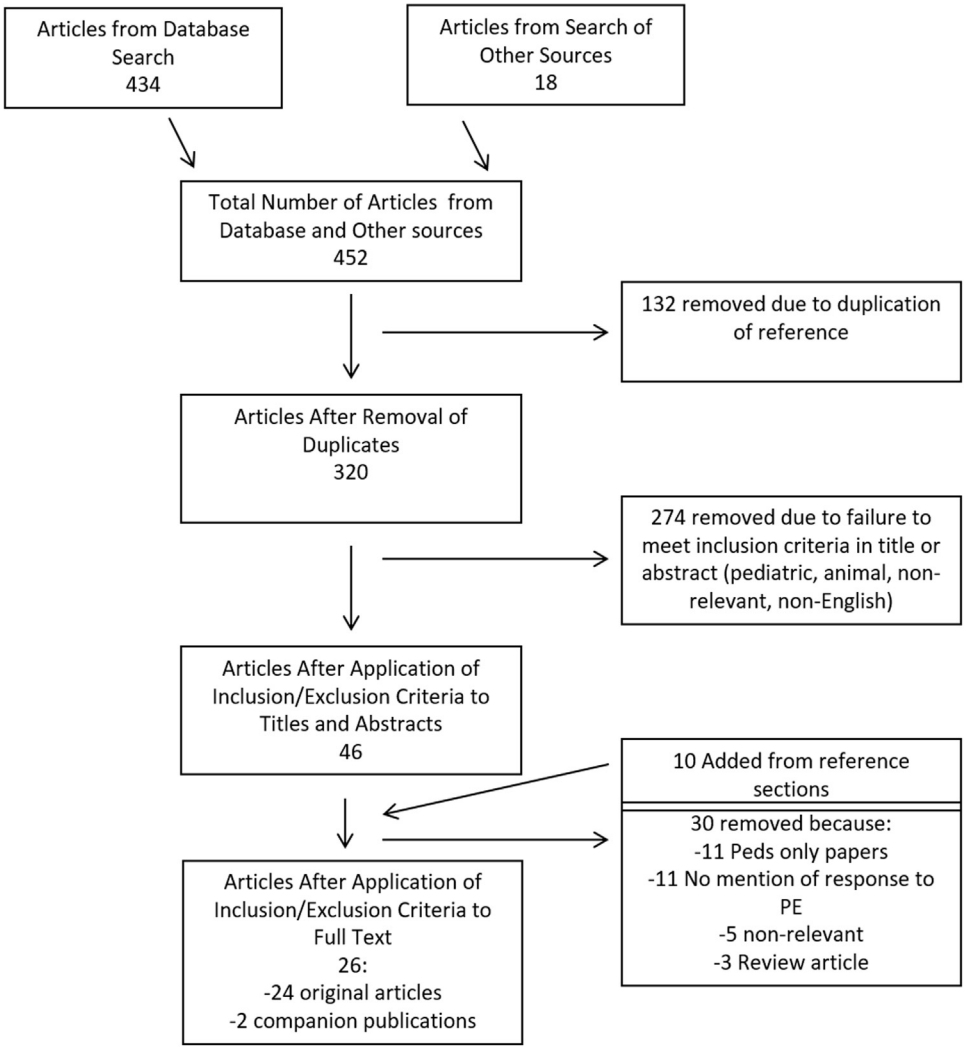

Fig 1. Flow diagram of search results.

not otherwise specified in 7 patients [13,15,21,29],*N*-methyl D-aspartate (NMDA) receptor encephalitis in 7 patients [18,23,24,26,27,30], anti-glutamic acid decarboxylase (anti-GAD) encephalitis in 2 patients [19,25], Rasmussen's encephalitis in 2 patients [8,28], viral encephalitis related (varicella zoster and Epstein-Barr) in 2 patients [18], lupus encephalitis in 1 patient [14], Hashimoto's encephalitis in 1 patient [9], anti-gamma amino butyric acid (anti-GABA) encephalitis in 1 patient [16], anit-voltage gated potassium channel (anti-VGKC) encephalitis in 1 patient [22], combined anti-VGKC and anti-voltage gated calcium channel (anti-VGCC) encephalitis in 1 patient [7], and unknown/idiopathic autoimmune encephalitis in 8 patients [10–12,17,18,20]. Study demographics and patient characteristics for all studies can be seen in Table 1.

