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Review

Dietary, immunological, surgical, and other emerging treatments for pediatric refractory status epilepticus

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ABSTRACT

Purpose: To summarize the evidence regarding dietary, immunological, surgical, and other emerging treatments for refractory status epilepticus (RSE)/super-RSE (SRSE).
Methods: Narrative literature review including relevant human studies.
Results: Hypothermia and brenaxolone were tested in randomized controlled trials for RSE/SRSE management, while other interventions have only limited evidence for their efficacy and safety. Clinical trials including the HYBERNATUS study found the efficacy of therapeutic hypothermia to be no better than placebo for RSE/SRSE, and raised concerns about its safety. Ketogenic diet has shown possible efficacy in RSE/SRSE in several case series, with electrographic seizure resolution within 7 days in 20%–90% patients in larger (n = 8–17) reports. A review of 37 pediatric patients reported seizure control with immunotherapy in only 7 patients. A phase 3 double-blind trial showed that brexanolone was no better than placebo for successful wean of 3rd line anesthetic agent(s) and freedom from RSE for ≥24 hours. Epilepsy surgery has been reported to successfully control seizures in small series; however, pre-surgical evaluation is confounded by ongoing ictal activity and anesthetic infusions. Vagus nerve stimulation was reported to be associated with cessation of RSE/SRSE in 21/28 patients in a review of anecdotal reports. There is no evidence for use of pyridoxine and magnesium outside of specific indications.
Conclusions: There is only anecdotal evidence for dietary, immunological, surgical, and other treatments for RSE/SRSE, often confounded by multiple concurrent treatments, and heterogeneity in their use and assessment of outcomes. Clinical trials for therapeutic hypothermia and brexanolone have not shown a significant advantage over comparators.

1. Introduction

Refractory status epilepticus (RSE) is often defined as a prolonged seizure which fails to respond to two or more anti-seizure medications (ASMs), including at least one non-benzodiazepine ASM [1]. In children, RSE is a devastating condition associated with considerable mortality and long-term neurological morbidity [2,3]. For example, the case fatality for convulsive status epilepticus (SE) was 11% in the North London cohort, with cumulative incidence of epilepsy, intellectual disability, and motor impairment of 25%, 12%, and 5% respectively in survivors after a median follow-up of 9 years [4,5]. Other relatively smaller studies of pediatric RSE have reported mortality from 16% to 44%, and sequelae in 25%–100% of survivors [2,6–8]. Although pediatric RSE is an emergent condition, there is lack of high-quality evidence to formulate a management protocol. Anesthetic agents, including continuous infusions of midazolam or pentobarbital, and ketamine, are often used for initial treatment of pediatric RSE. Depending on the resources available to the clinical team, other conventional ASMs or inhaled anesthetics are also used, instead of, or in addition to, the continuous infusions. However, about 15%–35% of patients with RSE fail to achieve desired therapeutic endpoint with these approaches, and progress to the super-RSE. Super-RSE (SRSE) is defined as SE that continues for 24 h or more despite anesthetic treatment, or recurs on attempted wean of the anesthetic regimen [9,10]. These cases represent a desperate situation for the clinical team and a myriad approaches are brought upon to control the SRSE, frequently based on limited experience.

The goals of SRSE management are distinct from those for the treatment of established SE or even RSE. In early/established SE, the

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focus is to rapidly control the seizures to avoid neuronal injury. However, after more than 24 h of continuous or intermittent seizures, the excitotoxic and other potentially neuro-detrimental mechanisms, are likely already initiated. Hence, the therapeutic goal in SRSE is to check these processes, prevent their downstream consequences, and salvage end-organ function as much as possible [11]. Clinically, this implies avoiding, anticipating, and pre-emptively managing multi-system dysfunction that occurs in such patients from ongoing seizure(s), anesthetic agents, other treatments, and from prolonged unconsciousness and immobility. These complications include, but are not limited to, hemodynamic compromise and cardiac rhythm disturbances; muscle breakdown from convulsive motor activity resulting in myoglobinuria which may lead to oliguria or acute tubular necrosis, hyperkalemia; other electrolyte abnormalities including hypoglycemia, hyponatremia, and metabolic acidosis; cerebral edema, central hyperthermia; non-cardiogenic pulmonary edema (rare in children); coagulopathy; gastrointestinal stasis; and intensive care neuropathy and/or myopathy (reviewed in [12]).

