Seizure 43 (2016) 14–22

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Review

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

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ARTICLE INFO

Article history:
Received 24 August 2016
Received in revised form 8 October 2016
Accepted 14 October 2016

Keywords:
Plasmapheresis
PLEX
Plasma exchange
Status epilepticus
Refractory seizures
Adults

ABSTRACT

Purpose: Our goal was to perform a scoping systematic review of the literature on the use of plasmapheresis or plasma exchange (PE) for refractory status epilepticus (RSE) in adults.
Methods: 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-two original articles were identified. Twenty-seven adult patients were described in these articles, with a variety of autoimmune conditions leading to RSE. Seizure response with the application of PE therapy occurred in 14 of the 27 patients (51.9%), with 1 (3.7%) and 13 (48.1%) displaying partial and complete responses respectively. Generalized RSE was the most likely seizure subtype to respond to PE therapy. One patient had recorded an adverse events related to PE therapy.
Conclusions: Oxford level 4, GRADE D evidence exists to suggest an uncertain response of adult autoimmune RSE to PE therapy. Thus, the routine application of PE therapy for adult autoimmune RSE cannot be recommended at this time.

1. Introduction

Status epilepticus (SE), refractory status epilepticus (RSE), and super refractory status epilepticus (SRSE) pose a significant therapeutic challenge. Numerous therapies have been implemented in attempts to control these refractory seizures [1,2]. The longer the seizures remain uncontrolled, the more difficult they can be to treat. Immunotherapies are one of the tools applied in the setting of RSE/SRSE and include: plasmapheresis, intravenous immunoglobulins (IVIG), corticosteroids, monoclonal antibodies, and other immuno-modulators [1,2].

Plasmapheresis or plasma exchange (PE) has been applied sparingly in severe cases of RSE [1,2]. Typically it is utilized within the setting of diagnosed or presumed autoimmune encephalitis leading to RSE/SRSE. The theory behind its application is that through filtering out pathologic antibodies, the trigger for encephalitis will be removed and seizures will improve.

To date, application of PE to RSE/SRSE has been eluded to in a few literature reviews on the topic of refractory seizure control. However, there are only a small number of cases describing the use of PE for adult RSE [3–27]. Our goal was to perform a scoping systematic review of the literature on the application of PE for adult RSE, in order to gain insight as to the breadth of literature available on the subject. This manuscript is Part I of a two part series on PE in RSE. Part II is a scoping systematic review focused on PE in pediatric RSE.

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http://dx.doi.org/10.1016/j.seizure.2016.10.012
1059-1311/

2. Materials and methods

A scoping systematic review was conducted utilizing the methods outlined in the Cochrane Handbook for Systematic Reviewers [28]. Data was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [29]. Search strategy and review questions were decided upon by the primary author (FZ) and supervisor (LG). The process undertaken was identical to that seen in the companion paper on the pediatric response to PE, hence nearly 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 this scoping systematic review was: What is the effectiveness of PE for RSE in adult patients? The definition of RSE was as per the Neurocritical Care Society guidelines on the management of SE [30]. We utilized the following sub-classification system of RSE: generalized refractory status epilepticus (GRSE) was used to refer to generalized tonic-clonic RSE, focal refractory status epilepticus (FRSE) was used to refer focal tonic-clonic RSE, multi-focal refractory status epilepticus (MFRSE) was used to refer to RSE that had a mutli-focal tonic-clonic nature, and 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 to PE.

Inclusion criteria were: All studies including human subjects whether prospective or retrospective, all study sizes, adult age category only (i.e. 18 years and older), and documented application of PE for the purpose of seizure control in the setting of RSE. Exclusion criteria were: animal and non-English studies, pediatric patients, any studies where the response to PE was unclear or unstated, and any studies where the application of PE was for non-specific encephalopathy symptoms and not seizure control.

2.2. 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.

Meeting proceedings for the last 5 years looking for ongoing and unpublished work based on PE for RSE/SRSE 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 PE or immunotherapy application for RSE that were missed during the database and meeting proceeding search.