3.1. IVIG treatment characteristics

Characteristics of the IVIG therapy were documented in only 8 of the 24 original articles [13,14,18–20,23,28,29]. The exact treatment regimen varied significantly. The most commonly quoted dosing was 0.4 gm/kg/day. The most common quoted duration of therapy was a 5 day course of IVIG.

The duration of treatment prior to IVIG therapy was documented in only 6 patients [12–14,18,20,21], ranging from 2 to 100 days (mean = 28.6 days; median = 16). The remaining articles failed to mention the duration of therapy prior to IVIG treatment. The number of AEDs administered prior to IVIG therapy was documented in 15 patients [9,11–21,23–26], with the total number ranging from 3 to 10 (mean = 7.1, median = 6). Treatment characteristics for the adult studies can be seen in Table 2.

Numerous other immunotherapies were administered in these patients (see Table 2). It was difficult from the information within the included studies to determine the exact sequence of these therapies. Thus, it is possible that the majority of these patients received combination immunotherapy as opposed to IVIG alone.

3.2. Seizure response

Seizure response to IVIG occurred in 15 of the 33 patients (45.4%) included in the review, with 1 patients [28] (3.0%)

Table 1
Adult IVIG study characteristics and patient demographics.

Reference	Number of patients treated with IVIG	Study type/ design	Article location	Mean age (years)	Etiology of seizures and type of status epilepticus	Mean # meds prior to IVIG	Mean time until IVIG administration (days)
Al-Ajlan et al. [7]	1	Retrospective case report	Journal manuscript	18	Etiology: autoimmune encephalopathy (anti-VGKC & anti-VGCC antibodies) Type: FRSE	NA	NA
Alam et al. [8]	1	Retrospective case report	Meeting abstract	20	Etiology: Rasmussen's encephalitis Type: MFRSE	NA	NA
Alam et al.[a] [9]	1	Retrospective case report	Meeting abstract	60	Etiology: Hashimoto's encephalitis (anti-TPO & anti-TG antibodies) Type: RSE (unknown subtype)	5	NA
Armas et al. [10]	1	Retrospective case report	Meeting abstract	69	Etiology: autoimmune Type: FRSE	NA	NA
Agirre-Arrizubieta and Moran [11]	1	Retrospective case report	Meeting abstract	28	Etiology: encephalopathy of unknown origin Type: FRSE	8	NA
Bobb et al. [12]	1	Retrospective case report	Meeting abstract	28	Etiology: unknown Type: MFRSE	5	25
Gall et al. [14]	2	Retrospective case series	Journal manuscript	30	Etiology: NORSE (presumed autoimmune). 1 → anti-TPO antibodies & ANA Type: 1 → MFRSE 2 → GRSE	1 → 7 2 → NA	1 → 18 2 → NA
Ghamande et al. [15]	1	Retrospective case report	Meeting abstract	41	Etiology: meningoencephalitis (SLE) Type: unknown type of RSE	5	2
Gonzalez et al. [16]	1	Retrospective case report	Meeting abstract	23	Etiology: NORSE Type: FRSE	6	NA
Hainsworth et al. [13]	1	Retrospective case report	Meeting abstract	23	Etiology: autoimmune encephalitis (anti-GABA(B) receptor antibodies) Type: MFRSE	NA	NA
Hoang et al. [17]	1	Retrospective case report	Meeting abstract	40	Etiology: unknown Type: NCRSE	9	NA
Khawaja et al. [18]	10 total (7 received IVIG)	Retrospective case series	Journal manuscript	35	Etiology: 1 → anti-NMDAr, anti-TPO antibodies 2 → EBV IgG 3 → anti-VGKC, VZV IgG/IgM 4,5,6 → unknown 7 → anti-VGCC, anti-NMDAr antibodies Type: All GRSE	5	13
Khawaja et al. [19]	1	Retrospective case report	Meeting abstract	22	Etiology: autoimmune (anti-GADb antibodies) Type: GRSE	3	NA

Table 1 (*Continued*)

