Current Trends in Treatment of Status Epilepticus and Refractory Status Epilepticus

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Abstract

Status epilepticus is a heterogeneous disorder with varied definitions and presentations. Taken together, all forms of status epilepticus carry significant morbidity and mortality, much of which is dictated by the underlying etiology. Generalized convulsive status epilepticus, which represents a common form, is a true neurologic emergency that requires emergent management. Treatment focuses on stabilizing the patient and aggressive medical management to achieve the timely termination of seizures. For other forms of status epilepticus including nonconvulsive and focal status epilepticus, the goal remains early seizure termination, but the use of intravenous medications should be weighed against the risks associated with these therapies. The diagnostic evaluation of status epilepticus is guided by the patient’s history and should be broad, including a screen for toxins, electrolytes, structural abnormalities, and central nervous system infectious and autoimmune/inflammatory etiologies. Considerable research is still needed to improve our understanding of the mechanisms, consequences, and therapy of status epilepticus.

Epidemiology and Prognosis

When broadly defined as a seizure lasting more than 30 minutes or recurrent seizures with incomplete return to baseline, the annual incidence of SE ranges from 10 to 41 per 100,000 persons, or roughly 125,000 to 195,000 new cases annually in the United States. 1-5 These figures may even be underestimates, particularly in the case of NCSE, which is only diagnosed through electroencephalographic (EEG) monitoring; recent studies of inpatient EEG monitoring, particularly in the intensive care unit (ICU), have demonstrated high rates of electrographic seizures that likely are underrecognized. 6-11 Owing in part to this increase in SE detection in the hospital, the incidence of SE is increasing. 12,13

Although greatly influenced by the etiology, overall mortality estimates related to SE approach 20% 1 and are not changing dramatically over time. 12,13 When considering the causes of SE, it can be helpful to divide cases into acute and chronic etiologies. Acute symptomatic causes (i.e., stroke, metabolic, infectious, anoxic injury) tend to be more common than chronic causes (i.e., low antiepileptic drug level, alcohol abuse, tumor, remote effects from stroke) and are generally associated with a higher mortality. 2,5,14 Given the increasing
incidence and associated morbidity and mortality, the costs of SE are substantial; direct inpatient costs related to SE are approximately $4 billion annually in the United States.\textsuperscript{15}

**Definitions of Status Epilepticus**

General agreement exists that SE should be treated promptly and effectively to minimize neuronal injury and overall morbidity and mortality. Although the majority of seizures self-terminate within 180 seconds,\textsuperscript{16} prolonged seizures become pharmacoresistant (especially to benzodiazepines) and are less likely to terminate spontaneously.\textsuperscript{17,18} Status epilepticus was previously defined as a seizure lasting more than 30 minutes based on studies of neuronal injury.\textsuperscript{19} However, the International League Against Epilepsy is considering a new operational definition advocating for the treatment of SE within 5 minutes of onset. Although this definition applies mainly to GCSE, in the future it may be extended to forms of focal motor SE and NCSE.

It is important to realize that the definitions of SE are continually changing and that significant overlap and limitations exist among the varied definitions. For this review, we will consider three main practical types of SE: GCSE, focal motor SE, and NCSE (\textit{\textit{\textbullet}} Table 1). Generalized convulsive SE and focal motor SE are characterized by overt rhythmic movements of the extremities and/or the face associated with an alteration in cognition. Nonconvulsive SE in adults is defined as prolonged epileptiform activity on EEG, though a generally accepted duration of epileptiform activity is not incorporated into the definition. There are many subdivisions of NCSE, which can be difficult to define,\textsuperscript{20} but for the purposes of this review we will focus on two main types: NCSE with coma, which is also commonly referred to as “subtle SE,” and NCSE without coma. Nonconvulsive SE with coma often follows overt GCSE or acute severe brain injury and is characterized by a severe alteration in mental status and ongoing focal or generalized epileptiform discharges. Although there may be subtle twitching movements accompanying NCSE with coma, the diagnosis requires EEG. Nonconvulsive SE without coma implies a patient with epileptiform activity on EEG resulting in relatively mild alteration in cognition or behavior, sometimes referred to as the “wandering confused” patient.\textsuperscript{21} When considering the treatment of SE, particularly the urgency of treatment and escalation to anesthetics, a distinction is often made between GCSE and other forms of SE, with focal motor SE and the subtypes of NCSE often treated in a similar and somewhat less-aggressive fashion than GCSE.

