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Management and prognosis of pediatric status epilepticus

Eroshini Swarnalingam · Kristine Woodward · Micheal Esser · Julia Jacobs
 Division of Pediatric Neurology, Alberta Children's Hospital, Calgary, Canada

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Abstract

Background: Pediatric status epilepticus is a neurological emergency with the potential for severe developmental and neurological consequences. Prompt diagnosis and management are necessary.

Objectives: To outline the existing best available evidence for managing pediatric and neonatal status epilepticus, in the light of emerging randomized controlled studies. We also focus on short and long-term prognoses.

Materials and methods: This is a systematic overview of the existing literature.

Results: Status epilepticus, its treatment, and prognosis are usually based on the continuation of seizure activity at 5 and 30 min. Refractory and super-refractory status epilepticus further complicates management and requires continuous EEG monitoring with regular reassessment and adjustment of therapy. Benzodiazepines have been accepted as the first line of treatment on the basis of reasonable evidence. Emerging randomized controlled trials demonstrate equal efficacy for parenterally administered phenytoin, levetiracetam, and valproic acid as second-line agents. Beyond this, the evidence for third-line options is sparse. However, encouraging evidence for midazolam and ketamine exists with further data required for immunological, dietary, and surgical interventions.

Conclusion: Our overview of the management of pediatric and neonatal status epilepticus based on available evidence emphasizes the need for evidence-based guidelines to manage status epilepticus that fails to respond to second-line treatment.

Keywords

Pediatric status epilepticus · Neonatal status epilepticus · Refractory status epilepticus · Prognosis

Status epilepticus (SE) generally has a bimodal distribution of incidence with the first peak observed during the first decade of life (14.3/100,000/year) and a second peak observed after the age of 60 years [1]. Pediatric SE is the most commonly observed pediatric neurological emergency worldwide, with a high rate of morbidity and a considerable rate of mortality [2, 3]. Each year, 20 per 100,000 children are affected by SE with an overall mortality of 3% [4]. In comparison with its adult counterpart, the mortality of pediatric SE is comparatively low (3% in children vs. 30% in adults), but the burden of short- and long-term morbidity that it carries is considerably higher [5–7].

The new diagnostic framework for classification of SE through different axes includes an age-group-based classification,

i.e., neonatal, infancy, childhood and adolescence, adulthood and older age. Nevertheless, the quality and quantity of evidence available to guide management of pediatric and neonatal SE remains sparse in comparison with the abundant evidence available for its adult counterpart [8].

This is an important distinction because pediatric SE can be considered a separate entity on its own for a myriad of different reasons.

There is a wide heterogeneity in the underlying etiologies and mechanisms driving adult and pediatric SE that differ widely between these two groups. Population-based studies show that the commonest underlying etiology for pediatric status epilepticus is non-CNS infection-related fever, commonly febrile SE, while in adults, SE occurs most often in the context of

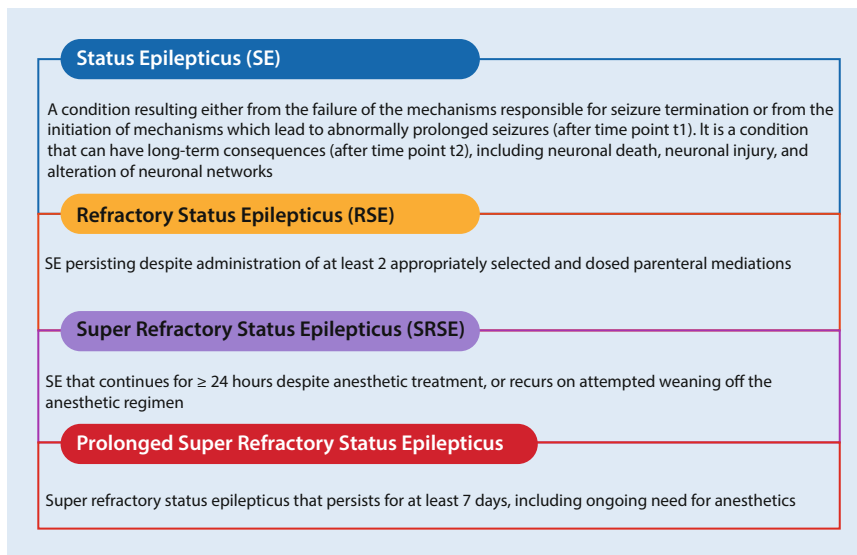


Fig. 1 ▲ Definitions of status epilepticus and its subtypes

remote symptomatic etiologies with cerebrovascular accidents accounting for the majority of cases [1, 2, 9]. Relatively rare but distinct entities such as febrile infection-related epilepsy syndrome (FIRES) and new-onset refractory status epilepticus (NORSE) show a variable incidence between the two age groups, with FIRES commonly observed within the pediatric age range but NORSE commonly occurring during early to mid-adulthood [10, 11]. Furthermore, certain treatment modalities such as propofol and thiopental, although widely used in the management of adult SE, are known to cause harm in children.

Taking all these factors into consideration, the available abundant data from the adult population cannot be safely extrapolated to the pediatric population.

In this article, we primarily aim to review the available evidence for management of pediatric and neonatal SE. However, investigating the underlying pathophysiology of pediatric SE, including analyzing the associated cellular and molecular disturbances in SE, is beyond the scope of this article.

Definitions

The definition of SE and its subtypes has evolved significantly over time. The International League Against Epilepsy (ILAE) classification and terminology task force has proposed a new framework of pathophysiology-based definitions (■ Fig. 1).

Status epilepticus is now defined conceptually as “a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of the mechanisms responsible, which lead to abnormally, prolonged seizures (after time point t1). It is a condition which can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures.”

The two operational dimensions or the time points stated above are defined as t1: the length of duration of seizure after which occurrence of “continuous seizure activity” is considered and treatment should be initiated and t2 or time point 2 as the time of seizure activity beyond which the risk of long-term consequences arise. Based on animal research, in convulsive SE, t1 and t2 are 5 min and 30 min, respectively, with no data available for timelines of the other forms of SE.

But both animal and human studies now confirm that the more prolonged the seizures are, the more likely that they are to become refractory leading to worse outcomes, which emphasizes the need for early treatment initiation and termination of seizures.

Prognosis

Although the overall prognosis ultimately depends on the underlying etiology, delay

in treatment will not only prolong the duration of seizures and its refractoriness to treatment but it is also known to be associated with increased morbidity and mortality and poor long-term outcomes, independent of the underlying etiology [12–16].

