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Review

Gaps and opportunities in refractory status epilepticus research in children: A multi-center approach by the Pediatric Status Epilepticus Research Group (pSERG)☆

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ABSTRACT

Purpose: Status epilepticus (SE) is a life-threatening condition that can be refractory to initial treatment. Randomized controlled studies to guide treatment choices, especially beyond first-line drugs, are not available. This report summarizes the evidence that guides the management of refractory convulsive SE (RCSE) in children, defines gaps in our clinical knowledge and describes the development and works of the 'pediatric Status Epilepticus Research Group' (pSERG).
Methods: A literature review was performed to evaluate current gaps in the pediatric SE and RCSE literature. In person and online meetings helped to develop and expand the pSERG network.
Results: The care of pediatric RCSE is largely based on extrapolations of limited evidence derived from adult literature and supplemented with case reports and case series in children. No comparative effectiveness trials have been performed in the pediatric population. Gaps in knowledge include risk factors for SE, biomarkers of SE and RCSE, second- and third-line treatment options, and long-term outcome.
Conclusion: The care of children with RCSE is based on limited evidence. In order to address these knowledge gaps, the multicenter pSERG was established to facilitate prospective collection, analysis, and

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sharing of de-identified data and biological specimens from children with RCSE. These data will allow identification of treatment strategies associated with better outcomes and delineate evidence-based interventions to improve the care of children with SE.

1. Introduction

Status epilepticus (SE) is one of the most common neurologic emergencies of childhood.[1–4] A major proportion of morbidity and mortality associated with SE occurs during episodes of refractory convulsive status epilepticus (RCSE),[5–8] a condition characterized by the persistence of convulsive seizures or evolution of the convulsive seizure to non-convulsive seizures despite initial, antiepileptic medication treatment.[7] This review aims to describe the main characteristics of pediatric RCSE, emphasizing opportunities to better understand and eventually improve care.

2. Literature search method

Since there is no MeSH term corresponding to refractory status epilepticus, we performed a PubMed search using a semi-structured string ("Status epilepticus" [Mesh] AND "refractory") in August 2013. The filter "age" was applied to include all patients ≤18 years. The initial search returned 268 papers. Additional 127 papers were identified from relevant articles known to the members of pSERG and a manual search of cited references. After screening and exclusion of abstracts (and when relevant, full-text manuscripts), 113 articles were included in this literature review (Fig. 1). Because randomized clinical trials in pediatric status epilepticus patients are rare, we also included randomized clinical trials performed exclusively or predominantly in adults in this systematic review.

3. Definitions

When medications fail to terminate SE, it is often termed refractory. However, although to date, there is no single, accepted operational definition of SE a consensus has developed that SE should be considered refractory after failure of an initial benzodiazepine followed by another class of antiepileptic drug[9] (Table 1).

3.1. Clinical presentation and evolution

When seizures persist for more than 5–10 min the preferred term is impending SE. When seizures persist for at least 30 min the preferred term is established SE.[10] The prolonged seizures of SE can evolve from a period of isolated seizures that become progressively longer and then fuse into a prolonged continuous seizure or continue to be repeated frequently enough so that a return to baseline does not occur between the seizures. Eventually, if the SE persists, a phase of electromechanical dissociation may pursue.

Super-refractory SE is defined as SE that continues 24 h or more after the onset of anesthetic therapy for SE, including those cases in which SE recurs during reduction or withdrawal of anesthesia.[11]

Additionally, SE has been also classified based on clinical features, such as convulsive SE or non-convulsive SE. Defining convulsive SE as a convulsive seizure that lasts for a period of at least 5 min is not only practical[9,12] but is supported by the finding that the probability of a seizure stopping spontaneously without intervention is quite low after this duration.[13]

3.2. Pathophysiology and etiology

One of the difficulties in developing a comprehensive definition of SE is related to the limited understanding of the pathogenesis of this neurological emergency. Recent advances outlining the cellular and molecular changes that occur during SE have focused on trafficking of receptors[14–17] and ion channels.[18,19] Yet, time course studies of these changes are limited and whether these changes reflect the consequences of an episode of SE or are necessary for an episode of SE to occur is not known, and etiologies are frequently multifactorial.

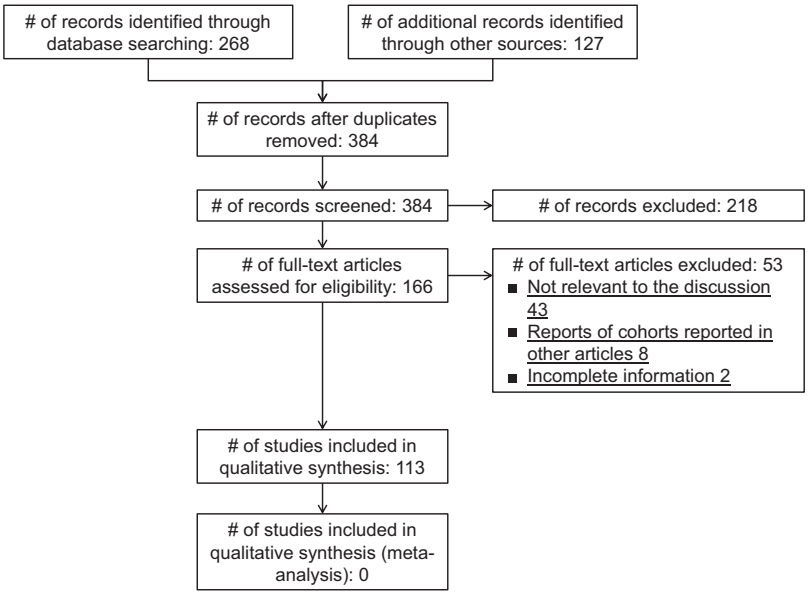

Fig. 1. Approach to literature review in our manuscript. This figure outlines the literature review in this manuscript that follows the PRISMA scheme.

