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Status Epilepticus and Refractory Status Epilepticus Management

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Abstract

Status epilepticus (SE) describes persistent or recurring seizures without a return to baseline mental status, and is a common neurologic emergency. SE can occur in the context of epilepsy or may be symptomatic of a wide range of underlying etiologies. The clinician's aim is to rapidly institute care that simultaneously stabilizes the patient medically, identifies and manages any precipitant conditions, and terminates seizures. Seizure management involves "emergent" treatment with benzodiazepines followed by "urgent" therapy with other anti-seizure medications. If seizures persist then refractory SE is diagnosed and management options include additional anti-seizure medications or infusions of midazolam or pentobarbital. This paper reviews the management of pediatric SE and RSE.

Keywords

Introduction

Status epilepticus (SE) describes a prolonged seizure or recurrent seizures without a return to baseline. It is the most common pediatric neurological emergency with an incidence of 18–23 per 100,000 children per year.[1] Care involves simultaneously identifying and managing systemic complications, identifying and managing precipitant etiologies, and administering anticonvulsants to terminate ongoing seizures(s).

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Historically, SE was defined as a seizure lasting longer than 30 minutes or a series of seizures without return to baseline level of alertness between seizures.[2] During the prodromal or incipient stage (<5 minutes) it is unknown whether the seizure will self-terminate or evolve into SE. Persisting SE has been divided into early SE (5–30 minutes), established SE (>30 minutes), or refractory SE (RSE) (seizures persist despite treatment with adequate doses of two or three anticonvulsants). Due to increasing recognition that most seizures are brief (3–4 minutes)[3] and anticonvulsant administration delays are associated with more refractory seizures, the temporal definition of SE has gradually shortened and the related terminology has been modified to convey a greater sense of urgency. The Neurocritical Care Society guideline for SE management in children and adults defines SE as "5 minutes or more of (i) continuous clinical and/or electrographic seizure activity or (ii) recurrent seizure activity without recovery (returning to baseline) between seizures" and opines that "definitive control of SE should be established within 60 minutes of onset."[4] Rather than labeling medications as first, second, and third line agents which provide no sense of timing urgency, the guideline uses the terms "emergent", "urgent", and "refractory" to help convey that medications should be administered sequentially and rapidly. RSE is defined as clinical or electrographic seizures which persist after an adequate dose of an initial benzodiazepine and a second appropriate anti-seizure medication; in contrast to prior definitions no specific time must elapse before initiation of RSE management.

Variability in SE management and treatment delays are common. Studies of SE management in children in emergency departments have described that laboratory parameters were often not checked and some results were only available after long delays,[5] the median time to administer a second-line anticonvulsant to a seizing child was 24 minutes,[6] and that benzodiazepine dosing was outside usual dosing guidelines in 23% of children with SE.[5] Excess benzodiazepine dosing (which often occurs when prehospital doses are administered) contributes to respiratory insufficiency and need for intensive care unit admission[5,7,8] while inadequate dosing may reduce the likelihood of seizure termination. Several studies have described associations between SE management delays and more prolonged seizures[9] as well as lower anticonvulsant responsiveness.[10–13] To expedite therapeutic decisions, a consensus document recommended that all units have a written management pathway with a clear structured time frame.[14] An example SE management pathway is provided in Figure 1 which is adapted from the Neurocritical Care Society guideline[4] and other recent publications.[15–17]

Medical Management and Precipitating Etiology Evaluation

Medical Stabilization of the acutely seizing patient should focus on airway, breathing and circulation with the goal maintain oxygenation, ventilation and adequate tissue perfusion while rapidly diagnosing and treating the source of the seizures. The Neurocritical Care Society guideline provides a timed treatment outline.[4] Steps to be completed in the initial 2 minutes include non-invasive airway protection and gas exchange with head positioning and vital sign assessment. Steps to be included in the initial 5 minutes include neurologic examination and placement of peripheral intravenous access for administration of emergent anti-seizure medication therapy and fluid resuscitation. Steps to be completed in the initial

10 minutes include intubation if airway or gas exchange is compromised or intracranial pressure is elevated. Intubation may be necessary due to seizure associated hypoventilation, medication associated hypoventilation, inability to protect the airway or other causes of oxygenation or ventilation failure. Steps to be completed in the initial 15 minutes include vasopressor support if needed.[4]

Multiple studies have characterized the various potential etiologies for SE.[1,18–20] The most common cause of pediatric SE is febrile SE, and SE may also occur in children with epilepsy.[21] However, in most situations acute precipitating conditions must be considered. Acute symptomatic conditions are identified in 15–20% of children with SE.[1,19,22] The American Academy of Neurology practice parameter addressing the diagnostic assessment of a child with convulsive SE reported that abnormal results among children who underwent testing included low anticonvulsant levels (32%), neuroimaging abnormalities (8%), electrolytes (6%), inborn errors of metabolism (4.%), ingestion (4%), central nervous system infections (3%), and positive blood cultures (3%).[23] Rapidly reversible causes of seizures should be diagnosed and treated within minutes of hospital arrival, specifically evaluating for electrolyte disturbances such as hyponatremia, hypoglycemia, hypomagnesemia and hypocalcemia. The Neurocritical Care Society guideline provides suggestions regarding etiologic testing including: bedside finger stick blood glucose (0–2 minutes) and serum glucose, complete blood count, basic metabolic panel, calcium, magnesium, and anti-seizure medication levels (5 minutes). In some patients, other diagnostic testing may include neuroimaging or lumbar puncture (LP) (0–60 minutes), additional laboratory testing (including liver function tests, coagulation studies, arterial blood gas, toxicology screen, and inborn errors of metabolism screening), and continuous electroencephalographic (EEG) monitoring if the patient is not waking up after clinical seizures cease (15–60 minutes).[4] These recommendations are similar to those of the prior American Academy of Neurology practice parameter.[23] Rarer infectious, metabolic, autoimmune and paraneoplastic etiologies may be considered in specific situations.[24]