Acute complications of SE are numerous and may include cerebral edema, hemodynamic compromise and cardiac arrhythmia, non-cardiogenic pulmonary edema, excessive convulsive motor activity leading to hyperthermia as well as myoglobinuria, which may progress to acute renal tubular necrosis and renal failure, life-threatening electrolyte disturbances such as hyperkalemia and hyponatremia, as well as metabolic disturbances including hypoglycemia and metabolic acidosis, coagulopathy, gastrointestinal paresis, intensive care neuropathy, and myopathy [17, 126].

The incidence of learning difficulties, neuro-disability, and de novo and drug-resistant epilepsy is also high in survivors.

Unfortunately, despite all the available evidence to the contrary, treatment delay is still a universal observation in the management of pediatric status epilepticus [18].

Management

Pharmacological management of SE can be approached as first, second, and third tiers of treatment options or as management of early or prehospital versus established SE. The first-line treatment approach for convulsive SE is usually with single or repeated doses of a benzodiazepines followed by a tier-two medication choice, either fosphenytoin or phenobarbital.

First-line treatment

Parenteral benzodiazepines remain the first-line treatment of choice in status epilepticus (■ Table 1). First-line treatment with benzodiazepines alone will successfully terminate 40–60% of convulsive SE [18]. However, establishing venous access in an actively convulsing child needs expertise and can be quite challenging particularly in a prehospital setting. Despite the emphasis on importance of initiating prehospital treatment for early SE, pedi-

Table 1 Pediatric treatment trials: first-line anti-seizure medication for status epilepticus				
Study, year (reference)	Study type	Number of pediatric cases	Medication compared	Outcome
Chamberlain et al. 2014 [19]	Class I RCT	273	IV diazepam vs. IV lorazepam	Equipoise in both meds at terminating seizures in 10 min (72%)
RAMPART [20]	Class I RCT	145	IV lorazepam vs. IM midazolam	No subgroup analysis. Overall, noninferiority of IM midazolam in comparison with IV lorazepam

RCT randomized controlled trial, *IV* intravenous, *IM* intramuscular

Table 2 Pediatric treatment trials: second-line antiseizure medication for status epilepticus				
Study, year (reference)	Study type	Number of pediatric cases	Medication compared	Outcome
ECLIPSE, 2019 [23]	Open-label RCT	286	IV levetiracetam 40 mg/kg vs. IV phenytoin 20 mg/kg	Equipoise: IV LEV – 70% seizure termination on average 35 min IV PHT – 65% seizure termination average 45 min
ConSEPT, 2019 [24]	Open-label RCT	233	IV or IO phenytoin 20 mg/kg infusion over 20 min vs. IV or IO levetiracetam 40 mg/kg infusion over 5 min	Cessation of seizures at 5 min was equivocal LEV – 50% PHT – 60%
ESETT, 2019 [25]	Class I RCT	225	Infusions of, levetiracetam 60 mg/kg vs. fosphenytoin 20 mg/kg vs. valproate 40 mg/kg	Seizure termination at 60 min was equivocal: LEV – 52% Fosphenytoin – 49% Valproic acid – 52%

RCT randomized controlled trial, *IO* intraosseous, *IV* Intravenous, *LEV* levetiracetam, *PHT* phenytoin

atric-specific data are lacking to compare the efficacy of different formulations and routes of benzodiazepine administration in an out-of-hospital setting.

A class I randomized control study enrolled 273 children to first-line treatment with either intravenously administered (IV) diazepam or IV lorazepam and derived equipoise in the efficacy of seizure cessation within 10 min between IV diazepam (101/140, 72.1%) and IV lorazepam (97/133, 72.9%) with similar side effect profiles in the two treatment arms [19].

The Rapid Anticonvulsant Medication Prior to Arrival (RAMPART) trial included 145 patients between the ages of 0 and 20 years alongside 748 participants above this age range, who were then randomized to prehospital treatment with either intramuscular (IM) midazolam or IV lorazepam upon presentation with convulsive seizures lasting longer than 5 min. Although an age-based subgroup analysis was not carried out, overall non-inferiority of IM midazolam was established in comparison with IV lorazepam in prehospital termination of status epilepticus with similar adverse effect profiles for both these medications [20].

Second-line treatment

Under familiar circumstances, second-line treatment is necessitated when convulsive SE persists after two doses of benzodiazepines [21]. An infusion of phenytoin is the most commonly utilized second-line approach in established SE with approximately 60% chance of seizure termination [22].

Phenytoin is known to cause severe adverse events when given as an infusion, including life-threatening cardiac arrhythmias and hypotension as well as severe extravasation injuries (purple glove syndrome) and liver toxicity. Fosphenytoin is of higher cost and is not universally available; however, it is preferred over phenytoin due to its better tolerability at higher infusion rates and relatively lower rates of adverse effects including fewer chances of cardiac arrhythmias and less extravasation-related harm. However, the benefit of higher rates of infusion of fosphenytoin is counteracted by the time necessary to transform the pro-drug into the active substance state.

Fortunately, randomized clinical trial-based evidence is emerging for other po-

tential candidates as a second tier of management of pediatric SE (■ Table 2).

Three treatment trials were published in 2019 assessing the treatment response to several different second-line antiseizure medication. The “Levetiracetam versus phenytoin for second-line treatment of pediatric convulsive SE” (ECLIPSE) trial was an open-label randomized clinical trial that was undertaken in United Kingdom. This study showed that out of 286 randomized participants aged between 6 months to under 18 years, receiving levetiracetam (40 mg/kg over 5 min) versus phenytoin (20 mg/kg over at least 20 min), convulsive SE was terminated in 106 of 152 (70%) children in the levetiracetam arm and in 86 of 134 (64%) in the phenytoin arm [23]. The median time from randomization to cessation of convulsive SE was 35 min in the levetiracetam group and 45 min in the phenytoin group (hazard ratio: 1.20, 95% CI: 0.91–1.60; $p=0.20$).