2. Literature search

We performed structured searches for the role of dietary, immunological, surgical, and other unconventional treatment modalities in the treatment of SE using appropriate MeSH terms, limiting our results to human subjects and English language studies (Table 1). These results, along with cited references, were reviewed to select most representative studies, using clinical judgement about relevance to pediatric RSE/SRSE. The level of evidence was classified according to the American Academy of Neurology scheme [13]. We have reviewed and summarized the available evidence for RSE/SRSE treatments other than anesthetic agents, with a focus on clinical utility (Table 2).

3. Ketogenic diet (Kd)

KD is a high-fat, low-carbohydrate diet with proven efficacy in certain drug-resistant epilepsies (DREs) including infantile spasms, childhood epileptic encephalopathies, and inborn errors of neuronal glucose uptake. Over the last few years, there has been emerging evidence for efficacy of KD in RSE/SRSE. A study including 14 pediatric patients reported electrographic seizure resolution along with ≥50% suppression (usual therapeutic target in RSE/SRSE) in 10/14 patients within 7 days of starting KD [14]. In 11/14 patients, continuous infusions could be weaned off within 2 weeks of starting KD. However, it was noted that KD was under-utilized, as this sample of 14 patients was derived from a cohort of 239 RSE patients; and there was a median delay of 14 days after SE onset, before KD was used. Another series also reported resolution of SRSE in 9/10 patients after a median of 7 days, and weaning off anesthesia in 8/10 patients within 15 days of KD initiation [15]. Similarly, seizure resolution in 2 patients, and > 50% decrease in seizure frequency in 5 patients, a mean of 5 days after starting KD was reported in another series of 10 patients [16]. KD has also been successfully used in febrile infection related epilepsy syndrome (FIRES) with 7/9 patients achieving seizure remission a mean 5 days after initiating KD [17]. In a majority of patients, KD was given via enteral route, though in some cases ketogenic total parenteral nutrition (TPN) was also used, both typically in a 4:1 ratio. Common adverse effects reported with the use of KD for RSE/SRSE in studies with n > 5 have included metabolic derangements like ketoacidosis and hypoglycemia; and gastrointestinal symptoms like emesis [14–16,18,19]. While the incidence of adverse effects associated with the use of KD for treatment of RSE/SRSE has reportedly been low, there are concerns about variability in the definition of ketosis, and representative outcomes in this population [14]. Also, there is lack of data whether KD decreases mortality or long-term morbidity associated with SRSE, which are important functional outcomes.

Table 1
Literature search and summary of available evidence.

Treatment	Structured search strings	Results reviewed	Included studies	Best evidence	Comments on available evidence
Ketogenic diet	("Diet, Ketogenic"[Mesh]) AND "Status Epilepticus"[Mesh]	41	4	IV	Case series (n < 17) of children and adults Studies included are case series with > 8 patients
Immunological treatments	("Immunoglobulins, Intravenous"[Mesh]) AND "Status Epilepticus"[Mesh] ("Glucocorticoids"[Mesh]) AND "Status Epilepticus"[Mesh] ("Plasmapheresis"[Mesh]) AND "Status Epilepticus"[Mesh]	17, 6, 12	10	I*	Phase I/II/III trials of brexanolone Systematic review of IVIg for RSE including 33 adults Only small series in children
Pyridoxine	("Pyridoxine"[Mesh]) AND "Status Epilepticus"[Mesh]	21	2	IV	Total n ~ 16 isolated cases, or small series
Magnesium	("Magnesium"[Mesh]) AND "Status Epilepticus"[Mesh]	7	5	I*	RCT in women with eclampsia Systematic review of 28 patients (9 children)
Therapeutic hypothermia	("Hypothermia, Induced"[Mesh]) AND "Status Epilepticus"[Mesh]	46	16	I*	RCTs in RSE, and special populations (post cardiac arrest, TBI) Systematic review of 40 patients
Epilepsy surgery	("epilepsy surgery" OR "neurosurgery" OR "callosotomy" OR "vagus nerve stimulation" OR "subpial transection") AND ("Status Epilepticus"[Mesh])	108	26	IV	Case series n ≤ 10 (majority single case reports)
DBS, TMS, ECT	("Deep Brain Stimulation"[Mesh]) AND "Status Epilepticus"[Mesh] ("Transcranial Magnetic Stimulation"[Mesh]) AND "Status Epilepticus"[Mesh] ("Electroconvulsive Therapy"[Mesh]) AND "Status Epilepticus"[Mesh]	7, 12, 50	15	IV	Small series (majority single reports) Majority of papers about ECT, actually reported SE as a complication of ECT

(DBS Deep Brain Stimulation; ECT Electroconvulsive Therapy; IVIg Intravenous Immunoglobulins; MeSH Medical Subject Headings; RCT Randomized Clinical Trial; RSE Refractory Status Epilepticus; SE Status Epilepticus; Small series n ≤ 5; TMS Transcranial Magnetic Stimulation; *not relevant to pediatric RSE).

