Status Epilepticus—Work-Up and Management in Children

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Abstract

Status epilepticus (SE) is one of the most common neurological emergencies in children and has a mortality of 2 to 4%. Admissions for SE are very resource-consuming, especially in refractory and super-refractory SE. An increasing understanding of the pathophysiology of SE leaves room for improving SE treatment protocols, including medication choice and timing. Selecting the most efficacious medications and giving them in a timely manner may improve outcomes. Benzodiazepines are commonly used as first line and they can be used in the prehospital setting, where most SE episodes begin. The diagnostic work-up should start simultaneously to initial treatment, or as soon as possible, to detect potentially treatable causes of SE. Although most etiologies are recognized after the first evaluation, the detection of more unusual causes may become challenging in selected cases. SE is a life-threatening medical emergency in which prompt and efficacious treatment may improve outcomes. We provide a summary of existing evidence to guide clinical decisions regarding the work-up and treatment of SE in pediatric patients.

Keywords
- pediatric status epilepticus
- diagnosis
- treatment

Status epilepticus (SE) is one of the most common neurologic emergencies in children and is associated with a short-term mortality of approximately 3%.[1–3] A recent meta-analysis, which reviewed all existing literature on mortality in SE, reported an overall mortality of 3.6%.[4] Although there was a trend toward lower mortality in more recent years, there has not been a substantial reduction in SE mortality over the last few decades.[4] The incidence of SE varies with age, showing a bimodal distribution, with the highest incidence in adults older than 50 years (28.4/100,000) and children younger than 10 years (14.3/100,000).[2] The large North London study estimated an overall incidence of SE in childhood of 14.5/100,000,[5] with the highest incidence in children younger than 1 year (51/100,000), and a progressive decrease with increasing age, until an incidence of 2/100,000 in the group aged 10 to 15 years.[5]

SE is a resource-consuming condition, particularly in refractory SE (RSE) and super-refractory SE (SRSE).[6,7] In a German study, SE admissions were approximately six times costlier than epilepsy admissions.[6] Further, the cost of admissions for RSE is approximately double that of the cost for non-RSE, and admissions related to SRSE are up to 18 times costlier than those for non-RSE.[6,8]

In this review, we will outline the main clinical characteristics of pediatric SE with a focus on diagnostic evaluation and treatment.

Pathophysiology

The current International League Against Epilepsy definition considers SE as a condition resulting either from the failure of the mechanisms responsible for seizure termination or from

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the initiation of mechanisms, which lead to abnormally prolonged seizures.[9] Animal models show changes in composition and surface expression of neurotransmitter receptors during prolonged seizures that may promote self-sustaining seizures.[10,11] After seizure onset, there is a progressive decrease of inhibitory transmission due to the internalization of synaptic gamma-aminobutyric acid (GABA) subtype A receptors.[10,12] This can contribute to drug resistance to benzodiazepines (BZDs) and other GABAergic positive allosteric modulators in late stages of SE.[10,11,13–15] In an animal model of SE, there was a 20-fold decrease in response to diazepam after 30 minutes of seizure activity.[15]

In addition, as SE evolves, excitatory receptors such as N-methyl-D-aspartate receptor (NMDA) and α-amino-3-hydroxy-5methyl-4-isoxazolepropionic acid (AMPA) receptors are trafficked toward the synapses.[16–18] This increase in excitatory receptors and decrease in inhibitory receptors in the synapse may contribute to the tendency of prolonged seizures to self-sustain.[16–18] The clinical relevance of these findings is that treatment with NMDA receptor antagonists (such as ketamine), AMPA receptor antagonists (such as GYKI-52466), or modulators of extrasynaptic $GABA_A$ receptors may be potentially more efficacious than $GABA_A$-positive allosteric modulators in prolonged seizures and SE.[18–20]

Prolonged convulsive seizures do not only alter neurotransmitter receptors in the synapse, but also alter systemic bodily functions,[21] possibly as a consequence of increased metabolic demands and disruption of the autonomic nervous system.[21] Early during convulsive seizures, blood pressure, heart rate, and glucose levels increase to maintain metabolic requirements, but as seizures last longer, anaerobic metabolism leads to lactic acidosis and electrolyte balance cannot be sustained.[21] These changes evolve to a secondary phase within approximately 30 minutes after seizure onset, when compensatory mechanisms are overwhelmed and blood pressure, glucose levels, cerebral perfusion, and oxygenation decrease progressively, and intense muscular activity is thought to contribute to hyperpyrexia.[21]

In animal models, neuronal ischemic changes in neocortex, cerebellum, and hippocampus appeared after at least 25 minutes of convulsive seizures.[22,23] It is important to note that these animals were in good cardiovascular and respiratory health at baseline.[23] Cardiorespiratory and metabolic decompensation may occur earlier in patients with already compromised cardiocirculatory and respiratory reserve at baseline. Management of physiological changes and reduction of cerebral hypoxia during early treatment may potentially decrease neuronal injury.[22,23] Available studies in humans describe similar physiological changes during convulsive SE.[24] Likewise, the histological examination of the human brain following SE in patients who died showed neuronal injury.[25] The main changes were neuronal destruction and gliosis and the most vulnerable areas in this study included hippocampus, cerebral cortex, cerebellum, thalamus, and caudate.[25] Injury was ascribed to acute hypoxic-ischemic damage or the underlying etiology: inflammatory or metabolic causes.[25] Cerebral vasoconstriction due to cardiorespiratory changes during convulsions may lead to a state of general brain hypoxia that selectively affects these vulnerable regions.[26]

Diagnostic Evaluation

Pediatric SE may often be related to prolonged febrile seizures, noncompliance with antiseizure drugs (ASDs) and other acute conditions such as metabolic disturbances or insults of the central nervous system (CNS), including infections.[5] In newborns, hypoxic-ischemic encephalopathy, hemorrhage/stroke, CNS infections, inherited metabolic diseases, hypoglycemia, and electrolyte imbalances are common causes of SE.[27]

The diagnostic evaluation of SE in children focuses on the identification of factors that may ideally help treat the cause of the condition and improve the prognosis.[28] There is very limited evidence to guide diagnostic recommendations in SE. Therefore, diagnostic protocols for SE are highly heterogeneous among centers.[29] Hence, the diagnostic work-up may need to be individualized according to the initial clinical evaluation and differential diagnoses. Basic laboratory tests including electrolytes and glucose are generally the first recommended procedures, followed by a more extensive battery of tests that may be guided by a thorough history of present illness and physical exam.[30] If the patient presents with fever or clinical signs of CNS infection, blood cultures and lumbar puncture are recommended.[30] Brain magnetic resonance imaging (MRI) is the most sensitive imaging test for detecting brain lesions or malformations, and may be considered if the etiology remains unknown.[30,31] Metabolic testing and toxicology screening may be contemplated for clinical suspicion of a metabolic disorder, drugs, or toxin ingestion, or when the etiology is not clear after the initial work-up.[30,31] ►**Fig. 1** suggests a diagnostic approach, although we acknowledge that (1) it is not evidence-based, (2) clinical adjustment is needed on a case-by-case basis, (3) it only considers more common etiologies, and (4) it focuses on the early stages of SE.

