

# Guidelines for the Evaluation and Management of Status Epilepticus

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**Abstract** Status epilepticus (SE) treatment strategies vary substantially from one institution to another due to the lack of data to support one treatment over another. To provide guidance for the acute treatment of SE in critically ill patients, the Neurocritical Care Society organized a writing committee to evaluate the literature and develop an evidence-based and expert consensus practice guideline. Literature searches were conducted using PubMed and studies meeting the criteria established by the writing committee were evaluated. Recommendations were developed based on the literature using standardized assessment methods from the American Heart Association and Grading of Recommendations Assessment, Development, and Evaluation systems, as well as expert opinion when sufficient data were lacking.

**Keywords** Status epilepticus · Seizure · Guideline · EEG · Antiepileptic treatment

## Introduction

Status epilepticus (SE) requires emergent, targeted treatment to reduce patient morbidity and mortality. Controversies about how and when to treat SE have been described in the literature [1–3]. The Neurocritical Care Society Status Epilepticus Guideline Writing Committee was established in 2008 to develop evidence-based expert consensus guidelines for diagnosing and managing SE. Co-chairs were selected by the Neurocritical Care Society, with ten additional neurointensivists and epileptologists from across the United States included on the committee. After the committee prepared an initial set of guidelines

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based on literature review and committee consensus, recommendations were reviewed by a group of external experts in SE management, whose comments were incorporated into the final document.

These guidelines were developed to address evaluation and management of SE in critically ill adults and children and will not address the management of SE in neonates. These guidelines will specifically describe SE definitions and classification, etiology, diagnostic evaluation, prognosis, treatment, monitoring, and future directions. Principles discussed will apply to both adults and children, unless specifically noted.

## Methodology

A PubMed/Medline literature search was performed for relevant articles published through August 2011, using the following search terms: status epilepticus, refractory seizures, and nonconvulsive status epilepticus plus individual seizure treatments, including standard medications and other anticonvulsive therapies (e.g., cooling and ketogenic diet). The search was limited to articles describing human subjects that were published in the English language. Clinical trials, meta-analyses, review articles, and practice guidelines were all eligible for inclusion. Studies describing treatment were limited to those that included at least 5 patients. Results were supplemented with literature recommended by the committee or identified from reference lists.

Articles selected for inclusion in the treatment recommendations underwent a review by the writing committee. Treatment recommendations were then assigned a level of evidence based on the American Heart Association statement and guideline development (Table 1) [4]. Diagnosis and management of SE were assigned a recommendation based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system [5]. The GRADE system offers two grades of recommendations:

“strong” and “weak.” Definitions for the quality of evidence are as follows:

- high quality—further research is very unlikely to change our confidence in the estimate of effect,
- moderate quality—further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate,
- low quality—further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate, and
- very low quality—any estimate of effect is very uncertain.

One advantage of the GRADE system is that a strong recommendation can be made using weak to moderate evidence based on these four factors:

- (1) Balance between desirable and undesirable effects if the effect is very desirable, a stronger recommendation is given.
- (2) Quality of evidence.
- (3) Values and preferences—if the values and preferences are similar, or there is greater certainty in them, then a stronger recommendation is given.
- (4) Costs (resource allocation)—lower costs of an intervention (e.g., the fewer the resources consumed) are linked to a higher likelihood that a strong recommendation is warranted.

All participants agreed with the recommendations presented in this guideline. Many management decisions lack prospective randomized controlled trials upon which SE treatment recommendations can be based. Therefore, we also present data obtained from previously published surveys [6] and a survey of an international panel of experts specifically conducted for the development of these guidelines. In addition, citations to several important review articles outside of the specified search criteria were included at the recommendation of external reviewers.