Another open-label, multicenter, randomized controlled trial conducted in 13 emergency departments in Australia and New Zealand, the ConSEPT trial, randomly assigned 233 children between the ages of 3 months and 16 years to receive either 20 mg/kg phenytoin (IV or

Table 3 Best available evidence: management of pediatric RSE and SRSE				
Study, year (reference)	Study type	Number of pediatric cases	Treatment	Outcome
Wilkes and Tasker (2014) [33]	Systematic review	521	IV midazolam	Sz control – 76% Average time for Sz cessation – 271 min Breakthrough Sz – 52% Sz recurrence – 12%
Wilkes and Tasker (2014) [33]	Systematic review	95	Barbiturate infusion	65% who failed midazolam respond to barbiturate Sz control or BS in 22.6 h Breakthrough Sz – 67% Sz recurrence – 22%
a. Invento et al., 2015 [62] b. Rosati et al., 2012 [121]	Case series	a. 11 b. 9	Ketamine	1. SE resolved – 14/19 episodes 2. 66% Sz control
Kofke et al., 1989 [67]	Case series	5	Isoflurane	Sz cessation or BS – 5/5 (100%) Mean duration of treatment – 7 days
Guilliams et al., 2013 [99]	Case series	5	Hypothermia (30–35.3 °C)	Sz control – 5/5 (100%) Relapses – 0%
Schoeler et al., 2021 [89]	Systematic review	147	Ketogenic diet	Ketosis in – 96% SRSE resolution – 60% Average time to Sz resolution – 6.3 days
Uberall et al., 2000 [56]	Case series	41	IV valproic acid as an adjunct to a 2nd-line agent	RSE termination in – 78%

IV intravenous, Sz seizure, BS burst suppression, SE status epilepticus, SRSE super-refractory status epilepticus, RSE refractory status epilepticus

intraosseous [IO] infusion over 20 min) or 40 mg/kg levetiracetam (IV or IO infusion over 5 min) [24]. The study showed that 68 of 114 (60%) patients in the phenytoin group and 60 of 119 (50%) patients in the levetiracetam group had cessation of SE within 5 min of cessation of the infusion (risk difference –9.2% [95% CI: –21.9–3.5]; $p=0.16$), with no difference in the rates of adverse events occurring within 2 h of receiving the study drug or subsequently during admission. Although both of these studies did not establish any superiority of one medication over the other, the findings show that levetiracetam is as an appropriate alternative to phenytoin as a second-line agent.

The established SE treatment trial (or ESETT trial) is a multicenter double-blinded, responsive-adaptive, randomized controlled trial carried out in the United States. Overall, 400 patient enrollments (384 individual patients) were included, and were stratified according to age, i.e., 39% were children and adolescents (up to 17 years of age), 48% were younger adults (18–65 years of age), and 13% were older adults (>65 years of age). They were randomized to receive levetiracetam 60 mg/kg (maximum 4500 mg), fosphenytoin 20 mg/kg (maximum 1500 mg), or valproate 40 mg/kg (maximum 3000 mg) infused

over 10 min [25]. Each of the three study medications showed approximately 50% effectiveness in aborting SE within 1 h in all of the age groups. Analyzing the results of the pediatric age group separately, the responses to levetiracetam, fosphenytoin, and valproic acid were 52%, 49%, and 52%, respectively. There was no difference in achieving seizure freedom at 60 min from the onset of study drug infusion and this was without the use of an additional antiseizure medication. The safety outcomes did not differ by treatment group in any of the age groups.

Third-line treatment

Failure of second-line treatment should lead to initiation of the third-line therapy phase when the seizure duration reaches 40 min, at which point the conservative practice is initiation of anesthesia. This requires endotracheal intubation with rapid sequence induction (RSI) to prevent the accompanying airway compromise [21]. All conventional anesthetics delivered through infusion require endotracheal intubation, which is an individual negative prognostic factor of morbidity and mortality in SE [26].

Although first- and second-line treatment for pediatric SE is based on high-grade evidence derived from randomized

controlled trials (RCTs) and meta-analyses with even better quality evidence on emergence, unfortunately the evidence for third-line agents remains controversial and is based on observational studies and expert opinion alone ([27], ■ Table 3).

Midazolam

Most adult SE treatment protocols include IV midazolam, short-acting barbiturates such as pentobarbital, or thiopentone infusions or propofol as the three most widely utilized options, with a less clear understanding of their effectiveness in comparison [28–31]. An even lower number of evidence-driven options are available for the pediatric population.

A prospective observational study carried out by the Pediatric Status Epilepticus Research Group (pSERG) between 2011 and 2013 identified 111 patients with refractory status epilepticus (RSE; median age: 3.7 years) of whom 54 patients (49%) required a continuous infusion of an anesthetic agent. A median of five bolus doses of antiseizure medication (interquartile range: 4–7) had been given with no effect prior to the start of the infusion medication. Midazolam was the most frequently administered first-choice anesthetic agent (78%) followed by pentobarbital. Overall, 94% patients achieved seizure

termination with either of these two therapies. Other agents that were used as third-line medications were propofol, ketamine, valproate, and isoflurane [32].

A systematic literature search and review by Tasker and colleagues identified that when midazolam was used as the initial agent for RSE, there was a 76% clinical seizure control achieved within 41 min on average after starting the infusion. However, when two studies with continuous EEG monitoring were included, the weighted mean time from beginning of the midazolam protocol to seizure control increased to 271 min, suggesting the possibility of ongoing subclinical seizures despite cessation of clinically evident seizures. Breakthrough seizures occurred in 52% of patients treated with midazolam infusion and seizures recurred in 12% [33].

The mechanism of action of midazolam is via positive allosteric modulation of gamma aminobutyric acid type A (GABA_A) receptors suppressing the neuronal excitability. Its rare but well-described side effects include hypotension, respiratory suppression, and hepatotoxicity as well as development of tolerance or tachyphylaxis with increasing doses [34]. Cumulative evidence suggests that an initial bolus of 0.1–0.5 mg/kg followed by increments of 1–2 µg/kg/min up to 30 µg/kg/min is efficient in controlling SE in the pediatric population [28].

Barbiturates

In those patients in whom midazolam has failed, barbiturate infusion was effective in terminating seizures in 65% of cases [33]. On average, a barbiturate infusion was initiated 66 h after the onset of RSE. Burst suppression, which remains the ultimate electroencephalographic goal, was achieved 22.6 h later. However, 67% of patients had breakthrough seizures and recurrence of seizures after weaning from barbiturates occurred in 22%.