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Table 1
Representative definitions of refractory status epilepticus in previous literature and comparison with our current definition.

Author and year	Definitions of refractory status epilepticus (SE)
Jagoda and Riggio, 1993 [111]	Cases in which seizure control is not attained with a benzodiazepine, phenytoin, and/or phenobarbital and thus requires the addition of a third-line antiepileptic drug
Lowenstein and Alldredge, 1998 [109]	SE that does not respond to a benzodiazepine, phenytoin, or phenobarbital is considered refractory
Stecker et al., 1998 [112]	All of the following criteria: (1) acute seizures persisting more than 2 h despite treatment with first-line antiepileptic drugs, (2) altered mental status, and (3) seizures recurring at a rate of at least two per hour without a recovery to baseline between seizures
Hanley and Kross, 1998 [113]	Sustained seizures that do not respond to initial drug therapy and persist longer than 60 min
Mayer et al., 2002 [7]	Seizures lasting longer than 60 min despite treatment with a benzodiazepine and an adequate loading dose of a standard intravenous antiepileptic drug
Loddenkemper and Goodkin, 2011 [21]	SE is considered refractory at the latest after failure of the second medication
Rossetti and Lowenstein, 2011 [20]	SE that continues despite treatment with benzodiazepines and one antiepileptic drug
Brophy et al., 2012 [9]	Refractory SE is considered when either clinical or electrographic seizures persist after receiving adequate doses of an initial benzodiazepine followed by a second acceptable antiepileptic drug
Present study	Prolonged seizures that fail to terminate after administration of two antiepileptic drugs with different mechanisms of action or that require continuously administered medication to abort seizures, regardless of seizure duration

3.3. Treatment and response to treatment

There are many different definitions for refractory SE, almost as many as manuscripts that have studied this topic (Table 1). Commonly, refractoriness is considered after failure of at least two appropriately chosen and administered antiepileptic drugs.[9,20,21] Based on this frequently used criterion, our group agreed to term SE refractory when SE does not respond to two different drugs with different mechanisms. The second definition meeting consensus with pSERG was use of a continuous infusion of AED regardless of the number or type of previously administered AEDs since this approach is usually used after failure of at least two different medications with two different mechanisms of action. Table 1 summarizes representative definitions of RCSE.

4. Epidemiology of pediatric convulsive status epilepticus

4.1. Incidence

The incidence of convulsive SE in children is approximately 10–27/100,000 per year, with the highest incidence in children less than one year of age.[1–4] If febrile SE is excluded, the incidence decreases by 25–40%.[4] The proportion of cases with RCSE is difficult to estimate because definitions vary. In a series of 193 children with SE, 26% had seizures lasting longer than 1 h.[22] Duration correlated with etiology: seizures lasting over 1 h occurred in 46% of patients with acute symptomatic seizures and in 17% of those with unprovoked seizures.[22]

4.2. Etiology

Most episodes of RCSE begin in previously healthy children in the out-of-hospital setting. A large prospective study of 226 children with convulsive SE of a median duration of 65 min in North London in the United Kingdom, found that 78% of cases were first-ever episodes of SE. Of those, 56% of patients had normal neurodevelopment at baseline, no history of epilepsy, and no neurological deficits prior to the SE episode.[3] Of the 176 first-ever episodes, 77% started out-of-hospital.[3,23,24] The most common cause of pediatric SE is febrile/infectious. The most common etiologies of SE in children are summarized in Table 2. The younger the patients, the more frequent an acute symptomatic etiology was found, especially in those under one year of age.[3] It is unknown why some febrile processes are associated with SE while others are not. Infection with the human herpesvirus 6 (HHV6) and herpesvirus 7 (HHV7) are being postulated as an additional potential risk factor for the development of SE and subsequent epilepsy in selected cases.[25,26] Gaps in information exist in the correlation between etiology, response to different treatment and long-term outcome after pediatric SE.

4.3. Genetics

A variety of genetic factors might promote or protect patients from developing uncontrolled seizures.[27] Genetic variants that predispose some individuals to prolonged seizures are yet to be discovered. A study on concordance rates for SE found a much higher rate in monozygotic than in dizygotic (0.38 versus 0) twins.[27] However, there are insufficient data to support or refute routine genetic testing (chromosomal or molecular studies) in children with SE.[24]

4.4. Outcome

Children with SE have an overall mortality rate of approximately 0–3%,[3,22,23,28–31] and surviving children are at risk of lifelong sequelae including cognitive and neurodevelopmental impairments, new-onset epilepsy, and recurrent SE.[22,32] RCSE is associated with a much higher mortality. In a retrospective series of 22 children (4.5 months to 18 years of age) with RCSE (refractory to a benzodiazepine followed by either phenytoin or phenobarbital, and lasting more than 60 min), mortality was 32%.[8] Studies on RCSE in adults also point toward a higher mortality when SE is refractory, although it probably reflects a more severe underlying cause.[33]

Table 2
Frequency of the most common etiologies of status epilepticus in children.