Table 2
Doses, regimens, or settings, derived from literature, and summary of efficacy and safety.

Treatment	Dose, regimen, and/or settings	Efficacy data summary	Potential adverse effects
Ketogenic diet	Ketogenic ratio 4:1 Target serum BHB 20 mg/dl (1.9 mmol/l) Prefer enteral administration	Resolution of SRSE within 7 days of starting KD: 20%–90% Weaning off anesthetic infusions within 2 weeks of starting KD: 77%–80% (in series with > 8 patients)	GI motility issues, hyperlipidemia, hypoglycemia, metabolic acidosis
Immunological treatments	IV methylprednisolone 30 mg/kg over at least 30 min (maximum dose 1000 mg) daily for 3–5 days; Oral prednisolone starting at 2 mg/kg/d (maximum 80 mg/d) with a gradual wean over several months IVIg 0.4 g/kg/d for 5 days Regimens: IV methylprednisolone followed by oral prednisolone Oral prednisolone only IVIg followed by oral prednisolone	Favorable outcome (no death, vegetative state, or significant disability) in 6/8 adults (nearly 2/3rds positive for anti-neuronal antibodies) Successful wean of 3rd line anesthetic and free of SE for ≥24 h in 44% of patients on brexanolone, compared to 42% of those on placebo in a double-blind phase III trial Seizure control in 7/37 pediatric patients with PEX/IVIg	Steroids: GI ulceration, fluid retention, hypertension, hyperglycemia, sodium imbalance IVIg: coagulopathy, screen for selective IgA deficiency before administration
VNS	Start at current strength of 0.25 mA, with rapid titration every 4–6 h up to 1–1.5 mA Starting duty cycle: 10%–16% Once current strengths of ~1.5 mA is reached, balance titration of current strength vs. duty cycle depending on electrographic response	Cessation of RSE in 21/28 patients (systematic review of anecdotal reports)	Most of the side effects are chronic and not relevant to its use in RSE
Epilepsy surgery	Not applicable.	Only isolated reports, and a series of 15 patients with successful outcomes, driven by candidate selection.	New neurological deficits, wound infections, meningitis, encephalitis, intracranial hemorrhage
Hypothermia	Endovascular cooling to 31–35 °C	Class I trial showed no significant difference in Glasgow outcome score of 5 at 90 days (aOR 1.22, 95% CI 0.75–1.99)	Coagulopathy, deep venous thrombosis, hypotension, electrolyte disturbances, cardiac arrhythmia, GI motility disturbances
Pyridoxine	15–30 mg/kg (maximum of 300 mg/d) single dose	Limited anecdotal evidence for efficacy other than in genetic pyridoxine dependency	Apnea, bradycardia
Magnesium	2–6 g/h infusion up to a target serum Mg level of 3.5 mmol/l	Class I evidence for superiority over diazepam (52%) and phenytoin (67%) in eclampsia (RRR) Seizure control in 12/28 (42.9%) patients with RSE/SRSE with recurrence in > 50% (systematic review of small series)	Hypotension, cardiac arrhythmia, neuromuscular conduction issues, avoid in renal failure

(aOR: Adjusted Odds Ratio; BHB: beta-hydroxy butyrate; GI: gastrointestinal; Ig: Immunoglobulins; IV: Intravenous; PEX: Plasma Exchange; RRR: Relative Risk Reduction; RSE: Refractory Status Epilepticus; SRSE: Super RSE; Small Series: case series with n ≤ 5; VNS: Vagus Nerve Stimulation].

Of the treatments discussed in this review, KD is perhaps the most promising and deserves prompt and rigorous studies to better characterize its place in the management of RSE/SRSE. This is partly because KD potentially interacts and undermines the pathophysiology of RSE at multiple levels including receptor trafficking; neurotransmitter localization and release with resultant excitotoxicity; blood brain barrier (BBB) permeability with downstream effects on access to drugs and inflammatory mediators; and mitochondrial dynamics in the face of oxidative stress [9,20,21]. However, KD has a relatively longer timeframe for treatment effect (1–2 weeks), compared to other non-surgical treatments reviewed here.

