

# Management of Status Epilepticus

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J Neuroanaesthesiol Crit Care 2019;6:267–274

## Abstract

### Keywords

- ▶ convulsive status epilepticus
- ▶ neurocritical care
- ▶ nonconvulsive status epilepticus
- ▶ refractory status epilepticus
- ▶ status epilepticus
- ▶ super-refractory status epilepticus

Status epilepticus (SE) is a life-threatening neurologic condition that requires immediate assessment and intervention. Over the past few decades, the duration of seizure required to define status epilepticus has shortened, reflecting the need to start therapy without the slightest delay. The focus of this review is on the management of convulsive and nonconvulsive status epilepticus in critically ill patients. Initial treatment of both forms of status epilepticus includes immediate assessment and stabilization, and administration of rapidly acting benzodiazepine therapy followed by nonbenzodiazepine antiepileptic drug. Refractory and super-refractory status epilepticus (RSE and SRSE) pose a lot of therapeutic problems, necessitating the administration of continuous infusion of high doses of anesthetic agents, and carry a high risk of debilitating morbidity as well as mortality.

## Introduction

Status epilepticus (SE) is a medical and neurologic emergency that requires immediate evaluation and treatment. It is associated with a variable period of apnea, cyanosis, metabolic acidosis, cerebral ischemia, and hemodynamic perturbation. Different types of SE are classified based on clinical presentation and electroencephalography (EEG) findings. A detailed management scheme for all types of SE in adults and children is beyond the scope of this article. The focus of this review is on convulsive status epilepticus (CSE), which is frequently encountered in adult neurocritical care. Pertinent points related to the management of refractory and super-refractory SE (RSE and SRSE) are also highlighted in the text. Nonconvulsive status epilepticus (NCSE) merits a separate discussion; NCSE in critically ill patients is only briefly discussed.

## Definitions

Traditionally, SE was defined as “seizure lasting more than 30 minutes or several distinct episodes without restoration of consciousness.”<sup>1</sup> This time cutoff suggested that irreversible neuronal damage and metabolic decompensation may

occur after 30 minutes of seizure activity. However, this working definition did not indicate the need to immediately commence treatment and that permanent neuronal injury could occur by the time a clinical diagnosis of SE was made. A more appropriate definition of SE is “≥5 min of continuous seizure, or two or more discrete seizures during which there is incomplete recovery of consciousness.”<sup>2</sup> In 2015, the International League Against Epilepsy proposed a conceptual definition of SE with two time-points: the first time-point ( $t_1$ ) indicating when the seizure should be considered as “abnormally prolonged” and the second time-point ( $t_2$ ) indicating “the time of ongoing seizure activity beyond which there are risks of long-term sequelae,” such as neuronal injury, alteration of neuronal networks and neuronal death.<sup>3</sup> These time-points have clinical implications in determining when and how aggressively treatment should be commenced to minimize long-term consequences (▶ **Table 1**). The time-points for CSE are clearly defined but they are less clear for other types of SE.

Refractory SE (RSE) is defined as ongoing CSE or NCSE even after sufficient dose of an initial benzodiazepine and a nonbenzodiazepine antiseizure drug (ASD) are administered. SRSE is defined as ongoing seizure activity for ≥24 hours despite

### received

August 20, 2019

### accepted after revision

September 17, 2019

### published online

November 21, 2019

DOI <https://doi.org/10.1055/s-0039-1700446>

ISSN 2348-0548.

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**Table 1** Conceptual definition of status epilepticus

Type of SE	Time point 1 (t1) (when seizure is likely to be prolonged)	Time point 2 (t2) (when seizure is likely to cause long-term consequences)
Tonic-clonic	5 min	30 min
Focal with impaired consciousness	10 min	>60 min
Absence	10–15 min	Data inadequate

Source: Table adapted from Trinka et al<sup>3</sup> with permission.

**Table 2** Clinical classification of status epilepticus

<ol style="list-style-type: none"> <li>1. With prominent motor symptoms               <ol style="list-style-type: none"> <li>a. Convulsive SE (CSE)                   <ol style="list-style-type: none"> <li>i. Generalized convulsive</li> <li>ii. Focal onset evolving into convulsive</li> <li>iii. Unknown whether focal or generalized</li> </ol> </li> <li>b. Myoclonic SE                   <ol style="list-style-type: none"> <li>i. With coma</li> <li>ii. Without coma</li> </ol> </li> <li>c. Focal motor SE                   <ol style="list-style-type: none"> <li>i. Repeated focal motor seizures</li> <li>ii. Epilepsia partialis continua</li> <li>iii. Adversive</li> <li>iv. Oculoclonic</li> <li>v. Ictal paresis</li> </ol> </li> <li>d. Tonic SE</li> <li>e. Hyperkinetic SE</li> </ol> </li> <li>2. Without prominent motor symptoms (nonconvulsive status epilepticus [NCSE])               <ol style="list-style-type: none"> <li>a. NCSE with coma</li> <li>b. NCSE without coma                   <ol style="list-style-type: none"> <li>i. Generalized                       <ol style="list-style-type: none"> <li>1. Typical absence</li> <li>2. Atypical absence</li> <li>3. Myoclonic absence</li> </ol> </li> <li>ii. Focal                       <ol style="list-style-type: none"> <li>1. Without impairment of consciousness</li> <li>2. Aphasic SE</li> <li>3. With impaired consciousness</li> </ol> </li> <li>iii. Unknown whether focal or generalized                       <ol style="list-style-type: none"> <li>1. Autonomic SE</li> </ol> </li> </ol> </li> </ol> </li> </ol>
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Source: Table adapted from Trinka et al<sup>3</sup> with permission.

anesthetic therapy or recurrence of seizure upon withdrawal of anesthetics. Despite optimum treatment, nearly one-fifth of all RSE patients may progress to develop SRSE.<sup>4</sup> New-onset RSE (NORSE) is a rare clinical presentation in otherwise healthy patients, without a clear acute or active structural, toxic, or metabolic cause.<sup>5</sup> Febrile infection-related epilepsy syndrome is a subcategory of NORSE where patients have a preceding febrile infection within 24 hours to 2 weeks of the onset of RSE.<sup>5</sup>

## Classification

Broadly, SE can present with or without prominent motor symptoms. A detailed classification based on clinical findings is presented in ► **Table 2**.