**Table 1** Evidence rating system based on American Heart Association/American College of Cardiology guidelines [4]

| Class category   | Level of evidence  |
|--|--|
| I Intervention is useful and effective. Treatment benefits clearly exceed risks  | A Adequate evidence is available from multiple, large, randomized clinical trials or meta-analyses   |
| IIa Evidence/expert opinion suggest intervention is useful/effective. Treatment benefits exceed risk   | B Limited evidence is available from less rigorous data, including fewer, smaller randomized trials, nonrandomized studies, and observational analyses |
| IIb Strength of evidence/expert opinion about intervention usefulness/effectiveness is less well established. More data are needed; however, using this treatment when warranted is not unreasonable | C Evidence relies on expert/consensus opinion, case reports, or standard of care   |
| III Intervention is not useful or effective and may be harmful. Benefit does not exceed risk   |  |

## Definition, Classification, and Evaluation of SE

For the purposes of these guidelines, SE was defined as 5 min or more of (i) continuous clinical and/or electrographic seizure activity or (ii) recurrent seizure activity without recovery (returning to baseline) between seizures. This definition was adopted for the following reasons:

- Most clinical and electrographic seizures last less than 5 min and seizures that last longer often do not stop spontaneously [7–10].
- Animal data suggest that permanent neuronal injury [11] and pharmacoresistance [12–14] may occur before the traditional definition of 30 min of continuous seizure activity have passed.
- More recently, experts have suggested a revised definition of SE which includes seizures lasting for 5 min or longer [8, 12, 15–19], although some controversy still remains [1, 20, 21].

As further evidence of the controversy in defining SE, some authors have labeled seizures lasting for at least 5 min as “impending status epilepticus,” [12] “early heralds of status,” or “early status epilepticus.” [22] The committee recognizes that the proposed 5-min definition will include some patients with prolonged seizures that would not meet traditional criteria for status epilepticus. However, this revised definition of SE builds on the recognition that emergent treatment is paramount in patients with prolonged seizure activity [12, 19].

Status epilepticus can be classified by semiology, duration and underlying etiology. For the purpose of these guidelines, we are focusing on convulsive, non-convulsive and refractory SE.

### Convulsive Status Epilepticus

- Defined as convulsions that are associated with rhythmic jerking of the extremities.
- Characteristic findings of generalized convulsive status epilepticus (GCSE):
  - Generalized tonic–clonic movements of the extremities
  - Mental status impairment (coma, lethargy, confusion)
  - May have focal neurological deficits in the post ictal period (e.g., Todd’s paralysis, a temporary neurological deficit lasting hours to days following a seizure)
- Focal motor status epilepticus and *epilepsia partialis continua* are not included in this definition.

### Non-convulsive status epilepticus (NCSE)

- Defined as seizure activity seen on electroencephalogram (EEG) without clinical findings associated with GCSE.
- Two rather distinct phenotypes of NCSE have been described:
  - (1) the “wandering confused” patient presenting to the emergency department with a relatively good prognosis [24] or chronic epileptic syndromes [25] or,
  - (2) the acutely ill patient with severely impaired mental status, with or without subtle motor movements (e.g., rhythmic muscle twitches or tonic eye deviation that often occurs in the setting of acute brain injury) [15, 25–29]. This term has also been labeled as “subtle status” [12 30].
- For the purposes of these guidelines we will focus on the acutely ill patient with impaired mental status. This type of SE frequently follows uncontrolled GCSE and is often encountered in the intensive care setting.
- Semiological spectrum of non-convulsive seizures is highly variable [31, 32].
  - Negative symptoms include anorexia, aphasia/mutism, amnesia, catatonia, coma, confusion, lethargy, and staring.
  - Positive symptoms include agitation/aggression, automatisms, blinking, crying, delirium, delusions, echolalia, facial twitching, laughter, nausea/vomiting, nystagmus/eye deviation, perseveration, psychosis, and tremulousness.

### Refractory SE (RSE)

- Patients who do not respond to standard treatment regimens for status epilepticus are considered to be in RSE [32]. For the purposes of these guidelines, patients who continue to experience either clinical or electrographic seizures after receiving adequate doses of an initial benzodiazepine followed by a second acceptable antiepileptic drug (AED) will be considered refractory.
- Controversies exist regarding the definition of RSE, including:
  - The number of AEDs patients need to have failed. Most experts agree that patients should be considered in RSE after failure of adequately dosed initial benzodiazepine and one AED.
  - Duration of SE after initiation of treatment. Most experts no longer consider duration to be a criterion for classification of RSE.

