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Review

Pediatric refractory and super-refractory status epilepticus

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ABSTRACT

Purpose: To summarize the available evidence related to pediatric refractory status epilepticus (RSE) and super-refractory status epilepticus (SRSE), with emphasis on epidemiology, etiologies, therapeutic approaches, and clinical outcomes.
Methods: Narrative review of the medical literature using MEDLINE database.
Results: RSE is defined as status epilepticus (SE) that fails to respond to adequately used first- and second-line antiepileptic drugs. SRSE occurs when SE persist for 24 h or more after administration of anesthesia, or recurs after its withdrawal. RSE and SRSE represent complex neurological emergencies associated with long-term neurological dysfunction and high mortality. Challenges in management arise as the underlying etiology is not always promptly recognized and therapeutic options become limited with prolonged seizures. Treatment decisions mainly rely on case series or experts' opinions. The comparative effectiveness of different treatment strategies has not been evaluated in large prospective series or randomized clinical trials. Continuous infusion of anesthetic agents is the most common treatment for RSE and SRSE, although many questions on optimal dosing and rate of administration remain unanswered. The use of non-pharmacological therapies is documented in case series or reports with low level of evidence. In addition to neurological complications resulting from prolonged seizures, children with RSE/SRSE often develop systemic complications associated with polypharmacy and prolonged hospital stay.
Conclusion: RSE and SRSE are neurological emergencies with limited therapeutic options. Multi-national collaborative efforts are desirable to evaluate the safety and efficacy of current RSE/SRSE therapies, and potentially impact patients' outcomes.

1. Introduction

Refractory status epilepticus (RSE) is a life-threatening neurological emergency associated with significant morbidity and mortality. RSE is defined as seizure activity that persists after administration of a first-line benzodiazepine (BZD) and a second-line antiseizure drug (ASD) [1]. Primarily encountered and treated in the intensive care unit (ICU), RSE patients usually receive additional boluses of second-line ASDs (e.g. fosphenytoin, levetiracetam, and valproate) or are placed in a medically induced coma with intravenous (IV) continuous infusions (CI) of an anesthetic (e.g. midazolam, propofol, barbiturates) for seizure control. Nevertheless, continuous or intermittent seizures may persist for 24 h or more following the administration of general anesthesia or recur after its withdrawal. The resulting condition is known as super-refractory status epilepticus (SRSE) [2]. Identifying the underlying etiology of RSE and SRSE can be challenging. Treatment decisions mainly rely on case series or experts' opinions. The comparative effectiveness of heterogeneous treatment strategies has not been systematically evaluated in large prospective series or randomized clinical trials.

The annual incidence of status epilepticus (SE) is estimated to be 17–23 episodes per 100,000 children [3,4]. Of these SE patients, between 10% and 40% develop RSE [5–7] with a mortality rate of 16–43.5% [8–10]. The few epidemiological studies on SRSE are based mainly in adult population [11] indicating that 10–15% of

Abbreviations: ASD, Anti-seizure drug; BZD, Benzodiazepine; CEEG, Continuous Encephalography; CI, Continuous infusions; CNS, Central Nervous System; FIRES, Febrile illness-related epilepsy syndrome; GCSE, Generalized convulsive status epilepticus; ICU, Intensive Care Unit; KD, Ketogenic diet; NCS, Neurocritical Care Society; NCSE, Non convulsive status epilepticus; NORSE, New onset refractory status epilepticus; RSE, Refractory status epilepticus; RCSE, Refractory convulsive status epilepticus; SRSE, Super-refractory status epilepticus; TBI, Traumatic brain injury.

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RSE cases progress to SRSE [12,13], and approximately one-third of RSE and SRSE patients die [12–14]. In children, a retrospective study showed that of 602 convulsive SE episodes, SRSE occurred in 7.14% [15]. In the United States, most data come from case series or case reports. Without large series, estimating the exact incidence and mortality of SRSE is challenging. In this review we present existing evidence on pediatric RSE/SRSE including clinical presentations and etiologies. We address current diagnostic and treatment approaches, as well as clinical outcomes of RSE/SRSE in children.

1.1. Clinical presentation

Patients who develop RSE/SRSE present clinically in different ways. The most common presentation is generalized convulsive SE (GCSE), the major seizure type for pediatric SE [16–18], or focal SE with impaired consciousness after failure to initial treatment. Other common clinical presentations are subtler and thus, are suggestive of non-convulsive SE (NCSE). In the latter clinical scenario, patients usually present with stupor/coma after a GCSE or after an acute brain insult [19,20]. Although convulsive SE often evolves to NCSE, the distinction between these two phenotypes is crucial as the therapeutic approaches and outcomes are different, being NCSE more often associated with medical refractoriness due to delayed recognition [20].