## Management of Convulsive Status Epilepticus

The management of CSE can be structured into emergent management and postictal management.

### Emergent Management

The emergent management of CSE can be divided into three phases: (i) immediate assessment and stabilization, (ii) therapy with rapidly acting benzodiazepine, and (iii) therapy for long-term seizure control.

#### Immediate Assessment and Stabilization

This phase begins with a rapid and focused neurologic assessment to understand the type of SE. Like with other acute emergencies, maintenance of airway, breathing, and circulation is of paramount importance. Supplemental oxygen should be provided, with a low threshold for endotracheal intubation. Intravenous (IV) catheters should be inserted/attempted and blood samples should be sent to the laboratory for obtaining levels of serum electrolytes, liver function, blood count, drug levels, and toxicology screen, as appropriate. Bedside finger-stick blood glucose estimation is mandatory. IV thiamine (100–250 mg) followed by glucose can be given if hypoglycemia or alcohol intoxication is suspected. This phase should be completed within 5 minutes and ideally be performed in parallel with the second phase of management.

#### Therapy with Rapidly Acting Benzodiazepine

Prompt termination of seizure with a rapidly acting benzodiazepine ASD is the cornerstone of managing CSE. IV lorazepam is the first-line therapy; IV diazepam is a suitable alternative when lorazepam is not available.<sup>6</sup> Intramuscular (IM) midazolam can be given if IV line has not been secured. Among other benzodiazepines, IV clonazepam is popular in some countries (especially Europe) as the first-line agent. There is also a recent effort to study whether add-on therapy to first-line benzodiazepine is better than benzodiazepine alone in CSE. The Prehospital Treatment with Levetiracetam plus Clonazepam or Placebo plus Clonazepam in Status Epilepticus (SAMUKeppra) trial was one such study that evaluated the effect of clonazepam and levetiracetam versus clonazepam and placebo in prehospital management of SE.<sup>7</sup> Even though this study did not show significant benefit of such add-on therapy, it is an intriguing area of future research.

- **Lorazepam:** Several studies have validated lorazepam as the first-choice drug for SE.<sup>8–10</sup> It is administered in the dose of 0.1 mg/kg IV (maximum 4 mg per bolus). This dose can be repeated if seizure is not controlled. Recently, intranasal preparation of lorazepam has also been proposed as a convenient and noninvasive route of drug delivery, on account of its favorable pharmacokinetics with rapid absorption and adequate serum concentration after intranasal administration.<sup>11,12</sup>
- **Diazepam:** Diazepam is as efficacious as lorazepam in aborting seizures.<sup>13</sup> However, it has a shorter duration

of action compared with lorazepam as there is significant redistribution to adipose tissue. The usual dose is 0.1 to 0.2 mg/kg IV (maximum 10 mg per dose). Rectal diazepam is useful when there is no IV access and IM injections are contraindicated.

- Midazolam: Midazolam is extremely useful when IV access is not available. The usual IM dose is 10 mg for patients with body weight exceeding 40 kg, or 5 mg for those between 10 and 40 kg. The Rapid Anticonvulsant Medication Prior to Arrival Trial found IM midazolam to be at least as safe and effective as IV lorazepam for seizure cessation.<sup>14</sup> Alternative routes such as nasal or buccal may lead to quicker drug absorption; however, there are very few studies assessing the effectiveness of such routes in treating SE.

### Therapy for Long-Term Seizure Control

Therapy with a nonbenzodiazepine ASD is necessary to prevent recurrence of SE even if the seizure is aborted by the initial benzodiazepine drug. Common choices include phenytoin, fosphenytoin, valproate, and levetiracetam. Fosphenytoin is better than phenytoin because of safer side effect profile and the possibility of a more rapid administration. IV valproic acid and levetiracetam are other suitable choices. IV phenytoin (or fosphenytoin) is the most commonly used drug for long-term seizure control, except in patients with a history of primary generalized epilepsy, where valproate is better.

- Phenytoin: IV phenytoin is a nonsedating ASD with a recommended loading dose of 15 to 20 mg/kg at the rate up to 50 mg/min. Hypotension, cardiac dysrhythmias, and venous thrombophlebitis preclude a quicker rate of administration. Propylene glycol, which is used to solubilize phenytoin, is implicated in cardiovascular side effects.
- Fosphenytoin: Fosphenytoin is the water-soluble prodrug that is rapidly converted to phenytoin. As propylene glycol is not required to solubilize the drug, cardiovascular side effects and thrombophlebitis are less frequent than with phenytoin. A quicker infusion rate of up to 150 mg/min is possible. Even though drug absorption may be erratic in patients with active convulsions, IM injections can be given if IV access is not available.
- Valproate: IV valproate is another nonsedating ASD that is useful in several types of seizures. It can be used for long-term seizure control instead of phenytoin. A typical loading dose is 20 to 40 mg/kg followed by an infusion of 1 to 3 mg/kg/h. Higher doses may be required in patients who are on enzyme-inducing drugs, such as phenytoin. A systematic review of five randomized trials concluded that valproic acid may be at least as effective as phenytoin and is probably better tolerated.<sup>15</sup> A systematic review of IV valproate use in SE reported an overall response rate of around 70% with a low incidence of adverse effects.<sup>16</sup> Prolonged use of high doses of valproate can cause hyperammonemia, acute encephalopathy, and pancreatic toxicity.<sup>16</sup>
- Levetiracetam: There is a growing body of evidence suggesting that levetiracetam may be effective as the first-line