**Table 2** Potential underlying etiology

## Acute processes [8, 12]

Metabolic disturbances: electrolyte abnormalities, hypoglycemia, renal failure  
 Sepsis  
 Central nervous system infection: meningitis, encephalitis, abscess  
 Stroke: ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, cerebral sinus thrombosis  
 Head trauma with or without epidural or subdural hematoma  
 Drug issues  
 Drug toxicity  
 Withdrawal from opioid, benzodiazepine, barbiturate, or alcohol  
 Non-compliance with AEDs  
 Hypoxia, cardiac arrest  
 Hypertensive encephalopathy, posterior reversible encephalopathy syndrome  
 Autoimmune encephalitis (i.e., anti-NMDA receptor antibodies, anti-VGKC complex antibodies), paraneoplastic syndromes

## Chronic processes

Preexisting epilepsy: breakthrough seizures or discontinuation of AEDs  
 Chronic ethanol abuse in setting of ethanol intoxication or withdrawal  
 CNS tumors  
 Remote CNS pathology (e.g., stroke, abscess, TBI, cortical dysplasia)  
 Special considerations in children  
 Acute symptomatic SE is more frequent in younger children with SE [33]  
 Prolonged febrile seizures are the most frequent cause of SE in children [34]  
 CNS infections, especially bacterial meningitis, inborn errors of metabolism, and ingestion are frequent causes of SE [34, 35]

AED antiepileptic drug; CNS central nervous system; NMDA N-methyl-D-aspartic acid; SE status epilepticus; TBI traumatic brain injury; VGKC voltage-gated potassium channel

**Table 3** Suggested diagnostic work-up [21]

The steps included in the diagnostic work-up should be completed as soon as possible and occur simultaneously and in parallel with treatment.

## All patients

1. Fingertick glucose
2. Monitor vital signs.
3. Head computed tomography (CT) scan (appropriate for most cases)
4. Order laboratory test: blood glucose, complete blood count, basic metabolic panel, calcium (total and ionized), magnesium, AED levels.
5. Continuous electroencephalograph (EEG) monitoring

## Consider based on clinical presentation

1. Brain magnetic resonance imaging (MRI)
2. Lumbar puncture (LP)
3. Comprehensive toxicology panel including toxins that frequently cause seizures (i.e. isoniazid, tricyclic antidepressants, theophylline, cocaine, sympathomimetics, alcohol, organophosphates, and cyclosporine)
4. Other laboratory tests: liver function tests, serial troponins, type and hold, coagulation studies, arterial blood gas, AED levels, toxicology screen (urine and blood), and inborn errors of metabolism

## AED antiepileptic drug

The etiology, diagnostic work-up, and prognosis for patients with SE are summarized in Tables 2, 3, and 4.

**Summary Recommendations for SE Definition and Classification**

1. SE should be defined as 5 min or more of continuous clinical and/or electrographic seizure activity or

- recurrent seizure activity without recovery between seizures (*strong recommendations, moderate quality*).
2. SE should be classified as either convulsive SE (convulsions that are associated with rhythmic jerking of the extremities) or non-convulsive SE (seizure activity seen on EEG without the clinical findings associated with convulsive SE) (*strong recommendation, high quality*).

**Table 4** Prognosis*Convulsive status epilepticus*

## Mortality

At hospital discharge: 9–21 % [19, 36–38]

At 30 days: 19–27 % [30, 39, 40]

At 90 days: 19 % [41]

Standardized 10-year mortality ratio: 2.8 in general population [42]

In children, the mortality ranges from 3 to 11 % in retrospective series [43]. In a prospective study, the mortality was 3 % [34]

## Morbidity

Severe neurological or cognitive sequelae: 11–16 % [19, 44–46]

Deterioration in functional status 23–26 % [19, 36, 38]