	Febrile seizures (%)	Acute metabolic derangement or central nervous system infection (%)	Remote symptomatic (%)	Acute symptomatic on remote symptomatic (%)	Low antiepileptic drug levels (%)
Chin et al., 2006 (N=226) [3]	33	17	16	16	
De Lorenzo et al., 1996 (N=166) [28]	52[a]		39		21
Singh et al., 2010 (N=144) [23]	32	9	18		

[a] Infections with fever.

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Younger children have the highest rates of morbidity and mortality.[8,22] In a series of 193 children with SE, neurologic sequelae occurred in 29% of infants younger than one year of age, 11% of children one to three years of age, and 6% of children older than three years of age.[22] Given that there was no difference in outcome when these data were stratified by etiology, these data reflect the greater incidence of acute neurologic disease (associated with worse outcome) in younger age groups.[22] Long-term mortality data suggest that the etiology of SE is one of the main predictors of long-term survival.[34] Apart from mortality, SE survivors have an increased risk of subsequent epilepsy, which is reported in 13–74%.[31] SE recurs in approximately 20% of cases within four years of initial presentation, with most recurrences during the first two years.[31] Seizures and SE recurrence risk is influenced by the underlying etiology, with structural or metabolic lesions associated with the highest risk.[31] In addition, current literature suggests subtle neurocognitive dysfunction in patients who have suffered a prior episode of SE, but the impact of etiology, duration and other potential confounders has not been clarified.[31,35]

There are gaps in data on outcome after pediatric SE. Specifically, there are limited data on the mortality and morbidity following RCSE. There is also scarce information on the relationship between SE duration and outcome, and on the long-term sequelae (in particular neurocognitive impairment) of pediatric patients following RCSE.

5. Current diagnostic strategies in pediatric status epilepticus

Diagnostic testing in children and adolescents with SE varies among centers and likely reflects the limited evidence supporting most diagnostic approaches in pediatric SE. Although blood cultures and a lumbar puncture have a high yield in children with SE and a clinical suspicion of infection, there is insufficient evidence to either support or refute whether these procedures should be routinely performed in children in whom there is no clinical suspicion of infection.[36] In addition, the clinical suspicion of infection is variably defined among studies and the yield of an infectious work-up has not been studied specifically for RCSE. The indications for performing toxicology screening or metabolic testing in children with SE have not been delineated.[24] Evidence to support the performance of most diagnostic tests relies on limited data collected in heterogeneous settings with different study objectives.[24] A large set of pediatric RCSE patients with homogeneous inclusion criteria may be able to address this gap in evidence-based practice and will provide valuable information regarding the diagnostic yield of different tests.

6. Current treatment strategies in pediatric status epilepticus

SE can be refractory to first- and second-line medications. Treatment choices, especially beyond first- and second-line choices, that is treatment choices for RCSE, are often made without class I evidence.

6.1. Current treatment strategies for SE

The treatments of choice during the first half of the twentieth century included paraldehyde, phenobarbital, and sodium amytal.[37] These medications became the established treatment of SE at a time when options were limited.[38] A more recent era of treating SE began soon after the discovery and synthesis of benzodiazepines in the late 1950s.[37] Medical convention suggested a stepwise treatment of SE[9,21,39] and RCSE[40] in children. Based on available studies, mostly performed in adults, and mostly at a time when intravenous medications and options were limited, the preferred first-line therapy is usually a benzodiazepine, most commonly lorazepam. Benzodiazepines have been shown to be safe first-line treatments in the in- and out-of-the-hospital setting.[3,41,42] If benzodiazepines fail to terminate SE, many reports describe the use of fosphenytoin (or phenytoin) or phenobarbital.[9,21,39] After failure of the second- or third-line medication, continuous administration of antiseizure medications such as midazolam or pentobarbital is advocated by established medical convention[9,21,39] (Supplementary Fig. S1). However, use of these continuous infusions are not without untoward effect.[43,44] It is unclear if adherence to SE treatment protocols influence outcome.[45]

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.seizure.2013.10.004.