Pentobarbital is a metabolite of thiopental, a barbiturate that depresses neuronal excitability by enhancing GABA-associated inhibitory responses. Compared with phenobarbital, pentobarbital readily penetrates the blood–brain barrier allowing for rapid onset of action and seizure control with a shorter half-life

thereby enabling faster recovery from coma and awakening upon weaning. It may accumulate in tissue with prolonged administration due to its lipid solubility and has a considerable side effect profile including significant severe respiratory suppression, myocardial depression, profound hypotension, immune suppression, and risk of multiorgan failure, among others.

A retrospective data analysis of 26 children between the ages of 1 day and 13 years with RSE showed a response rate of 52% when a loading dose of 5 mg/kg of pentobarbital followed by an infusion of 1–3 mg/kg/h was used [35]. Seizure relapse was observed in 22% of cases.

Propofol and thiopental

Propofol is an IV general anesthetic agent with the property of a positive modulator of GABA receptors. It generally has a short half-life and is easily titratable; it is rapid acting, enabling rapid recovery after drug discontinuation, although with prolonged administration, the terminal half-life may amount to several days.

In adults, propofol has evidence-based utility in management of RSE or super-refractory status epilepticus (SRSE) due to its aforementioned rapid onset of action and prompt awakening of patients upon withdrawal. Propofol induces burst-suppression within 35 min of initiation; however, frequent titration is required to maintain adequate suppression. Adult studies have shown that propofol infusion terminates RSE/SRSE in 67% of cases [36, 37].

Unfortunately, the high risk of “propofol infusion syndrome” (PRIS) often limits its use in children [38]. It has been reported that PRIS could lead to early Brugada–Brugada-like ECG changes, cardiac failure, rhabdomyolysis, metabolic acidosis, renal failure, and sometimes even death [39, 40, 127, 128]. Propofol also has a propensity to induce hyperkinesias, which can mimic breakthrough seizures [41]. However, these are not true seizures, but extrapyramidal hyperkinesias given their pathomechanism: Propofol inhibits cortical than basal ganglia excitatory activity much faster, which leads to disinhibition of basal ganglia motor programs and the hyperkinesias [129, 130].

Reported risk factors associated with a higher risk of PRIS include younger age, higher doses, prolonged use, concurrent use of with catecholamines and corticosteroids, and a low body mass index or presence of malnutrition [42, 43]. There have been descriptions of PRIS in patients receiving propofol doses greater than 5 mg/kg/h for more than 48 h. However, more recent data suggest that even shorter durations or lower doses of propofol (less than 4 mg/kg/h) can also result in development of PRIS, exposing pediatric patients to high risk of death and morbidity [44–46]. When propofol was administered in conjunction with a ketogenic diet, more severe adverse events including case fatalities were reported [47]. It also worth noting that the propofol syndrome may not be caused by propofol in entirety but may have resulted from drug-induced cerebral suppression.

A retrospective study assessed the effectiveness of propofol in comparison with thiopental in 33 children aged between 4 months and 15 years with RSE and concluded that propofol was more effective than thiopental, with propofol being successful in terminating seizures in 64% and thiopental in only 55% of cases [48]. However, propofol had to be discontinued in 18% of patients due to adverse events, which included rhabdomyolysis and hypertriglyceridemia.

All these factors may limit the utility of propofol as a third-tier agent in the management of pediatric SE, and stronger evidence is required to assess the associated safety concerns.

Refractory status epilepticus

Refractory status epilepticus is defined as SE that persists despite administration of at least two appropriately selected and dosed parenteral medications including benzodiazepines. No specific seizure duration is required for this diagnosis. Approximately 15–35% of patients with RSE fail to achieve the desired therapeutic endpoint and progress to SRSE.

Super-refractory status epilepticus

Super-refractory status epilepticus is defined as SE that continue for 24 h or more, despite anesthetic treatment, or recurs on

attempted weaning off the anesthetic regimen requiring reintroduction of anesthetic agents [49, 50].

By the time SRSE ensues, it is presumed to be very likely that the neuronal damage has been already established and the goal of management thus deviates from simply halting and preventing seizures to anticipatory monitoring and pre-emptive managing down-stream consequences, which include multiorgan dysfunction [17].

Based on a variety of pathophysiological mechanisms, resistance to conventional medication is established by the time SRSE is established [51]. Almost all conventional anesthetic agents used in treatment of SRSE act on inhibitory GABA_A receptors [51]. Experimental models suggest that with continuing seizures, GABA_A receptors composed of alpha, beta, and gamma subunits are internalized while those receptors containing delta subunits and localized extrasynaptically remain pharmacologically responsive to very high doses of midazolam and neurosteroids [131]. By contrast, excitatory *N*-methyl-*D*-aspartate (NMDA) receptors are mobilized to the cellular membrane, which results in a clearly hyperexcitable state at the synapse [52]. This excess glutamate release with ongoing seizure activity lasting for longer than 1 h is postulated to unfavorably alter the balance between neuronal excitation and inhibition and to sustain seizure activity.

Neurological sequelae are expected in more than 50% of the pediatric population with refractory convulsive SE despite best available care; refractory convulsive SE has a mortality rate of 2.7–5.2% [15, 53].

There is a significant lack of consensus or a clear evidence-based guidelines on how to approach pediatric RSE and/or SRSE. A variety of different approaches are utilized worldwide.

A retrospective cohort study demonstrated that in a group of 31 pediatric patients with SRSE, a single continuous drug infusion was effective in 48.4% of cases for resolution of SE. Two infusions with different drugs were utilized in 32.3% and three or more different drugs were used in 19.4% of cases. Most of the patients with SR SE (96.8%) received midazolam as the first choice [54]. The same study observed that SRSE patients had delayed initiation of first non-ben-

zodiazepine antiseizure medication in comparison with the non-SRSE patients (149 min vs. 62 min; $p = 0.030$). Additional therapies that were administered in 17 out of 31 patients (54.8%) in this study cohort included corticosteroids, ketogenic diet, and intravenous immunoglobulin (IVIg) as the most favored options.

Some of the other nonconventional or debated management modalities that are available for treatment of SRSE are discussed next.

Intravenous valproic acid

Valproic acid is a conventional antiseizure medication that is used as maintenance therapy, but several case reports are available to demonstrate that valproic acid given as a continuous infusion can be effective in terminating RSE [55]. In a case series of 41 children with RSE, a continuous infusion of valproic acid successfully terminated seizures in 78% when used in addition to a conventional second-line medication such as phenobarbital [56].