A precise definition of refractory SE (RSE) is also lacking. A generally agreed-upon definition for RSE is any type of SE that persists despite adequate treatment with a first-line agent (benzodiazepines) and at least one second-line antiepileptic drug (AED).\textsuperscript{22} Refractory SE encompasses both convulsive and nonconvulsive SE; as in both, an EEG is often required to confirm the presence of ongoing seizure activity. Superrefractory SE (SRSE) is commonly defined as SE that persists for more than 24 hours after anesthetics have been introduced, and includes cases where SE was initially controlled by an anesthetic, but returns upon weaning the anesthetic.

**Table 1** Definitions of status epilepticus

<table>
<thead>
<tr>
<th>Type of SE</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Generalized convulsive</td>
<td>Overt generalized convulsive activity with altered cognition</td>
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<tr>
<td>Focal motor</td>
<td>Overt focal convulsive activity with altered cognition (previously complex partial SE)</td>
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<tr>
<td>Nonconvulsive</td>
<td>Prolonged focal or generalized electrographic seizure activity</td>
</tr>
<tr>
<td>NCSE without coma</td>
<td>Typically focal electrographic seizure activity resulting in altered cognition described as the “wandering confused patient.” Also referred to as dyscognitive focal SE</td>
</tr>
<tr>
<td>NCSE with coma</td>
<td>Also referred to as “subtle SE,” often occurs following GCSE or an acute severe brain injury and is characterized by focal or generalized electrographic seizure activity and severely altered cognition (i.e., coma)</td>
</tr>
<tr>
<td>Refractory</td>
<td>SE that persists despite appropriate treatment with benzodiazepines and a second-line AED</td>
</tr>
<tr>
<td>Superrefractory</td>
<td>SE persisting for more than 24 hours after the introduction of anesthetics including SE that was initially controlled by an anesthetic but returns upon weaning the medication.</td>
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Abbreviations: AED, antiepileptic drug; NCSE, nonconvulsive status epilepticus; SE, status epilepticus.
double-blind comparison of four intravenous (IV) treatments: lorazepam, phenytoin, phenobarbital, or diazepam plus phenytoin. Status epilepticus was terminated in 65% of patients treated with lorazepam, similar to the results seen with phenobarbital and diazepam plus phenytoin and superior to the phenytoin monotherapy arm. Intravenous lorazepam has therefore served as the initial medication of choice for SE.

Two randomized, double-blind trials examined the efficacy and safety of benzodiazepines administered by paramedics in the prehospital setting. The first compared IV diazepam (5–10 mg), IV lorazepam (2–4 mg), and placebo, and found that patients who received either lorazepam or diazepam were more likely to have their SE terminated upon arrival to the emergency room than patients receiving placebo. In addition, those receiving a benzodiazepine were less likely to experience respiratory compromise. The more recent Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) compared IV lorazepam (4 mg in adults, 2 mg in children) to intramuscular (IM) midazolam (10 mg in adults, 5 mg in children) and concluded that IM midazolam was at least as safe and effective for terminating SE in the prehospital setting. Based on the findings of these pivotal trials, the first-line treatment of SE begins with either IV lorazepam or IM midazolam prior to arrival in the emergency room.

Numerous studies have also examined the efficacy of benzodiazepine abortive medications to be administered by paramedics and caregivers for acute repetitive seizures and SE. Early studies demonstrated the efficacy of rectal diazepam, but more recently, the development of buccal and IM preparations of midazolam have allowed for easier and more socially acceptable routes of administration.