2.3. Study selection

Two reviewers (FZ and MM) performed 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, PE treatment characteristics, timing to application of PE, other immunotherapies administered, other AED were utilized prior to implementation of PE, 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 [31] and the Grading of Recommendation Assessment Development and Education (GRADE) criteria [32–37] 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 MM) were resolved via a third party (LG).

2.6. Statistical analysis

The main goal of this study was to produce a systematic scoping review on the topic of PE for adult RSE. A meta-analysis was not performed in this study due to the heterogeneity of data within the articles and the presence of only low quality retrospective studies.

3. Results

A flow diagram depicting the search strategy and results can be seen in Fig. 1. Overall a total of 379 articles were identified, with 364 from the database search and 15 from published meeting proceedings. Removing duplicate results, there were 287 articles for the first filtering process. Applying the previously outlined inclusion/exclusion criteria, we identified 61 articles with 46 from the database search and 15 were from published meeting proceedings. Applying the inclusion/exclusion criteria to the full text documents, and adding 8 references from the reference sections of the fully reviewed manuscripts, only 25 articles were eligible for inclusion in the systematic review, with 10 from database and 15 from meeting proceeding sources.

Of the 25 articles included in the review [3–27], 22 were original studies [3–24] and 3 were companion publications [25–27] with duplicate patient data. Allam et al. [5] and Allam et al. [25] were meeting proceedings describing the same patient. Similarly, Calabrace and Witherspoon [26] was a meeting proceeding containing duplicate patient data from the case report from Kirkpatrick et al. [14]. Finally, Madisi et al. [27] contained exact duplicate patient data to Madisi and Berkeley [16]. The duplicate publication data [25–27], was included in the tables only for completeness and was not included in the final summarization of data in order to avoid counting the same patients multiple times.

All 22 original studies were retrospective studies [3–24], with 2 retrospective case series [12,15] and 20 retrospective case reports [3–11,13,14,16–24]. All were single center reports.

A total of 27 patients were documented as having received PE for RSE (mean 1.2 patients/study; range: 1–4 patients/stud.). The mean age of the patients was 30.7 years (range: 18–74 years). Seizures were classified as GRSE in 15 patients [3,5–7,9,1213,15–18], FRSE in 6 patients [4,8,10,15,19,24], and NCRSE in 6 patients [11,14,20–23].

The etiology of SE/RSE varied significantly and were as follows: unknown suspected autoimmune etiology [3,4,7,11,12,15] in 8 patients, *N*-methyl D-aspartate (NMDA) receptor encephalitis in 6 patients [6,12,14,18,22,23], anti-glutamic acid decarboxylase (GAD) [12,13,21] in 3 patients, Hashimoto's encephalitis [5,20] in 2 patients, anti-voltage gated calcium channel (VGCC) [12] encephalitis in 1 patient, anti-voltage gated potassium channel