4. Therapeutic hypothermia

Although the anti-seizure and neuroprotective effects of hypothermia have been well-documented in experimental SE in animal models, the data in human RSE is not encouraging [22–26]. In 1970, intraoperative local brain cooling in conjunction with thiopental was first shown to achieve seizure remission [27]. This prompted the use of intraoperative local hypothermia, now usually achieved through cold saline irrigation, and used for seizure control during epilepsy surgery. In another early report, three pediatric patients with generalized SE were successfully treated by hypothermia (30–31 °C) along with 5–55 mg/kg/h thiopental infusion (cumulative dose 15–50 g) [28]. Electrographic burst suppression was achieved with plasma thiopental levels of 25–40 mg/dl and sustained for 48–120 h. Similarly, endovascular cooling (31–35 °C) successfully controlled RSE in four patients, allowing midazolam infusions to be discontinued [29]. After controlled rewarming, two patients remained seizure-free, and all four demonstrated reduced seizure frequency. This report highlighted the adverse events associated with the use of even mild hypothermia for RSE including coagulopathy, venous thromboembolism, renal tubular dysfunction with attendant acid-base and electrolyte abnormalities, bradyarrhythmias, and intestinal paresis. Two deaths were also reported, including one from sepsis, which was partly attributable to immunosuppression from the use of barbiturates and hypothermia. Other reports have included decreased seizure frequency with mild hypothermia (~36 °C) in an infant with RSE due to hemimegalencephaly [30]; prompt and sustained control of RSE in two pediatric cases of FIRES with moderate hypothermia (33 °C) [31]; and successful management of SRSE with mild hypothermia and inhaled isoflurane in a single adult [32]. In five pediatric patients with RSE, including four with relapse on attempted discontinuation of pentobarbital; hypothermia (32–35 °C) achieved sustained decrease in seizure burden [33]. One death was reported after redirection of care. A systematic review from 2015 reported seizure cessation in 62.5% of patients (total n = 40), most of whom received external cooling to a modal temperature of 33 °C [34].

The best evidence comes from the multicenter HYBERNATUS trial including 270 patients with convulsive RSE who were on assisted ventilation [35]. The primary endpoint of Glasgow outcome score of five (minimal/no neurologic deficit) at 90 days, was achieved in 67/138 (49%) patients in the hypothermia (32–34 °C) group, compared to 56/130 (43%) in the control group. The adjusted odds ratio was 1.22 (95% confidence limits 0.75–1.99) with the comparison not being significant. However, there is a concern that Glasgow outcome scale may not capture more subtle neurological deficits, such as in global cognitive functioning, seen in patients after RSE/SRSE. Furthermore, the

adverse events were more frequent in the hypothermia group compared to those allocated to receive standard care only.

Hypothermia has been shown in experimental conditions to antagonize multiple pathophysiological changes related to RSE/SRSE including decreased cerebral oxygen utilization, metabolic rate, excitotoxicity, calcium release, free radical production, reactive oxidative molecular species, and BBB permeability particularly for inflammatory intermediates [36]. However, the extent to which these potential mechanisms can be translated to human RSE, is unclear. Both in terms of its putative mechanisms and associated adverse effects, hypothermia is somewhat similar to KD. This supports investigating cellular and molecular disturbances in RSE/SRSE and effect of these treatment modalities on them. While laboratory investigators pursue these lines of research, the efficacy and safety of therapeutic hypothermia is presently not supported by well-designed clinical trials [35,37,38].