1.2. Etiology

The etiologies for pediatric RSE and SRSE reported in the literature vary. The most commonly reported etiologies include: acute symptomatic causes (e.g. presumed infectious or immune mediated encephalitis, central nervous system (CNS) infections, traumatic brain injury (TBI), brain ischemia), remote symptomatic with acute precipitant causes (e.g. CNS lymphoproliferative disease, human immunodeficiency virus (HIV) infection, hypoxic-ischemic encephalopathy, developmental delay, epilepsy), remote symptomatic and progressive encephalopathies (e.g. Alpers disease, metabolic diseases such as medium chain acyl-CoA dehydrogenase deficiency, epileptic encephalopathies), febrile SE (excluding CNS infections), and unknown etiologies (e.g. cryptogenic) [3,8,21,22]. Nonetheless, previous studies show that etiology varies according to age groups and geographic location. In a study of 151 refractory convulsive SE (RCSE) episodes, the most common etiology was acute symptomatic (28.5%) in neonates and infants; prolonged febrile convulsions (33.8%) in children 1–5 years; and remote symptomatic etiologies in 40% of patients between 5 and 10 years old, and in 36.8% patients between 10 and 16 years old [23]. In contrast, the etiologies contributing to RSE and SRSE development in the adult population include acute brain injury (e.g. cerebrovascular disease, CNS infections, brain tumor, traumatic brain injury), intoxication/withdrawal syndromes, low levels of antiepileptic drugs, metabolic distrubances, and systemic infections [19]. In developing countries, acute symptomatic etiology remains the most frequent etiology in children, followed by remote symptomatic and unknown etiologies. Within the acute symptomatic etiology, CNS infections (e.g. herpes simplex virus (HSV), HIV, neurocysticercosis, malaria, tuberculosis), viral/autoimmune encephalitis and meningitis are common causes [7,24–30].

New Onset RSE (NORSE), on the other hand, is a clinical presentation described in patients without epilepsy or a relevant preexisting neurological disorder, who present with RSE without an identifiable acute cause or active structural, toxic or metabolic cause [31]. A subcategory of NORSE known as febrile infection-related epilepsy syndrome (FIRES) commonly presents in previously healthy school-aged children [32,33]. These patients usually have a preceding febrile illness, with fever starting between 2 weeks and 24 h prior to the onset of SE, and can present with or without fever at the onset of SE [31]. The etiology of this syndrome remains unknown, and the seizures in this patient population are notoriously difficult to control in both the acute and chronic settings. While NORSE and FIRES are relatively rare epilepsy syndromes, they are frequent in the SRSE population. In a small study of ketogenic diet (KD) usage for SRSE, the most common etiologies included encephalitis/FIRES (55.55%), followed by FIRES (22.22%), epileptic encephalopathy (11.11%), and central nervous system-hemophagocytic lymphohistiocytosis (11.11%) [34]. Another study showed that 40% patients with SRSE had a diagnosis of immune-mediated encephalitis (Rasmussen's syndrome, post-infectious mycoplasma encephalitis and Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis), followed by FIRES (20%), genetic epilepsies (PCDH19 and GABRG2 mutations) (20%), epilepsy of a known metabolic etiology (10%) and NORSE (10%) [35]. Therefore, when initial diagnostic workup reveals negative results, these epilepsy syndromes should be considered in the differential diagnosis.

1.3. Pathophysiology

In RSE and particularly SRSE, mechanisms responsible for seizure termination fail and additional pathophysiologic processes develop leading to persistence of SE. At a cellular level, SE intensifies the internalization of synaptic γ-amino butyric acid type A (GABA-A) receptors whereas the function of extra synaptic receptors is preserved. This synaptic "receptor trafficking" leads to an overall reduction of the inhibitory activity of GABA, playing a key role in the development of pharmacoresistance [36]. Additionally, increased number of glutaminergic receptors at the neuronal surface may contribute to seizure perpetuation due to changes in concentrations of ions, like chloride, in the cellular environment. Furthermore, the persistence of seizures and development of SRSE may be explained by sensitivity to NMDA-mediated neuronal stimulation [37], mitochondrial failure [38], blood-brain barrier damage, and neuro inflammation (i.e. pro-inflammatory cytokines, autoantibodies to neural elements) [2]. All of these factors result in excitotoxicity [39], which is directly responsible for neuronal injury and cell loss, and ultimately poor clinical outcomes. Finally, previous studies demonstrate the important role of time from seizure onset to treatment administration on seizure duration [40,41]. If treatment is delayed or inadequate, seizures can rapidly become self-sustained and fail to respond to the intrinsic mechanisms normally involved in seizure termination [42].

2. Diagnosis & treatment

2.1. Diagnostic approach

Approximately 15% of patients with a prolonged convulsive seizure episode (>5 min) may achieve seizure cessation without medical intervention [6]; however, the majority of patients experience a seizure lasting more than 30 min. Therefore, RSE recognition is crucial and requires prompt diagnostic evaluation and treatment in order to prevent long-term sequelae. At this point in time, SE patients may have already completed a battery of testing [43–45], yet efforts should remain focused on identifying the etiology of RSE/SRSE (Table 1) [22,43–45]. Laboratory investigations for inflammatory and immune-related etiologies (e.g. serum and CSF-autoantibodies, IgG index) should be tiered according to the disease phenotype [45,46]. With more readily available genetic testing, evaluations for genetic epilepsy

Table 1
Recommended diagnostic workup for pediatric RSE/SRSE.