6.2. Evidence to support first-line treatment with benzodiazepines in children

The administration of 0.5–1 mg/kg of rectal diazepam solution results in therapeutic concentrations within minutes, which makes it useful for SE treatment.[46] The few controlled studies that have compared the efficacy of different first-line treatments for SE have either not included children,[41,42,47,48] or children represented only a minor proportion of the study population (16% of patients were younger than 20 years in a large series of 893 patients).[49]

The Veterans Affairs (VA) cooperative trial has a randomized treatment trial that aimed to determine optimal first-line treatment in SE comparing four choices: intravenous diazepam followed by intravenous phenytoin, intravenous lorazepam, intravenous phenobarbital, and intravenous phenytoin.[41] In that study lorazepam was superior to phenytoin, but in an intention-to-treat analysis there were no differences among the four treatment groups.[41] The conclusions from the VA cooperative trial are often extrapolated to the management of children with SE even though there were no children in the study.[41] In a double-blind study of SE in 78 adults with 81 episodes seizures were controlled in 76% of the episodes treated with 10 mg of diazepam intravenously and in 89% treated with 4 mg of lorazepam intravenously.[42] Adverse effects occurred in 12.5% of the diazepam-treated patients and in 13% of the lorazepam-treated patients.[42] In a series of 205 adults with out-of-hospital SE, patients were randomized to receive intravenous lorazepam, intravenous diazepam, or intravenous placebo.[47] On arrival at the emergency department SE was terminated in more patients treated with lorazepam (59.1%) or diazepam (42.6%) than with placebo (21.1%).[47]

Several studies show efficacy of benzodiazepines as first-line treatment of pediatric SE without a clear benefit of one benzodiazepine over the others.[50] In a series of 77 children and young adults with SE or serial seizures, lorazepam stopped seizures in 79% and decreased seizure intensity in an additional 4%.[51] In a prospective study, 44 children (6 months to 5 years of age) were treated with rectal diazepam during 59 generalized seizures with a rate of seizure resolution of 80%.[52] In 10% rectal diazepam failed, while intravenous diazepam was effective, and in 10% diazepam failed after rectal and intravenous administration.[52] The therapeutic effect was significantly correlated with the duration of convulsions before treatment: early treatment (convulsions $\leq$15 min) had effect in 96%, and late treatment (convulsions $>$15 min) had effect in 57% of the cases.[52] No respiratory depression or serious side effects were observed.[52] In a randomized trial of 178 children with convulsive SE (defined as convulsive activity lasting for 5 min or more), intravenous lorazepam was compared to the combination of diazepam and phenytoin with no differences between the treatment groups and 100% seizure control in both groups.[53] This response rate, however, does not match experiences from others with less than 100% response rate

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to these medications, raising concerns about potential selection bias.[53] Diazepam and lorazepam showed no difference in efficacy in a series of 48 children with SE treated in the emergency department.[54] In a series of 76 episodes of pediatric seizures lasting more than 5 min, three bolus doses of intravenous midazolam controlled 89% of the events with minimal chance of additional response with further drug boluses.[55] A meta-analysis demonstrated that non-intravenous midazolam was at least as safe and effective as diazepam administered by different routes.[56] A series of 28 children (5–19 years of age) with severe epilepsy who presented with seizures of more than 5 min duration, were randomized to receive buccal midazolam or rectal diazepam.[57] In this series, buccal midazolam was shown to be at least as effective as rectal diazepam.[57] A series of 92 children with seizures did not find differences in efficacy between intranasal midazolam and rectal diazepam as a first-line treatment.[58] In a series of 24 children with convulsive seizures of more than 10-min duration, intramuscular midazolam was administered earlier and led to more rapid cessation of seizures than intravenous diazepam.[59]

Lorazepam is commonly recommended over other benzodiazepines. For children, this recommendation is essentially based on the large North London series of 182 pediatric patients (1 month to 16 years of age) with convulsive SE, in which treatment with intravenous lorazepam was associated with a 3.7 (95%CI 1.7–7.9) times greater likelihood of seizure cessation than was treatment with rectal diazepam.[6] However, a recent series of 893 patients (145 of them younger than 20 years of age) demonstrated that intramuscular midazolam is at least as safe and effective as intravenous lorazepam.[49] Gaps in knowledge include comparative effectiveness and randomized trial data of first-line treatment of pediatric SE.

6.3. Evidence to support second- and third-line treatment options in children

The available evidence supporting the use of any particular second- or third-line therapy is weaker than for first-line therapies. Likely more reports on the use of benzodiazepines, phenobarbital, and phenytoin for SE exist, because these medications were, until recently, the only available antiepileptic drugs. In a series of 122 children with generalized convulsive SE treated with a stepwise combination of a midazolam bolus followed (if needed) by phenytoin followed (if needed) by a continuous infusion of midazolam showed that seizures stopped with midazolam given as a bolus in 58 patients (percentage: 48%). When phenytoin was added to the midazolam bolus, it stopped seizures in 19 additional patients (cumulative percentage: 63%), and with continuous midazolam added to midazolam bolus and phenytoin seizures stopped in another 32 patients (cumulative percentage: 89%).[60]

In the North London series of 182 pediatric patients (ages 1 month to 16 years) with convulsive SE, treatment with intravenous phenytoin as a second-line therapy was associated with a 9 (95%CI 3–27) times greater likelihood of seizure cessation as compared to treatment with rectal paraldehyde.[6] Yet, a study of 68 pediatric and adult patients with convulsive SE randomly assigned phenytoin or valproate demonstrated higher efficacy for valproate.[61] In this study phenytoin or valproate were given as first-line drugs without previous administration of benzodiazepines and only 12 patients (17.6%) in this series were under 15 years of age.[61]