**Hospital Management**
The initial management of a patient in GCSE begins with vital sign stabilization and airway management. Although the initial treatment of SE begins with the use of benzodiazepines, significant practice variability exists in the treatment of SE refractory to adequate benzodiazepines alone. Second-line AEDs that have been investigated include IV phenytoin, fosphenytoin, valproic acid, phenobarbital, levetiracetam, and lacosamide. Convention in the United States leans toward the use of phenytoin or fosphenytoin. Although fosphenytoin is more costly, it offers the advantages of a lower risk for adverse reactions related to IV extravasation and can be administered at a faster rate than phenytoin with no increased risk of arrhythmias or hypotension. Dosing for phenytoin and fosphenytoin is weight-based (20 mg/kg). A second smaller dose of 5 to 10 mg/kg can be administered if the patient is still suspected to be seizing. Common practice is to aim for a slightly supratherapeutic corrected phenytoin level (20–30 μg/ml), though further escalation of treatment should not be delayed for laboratory results if the patient continues to seize.

Numerous studies have attempted to compare these second-line agents, but small sample sizes and methodological variability limit their interpretation and applicability. It is important to note that no class I data exist comparing the efficacy of these second-line AEDs. A recent meta-analysis of the most commonly used second-line AEDs found that valproic acid was most efficacious, stopping SE in 75.7% of patients, followed by phenobarbital 73.6%, levetiracetam 68.5%, and phenytoin 50.2%; lacosamide had insufficient evidence to analyze. The authors advise caution when interpreting the data, noting several limitations including the relatively small number of studies comparing these AEDs, a preponderance of observational studies, and heterogeneous methodologies. A Cochrane review summarizing studies comparing these second-line AEDs concluded that the results are uncertain and further study is needed.

These findings underscore the importance of the Established Status Epilepticus Treatment Trial (ESETT; NCT01960075). Funded by the National Institute of Neurologic Disorders and Stroke, ESETT...
is to begin enrollment in late 2015 and will compare fosphenytoin, valproic acid, and levetiracetam in a blinded, randomized fashion for the treatment of SE refractory to benzodiazepines.  

When SE is refractory to benzodiazepines and a second-line AED, a decision must be made regarding the next step in treatment. Prior convention may have included another trial of a second-line AED, but more recent practice patterns indicate a shift toward early anesthetic use in adults with refractory GCSE.

Although no absolute consensus exists, the updated treatment algorithm presented in Fig. 1 advocates for early escalation (within 30–60 minutes of seizure onset) to an anesthetic agent such as propofol or midazolam rather than another trial of a second-line AED. The rationale behind this recommendation is based on evidence of systemic and neuronal injury from continued GCSE, as well as the development of pharmacoresistance to medications with prolonged seizures. The decision to use an anesthetic agent must be weighed against its potentially serious complications.

**Fig. 1** Generalized convulsive status epilepticus treatment algorithm. ABCs, airway, breathing, circulation; IV, intravenous. (Reprinted with permission from Betjemann JP, Lowenstein DH. Status epilepticus in adults. Lancet Neurol 2015;14:615).

**Treatment of Focal Motor Status Epilepticus and Nonconvulsive Status Epilepticus**

A relative lack of data exists to guide the management of focal motor SE and NCSE. Often their treatment strategy is similar, as these forms of SE are felt to be less of a true medical emergency because they lack the generalized convulsive activity that can result in severe metabolic dysfunction; however, some evidence exists demonstrating that even NCSE can result in neuronal injury, questioning this less time-pressured approach. In the VA Cooperative Study, subtle SE was terminated in only 8 to 24% of cases, with no significant difference found between treatment arms of lorazepam alone, diazepam plus phenytoin, phenytoin alone, and phenobarbital alone. The treatment of focal motor SE and forms of NCSE still focuses on timely management and early seizure cessation, and begins with one or two rounds of benzodiazepines according to the GCSE treatment algorithm. Similarly, if seizures persist, a second-line AED is the next step in management. When focal motor SE or NCSE is refractory to first- and second-line treatments, consideration should be given to scheduled benzodiazepines and additional AED trials prior to escalating to intubation and IV anesthetics, particularly in cases of SE when consciousness is relatively preserved. Phenytoin/fosphenytoin, valproic acid, levetiracetam, and phenobarbital can all be considered as potential adjunct second-line therapies. Intravenous lacosamide and oral topiramate have also been suggested for refractory SE.