Always recommended
Finger stick blood glucose
Monitor vital signs
CT/MRI (almost always appropriate except in epileptic patients with a prior normal neuroimaging or with a generalized seizure syndrome and generalized seizures)
Serum electrolytes including calcium and magnesium
cEEG monitoring
Specific circumstances
Known epilepsy patient
ASD levels
Consider CT/MRI
Consider Electrolytes
*Decision making largely dependent on the patient's seizure history and associated comorbidities.
Febrile patient
SE with fever (presumed Febrile SE) in a patient ≤5 years, improved clinical state and SE resolving (no concerns for CNS infection)
Identification of primary source of fever
SE with fever in a patient>5 years, improved clinical state and SE resolving
Identification of primary source of fever
CT/MRI consider giving IV contrast if possible
SE with fever of unknown etiology and no improvement of clinical state
CBC
Lumbar puncture with CSF investigation of infectious etiologies
CT/MRI consider giving IV contrast if possible
Suspected non-infectious encephalitis (immune/inflammatory)
CRP
ESR
Auto-antibodies including ANA, anti-dsDNA, ANCA, APS & ENA panel
Serum anti-neuronal antibodies including anti-NMDAR, –AMPA & –VGKC, –GABA
Lumbar puncture with oligoclonal bands, and CSF anti-neuronal antibodies (as above)
Paraneoplastic evaluation if appropriate
Suspected genetic syndrome
Genetic consultation
Tiered genetic testing per age, clinical exam and seizure phenotype
Additional considerations
Toxicology screen
Consider medication side effect (chemotherapeutics, immune-modulators, etc.)
In rheumatologic disease consider: CRP, ESR, CMP, ANA, ANCA, APS panel, ENA panel

Abbreviations: CT: computed tomography, MRI: magnetic resonance imaging, cEEG: continuous electroencephalogram, ASD: anti-seizure drug, SE: status epilepticus, CNS: central nervous system, IV: intravenous, CBC: complete blood count, CSF: cerebrospinal fluid, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, ANA: anti-nuclear antibody, ANCA: anti-neutrophil cytoplasmic antibody, APS: anti-phospholipid syndrome (lupus anticoagulant, anti-β2-glycoprotein,-cardiolipin), ENA: extractable nuclear antigen (anti-Smith, –RNP,-Ro,-La), NMDAR (N-methyl-D-aspartate), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), VGKC (voltage gated potassium channel), GABA (γ-Amino butyric acid)

syndromes should be considered in patients in whom an etiology is not established with the initial testing. These should be suspected particularly in patients that present at young ages, or with a history of dysmorphic features, developmental delay or a family history of epilepsy.

Lastly, continuous electroencephalography (cEEG) monitoring is essential for the diagnosis and management of RSE/SRSE [43,47,48]. Monitoring with cEEG allows clinicians to target electrographic seizure cessation or achievement of burst-suppression as the case requires [43,47,48]. It is helpful to guide the induction of pharmacological coma as well as the identification of subsequent electrographic seizures, often recurring during titration or weaning of anesthetic agents [49]. Furthermore, there is evidence that approximately 1/3 of the children with convulsive SE may develop electrographic seizures and of these, almost half evolve to electrographic SE [50]. There is certainly an increased awareness of the valuable aid of cEEG in the initial treatment and diagnosis of RSE/SRSE [51,52]; however, not all of the available pediatric studies include it in their RSE/SRSE management. This highly limits the generalizability of results and comparison of clinical outcomes across studies, particularly in NCSE.

2.2. Treatment

The therapeutic approach in RSE/SRSE aims to achieve seizure control with prevention of excitotoxicity, neuroprotection and avoidance of systemic complications [53]. Coma induction with anesthetic agents is the most common treatment after failure of first- and second-line ASDs. The choice of anesthetic agent is often individualized. Unfortunately, due to the lack of randomized clinical trials to guide clinical practice, the goal of pharmacological induced coma (termination of seizures, burst-suppression or complete suppression of EEG activity [54]), duration, and weaning parameters remain unclear. In general, CIs should be titrated to achieve electrographic seizure cessation or burst-suppression; which should be maintained for at least 24–48h before withdrawal of CI agents [43]. If seizures recur after the weaning period, CIs are usually up-titrated until cessation is re-attained and for additional 24–48h. In addition to coma induction with anesthetic agents, the use of adjunctive therapies such as immunomodulation, ketogenic diet, hypothermia, electroconvulsive therapy and vagus nerve stimulation might be considered despite their low level of evidence. The treatment approaches for RSE/SRSE are heterogeneous and usually employed in a trial and error fashion until a response is achieved. Table 2 summarizes the most common pharmacological and non-pharmacological therapies for the treatment of RSE/SRSE [43,55,56] and their corresponding level of evidence.