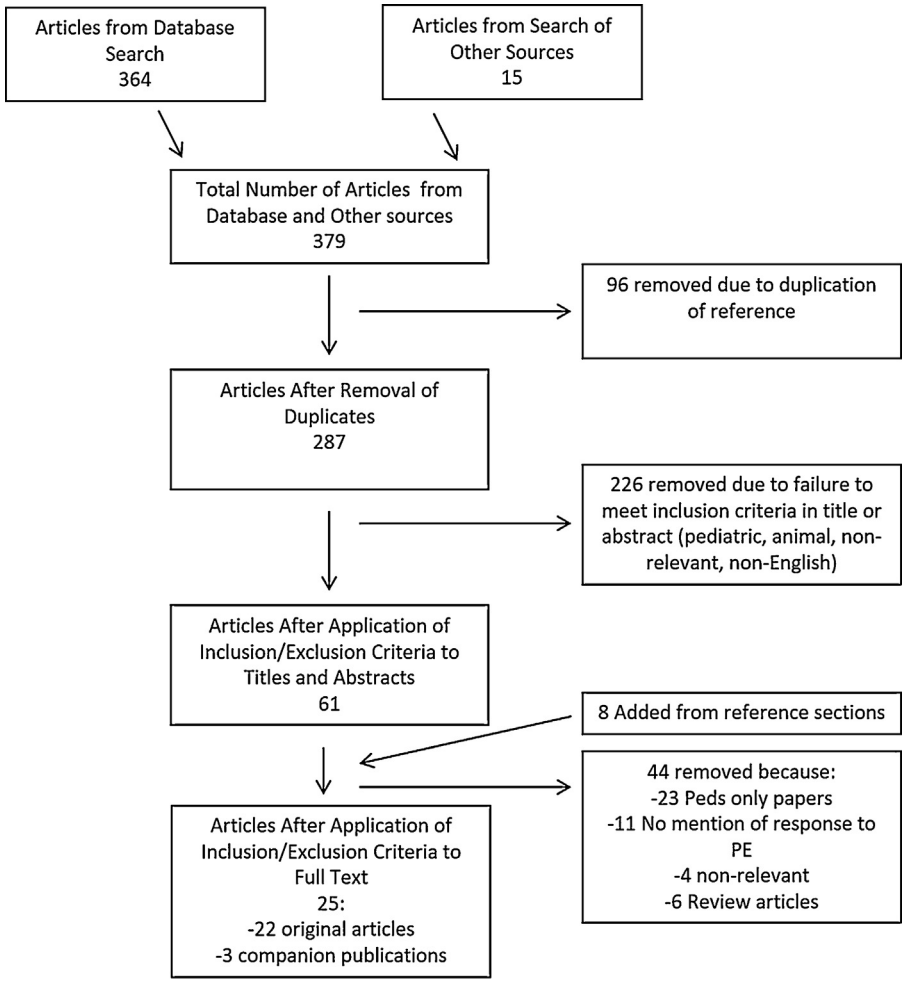

Fig 1. Flow diagram of search results.

Table 1
Adult study characteristics and patient demographics.

References	Number of patients treated with PE	Study type/ design	Article location	Mean age (years)	Etiology of seizures and type of status epilepticus	Mean # meds Prior to PE	Mean time until PE (days)
Agan et al. [3]	1	Retrospective case report	Journal manuscript	19	Etiology: autoimmune encephalitis Type: generalized RSE	3	8
Agirre and Moran [4]	1	Retrospective case report	Meeting abstract	28	Etiology: unknown Type: focal RSE	7	NA
[a]Allam et al. [5]	1	Retrospective case report	Meeting abstract	60	Etiology: Hashimoto's encephalitis (anti-TPO & anti-TG antibodies) Type: generalized RSE	5	NA
Amer et al. [6]	1	Retrospective case report	Letter	21	Etiology: anti-NMDAr encephalitis Type: generalized RSE	6	NA
Barnes et al. [7]	1	Retrospective Case Report	Meeting abstract	33	Etiology: encephalitis of unknown cause Type: generalized RSE	9	NA
Buerger et al. [8]	1	Retrospective case report	Journal manuscript	74	Etiology: herpes simplex encephalitis Type: focal RSE	6	12
Hainsworth et al. [9]	1	Retrospective case report	Meeting abstract	23	Etiology: autoimmune limbic encephalitis (anti-GABA-(B) receptor antibodies) Type: generalized RSE	NA	NA
Hakimi et al. [10]	1	Retrospective case report	Meeting abstract	44	Etiology: Creutzfeld–Jakob disease Type: focal RSE	11	NA
Hoang et al. [11]	1	Retrospective case report	Meeting abstract	40	Etiology: unclear Type: non-convulsive RSE	11	NA
Kawaja et al. [12]	4	Retrospective case series	Journal manuscript	23	Type: generalized RSE Etiology: autoimmune. Antibodies in each patient: 1 → anti-NMDAr 2 → anti-GAD 3 → cryptogenic 4 → anti-VGCC, anti-NMDAr	4	11
Khawaja and Amara [13]	1	Retrospective case report	Meeting abstract	22	Etiology: autoimmune (anti-GAD decarboxylase antibodies) Type: generalized RSE	3	NA
[b]Kirkpatrick et al. [14]	1	Retrospective case report	Journal manuscript	19	Etiology: anti-NMDAr encephalitis (mediastinal teratoma) Type: non-convulsive RSE	11	NA
Li et al. [15]	3	Retrospective case series	Journal manuscript	44 (39, 43, 51)	Etiology: unknown Type: 1, 3 → generalized RSE 2 → focal RSE	8	17
[c]Madisi and Berkeley [16]	1	Retrospective case report	Meeting abstract	23	Etiology: NORSE Type: generalized RSE	5+	>100
Mann et al. [17]	1	Retrospective case report	Meeting abstract	20	Etiology: autoimmune encephalitis (anti-VGKC antibodies) Type: generalized RSE	NA	NA
Marques et al. [18]	1	Retrospective case report	Journal manuscript	30	Etiology: anti-NMDAr encephalitis Type: generalized RSE	4	>30
Moeller et al. [19]	2 (1 adult)	Retrospective case report	Journal manuscript	27	1 → Etiology: autoimmune (anti-SSA & SSB antibodies) Type: focal RSE	7	1 → NA