drug in benzodiazepine-resistant SE. A meta-analysis of 22 studies concluded that its efficacy to terminate benzodiazepine-resistant CSE is nearly 70%, which is comparable to that of phenobarbital and valproate.<sup>17</sup> A small randomized study reported similar efficacy of levetiracetam and lorazepam in stopping CSE, as well as similar 24-hour seizure freedom.<sup>18</sup> The ongoing multicentric Established Status Epilepticus Treatment Trial (ESETT), which is designed to find out the most effective and/or least effective drug among valproate, levetiracetam, and fosphenytoin in patients with benzodiazepine-resistant SE may be able to guide treatment decisions in the future.<sup>19</sup> The results of this trial are expected by the end of 2019. There are wide variations in the reported initial dose of IV levetiracetam in SE, ranging from 20 mg/kg to 60 mg/kg (maximum 4,500 mg).

There are many other drugs that are used as second or third-line therapy for SE.

- Phenobarbital: The Veterans Affairs Status Epilepticus Cooperative Study Group found a comparable rate of seizure control with phenobarbital and lorazepam.<sup>10</sup> The initial dose of IV phenobarbital is 15 to 20 mg/kg, which is given as a slow infusion at 25 to 60 mg/min. However, phenobarbital is not popular as the first-choice therapy in adults because of complications such as excessive sedation, hypotension, immunosuppression, reduced gastrointestinal motility, and blunting of respiration.
- Lacosamide: Lacosamide is commonly used for the treatment of focal epilepsy.<sup>20</sup> Recent evidence suggests that its efficacy and safety in SE are similar to that of other drugs commonly used for the treatment of SE.<sup>21,22</sup> IV lacosamide is administered at a typical dose of 200 to 400 mg/day. An important side effect is dose-dependent prolongation of PR interval, so it is contraindicated in the presence of heart blocks and significant dysrhythmias.<sup>23</sup>
- Topiramate: Topiramate is a broad-spectrum oral ASD administered up to 1,600 mg/day. The efficacy of topiramate in treating SE is not established in large studies. Most of the evidence is derived from small nonrandomized studies and case reports.<sup>24-28</sup> Metabolic acidosis is commonly seen after topiramate therapy, so concurrent administration with propofol is not recommended.

### Postictal Management

Patients with CSE have a variable course with treatment. CSE engenders major physiological changes with the potential for severe morbidity and even mortality. Despite optimum treatment, some patients may develop RSE, NCSE, or other types of electrographic seizures. However, most patients begin to recover consciousness after 10 to 20 minutes. Postictal period begins when seizure ends and lasts till the time the patient returns to neurological baseline.

Postictal management begins with a full neurologic examination and additional laboratory or imaging studies. Rest of the postictal management is based on complications or co-existing medical conditions such as dyselectrolytemia,

arrhythmia, circulatory disturbances, infection, or long-term disability. If the patient is intubated, ventilatory parameters should be optimized.

In many instances, the differentiation between ongoing seizure (ictus) and postictal confusion is not straightforward. This is particularly true for complex partial SE and NCSE where patients may have a lot of cognitive, behavioral, and sensorineural impairments in the postictal stage. Routine EEG readings may provide useful adjunctive information, but are not always helpful because ictal discharges arising from deep brain structures may not be recorded by the scalp electrodes.<sup>29</sup> Furthermore, several types of epileptiform EEG discharges are similar in both ictal and postictal states.<sup>30</sup> For practical purposes, most of these clinical decisions are based on careful behavioral observation.

## Management of Refractory Convulsive Status Epilepticus

There is no common consensus for the management of RSE and the choice of pharmacotherapy may differ between institutes. Midazolam, propofol, and thiopental (or pentobarbital) infusions are most commonly used drugs in RSE. All three drugs modulate gamma-aminobutyric (GABA<sub>A</sub>) receptors in different ways. With prolonged seizure activity in RSE, GABAergic mechanisms fail, pharmacoresistance increases, and seizure becomes self-sustaining and difficult to interrupt.<sup>31</sup> Thus, it is important to implement aggressive therapy of “third-line” agents to promptly terminate RSE. A systematic review comparing these three drugs in RSE found that pentobarbital was associated with a lower frequency of short-term treatment failure, but there was no mortality benefit with one drug compared with another.<sup>32</sup> High-intensity therapy to induce therapeutic coma entails several side effects, so maintenance of hemodynamic parameters, metabolic profile, and other organ-system support is crucial. Continuous EEG (cEEG) monitoring is extremely useful to titrate drug doses to electrographic seizure suppression and to assess the effectiveness of treatment, even though there is a lot of controversy in EEG end-point for RSE treatment. Nearly 15% patients with convulsive RSE may continue to have NCSE with non-specific signs even after active convulsions have ceased.<sup>33</sup> EEG monitoring during aggressive management is essential in picking up such cases. There is no agreement on when to stop drug infusion, but ASD infusions are generally continued for 24 to 48 hours of clinical and electrographic seizure control, and then gradually tapered over the next 24 hours with cEEG guidance.