2.2.1. Anesthetics and continuous infusions

The most commonly used agents for coma induction are midazolam [15,26,57–59], barbiturates and propofol [53,60]. Midazolam is a fast-acting BZD that enhances the action of GABA on the GABA-A receptors in the CNS [61,62]. It has a short duration

Table 2
Pharmacological and non-pharmacological therapies for the treatment of RSE/SRSE.

	Mechanism of action	Dose	Adverse Events	Clinical Considerations	Level of evidence	References
Pharmacological therapies						
Benzodiazepines						
Midazolam	Positive allosteric modulation of GABA-A receptors, Increases frequency of CI channel opening	Loading dose: 0.2 mg/kg; administer at an infusion rate of 2 mg/min Infusion rate: 0.05–2 mg/kg/h Breakthrough SE: 0.1–0.2 mg/kg bolus, increase rate by 0.05–0.1 mg/kg/h. every 3–4 h	Hypotension, respiratory depression	Prolonged use may cause tachyphylaxis and drug accumulation	Class IIA, Level B Class IV	[43] [9,153]
IV anesthetic agents						
Barbiturates						
Pentobarbital	Activation of GABA receptors-increase mean CI channel opening duration, inhibition of NMDA receptors, alteration in conductance of Cl^-, K^+, Ca^{2+} ion channels.	Loading dose: 5–15 mg/kg; infusion rate $\leq$ 50 mg/min Infusion rate: 0.5–5 mg/kg/h Breakthrough SE: 5 mg/kg bolus, increase rate by 0.5–1 mg/kg/h. every 12 h	Hypotension, cardiac and respiratory depression, paralytic ileus, infection	Long half-life (15–50 h) Requires mechanical ventilation. Can exacerbate porphyria Hepatic enzyme inducer Drug accumulation with prolonged use	Class IIB, Level B Class IV	[43] [10,65].
Thiopental	Same as the mechanism described above	2–7 mg/kg, infusion rate $\leq$ 50 mg/min Infusion/ maintenance rate: 0.5–5 mg/kg/h Breakthrough SE:1–2 mg/kg bolus, titrate by 0.5–1 mg/kg/h. every 12 h.	Hypotension, cardiac and respiratory depression	Requires mechanical ventilation, titrate infusion rates to EEG burst-suppression	Class IV	[66]
Propofol	Chloride channel conductance, enhances GABA-A receptor	Initial loading dose: 1–2 mg/kg Initial infusion rate 20 mcg/kg/min titrated by 5–10 mcg/kg/min Use with caution with doses > 65 mcg/kg/min Breakthrough SE: Increase infusion rate by 5–10 mcg/kg/min every 5 min	PRIS, hypotension, cardiac and respiratory depression	Requires mechanical ventilation Prolonged infusion of propofol is a relative contraindication in children (due to risk of PRIS) and in patients with metabolic acidosis, mitochondrial disorders or hypertriglyceridemia Reduces ICP Caution with concomitant use of steroid or catecholamine therapy	Class IIB, Level B Class IV	[43] [66]
Ketamine	Noncompetitive NMDA glutamate receptor antagonist-reduces neuronal excitability	0.5–3 mg/kg Infusion rate: 1–10 mg/kg/h	Tachycardia, hypertension, ICP elevation	Relative contraindication in patients with ICP. Ketamine is an enzyme inducer and inhibitor (CYP2C9)	Class IV	[73,154]
Inhalational anesthesia						
Isoflurane	Enhancement of GABA-A receptors, noncompetitive antagonist of NMDA receptor	Concentration 1–5% Titrate to achieve burst-suppression on EEG	Hypotension requiring use of vasopressors, atelectasis, paralytic ileus, infection, deep vein thrombosis	High seizure recurrence rate	Class IV	[83,84,87]
Immunomodulatory therapy						
IVIG	Alteration of IgG-specific receptors (FcγR) expression and function (decreases cytokine production), attenuation of complement mediated cell damage	1–2 g/kg divided over 3–5 days	Hypersensitivity reactions, transfusion related acute lung injury, thromboembolic events, renal dysfunction with concentrated solutions, aseptic meningitis	Immunomodulatory therapies may be considered in patients with cryptogenic, autoimmune etiologies of RSE/SRSE.	Class IV	[33,93,94,155]
Corticosteroids:						
Methyl prednisolone	Inhibition of inflammation-associated proteins (e.g. cytokines, chemokines) and immunosuppressive action	1 g/day for 3–5 days	Glucose intolerance, psychiatric disturbances, altered immune function, adrenal suppression		Class IV	[91–94,156,157]
Prednisone	Same as the mechanism described above	60 mg daily				

Table 2 (*Continued*)