Neuroimaging abnormalities have been reported in 30% of children with SE and described to alter acute management in 24%.[19] If no etiology is identified by computerized tomography (CT), magnetic resonance imaging (MRI) may still identify lesions. One study described that among 44 children who underwent head CT and MRI, 14 had a normal head CT but an abnormal MRI, leading to the conclusion that MRI had a superior yield and should be considered whenever available if head CT is non-diagnostic.[19]

There are two main urgent EEG indications. First, if the diagnosis of psychogenic SE is suspected, then rapid diagnosis using EEG monitoring may avoid continued exposure to anticonvulsants with potential adverse effects. Second, if there is concern that EEG-only (non-convulsive) seizures are ongoing despite cessation of clinically evident seizures, then EEG monitoring may be required for identification and to assess the impact of continued management.[25,26] A multi-center study of children who underwent EEG monitoring while in the ICU reported that 33% of 98 children who presented with convulsive SE had electrographic seizures identified. The seizure burden was often high with electrographic SE in 47%. Further, 34% of children with seizures had exclusively EEG-only seizures which would not have been identified without EEG monitoring.[27] Observational studies have

reported that in multivariable analyses aiming to account for encephalopathy etiology and severity, high electrographic seizure burdens in critically ill children are associated with worse outcomes.[26,28–31] The Neurocritical Care Society guideline states that in order to identify electrographic seizures, "continuous electroencephalographic monitoring should be initiated within one hour of SE onset if ongoing seizures are suspected" and that the management goal be termination of both convulsive and electrographic seizures.[4] Further study is needed to determine whether efforts to identify and manage these electrographic seizures improve patient outcomes.

If no etiology is identified by the initial testing, then additional testing may be indicated. A targeted approach may be useful for some patients, but in some patients sending a full panel of tests initially may be optimal.

Central nervous system infections are a common cause of acute symptomatic SE[19], accounting for 0.6%–40% of all SE in different series.[32,33] In addition, SE occurs in 15% of encephalitis cases overall. Development of RSE in encephalitis has been associated with younger age, fever, the presence of a prodromal gastrointestinal illness, normal peripheral white blood cell count, and normal neuroimaging.[34] The clinical presentation of encephalitis and other central nervous system infections is highly variable depending on the pathogen involved and specific host factors. In some cases, particularly in young children, individuals who are immunocompromised, or individuals who have received recent antibiotics, fever may be absent and clinical signs of infection very subtle. Therefore, LP and magnetic resonance imaging (MRI) should be performed in all cases of SE without an obvious non-infectious etiology. A diagnostic strategy to evaluate for possible infectious etiologies is outlined in Table 2 (adapted from prior publications[35,36]). Detailed consideration of potential infectious etiologies may lead to focused testing and in some etiologies, specific effective treatment (such as Bartonella in cat-scratch disease).

If an autoimmune etiology for RSE is suspected, a LP should be performed to evaluate for evidence of central nervous system inflammation. Routine studies from the cerebrospinal fluid (CSF) including a cell count and protein are useful as patients with underlying neuro-inflammatory processes will often have a pleocytosis and elevated CSF protein. Intrathecal immunoglobulin synthesis is a hallmark of central nervous system inflammation and should be evaluated with an oligoclonal band profile, IgG index, and IgG synthesis rate when a neuro-immune etiology is being considered. Oligoclonal bands are positive when two or more immunoglobulin bands are detected in CSF but not in accompanying serum.

Many causes of autoimmune encephalitis may be associated with neoplasm, although the frequency of tumor detection varies. Depending on the auto-antibody, distinct brain regions may be targeted, with seizures or SE resulting from autoimmunity to either the limbic system or cerebral cortex.[37] Paraneoplastic antibodies may target intracellular antigens or antigens on the neuronal surface. Antibodies to intracellular neuronal antigens include Hu, Ma2, CV2/CRMP5, and amphiphysin; such antibodies have rates of tumor association (>90%).[38] In general, for intracellular paraneoplastic antibodies, cytotoxic T-cell responses are believed to mediate neural inflammation and destruction, and there is poor response to immunotherapy.[39] One exception is encephalitis associated with anti-GAD65 antibodies.

Although GAD65 is an intracellular antigen, there less brain inflammation/destruction, a lower association with tumor (<5%), and greater response to immunotherapy.[38,39] Of the intracellularly targeted antibodies, anti-Hu antibodies have the strongest association with isolated seizures and limbic encephalitis, but are rarely detected in children and most often they occur in association with neuroblastoma. Patients with anti-CRMP5 antibodies may have associated chorea, while anti-Ma2 antibodies often result in a diencephalic syndrome, and anti-GAD-65 and anti-amphiphysin both may associate with stiff person syndrome.[40]