The American Academy of Neurology and the Child Neurology Society suggested a practice parameter on diagnostic evaluation by summarizing the work-up on published cases of pediatric SE.[29] They reported insufficient data to support or refute the performance of blood cultures or lumbar puncture when there are no infectious symptoms.[29] Likewise, review of routine neuroimaging, metabolic studies, and genetic testing came to the same conclusion.[29] Electroencephalogram (EEG) may help by differentiating generalized and focal origin of SE or may show specific abnormal findings.[29] Regarding toxicology testing, the practice parameter supports it when the etiology remains unknown after the initial evaluation.[29] In conclusion, this evidence-based review highlights the lack of strong data to recommend specific diagnostic tests, requiring a tailored approach to each patient.[29]

Autoimmune or inflammatory etiologies and the new-onset RSE (NORSE)-febrile infection-related epilepsy syndrome (FIRES) continuum may need to be considered, when SE progresses to refractory or super-refractory, and when the etiology remains unknown after initial work-up.[32,33] An international

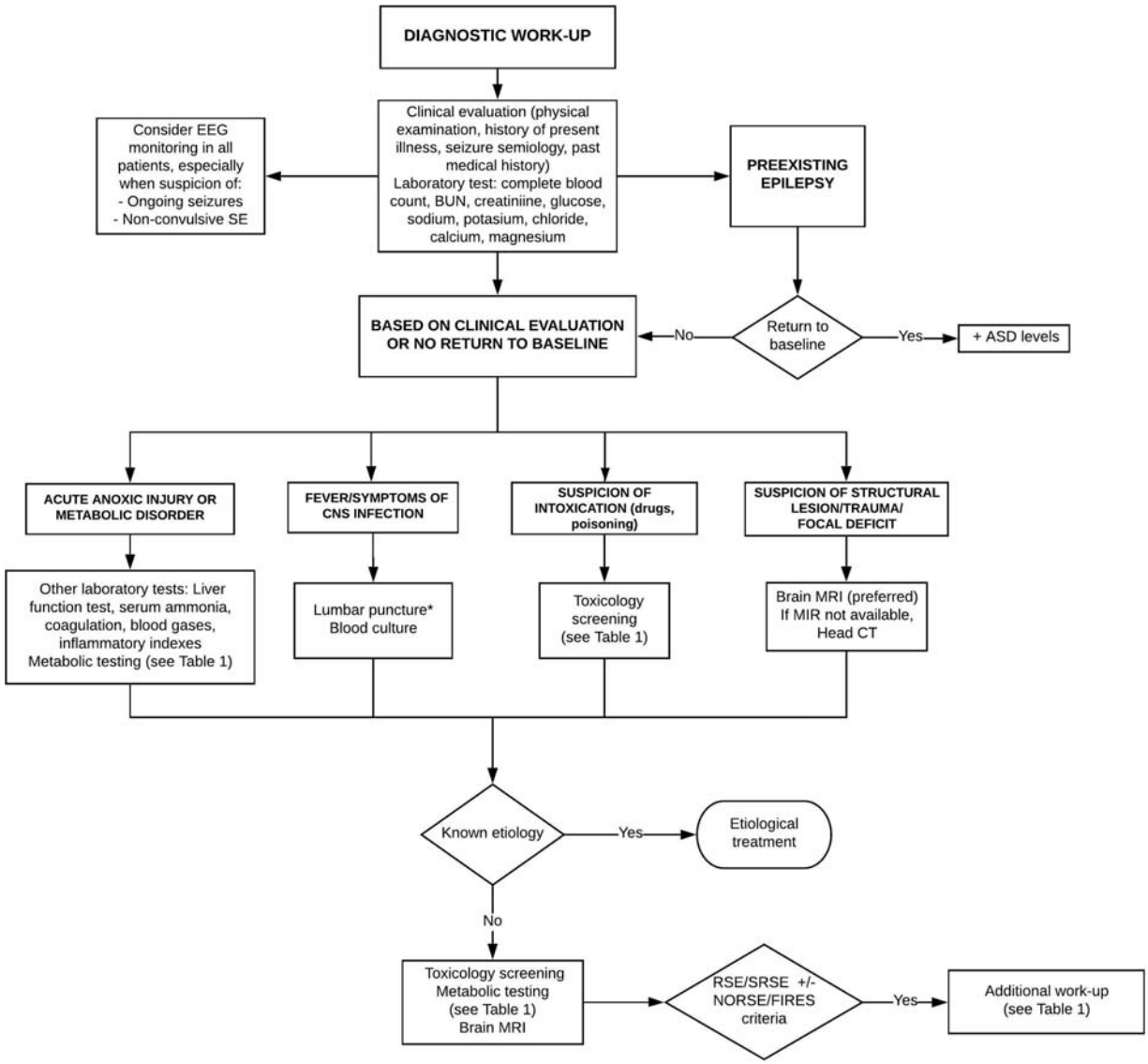

Figure 1 Diagnostic work-up algorithm for status epilepticus in children.[28,30,31,34,145] *Consider CT prior to lumbar puncture. ASD, antiseizure drug; BUN, blood urea nitrogen; CNS, central nervous system; CT, computed tomography; CSF, cerebrospinal fluid; EEG, electroencephalogram; FIRES, febrile Infection-related epilepsy syndrome; MRI, magnetic resonance imaging; NORSE, new-onset refractory status epilepticus; RSE, refractory status epilepticus; SE, status epilepticus; SRSE, super-refractory status epilepticus.

consensus defined NORSE as a clinical presentation, not a specific diagnosis, in a patient without active epilepsy or other preexisting relevant neurological disorder, with new onset of RSE without a clear acute or active structural, toxic, or metabolic cause.[32] This proposal also suggested that FIRES is a subcategory of NORSE that requires a febrile infection starting between 2 weeks and 24 hours prior to onset of RSE, with or without fever at onset of SE.[32] The most common cause of NORSE and FIRES is inflammatory and autoimmune encephalitis; other causes are uncommon infectious encephalitis, genetic disorders, and toxic disorders, with 50% of cases remaining unknown in adults.[33] Consequently, the diagnostic work-up of patients within the RSE, NORSE, FIRES realm may need to be more extensive, as shown in ►**Table 1**, which modifies a checklist from the NORSE Institute based on our clinical experience.