Reference	Number of patients treated with IVIG	Study type/ design	Article location	Mean age (years)	Etiology of seizures and type of status epilepticus	Mean # meds prior to IVIG	Mean time until IVIG administration (days)
Li et al. [20]	1	Retrospective case series	Journal manuscript	39	Etiology: unknown Type: NCRSE	6	14
Madisi and Berkeley[b] [21]	1	Retrospective case report	Meeting abstract	23	Etiology: NORSE Type: GRSE	5	100
Mann et al. [22]	1	Retrospective case report	Meeting abstract	20	Etiology: autoimmune encephalitis (anti-VGKC antibodies) Type: GRSE	NA	NA
Marques et al. [23]	1	Retrospective case report	Meeting abstract	30	Etiology: anti-NMDAr encephalitis Type: FRSE	7	NA
Neligan et al. [24]	1	Retrospective case report	Meeting abstract	33	Etiology: anti-NMDAr encephalitis Type: unknown type of RSE	6	NA
Sawicka et al. [25]	1	Retrospective case report	Meeting abstract	18	Etiology: autoimmune (anti-GAD antibodies) Type: NCRSE	9	NA
Shatzmiller et al. [26]	1	Retrospective case report	Meeting abstract	19	Etiology: autoimmune (anti NMDAr antibodies) Type: NCRSE	10	NA
Thomas et al. [27]	1	Retrospective case report	Meeting abstract	19	Etiology: autoimmune (anti-NMDAr antibodies) Type: NCRSE	NA	NA
Villani et al. [28]	1	Retrospective case report	Journal manuscript	45	Etiology: Rasmussen's encephalitis Type: FRSE	NA	NA
Wilder-Smith et al. [29]	3	Retrospective case series	Journal manuscript	NA	Etiology: NORSE Type: GRSE	NA	NA
Yeo et al. [30]	1	Retrospective case report	Meeting abstract	32	Etiology: autoimmune (anti-NMDAr antibodies) Type: unknown type of RSE	NA	NA
Alam et al.[a] [31]	1	Retrospective case report	Meeting abstract	60	Etiology: Hashimoto's encephalitis (anti-TPO & anti-TG antibodies) Type: NCRSE	5	NA
Madisi et al.[b] [32]	1	Retrospective case report	Meeting abstract	23	Etiology: autoimmune, post-infectious Type: GRSE	5	100

AED = anti-epileptic drug, IV = intravenous, RSE = refractory status epilepticus, GRSE = generalized refractory status epilepticus, FRSE = focal refractory status epilepticus, NCRSE = non-convulsive refractory status epilepticus, MFRSE = multi-focal refractory status epilepticus, NORSE = new onset resistant status epilepticus, min = minute, hrs = hours, NMDAr = *n*-methyl D-aspartate receptor, GABA = gamma amino butyric acid, anti-VGKC = anti-voltage gated potassium channel, anti-VGCC = anti-voltage gated calcium channel, anti-TPO = anti-thyroperoxidase, anti-TG = anti-thyroglobulin, GAD = glutamic acid decarboxylase, VZV = varicella zoster virus, EBV = Epstein–Barr virus.

[a] Alam et al. [31] contains duplicate patient data to Alam et al. [9].

[b] Madisi et al. [32] contains duplicate patient data to Madisi and Berkeley [21].

displaying partial EEG based response and 14 patients [7,10,13,16,18,19,24,27] (42.4%) displaying complete resolution of seizures. Eighteen of the 33 patients (54.5%) had no response [8,9,11,12,14,15,17,18,20–23,25,26,29,30].

Through evaluating seizure subtype and response: 8 of the 14 (57.1%) GRSE patients responded, 3 of the 7 FRSE (42.9%) responded, 2 of the 3 (66.6%) MFRSE patients responded, 1 of the 5 NCRSE patients (20.0%) responded, and 1 of the 4 "unknown type" RSE patients (25.0%) responded.

Seizure recurrence in initial responders occurred in 2 of the 15 (13.3%). Eight of the initial responders had no clear documentation of whether seizures remained controlled post-IVIG [13,18,19].

Evaluating seizure etiology, we split the patients into two groups: antibody defined etiology (i.e. NMDA, GAD, GABA, SLE, Hashimoto's, VGKC or VGCC) and non-specific encephalitis (i.e. NORSE, Rasmussen's, suspected post-viral, and unknown). There were 14 patients with antibody defined etiologies, [7,9,14,16,18,22–27,30] of which 6 (42.9%) displayed completed seizure resolution with IVIG therapy. The remaining 8 (53.1%) patients with antibody defined disease failed to responds to IVIG. Similarly, there were 19 patients with non-specific encephalitis, [8,10–13,15,17–21,28,29] with 9 (47.4%) displaying seizure response (8 with complete; 1 with partial seizure reduction). Finally, in those patients with non-specific encephalitis, 10 (52.6%) failed to respond to IVIG.