Table 1 (*Continued*)

References	Number of patients treated with PE	Study type/ design	Article location	Mean age (years)	Etiology of seizures and type of status epilepticus	Mean # meds Prior to PE	Mean time until PE (days)
Pari et al. [20]	1	Retrospective case report	Journal manuscript	19	Etiology: Hashimoto encephalitis (anti-TPO & anti-TG antibodies) Type: non-convulsive RSE	2	NA
Sawicka et al. [21]	1	Retrospective case report	Meeting abstract	18	Etiology: autoimmune encephalitis (anti-GAD antibodies) Type: non-convulsive RSE	9	NA
Shatzmiller et al. [22]	1	Retrospective case report	Meeting abstract	19	Etiology: autoimmune encephalitis (anti-NMDAr antibodies) Type: non-convulsive RSE	10	NA
Thomas et al. [23]	1	Retrospective case report	Meeting abstract	19	Etiology: autoimmune encephalitis (anti-NMDAr antibodies) Type: non-convulsive RSE	NA	NA
Villani et al. [24]	1	Retrospective case report	Journal manuscript	45	Etiology: Rasmussen's encephalitis Type: focal RSE	NA	NA
[a]Allam et al. [25]	1	Retrospective case report	Meeting abstract	60	Etiology: Hashimoto's encephalitis (anti-TPO & anti-TG antibodies) Type: generalized RSE	5	NA
[b]Calabrace and Witherspoon [26]	1	Retrospective case report	Meeting abstract	19	Etiology: anti-NMDAr encephalitis Type: non-convulsive RSE	7+	NA
[c]Madisi et al. [27]	1	Retrospective case report	Meeting abstract	23	Etiology: autoimmune, post infectious Type: generalized RSE	5+	>100

NA = not applicable, AED = anti-epileptic drug, PE = plasma exchange, RSE = refractory status epilepticus, GABA = gamma aminobutyric acid, NMDAr = n-methyl d-aspartate receptor, GAD = glutamic acid decarboxylase, VGCC = voltage gated calcium channel, NORSE = new onset resistant status epilepticus, TPO = thyroid peroxidase, TG = thyroglobulin.

[a] Alam et al. [25] contains duplicate patient data to Allam et al. [5].

[b] Calabrace and Witherspoon [26] contains duplicate patient data to Kirkpatrick et al. [14].

[c] Madisi et al. [27] contains duplicate patient data to Madisi and Berkeley [16].