Treatment Strategies

Overview

SE treatment starts with general stabilization through the management of circulation, airway, and breathing.[34] Pharmacological treatment may need to follow immediately to achieve the goal of controlling clinical and electrographic seizures as soon as possible.[34] Most guidelines propose a sequential approach with three levels of treatment.[34–36] In a survey of experts, most favor intravenous (IV) lorazepam for initial treatment, while phenytoin/fosphenytoin and levetiracetam were the preferred options as urgent control therapy, followed, if needed, by midazolam or pentobarbital for RSE.[35] An evaluation of 10 hospital protocols reflects current clinical practice in the United States and revealed BZDs as first-line treatment, fosphenytoin as second-line choice, and

Table 1 Diagnostic work-up in RSE or SRSE with unknown etiology in children, especially if suspicion of autoimmune/inflammatory etiologies (NORSE/FIRES)[a]

Initial work-up (all patients within the first 24 hours)	
• History of present illness, with special attention to recent travels, contact with animals, drug or toxic exposure, past medical history, and immune state. • Continuous EEG monitoring. • Laboratory testing: CBC, electrolyte panel, venous blood gas, glucose, BUN, Cr, Ca, P, Mg, albumin, coagulation, PCR, vitamins (B12, folate, A, E), liver function test, urine analysis, CSF analysis (cell counts, protein, and glucose). • Brain MRI.	
Suspected entity	**Recommended test**
Infectious diseases	• Serologic: CBC, bacterial and fungal cultures. RPR-VDRL, HIV-1/2 immunoassay with confirmatory viral load if appropriate. PPD placement or IGRAs (only screening) • Serum and CSF: IgG and IgM testing for *Chlamydia pneumoniae*, *Bartonella henselae*, *Mycoplasma pneumoniae*, *Coxiella burnetii*, *Shigella* species, and *Chlamydia psittaci*. Parvovirus, enteroviruses (*Enterovirus*, *Coxsackie*, Poliovirus, *Echovirus*, *Parechovirus*). HSV1, HSV2, VZV, CMV, HHV6, HHV7, influenza A/B. • Nares/nasopharynges: Respiratory viral DFA panel. PCR for *Bordetella pertussis*, *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae*. • CSF: Cell counts, protein, and glucose Bacterial and fungal stains and cultures PCR for HSV1, HSV2, VZV, EBV, HIV, HHV6, HHV7, *Enterovirus*, *Parechovirus*, influenza A/B, *Mycoplasma pneumoniae*. Send VDRL, *M. tuberculosis* PCR. Gene Xpert MTB/Rif. To note, diagnosis of Tb meningitis in CSF. Metagenomic next-generation sequencing (NGS) panel for meningitis or encephalitis diagnosis (unexpected pathogens). • Urine: bacterial and fungal stains and cultures. • Saliva: IgG and IgM testing for rabies. • Sputum: bacterial and fungal stains and cultures. • Imaging: chest-X-ray Immunocompromised patients: • Serologic: IgG *Cryptococcus* species, IgM and IgG *Histoplasma capsulatum*, IgG *Toxoplasma gondii* • Sputum: M Tb Gene Xpert MTB/Rif • Serum and CSF: Toxoplasma IgG • CSF: eosinophils, silver stain for CNS fungi, PCR for JC virus, CMV, EBV, HHV6, EEE, enterovirus, influenza A/B, HIV, WNV, parvovirus. Listeria Ab, measles (rubeola), • Stool: adenovirus PCR, enterovirus PCR If geographic/seasonal/occupational risk of exposure: Serum buffy coat and peripheral smear Rabies IgG and IgM Lyme EIA with IgM and IgG reflex Send further serum and CSF samples to CDC DVBID Arbovirus Diagnostic Laboratory, CSF and serum Rickettsial disease panel, Flavivirus panel, Bunyavirus panel Serum testing for *Acanthamoeba* spp., *Balamuthia mandrillaris*, *Baylisascaris procyonis* Other
Autoimmune and paraneoplastic disorders	• Serum and CSF: paraneoplastic and autoimmune encephalitis antibody panel: To include antibodies to: VGKC-complex (LGI-1, CASPR2), Ma2/Ta, DPPX, GAD65, NMDA, AMPA receptor, GABA-B, GABA-A, anti-AQ4 receptor and MOG, glycine receptor (GlyR), D1R, D2R, GLUT3, Tr/DNER, amphiphysin, CV-2/CRMP-5, neurexin-3α, adenylate kinase, antineuronal nuclear antibody types 1/2/3 (Hu, Yo, and Ri), Purkinje cell cytoplasmic antibody types 1,2. TNF-α, IFN-gamma, interleukines; neopterin in CSF and oligoclonal IgG bands in serum and CSF. Measure albumin and IgG in serum and CSF on the same analytical set and with the same method. Calculate albumin quotient. • Serologic: ANA, ANCA, antithyroid antibodies, anti-dsDNA, ESR, CRP, ENA, SPEP, IFE. Antibodies for Jo-1, Ro, La, Scl-70. Check RF,ACE. Anti-tTG, antiendomysium antibodies, cold and warm agglutinins. Consider ab-negative autoimmune encephalitis. Consider storing extra frozen CSF and serum for possible further autoimmune testing in a research laboratory.
Neoplastic	CT: chest/abdomen/pelvis, ultrasound scrotal/abdominal CSF cytology, and flow cytometry Pelvic MRI

Table 1 (*Continued*)