5. Immunological treatments

Despite the full armamentarium of sophisticated investigations available to the modern neurologist, a definite etiology for seizures can be established only in < 50% of patients with epilepsy [39,40]. Historically, this proportion has been even lower, which led astute clinicians to observe the beneficial role of steroids and other immunomodulatory treatments in some patients with epilepsy. A review of 32 children with epilepsy (excluding infantile spasms), found 8 patients to achieve seizure freedom, and 15 others to have decreased seizure frequency [41]. There is an increasing recognition of autoimmune epilepsies for last 10–15 years, both as paraneoplastic syndromes and without any neoplastic associations [42]. Consensus diagnostic criteria for various autoimmune encephalitis have also been proposed [42]. Relevant to the discussion here, cortical stage of anti-NMDA receptor encephalitis, and other limbic encephalitis including those associated with antibodies against GAD65, GABA-B receptor, AMPA receptor, and components of voltage-gated potassium channel complex, sometimes present with RSE/SRSE or with new-onset RSE (NORSE) [43,44]. This subgroup of patients with RSE may be uniquely amenable to treatment with immune-modulation. In a series of 11 adults (mean age 48 years), seven of whom were positive for anti-GAD or anti-NMDA receptor antibodies, eight patients received some combination of steroids, IVIg, or plasmapheresis [45]. Of these eight patients, six achieved favorable outcome, which was defined as any outcome other than death, vegetative state, or inability to take care of oneself; compared to 0/3 patients who did not receive any immunotherapy.

Given that not all anti-neuronal antibodies have been identified, and there may be patients with immune-responsive RSE/SRSE which may be antibody negative by commercially available panels, immunotherapies are worth trying in the treatment of pediatric RSE/SRSE with suspected limbic localization or autoimmune basis. This is supported, partly, by increasing recognition of the role of inflammation in human epileptogenesis [46]. Converging evidence from such studies and recognition of altered cortical excitability from endogenous steroids, have led to a trial of neuro-active steroids for RSE. In the phase I/II open-label trial of brexanolone, an aqueous formulation of allopregnanolone, 17/25 patients (age: 47.6 ± 19.5 years) were successfully weaned off 3rd-line anesthetic before tapering the study medication [47]. Although 16/25 patients experienced serious adverse events, none were attributed to brexanolone by the safety review committee. The phase 3 trial of brexanolone recently reported that the primary endpoint was not significantly different between the study drug (43.9%) and placebo (42.4%, $p = 0.88$) at the end of the double-blind period [48]. The primary endpoint in this trial included successful wean from 3rd-line agents, and remaining free of SE activity for at least 24 h without restarting the 3rd-line treatment. During the open-label extension period, 37% of patients on brexanolone achieved treatment response.

There is similar limited data for IVIg and plasmapheresis also. A recent systematic review found 33 adults who had received IVIg for RSE, 14 of whom achieved seizure control without any reported adverse events [49]. Use of plasmapharesis for RSE has been reported in 27 adults with autoimmune conditions, with 13 patients achieving seizure control [50]. Authors reported generalized RSE to more likely respond to plasma exchange. The reports have been less encouraging in children, with only 7/37 patients achieving seizure control, and two other patients experiencing a decrease in seizure burden [51]. Another recent review has reported “positive effects” of methylprednisolone pulse in 11/63 (17%) treatments in patients with FIRES and 15/40 (38%) treatments in cases with NORSE [52]. Similar outcomes were also reported for IVIg (5/94 for FIRES and 5/17 for NORSE), and plasmapheresis (2/18 for FIRES and 6/15 for NORSE). However, authors did not define “positive effects” but commented that the effects were transient in some cases. Overall, it may be desirable to empirically try some combination of steroids, IVIg, or plasma exchange in RSE/SRSE patients without any obvious etiology. Using these immunological treatments can be considered in RSE/SRSE patients without obvious contraindications and in settings with adequate resources for their management. In some cases, steroids may have additional beneficial effects on cerebral edema and intracranial pressure. Future studies, besides defining the clinical role of steroids and other immunotherapies, would benefit from studying the effects of these treatments on BBB permeability and function.