### Pharmacotherapy

- **Midazolam:** Midazolam is usually the first-line drug for RSE. It is a rapidly acting benzodiazepine administered as an IV bolus of 0.1 to 0.2 mg/kg. Additional boluses can be given every 5 minutes. Midazolam infusion can be started at a low dose of 0.1 mg/kg/h and gradually increased up to 2 mg/kg/h. Intubation and mechanical ventilation are usually required when midazolam infusion is started.

Hypotension occurs in up to 50% of patients on high doses of midazolam.<sup>34</sup> Tachyphylaxis is another common problem after 24 to 48 hours that often necessitates continuous dose escalation of midazolam.<sup>35</sup>

- **Propofol:** Propofol is a potent IV anesthetic that is loaded in a dose of 1 to 2 mg/kg and maintained at 2 to 5 mg/kg/h. High doses (>5–10 mg/kg/h) may be required in RSE, which can cause severe hypotension requiring vasopressors. A small study found that propofol controls RSE more rapidly than high-dose barbiturates.<sup>36</sup> A retrospective case series in adults with RSE reported successful termination of 67% seizure episodes with propofol.<sup>37</sup> A recent meta-analysis of seven studies that compared propofol and barbiturates for controlling RSE found that propofol shortened the average seizure control time but there was no difference in case fatality rate or the incidence of hypotension.<sup>38</sup> Use of high doses of propofol for prolonged periods (>48 hours) should be avoided because of the risk of propofol infusion syndrome. Careful monitoring of serum lactate, triglycerides, and creatine kinase is required if prolonged propofol infusion is planned.
- **Thiopental (or pentobarbital in some countries):** Thiopental and its metabolite, pentobarbital, are potent ASDs. Thiopental is administered as a loading dose of 2 to 5 mg/kg followed by a continuous infusion of 1 to 5 mg/kg/h. It is useful in RSE because in addition to modulating GABA<sub>A</sub>, it is also an N-methyl-D-aspartate (NMDA) antagonist.<sup>39</sup> High doses of barbiturates almost always terminate seizures. A retrospective study found that over 90% patients with RSE had seizure control with pentobarbital, even though nearly half of them had seizure recurrence after drug weaning. Extremely long elimination time, drug accumulation and subsequent cardiovascular depression, metabolic complications, and infection are major problems with prolonged infusions of thiopental/pentobarbital. Other notable adverse effects include ileus and lingual edema.
- **Clobazam:** Clobazam is a long-acting oral ASD, which causes less sedation compared with other benzodiazepines. The drug is usually well-tolerated and may be useful as an adjunctive therapy for RSE.<sup>40</sup> A recent systematic review concluded that even though there is insufficient evidence to determine the long-term safety and efficacy of clobazam in SE, it may be considered as an add-on drug in dosages of 10 to 60 mg/day.<sup>41</sup>

## Management of Super-Refractory Status Epilepticus

Several other drugs or treatment modalities have been described for RSE and SRSE. Some of these are experimental, others have an established place in the management of SRSE.

- **Ketamine:** With continued seizure activity, many ASDs such as benzodiazepines and barbiturates that act through the GABAergic system lose their activity. Ketamine decreases excitatory glutamate activity by NMDA receptor antagonism and has been found to be useful

in patients with SRSE. Evidence supporting its use has been mainly derived from case reports and small prospective and retrospective studies.<sup>42-44</sup> A retrospective study found that the response to ketamine therapy in SRSE is probably best when instituted early in the course of treatment.<sup>45</sup> Another small retrospective study found that treatment of adults with SRSE leads to resolution of status in nearly 60% cases.<sup>43</sup> No consensus exists on the dosing protocol of ketamine for SRSE. A typical loading dose is 1 to 2 mg/kg IV followed by an infusion of 2 to 7.5 mg/kg/h.

- **Neurosteroids:** Allopregnanolone and allotetrahydrocorticosterone are endogenous metabolites of steroid hormones that cause allosteric modulation of GABA<sub>A</sub> receptors. In animal models, they have been found to potentiate GABA<sub>A</sub> receptor currents in low concentrations and directly activate the receptor in high doses, with the potential to confer protection from refractory forms of seizure.<sup>46</sup> There are only a few published human studies examining the safety and efficacy of neurosteroids in the management of SRSE. Brexanolone is an aqueous formulation of allopregnanolone that has been evaluated in a few studies. A cohort study of 25 patients who received brexanolone as an adjunctive therapy to anesthetic third-line agent found that over 70% patients were successfully weaned off the third-line agent within 5 days of starting brexanolone without the need to restart the anesthetic drug in the following 24 hours.<sup>47</sup> However, initial enthusiasm has dampened after the preliminary results of the first randomized trial on brexanolone use in SRSE failed to show any difference in treatment outcome compared with placebo.<sup>48</sup>
- **Immunomodulatory therapy:** Early administration of immunomodulatory therapies such as immunosuppressants, IV immunoglobulins (IVIG), and plasma exchange may be useful in autoimmune or inflammatory pathologies. If the clinical presentation of RSE suggests a possible autoimmune syndrome, immunomodulatory therapy can be started at the onset. However, large studies are lacking. A recently published systematic review concluded that based on current evidence, the routine use of IVIG in adult RSE cannot be recommended at this time.<sup>49</sup>
- **Ketogenic diet:** Early induction of ketosis is a novel strategy to treat SRSE. A ketogenic diet is a high fat, low carbohydrate, and adequate protein diet aimed to alter the primary source of cerebral metabolism from glucose to ketone bodies. Although the precise antiepileptic mechanisms of ketogenic diet are not clear, it is believed to exert neuroprotective, antioxidant, and anti-inflammatory effects against diverse types of cellular injuries.<sup>50</sup> Most of the early evidence for the use of ketogenic diet in SRSE was derived from isolated case reports and small case series.<sup>51,52</sup> A retrospective review of 10 adults with SRSE found resolution of seizure in nine patients within 3 days of initiating ketogenic diet.<sup>53</sup> A prospective multicenter

study that enrolled 15 patients with SRSE reported seizure cessation in 70% patients with ketogenic diet treatment.<sup>54</sup> Hypertriglyceridemia, hyponatremia, acidosis, and episodes of hypoglycemia frequently complicate the successful implementation of ketogenic diet regimen.