If multiple trials of AEDs are unsuccessful over the course of a few days, anesthetics should be more strongly...
Refractory Status Epilepticus and Superrefractory Status Epilepticus

Refractory SE (RSE) is defined as SE that persists despite an appropriately dosed first-line agent (benzodiazepines) and a second-line AED; superrefractory SE (SRSE) refers to SE that persists for more than 24 hours following the introduction of anesthetics. A study of patients appropriately treated for convulsive SE found that 48% went on to have continued nonconvulsive seizures and 15% were diagnosed with NCSE, underscoring the importance of continuous EEG to identify RSE and guide its treatment.42

Although data are limited, more recent studies estimate that 23 to 43% of patients in SE will progress to RSE, and the mortality of RSE ranges from 17 to 39%.22,43–46 Similar to nonrefractory SE, mortality is largely dependent on the underlying etiology for RSE and the patient’s age. Refractory SE tends to be more commonly associated with acute severe brain injuries such as ischemic stroke and CNS infection, and less likely to be associated with more “benign” etiologies such as chronic epilepsy and low AED levels.43,44 Patients in RSE are less likely to return to baseline, have significantly longer hospital stays, and are significantly more likely to require inpatient rehabilitation than are patients who experience nonrefractory SE.44 In addition, patients who survive RSE are more likely develop symptomatic epilepsy following SE compared with those who experience nonrefractory SE.43

The treatment of RSE and SRSE centers around rapid seizure control to minimize systemic and neurologic compromise while balancing the risks associated with prolonged intubation and anesthetics. A concurrent, extensive diagnostic investigation should be undertaken to identify potentially reversible causes such as metabolic, infectious, or inflammatory etiologies. Detailed reviews of the treatment of RSE and SRSE are provided elsewhere.47,48 Propofol, midazolam, and thiopental are commonly used first-line anesthetics for SE, with pentobarbital often being reserved for use as a second-line anesthetic for those patients still refractory after these initial medications. All of these medications should be given as an initial bolus followed by a maintenance infusion to assure adequate serum levels of the drugs. A systematic review comparing pentobarbital, midazolam, and propofol found no significant difference in overall mortality, and noted that treatment with pentobarbital was associated with fewer breakthrough seizures, but was also associated with an increased risk of hypotension.49 Propofol has been associated with a life-threatening infusion syndrome, particularly during prolonged infusions and in children. Midazolam has been associated with tachyphylaxis, often necessitating frequent dosage adjustments. Both propofol and midazolam have relatively short half-lives, as opposed to pentobarbital, which is advantageous when frequent neurologic exams need to be performed. In the absence of randomized data to guide management decisions, selection of an anesthetic should be individualized and based on factors including comorbidities, cardiovascular status, drug interactions, and institutional experience.

When treating RSE with an anesthetic, continuous EEG is needed to help guide therapy. The goal is to achieve electrographic seizure suppression and potentially a burst-suppression EEG pattern. No definitive data exist to determine what adequate burst-suppression entails and how long it should be maintained. Convention is to aim for 1 to 2 seconds of cerebral activity with 10-second interburst intervals of background suppression for a total of 24 to 48 hours before attempting to lighten sedation. This period of electrographic suppression also provides an opportunity to add on maintenance AEDs and quickly bring them to therapeutic levels before weaning sedation.