Initial work-up (all patients within the first 24 hours)	
Metabolic disorders	• Serum: BUN/Cr, LDH, liver function tests, Electrolytes, Ca/Mg/Phos. Amino acids, lactate, pyruvate, ammonia. • CSF: amino acids, lactate, pyruvate • Urine: organic acids. Urinalysis with microscopic urinalysis. Porphyria screen.
Intoxications	• Blood: carboxyhemoglobin, acetaminophen, salicylates. • Urine: toxicology screening (alcohol, amphetamines, barbiturates, benzodiazepines, cocaine, opioids, phencyclidine, ecstasy, heavy metals, synthetic cannabinoids, bath salts).
Genetic disorders	Genetics consult, if possible. Genetic screens for MERRF, MELAS, POLG1, and VLCFA screen. Consider ceruloplasmin and 24-hour urine copper.
Cerebrovascular disorders (Ischemic/ hemorrhage/ thrombotic)	• Imaging: head CT, head MRA/MRV

Abbreviations: Ab, antibody; ACE, angiotensin-converting enzyme; anti-dsDNA, anti-double-stranded DNA; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; anti-AQ4, anti-aquaporin-4; anti-GAD, anti-glutamic acid decarboxylase; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; Anti-tTG, antitissue transglutaminase; BUN, blood urea nitrogen; CASPR2, contactin-associated protein 2; CBC, complete blood count; CDC, Centers for Disease Control and Prevention; CMV, cytomegalovirus; CNS, central nervous system; CRP, C-reactive protein; CSF, cerebrospinal fluid; CT, computed tomography; CRMP-5, collapsin response mediator protein 5; DPPX, dipeptidyl-peptidase–like protein 6; DVBID, division of vector–borne infectious diseases; EBV, Epstein–Barr virus; EEEV, Eastern equine encephalomyelitis virus; ENA, extractable nuclear antigen; ESR, erythrocyte sedimentation rate; GABA, gamma aminobutyric acid; GAD65, glutamic acid decarboxylase 65; GLUT3, glucose transporter 3; HHV6, human herpes virus 6; HHV7, human herpes virus 7; HIV, human immunodeficiency virus; HSV1, herpes simplex virus 1; HSV2, herpes simplex virus 2; IFE, immunofixation electrophoresis; IFN-gamma, interferon gamma; IgG, immunoglobulin G; IgM, immunoglobulin M; IGRAs, interferon-gamma release assays; JC virus, John Cunningham virus; LDH, lactate dehydrogenase; LGI-1, leucine-rich, glioma inactivated 1; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonic epilepsy with ragged-red fibers; MOG, myelin oligodendrocyte glycoprotein; MRA, magnetic resonance angiogram; MRV, magnetic resonance venogram; MTB/Rif, mycobacterium tuberculosis/rifampicin; NMDAR, N-methyl-D-aspartate receptor; PCR, polymerase chain reaction; PET-CT, positron emission tomography computed tomography; POLG1, DNA polymerase gamma 1; PPD, purified protein derivative; RF, rheumatoid factor; RPR, rapid plasma reagin; SPEP, serum protein electrophoresis; SRSE, super-refractory status epilepticus; TNF-α, tumor necrosis factor α; Tb, tuberculous; Tr/DNER, delta/notch-like epidermal growth factor-related receptor ; VDRL, venereal disease research laboratory; VGKC, voltage-gated potassium channel; VLCFA, very long chain fat acids; VZV, varicella zoster virus; WNV, West Nile virus.

[a]This is not a complete list of tests to be done, but is a sample of suggested tests. (Table adapted from http://www.norseinstitute.org/, with permission. Please see that Web site for the full table, as well as other helpful tables including a sample status epilepticus protocol, zoonotic/geographic tips, diagnostic clues to specific organisms or syndromes, and list of medications, drugs, and toxins that can cause status epilepticus.)

additional bolus of a second-line ASDs or continuous infusion of midazolam as the most common third-line therapy.[37] These practices are consistent with recommendations in most recent treatment guidelines for SE,[34,36] although evidence to support them is scarce.

Time to Treatment

BZDs are effective in early stages of SE, both in animal models and humans.[15] A reduction of the functional $GABA_A$ postsynaptic receptors may in part explain the decrease of sensitivity to BZDs as seizures evolve.[10,13,15] Studies show progressive endocytosis of $GABA_A$ receptors as seizures become longer, and as the number of functional $GABA_A$ receptors in the synaptic membrane is decreasing.[10,38] At the same time, the externalization of NMDA receptors may contribute to glutamatergic excitation that leads to further excitatory responses and additional seizures.[17] The time-dependent feature of SE highlights the importance of using $GABA_A$-positive allosteric modulators early and also potentially considering drugs with other mechanisms of action, once seizures last longer.

Etiology, age, and SE duration are the main predictors of SE outcome. Among them, SE duration is a possible modifiable factor that can be controlled by timely intervention.[39] Longer time intervals to treatment may lead to more prolonged SE and poorer prognosis.[39–42] Once a seizure lasts more than 5 minutes, the probability of stopping spontaneously without medication greatly decreases and the probability of worse outcomes increases.[9] In a study of 218 pediatric patients, receiving initial treatment more than 10 minutes from seizure onset was independently associated with longer convulsion duration, increased need for continuous infusions of anesthetics, and higher mortality.[40]

In spite of the importance of timely treatment, several studies showed that time periods from seizure onset to ASD administration exceed ideal time frames,[41–44] even in patients with a prior diagnosis of epilepsy.[45] These studies suggested potential targets for improvement such as education of families and physicians for rapid detection and treatment and standardization of evidence-based SE treatment protocols.[42,43,46]

Benzodiazepines as Initial Treatment

BZDs are typically used as first-line treatment due to their efficacy, fast mechanism of action, and multiple routes of administration, with alternative routes when an IV line is not

feasible.[36,47] Repeating the dose after 5 to 10 minutes is recommended when seizures persist.[34,36]

Controlled trials and meta-analysis supported BZDs as an effective and safe option as initial treatment of SE.[48,49] Recent guidelines, such as the American Epilepsy Society (AES) guideline, concluded that IV lorazepam and IV diazepam are often effective at stopping seizures lasting at least 5 minutes in children (level A).[36] Also, alternative routes for BZD—rectal diazepam, intramuscular midazolam, intranasal midazolam, and buccal midazolam—showed effectiveness at seizure control (level B).[36] The Neurocritical Care Society guideline supports BZD as first agent, with IV lorazepam as preferred choice.[34] Midazolam is proposed as a favorite option by the intramuscular route and diazepam for the rectal route.[34] A randomized double-blind trial of 205 adults compared IV lorazepam, IV diazepam, and placebo for treatment of SE in the prehospital setting.[49] Lorazepam (59%) and diazepam (43%) stopped SE before arrival at the emergency department in more patients than those treated with placebo (21%).[49] Therefore, treatment with BZDs is more effective than not treating SE, and the study suggested a trend in favor of lorazepam compared with diazepam, although differences were not statistically significant.[49]