A series of 167 patients with SE (defined as continuous occurrence of seizures for more than 5 min or repeated epileptic seizures without intercurrent baseline recovery) compared phenytoin, valproate, and levetiracetam as second-line drugs (after administration of benzodiazepines).[62] This study showed that valproate was more effective than levetiracetam while there was no difference in the efficacy of phenytoin compared to valproate or phenytoin compared to levetiracetam.[62] However, no patients younger than 16 years were included in this series.[62] A study of 48 patients with convulsive SE refractory to prior treatment with diazepam and phenobarbital found that seizures were controlled in 87.5% of patients after valproate administration.[63] Only five patients (10.4%) in this study were under 15 years of age.[63] In another series of 60 children with generalized convulsive seizures lasting more than 5 min that did not respond to a bolus of intravenous diazepam were randomly assigned to either phenobarbital or valproate.[64] In this study, there was a tendency toward a higher rate of seizure cessation with valproate than with phenobarbital (90% versus 77%) with fewer associated adverse events (24% versus 74%).[64]

A developing, comparative, randomized, controlled trial intends to investigate whether valproate and levetiracetam are superior to phenytoin as second-line treatment options of SE.[65] The extrapolation of safety results from adult series directly into children can be misleading for valproate, which disrupts organic acid metabolism, and therefore can lead to serious toxicity in children with underlying metabolic disorders (often unknown at the time of SE presentation) and in children under two years of age.[66]

In a series of 53 episodes of convulsive SE in 37 children, lidocaine achieved seizure control in 36%.[67] In a series of 53 episodes of prolonged tonic-clonic seizures in 30 children, rectal paraldehyde terminated convulsions in 63%.[68]

In summary, there is limited evidence to guide the choice regarding commonly used second- and third-line treatment options for pediatric SE. The answer to this problem is further compounded by the broadening of choice as a result of new intravenous preparations of antiepileptic drugs such as valproate, levetiracetam, or lacosamide.

6.4. Evidence to support continuous infusion options in children

Administering continuous infusions of medications at anesthetic doses in RCSE is considered after failure of previous treatments. Current evidence supports benzodiazepines as the most efficacious and safe continuous infusion in children. In a series of 20 children with SE, continuous infusion of midazolam controlled seizures in 19 children after a mean time interval of 0.9 h after treatment initiation.[69] In a study of 27 children (8 months to 14 years of age) with RCSE (persistence of seizures for longer than 60 min despite receiving at least diazepam, phenytoin, and phenobarbital) a continuous infusion of midazolam controlled seizures in 26 cases within 65 min of the start of the midazolam infusion.[70] In another series, 40 children (2–12 years of age) with SE refractory to diazepam bolus and phenytoin were randomized to a continuous infusion of diazepam or midazolam.[71] Control of RCSE (89% of patients on diazepam and 86% of patients on midazolam) and median time to seizure control (16 min in both groups) were not different.[71] However, more seizures recurred in the midazolam group (57%) than in the diazepam group (16%).[71] Infusion of benzodiazepines was associated with a low rate of adverse effects.[69–71]

Even less information is available on other types of continuous infusion and anesthetic therapies. Three pediatric patients with RCSE responded to moderate hypothermia and thiopental-induced coma.[72] Propofol in continuous infusion controlled 14 out of 22 episodes of RCSE in children.[73] In the same study, thiopental in continuous infusion controlled 11 out of 20 episodes of SE.[73] Thiopental was associated with more frequent, severe side effects than propofol and based on these data the authors recommended use of propofol over thiopental.[73] Despite this recommendation, it is important to be aware that propofol has been associated in children with lactic acidosis, lipemia, rhabdomyolysis and

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cardiovascular collapse in a severe condition known as propofol infusion syndrome.[74]

Pentobarbital is another option for a continuous infusion.[75] In a retrospective series of 30 children with refractory SE treated with continuous pentobarbital infusion, 33% of patients achieved sustained burst suppression without relapse during treatment, 67% experienced relapse of epileptiform activity during treatment, but 60% of those eventually achieved burst suppression with pentobarbital.[76] The rate of adverse effects with pentobarbital infusion was particularly high with hypotension requiring inotropes in 93% of patients, an infection in 66%, metabolic acidosis in 10%, and pancreatitis in 10%.[76] Isoflurane has also been reported to be effective in pediatric SE.[77]

In summary benzodiazepines appear to be the safest and most frequently used continuous infusion, but literature on this topic is scarce, indicating a gap in knowledge, and a comparison of efficacy of different continuous infusions is not available.

6.5. Emerging therapies

Several alternative therapies for RCSE have been reported as effective in individual patients or small series, but larger confirmatory trials are not available in children. Topiramate loading was able to control seizures in a series of three children with refractory SE.[78] The ketogenic diet has been reported as efficacious in a limited number of children with refractory nonconvulsive[79] and convulsive[80] SE. Several cases of refractory SE have responded to hypothermia both in adults[81] and children.[82]

Preliminary case series suggest that epilepsy surgery may be an effective alternative in children with refractory SE not responsive to conventional treatment and with an identifiable focus.[83] Brain stimulation is emerging as a potentially useful therapy for refractory epilepsy. Invasive brain stimulation methods such as vagus nerve stimulation and deep brain stimulation[84] are presently options to be considered as well as the non-invasive transcranial magnetic stimulation.[85] A common limitation to the proper evaluation of emerging therapies is the rarity of their use. This leads to case reports and small series with probable publication bias of more positive results. Only a large multicenter study of reference centers will gather enough information to provide an objective evaluation of these treatments.