In cases where seizures return upon lightening sedation (SRSE), further therapeutic pharmacological options can be considered, though data are extremely limited. Case reports suggest the efficacy of IV ketamine infusion even in cases where traditional GABAergic anesthetics fail.50–52 Ketamine has theoretical advantages, including its potential to be neuroprotective via modulation of N-methyl-D-aspartate (NMDA) activity and its lack of cardiovascular side effects.48 A multicenter retrospective study concluded that ketamine infusion was safe and potentially efficacious when administered via a loading dose followed by a continuous infusion.53 The inhalated anesthetics isoflurane and desflurane have been discussed in case reports, but should be used with caution given their potential for serious adverse events including hypotension, atelectasis, infections, and ileus.34 Reports, especially in the pediatric literature, have also suggested IV lidocaine as being potentially efficacious.55–57 Magnesium can control seizures related to eclampsia, and more recently in cases of mitochondrial encephalopathy and RSE related to a POLG1 mutation.58 Similarly, IV pyridoxine has a role in patients with an inborn error in metabolism of pyridoxine, but should be also considered in other patients owing to its low-risk profile.59

There are numerous reports, primarily in children, of successfully using the ketogenic diet in aborting RSE.60–62 The diet is relatively easy to administer via nasogastric tube, but does require interdisciplinary teamwork with a nutritionist. The diet is contraindicated in patients with pyruvate carboxylase and β-oxidation deficiencies, and is probably best avoided when patients are receiving concurrent propofol or steroids.

Recently, immunologic therapy including steroids, IV immunoglobulin, and plasma exchange has gained enthusiasm for the treatment of new-onset RSE (NORSE) in light of increased appreciation for immunomediacted causes of SE, including anti-NMDA receptor encephalitis and voltage-gated potassium antibody-mediated encephalitis. It is important to attempt to rule out infections and perform a thorough diagnostic workup prior to initiating immune therapy, as treatment can impact the ability to make an alternative diagnosis.
There are also several nonpharmacologic options for SRSE, including electroconvulsive therapy (ECT) and surgery. A few published reports have suggested that ECT typically administered in 1 to 6 sessions over nearly consecutive days can terminate SRSE.\textsuperscript{63,64} Electroconvulsive therapy requires an experienced multidisciplinary team and also requires continuous EEG monitoring to ensure that the patient experiences an induced seizure during the treatment. There are numerous surgical options including focal resective surgery, vagal nerve stimulator placement, multiple subpial transection, and corpus callosotomy. Surgical approaches require a highly specialized multidisciplinary team who can develop a surgical plan, and in the case of resective surgery, requires evidence of a focal epileptogenic focus.

**Diagnostic Evaluation of a Patient in Status Epilepticus**

The initial diagnostic evaluation of a patient in SE should be occurring in conjunction with treatment and should not delay emergent therapy (\textsuperscript{2}Table 3). The evaluation begins with a careful history aimed at identifying potential etiologies, including a prior history of seizures and medication noncompliance, which remains the single most common etiology of SE.\textsuperscript{14} The history should also focus on new medications, illicit substances, and recent or remote injuries that may have triggered SE. An urgent laboratory evaluation should focus on reversible etiologies, including signs of infection, metabolic disturbances, renal and liver failure, toxin ingestion, and low AED levels. In most instances, AED levels for phenytoin, carbamazepine, valproic acid, and phenobarbital can be obtained relatively quickly, but most other AED levels will take days to result. Brain imaging should be obtained once convulsions are controlled. Practically, this often begins with a contrasted computed tomography (CT) scan of the head, but if an explanation is not elucidated, an MRI should be performed once the patient is stabilized. Status epilepticus is a clinical diagnosis that does not require an EEG; importantly, treatment should not be delayed to obtain one.

Electroencephalography becomes increasingly important in instances where a patient remains persistently altered, raising concern for ongoing electrographic seizures, and when titrating medications to treat a patient with RSE. A lumbar puncture is an important early test in patients with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) and when suspicion exists for a life-threatening infection such as bacterial meningitis or herpes simplex virus encephalitis. Treatment with AEDs, antibiotics, and other supportive care, Table 3 Diagnostic evaluation for status epilepticus