However, superiority of BZD over other non-BZD drugs for initial treatment options remains unclear, and several studies in adults used non-BZD ASDs as first-line agents.[50–55] The Veterans Affair Cooperative Study, a double-blind study in adults, compared BZDs with non-BZD drugs as initial treatment (lorazepam, phenobarbital, phenytoin, and diazepam followed by phenytoin) with the aim of establishing the optimal first-line medication.[50] Lorazepam was more effective than phenytoin (64.9 vs. 43.6%, respectively), but there were no significant differences between the four treatment arms in an intention-to-treat analysis.[50] Another study randomized 178 children to receive either lorazepam or a combination of diazepam and phenytoin.[51] They found no differences between the two groups regarding efficacy and safety, with a success rate in seizure control of 100% in both groups.[51] Moreover, one randomized trial compared valproic acid with phenytoin as first-line treatment in 68 adults with SE, without previous administration of BZD.[52] Valproic acid stopped 66% of episodes and phenytoin 42%.[52] If patients did not respond to the first agent, the other medication was used. Valproic acid was effective as a second drug in 79% and phenytoin in 25%.[52] Levetiracetam was efficacious when administered as first-line treatment, in combination with BZD or alone, with seizure cessation in 78.5% of cases.[53] A different study showed positive response in eight out of nine patients with levetiracetam given as the first drug.[54] Lacosamide was tested as first- or second-line therapy, stopping seizures in 60% of patients of this group.[55] Overall, based on available data, the proportion of patients who respond to non-BZD ASDs used as first-line therapy may be in many series at least similar to the proportion of patients who respond to BZDs as first-line therapy.

BZDs can be given through multiple routes of administration, but the superiority of one BZD route over another remains unclear. A meta-analysis aimed to compare lorazepam, midazolam, and diazepam by any route including 16 randomized clinical trials in pediatrics.[56] It concluded that non-IV midazolam was at least as effective regarding seizure control as IV diazepam, and superior to non-IV diazepam.[56] Thus, rectal diazepam showed inferiority in terms of efficacy compared with buccal, intranasal, or intramuscular midazolam, recommending the non-IV routes of midazolam for prehospital treatment of SE.[56] The RAMPART study, a double-blind, randomized, noninferiority trial, evaluated the prehospital treatment of 893 children and adults, and found seizure termination after intramuscular midazolam in 73.4%, as compared with 63.4% in the IV lorazepam group. This study concluded that intramuscular midazolam was at least as safe and effective as IV lorazepam.[57] Another network meta-analysis compared the effectiveness of non-IV treatments for acute convulsive seizures and SE, including 16 pediatric and adult studies. Intramuscular midazolam was the most efficacious drug regarding time to seizure termination after administration. Intranasal midazolam was the most efficacious for seizure cessation within 10 minutes of administration and for persistent seizure cessation for at least 1 hour. Buccal midazolam was the second most efficacious non-IV drug regarding time to administration, seizure cessation within 5 and 10 minutes of administration, and with regards to sustained seizure treatment response.[58] Moreover, rectal diazepam showed inferiority compared to intramuscular midazolam and intranasal midazolam in relation to time to seizure cessation and persistent seizure cessation, also showing lower efficacy in time to initiate treatment compared with buccal midazolam.[58] A cost-effectiveness analysis in the United States suggested that buccal midazolam and intranasal midazolam were the most cost-effective non-IV alternatives, and rectal diazepam was not a cost-effective choice by a large margin.[59] Another study compared intranasal midazolam and rectal diazepam and found a better cost-effectiveness profile in the intranasal midazolam group.[60] Regarding preferences of caregivers about the use of one drug or another, one study revealed an overall better acceptance of intranasal midazolam over rectal diazepam due to the ease of use, efficacy, and comfort of the intranasal formulation.[61]

Remarkably, the Food and Drug Administration (FDA) approved rectal diazepam only for the treatment of acute repetitive seizures.[59,61–64] Therefore, its use for prolonged seizures and SE remains off-label.[59,61] Its FDA approval was based on clinical trials that looked at the response of rectal diazepam reducing the frequency of acute repetitive seizures over many hours.[62,63] The specific clinical trials evaluated the use of rectal diazepam for acute repetitive seizures compared with placebo and concluded a reduction of the number of seizures during an observation period of 12 hours.[62,63] Despite rectal diazepam not being FDA-approved for SE, a large proportion of the literature states that it is approved for prolonged seizures and SE. Intranasal midazolam is another alternative non-IV BZD considered for acute repetitive seizures and prolonged seizures, but not currently approved by the FDA.[65,66] A recent study assessed the efficacy of a nasal spray formulation of midazolam for seizure clusters, with seizure termination as the primary outcome.[66] It concluded seizure control and no seizure recurrence in a higher proportion of patients than those treated with placebo.[66] This study also showed a lower

efficacy than similar studies, probably related to a lower dose.[66]

Alternative routes of BZD administration allow seizure treatment before hospital arrival. This is a great advantage because most seizures start out of the hospital and may be more responsive to treatment during the first minutes after seizure onset.[67,68] Therefore, providing families with a seizure action plan using rescue medications may help reduce treatment delays.[67,68] Many patients do not receive any rescue medication before hospital arrival and this is associated with treatment delays and more prolonged seizures.[41,49,69,70] A quality improvement program that educated caregivers on rescue medication dosing and administration within a seizure action plan has shown reductions of cost and health care utilization.[71] After the application of this program in children with epilepsy, seizure-related visits to the emergency department decreased by 28% and inpatient hospitalizations by 43%.[71]

Nonbenzodiazepine Antiseizure Medications

If one or two doses of BZDs fail to control SE, or SE lasts more than 10 minutes, current guidelines recommend escalating treatment and using a non-BZD medication.[34,36] Fosphenytoin, phenobarbital, valproic acid, and levetiracetam are the most frequently used ASDs,[34,36] and other options such as lacosamide are also being used.[72–75] Most of the studies on second-line treatment of SE aimed to compare the classic agents—phenytoin and phenobarbital—with newer ASDs.[52,76–87] Evidence supporting the superiority of one of these non-BZD ASDs over the others was mostly based on retrospective observational studies, but the recently published Established Status Epilepticus Treatment Trial (ESETT) provided more information on the relative efficacy and safety of fosphenytoin, levetiracetam, and valproic acid.[88]