6.6. Summary of the evidence on management of status epilepticus in children

While most SE management protocols advise a stepwise treatment (Supplementary Fig. S1),[86] the data to support the order of medications in this approach and the stepwise sequence is scarce, and mostly restricted to first-line drugs.[9] The best evidence coming from multiple, large, randomized clinical trials or meta-analysis is limited to essentially analysis of benzodiazepines, fosphenytoin (or phenytoin), phenobarbital, and valproate given as initial treatments in those studies.[9] The more refractory the SE becomes, the less scientific data exist to support any particular treatment choice.

An example that illustrates the limited scientific evidence is the lack of studies that compare fosphenytoin (or phenytoin) with phenobarbital as second-line medication,[87] although both medications have been widely used for decades. The data and experience are even more limited for newer, alternative second-line intravenous treatment options, such as levetiracetam or lacosamide. Further, the best quality evidence on the management of RCSE is mostly derived from studies in adults[41,47,49] with these conclusions directly extrapolated to the clinical management of RCSE in children, which might not always apply.[88] Additionally, dosing recommendations are based on limited observational data because controlled trials comparing different doses are lacking, even in adults.[9]

6.7. Timing of interventions

A timely escalation of antiepileptic drugs when initial treatments fail is advocated.[9,21,39,40,87,89–92] Basic research results[14–16,93–99] as well as clinical evidence[5,6] suggests that the longer SE persists, the more resistant it becomes to treatment. In a study of 157 children (1 month to 16 years of age) with SE, a treatment delay of more than 30 min was associated with delayed seizure control.[100] In a study of 27 children, first- (benzodiazepine) and second-line (phenytoin or phenobarbital) medications were effective in terminating SE in 86% when seizure duration was less than 20 min at presentation and only in 15% when seizure duration exceeded 30 min.[101] The North London pediatric convulsive SE population showed that for each minute delay from onset of SE to arrival at the emergency department, there was a 5% cumulative increase in the risk of the episode lasting more than 60 min.[6] Together, these studies suggest that seizures must be treated quickly before they become resistant to treatment and associated with higher mortality.

As most cases of SE begin out-of-hospital, treatment plans for SE should be easily applicable by families and school personnel emphasizing the need of a timely intervention.[50] A large series of 889 patients (625 adults and 264 children) categorized the timing of administration of the first antiepileptic drug as occurring in the following broad time frames: 0–29, 30–59, 60–89, 90–119, 120–179, 180–239, $\geq$240 min.[102] Approximately 60% of the patients received their first medication after 30 min and 30% after 60 min with no significant differences between adults and children.[102] However, to date there is a gap of pediatric and adult studies that specify the timing of administration of the individual medications and therefore there are no correlations between timing of antiepileptic drug administration with outcome. As a consequence, it is not possible to make evidence-based recommendations on how fast antiepileptic drugs should be administered and when to transition from one antiepileptic drug type to the next or whether antiepileptic drugs should be given simultaneously.

7. The need of high-quality data to develop evidence-based treatment strategies

Based on a formal series of discussions that culminated at the Child Neurology Society and American Epilepsy Society meetings in 2010, the pSERG was established. The guiding purpose of the group is to delineate strategies for improving the management and eventually the prognosis of children with SE, especially those episodes that are not responsive to first-line treatments and become RCSE. The group concluded that in order to best understand the relationship between variation in care and outcome, pediatric SE data needed to be prospectively collected and analyzed with a comparative effectiveness research approach.[103,104] Furthermore, a large number of RCSE cases would be necessary to:

(1) Describe how children with RCSE are currently managed in clinical practice.
(2) Identify clinical findings, biomarkers, and treatment strategies associated with more favorable outcomes (medication effectiveness), and ultimately.
(3) Develop clinical predictors and biomarkers of care that permit evidence-based clinical decision-making.

The number of RCSE cases needed for this scope of analysis is beyond the capabilities of any individual center and is only feasible

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Table 3
Summary of the main gaps in pediatric status epilepticus literature and how pSERG is aiming to address them.

Areas	Main knowledge gaps in pediatric status epilepticus literature	pSERG strategies to address these gaps
Epidemiology	Clinical and genetic risk factors that contribute to refractoriness	Genetic analyses of patients with RCSE
	Correlation between etiology, response to different treatments and long-term outcome	Long-term outcome evaluation with a particular focus in function and neurocognitive function
	Data on receptor changes during status epilepticus in human brain	Collection of human brain samples from epilepsy surgery and autopsies
	Long-term clinical and developmental sequelae and mortality	Long-term follow-up with a focus on mortality and function
Diagnosis	Indications and yield of lumbar puncture, toxicologic studies	Collection of data on the yield of these tests when clinically used
Treatment	Optimal first-line therapy	Comparative effectiveness of first-line therapies
	Optimal second-line therapy	Comparative effectiveness of second-line therapies
	Optimal third-line therapy	Comparative effectiveness of third-line therapies
	Optimal continuous infusion	Comparative effectiveness of continuous infusions
	Role of emerging therapies	Descriptive analysis of the efficacy of emerging therapies in a large population
	Timing and escalation of treatments	Observational studies on the timing and escalation of drugs
	Potential role of polytherapy and combinations of different treatments	Descriptive analysis of the efficacy of polytherapy when clinically used
	Lack of comparative effectiveness studies	Performance of comparative effectiveness studies
	Lack of interventional treatment trials	Performance of interventional treatment trials

within a large multi-center collaborative network of hospitals. There is a general consensus in the adult and, especially pediatric literature regarding the need for high-quality data on SE[9,20,105] (Table 3). Randomized controlled trials are difficult, but prospective observational study protocols assessing variation in care using a comparative effectiveness approach are more feasible, help refine the key issues for future studies, and need to be developed.[105]