- **Inhalational anesthetics:** Isoflurane and less commonly, desflurane, have been described for the treatment of SRSE.<sup>55,56</sup> There are several problems associated with the use of volatile anesthetics such as hypotension and frequent relapse of seizures upon termination of the anesthetic. There are also concerns of direct neurotoxicity with the use of high doses of isoflurane.<sup>57</sup> Additionally, there are logistical problems as standard intensive care unit ventilators cannot deliver volatile anesthetics.
- **Hypothermia:** The Hypothermia for Neuroprotection in Convulsive Status Epilepticus (HYBERNATUS) trial, which was a large multicentric study evaluating the effect of induced hypothermia on neurologic outcomes in 268 critically ill patients with CSE, found that hypothermia did not confer any neuroprotection and was not useful as a treatment modality.<sup>58</sup>
- **Surgery:** Most of the patients eligible for surgery have documented structural lesions on imaging. Different types of surgeries for SRSE such as focal cortical resection, anatomic and functional hemispherectomy, multiple subpial transection, corpus callosotomy, and vagal nerve stimulator implantation have been described.<sup>59-62</sup> Clear guidelines on the timing and type of surgery for SRSE do not exist. Surgery is generally a therapeutic option at experienced epilepsy centers in only small subset of patients with SRSE.
- **Miscellaneous:** Transcranial magnetic stimulation, lidocaine, verapamil, pregabalin, perampanel, magnesium, and electroconvulsive therapy have all been described in small studies and case reports.<sup>63-68</sup> Strong evidence for their routine use does not exist.

## Management of Nonconvulsive Status Epilepticus in Critically Ill

Non-convulsive status epilepticus is a diverse electroclinical entity with varied causes and protean manifestations. A detailed review of management of NCSE and its variants is beyond the scope of this review. Common etiologies in critically ill patients include subarachnoid hemorrhage, infection, stroke, trauma, space-occupying lesions, hypoxia, dyselectrolytemia, drug-intake/withdrawal, and metabolic derangements. Critically ill patients with NCSE may show altered consciousness or behavior, autonomic and hemodynamic disturbances, and dip in sensorium. Pharmacotherapy for NCSE is extremely heterogeneous compared with CSE, where protocol-based algorithms are available. Quite often, NCSE goes unrecognized leading to diagnostic and treatment delays. Most of the literature on NCSE is available for patients who are critically ill or NCSE following CSE. A brief outline is presented here.

## Emergent Management

Emergent management of NCSE begins with stabilization of the airway, breathing, and circulation, and prompt neurological assessment to identify the cause of seizure. Early cEEG monitoring is indicated to guide further therapy. The initial pharmacologic therapy for NCSE consists of a rapidly acting IV benzodiazepine in conjunction with a nonbenzodiazepine ASD. Drug dosages used for emergent therapy in NCSE are similar to those in CSE. Common choices are lorazepam followed by phenytoin, fosphenytoin, valproate, levetiracetam, or lacosamide. Large studies assessing the efficacy of one drug over another in NCSE are lacking and most of the treatment modalities are extrapolated from studies in CSE.

Considerable controversy exists over how aggressively to approach NCSE, and how appropriately to apply cEEG findings to patient management. There are proponents of both aggressive and less-aggressive therapy. Studies have found that NCSE after intracerebral hemorrhage can cause brain hypoxia, rise in intracranial pressure, and even increase in midline shift and hematoma size.<sup>69,70</sup> There are also suggestions that nonconvulsive seizure duration and delay in diagnosis are independent predictors of increased mortality.<sup>71</sup> In contrast, there are also studies indicating that aggressive pharmacotherapy for NCSE may be detrimental. A small prospective study in elderly critically ill patients with NCSE found that treatment with higher number or greater doses of drugs did not improve outcome and that treatment with IV benzodiazepines was associated with increased mortality.<sup>72</sup> Another retrospective study in patients with NCSE concluded that mortality depends on severe mental state alteration, underlying etiology and acute complications, but not on the type of EEG discharge.<sup>73</sup>

## Management of Refractory NCSE

Most of the data regarding drug efficacy and safety in refractory NCSE are extrapolated from studies in refractory CSE. A typical approach in refractory NCSE is to administer IV drugs that were not used in the initial phase. These may include phenytoin, fosphenytoin, valproate, lacosamide, and levetiracetam. Several oral antiepileptics have also been found to confer some benefit in refractory NCSE. In a small retrospective study, perampanel, which is the first antiepileptic in the category of selective noncompetitive antagonist of  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, was found to be beneficial for NCSE termination.<sup>74</sup> Other oral choices include topiramate, pregabalin, oxcarbazepine, and clobazam. Institution of therapeutic coma with anesthetics is less commonly practiced for refractory NCSE. If required, common options include continuous infusions of midazolam, propofol, and thiopental (or pentobarbital).