	Mechanism of action	Dose	Adverse Events	Clinical Considerations	Level of evidence	References
Plasmapheresis	Removal of circulating autoantibodies, immune factors or high weight proteins that may participate in inflammatory process	5 exchanges over 5 days			Class IV	[33,94,96,140,158–160]
Non-pharmacological alternatives						
Ketogenic diet	Ketosis mediated decreased glycolysis, increase in free and polyunsaturated fatty acids, anti-inflammatory action, stabilization of neuronal membrane	4:1 (ratio fat to carbohydrates and proteins)	Hypoglycemia, hyperlipidemia, weight loss, acute pancreatitis, metabolic acidosis	Contraindicated in pyruvate carboxylase deficiency, disorders of fatty acid oxidation and metabolism, or porphyria	Class IV	[34,35,101,107–115]
Hypothermia	Reduction of Na^+ exchange, decreased K^+ conductance, regulation of glutamatergic synaptic transmission, disruption of synchronized discharges	32–35°C x 24h Rewarming $\leq$ 0.5 °C/h	Deep venous thrombosis, infections, cardiac arrhythmias, electrolyte disturbances, acute intestinal ischemia, coagulation disorders	Requires EEG monitoring	Class IV	[123,124,126,127,161–163]
Electroconvulsive therapy	Enhancement of GABA neurotransmission, increase of seizure threshold and reduction of neural metabolic activity	Variable protocols	May induce seizures and non-convulsive SE after treatment, amnesia, headache, cognitive impairment	Relative contraindication in patients with cardiovascular conditions Requires EEG monitoring	Class IV	[134–136,164]
Vagus nerve stimulation	Modulation of the locus coeruleus, thalamus and limbic circuit through noradrenergic and serotoninergic projections, elevation of GABA levels in brainstem	Surgical implantation	Hoarseness, surgical infection, rarely asystole or bradycardia		Class IV	[137–142]

Abbreviations: RSE: Refractory status epilepticus; SRSE, Super-refractory status epilepticus GABA-A, Υ-amino-butyric acid type A; mg, milligrams; MCG, micrograms; kg, kilograms; PRIS: Propofol related infusion syndrome; NMDA, N-methyl-D-aspartate; EEG: Electroencephalogram.

of action and is generally administered as an initial loading dose of 0.2 mg/kg followed by an infusion rate of 0.05–2 mg/kg/h. It is used to achieve electrographic/clinical seizure cessation or burst-suppression [43,55]. A randomized, open label study showed that the efficacy of continuous midazolam in controlling RSE was similar to infusion of diazepam (86% vs 89% with diazepam). Midazolam however, was associated with a higher recurrence rate (57% vs. 16% with diazepam) [43,63]. Similarly, a study of 27 children with refractory generalized convulsive SE, demonstrated that midazolam infusion (0.2 mg/kg as bolus followed by 5 mcg/kg/min as CI) was effective in the control of RSE in 26 (96%) children within 65 min, with no adverse events [28]. Even though the use of CI midazolam may cause cardiorespiratory depression and hypotension; the risk is still low compared to other anesthetics [64]. Another important aspect to consider is the risk of tachyphylaxis, which may occur after prolonged midazolam use. Thus, requiring constant monitoring and adjustment of the dosing [43].

If midazolam fails to control SE, clinicians typically resort to using barbiturates as a second agent. Pentobarbital and thiopental are both barbiturates that act similar to midazolam, through the enhancement of GABA activity. Additionally, they inhibit glutamate NMDA receptors and alter the ion conductance in the axonal membrane. Pentobarbital is administered with an initial bolus of 5–15 mg/kg (may give additional 5–10 mg/kg) followed by an infusion rate of 0.5–5 mg/kg/h. to achieve electrographic/clinical seizure cessation or burst-suppression. A case series of 26 children treated with pentobarbital showed that 75% of patients achieved burst-suppression pattern on EEG, with a relapse rate of 22% upon its weaning [10]. Another study of 30 patients presenting RSE showed that 33% achieved burst-suppression with pentobarbital without relapse; while 66.7% required titration of pentobarbital to reachieve burst-suppression. The authors also found that patients older than five years and those who achieved burst-suppression within one day of pentobarbital initiation were more likely to have positive outcomes [65]. Thiopental is less commonly used, but can be administered with an initial bolus of 2–7 mg/kg followed by an infusion rate of 0.5–5 mg/kg/h. [43]. Its efficacy in terminating seizures showed to be lower (55%; 11/20 patients) than propofol (64%; 14/22 patients) in a retrospective study [66]. A major drawback of barbiturates is the long half-life, which leads to a delayed recovery time. In addition, barbiturates are associated with a high rate of side effects including hypotension, respiratory depression, infections, anemia and prolonged length of ICU stay [64,67]. Reported effectiveness in SE termination with barbiturates varies between 64% and 69% with an estimated seizure recurrence rate of 22% [10,64,65,67]. Because the majority of patients initiated on pentobarbital infusions have failed to stop ongoing seizure activity with midazolam, showing the potential for a more severe form of SRSE, the higher seizure recurrence rate associated with pentobarbital infusions should be interpreted cautiously.

The use of propofol is reported in the treatment of adult RSE [68]. Although the mechanism of action is similar to midazolam and barbiturates (GABA-A receptor agonist), its use in children is limited. A previous report showed that children have increased risk of propofol infusion syndrome (PRIS), a life-threatening condition characterized by metabolic acidosis, rhabdomyolysis, arrhythmias, myocardial and renal failure, that results from administering a dose higher than 4 mg/kg/h. during 48 or more hours [69]. Thus, propofol should be used with caution in pediatric patients, particularly with doses greater than 65 mcg/kg/min.