In contrast to intracellularly targeted antibodies, disorders associated with antibodies to neuronal surface antigens have a distinct pathophysiology as these antibodies are thought to be directly pathogenic. Antibodies bind to the target antigen at synapses and result in altered synaptic function. There is less neuronal destruction and tissue inflammation, likely resulting in the more robust responses to immunotherapy, typically with agents targeting B-cells.[39] Of these disorders, the most well established in the pediatric population is anti-NMDAR encephalitis, which is often associated with ovarian teratoma. This encephalitis usually begins with behavioral change or psychosis and then progresses to seizures in 70%, as well as decline of the level of consciousness, catatonia, dyskinesias, autonomic instability, and hypoventilation.[37] Children comprise nearly half of identified patients, are more likely than adults to have seizure as the first presenting sign, and are less likely to have associated ovarian teratoma.[41,42] Antibodies against the voltage gaited potassium channel (VGKC) complex, which includes leucine-rich glioma-inactivated protein 1 (LGI1) and contactin-associated protein-like 2 (CASPR2), are established as a cause of autoimmune epilepsy and limbic encephalitis in adults and case series of pediatric patients with likely autoimmune encephalitis have detected these antibodies in 4–15% of subjects. In these case series, a few patients with anti-CASPR2 encephalitis have been reported but no anti-LGI1 cases have yet been found. Similarly, although antibodies to the AMPA subtype of glutamate receptor have been reported as a cause of limbic encephalitis in adults, but these have not yet been found in children.[43,44] Recently described autoantibodies to other synaptic proteins such as mGluR5, glycine receptors, GABA-A receptors and GABA-B receptors have been associated with seizures and refractory SE in children.[40,45,46] Reports of these antibodies remain rare, but this is an emerging field, and both the spectrum of associated diseases and number of cases are expected to grow.

As discussed above, LP should be performed if autoimmune or paraneoplastic encephalitis is suspected. Elevated oligoclonal bands and CSF pleiocytosis support an autoimmune process with intrathecal synthesis of anti-neuronal antibodies, but these findings are not necessary for the diagnosis. Specific autoantibody testing for some of these disorders is available and should be pursued. In general, testing of CSF has superior sensitivity and specificity as compared to serum. Anti-NMDAR antibody testing can be send to a number of clinical laboratories. As the most commonly identified cause of encephalitis, testing for anti-NMDAR antibodies has higher diagnostic yield that other autoantibody testing or even testing for specific viral etiologies.[47,48] If this test is negative or symptoms are atypical, additional autoantibody testing is commercially available with paraneoplastic autoantibody panels. In addition, any patient with known or suspected paraneoplastic disease should have appropriate tumor screening, which should include imaging of the chest and abdomen if ovarian teratoma is not detected in the pelvis.

Aside from paraneoplastic processes, Rasmussen's encephalitis and Hashimoto's encephalopathy are two of the most common autoimmune causes of SE. There are no specific diagnostic tests for Rasmussen's encephalitis though patients will clinically present with focal seizures and unilateral cortical deficits and are found to have progressive unihemispheric cortical atrophy.[49] If a biopsy is obtained, histopathology generally reveals T-cell dominated encephalitis with activated microglia.[49] Hashimoto's encephalopathy is an acute or subacute encephalopathy that occurs most commonly in women, and is associated with serum anti-thyroid peroxidase antibodies or anti-thyroglobulin antibodies. The majority of patients have seizures and cases of RSE have been reported.[50] Anecdotal reports of patients with Hashimoto's encephalopathy describe benefit with immunotherapy, and screening for anti-thyroid antibodies should be considered in patient with unexplained RSE.

Some genetic epilepsies may present with new-onset SE that do not produce obvious metabolic or imaging changes. While screening for genetic epilepsies in new-onset SE is usually not considered in the acute work-up, the question of an underlying genetic etiology is often considered in the subacute phase of the treatment, particularly when no other etiologies can be identified. So far, reports of patients with genetic epilepsies presenting with new-onset SE are anecdotal. Two genetic epilepsies commonly considered are epilepsies due to mutations in *SCN1A*[51] or *POLG1*.[52] Beyond the classical phenotypes of Dravet Syndrome and Alpers Syndrome, patients may present atypically with SE. However, in patients with severe epilepsies with new-onset SE such as febrile infection related epilepsy syndrome, these mutations seem to be rare.[53]

With increasing availability and decreasing costs of genetic testing, many genetic epilepsies are found to have a wider phenotypic spectrum than initially anticipated. Given that the genetic basis of a sizable fraction of genetic epilepsies may only be identified by parallel screening of a panel of candidate genes[54] or through genome-wide approaches such as exome or genome sequencing,[55] clinicians may consider adding either gene panel analysis or exome sequencing approaches into the systematic work flow of new onset SE, rather than only evaluating for them during a later stage of the workup. Improving the turnaround time for genetic tests will be crucial in establishing genetic testing as a routine part of the diagnostic workflow.

Status Epilepticus Management

The guideline states that "definitive control of SE should be established within 60 minutes of onset"[4] with termination of both clinical and electrographic seizures. Benzodiazepines are the "emergent" medications of choice; lorazepam for intravenous administration, midazolam for intramuscular or intranasal administration, and diazepam for rectal administration.[4] Repeat dosing may be provided in 5–10 minutes if needed. A double-blind randomized trial of 273 children with SE compared intravenous lorazepam (0.1mg/kg) and diazepam (0.2mg/kg) in the emergency department. A half-dose of either medication could be administered at 5 minutes if seizures persisted. The primary outcome was SE cessation by 10 minutes without recurrence in 30 minutes, and it was not significantly different in the two groups (72.1% with diazepam and 72.9% with lorazepam). Patients receiving lorazepam were more likely to be sedated (67% with lorazepam, 50% with diazepam) but there was no

difference in requirement for assisted ventilation (18% with lorazepam, 16% with diazepam).[56] If intravenous access cannot be obtained, then providers should administer rectal, intramuscular or buccal benzodiazepines. Providers can consider obtaining intraosseus access if prolonged intravenous access is unable to be obtained and the patient had respiratory or circulatory instability. Care should be taken to assess whether any pre-hospital benzodiazepines were administered since excess benzodiazepines may produce respiratory insufficiency.[5,7,8] Unless the SE etiology has been identified and definitively corrected, all children should also receive an "urgent" category anticonvulsant in addition to a benzodiazepine.[4]