8. Goals of pSERG

The overall goal of pSERG is to foster an evidence based approach to assessing the current variation in care and converting that information to knowledge for improving the management and prognosis of children with RCSE.[103] The data obtained from prospective collection of current clinical practice can inform future decisions about care and treatment trials. This overall goal will be attained by completing the following aims.

Aim 1. Build a standardized infrastructure that fosters collaboration between hospitals that care for children with RCSE by introducing common measurement indicators, common terminology for documenting care, and a computerized online database that facilitates data entry, data maintenance, and data analysis.

Aim 2. Generate observational data on current acute care of children with RCSE, including collection and analysis of clinical data, treatment approaches, electroencephalography (EEG) findings, magnetic resonance imaging (MRI) findings, and biological specimens in order to identify biomarkers and predictors of treatment response and short-term outcome based on variation in care.

Aim 3. Record and analyze observational data on the follow-up of children with RCSE in order to identify biomarkers and predictors of treatment response and long-term outcome based on variation in care.

These three inter-related and ongoing aims will inform evidence-based treatment approaches, and will provide information on areas of greatest need for interventional treatment trials.[104]

9. Development of the pSERG network

Since December 2010, phone and in-person conferences have been established in order to assign specific tasks, share problem-solving strategies, update the group on achieved objectives, and constitute a forum for exchange of ideas. Currently, the group is composed of 12 tertiary care hospitals with large patient populations and infrastructure to diagnose, treat and study RCSE (Supplementary Table S1).

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.seizure.2013.10.004.

The organizational structure of pSERG (Supplementary Fig. S2) consists of different committees and promotes involvement of participants from each center and development of ancillary studies. The *executive committee* establishes lines of research inquiry and maintains a research infrastructure that facilitates data collection. The *database management working group* facilitates data entry and data analysis by creating and updating a computerized web-based database. The *quality control working group* ensures that the information in the database is as complete as possible and that all the included RCSE episodes meet the inclusion/exclusion criteria.

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The data collection and publication working group oversees data analysis and distributes data collected among the different investigators in order to promote optimal analysis, timely dissemination of results, and fair distribution of authorship. The *operations advisory working group* assures that the research is conducted according to ethical guidelines and that complies with the Institutional Review Board (IRB) requirements at all centers.

10. Development of a computerized database with common terminology

A secure, Health Insurance Portability and Accountability ACT (HIPPA)-compliant web-based interface is used to promote multicenter, anonymized data entry. This system is designed with the same approach implemented by the Childhood Absence Epilepsy Study Group[106] and in Cincinnati Children's Hospital Medical Center's Comprehensive Epilepsy Center. A modular plug-and-play approach ensures generalizability of data while allowing appropriate enhancements. Our web-based data entry and management system uses MySQL, an open-source database management system and CHRISTINE, a web-based data collection system developed for multi-site neuropsychiatric research.[107]

Based on NIH/NINDS common data elements and case reports forms for epilepsy (http://www.commondataelements.ninds.nih.gov/epilepsy.aspx#tab=Data_Standards),[108] the pSERG network has developed a set of demographic, clinical, EEG, neuroimaging,

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and outcome variables which captures the main aspects of pediatric RCSE diagnosis, management and outcome.

11. Patients

11.1. Inclusion/exclusion criteria

Patients with RCSE are eligible if they: (1) are between 1 month to 21 years of age, (2) have convulsive seizures at onset, and (3) experience failure of two or more antiepileptic drugs or require a continuously administered medication to stop seizures (Table 1).[9,20,109] Patients are excluded if they: (1) have non-convulsive SE detected on EEG only (without convulsive seizures at onset) or (2) have non-convulsive SE with infrequent myoclonic jerks. Patients with complex partial SE were included as long as they had convulsive movements at onset.

We include age ranges from 1 month to 21 years in order to exclude both neonates and older adults in whom the etiology, natural history, and prognosis appear to follow a different trajectory than in children.[28,110] We define SE as prolonged self-sustaining seizures and classified the episode of SE as "continuous" if there was a continuous clinical seizure or "intermittent" if there were repeated clinical seizures without interval return to baseline.[12] We define RCSE as prolonged seizures that fail to terminate after administration of two antiepileptic drugs with different mechanisms of action or if a continuous medication infusion was commenced to abort seizures, independent of seizure duration.[9,20,109] For the purposes of antiepileptic drug assessment, different benzodiazepines given as a bolus (for example, rectal diazepam followed by intravenous lorazepam) are counted as one antiepileptic drug. The rationale for this decision is that different benzodiazepines administered by different routes do not have differences in mechanism of action or efficacy.[41,47,49] Benzodiazepines in continuous administration (for example, continuous infusion of midazolam) are quantified as continuous medication administration.