Ketamine is an alternative therapy for control of RSE [70]. It acts as a noncompetitive antagonist of NMDA receptor and has been postulated to reduce epileptiform burst discharges and prevent glutamate-mediated neuro-toxicity [71,72]. Since, in late stages of SE, there is a decrease in the number of active GABA-A receptors and up-regulated glutamate NMDA receptors, ketamine emerged as a promising treatment. A retrospective multicenter study including 46 adults and 12 children reported that permanent SE control was likely attributed to ketamine in 32% (19/60) of patients, and transient

control in 13% (8/60) when used early. When ketamine was administered as third- or fourth-line treatment, SE control was achieved in 60% (6/10) of patients [73]. Similarly, a systematic review of 162 adults and 52 children, showed that ketamine was effective in 56.5% and 36.5%, of the adults and children, respectively. From the pediatric studies included in the review, those who reported ketamine dosing indicated either an initial bolus followed by CI, isolated CI or oral administration. The initial bolus dosing ranged between 2 and 3 mg/kg, followed by an infusion rate of 7.5 mcg/kg/h. to 10 mg/kg/h. When ketamine was administered as isolated CI, the dose ranged between 7 and 60 mcg/kg/min [74]. Despite the sympathomimetic properties, ketamine has a relative safe profile [74]. Compared to other anesthetics, it has the advantage of avoiding endotracheal intubation due to lack of respiratory compromise [75]. There is a current ongoing multicenter, randomized, controlled trial [76] evaluating the efficacy of ketamine in pediatric RSE. We anticipate that the results will be essential to stratify anesthetic utilization for the treatment of RSE/SRSE. They could help to overcome current limitations of retrospective data particularly, heterogeneity of medications prior to ketamine use, dosing and timing of administration.

One of the last resorts of the SE/RSE treatment protocols is inhalational anesthesia. The antiepileptic effects of inhaled anesthetics likely involve potentiation of GABA-A receptors and inhibition of glutamate NMDA receptors [77,78]. Isoflurane and desflurane are commonly used for the treatment of RSE and have shown to be effective in inducing burst-suppression that is easily titratable [79,80]. In the children, the most common inhalational anesthetic used is isoflurane [81–86]. It is administered with end-tidal concentrations of 0.5–2.3% [82,83] through an anesthetic machine. This poses a potential logistical limitation in the ICU [81,82]. A clinical series of 11 RSE episodes in 9 patients (4 adults, 5 children) demonstrated achievement of seizure cessation (EEG burst-suppression pattern) with isoflurane in all patients. Nonetheless, 8/11 (72.7%) episodes relapsed upon discontinuation of isoflurane and 6/9 (66.7%) patients died [83]. Another series of 5 adults and 2 children presenting RSE, showed that isoflurane and desflurane stopped seizures in 100% of cases, with sustained EEG burst-suppression pattern [87]. Overall, the efficacy of inhalational anesthetics seems to be transient and thus, should be considered as a temporary measure while additional workup is done to establish the etiology and/or adjunctive therapy is administered. The most commonly reported side effect of inhalational anesthetics is hypotension, requiring use of vasopressors. Other common side effects include atelectasis, deep vein thrombosis, infections and paralytic ileus [2], all of which are limiting factors for their use.

2.2.2. Immune modulators

In cases of RSE of a presumed autoimmune/inflammatory etiology or in cryptogenic NORSE, clinicians frequently use immunomodulatory therapies as trial in attempts to control seizures. In this scenario, their use is supported by recent discoveries on immunologic (antibodies against neural receptors such as voltage-gated potassium channels and NMDA receptors) and inflammatory (activation of inflammatory signaling pathways such as Interleukin-1 receptor/toll-like receptor pathway) processes that may contribute to their underlying pathophysiology [53,88,89]. The most commonly used therapies include corticosteroids, IV immunoglobulin (IVIG) and plasmapheresis [33,90–94]; however, their efficacy remains controversial. A series of 5 young adults with new onset SRSE, showed that early administration of immunotherapy (steroids, IVIG, and/or azathioprine) achieved seizure control in 3 patients with subsequent AEDs, and was associated with good outcomes [95]. Nonetheless, a review including 21 RSE/SRSE cases treated with adjunctive immunomodulatory therapy showed adequate seizure control in only 5% of cases [68].

Plasmapheresis is often used in parallel to other immunotherapies, particularly in RSE/SRSE etiologies such as FIRES, anti-NMDA encephalitis, and autoimmune paraneoplastic encephalitis. A previous series showed the potential benefit of early administration of plasmapheresis in FIRES. In this series, 4 patients received plasmapheresis at days 11, 12, 20 and 30, respectively, after seizure onset. The two patients that received plasmapheresis at days 11 and 12 presented better clinical outcomes than those who received it later [96]. On the contrary, a retrospective case series showed that plasmapheresis was no efficacious in two patients with FIRES [94].