NCSE is a common entity in neurocritical care units and yet, compared with CSE, very little information exists. NCSE carries a similar or probably even worse prognosis compared with CSE.<sup>10,33</sup> Mortality rate in critically ill patients with NCSE exceeds 30%.<sup>75</sup>

## Conclusion

Despite considerable progress in the identification and treatment of SE, it remains a common neurologic problem with high morbidity and mortality. A lot of heterogeneity in treatment approach exists among physicians managing these patients. Future research is needed to ascertain the efficacy of second-line and third-line ASDs as well as the impact of add-on therapy for CSE. There is a clear dearth of adequately powered studies evaluating pharmacotherapy for NCSE. Optimal pharmacotherapy as well as the effect of immunomodulatory compounds and nonpharmacological modalities, drug escalation/de-escalation, and the impact of extended EEG monitoring for refractory cases is still unclear. Continuous EEG monitoring is a cumbersome procedure; availability of dry EEG devices that can be applied without a trained technician can be useful for both clinical and research work.

### Conflict of Interest

None declared.

## References

- 1 Brodie MJ. Status epilepticus in adults. *Lancet* 1990;336(8714):551–552
- 2 Lowenstein DH, Bleck T, Macdonald RL. It's time to revise the definition of status epilepticus. *Epilepsia* 1999;40(1):120–122
- 3 Trinka E, Cock H, Hesdorffer D, et al. A definition and classification of status epilepticus—Report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia* 2015;56(10):1515–1523
- 4 Kantanen AM, Reinikainen M, Parviainen I, et al. Incidence and mortality of super-refractory status epilepticus in adults. *Epilepsy Behav* 2015;49:131–134
- 5 Hirsch LJ, Gaspard N, van Baalen A, et al. Proposed consensus definitions for new-onset refractory status epilepticus (NORSE), febrile infection-related epilepsy syndrome (FIREs), and related conditions. *Epilepsia* 2018;59(4):739–744
- 6 Brophy GM, Bell R, Claassen J, et al. Neurocritical Care Society Status Epilepticus Guideline Writing Committee. Guidelines for the evaluation and management of status epilepticus. *Neurocrit Care* 2012;17(1):3–23
- 7 Navarro V, Dagrón C, Elie C, et al. SAMUKeppra investigators. Prehospital treatment with levetiracetam plus clonazepam or placebo plus clonazepam in status epilepticus (SAMUKeppra): a randomised, double-blind, phase 3 trial. *Lancet Neurol* 2016;15(1):47–55
- 8 Alldredge BK, Gelb AM, Isaacs SM, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. *N Engl J Med* 2001;345(9):631–637
- 9 Sreenath TG, Gupta P, Sharma KK, Krishnamurthy S. Lorazepam versus diazepam-phenytoin combination in the treatment of convulsive status epilepticus in children: a randomized controlled trial. *Eur J Paediatr Neurol* 2010;14(2):162–168
- 10 Treiman DM, Meyers PD, Walton NY, et al. Veterans Affairs Status Epilepticus Cooperative Study Group. A comparison of four treatments for generalized convulsive status epilepticus. *N Engl J Med* 1998;339(12):792–798
- 11 Anderson M, Tambe P, Sammons H, Mulla H, Cole R, Choonara I. Pharmacokinetics of buccal and intranasal lorazepam in healthy adult volunteers. *Eur J Clin Pharmacol* 2012;68(2):155–159
- 12 Arya R, Gulati S, Kabra M, Sahu JK, Kalra V. Intranasal versus intravenous lorazepam for control of acute seizures in children: a randomized open-label study. *Epilepsia* 2011;52(4):788–793