3.3. Adverse effects of IVIG

Only 1 study [28] documented that there were no adverse events related to IVIG therapy. The remaining 23 studies did not document adverse events, nor make comments as to whether this was considered in their data collection processes.

3.4. Outcome

Outcome data was scarce, but we were able to make some general conclusions as to outcome in the majority of patients. Four patients lacked significant long term follow up data and their studies just focused on the subacute phase post-RSE [19,21,23,26]. Fifteen patients were recorded as returned or returning to baseline function [7,9,10,12–14,16,18,20,24,28]. Two patients were recorded with mild deficits [25,27]. Seven patients were recorded with severe deficits [8,11,17,18,29]. Five patients were reported as dead

Table 2
Adult IVIG treatment characteristics, seizure response, and outcome.

Reference	Number of patients treated with IVIG	IVIG dosing	Other immunotherapies	Other AED on board	Electrographic seizure response	Seizure recurrence	Adverse effects to IVIG	Patient outcome
Al-Ajlan et al. [7]	1	NA	IV steroids	None	Resolved	No	NA	Good: returned to baseline
			Prior to IVIG					
Alam et al. [8]	1	NA	None	Various unknown + barbiturate coma	Failed to improve	NA	NA	Poor: seizures were controlled with left hemispherectomy & on maintenance AED
Allam et al.[a] [9]	1	NA	IV steroids prior to IVIG, followed by repeat treatments on steroids, PLEX, RTX	PHT, LVT + various other unknown	Failed to improve	NA	NA	Good: improved post total thyroidectomy
Armas et al. [10]	1	NA	Steroids concurrently, followed with azathioprine	PHT, VPA, LVT, LCS + general anesthesia	Resolved	Yes	NA	Good: complete resolution, however SE would eventually relapse
Agirre-Arrizubieta et al. [11]	1	NA	PLEX	Various unknown + thiopentone	Failed to improve	NA	NA	Poor: persistent vegetative state
Bobb et al. [12]	1	NA	Allopregnalone	PTB	Failed to improve	NA	NA	Good: gradual reduction in seizures
			Not concurrent					
Gall et al. [14]	2	150 g over 5 days	1 → concurrent with steroids	1 → PRO, PHT, VPA, LVT, thiopentone, PB, CLB	1 → Seizures improved	1 → yes, controlled with azathioprine	NA	1,2 → Good: returned to baseline, on maintenance AEDs
			2 → steroids	2 → various unknown	2 → Improved	2 → Unknown		
Ghamande et al. [15]	1	3 day course	Prior: steroids	PRO, MDZ	Failed to improve	NA	NA	Good: gradually recovering post RTX treatment
Gonzalez et al. [16]	1	NA	Steroids concurrently, pyridoxine	MDZ, PTB, PRO, fPHT, VPA, LVT	Failed to improve	NA	NA	Poor: died
Hainsworth et al. [13]	1	NA	IV steroids, plasmapheresis, RTX	Various unknown	Seizures resolved	No	NA	Good: gradually returned to baseline
			All were given prior to seizure resolution—potential overlap					
Hoang et al. [17]	1	NA	High-dose steroids, plasmapheresis	LCS, TPM, DZP, PB, PTB	Failed to improve	NA	NA	Poor: seizures resolved with perampanel but discharged to long-term care facility
Khawaja et al. [18]	10 total (7 received IVIG)	5 days	1 → IV steroids & plasmapheresis	ALL:	1 → Improved	Unknown	NA	Good:
			2 → IV steroids, plasmapheresis, RTX, CPH	LRZ, fPHT	2 → Improved			1,2,4,5 → discharged home
			3 → steroids	1,2 → PRO, MDZ, PTB, KTM	3 → Failed to improve			Poor:
			4 → steroids, plamsapheresis	3 → PRO, MDZ	4 → Improved			3 → died
			5 → steroids, tacrolimus, everolimus, cyclosporin	4 → PRO, MDZ, PTB, KTM	5 → Improved			6 → nursing home
			6 → steroids	5 → PRO, PTB, KTM	6 → Improved			7 → hospitalized
			7 → plasmapheresis, RTX	6 → MDZ, KTM, fentanyl	7 → Improved			