There are less conventional immune therapies that target pro-inflammatory cytokines, which are considered to play an important role in the etiopathology of resistant epilepsies [97]. Recently, the use of Anakinra has gained attention for the treatment of FIRES [98]. Anakinra is an antagonist of the interleukin (IL) 1 receptor type 1, which inhibits the biological actions of IL-1β [99]. IL-1β is a pro-inflammatory cytokine with ictogenic properties. In animal models with refractory seizures, microglia and astrocytes exhibit overexpression of IL-1β [100], which makes of Anakinra a potential therapeutic approach for new onset RSE/SRSE.

Similarly, the potential involvement of toll-like receptors and IL receptors in the role of innate immunity as a precipitating factor of seizures makes inflammatory mediators appealing therapeutic targets. Drugs such as Pralnacasan (inhibitor of IL-1β converting enzyme), Belnacasan (selective inhibitor of the interleukin converting enzyme/caspase-1 family), VX765 (selective inhibitor of interleukin converting enzyme), Resveratrol (suppressor of nuclear factor κB induced by toll like receptors) and Ifenprodil (sensitive blocker of NR2B-contaning NMDA receptors) are experimental inflammatory modulating therapies that deserve further exploration for the treatment of RSE/SRSE [97].

2.2.3. Other therapies

Ketogenic diet (KD) is a high-fat, low-carbohydrate, and adequate-protein diet considered a safe and effective optional therapy for patients with drug-resistant epilepsy [101]. It has gained significant attention in recent years for the treatment of SE [102–104] as an adjunctive therapy due to its anti-inflammatory and anti-seizure properties. In the pediatric population, small series report a collective efficacy rate of approximately 54% [34,35,105–107]. In a series of 9 children with FIRES, KD was administered with a ratio of fat to combined protein and carbohydrate of 4:1 between days 4 and 55 of seizure onset. Seizure cessation was achieved in 7 of 8 (87.5%) patients that reached ketosis, within 2–4 days of ketonuria. Six of the 7 patients were maintained on the diet and re-experienced mild seizures (~2 seizures per week) only after few months. The remaining patient returned to RSE after termination of KD, dying 10 days later [108]. Overall, there is heterogeneity regarding timing of implementation of KD, time to ketosis and clinical outcomes [34,35,101,107–115]. Moreover, the simultaneous use of pharmacologic and non-pharmacologic therapies challenges the full understanding of the impact of KD efficacy in RSE/SRSE as well as the optimal parameters of administration. An important consideration is the involvement of a dietitian in the multidisciplinary team, as they will be crucial for achieving and maintaining ketosis in these patients. In children who are unable to take enteral feeds, implementation of KD can become complicated. Thus, IV KD can be used in these patients as a temporary measure [34,105]. Contraindications to KD implementation include carnitine deficiencies, beta-oxidation metabolic defects, pyruvate carboxylase deficiency and porphyria [116]. In the absence of a contraindication, KD could be considered in earlier stages of RSE and SRSE management.

The use of neurosteroids (e.g. allopregnanolone) in RSE/SRSE was initially supported by their action on extrasynaptic GABA-A receptors. These are different to BZDs' receptors as they do not

undergo internalization with prolonged seizures [117], and thus, represented a promising therapy for RSE/SRSE. Their use was reported in adults [118] and two pediatric patients [119], in whom the neurosteroids allowed the general anesthetic infusions to be successfully weaned. Nonetheless, a recent randomized controlled trial in adults and children failed to demonstrate the efficacy of IV allopregnanolone (brexanolone) compared to placebo (43.9% vs. 42.4%; p = 0.877) in the resolution of SRSE, when it was added to the standard care [120]. These results highlight the importance of data derived from randomized clinical trials to inform and guide current clinical RSE/SRSE management.

Therapeutic hypothermia is described mainly for the treatment of TBI. Currently, it is considered as an adjunctive therapy for RSE/SRSE due to its neuroprotective and antiepileptic properties demonstrated in animal studies. Moreover, it has the capacity to reduce cerebral metabolic rate, cerebral edema, inflammation, oxidative stress, and glutaminergic drive [121,122]. In children, multiple case reports describe resolution of RSE with adjunctive hypothermia [123–126]. In a series of 5 children with RSE, mild hypothermia (32–35 °C) was beneficial in reducing seizure burden, and prevented RSE relapse in all the patients [127]. Nonetheless, more robust evidence of its efficacy emerged with a multicenter randomized clinical trial comparing therapeutic hypothermia to the standard medical treatment. This study included 270 patients with convulsive SE and concluded that hypothermia was not associated with a lower rate of progression to RSE or SRSE, or improved clinical outcomes [128]. Important considerations before its implementation include the possible interaction with anesthetics and ASDs clearance [121], as well as awareness of common side effects: deep venous thrombosis, infections, cardiac arrhythmias, electrolyte disturbances, acute intestinal ischemia and coagulation disorders [55,129].