Nearly half of children will have persisting SE after receiving benzodiazepines,[6,10] yet there are few comparative data evaluating the medication options available. Phenytoin is reported as the second-line agent by most respondents in surveys of pediatric emergency medicine physicians[57] and neurologists.[58] Fosphenytoin is a pro-drug of phenytoin, and while it may be administered more rapidly it must then be converted to phenytoin internally, so they likely reach therapeutic concentrations in the brain in about the same time. The Neurocritical Care Society guideline considers phenytoin/fosphenytoin to be an emergent treatment option, urgent treatment option, and refractory treatment option.[4] Cardiac arrhythmias are rare, especially with fosphenytoin, but may occur with both. Fosphenytoin is associated with less tissue injury if infiltration occurs. Both are considered focal anticonvulsants, and they may be ineffective in treating SE related to generalized epilepsy. There are numerous drug interactions due to strong hepatic induction and high protein binding.

Phenobarbital is often considered a third or fourth line drug in most pediatric SE pathways. The Neurocritical Care Society guideline considers phenobarbital to be an emergent treatment option and an urgent control treatment option.[4] Dosing is generally 20mg/kg followed by another 5–10mg/kg if needed. One study of 36 children with SE indicated that phenobarbital stopped seizures faster than a combination of diazepam and phenytoin and safety was similar,[59] and several reports have described the use of high dose phenobarbital to control RSE and allow withdrawal of pharmacologic coma.[60–62] Phenobarbital may cause sedation, respiratory depression and hypotension so cardiovascular and respiratory monitoring is generally required. It is a hepatic enzyme inducer leading to drug interactions.

Valproate sodium is a broad spectrum anticonvulsant and has been reported to be safe and highly effective in terminating SE and RSE. It is a broad spectrum anticonvulsant with multiple mechanisms of action including modulation of sodium and calcium channels and inhibitory GABA transmission.[63] Because it has mechanisms independent of GABA receptors, valproate may be effective later in RSE once GABA receptors have been targeted by other agents. The Neurocritical Care Society guideline considers valproate sodium to be an emergent treatment option, an urgent control treatment option and a refractory treatment option.[4] Several studies and reports have reported that valproate sodium at doses of 20–40 mg/kg is effective in terminating RSE in children without adverse effects.[64–68] Black box warnings include hepatotoxicity (highest risk in children younger than two years, receiving anticonvulsant poly-therapy, and with suspected or known metabolic/mitochondrial disorders), pancreatitis, and teratogenicity. Other adverse effects include pancytopenia, thrombocytopenia, platelet dysfunction, hypersensitivity reactions (including Stevens-

Johnson syndrome and toxic epidermal necrolysis), and encephalopathy (with or without elevated ammonia). There are numerous drug interactions due to strong hepatic inhibition.

Levetiracetam is a broad spectrum anticonvulsant and there is increasing evidence that levetiracetam may be safe and effective for treating SE. The Neurocritical Care Society guideline considers levetiracetam to be an urgent therapy option.[4] Several observational studies in children have reported that levetiracetam may be safe and effective for managing SE and acute symptomatic seizures in children at doses of 20–60mg/kg.[69–73] Levetiracetam has no hepatic metabolism, which may be beneficial in complex patients with liver dysfunction, metabolic disorders, or in those at risk for major drug interactions. In comparison to other intravenous anticonvulsants, levetiracetam has a low risk of sedation, cardio-respiratory depression, or coagulopathy. Since levetiracetam clearance is dependent on renal function, maintenance dosage reduction is required in patients with renal impairment.

Refractory Status Epilepticus

RSE is characterized by seizures that persist despite treatment with adequate doses of initial anticonvulsants. Definitions for RSE have varied in seizure durations (no time criteria, 30 minutes, one hour, or two hours) and/or lack of response to different numbers (two or three) and types of anticonvulsants. The Neurocritical Care Society guideline states that "patients who continue to experience either clinical or electrographic seizures after receiving adequate doses of an initial benzodiazepine followed by a second acceptable anticonvulsant will be considered refractory."[4] In contrast to prior definitions of RSE, there is no specific time that must elapse to define RSE, thereby emphasizing the importance of rapid sequential treatment. In the guideline, "refractory therapy" refers to anticonvulsants administered immediately if seizures persist after administration of an urgent control therapy medication, and the guideline discusses that "the main decision point at this step is to consider repeat bolus of the urgent control anticonvulsant or to immediately initiate additional agents."[4] Additional urgent control anticonvulsants may be reasonable if they have not yet been tried or if the patient needs to be transferred or stabilized prior to administration of continuous infusions. However, if an initial urgent control medication fails to terminate seizures then preparations should be initiated to achieve definitive seizure control with continuous infusions. Depending on RSE definitions and the cohorts described, RSE occurs in about 10–40% of children[11,12,74] with SE. Studies in children have indicated that SE lasted more than one hour in 26–45% of patients,[75,76] longer than two hours in 17–25% of patients,[76,77] and longer than four hours in 10% of patients.[76]