Table 2 (*Continued*)

Reference	Number of patients treated with IVIG	IVIG dosing	Other immunotherapies	Other AED on board	Electrographic seizure response	Seizure recurrence	Adverse effects to IVIG	Patient outcome
				7 → unknown				
Khawaja et al. [19]	1	2 sessions	Steroids, PLEX, RTX, Cytoxan	KTM, MDZ, PTB	Burst suppression	unknown	NA	Good: burst suppression maintained
Li et al. [20]	1	5 day course	Steroids	LRZ, fPHT, LVT, PRO, VPA, LCS, PTB	Failed to improve	NA	NA	Poor: died
			After IVIG					
Madisi and Berkeley[b] [21]	1	NA	Steroids (concurrently), followed by PLEX & RTX	Various unknown	Failed to improve	NA	NA	Good: recovering gradually with PLEX & RTX
Mann et al. [22]	1	NA	Steroids, PLEX	PRO, MDZ, PB + various unknown AEDs	Failed to improve	NA	NA	Good: returned to baseline with PLEX
Marques et al. [23]	1	25 g/d for 5 days	Prior: steroids	MDZ, PRO	Failed to improve	NA	NA	Good: slow recovery with PLEX
			Followed by: PLEX					
Neligan et al. [24]	1	NA	RTX	VPA, PHT, PB, TPM, CLP, LVT, IV Mg	Improved	No	NA	Good: seizures resolved with gradual recovery
Sawicka et al. [25]	1	NA	Steroids, RTX, PLEX	LVT, CLB, TPM, CLP, LCS, VGB, PB	Failed to improve	NA	NA	Good: recovered with mild deficits
Shatzmiller et al. [26]	1	NA	Steroids, PLEX	Various unknown	Failed to improve	NA	NA	Good: recovering after CPH
Thomas et al. [27]	1	NA	Steroids, PLEX	Various unknown	Improved (unknown to which therapy directly)	No	NA	Good: mild neurological deficits (post ovarian teratoma resection)
Villani et al. [28]	1	400 mg/kg for 5 days (4 sessions, monthly)	Prior: steroids, PLEX	Unknown	>75% reduction in seizures	No	No	Good: gradual recovery in neurological function
Wilder-Smith et al. [29]	3	0.4 g/kg for 3 days	None	Various unknown	Failed to improve in all	NA	NA	Poor: severe vegetative state, death
Yeo et al. [30]	1	NA	None	Various unknown	Failed to improve	NA	NA	Poor: severe neurological deficits
Allam et al.[a] [31]	1	NA	IV steroids, plasmapheresis, rituximab	Various unknown	Failed to respond	NA	NA	Good: improved post total thyroidectomy
Madisi et al.[b] [32]	1	NA	Concurrent: steroids	Various unknown	Failed to improve	NA	NA	Good: recovering gradually with PLEX & RTX
			Followed by: PLEX, RTX					

AED = anti-epileptic drug, NA = not applicable, IV = intravenous, gm = gram, mg = milligram, kg = kilogram, hr = hour, min = minute, IV = intravenous, SE = status epilepticus, RSE = refractory status epilepticus, *PLEX = plasmapheresis, RTX = rituximab. AEDs: (CLB = clobazam, CLP = clonazepam, CPH = cyclophosphamide, DZP = diazepam, fPHT = fosphenytoin, KTM = ketamine, LCS = lacosamide, LRZ = lorazepam, LVT = levetiracetam, MDZ = midazolam, PB = phenobarbital, PHT = phenytoin, PRO = propofol, PTB = pentobarbital, RTX = rituximab, TPM = topiramate, VGB = vigabatrin, VPA = valproate.

[a] Alam et al. [31] contains duplicate patient data to Alam et al. [9].

[b] Madisi et al. [32] contains duplicate patient data to Madisi and Berkeley [21].

Table 3
Oxford and GRADE Level of Evidence.