At 90 days after SE, 39 % had marked functional impairment (glasgow outcome scale score 2–4) and 43 % had good recovery (glasgow outcome scale score 5) [41]

## Factors associated with poor outcome after GCSE

Underlying etiology, de novo development of SE in hospitalized patients, older age, impairment of consciousness, duration of seizures, at onset focal neurological signs, and the presence of medical complications [36, 37, 40, 41, 47–49]

Mortality rate is higher (61 %) when SE develops de novo in hospitalized patients [49]

In patients with adequate therapy, the mortality rate may be as low as 8 % while it may be as high as 45 % in those with insufficient therapy (insufficient dose given, wrong route of administration, unnecessary delay between treatments, inadequate ventilation, medical complications, or lack of EEG monitoring to guide treatment) [47]. Adherence to a treatment protocol was associated with better seizure control and shorter ICU and hospital length of stay [50]

*Nonconvulsive status epilepticus*

## Mortality

At hospital discharge: 18–52 % [51–53]

At 30 days: 65 % [30]

## Factors associated with poor outcome after NCSE:

Underlying etiology, severe mental status impairment, longer seizure duration [28, 51, 53, 54]

For patients diagnosed within 30 min of seizure onset, mortality was 36 % compared with 75 % for those patients diagnosed  $\geq$ 24 h after seizure onset seizures [51]

Patients with NCSE treated and resolved within 10 h had 10 % mortality vs. 85 % mortality if seizures continued longer than 20 h [51]

Mortality at hospital discharge in NCSE was 27 % vs. 3 % comparing patients with vs. without known acute medical cause [53]

*Refractory status epilepticus*

## Mortality

At hospital discharge: 23–61 % [26–28, 38, 55–67]

At 3 months: 39 % in RCT comparing propofol with barbiturate infusions [68]

In children with RSE, the mortality rate was very low [69] to 32 % [70], but greatest in those with acute symptomatic SE [70, 71]

In a meta-analysis of RSE in children, the mortality rate was 20 % in symptomatic SE and 4 % in idiopathic SE [72]

## Morbidity

Return to functional baseline is more likely for SE patients than for RSE patients [66] and was seen in 39 % of RSE patients at 3 months [68].

At hospital discharge among 13 survivors: 23 % vegetative state, 62 % severely disabled, 15 % independent but moderately disabled [28, 73]. Post-SE epilepsy may be seen more frequently in long-term survivors with RSE than in those with non-refractory SE (88 % vs. 22 %) [65]

In children with RSE, a new deficit occurred in 36 and 32 % returned to baseline [70]. Motor and visual deficits may be seen at 1 year after SE [69]. However, no child with acute symptomatic RSE returned to baseline [71] and the morbidity and mortality is highest in those with symptomatic SE or a progressive encephalopathy [34, 74]

## Factors associated with poor outcome after RSE:

Underlying etiology, older age (e.g., >50 years), long seizure duration, and high Acute Physiology and Chronic Health Evaluation-2 (APACHE-2) scale scores [51, 63, 67, 75]

Recently one study reported that after correcting for underlying etiology, coma, and type of SE seizure, duration was not associated with outcome [64]

*EEG* electroencephalogram; *GCSE* generalized convulsive status epilepticus; *NCSE* nonconvulsive status epilepticus; *ICU* intensive care unit; *RCT* randomized clinical trial; *RSE* refractory status epilepticus; *SE* status epilepticus

3. Refractory SE should be defined as SE that does not respond to the standard treatment regimens, such as an initial benzodiazepine followed by another AED (*strong recommendations, moderate quality*).
4. The etiology of SE should be diagnosed and treated as soon as possible (*strong recommendation, high quality*).

treatment strategy includes simultaneous assessment and management of airway, breathing, and circulation (obtain IV access, administer O<sub>2</sub>, and secure the airway as needed), seizure abortive drug treatment (i.e., benzodiazepine), screening for the underlying cause of SE, and immediate treatment of life-threatening causes of SE (e.g., meningitis, intracranial mass lesion).