(VGKC) [17] encephalitis in 1 patient, anti-SSA encephalitis [19] in 1 patient, anti-gamma amino butyric acid (GABA) encephalitis [9] in 1 patient, herpes simplex encephalitis [8] in 1 patient, Creutzfeldt-Jakob disease [10] in 1 patient, Rasmussen's encephalitis [24] in 1 patient, and new onset refractory status epilepticus (NORSE) [16] not otherwise specified in 1 patient.

Study demographics and patient characteristics for all studies can be seen in Table 1, while treatment characteristics and seizure outcome are reported in Table 2.

3.1. PE treatment characteristics

Only 8 studies documented details around PE therapy [3,12,15,16,18,19–21]. The remaining studies only documented the application of PE therapy and some response. The number of PE sessions ranged from 2 sessions [3], up to 2 groups of 5 sessions [12]. The most commonly quoted regiment was a 5 session course that consisted of a single PE therapy on 5 consecutive days.

Duration of treatment prior to implementation of PE therapy was documented in 7 manuscripts [3,8,12,15,16,18,19], ranging from 8 to over 100 days (mean = 16.2 days). The remaining 15 articles failed to mention the exact duration of therapy prior to the initiation of PE. The number of AEDs administered prior to PE therapy was documented in 18 studies [3–8,10–16,18–22], with the total number ranging from 2 to 11 (mean = 6.5). The exact AEDs implemented prior to PE therapy varied significantly between studies, and can be seen summarized in Table 2, along with other treatment/response characteristics.

In addition to the other AED therapy administered, there were other immunotherapies administered in all but 1 study [3], consisting of: corticosteroids, IVIG, and rituximab. It was unclear from the majority of the studies whether these therapies were co-administered during PE therapy, or trialed in succession. The available details of these therapies can be seen in Table 2.

3.2. Seizure response

Seizure response to the application of PE therapy occurred in 14 of the 27 patients (51.9%) included in the review, with 1 patient [10] (3.7%) displaying partial temporary EEG based response and 13 patients [3,12,13,15–18,20,23] (48.1%) displaying complete resolution of seizures. 13 of the 28 patients (48.1%) had no response to the application of PE for their RSE [4–9,11,12,14,19,21,22,24].

Looking at seizure subtype: 10 of the 15 (66.6%) GRSE patients responded, 2 of the 6 (33.3%) FRSE patients responded, and 2 of the 6 (33.3%) NCRSE patient responded. Seizure recurrence upon completion of PE therapy occurred in 4 of the 14 (28.6%) of those patients whom initially responded [10,16,18,20].

No identified trend in seizure response could be identified based on autoimmune etiology.

3.3. Adverse effects of PE

One study documented a complication to PE therapy in 1 patient [18]. This complication consisted of hypofibrinogenemia