Reference	Study type	Oxford [36] level of evidence	GRADE [37–42] level of evidence
Al-Ajlan et al. [7]	Retrospective case report	4	D
Alam et al. [8]	Retrospective case report	4	D
Alam et al.[a] [9]	Retrospective case report	4	D
Armas et al. [10]	Retrospective case report	4	D
Agirre-Arrizubieta et al. [11]	Retrospective case report	4	D
Bobb et al. [12]	Retrospective case report	4	D
Gall et al. [14]	Retrospective case series	4	D
Ghamande et al. [15]	Retrospective case report	4	D
Gonzalez et al. [16]	Retrospective case report	4	D
Hainsworth et al. [13]	Retrospective case report	4	D
Hoang et al. [17]	Retrospective case report	4	D
Khawaja et al. [18]	Retrospective case series	4	D
Khawaja et al. [19]	Retrospective case report	4	D
Li et al. [20]	Retrospective case series	4	D
Madisi and Berkeley[b] [21]	Retrospective case report	4	D
Mann et al. [22]	Retrospective case report	4	D
Marques et al. [23]	Retrospective case report	4	D
Neligan et al. [24]	Retrospective case report	4	D
Sawicka et al. [25]	Retrospective case report	4	D
Shatzmiller et al. [26]	Retrospective case report	4	D
Thomas et al. [27]	Retrospective case report	4	D
Villani et al. [28]	Retrospective case report	4	D
Wilder-Smith et al. [29]	Retrospective case series	4	D
Yeo et al. [30]	Retrospective case report	4	D
Alam et al.[a] [31]	Retrospective case report	4	D
Madisi et al.[b] [32]	Retrospective case report	4	D

[a] Alam et al. [31] contains duplicate patient data to Alam et al. [9].
[b] Madisi et al. [32] contains duplicate patient data to Madisi and Berkeley [21].

[15,18,20,29,30]. No identifiable trend in outcomes could be seen based on seizure subtype or etiology of seizures.

3.5. Level of evidence for IVIG

All 24 original studies [7–30] fulfill Oxford level 4, GRADE D evidence to an unclear impact of IVIG therapy for adult RSE. Summary of the level of evidence can be seen in Table 3.

4. Discussion

Some important points can be seen within our review. First, IVIG has an uncertain impact on seizure control in adult RSE. This is despite the majority of patients having either diagnosed, or suspected, autoimmune pathology leading to seizures in the first place. Second, there were no identified trends in RSE subtype, or seizure etiology, in terms of seizure control or outcome. This point is further emphasized by the fact that there was no difference in IVIG responders between those patients with antibody defined disease and those with non-specific encephalitis. Third, the seizure recurrence rate cannot be commented on in the "responder" group since the majority of patients in this group had insufficient data to determine recurrence or not. Fourth, the patients whom responded likely did so based on the combination of AED therapy and not IVIG alone. Fifth, there was typically a combination of immunotherapy administered in most patients, as seen in Table 2. It was difficult to determine the exact sequence immunotherapy, with some patients potentially receiving a combination of therapies during their IVIG treatment. Thus, those patients whom "responded" may have done so secondary to the combination of immunotherapy and not IVIG in isolation. Sixth, complications were not reported. This is likely secondary to underreporting. Finally, the patient outcomes were overly positive for an RSE population. This raised the concern of significant publication bias.

Our review has significant limitations. First, there were a small number of studies identified, all with small retrospectively collected patient populations. This fact alone makes it difficult to generalize this data to all RSE. Second, the retrospective heterogeneous nature of the data makes it difficult to perform a meaningful meta-analysis. We are thus left with only descriptive statistics to summarize the available data. Third, the seizure response IVIG described may not be related to IVIG at all. As described above, it may be related to the combination of AED or immunotherapies administered. The data from within the original studies left us unable to completely exclude these other therapies as the cause of seizure response. Fourth, our comments on the dosing and treatment regimen for IVIG are limited, as most studies did not divulge the exact details of the regimen. Finally, the potential for publication bias in the articles reviewed is extremely high. It is likely that there are many more negative results IVIG therapy that haven't made it to the literature.

Currently, the routine use of IVIG for adult RSE cannot be recommended at this time. At this moment, IVIG therapy for adult RSE should be considered experimental. There needs to be extensive prospective study of this drug, and other immunotherapies, for RSE prior to widespread implementation.

5. Conclusions

Oxford level 4, GRADE D evidence exists to suggest an unclear impact of IVIG therapy in adult RSE. Routine use of IVIG in adult RSE cannot be recommended at this time.

Conflict of interest statement

None of the authors have any conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.seizure.2016.12.017.

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