6. Epilepsy surgery

The basic principles of surgical decision making for RSE/SRSE are similar to those for DRE. If neuroimaging identifies a potentially epileptogenic lesion and there is neurophysiologic evidence for seizure-onset from that lesion, then a decision for resection of the lesion, sometimes including the adjacent cortex, may be relatively straightforward. These decisions would also incorporate location, size, and nature of such lesion(s); and functional significance of the surrounding cortex; which may require intracranial EEG monitoring and/or electrical stimulation mapping. At least in our center, such resections are performed with electrocorticographic (ECoG) guidance [53,54]. The decision making is more complicated and nuanced if the brain magnetic resonance imaging (MRI) does not show a lesion specific enough to guide neurosurgery (MRI-negative epilepsy), or shows multiple potential lesions [55,56]. In such cases, additional tests are often required including positron emission tomography (PET), ictal and inter-ictal single photon emission computed tomography (SPECT) with digital subtraction and MRI co-registration (SISCOM), and magneto-encephalography (MEG) to look for concordance and define the seizure-onset zone. Additional non-invasive functional mapping using functional MRI, MEG, or transcranial magnetic stimulation (TMS) may also be necessary. However, many of these studies can be confounded by ongoing seizure activity in patients with RSE/SRSE, or simply not feasible due to their medical condition and potential hazards associated with transportation. The safety and time available to perform, analyze, and cogitate over these studies for the clinical team is also limited when emergency epilepsy surgery is being considered for RSE/SRSE. Finally, such MRI-negative or multi-lesion patients are usually candidates for intracranial EEG monitoring using subdural and/or stereotactic depth electrodes. Such an endeavor is particularly challenging and often impractical given the medical and anesthetic considerations in RSE/SRSE. In many patients with RSE/SRSE such a localization is either not feasible or not achieved, which leads to consideration of palliative surgical options including vagus nerve stimulation (VNS) and complete corpus callosotomy (CCC).

There are small reports of successful seizure termination with resective surgery using a decision process similar to that summarized above. Acute termination of SRSE was achieved with epilepsy surgery in 10 patients who had been on continuous infusions for two weeks,

with 7/10 being seizure-free after a median seven month follow-up [57]. Another series of adults aged 20–68 years, evaluating chronic outcomes after SRSE, found 5/9 patients to be seizure-free 1 month to 7 years after ECoG-guided resections [58]. Unfortunately, three patients in this series died, allegedly after institution of "post-contrast", something which remained unclear and not adequately explained by the authors. In another report of three patients (including two children) with acute resolution of RSE after surgery, one patient underwent presurgical evaluation with stereo-EEG [59]. Other studies have reported seizure termination in 4/5 children with RSE after focal resections [60]; and, urgent surgery to achieve termination of RSE in 2/3 children having malformations of cortical development [61]. Interestingly, the patient who did not have seizure termination in this latter report, had histological evidence of aberrant cell-mediated immunity, leading the authors to suspect bilateral Rasmussen's encephalitis. In a larger series of 15 children, surgery guided by PET, ictal SPECT, and intraoperative ECoG achieved seizure control and facilitated transition out of the intensive care, after a mean pre-operative RSE duration of eight weeks [62]. Four patients had neurological worsening, having developed hemiparesis and dysphasia.

Single case reports also include termination of RSE with right anterior temporal lobectomy (ATL) in a 10-year-old boy with generalized convulsive RSE after a mild febrile illness and restricted diffusion in right hippocampus [63]; left occipital lobectomy 3 months after onset of RSE in a 7-years-old boy with anti-NMDA receptor encephalitis [64]; right ATL in a 45-year-old woman with limbic encephalitis due to antibodies against N-type voltage-gated calcium channels and a small cell carcinoma of the lung [65]; ECoG-guided resection of right dorsolateral frontal cortex in a 20-year-old man with nervous system vasculitis [66]; left temporal lesionectomy in a 56-year-old man with NORSE, where post-operative histology showed reactive gliosis and inflammatory biomarkers [67]; and, right ATL in a 60-year-old man with retrospective diagnosis of herpes simplex encephalitis [68]. It is notable that many patients with infectious or autoimmune epilepsies had undergone epilepsy surgery for RSE. As the awareness and recognition of these syndromes improves, it is likely that many such patients will be treated with immune-modulatory treatments and have more favorable outcomes.

Multiple subpial transections (MST) have also been tried, usually as an adjunct to the resection, in rare cases. Seizure termination was reportedly achieved in an adult with NORSE after resection of left middle frontal gyrus and MST of surrounding cortex [69]; and, in a 48-year-old man with a neoplasm involving right primary motor cortex with lesionectomy and MST of primary sensorimotor cortex [70]. Also, isolated MST of sensorimotor cortex was successful in a 6-year-old patient with MRI-negative SRSE of 60 days duration, where seizure-onset zone was localized by EEG and ictal SPECT [71].