However, the use of valproic acid in children can be problematic with metabolic conditions being a more common underlying etiology of SE in children than in adults, predisposing them to hepatotoxicity and pancreatitis as a consequence. Certain mitochondrial metabolic conditions such as mutations of the *POLG* gene or in the urea cycle enzyme system, such as ornithine transcarbamylase (OTC) deficiency, are accepted contraindications for its use, which may remain undiagnosed at the time of presentation. There is also a known age restriction where children below the age of 2 years are generally excluded from receiving valproic acid. Universal unavailability of IV formulations can also act as another limiting factor.

Ketamine

There is increasing evidence to suggest that ketamine may be effective in treating refractory convulsive SE compared to conventional anesthetics in adults [57]. Ketamine is a potent *N*-methyl-*D*-aspartate (NMDA) antagonist. The NMDA receptors are still functional at later stages of SE even after the GABA receptors have been internalized rendering conventional anes-

thetics that utilize this pathway ineffective [58]. It also has sympathomimetic properties with utility in neuroprotection [59]. Ketamine has neither cardiac nor respiratory depressant properties. Therefore, endotracheal intubation may not be required with ketamine in comparison with other conventional anesthetics, especially considering that mechanical ventilation itself is considered a factor that increases morbidity and mortality risk in critically ill pediatric patients [60, 61]. It is tempting to speculate that earlier, i.e., before it enters the refractory stage, use of ketamine in SE may be more effective than the administration in the (super-)refractory phase only.

Ilveto et al., in their study of 13 children, aged between 2 months and 11 years 5 months, with a total of 19 treatment episodes using ketamine at a median dose of 30 µg/kg/min, observed that refractory convulsive SE was resolved in 14 out of 19 episodes. Four patients who received ketamine in lieu of conventional anesthetics achieved resolution of status and thus did not require endotracheal intubation [62]. A burst suppression EEG pattern was obtained in 10 of 19 episodes. Aside from a slight increased saliva production and a transient mild increase of liver enzymes in some of the children receiving concomitant phenobarbital, no serious adverse events were observed. Add-on midazolam at 1 mcg/kg/min was administered as per protocol to prevent hallucinations, which are an expected side effect.

The KETASERO1 trial (Ketamine in Refractory Convulsive Status Epilepticus in Pediatric Convulsive RSE) was planned to evaluate the efficacy of ketamine in this population of interest. This multicenter, randomized controlled trial had to be halted because of much too slow recruitment [63, 132].

Inhaled anesthetics

The mechanisms of action of inhaled anesthetics are not well established, but both isoflurane and desflurane are known to produce dose-dependent changes in the EEG. The postulated mechanism of action is likely via potentiation of inhibitory postsynaptic GABA_A receptor-mediated currents or through its effects on the thala-

nocortical pathways [64]. Isoflurane and desflurane both are easily titratable and they both have favorable pharmacokinetic and pharmacodynamic properties that are effective in achieving burst-suppression patterns on EEG [65].

However, only limited data are available for the use of isoflurane and desflurane and their efficacy in the management of pediatric RSE with most of the validated data coming from the adult population. In addition, many hospitals stopped or heavily restricted the use of fluoranes because of their catastrophic effect on the environment.

In a case series of seven patients with RSE aged between 17–71 years, isoflurane with and without desflurane was effective in seizure cessation and achieving burst suppression [66]. Complications were frequent, the commonest complication being hypotension with all of the patients in the series requiring volume resuscitation and vasopressors. Among other complications were atelectasis (7/7), infections (5/7), paralytic ileus (3/7), and deep venous thrombosis (2/7).

In another case series where five pediatric patients were included, Kofke et al. reported seizure response and achievement of burst suppression in all five patients with isoflurane [67]. However, potential neurotoxicity with inhaled anesthetics is worth considering in light of recent case reports of magnetic resonance imaging (MRI) changes observed in variable brain regions with prolonged isoflurane exposure [68, 69].

These MRI changes were particularly observed in the hippocampal region, hypothalamus and the cerebellum associated with prolonged use in RSE compared with those who received only an intravenous anesthetics.

Under these circumstances risks versus benefits need to be considered in using inhaled anesthetics in the pediatric population.

Immunomodulatory therapy

Immunomodulatory therapy in the management of epilepsy and SE is a relatively novel approach gaining popularity over the years, especially in the management of immune-mediated epilepsies and au-

toimmune encephalitis. It has been identified that immune-mediated processes may modulate epileptogenicity. Evidence has emerged on the use of immune modularity therapy in successful treatment of intractable childhood epilepsies and epilepsies with a known or a presumed underlying inflammatory or autoimmune pathology [70–75].

Immunomodulatory therapy may also be efficacious in patients with no established underlying immune-mediated etiology primarily because not all anti-neuronal antibodies can be identified by current commercially available panels. Therefore, a trial of immunomodulatory therapy can be justified in pediatric RSE/SRSE patients with no obvious contraindication, particularly for those presenting with temporal lobe seizures without a known underlying immune-mediated pathology.

Steroids in particular may have an additional benefit in managing cerebral edema and raised intracranial pressure that may occur concomitantly with prolonged seizures [76].

Based on a literature review by Ferlisi et al., only 5% of patients with RSE and SRSE have adequate seizure control with steroids, IVIG, and plasma exchange [77].

Neurosteroids

Neuroactive steroids have been studied in experimental epilepsies in animals and were shown to alter their cortical excitability and therefore reduce seizure propensity.

Brexanolone, an aqueous formulation of allopregnanolone, was experimented in adults with SRSE as an adjunctive medication in a phase I/II open-label trial. Out of 25 patients with a median age range of 47.6 ± 19.5 years, 17 were successfully weaned off third-line anesthetics with the use of the study medication. No brexanolone-specific serious safety concerns were identified. However, the phase 3 trial reported that the primary endpoint was not significantly different between the study drug (43.9%) and the placebo (42.4%, $p=0.88$) at the end of the double-blind period [78].

Methylprednisolone pulse therapy was observed to be beneficial for presumed immunologically driven epilepsies such as FIRES and NORSE [79].

Intravenous immunoglobulins

It has been shown that IVIG may be of benefit in some of the antibody-mediated epilepsies and CNS neuroinflammatory processes as well as other types of epilepsies that are not yet proven to be immune mediated such as Continuous Spike and Wave during Slow wave sleep (CSWS) and refractory focal epilepsies.