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

References	Number of patients treated with PE	PE regimen	Other immunotherapies	Other AED On board	Electrographic seizure response	Recurrence after PE	Adverse effects to PE	Patient outcome
Agan et al. [3]	1	2 sessions	NA	PHT, LVT, MDZ	Improved (Resolved RSE)	No	NA	Good: returned to baseline
Agirre and Moran [4]	1	NA	IVIG	Multiple unknown	Failure to improve	NA	NA	Poor: vegetative state
[a]Allam et al. [5]	1	NA	Steroids, IVIG, rituximab	PHT, LVT	Failure to improve	NA	NA	Good: resolved with thyroidectomy
Amer et al. [6]	1	NA	Steroids, IVIG	Multiple unknown	Failure to improve	NA	NA	Poor: long term care facility
Barnes et al. [7]	1	NA	Steroids	PB, KTM, KGD	Failure to improve	NA	NA	Good: returned to baseline
Buerger et al. [8]	1	NA	Dexamethasone (concurrently)	fPHT, LCS, steroids, others	Failure to improve	NA	NA	Poor: died
Hainsworth et al. [9]	1	NA	Methylprednisone, IVIG, rituximab	Multiple unknown	Failure to improve	NA	NA	Good: gradual improvement to baseline
Hakimi et al. [10]	1	NA	IVIG, steroids	LRZ, LVT, VPA, fPHT, CLB, MDZ, DZP, PB, KTD	Mild temporary improvement	yes	NA	Good: resolved with ketogenic diet
Hoang et al. [11]	1	NA	Steroids, IVIG	PTB, PRO, LRZ, KTM, LCS, TPM, DZP, PB, KTD	Failure to improve	NA	NA	Poor: severe neurological deficits
Khawaja et al. [12]	4	1,3,4 → 5 sessions 2 → 2 × 5 sessions	Steroids: 1 g/d/5d IVIG: 0.4 g/kg/d/5d IVIG → 1,2,3,4 Steroids → 1,2,3 Rituximab → 2,4 CPH → 2	1,2,3 → PRO, MDZ, PTB, KTM, LRZ, fPHT 4 → unknown	1,2,3 → improved 4 → failed to improve	unknown	NA	1,2,3 → Good. Returned to baseline 4 → poor
Khawaja and Amara [13]	1	NA	Corticosteroids, 2x IVIG, rituximab, cytoxan (concurrently)	Multiple unknown	Minimally improved	No	NA	Unknown Long term
[b]Kirkpatrick et al. [14]	1	NA	Rituximab, steroids (concurrent)	LRZ, DZP, PHT, LVT, VPA, PTB, OXB, PB	Failure to improve	NA	NA	Good: returned to baseline after felbamate
Li et al. [15]	3	5 days	1 → steroids 1 g QC/3d 2 → none 3 → IVIG, steroids for 5d each	1 → fPHT, LVT, PB, PRO, PTB, MDZ 2 → CBZ, fPHT, LVT, LCS 3 → fPHT, LVT, LCS, VPA, PB, LRZ, PRO, PB, KTM, MDZ	Improved in all	No	NA	1—good: mild neurological deficit 2—good: moderate neurological deficit 3—poor: died 2° to bowel necrosis
[c]Madisi and Berkeley [16]	1	2 sessions (concurrent with rituximab)	Steroids, IVIG. Rituximab (with PLEX)	Multiple unknown	Mild Decrease in Seizures	yes (after 2–3 w)	NA	Good: recovered slowly
Mann et al. [17]	1	NA	Steroids & IVIG	PRO, MDZ, PB +others	Improved	No	NA	Good: dramatic improvement
Marques et al. [18]	1	4 sessions (discontinued due to adverse effect)	IVIG (25 g/d × 5 d) Steroids high dose for 5d followed by 1 g/d × 5 d	MDZ, PRO	Improved	Yes	Hemoptysis 2° to hypofibrinogenemia & severe anemia	Good: slow recovery
Moeller et al. [19]	2 (1 Adult)	5 sessions	1 → IVIG 1 g/d × 5 d	1 → PRO, MDZ, PTB, LVT, LCS, TPM, PB	1 → Failure to improve	NA	NA	1 → poor: moderate neurological deficit
Pari et al. [20]	1	5 sessions	Steroids 1 g/d × 8 d	DZP	Improved	yes	NA	Good: returned to baseline
Sawicka et al. [21]	1	NA	Steroids, IVIG, rituximab	LVT, CLB, TPM, CLP, LCS, VGB, PB, PTB	Failure to improve	NA	NA	Good: mild deficits
Shatzmiller et al. [22]	1	NA	IVIG, steroids	Multiple unknown	Failure to improve	NA	NA	Good: gradual recovery with CPH
Thomas et al. [23]	1	NA	IVIG, steroids	Multiple unknown	Improved	No	NA	Good: mild neurological deficits. Also had ovarian teratoma resected

Table 2 (*Continued*)