- 13 Chamberlain JM, Okada P, Holsti M, et al. Pediatric Emergency Care Applied Research Network (PECARN). Lorazepam vs diazepam for pediatric status epilepticus: a randomized clinical trial. *JAMA* 2014;311(16):1652–1660
- 14 Silbergleit R, Durkalski V, Lowenstein D, et al. NETT Investigators. Intramuscular versus intravenous therapy for prehospital status epilepticus. *N Engl J Med* 2012;366(7):591–600
- 15 Liu X, Wu Y, Chen Z, Ma M, Su L. A systematic review of randomized controlled trials on the therapeutic effect of intravenous sodium valproate in status epilepticus. *Int J Neurosci* 2012;122(6):277–283
- 16 Trinka E, Höfler J, Zerbs A, Brigo F. Efficacy and safety of intravenous valproate for status epilepticus: a systematic review. *CNS Drugs* 2014;28(7):623–639
- 17 Yasiry Z, Shorvon SD. The relative effectiveness of five antiepileptic drugs in treatment of benzodiazepine-resistant convulsive status epilepticus: a meta-analysis of published studies. *Seizure* 2014;23(3):167–174
- 18 Misra UK, Kalita J, Maurya PK. Levetiracetam versus lorazepam in status epilepticus: a randomized, open labeled pilot study. *J Neurol* 2012;259(4):645–648
- 19 Cock HR; ESETT Group. Established status epilepticus treatment trial (ESETT) *Epilepsia* 2011;52(Suppl 8):50–52
- 20 Ben-Menachem E. Lacosamide: an investigational drug for adjunctive treatment of partial-onset seizures. *Drugs Today (Barc)* 2008;44(1):35–40
- 21 Kellinghaus C, Berning S, Immisch I, et al. Intravenous lacosamide for treatment of status epilepticus. *Acta Neurol Scand* 2011;123(2):137–141
- 22 Höfler J, Unterberger I, Dobesberger J, Kuchukhidze G, Walser G, Trinka E. Intravenous lacosamide in status epilepticus and seizure clusters. *Epilepsia* 2011;52(10):e148–e152
- 23 Krause LU, Brodowski KO, Kellinghaus C. Atrioventricular block following lacosamide intoxication. *Epilepsy Behav* 2011;20(4):725–727
- 24 Reuber M, Evans J, Bamford JM. Topiramate in drug-resistant complex partial status epilepticus. *Eur J Neurol* 2002;9(1):111–112
- 25 Bensalem MK, Fakhoury TA. Topiramate and status epilepticus: report of three cases. *Epilepsy Behav* 2003;4(6):757–760
- 26 Hottinger A, Sutter R, Marsch S, Rüegg S. Topiramate as an adjunctive treatment in patients with refractory status epilepticus: an observational cohort study. *CNS Drugs* 2012;26(9):761–772
- 27 Asadi-Pooya AA, Jahromi MJ, Izadi S, Emami Y. Treatment of refractory generalized convulsive status epilepticus with enteral topiramate in resource limited settings. *Seizure* 2015;24:114–117
- 28 Stojanova V, Rossetti AO. Oral topiramate as an add-on treatment for refractory status epilepticus. *Acta Neurol Scand* 2012;125(2):e7–e11
- 29 Block A, Fisher RS. Can patients perform volitional motor acts at the start of a seizure? *J Clin Neurophysiol* 1999;16(2):141–145
- 30 Kaibara M, Blume WT. The postictal electroencephalogram. *Electroencephalogr Clin Neurophysiol* 1988;70(2):99–104
- 31 Naylor DE, Liu H, Wasterlain CG. Trafficking of GABA(A) receptors, loss of inhibition, and a mechanism for pharmacoresistance in status epilepticus. *J Neurosci* 2005;25(34):7724–7733
- 32 Claassen J, Hirsch LJ, Emerson RG, Mayer SA. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. *Epilepsia* 2002;43(2):146–153
- 33 DeLorenzo RJ, Waterhouse EJ, Towne AR, et al. Persistent non-convulsive status epilepticus after the control of convulsive status epilepticus. *Epilepsia* 1998;39(8):833–840
- 34 Fernandez A, Lantigua H, Lesch C, et al. High-dose midazolam infusion for refractory status epilepticus. *Neurology* 2014;82(4):359–365
- 35 Claassen J, Hirsch LJ, Emerson RG, Bates JE, Thompson TB, Mayer SA. Continuous EEG monitoring and midazolam infusion for refractory nonconvulsive status epilepticus. *Neurology* 2001;57(6):1036–1042
- 36 Stecker MM, Kramer TH, Raps EC, O'Meeghan R, Dulaney E, Skaar DJ. Treatment of refractory status epilepticus with propofol: clinical and pharmacokinetic findings. *Epilepsia* 1998;39(1):18–26
- 37 Rossetti AO, Reichhart MD, Schaller MD, Despland PA, Bogousslavsky J. Propofol treatment of refractory status epilepticus: a study of 31 episodes. *Epilepsia* 2004;45(7):757–763
- 38 Zhang Q, Yu Y, Lu Y, Yue H. Systematic review and meta-analysis of propofol versus barbiturates for controlling refractory status epilepticus. *BMC Neurol* 2019;19(1):55
- 39 Zhan R-Z, Qi S, Wu C, Fujihara H, Taga K, Shimoji K. Intravenous anesthetics differentially reduce neurotransmission damage caused by oxygen-glucose deprivation in rat hippocampal slices in correlation with N-methyl-D-aspartate receptor inhibition. *Crit Care Med* 2001;29(4):808–813
- 40 Sivakumar S, Ibrahim M, Parker D Jr, Norris G, Shah A, Mohamed W. Clobazam: an effective add-on therapy in refractory status epilepticus. *Epilepsia* 2015;56(6):e83–e89
- 41 Mahmoud SH, Rans C. Systematic review of clobazam use in patients with status epilepticus. *Epilepsia Open* 2018;3(3):323–330
- 42 Kramer AH. Early ketamine to treat refractory status epilepticus. *Neurocrit Care* 2012;16(2):299–305
- 43 Höfler J, Rohrer A, Kalss G, et al. (S)-ketamine in refractory and super-refractory status epilepticus: a retrospective study. *CNS Drugs* 2016;30(9):869–876
- 44 Synowiec AS, Singh DS, Yenugadhathi V, Valeriano JP, Schramke CJ, Kelly KM. Ketamine use in the treatment of refractory status epilepticus. *Epilepsy Res* 2013;105(1)(2):183–188
- 45 Gaspard N, Foreman B, Judd LM, et al. Intravenous ketamine for the treatment of refractory status epilepticus: a retrospective multicenter study. *Epilepsia* 2013;54(8):1498–1503
- 46 Kokate TG, Svensson BE, Rogawski MA. Anticonvulsant activity of neurosteroids: correlation with gamma-aminobutyric acid-evoked chloride current potentiation. *J Pharmacol Exp Ther* 1994;270(3):1223–1229
- 47 Rosenthal ES, Claassen J, Wainwright MS, et al. Brexanolone as adjunctive therapy in super-refractory status epilepticus. *Ann Neurol* 2017;82(3):342–352
- 48 Rosenthal E, Wainwright MA. Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus. 2019. Available at: <https://clinicaltrials.gov/ct2/show/study/NCT02477618>. Accessed September 4, 2019
- 49 Zeiler FA, Matuszczak M, Teitelbaum J, Kazina CJ, Gillman LM. Intravenous immunoglobulins for refractory status epilepticus, part I: A scoping systematic review of the adult literature. *Seizure* 2017;45:172–180
- 50 Gasior M, Rogawski MA, Hartman AL. Neuroprotective and disease-modifying effects of the ketogenic diet. *Behav Pharmacol* 2006;17(5-6):431–439
- 51 Lin JJ, Lin KL, Chan OW, Hsia SH, Wang HS; CHEESE Study Group. Intravenous ketogenic diet therapy for treatment of the acute stage of super-refractory status epilepticus in a pediatric patient. *Pediatr Neurol* 2015;52(4):442–445
- 52 Appavu B, Vanatta L, Condie J, Kerrigan JF, Jarrar R. Ketogenic diet treatment for pediatric super-refractory status epilepticus. *Seizure* 2016;41:62–65
- 53 Thakur KT, Probasco JC, Hocker SE, et al. Ketogenic diet for adults in super-refractory status epilepticus. *Neurology* 2014;82(8):665–670