Electroconvulsive therapy (ECT) is also documented for the treatment of SRSE [130] in case series and reports. ECT increases GABA levels, leading to reduction of neuronal metabolic activity and interruption of seizures through the induction of a refractory period [131–133]. It is considered in children with focal and generalized RSE, with variable etiology (e.g. structural, intractable epilepsy) in whom more than five ASDs have been administered prior to ECT [134–136]. In these case reports the patients' outcomes are variable ranging from transient response to ECT and mild improvement of seizure frequency [135] to no clinical improvement followed by death [134]. Administering acute ECT is logistically challenging because its availability in some centers is limited. The side effects reported in the literature include transient lethargy or amnesic events [135], though most of the studies fail to document this information.

Another non-pharmacological option includes the vagus nerve stimulation [137–142]. Similar to ECT, there is certainly no evidence that suggest consistent improvement in seizure control based on the current data.

Emergency epilepsy surgery should be considered for RSE and SRSE treatment in two scenarios: failure to maximal medical therapy for at least two weeks or when a structural abnormality is identified [143]. Although surgery is generally contemplated in the late course of RSE, patients may undergo surgery as early as eight days after SE onset [84]. Since typical pre-operative diagnostic tools such as cortical mapping are challenging to obtain in an ICU setting, emergency surgery must be carefully weighed. The initial diagnostic approach includes the identification of the epileptogenic focus on EEG. Prior literature in children with RSE treated with surgery showed that common EEG features include generalized or non-focal lateralized discharges [144]. However, in some cases these findings can be hindered by the use of barbiturates and BZDs. If that is the case, ancillary testing such as ictal single-photon emission computerized tomography (SPECT), MRI and possibly magneto-encephalogram (MEG) should be utilized. If a structural lesion is identified, the extent of the lesion should be further characterized through the mapping of the eloquent cortex and definition of the epileptogenic zone [143].

3. Outcomes of RSE and SRSE in children

3.1. Clinical outcomes

The nature of RSE/SRSE is highly heterogeneous and several factors may contribute to the patients' prognosis. Mortality estimates in pediatric RSE are 13.7–43.5% [8–10,24], related to etiology, patients' age (<3 years old), and initial EEG findings (i.e. multifocal or generalized abnormalities) [8]. The underlying etiology is usually recognized as a primary predictor of outcomes [6,7,24,145,146]. Patients presenting with RSE due to acute symptomatic etiologies are less likely to return to baseline neurological function and are at higher risk of developing drug-resistant epilepsy [145]. Similarly, existing evidence shows that patients with treatment delays [147], longer RSE duration [41,148], and those who present with non-convulsive SE have worse clinical outcomes [149].

Not only are patients with RSE/SRSE at risk for higher mortality, they are also at risk for neurological and systemic complications as a consequence of the prolonged length of ICU stay and anesthetic use. While the data for SRSE is scarce, a series of 10 children with SRSE showed a median ICU and hospital length stay of 27 and 62 days, respectively; and a mortality rate of 11.1% [35]. Another study identified 43 SRSE patients out of 305 children with SE. The patients in the SRSE cohort presented more often with adverse events due to medications. This cohort had a case fatality rate of 21.3% when compared to the 5.1% in all the analyzed SE children [15]. ICU related comorbidities include hypotension, prolonged respiratory failure, sepsis, pneumonia, urinary tract infections and prolonged immobility [53]. Moreover, as these patients are often on multiple therapies, systemic complications may arise from interactions between medications or their adverse effects. A study of 171 adult patients with SE evaluated the outcome of patients who were treated with IV anesthetic drugs (37%). After controlling for confounders, the authors found that the use of CIs was associated with increased frequency of infections during SE as well as a 2.9-fold relative risk for death. Additionally, these patients had higher rates of intubation, severe hypotension and poor functional outcome on the Glasgow Outcome Score at long-term follow-up [150].

Similarly, there is evidence in children with febrile RSE that induction of therapeutic burst-suppression may lead to increased risk of hemodynamic instability and poor outcomes as compared to electrographic seizure control [151]. Two retrospective case series showed that recurrence of SE after initiation of pentobarbital was associated with worse neurologic outcomes, suggesting that it should be considered as a poor prognostic factor [10,152]. The direct association between CIs use and clinical outcomes in RSE/SRSE warrants further investigation. It remains unclear whether worse outcomes are a result of the administration of CIs and their side effects, the natural progression of a more severe case of RSE/SRSE or a combination of these two. We consider urgent that future studies address the adequate approach to CI administration regarding dosing, up titration versus substituting for another anesthetic infusion, as well as the treatment goals in view of a potential impact on clinical outcomes.

4. Conclusion

RSE is a neurological emergency in the pediatric population. Literature on SRSE in children is limited despite the morbidity

associated with this disorder. Current clinical practice is challenged by the heterogeneous etiologies and multiple factors involved in the progression from SE to RSE and SRSE. Moreover, there is a need to understand how aggressively RSE/SRSE patients should be treated initially, as the intrinsic risks of treatment and their effect on clinical outcomes should be taken into consideration. A multicenter and multinational collaborative effort is desirable to evaluate epidemiological data on pediatric RSE/SRSE, prevention strategies and available therapeutic options in order to provide more definitive evidence for their efficacy and safety in RSE and SRSE.

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