References	Number of patients treated with PE	PE regimen	Other immunotherapies	Other AED On board	Electrographic seizure response	Recurrence after PE	Adverse effects to PE	Patient outcome
Villani et al. [24]	1	3 sessions	High dose steroids (concurrently), IVIG	Unknown	Failure to improve	NA	NA	Good: gradual recovery over 10 months after IVIG
[a]Allam et al. [25]	1	NA	Steroids, IVIG, rituximab	Multiple unknown	Failure to improve	NA	NA	Good: resolved with thyroidectomy
[b]Calabrace and Witherspoon [26]	1	NA	IV steroids, rituximab	LVT, OXB, PB, PHT, VPA	Failed to improve	NA	NA	Good: removal of teratoma + felbamate
[c]Madisi et al. [27]	1	2 sessions with rituximab	Steroids, IVIG, rituximab	Multiple unknown	Decreased seizure activity	Yes	NA	Good: seizures ceased

NA = not applicable, AED = anti-epileptic drug, PE = plasma exchange, g = gram, kg = kilogram, d = day, IV = intravenous, RSE = refractory status epilepticus, CBZ = carbamazepine, CLB = clobazam, CLP = clonazepam, CPH = cyclophosphamide, DZP = diazepam, fPHT = fosphenytoin, FBM = felbamate, KGD = ketogenic diet, KTM = ketamibne, LCS = lacosamide, LRZ = lorazepam, LVT = levetiracetam, MDZ = midazolam, OXB = oxcarbazepine, PB = phenobarbital, PHT = phenytoin, PRO = propofol, PTB = pentobarbital, TPM = topiramate, VGB = vigabatrin, VPA = valproate.

[a] Alam et al. [25] contains duplicate patient data to Allam et al. [5].

[b] Calabrace and Witherspoon [26] contains duplicate patient data to Kirkpatrick et al. [14].

[c] Madisi et al. [27] contains duplicate patient data to Madisi and Berkeley [16].

leading to hemoptysis and severe anemia. All other studies failed to document any adverse events, though it must be acknowledge this was not the main purpose of most of the studies included in this review.

3.4. Outcome

Some degree of outcome data was recorded for all but one patient [13]. Fifteen patients were recorded as recovered to baseline [3,5,7,9,10,12,14,16–18,20,22,24]. Three patients were recorded to be left with mild deficits [15,21,23]. Two patients had moderate deficits [15,19]. Four patients had severe deficits [4,6,11,12]. Two patients died [8,15]. No identifiable trend in outcomes could be seen based on seizure subtype, etiology of seizure, or comparing PE responders to non-responders.

3.5. Level of evidence for PE

Based on the 22 original articles included in the final review, all fulfill Oxford level 4, GRADE D evidence to suggest an uncertain impact on seizure control with the application of PE for adult autoimmune RSE. Summary of the level of evidence can be seen in Table 3.

4. Discussion

Despite the interesting trends identified within this review and outlined in the results section, there are significant limitations which should be addressed. First, given the paucity of literature on the subject, we were only able to identify retrospective studies documenting the application of PE for adult RSE in a small total number of patients. Furthermore, a large number of the literature identified was from published meeting abstracts. Given this, the data present on the individual patients and their response to PE was quite limited. Second, the seizure response to PE was only 51.9% in the setting of a significantly heterogeneous group of patients with varied autoimmune etiology. This makes the extrapolation of this data to other patients and populations extremely difficult. Third, the sequence of AED administered prior to the implementation of PE therapy was not well documented. Thus, in those circumstances where a positive seizure response to PE therapy was documented, it is hard to know whether PE alone led to improved seizure control. Given the combination of AED involved in the described patients, it is likely the seizure response was related to the entire regimen and not just PE alone. Fourth, other immunotherapies were administered in the majority of patients described within this review. The exact details surrounding the timing of these alternative immunotherapies was not clear. Thus, any seizure response recorded could potentially be related to an interaction amongst PE and the other immunotherapies recorded. Fifth, documentation around the details of PE therapy were lacking in the majority of the manuscripts included in this review. Therefore we cannot make any conclusions as to a PE regimen which may be efficacious in the setting of adult RSE. Sixth, despite screening the articles for the application of PE in the setting of RSE, it is possible that some of the included articles actually implemented PE for autoimmune encephalitis and not seizure control. This could skew our summarized results for seizure response. Seventh, given the limited number of patients and heterogeneous etiology of seizures, we could not identify trends in response to PE based on individual pathology. Eighth, the lack of described complications to PE therapy identified within this review is questionable. It is likely that such complications as venous thrombosis, line infections, and catheter insertional errors were underreported as the main focus of these studies was the therapies directed at RSE. Finally, patient outcomes reported in the

Table 3
Oxford and GRADE Level of Evidence.