In a subgroup of patients, RSE may last for weeks to months, despite treatment with multiple anticonvulsant medications. This lengthy course has been referred to as malignant RSE[78] or super-refractory SE.[79,80] Malignant RSE is associated with an infectious or inflammatory etiology, younger age, previous good health, and high morbidity and mortality.[78,81,82] It has also been referred to as de-novo cryptogenic refractory multi-focal SE,[82] new-onset refractory SE (NORSE),[81,83,84] and febrile infection related epilepsy syndrome (FIRES).[85–87] Some of these entities in which RSE occurs in a previously healthy

person with no identified cause except a recent infection may represent overlapping terms describing similar or identical entities.[88]

The management of RSE has been reviewed previously in children[89–92] and while there is variability in suggested pathways, all either administer additional anticonvulsants such as phenytoin/fosphenytoin, phenobarbital, valproate sodium, or levetiracetam, or they proceed to pharmacologic coma induction with intravenous or inhaled medications. A survey of 60 experts in SE management conveyed that there was substantial variability in the selected medications which included phenytoin, levetiracetam, valproate, and midazolam.[93] Children who are treated for RSE should be done so in an intensive care unit under the supervision of a neurology and critical care team with experience in managing these patients. The Neurocritical Care Society guidelines recommend rapid advancement to pharmacologic coma induction rather than sequential trials of many urgent control anticonvulsants.[4] Midazolam is a fast acting benzodiazepine that rapidly penetrates the blood brain barrier and has a short duration of action. Midazolam dosing usually involves an initial loading dose of 0.2 mg/kg followed by an infusion at 0.05–2 mg/kg/hour titrated as needed to achieve clinical or electrographic seizure suppression or EEG burst suppression. If seizures persist, escalating dosing through additional boluses is needed to rapidly increase levels and terminate seizures. Increasing the infusion rate without bolus dosing will lead to very slow increase in serum levels which is inconsistent with the goal of rapid seizure termination. A meta-analysis of 111 children indicated that midazolam was as effective as other coma inducing medications and had lower mortality[94] and a multi-center, retrospective study suggested efficacy of both midazolam boluses and continuous infusion.[13] An open label randomized study comparing midazolam and diazepam in 40 children indicated similar efficacy (86% and 89%), but midazolam was associated with higher recurrence (57% versus 16%) and higher mortality (38% versus 10.5%).[95] Studies describe breakthrough seizures and seizures on weaning in 25–50% of children.

Pentobarbital is a barbiturate that may be used to to treat RSE. Dosing usually involves an initial loading dose of 5–15mg/kg (followed by another 5–10mg/kg if needed) followed by an infusion at 0.5–5 mg/kg/hour titrated as needed to achieve seizure suppression or EEG burst suppression. If seizures persist, escalating dosing through additional boluses is needed to rapidly increase levels and terminate seizures. Pentobarbital is long acting medication and therefore increasing the infusion rate without continue bolus dose administration will lead to very slow increases in pentobarbital levels which is inconsistent with the goal of rapid seizure termination. One case series of 26 children who received pentobarbital for RSE years provided a loading dose of 5 mg/kg followed by an infusion of 1–3 mg/kg/hour. Efficacy was 74% but 22% had relapse of seizures upon pentobarbital weaning.[96] A case series of 30 patients who received pentobarbital for RSE described sustained burst suppression without relapse in 33%.[97] Adverse effects include respiratory depression, hypotension, cardiac depression, paralytic ileus, infection, and suppression of brainstem reflexes. Anesthetics such as isoflurane are effective in inducing a burst suppression pattern and terminating seizures, but only case reports are available.[98,99] Management of a RSE patient with volatile anesthetics should be performed the with support and guidance of an anesthesiologist. Propofol may also be used to terminate seizures, but is rarely used in

children due to its FDA black box warning because of the risk of propofol infusion syndrome.

Patients treated with continuous infusions or inhaled anesthetics require intensive monitoring. All will require invasive continuous mechanical ventilation for both airway protection and to maintain appropriate oxygenation and ventilation as medications are titrated. Central venous access and arterial access should be considered as these patients require frequent laboratory sampling and are at high risk for developing hypotension requiring vasopressor or inotropic support. Because high dose sedatives and anesthetics can blunt the shivering response and endogenous thermoregulation, continuous core temperature monitoring should be employed and when needed external thermoregulation. Patients should undergo continued evaluation for the development lactic acidosis, anemia, thrombocytopenia, and end organ dysfunction such as acute liver or renal injury. Finally, these patients are at increased risk of secondary infections due to indwelling catheters (central catheters, endotracheal tubes, foley catheters) as well as some medications (pentobarbital). Clinicians should maintain a high index of suspicion for infection as hypotension and hypothermia can be perceived to be due to seizure treatment, when they may be due the onset of sepsis.

When coma inducing agents are employed, it remains unclear whether the treatment goal should be termination of seizures, burst suppression, or complete suppression of EEG activity. The Neurocritical Care Society guideline states that "dosing of continuous infusions anticonvulsants for RSE should be titrated to cessation of electrographic seizures or burst suppression."[4] Patients may have seizures, even when the inter-ictal background is primarily a burst suppression pattern or even complete suppression, so this level of suppression does not guarantee seizure suppression. Adult reports comparing treatment goals of burst suppression versus seizure termination are inconclusive[100–102] and there are no data in children.