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Importance</th>
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<tbody>
<tr>
<td>Detailed history</td>
<td>Known epilepsy and poor AED compliance</td>
</tr>
<tr>
<td>Medications</td>
<td>Examples: bupropion, β-lactams, clozapine, isoniazid, theophylline</td>
</tr>
<tr>
<td>Illicit drugs</td>
<td>Stimulants: cocaine, methamphetamine</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>Alcohol, benzodiazepines, barbiturates</td>
</tr>
<tr>
<td>Brain injury</td>
<td>Stroke, infection, tumor, traumatic brain injury</td>
</tr>
<tr>
<td>Screening labs</td>
<td></td>
</tr>
<tr>
<td>CBC</td>
<td>Leukocytosis suggesting infection</td>
</tr>
<tr>
<td>CMP</td>
<td>Hyponatremia, hypocalcemia, hypercalcemia, hypomagnesemia, hyper-hypoglycemia, renal failure, liver failure</td>
</tr>
<tr>
<td>AED levels</td>
<td>Phenytoin, valproic acid, carbamazepine, phenobarbital</td>
</tr>
<tr>
<td>Urine toxicology</td>
<td>Evidence of illicit substances</td>
</tr>
<tr>
<td>Imaging</td>
<td></td>
</tr>
<tr>
<td>Contrast CT MRI</td>
<td>Evidence of obvious structural abnormalities</td>
</tr>
<tr>
<td>MRI</td>
<td>Preferred method for identifying numerous abnormalities including encephalitis, abscess, ischemic stroke and tumor</td>
</tr>
<tr>
<td>EEG</td>
<td>Not a necessary initial step but should be obtained for patients with persistent altered mental status following SE or to titrate anesthetics for burst suppression</td>
</tr>
<tr>
<td>CSF</td>
<td>Should be done early if suspicion exists for bacterial meningitis or HSV encephalitis. For persistently unexplained SE, CSF testing should include screening for atypical infections and evidence of inflammation (oligoclonal bands and IgG index)</td>
</tr>
<tr>
<td>Secondary laboratories</td>
<td>HIV, autoimmune/inflammatory etiologies including thyroid antibodies, serum/CSF paraneoplastic panel</td>
</tr>
</tbody>
</table>

Abbreviations: AED, antiepileptic drug; CBC, complete blood count; CMP, comprehensive metabolic panel; CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalography; HIV, human immunodeficiency virus; HSV, herpes simplex virus; MRI, magnetic resonance imaging; SE, status epilepticus.
and acyclovir should not be delayed to obtain cerebrospinal fluid.

If no cause for SE is identified during the initial evaluation, a more thorough workup can be entertained. This should include a careful search for causes of immunosuppression including HIV, as well as further cerebrospinal fluid testing for atypical bacterial, viral, fungal, and protozoal infections that are extensively reviewed elsewhere. A constellation of symptoms including seizures, ophthalmoplegia, ataxia, and myoclonus in a child or young adult should prompt consideration of a genetic defect, particularly a mitochondrial disorder. Recently, immune disorders have been increasingly recognized as the cause of previously unexplained cases of new-onset SE, and often RSE. It is extremely important to identify these syndromes as the treatment of SE involves immunotherapy in addition to AEDs. Two of the more commonly described autoimmune syndromes leading to SE are anti-NMDA receptor encephalitis and voltage-gated potassium channel antibody autoimmunity, though numerous other autoantibodies can cause SE.66 When SE remains unexplained, serum thyroperoxidase antibodies and antithyroglobulin antibodies as well as serum and CSF paraneoplastic antibody levels should be considered, especially in the setting of an unexplained lymphocytic pleocytosis in the spinal fluid or other signs of CSF inflammation such as an elevated IgG index or unique oligoclonal bands. If an autoantibody is identified, systemic imaging to look for an occult malignancy should be undertaken, as many paraneoplastic syndromes will respond best to treatment of the underlying malignancy.

Conclusion

Although SE is a relatively common neurologic disorder with significant morbidity and mortality, many management questions remain. Further research should focus on the most appropriate algorithm for the treatment of SE. Additional studies are also needed to examine the utility and cost-effectiveness of EEG monitoring to identify SE in hospitalized patients and its impact on outcomes. Finally, continued efforts to identify the myriad causes of SE, particularly novel autoimmune/inflammatory etiologies, are critical as their successful treatment often depends on prompt identification and treatment.

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