References	Study type	Oxford [31] level of evidence	GRADE [32–37] level of evidence
Agan et al. [3]	Retrospective case report	4	D
Agirre and Moran [4]	Retrospective case report	4	D
[a]Allam et al. [5]	Retrospective case report	4	D
Amer et al. [6]	Retrospective case report	4	D
Barnes et al. [7]	Retrospective case report	4	D
Buerger et al. [8]	Retrospective case report	4	D
Hainsworth et al. [9]	Retrospective case report	4	D
Hakimi et al. [10]	Retrospective case report	4	D
Hoang et al. [11]	Retrospective case report	4	D
Kawaja et al. [12]	Retrospective case series	4	D
Khawaja and Amara [13]	Retrospective case report	4	D
[b]Kirkpatrick et al. [14]	Retrospective case report	4	D
Li et al. [15]	Retrospective case series	4	D
[c]Madisi and Berkeley [16]	Retrospective case report	4	D
Mann et al. [17]	Retrospective case report	4	D
Marques et al. [18]	Retrospective case report	4	D
Moeller et al. [19]	Retrospective case report	4	D
Pari et al. [20]	Retrospective case report	4	D
Sawicka et al. [21]	Retrospective case report	4	D
Shatzmiller et al. [22]	Retrospective case report	4	D
Thomas et al. [23]	Retrospective case report	4	D
Villani et al. [24]	Retrospective case report	4	D
[a]Allam et al. [25]	Retrospective case report	4	D
[b]Calabrace and Witherspoon [26]	Retrospective case report	4	D
[c]Madisi et al. [27]	Retrospective case report	4	D

[a] Alam et al. [25] contains duplicate patient data to Allam et al. [5].
[b] Calabrace and Witherspoon [26] contains duplicate patient data to Kirkpatrick et al. [14].
[c] Madisi et al. [27] contains duplicate patient data to Madisi and Berkeley [16].

identified studies were overly positive, with only two deaths. These results do not accurately reflect the outcomes in severe RSE. It is likely that these outcomes are the reason these particular patient cases were written for publication. We believe there is significant publication bias within the articles included in the review, within only articles documenting positive patient outcome and seizure response reaching publication.

Based on the results of this comprehensive review, we currently cannot recommend the routine application of PE for adult autoimmune RSE. More prospective analysis on the application of immunotherapies, including PE, in the setting of adult autoimmune RSE need to be conducted. With the implementation of international RSE databases, further light may also be shed on the application of PE and related therapies.

5. Conclusions

Oxford level 4, GRADE D evidence exists to suggest an uncertain response of adult autoimmune RSE to PE therapy. Thus, the routine application of PE therapy for adult autoimmune RSE cannot be recommended at this time.

Conflict of interest statement

None of the authors (FZ, MM, JT, CK or LG) have any conflicts of interest to disclose.

Disclosures

FZ has received salary support for dedicated research time, during which this project was partially completed. Such salary support came from: the University of Manitoba Clinician Investigator Program,R. Samuel McLaughlin Research and Education Award, the Manitoba Medical Service Foundation, and the University of Manitoba—Faculty of Medicine Dean's Fellowship Fund.

Funding

None.

Acknowledgments

This work was made possible through salary support through the University of Manitoba Clinician Investigator Program, R. Samuel McLaughlin Research and Education Award, the Manitoba Medical Service Foundation, and the University of Manitoba Faculty of Medicine Dean's Fellowship Fund.

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.2016.10.012.

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