It remains unclear how long the patient should be maintained in pharmacologic coma. The Neurocritical Care Society guideline states that "a period of 24–48 hours of electrographic control is recommended prior to slow withdrawal of continuous infusion anticonvulsants for RSE"[4] and a survey of experts in SE management across all age groups reported they would continue pharmacologic coma for 24 hours.[93] Electrographic or electro-clinical seizures frequently recur during weaning of pharmacologic coma medications[95,96,103,104] indicating that pharmacologic coma should be considered as a temporizing measure, and during this period other anticonvulsants should be initiated which may provide seizure control as coma inducing medications are weaned. Often coma inducing medications are weaned over 1–2 days, although this is not evidence based. If definite seizures occur, reinitiating pharmacologic coma may provide additional time to adjust other anticonvulsants. A survey of experts on SE management reported that if seizures recurred during weaning of the pharmacologic coma they would reintroduce pharmacologic coma for 24–48 hours.[93] However, after several weaning attempts, reinitiating pharmacologic coma for recurrent seizures may not be optimal. First, continued pharmacologic coma use is associated with adverse effects. Second, in a report of prognosis of 22 children with RSE, all survivors had intractable epilepsy and many children had persisting seizures during or shortly after

weaning of anti-seizure medications.[105] Since future seizures are so likely, some seizures may be tolerated during weaning from pharmacologic coma.

Case reports and series have described several add-on medications and other techniques have been reported useful in reducing seizure recurrence as pharmacologic coma is weaned, but there are no large studies. These options include topiramate, ketamine, pyridoxine, the ketogenic diet, epilepsy surgery, immunomodulation, hypothermia, and electroconvulsive therapy.

Topiramate is a broad spectrum anticonvulsant with several mechanisms of action and may be logical to use in RSE once GABA receptors have been targeted by other medications. While not available in an intravenous form, tablets can be crushed for use with feeding tubes. Studies have not evaluated topiramate for early SE, but reports suggest it may a useful add-on medication for RSE.[62,106–108] Dosing is varied in these reports, but often starts at 1–5mg/kg/day with escalation to 20–25mg/kg/day. Topiramate is a carbonic anhydrase inhibitor and may result in metabolic acidosis by preventing bicarbonate formation. Rare adverse reactions include nephrolithiasis, pancreatitis, acute angle closure glaucoma, and oligohydrosis with resulting hyperthermia.

Ketamine is a non-competitive N-methyl D-aspartate (NMDA)-type glutamate receptor antagonist that may be effective in later stages of RSE since it acts independently of GABA-related mechanisms. Only case reports and series are available reporting 0.5–2 mg/kg loading doses followed by continuous infusions. The largest case series described 9 children with RSE with ketamine administered at a median of 6 days of RSE at a median dose of 40 mcg/kg/min. RSE was controlled in 66% and no major adverse effects were reported.[109] Ketamine's sympathomimetic properties may produce hypertension and tachycardia.

Pyridoxine-dependent seizures are typically related to a rare autosomal recessive mutation in the ALDH7A1 gene which encodes antiquitin. While generally considered in neonates with seizures, there have been reports of older patients including infants and even adults with SE controlled by pyridoxine.[110–114] The diagnosis of pyridoxine-responsive seizures is made when administration of intravenous pyridoxine (100mg given for one to five doses) terminates seizures, typically within hours of administration. Pyridoxine responsiveness may occur in children with ALDH7A1 mutations, pyridoxine 5′-phosphate oxidase (PNPO) deficiency, hypophosphatasia, nutritional pyridoxine deficiency, and some children with idiopathic epilepsy. Some children who do not respond to pyridoxine may respond to pyridoxal-5-phosphate (PLP, also known as P5P, 50–100 mg/kg/day) or to folinic acid (3–5 mg/kg/day).[115,116] Diagnosis of pyridoxine dependent epilepsy may be established by evaluating for elevated urinary alpha-aminoadipic semialdehyde or a specific marker on neurotransmitter testing. For patients who have responded to therapy testing can be performed for mutations in known genes.[117] Other vitamin response epilepsies will typically present during infancy, but late onset PNPO deficiency responding only to PLP as well as late onset biotinidase deficiency responding to biotin have both been described.[118,119] Thus, a trial of PLP or biotin could be considered in refractory SE.

The ketogenic diet is a high fat, low carbohydrate diet which can be administered by parenteral nutrition of intravenously. It is considered the treatment of choice for GLUT-1 transporter deficiency and pyruvate dehydrogenase deficiency while it is contraindicated in patients with porphyria, pyruvate carboxylase deficiency, disorders of fatty acid oxidation and metabolism, and some other metabolic disorders. Screening labs include serum acylcarnitine profile, amino acids, lactate, ammonia, complete blood count, electrolytes, liver function tests, and urine organic acids.[120,121] Implementation is complex and multiple adverse effects may occur, necessitating an experienced team.[122] Adverse effects include hypoglycemia, metabolic acidosis, hypertriglyceridemia, gastroesophageal reflux, emesis, constipation, nephrolithiasis, esophagitis, renal tubular acidosis, hepatitis, lipoid pneumonia, pancreatitis, and metabolic abnormalities. Several case reports and series describe benefit with the ketogenic diet including benefit in 7 of 9 patients with febrile infection related epilepsy syndrome in a mean of 5 days after starting the diet.[123] A literature review summarized 32 reported cases in which children and adults with SE were treated with dietary therapy and reported that 78% became seizure-free, with a response usually evident in 7–10 days.[122]

Immunomodulatory therapies may be useful in the context of cryptogenic RSE or when there is a confirmed autoimmune or inflammatory etiology, such as Rasmussen encephalitis, central nervous system vasculitis, NMDA receptor encephalitis, or Hashimoto's encephalopathy. Though there have been no controlled studies of the use of corticosteroids, intravenous immunoglobulin (IVIG), or plasma exchange for RSE, small observational studies have described benefit. For example, in one case series of 5 adults with cryptogenic RSE, the 3 patients with good outcomes were all treated with early immunotherapy.[124]