11.2. Collection of clinical information

Episodes of RCSE are prospectively identified at each center through daily review of admissions to the Neurology services and Neurology consultations in the emergency department and intensive care unit as well as through collaboration with inpatient care teams. The process of patient identification varies little between institutions to adjust for individual service designs. In order to collect all pSERG variables, medical records are reviewed during the hospitalization and, if deemed necessary, directed interviews with the family and medical team are performed. Study variables are de-identified by the study personnel at each individual center and entered into the secure centralized database. Management decisions are made by individual caretakers, paramedics, and treating physicians, with no influence from the research team. There is currently no specific management protocol for the study and each center/provider cared for the patient based on their own clinical decision-making strategies. The Institutional Review Boards at each center approved the performance of this study and each individual patient signed the consent form.

12. Ongoing projects

Considering the above summarized gaps in literature, the group has now started clinical data collection within this database and variables are being analyzed to generate and disseminate results on the following topics.

How are children with RCSE managed in clinical practice? While literature recommendations on treatment of SE abound, there is remarkable lack of data addressing antiepileptic drug choices, dosing, and on the timing of antiepileptic drug administration in real clinical management of pediatric RCSE[9,21,40] We will describe antiepileptic drug choices, and their timing of administration.

EEG monitoring findings. We will analyze EEG findings and in conjunction with the pediatric critical care EEG group (PCCEG) will identify neurophysiological biomarkers that influence care and predict outcome.

Neuroimaging. We will describe neuroimaging findings to identify imaging criteria that help influence care and predict outcome.

Continuous medication administration, PICU management and complications. In close collaboration with neurointensivists, we will describe the management of RCSE in the ICU and, specifically the use of continuous infusions to identify factors that influence management and prognosis.

Short-term outcome in RCSE and identification of risk factors. We will describe the clinical and developmental outcomes in our patients and will aim to identify the different treatment strategies associated with better outcomes through comparative effectiveness.[104] Children with RCSE are historically difficult to enroll in randomized clinical trials for ethical and/or organizational reasons including the lack of strong observational data in children in which to base clinical trials, and thus this observational study design is likely the best fit for this rare but important disease process.[104] Although clinical trials are considered the best available evidence, comparative effectiveness incorporates the complexities and vagaries of real-life clinical practice across a wide range of patients.[104]

Long-term outcome. We will follow-up our cohort and will describe the long-term outcome in terms of subsequent seizure and SE occurrence, neurocognitive features, and disability rates in RCSE survivors.

Genetic predisposition. pSERG is collaborating with The Duke Center for Human Genomic Variation (CHGV) to collect blood samples from our population of children with RCSE in order to identify variants associated with a higher risk of self-sustaining and pharmacologically intractable seizures. The Duke CHGV also runs the Sequencing, Biostatistics, and Bioinformatics core of the NIH-funded Epilepsy Center without Walls Human Genetic Initiative called Ep4 K and it is anticipated that the pSERG consortium will also collaborate with Ep4 K consortium in studies of genetic predisposition. The study of genetic risk factors for a certain condition benefits from the evaluation of genotypes of both affected and unaffected family members. Therefore, we will collect and keep information on the occurrence of epilepsy and SE in the parents and siblings of children with RCSE and we will collect blood samples from these family members. We will also request permission from the families to re-contact them in case that a more detailed phenotype and genotype study is deemed of scientific interest within a particular family.

13. Challenges and progress

During the development of this network we faced challenges regarding the development of a common terminology, the implementation of common inclusion and exclusion criteria, and the development and optimization of a centralized database. We decided to implement the NIH/NINDS common data elements for epilepsy, and will continue to implement the newly developed NIH Toolbox and PROMIS (http://www.nihpromis.org/?AspxAutoDetectCookieSupport=1). This approach will not only satisfy the need for a common language within our research network, but will generate literature with a terminology that has been developed for the mutual understanding of different subspecialties in neurology and that is expected to become standard in the coming years. The

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development of inclusion and exclusion criteria was a highly interactive process. The development of a centralized database implies frequent communication between the different clinical centers and the database management working group. Release of several preliminary formats of the database with a feedback and optimization loop from the different participating centers was necessary to achieve a fully functional and optimized database. We have launched the pSERG project in the United States of America. However, pediatric status epilepticus is a medical emergency that occurs in all regions of the world and we sincerely hope that our experience will alert other centers and fuel the development of similar collaborative research networks in other regions of the world that may eventually connect with pSERG.

14. Conclusions

pSERG is a research consortium that prospectively collects standardized data from a large population of children with RCSE to generate a high-quality data and biomarker repository that will provide much needed information on variation of care in RCSE, and will assess outcomes based on this variation. The strength of the pSERG network derives from the collaboration to identify a large number of patients in a relatively short time period including prospective clinical data, continuous EEG monitoring, neuroimaging, genetic information and ultimately the ability to implement interventional clinical trials at multiple sites. The overall purpose is to improve the management and ultimately the prognosis of children with SE.

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