Out of 33 adults in a systematic review who had received IVIG for RSE, 14 achieved seizure freedom with no reported adverse effects [80]. Furthermore, IVIG also demonstrated some efficacy in managing FIRES- (16.6%) and NORSE-related (29.4%) SE [79].

Plasmapheresis

Use of plasmapheresis for RSE has been reported in 27 adults with autoimmune conditions, with 13 patients achieving seizure control [81]. Plasmapheresis was effective in two of 18 patients with FIRES and six of 15 patients with NORSE [79]. However, the reports have been less encouraging in children, with only seven of 37 patients achieving seizure control and two other patients experiencing a decrease in seizure burden [82].

In the realm of pediatric SE, more evidence is required with regard to potential long- and intermediate-term side effects as well as evidence on whether any particular combination of different immunomodulatory therapies, rather than relying on one modality, might be of more benefit [83].

Dietary therapy

Ketogenic diet (KD) is a therapeutic diet that is high in fat and low in carbohydrate with proven efficacy in certain drug-resistant epilepsies such as infantile spasms, childhood epileptic encephalopathies, inborn errors of metabolism, as well as drug-resistant focal epilepsies. Over the past several years there is emerging evidence for the use of KD in the context of RSE and SRSE.

The exact mechanism of action of KD, especially in abolishing refractory seizures, is not precisely understood, but it has been postulated that KD potentially disrupts the pathophysiology of RSE at multiple levels including, but not limited to, neu-

rotransmitter receptor trafficking, neurotransmitter localization and release, excitotoxicity, alteration in the gut microbiome, and blood–brain barrier (BBB) permeability with downstream effects on action of various inflammatory mediators and on mitochondrial dynamics [84, 85, 133].

Fortunately, most of the studies investigating the efficacy of KD on RSE are pediatric studies, possibly due to its ease of administration in this population. In most cases, KD is delivered via the enteral route in a ratio of 4:1 and occasionally in the form of ketogenic total parenteral nutrition (TPN).

A case series reported that 10 of 14 pediatric patients had electrographic seizure resolution and $\geq 50\%$ suppression within 7 days of initiating KD [86]. The median delay in starting KD after the onset of SE in this series was 14 days.

Another pediatric case series reported resolution of SRSE in nine out of 10 patients after a median of 7 days' KD duration [87]. Anesthesia could be weaned off in eight of these 10 patients within 15 days of KD initiation.

In another series of 10 pediatric RSE patients, two patients had seizure resolution and five patients had $> 50\%$ decrease in seizure frequency over a mean duration of 5 days after initiating KD [88].

A more recently published systematic review assessed 147 pediatric patients who were started on a KD with 96% of them achieving ketosis and SRSE resolution in 60% over an average of 6.3 days [89]. A total of 34% were reported to have mild side effects in this analyzed population and 4% had side effects categorized as being severe or serious.

However, KD takes relatively longer time to take effect in comparison with other nonsurgical approaches of RSE management (weeks vs. days). There are also concerns about variability in the definition of ketosis and representative outcomes in this population.

While the incidence of adverse effects associated with the use of KD for treatment of RSE/SRSE has reportedly been low, commonly observed adverse effects include metabolic derangements such as keto acidosis and hypoglycemia and common gastrointestinal symptoms such as emesis and constipation [86, 89, 90].

Therapeutic hypothermia

Therapeutic hypothermia has demonstrated antiseizure and neuroprotective properties under experimental conditions, which are presumed to be exerted via several different pathways including decreasing cerebral oxygen utilization, metabolic rate, excitotoxicity, calcium release, free radical production, release of reactive oxidative molecular species, and altering BBB permeability to inflammatory intermediates [91–93].

Although hypothermia was used in isolation to control SE in the first reported series of patients, today therapeutic hypothermia is almost never used alone in the management of RSE and is usually used in conjunction with other available modalities.

In an adult case series of four adult patients in a neurology/neurosurgery critical care setting, endovascular cooling (31–35 °C) successfully controlled RSE, allowing for gradual withdrawal of IV anticonvulsants and vasopressors [94]. Two out of four patients had sustained seizure freedom, and all patients showed a marked reduction in seizures.

The only class-1 evidence for the use of hypothermia in management of RSE comes from the HYBERNATUS study, which is a multicenter study recruiting 270 patients with convulsive RSE who were on assisted ventilation. The trial found that the efficacy of therapeutic hypothermia was not better than placebo for RSE/SRSE, and there was no difference in achieving the primary endpoint of a Glasgow outcome score of 5 (minimal or no neurologic deficit) at 90 days between the intervention and control groups (49 vs. 43%; [95]).

With most of the available evidence coming from descriptive studies, a very early pediatric case series describes three patients with generalized SE who were treated successfully with induction of therapeutic hypothermia of 30–31 °C in conjunction with 5–55 mg/kg/h of thiopental infusion [96].

A case report of an infant with RSE due to hemimegalencephaly described decreased seizure frequency with induction of mild hypothermia at 36 °C [97]. Two additional case reports described prompt and sustained control of RSE in two pedi-

atric patients diagnosed with FIRES with induction of moderate hypothermia at 33 °C [98]. In another case series of five pediatric patients with RSE, including four with relapse on attempted discontinuation of pentobarbital, Guillems et al. reported that therapeutic hypothermia of 32–35 °C could bring about sustained decrease in seizure burden even when midazolam, pentobarbital, and ketamine had failed [99].

The adverse effects that were highlighted in these case series associated with even mild hypothermia included coagulopathy, venous thromboembolism, renal tubular dysfunction with attendant acid–base and electrolyte abnormalities, bradyarrhythmias, and intestinal paresis.

Further questions that remain unanswered with regard to the practicality of this approach are the optimal core body temperature to be targeted, optimal time lag to achieve this target temperature, optimal duration of hypothermia to be sustained, and the target percentage suppression of EEG as an electrographic goal. Other management questions also remain unanswered, such as the routine use of prophylactic heparin for prevention of coagulopathy, the mode of induction of the hypothermia such as surface cooling versus endovascular cooling, and the benefits versus the risks of each of these methods. Although very few of these questions could be answered with evidence extrapolated from the neonatal age group who underwent therapeutic hypothermia for perinatal ischemic injury, these may not be applicable to older age groups.