When steroids are used for RSE, initial treatment consists of intravenous methylprednisolone at a dose of 30mg/kg/day (maximum of 1 gram) for 3 days. If infection is being considered as an etiology for RSE, infectious disease specialists should be involved before initiation of steroids, and patients should be covered with appropriate antiviral and antibiotic agents until infectious studies have resulted. IVIG has also been used in refractory epilepsy if an underlying autoimmune etiology is suspected.[124,125] This therapy is typically employed if a patient has an inadequate response to steroids or if steroids are contraindicated. Standard dosage for IVIG is 2g/kg divided over 2–5 days. All diagnostic serum antibody testing should be obtained prior to initiation of IVIG. Though plasma exchange is more invasive than intravenous methylprednisolone and IVIG as it requires placement of an indwelling catheter, patients with RSE have had reported benefit from this treatment.[126,127] While the mechanism of action of plasma exchange is likely multifactorial, it is thought to have an effect by removing pathogenic antibodies and immune complexes from blood, and by modulating pro-inflammatory cytokines. A typical course of plasma exchange consists of 5–7 exchanges over 14 days. A patient's coagulation factors, electrolytes, and fluid balance must be closely monitored over this time period and levels of anti-epileptic medications should be checked regularly to ensure that they remain therapeutic. As with IVIG, all diagnostic serum antibody testing should be obtained before initiation of plasma exchange. If an autoimmune or paraneoplastic etiology is confirmed as the cause for RSE and a patient does not respond to initial treatment with methylprednisolone, IVIG, or plasma exchange, second-line treatment with rituximab or

cyclophosphamide should be considered. As these second-line therapies are associated with potentially severe adverse effects, clinical response should closely monitored after initiation of these treatments to help determine whether subsequent maintenance immunosuppression is warranted. While response to immunotherapy can support a diagnosis of autoimmune epilepsy, direct benefit is often difficult to prove as patients are often concurrently being treated with conventional anti-epileptic agents. It is also important to note that steroids have also been found to be beneficial in epilepsies that are not autoimmune such as Landau-Kleffner syndrome, and in infantile spasms.

Case reports and series have reported efficacy of a variety of surgical procedures for many types of lesions when all seizures have onset in an identifiable location. One case series of 15 children with RSE who underwent surgical procedures reported that all had seizure control ranging from seizure freedom to substantial reductions, allowing transition out of the ICU.[128] Vagus nerve stimulation has been reported effective in several case reports, but efficacy generally occurs over a prolonged period.

When used as a neuroprotective strategy for multiple types of brain injury, therapeutic hypothermia may reduce many destructive processes due to excitotoxicity, neuroinflammation, apoptosis, free radical production, seizures, and blood- brain barrier disruption. Only case reports and small case series have described the use of therapeutic hypothermia for SE and some indicate that 1–5 days of hypothermia to 32–36°C may terminate seizures and that some patients do not have seizure recurrence upon rewarming.[129,130]

RSE is considered an indication for electroconvulsive therapy by the American Psychiatric Association Task Force Report.[131] Only case reports and small series are available but they indicate some patients have temporary improvement and rare patients have full functional recovery.[132] Cardiovascular conditions are a relative contraindication, and in some patients electroconvulsive therapy may also provoke SE.

Conclusions

SE is a common neurologic emergency. Rapid efforts are needed to manage systemic complications, identify and manage precipitating conditions, and terminate seizures. A predetermined management plan that stresses urgent progression through appropriately dosed anticonvulsants may avoid delays. While data are limited regarding RSE management, a logical stepwise approach using available options is needed. Pharmacologic coma induction offers a window to identify and manage precipitant etiologies and to put in place anti-seizure strategies aiming to provide seizure control during pharmacologic coma weaning. While studies have compared benzodiazepines and administration strategies, there has been little study of medications used when seizures persist after administration benzodiazepines. However, research consortia are developing to identify and develop evidence-based interventions to improve the care of children with SE.[133]