Prospective and retrospective studies in children and adults suggested efficacy of valproic acid in SE treatment after BZD failure.[89–91] Further, most clinical trials comparing valproic acid and phenytoin concluded a higher efficacy for valproic acid, although the differences were frequently not statistically significant because of the limited sample size of individual studies.[79,81,83,84] A controlled randomized trial reported similar efficacy of phenytoin, valproic acid, and levetiracetam, with no different rates of seizure control (68, 68, and 78%, respectively).[79] A clinical trial randomized 30 children and adults to receive either phenytoin or valproic acid, with a response rate of 60 and 73.3%, respectively.[81] The authors concluded no significant differences between these treatments, although the study may have been underpowered to detect differences.[81] In a randomized study of 100 children and adults, 88% of patients on valproic acid and 84% on phenytoin achieved seizure control; this was not statistically significantly different and demonstrated that the efficacy of phenytoin was similar to that of valproic acid.[83] A series of 68 patients was randomized to receive valproate or phenytoin as first-line treatment and reported 66% efficacy for valproate, compared with 42% in the phenytoin group.[52] When treatment failed to stop seizures, patients received the opposite drug as second-line, and valproic acid stopped 79% compared with phenytoin stopping 25%.[52] The authors concluded superiority of valproic acid both as first and second choice.[52] Similarly, valproic acid was compared with phenobarbital in a randomized clinical trial in 60 children, and valproic acid stopped seizures in 90% and phenobarbital in 77%.[86] This study concluded no significant differences between the two drugs.[86] In contrast, in a randomized trial in 73 adults, phenobarbital was more successful than valproic acid (81.1 vs. 44.4%, respectively) in controlling seizures.[87] However, respiratory and circulatory adverse events occurred more frequently in the phenobarbital group.[87] Overall, the available evidence suggests that valproic acid and phenobarbital can be efficacious and safe options for the BZD-RSE treatment, with higher efficacy compared with phenytoin.

Several studies also examined the efficacy of levetiracetam in comparison with phenytoin or phenobarbital, concluding a comparable efficacy.[76,77,79,80,82,84] A randomized trial looked at the differences between levetiracetam and phenytoin for SE and seizure cluster treatment and observed seizure control in 82% with levetiracetam and 73.3% with phenytoin, reporting similar efficacy.[80] In addition, several retrospective studies assessed the efficacy of levetiracetam on SE treatment.[84,85,92–97] One study found similar efficacy of levetiracetam (57.9%) and phenobarbital (74%), with no significant differences in adverse events.[85] Another retrospective study including 167 adults compared phenytoin, valproate, and levetiracetam, and the efficacy was 74.4% for valproate, 59% for phenytoin, and 52% for levetiracetam.[84] Levetiracetam was less effective than valproate after adjusting for SE severity, but there was no difference when comparing phenytoin to valproate and levetiracetam.[84] Markedly, two novel randomized clinical trials compared levetiracetam with phenytoin as second-line agents.[76,77] The multicenter, randomized, controlled trial in Australia and New Zealand, ConSEPT, included 233 children and a clinical response (seizure cessation after 5 minutes) occurred in 60% in the phenytoin group and 50% in the levetiracetam group.[76] The authors concluded that levetiracetam was not superior to phenytoin.[76] In another multicenter, open-label, randomized trial in the United Kingdom (EcLipSE), 286 children received either levetiracetam or phenytoin, with seizure termination in 70 and 64%, respectively.[77] This study was consistent with the previous clinical trial, showing no significant differences between both treatments.[77] The primary endpoint in the ESETT was the absence of clinically evident seizures and improved responsiveness at 60 minutes.[88] Patients were randomized to fosphenytoin (20 mg/kg), valproic acid (40 mg/kg), or levetiracetam (60 mg/kg). There were no differences regarding efficacy or safety, and response to levetiracetam (47%), fosphenytoin (45%), and valproic acid (46%) was similar.[88]

Lacosamide was recently approved for focal drug-resistant epilepsy in children older than 17 years,[74] and there is growing evidence of its efficacy and safety for SE treatment in children.[73,98] However, the available literature regarding the indication in SE in children is mainly based on small retrospective studies. A systematic review analyzed 27 studies in drug-resistant epilepsy and RSE, with seven of them focused on pediatric RSE.[98] One study of 40 children showed a global

seizure cessation rate of 53% with lacosamide administration after one or more ASD or, less frequently, after anesthetic drugs.[99] Another study randomized 66 adults either to receive lacosamide or valproate and revealed similar efficacy in both groups (66.7 vs. 69.7%, respectively).[100] A prospective study in 38 adults with seizure clusters and SE analyzed lacosamide response, and concluded effectiveness and safety of lacosamide for both indications (87% rate of response in seizure clusters and 80% in SE).[75] A recent noninferiority trial randomized lacosamide or fosphenytoin to 74 adults with nonconvulsive seizures and concluded that lacosamide was not inferior to fosphenytoin (seizure cessation: 63.3 vs. 50%, respectively).[101]