Pyridoxine

Pyridoxine-dependent epilepsy results from pathogenic mutations in the *ALDH7A* gene causing a functional antiquation deficiency. Pyridoxine has been effectively used to treat SE associated with pyridoxine-dependent epilepsy [49, 100]. Pyridoxine has also been reported to be helpful for SE occurring in the context of isoniazid toxicity or with pyridoxine deficiency associated with prolonged isoniazid therapy [101, 102].

An empiric trial with pyridoxine may be considered in the management of RSE in infants or younger children. Side effects

of acute IV pyridoxine infusion include potential respiratory depression and hypotonia. However, most RSE/SRSE patients are likely to be ventilated at the stage where pyridoxine is given as a trial.

Magnesium

The mechanism of action of magnesium in the management of RSESE has not been completely elucidated. Magnesium—at the resting potential in mammalian (also human) neurons—blocks the ionophore of the glutamatergic NMDA receptor. During physiological depolarization, the magnesium ion exits and renders the ionophore permeable, i.e., excitable. Hypomagnesemia, as a consequence, facilitates hyperexcitability because the neurons became excitable already at the resting state potential voltage [134]. Nevertheless, magnesium is rarely used in light of the very limited evidence outside of specific contexts such as treatment of eclampsia or in patients with provoked seizures due to hypomagnesemia from gastrointestinal or renal losses [103].

A single case report of two teenage girls with juvenile-onset Alper's syndrome due to POLG1 variants describes remission of SE in response to IV magnesium [104].

In a systematic review including 28 patients (including nine children), seizure control was achieved in 12 patients but half of them had seizure recurrence after withdrawal of magnesium [105].

Significant side effects that are reported with hypermagnesemia (with serum levels >4.5 mg/dL) are hypotonia, weakness, or even paralysis resulting from the inhibition of acetylcholine release at the neuromuscular junctions. Vasodilation is also known to occur at higher concentrations (with magnesium concentrations exceeding >15 mg/dL) and can result in complete heart block or cardiac arrest.

Surgical management

Surgical resection of an area of the cortex with or without an identified epileptogenic lesion, with the presence of clear evidence to indicate that the seizures are originating from this particular region or lesion, can be curative in RSE. This may not be a straightforward decision if the imaging is

negative or is discordant with electrophysiological data and may mandate extensive work-up including intracranial EEG monitoring and/or electrical stimulation mapping, quite similar to a presurgical evaluation to assess surgical candidacy. However, carrying out a presurgical evaluation on an emergent basis in a medically unstable patient is not only difficult but also is confounded by ongoing ictal activity and by the effects of concomitantly administered anesthetic infusions.

Surgical planning and decision-making should also incorporate the location, size, and nature of such lesions as well as the functional significance of the surrounding eloquent cortex.

In a series of adults between the ages of 20 and 68 years, five out of nine patients were found to be seizure free at 1 month to 7 years after electrocorticographically guided resections [106]. Five out of nine patients had focal or diffuse nonspecific hyperintense lesions and three patients had solitary lesions, which included an intra-parenchymal hemorrhage, a resection cavity, and evidence of mesial temporal sclerosis with unilateral hippocampal atrophy.

As for evidence on pediatric patients, a case report of a 10-year-old boy with generalized convulsive RSE after a mild febrile illness and restricted diffusion in the right hippocampus described termination of RSE with right anterior temporal lobectomy [107].

Furthermore, left occipital lobectomy in a 7-year-old boy with anti-NMDA receptor encephalitis 3 months after onset of RSE led to seizure resolution and so did Electro Corticography (ECoG)-guided resection of the right dorsolateral frontal cortex in a 20-year-old man with CNS vasculitis [108, 109].

On rare occasions, multiple subpial transections have also been tried, usually as an adjunct to cortical resection [110]. An isolated multiple subpial transection of the sensorimotor cortex was successful in abolishing seizures in a 6-year-old child with MRI-negative SRSE of 60 days' duration, with a clearly localizable seizure-onset zone [110].

Palliative surgical options include neurostimulatory options such as vagus nerve stimulation (VNS) and complete corpus

callosotomy and functional hemispherectomy with several case reports of successful control of RSE [111, 112].

Neurostimulation

Delivery of an external electrical stimulus that is of adequate voltage and is properly timed in refractory epilepsy can prolong the post-excitation refractory period of the hyper-synchronous discharges and has the potential to interrupt an ongoing seizure.

Vagus nerve stimulation

There are case reports of young adults who underwent VNS surgery for prolonged RSE refractory to infusions of anesthetics resulting in seizure termination after the procedure enabling the tapering of other infusions [113, 114].

A 13-year-old boy with a history of previous 90% callosotomy underwent left VNS implantation 15 days after onset of RSE with a rapid response of seizures with the VNS settings of 30 Hz of frequency, pulse width 500 ms, on time 7 s, off time 120 s and current 0.25 mA [115].

Other pediatric case reports suggesting efficacy of neurostimulation in SE include a case report of a 17-year-old girl with generalized convulsive RSE demonstrating electro-clinical improvement of RSE after deep brain stimulation targeting the anterior thalamic nucleus [116, 117].

Electroconvulsive therapy

Electroconvulsive therapy (ECT) is an unpopular modality of neurostimulation that is hypothesized to be effective in terminating seizures by increasing presynaptic release of GABA resulting in a prolonged postictal refractory period [118].

In a 13-year-old boy with polymicrogyria and epileptic encephalopathy, consecutive ECT sessions over 3 days were successful in controlling RSE [119].

Another case report describes termination of SRSE with ECT in a 4-year-old boy with FİRES after multiple other therapeutic strategies failed including benzodiazepines, phenytoin, barbiturates, corticosteroids, plasmapheresis, immunoglobulins, propofol, lidocaine, ketamine, in-

haled desflurane, KD, lacosamide, and even therapeutic hypothermia [120].

Overall, neurostimulation (transcranial magnetic stimulation, Deep Brain Stimulation (DBS), and ECT) in treatment of RSE/SRSE remains poorly understood and utilized at present. Candidate selection, identifying stimulation targets, stimulation frequency, dose and regimen as well as the safety profile need to be evaluated prior to adaptation [83].

Noninvasive neurostimulation

Noninvasive methods of neurostimulation such as transcranial magnetic stimulation are emerging modalities for treating RSE/SRSE, which may be of use in the future, but they require better quality evidence prior to adaptation.