Acknowledgments

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Immediate Management
Non-invasive airway protection and gas exchange with head positioning
Intubation if needed.
Monitoring O2 saturation, blood pressure heart rate, temperature.
Finger stick blood glucose.
Peripheral IV access
Medical and Neurologic Examination.
Labs including basic metabolic panel, calcium, magnesium, complete blood count, liver function tests, coagulation tests, arterial
    blood gas, and anticonvulsant levels.
Evaluate for specific immediate reversible causes of seizures: hyponatremia, hypoglycemia, hypocalcemia, hypomagnesemia
    and malignant hypertension.
Emergent Initial Therapy
IV Access: Lorazepam 0.1mg/kg IV (max 4 mg) - may repeat if seizures persist.
No IV Access: Diazepam   Rectal   2-5 years 0.5mg/kg, 6-11 years 0.3mg/kg, ≥12 years 0.2g/kg (max 20mg)
                            Midazolam   Intramuscular (13-40kg = 5mg; >40kg = 10mg), Intranasal (0.2mg/kg), Buccal (0.5mg/kg)
Consider whether out-of-hospital benzodiazepines have been administered when considering how many doses to administer.
Urgent Management
Additional diagnostic testing as indicated:
        Lumbar puncture (opening pressure, cell count with differential, protein, glucose, gram stain and culture)
            Consider: oligoclonal band profile, IgG index, IgG synthesis rate, fungal culture, herpes simplex virus 1/2 PCR
                    enterovirus PCR, parechovirus PCR
        Imaging: computerized tomography, magnetic resonance imaging
            Consider: toxicology lab, inborn errors of metabolism, anti-thyroid peroxidase antibodies, anti-thyroglobulin
                    antibodies, bacterial cultures
Consider EEG monitoring to evaluate for psychogenic SE or persisting EEG-only seizures after convulsive SE terminates.
Neurology Consultation
Urgent Control Therapy
Phenytoin   20mg/kg IV (plus another 10mg/kg if needed)
OR Fosphenytoin 20 PE/kg IV (may given another 10 PE/kg if needed)   PE = phenytoin equivalents
OR consider phenobarbital, valproate sodium, or levetiracetam.
If < 2 years, consider pyridoxine (100mg IV).
Refractory Status Epilepticus Management
If seizure continue after benzodiazepines and a second anti-seizure medication, the patient is in refractory status epilepticus
regardless of elapsed time. Continue management as plan for ICU admission/transfer and likely continuous EEG monitoring.
Administer another Urgent Control anticonvulsant or proceed to pharmacologic coma.
    Levetiracetam 20-60 mg/kg IV
    Valproate Sodium 20-40 mg/kg IV.
    Phenobarbital 20-40 mg/kg IV
Pharmacologic Coma Medications
    Midazolam 0.2mg/kg bolus (max 10mg) and then initiate infusion at 0.1mg/kg/hr.
    Pentobarbital 5 mg/kg bolus and then initiate infusion at 0.5mg/kg/hour.
    For both medications, if dose escalation is needed, then re-bolus and do not just increase the infusion rate.
Pharmacologic Coma Management
    Titrate to either seizure suppression or burst suppression based on continuous EEG monitoring.
    Continue pharmacologic coma for 24-48 hours.
    Modify anti-seizure medications so additional coverage is in place for infusion wean.
    Continue diagnostic testing and implementation of etiology directed therapy.
Add-On Options
    Medications: phenytoin, phenobarbital, levetiracetam, valproate sodium, topiramate, lacosamide, ketamine, pyridoxine,
                pyridoxal-5-phosphate, folinic acid, biotin.
    Other: epilepsy surgery, ketogenic diet, vagus nerve stimulator, immunomodulatory therapy (methylprednisolone, IVIG, plasma
                exchange), hypothermia, electroconvulsive therapy.

Figure 1.
Status epilepticus evaluation and management pathway. Adapted from prior pathways.[15–17]

Urgent Evaluation

	Cerebrospinal fluid:	
		Collect up to 10-20mL CSF for immediate analysis and freeze remainder for later testing.
		Opening pressure on lumbar puncture
		White blood cell count with differential, red blood cell count, protein, glucose
		Gram stain, bacterial culture, fungal cultures (if immunocompromised)
		PCR: herpes simplex virus 1/2, enterovirus, parechovirus (if age < 3)
	Serum	
		Basic Studies: complete blood count with differential, electrolytes and liver function, coagulation studies
		Bacterial cultures
		Serologies: Epstein-Barr virus (VCA IgG and IgM and EBNA IgG), *Mycoplasma pneumoniae*
		Hold acute serum and collect convalescent serum 10-14 days later for paired antibody testing
	Other Samples	
		Mycoplasma pneumoniae PCR from throat swab
		Enterovirus PCR and/or culture of throat and stool
	Radiology	
		Magnetic resonance imaging of the brain with and without gadolinium
		Chest imaging (Chest x-ray and/or CT)

If RSE persists without clear etiology for ≥24 hours, consider adding:

	Cerebrospinal fluid:	
		CSF serologies (IgM and IgG): herpes simplex virus, varicella zoster virus, human immunodeficiency virus, arboviruses (including St. Louis encephalitis virus, California encephalitis group, Eastern equine encephalitis virus, Western equine encephalitis virus, West Nile virus), lymphocytic choriomeningitis.
		Acid fast bacilli (AFB) smear and *Mycobacterium tuberculosis* culture
		PCR: Epstein-Barr virus, cytomegalovirus, human herpes virus 6, rotavirus
		Oligoclonal bands and IgG index
		Consider repeat herpes simplex virus testing 3-7 days after initial test if clinical suspicion remains
	Serum	
		Serologies: adenovirus, arbovirus panel (including St. Louis encephalitis virus, California encephalitis group, Eastern equine encephalitis virus, Western equine encephalitis virus, West Nile virus), Lymphocytic choriomeningitis, HHV6, *Borrelia* sp., *Toxoplasma gondii*, and influenza.
		Human immunodeficiency virus serology (consider RNA)
		PCR: herpes simplex virus 1/2, varicella zoster virus
	Other Samples	
		Consider: viral cultures and analysis (antigen detection, PCR) of other potentially affected body fluids (tracheal aspiration, urine, stool) or mucosal sites (throat, nasopharynx, rectum)
		Consider: Brain biopsy in subjects with a progressive deterioration over time despite empiric therapy

Consider additional testing for selected patients based on exposure and travel history, and other specific clinical symptoms. Examples include, but are not limited to:

	Culture or PCR of skin lesions if present for herpes simplex virus, varicella zoster virus, and/or Rickettsial infection
	Naegleria fowleri (CSF wet mount and PCR) if swimming in warm freshwater
	Bartonella (serum) and Ophthalmologic exam if exposure to cats
	Rabies serology (serum)
	Treponemal testing (serum: rapid plasma reagin (RPR), specific treponemal test)
	Measles virus testing if unvaccinated
	Tick borne disease testing based on geographic region (ie *Borrelia, Ehrlichia, Rickettsia* sp.*, Anaplasma phagocytophilum* serology)
	Consider region-specific pathogens (e.g. malaria based on travel history)

Figure 2.

Suggested Infectious Disease Evaluation for Children with Refractory Status Epilepticus (RSE). Adapted from prior tables.[35,36]