Regarding palliative surgeries, there are rare reports of successful control of RSE with CCC, including a patient who remained seizure-free for up to two years, and another 9-year-old boy with seizure termination [72,73]. Functional hemispherectomy has also been used as a palliative measure in a child with Alper's disease, allowing extubation and discharge from intensive care unit [72]; and improved quality-of-life outcomes in two adults with RSE [74]. VNS has also been anecdotally effective both in children and adults for acute management of RSE. Reported cases include a 23-year-old man who had prompt termination of RSE of 3 weeks duration, allowing continuous infusions to be weaned [75]; a 30-years-old man with RSE after ASM withdrawal who underwent left VNS 9 days after unsuccessful barbiturate infusions, with electrographic improvement within 24 h [76]; and, a 67-year-old with RSE after evacuation of a spontaneous subdural hematoma, who was unresponsive to phenobarbital and propofol infusion but responded within a few days after VNS implantation [77]. In a single pediatric report, a 13-year-old boy with previous 90% callosotomy was implanted left VNS 15 days after onset of RSE. The VNS was activated at the following settings: frequency 30 Hz, pulse width 500 ms, on time 7 s, off time 120 s and current 0.25 mA. The current was increased by 0.25 mA/d for 2 days resulting in resolution of RSE within 24 h, with only a few (n = 11) brief (5–15 s) seizures during first 12 h [78]. A systematic review found 28 patients of VNS implantation for RSE with reported cessation of RSE in 21 cases (76%) [79].

7. Other neuro-stimulation modalities

A properly timed external electrical stimulus can prolong the post-excitation refractory period of abnormal hyper-synchronous discharges and may potentially interrupt an ongoing seizure [80]. However, such considerations should incorporate altered cortical excitability resulting from the underlying disease process that potentially caused the RSE, the ongoing seizure activity itself, and ASMs or other treatment modalities being used. At present, there is little evidence for clinical use of TMS or deep brain stimulation (DBS) in RSE/SRSE. TMS has shown some promise in epilepsia partialis continua but not in convulsive RSE [81–84]. In a 26-year-old female, 0.5 Hz electrical stimulation was performed through chronically implanted subdural electrodes over potential seizure-onset zones, with initial success in weaning an anesthetic agent, but subsequent recurrence of RSE and death of the patient [84]. Similarly, although there is evidence that DBS of anterior thalamic nucleus (ATN) can inhibit seizures in pilocarpine rat SE model [85], there are only a few reports of successful termination of RSE in humans. In one patient with focal RSE, stimulation of caudal zona incerta resulted in 70% decrease in seizure frequency and partial remission of RSE [86]. Other reports include clinical and EEG improvement in a 17-year-old girl with generalized convulsive RSE after ATN DBS [87]; and, resolution of SRSE in a 17-year-old boy after DBS of the centromedian nucleus of the thalamus, with immediate relapse on attempted reduction in stimulation settings [88].

Electroconvulsive therapy (ECT) has also been used in occasional patients with non-convulsive SE, based on anecdotal termination of non-convulsive SE after a spontaneous convulsive seizure [89]. In an early report, 3 bilateral ECT sessions (201–403 milli-Coulombs) given over 3 days effectively terminated non-convulsive SE in a 13 -year-old boy with microgyria and epileptic encephalopathy [90]. Recently, a 4-year-old boy with FIRES was reported to achieve termination of SRSE with ECT, who had been refractory to benzodiazepines, phenytoin, barbiturates, corticosteroids, plasmapheresis, immunoglobulins, propofol, lidocaine, ketamine, inhaled desflurane, ketogenic diet, lacosamide, and therapeutic hypothermia tried at different times over 8 weeks [91]. Based on studies in depressed subjects, ECT is hypothesized to increase pre-synaptic release of GABA resulting in prolonged post-ictal refractory period [92]. However, there is an unresolved issue given that concurrent ASMs and anesthetics can severely decrease cortical excitability, and seizure induction is required for the effect of ECT. This was noted in a patient where despite use of very high dosage, ECT could induce a seizure only after administration of flumazenil to antagnoize the effect of benzodiazepines and weaning off phenobarbital and phenytoin [93]. However, in another 7-year-old female with extensive bilateral polymicrogyria, 3 sessions of ECT (800 mA constant current at 60 Hz given as 1–2 millisecond pulses for 6–43 s) were able to terminate non-convulsive SE with no recurrence over an 11 weeks follow-up. In this patient, pentobarbital and ketamine drips were weaned off during ECT sessions, midazolam was reversed with flumazenil, but other ASMs (valproic acid, topiramate, levetiracetam, and clonazepam) were continued [94]. A recent review identified 8 case reports of use of ECT for RSE/SRSE, with electrographic resolution in six, but recovery to baseline in only two patients [95].