Traditionally, the recommended drugs after BZD failure in the United States are phenytoin or its prodrug fosphenytoin, followed in frequency by phenobarbital.[34,74,102] This recommendation is mostly based on longer experience with these two drugs. Before the ESETT, individual studies assessing the efficacy of newer drugs compared with classic ones were underpowered, which led to the need for meta-analyses on this topic. A meta-analysis on non-BZD ASDs for SE focused on adults included 22 studies and showed valproate effectiveness at 75.7% of episodes, phenobarbital at 73.6%, levetiracetam at 68.5%, and phenytoin at 50.2%.[103] In this study most non-BZD ASDs were given as second-line after the failure of one or two doses of BZDs, but some were given as initial medication, and some as third, fourth or fifth-line after other non-BZD ASDs.[103] These results supported the use of valproate, levetiracetam, and phenobarbital as second-line treatment for SE over phenytoin.[103] However, this meta-analysis is mostly based on retrospective and observational studies.[103] A more recent meta-analysis included 24 studies to compare effectiveness and cost-effectiveness of non-BZD ASDs as given exclusively as second-line treatment.[104] This meta-analysis, which included observational studies and randomized clinical trials, represents class II and class III evidence of the effectiveness of non-BZD ASDs for SE. Remarkably, it highlights the lack of studies investigating the effectiveness of fosphenytoin as second-line therapy.[104] Results showed that phenytoin was the least effective drug for this indication, with a probability of stopping seizures of 53%.[104] The highest probability was 80% for phenobarbital, followed by valproic acid at 71%, lacosamide at 66%, and levetiracetam at 62%.[104] As the prior meta-analysis, this reflects a marked difference in effectiveness among these drugs, with a difference of more than 20 percentage points between the most and the least efficacious drug.[104] In addition, this study concluded that the most cost-effective option was levetiracetam, followed by valproic acid and phenobarbital.[104] In contrast, phenytoin and lacosamide were not cost-effective compared with the other options.[104] Despite this evidence, phenytoin and fosphenytoin still appear in many SE hospital protocols in the United States as the recommended first choice for BZD-resistant SE.[37] A review of current practice protocols in 10 pediatric tertiary hospitals in the United States found that fosphenytoin was the first choice second-line ASD in nine of the 10 analyzed pathways.[37] The remaining pathway proposed levetiracetam or phenytoin as first choices, which are the least efficacious options based on existing literature.[37]

In summary, the effectiveness of phenytoin is much lower than other alternatives, and this finding is robust to multiple sensitivity analyses,[104] and effectiveness of fosphenytoin may be similar to those of valproic acid and levetiracetam based on ESETT findings. Safety profiles of valproic acid and levetiracetam have shown advantages, with lower risk of respiratory and circulatory adverse events compared with phenytoin or phenobarbital.[82,87] Of note, valproic acid has a safe profile in adults and children, but children can present with serious hepatic toxicity when they have underlying metabolic disorders, or are below 2 years of age.[105] The efficacy of second-line treatment options presented in the latest randomized clinical trials and the effectiveness and cost-effectiveness showed in recent meta-analyses, together with the safety profile of each drug, may guide clinical decisions in individual patients.

Refractory SE and Continuous Infusions with Anesthetics

SE can be defined as refractory when it fails to terminate after the administration of two ASDs with different mechanisms of action; continuously administered medications are required to abort seizures, regardless of seizure duration.[106] At this point, induced coma with anesthetic agents is the most common management, optionally preceded by repeated boluses of non-BZD ASDs.[107,108] While case series suggest the use of anesthetics, there is lack of randomized controlled trials evaluating their comparative effectiveness.[36] Therefore, clinical decisions among the available therapeutic options mostly rely on scarce evidence, and clinical goals during treatment are uncertain.[107,108]

Moreover, a balance between the aim of controlling SE and the potential damage secondary to anesthetic therapies may need to be considered. Recent studies have focused on the increased risk of mortality related to continuous infusion treatments. It is known that continuous infusions can predispose to treatment-related complications such as infections, hypotension, or propofol infusion syndrome.[108] Of note, this situation may be confounded by indication, as patients who are more seriously ill may be more likely to receive continuous infusions. Observational studies in adults suggested an independent negative effect on outcome with increased mortality, as well as both higher infection rates and length of hospital stay.[109–111] In contrast, another prospective study in adults found an association between mortality after SE and severity, etiology, comorbidities, and refractoriness, excluding an independent effect of anesthetic agents.[112] A study on pediatric RSE found higher mortality, longer intensive care unit (ICU) length of stay, and failure to return to baseline in patients who received continuous infusions, after adjusting for potential confounders with a propensity score approach.[113]

The most frequently used drugs for coma induction are midazolam, pentobarbital, thiopental, and propofol.[36] Ketamine is an alternative treatment for RSE, increasingly popular in children.[114] Current literature describes midazolam as the first choice for anesthetic treatment in pediatric RSE, followed

Table 2 Anesthetic treatments for RSE and SRSE[34,47,74,121]

Treatment	Advantages	Disadvantages
Midazolam	• Fast action and short duration of action • Less hypotension than barbiturates	• Tachyphylaxis and accumulation with prolonged use • Respiratory depression and hypotension
Pentobarbital/ thiopental	• Strong antiseizure action • Long experience of use • Potential neuroprotective effect • Lowers body temperature	• Adverse events: coagulation disorders, hypotension, cardiac arrhythmia, infection, acid–base and electrolyte disorders, ileus, bowel ischemia • Interaction with anesthetics and ASD clearance
Propofol	• Fast action and short duration of action (short half-life) Little accumulation	• Propofol infusion syndrome (high-risk young children) • Respiratory depression and hypotension
Ketamine	• Safer cardiorespiratory profile • May reduce excitotoxic neuronal damage	• Risk of increase of intracranial pressure • Drug–drug interactions

Abbreviation: ASD, antiseizure drug; SRSE, super-refractory status epilepticus.

by pentobarbital.[107,115] In a study of 51 children, midazolam infusion controlled SE in all patients except one.[116] Another study analyzed 111 children and found that midazolam controlled SE in 71% patients.[115] A systematic review of 16 studies evaluated RSE treatment in the pediatric ICU, with high dose of BZDs or anesthetic drugs. Midazolam as first anesthetic drug controlled 76% of RSE episodes. Barbiturate coma showed an overall seizure control rate for pentobarbital and thiopental of 69%.[117] Another systematic review in adults included 28 studies and compared pentobarbital, propofol, and midazolam for RSE. Pentobarbital was associated with overall better treatment response.[118] A retrospective study of 33 children concluded that propofol was more effective than thiopental in seizure control (64 vs. 55%, respectively). However, propofol had to be suspended in four cases due to adverse events, which reversed after stopping the infusion.[119] A retrospective multicenter study of 60 episodes of convulsive and nonconvulsive RSE (46 adults and 12 children) found that ketamine was more effective in early stages of RSE and SRSE treatments, with a higher response rate when introduced as fourth-line medication.[120] A summary of anesthetic treatments for RSE can be found in ►**Table 2**.[34,36,74]

Super-Refractory SE and Alternative Treatments

When SE persists for 24 hours or more after the administration of general anesthesia, or when it recurs after its withdrawal, it is considered SRSE.[121] In this stage, alternative treatments in combination with continuous infusions of anesthetics are available.[122] The evidence of these adjunctive therapies is mostly limited to small case series or case reports. Options consist of pharmacological treatments, such as pyridoxine, magnesium or immunological therapies (steroids and IV immunoglobulins), or nonpharmacological therapies, such as hypothermia, ketogenic diet, or epilepsy surgery.[121,123–125] ►**Table 3** summarizes the advantages and disadvantages of most frequently used treatments in SRSE.