- 54 Cervenka MC, Hocker S, Koenig M, et al. Phase I/II multicenter ketogenic diet study for adult superrefractory status epilepticus. *Neurology* 2017;88(10):938–943
- 55 Ikeda KM, Connors R, Lee DH, Khandji AG, Claassen J, Young GB. Isoflurane use in the treatment of super-refractory status epilepticus is associated with hippocampal changes on MRI. *Neurocrit Care* 2017;26(3):420–427
- 56 Mirsattari SM, Sharpe MD, Young GB. Treatment of refractory status epilepticus with inhalational anesthetic agents isoflurane and desflurane. *Arch Neurol* 2004;61(8):1254–1259
- 57 Fugate JE, Burns JD, Wijidicks EFM, Warner DO, Jankowski CJ, Rabinstein AA. Prolonged high-dose isoflurane for refractory status epilepticus: is it safe? *Anesth Analg* 2010;111(6):1520–1524
- 58 Legriel S, Lemiale V, Schenck M, et al. HYBERNATUS Study Group. Hypothermia for neuroprotection in convulsive status epilepticus. *N Engl J Med* 2016;375(25):2457–2467
- 59 Loddenkemper T, Cosmo G, Kotagal P, et al. Epilepsy surgery in children with electrical status epilepticus in sleep. *Neurosurgery* 2009;64(2):328–337
- 60 Botre A, Udani V, Desai N, Jagadish S, Sankhe M. Emergency surgery for refractory status epilepticus. *Indian Pediatr* 2017;54(8):678–680
- 61 Jeong A, Strahle J, Vellimana AK, Limbrick DD Jr, Smyth MD, Bertrand M. Hemispherotomy in children with electrical status epilepticus of sleep. *J Neurosurg Pediatr* 2017;19(1):56–62
- 62 Zeiler FA, Zeiler KJ, Teitelbaum J, Gillman LM, West M. VNS for refractory status epilepticus. *Epilepsy Res* 2015;112:100–113
- 63 Novy J, Rossetti AO. Oral pregabalin as an add-on treatment for status epilepticus. *Epilepsia* 2010;51(10):2207–2210
- 64 Dibué-Adjei M, Brigo F, Yamamoto T, Vonck K, Trinka E. Vagus nerve stimulation in refractory and super-refractory status epilepticus - a systematic review. *Brain Stimul* 2019;12(5):1101–1110
- 65 Yildiz B, Citak A, Uçsel R, Karaböcöoğlu M, Aydinli N, Uzel N. Lidocaine treatment in pediatric convulsive status epilepticus. *Pediatr Int* 2008;50(1):35–39
- 66 Arya R, Rotenberg A. Dietary, immunological, surgical, and other emerging treatments for pediatric refractory status epilepticus. *Seizure* 2019;68:89–96
- 67 Brigo F, Lattanzi S, Rohrer A, et al. Perampanel in the treatment of status epilepticus: a systematic review of the literature. *Epilepsy Behav* 2018;86:179–186
- 68 Ahmed J, Metrick M, Gilbert A, et al. Electroconvulsive therapy for super refractory status epilepticus. *J ECT* 2018;34(1):e5–e9
- 69 Claassen J, Perotte A, Albers D, et al. Nonconvulsive seizures after subarachnoid hemorrhage: multimodal detection and outcomes. *Ann Neurol* 2013;74(1):53–64
- 70 Vespa PM, O'Phelan K, Shah M, et al. Acute seizures after intracerebral hemorrhage: a factor in progressive midline shift and outcome. *Neurology* 2003;60(9):1441–1446
- 71 Young GB, Jordan KG, Doig GS. An assessment of nonconvulsive seizures in the intensive care unit using continuous EEG monitoring: an investigation of variables associated with mortality. *Neurology* 1996;47(1):83–89
- 72 Litt B, Wityk RJ, Hertz SH, et al. Nonconvulsive status epilepticus in the critically ill elderly. *Epilepsia* 1998;39(11):1194–1202
- 73 Shneker BF, Fountain NB. Assessment of acute morbidity and mortality in nonconvulsive status epilepticus. *Neurology* 2003;61(8):1066–1073
- 74 Redecker J, Wittstock M, Benecke R, Rösche J. Efficacy of perampanel in refractory nonconvulsive status epilepticus and simple partial status epilepticus. *Epilepsy Behav* 2015;45:176–179
- 75 Laccheo I, Sonmez Turk H, Bhatt AB, et al. Non-convulsive status epilepticus and non-convulsive seizures in neurological ICU patients. *Neurocrit Care* 2015;22(2):202–211