Management and prognosis of neonatal status epilepticus

Neonates are considered a special subgroup within the pediatric population, taking into consideration a variety of physiological and maturational factors. Likewise, neonatal seizures are considered an entity on their own based on the electro-clinical characteristics that differ widely from the rest of the pediatric population. Therefore, it is only fair that neonatal seizures and their management are considered separately, adapting a distinct approach.

Neonates are at a greater risk of developing seizures in comparison with the older children or adults, with acute provoked seizure being the commonest in this age group. The International League Against Epilepsy (ILAE) defines a neonatal seizure as an electrographic event with a definitive beginning and an end and clear electrographic evidence of evolution, but with no defined minimum duration, which is a significant deviation from seizures defined in other age groups [122]. Also, no universally accepted definition exists for neonatal SE, although neonatal SE is quite common and is associated with a higher burden of neurodevelopmental disability [123]. A cohort study by Pisani and colleagues observed that only one out of eight newborns with neonatal SE would have a normal developmental outcome and six out of eight of them went on to

develop cerebral palsy later in life. In this study, a mortality rate of 19% was observed with the presence of either SE or recurrent neonatal seizures, emphasizing the degree of associated disability [124].

The NEOLEV2 trial is a multicenter, randomized, blinded, phase IIb trial investigating the efficacy and safety of levetiracetam (40 mg/kg bolus followed by maintenance) compared with phenobarbital (20 mg/kg bolus followed by maintenance) as a first-line treatment of seizures in 83 neonates. In total, 80% of neonates who received phenobarbital were electrographically seizure free at 24 h while only 28% in the levetiracetam arm were able to achieve a similar outcome [125]. Beyond this, there is no evidence-driven data to guide management of SE in this specific population of patients.

Future directions

It is abundantly clear that the burden of disability and acute and long-term morbidity risks that are associated with pediatric SE (SE) is significant. Large knowledge gaps exist in the management of pediatric SE with several questions remaining unanswered. In contrast to 5–10 years ago, we now have a substantial amount of evidence to support the use of several treatment options as first- and second-line agents in managing pediatric SE. However, beyond this point the evidence is sparse and the management protocols and guidelines are largely institutional based and expert opinion driven.

The challenge of developing evidence-based guidelines beyond this point is in the lack of properly designed trials to assess each of the available modalities individually for efficacy and safety. By the time refractory SE ensues, ongoing management in a critical care setting includes multiple other instituted medication regimens, which will invariably confound the efficacy and safety profile of the trial medication. It is often hard to overcome this barrier in designing good-quality trials.

Prehospital treatment initiation of pediatric SE aiming to prevent progression into established SE is another area that lacks clear guidelines or protocols.

It is also worthwhile to explore other potential therapeutic targets in the treat-

ment of SE, which expands beyond the realms of extensively explored current targets. Some of the potential candidates include but are not limited to targeting specific inflammatory mediators exploring the benefits of utilizing therapeutic agents such as anakinra or tocilizumab. Exploring and managing altered gene expression in SE such as alterations of the mammalian target-of-rapamycin (mTOR) pathway with the use of agents such as rapamycin, and exploring dysregulations in cholesterol synthesis, cholinergic pathways, and mitochondrial oxidation are other potential options.

Incorporating machine learning to develop predictive models and reliable biomarkers to predict and identify risk factors for progression into refractory SE and super-refractory SE will also hasten the management of SESE and improve outcomes.

Developing universally accepted, evidence-based clear guidelines leading to rational use of polytherapy targeting one or more etiology-specific targets with minimal adverse events would be the ultimate goal to pursue.

Corresponding address

Eroshini Swarnalingam
Division of Pediatric Neurology, Alberta
Children's Hospital
28 Oki Drive NW, T3B 6A8 Calgary, Alberta,
Canada
Eroshini.Swarnalingam@
albertahealthservices.ca

Declarations

Conflict of interest. E. Swarnalingam, K. Woodward, M. Esser and J. Jacobs declare that they have no competing interests.

For this article no studies with human participants or animals were performed by any of the authors. All studies mentioned were in accordance with the ethical standards indicated in each case.

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Management und Prognose des Status epilepticus im Kindesalter

Hintergrund: Ein Status epilepticus im Kindesalter bedeutet immer eine kritische neurologische Notfallsituation, die sofort diagnostiziert und behandelt werden muss, um schwere neurologische Langzeitschäden zu vermeiden.

Ziel: Diese Studie fasst den aktuellen Stand der Literatur für die Behandlung des Status epilepticus im Kindes- und Neugeborenenalter zusammen mit einem Schwerpunkt auf neuen randomisierten kontrollierten Studien. Außerdem werden Prognose und Langzeitfolgen diskutiert.

Methoden: Dazu erfolgte eine systematische Analyse der existierenden Studien.

Ergebnisse: Beim Status epilepticus wird in Bezug auf die Behandlung und Prognose unterschieden, ob die Anfallsaktivität länger als 5 oder länger als 30 min anhält. Die Behandlung des refraktären und superrefraktären Status epilepticus kann generell als komplizierter angesehen werden und benötigt normalerweise kontinuierliches EEG-Monitoring und eine ständige Anpassung des Therapieregimes. Der Einsatz von Benzodiazepinen ist weitgehend als erste Behandlungsmaßnahme etabliert. Neue randomisierte kontrollierte Studien deuten darauf hin, dass im Kindesalter i.v. verabreichtes Phenytoin, Valproat und Levetiracetam als Zweitlinientherapie eine vergleichbare Wirksamkeit haben, wenn durch Benzodiazepine der Status epilepticus nicht unterbrochen werden konnte. Darüber hinaus, als für Drittlinientherapieansätze, ist die Studienlage nicht überzeugend. Einige Daten weisen darauf hin, dass Midazolam oder Ketamin bei refraktärem Status wirksam sind, ebenso werden Immunsuppressiva, ketogene Diät und in seltenen Fällen chirurgische Interventionen diskutiert.

Schlussfolgerung: In der vorliegenden Übersichtsarbeit wird die aktuelle Studienlage zum Thema pädiatrischer Status epilepticus zusammengefasst. Hierbei wird deutlich, dass v. a. Studien zum schwer behandelbaren Status epilepticus immer noch dünn gesät sind und weitere hochqualitative Studien sowie evidenzbasierte Leitlinien benötigt werden, um betroffene Kinder optimal zu behandeln.

Schlüsselwörter

Pädiatrischer Status epilepticus · Neonataler Status epilepticus · Refraktärer Status epilepticus · Prognose

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