Overall, the role of neuro-stimulation (TMS, DBS, and ECT) for the treatment of RSE/SRSE remains poorly defined at present. Selection of the candidates who are likely to respond to these modalities, targets of stimulation, dose/regimen, and safety considerations need better evaluation before any recommendations can be formulated.

8. Magnesium

There is class I evidence for efficacy of magnesium for control of acute seizures in one specific context. The international collaborative eclampsia trial including 1680 women, showed a lower risk of recurrent seizures with magnesium infusion compared to diazepam (relative risk 52%) and phenytoin (67%) [96]. Although maternal mortality was lower in patients who received magnesium, the differences were not significant. Hence, magnesium is often regarded as the drug of choice for acute seizure management in eclampsia. However, there is little evidence for its use in other RSE/SRSE patients. In 1933, a series of 8 patients with use of magnesium for SE was reported, at a time when the "standard treatment" for SE was morphine, with atropine, ether, or chloroform anesthesia [97]. Subsequently, a single patient where intravenous magnesium failed to achieve termination of myoclonic SE, despite cerebrospinal fluid magnesium level of 3.5 mEq/L, was reported [98]. Recently, seizure remission was reported in 1 of 2 patients with FIRES with serum magnesium level above 3.0 mmol/l [99]. Importantly, the authors did not report any adverse effects associated with the infusion. Also, there is a report of 2 teenage girls with juvenile-onset Alper's syndrome due to POLG1 variants, whose SE responded to intravenous magnesium, allowing rapid extubation [100]. A systematic review of 28 patients (including 9 children), reported seizure control in 12 patients, with approximately half of them experiencing seizure recurrence after withdrawal of magnesium therapy [101].

Besides limited evidence for efficacy, safety of intravenous magnesium infusion is also a concern. Hypermagnesemia (serum levels > 4.5 mg/dl) may result in the inhibition of acetylcholine release at neuromuscular junctions causing hypotonia, weakness, and even overt paralysis. At higher concentrations, vasodilation is known to occur, with more severe hypermagnesemia (> 15 mg/dl) potentially risking complete heart block and cardiac arrest. Hence, the role of magnesium in patients with RSE/SRSE is unclear, especially as some of these patients may have limited renal clearance. The only exceptions are acute seizures occurring in women with eclampsia and in patients with hypomagnesemia from gastrointestinal or renal losses.

9. Pyridoxine

There are anecdotal (approximately 16) reports of patients with SRSE where intravenous pyridoxine infusion achieved seizure remission. Specifically, these patients did not require long-term pyridoxine supplementation, and probably did not have the genetic pyridoxine-dependent epilepsy, which results from pathogenic mutations in ALDH7A gene causing functional antiquitin deficiency, and require lifelong pyridoxine therapy [9,102]. Pyridoxine is also reported to be helpful for SE occurring in the context of isoniazid toxicity [103–107]. SE is known to be associated with both pyridoxine depletion in acute isoniazid toxicity, and chronic deficiency that occurs with prolonged isoniazid therapy. Typically, SE due to isoniazid toxicity may be refractory to other ASMs but responds well to intravenous pyridoxine supplementation. This consideration is especially relevant for regions with high prevalence of tuberculosis. Although acute intravenous pyridoxine infusion may be associated with respiratory depression and hypotonia, most RSE/SRSE patients are likely to be ventilated at this stage [108]. Overall, an empiric pyridoxine trial may be considered in infants, younger children, or those with predisposing factor(s) for pyridoxine deficiency.

10. Discussion

Although largely anecdotal, there is encouraging emerging evidence for dietary, immunological, surgical, and neuro-stimulation therapies in RSE/SRSE. Evaluation of the efficacy and safety of these modalities is confounded by the use of multiple other concurrent treatments in these patients with RSE/SRSE, heterogeneity in the timing of administration of these treatments, and evaluated outcomes. Also, there is likely a publication bias where cases with unsuccessful outcomes may not be reported or accepted. In near future, it is likely that the ongoing Established Status Epilepticus Treatment Trial (ESETT) will standardize the management of status epilepticus up to the second drug choice [109]. It will then be pertinent to conduct a series of adequately powered, well-designed, clinical trials looking at the differential efficacy and safety of various interventions for RSE and SRSE with emphasis on representative acute and chronic outcomes, to evolve a data-driven protocol.

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Conflict of interest

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Authors' contributions

RA: concept, data acquisition, data interpretation, and first draft of the manuscript. AR: critical review of the manuscript. Both the authors approved the final version.

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