Table 3 Alternative treatments for RSE and SRSE[47,74,107,121,144]

Treatment	Advantages	Disadvantages
Ketogenic diet	• May help reduce excitotoxic damage	• Long time frame for treatment effect (1–2 weeks) • Adverse events: constipation, acidosis, hypoglycemia, hypercholesterolemia, pancreatitis
Hypothermia	• Neuroprotective properties	• Adverse events: coagulation disorders, hypotension, cardiac arrhythmia, infection, acid–base and electrolyte disorders, ileus, bowel ischemia • Interaction with anesthetics and ASD clearance
Epilepsy surgery	In selected cases, can lead to SE control or even seizure freedom	• Difficult to detect SE focus on EEG after days/weeks of onset • Risk of neurological deficits and postsurgical complications
Steroids	• Potentially beneficial effects on cerebral edema and intracranial pressure	• Adverse events: glucose intolerance, psychiatric disturbances, altered immune function, adrenal suppression
Immunoglobulins	• May be useful for selected etiologies(autoimmune)	• Adverse events: coagulation disorders, hypertension, hypersensitivity, aseptic meningitis, renal complications
Pyridoxine	• No significant toxicity	• Adverse events: bradycardia, hypothermia, apnea, sensory neuropathy
Magnesium	• Potential benefits in mitochondrial disease (POLG1) and magnesium deficiencies	• Adverse events (high dose): arrhythmia, neuromuscular blockage, hypotension

Abbreviations: ASD, antiseizure drug; EEG, electroencephalogram; POLG1, DNA polymerase gamma 1; SE, status epilepticus; SRSE, super-refractory status epilepticus.

Combined Treatments

The most common treatment combinations assessed in animal models and humans were a BZD and a non-BZD ASD or NMDA receptor antagonists.[126] The rationale behind the recommendation of early polytherapy lies in targeting several pathways to stop seizures before SE becomes more difficult to treat. Thus, early polytherapy may serve as a potentially useful approach for SE treatment.[127,128] Likewise, later combinations of anesthetic drugs in RSE and SRSE showed favorable outcomes.[129] However, studies on combined treatments for SE management in humans are scarce and yield mixed results.

A cohort study on management evaluation of generalized convulsive SE episodes in adults (100 episodes) found a higher rate of SE control in patients treated with a combination of diazepam or clonazepam with fosphenytoin (71%) compared with those treated with BZD alone (30%).[130] This study related the better response of the combined treatment to the early use of long-acting ASD other than BZDs.[130] In contrast, a double-blind phase 3 adult trial randomized two groups of 68 patients each to receive a combination of clonazepam and levetiracetam or clonazepam and placebo as prehospital treatment.[131] This study found no differences in seizure control: 74% of patients who received clonazepam and levetiracetam and 84% in those with clonazepam and placebo.[131] Another randomized controlled trial in 178 children comparing lorazepam with a combination of diazepam and phenytoin showed no differences in efficacy and safety between the two groups (100% rate of seizure termination within 10 minutes from treatment administration and 20 seconds to seizure control in both arms).[51] In conclusion, combined treatments may lead to better control of SE, but current results on this topic are too scarce and inconclusive to support its clinical adoption.

Outcome

SE is associated with substantial mortality and morbidity. The main predictors of unfavorable outcomes are etiology, pre-existence of neurological abnormalities, age, and SE duration.[132–134] Etiology is the main predictor of mortality, especially in the long term.[3,133] Acute symptomatic etiology, more common in younger patients, is associated with higher morbidity and mortality.[134,135] In contrast, previously neurologically normal children and nonsymptomatic cases show lower proportions of neurological sequelae and death after SE.[133]

The short-term mortality of pediatric SE (during admission or within 30 days of SE) is approximately 3%.[3,5,132,136,137] Long-term mortality after an 8-year follow-up period was 11% in the North London cohort,[132] and 16% among patients less than 1 year old at 10 years of follow-up,[138] much higher than the 3% rate in the 1 to 19 age group.[138] Besides mortality, SE is associated with morbidity in the long term, although there is major variability in adverse outcomes depending on the population studied. Thus, the proportion of new-onset epilepsy after SE ranged from 5 to 36%, and of SE recurrence from 3.7 to 56%, both higher during the first year after SE.[3,133,139] The proportion of behavioral problems following SE was 37%, and of cognitive disability was 10.2% in the prospective North London cohort.[133,140] In a recent literature review, the functional outcome in children was heterogeneously defined, with most studies evaluating impairment clinically and only one study using the Glasgow Outcome Scale Extended.[139,141] Consequently, the proportions of negative functional outcomes ranged widely from 0 to 79%.[139]

The association of SE with mesial temporal sclerosis and secondary temporal lobe epilepsy is a controversial topic. In the FEBSTAT study ("Consequences of Prolonged Febrile Seizures in Childhood"), 9.7% of children had abnormal hippocampal signal in the initial MRI, and 71% showed hippocampal sclerosis on the follow-up MRI (median follow-up of 1 year).[142] However, a longer follow-up is needed to relate it with temporal lobe epilepsy.[142] Another prospective study demonstrated hippocampal volume loss after SE due to any etiology.[143]

Conclusion

A growing understanding of SE pathophysiology may help improve the treatment and outcomes of SE. There may be opportunities for further improvement of medication choices and timing of medication administration. As highlighted in this review, the main goals of SE management would be a timely recognition and treatment of SE, as well as early awareness of potentially treatable etiologies with the overall goal of potentially improving outcomes.

Conflict of Interest
None declared.

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He is part of patent applications to detect and predict seizures and to diagnose epilepsy. Dr. Loddenkemper is co-inventor of the TriVox Health technology. Dr. Loddenkemper and Boston Children's Hospital may receive financial benefits from this organization in the form of compensation in the future.

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He served as a consultant for UCB, Grand Rounds, and Advance Medical. He performs video electroencephalogram long-term and ICU monitoring, electroencephalograms, and other electrophysiological studies at Boston Children's Hospital and affiliated hospitals and bills for these procedures and he evaluates pediatric neurology patients and bills for clinical care. He has received speaker honorariums from national societies including the AAN, AES, and ACNS, and for Grand Rounds at various academic centers.

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