The treatment of status epilepticus should include the appropriate elements of critical care as outlined in Table 5. Treatment of SE should mirror other resuscitation approaches with direct, close supervision of the patient by a treatment team including a physician and nurse. Elements

## Treatment of SE

The principal goal of treatment is to emergently stop both clinical and electrographic seizure activity. The initial

**Table 5** Critical care treatment outline for convulsive and non-convulsive SE that should be completed prior or upon arrival to the intensive care unit (Note: timing is merely a guide as all interventions should be done as soon as possible.)

| Critical care treatment   | Timing (minutes post seizure onset)          | Goals   | Rationale/references |
|---|--|---|----------------------|
| Non-invasive airway protection and gas exchange with head positioning     | Immediate (0–2 min)                          | Maintain airway patency, avoid snoring, administer O <sub>2</sub>   | [40, 76–79]          |
| Intubation (if airway/gas exchange compromised or elevated ICP suspected) | Immediate (0–10 min)                         | Establish secure oxygenation and ventilation  | Expert opinion       |
| Vital signs: O <sub>2</sub> saturation, BP, HR                            | Immediate (0–2 min)                          | Establish and support baseline vital signs  | [80–81]              |
| Vasopressor support of BP if SBP <90 mmHg or MAP <70                      | Immediate (5–15 min)                         | Support CPP   | Expert opinion       |
| Finger stick blood glucose  | Immediate (0–2 min)                          | Diagnose hypoglycemia   |                      |
| Peripheral IV access  | Immediate (0–5 min)                          | Establish medication route  | [80–82]              |
| 1. Emergent initial AED therapy (i.e. benzodiazepine)                     |  | 1. Stop seizure   |                      |
| 2. Fluid resuscitation  |  | 2. Establish euvoolemia   |                      |
| 3. Nutrient resuscitation (thiamine given before dextrose; dextrose)      |  | 3. Reverse thiamine deficiency, treat hypoglycemia  |                      |
| Urgent SE control therapy with AED  | Immediate after initial AED given (5–10 min) | Stop seizure  | [80–82]              |
| Neurologic exam   | Urgent (5–10 min)                            | Evaluate for mass lesion, acute intracranial process  | Expert opinion       |
| Triage lab test panel (see Table 2)                                       | Immediate (5 min)                            | Diagnose life threatening metabolic condition   | Expert opinion       |
| Refractory SE treatment   | Urgent (20–60 min after 2nd AED)             | Stop seizures; treatment strategies based on individual patient response and AED concentrations (if applicable) | Expert opinion       |
| Urinary catheter  | Urgent (0–60 min)                            | Evaluate systemic circulation   | Expert opinion       |
| Continuous EEG  | Urgent (15–60 min)                           | Evaluate for NCSE if not waking up after clinically obvious seizures cease                                      | [50, 73, 75]         |
| Diagnostic testing (selection depends on clinical presentation)           | Urgent (0–60 min)                            | Evaluate for mass lesions, meningitis, encephalitis   | Expert opinion       |
| CT  |  |   |                      |
| LP  |  |   |                      |
| MRI   |  |   |                      |
| Intracranial pressure monitoring (depending on clinical presentation)     | Urgent (0–60 min of imaging diagnosis)       | Measure and control ICP   | Expert opinion       |

AED antiepileptic drug; BP blood pressure; CPP cerebral perfusion pressure; CT computed tomography; EEG electroencephalogram; HR heart rate; ICP intracranial pressure; LP lumbar puncture; MAP mean arterial pressure; MRI magnetic resonance imaging; SBP systolic blood pressure

of resuscitation including airway protection, hemodynamic resuscitation, and intravenous access are outlined. Airway protection may be facilitated by careful noninvasive methods initially, but early intubation is advisable if continuous intravenous AEDs are necessary. Further treatment should then be guided by the diagnostic workup, as discussed earlier.

Once it is determined that SE is under control and vital signs are stable, specific diagnostic studies can be performed. These diagnostic studies are selected depending on the patient's history and physical examination. Not every diagnostic study is required in every patient. For example, a lumbar puncture is generally needed if there is any suspicion of a central nervous system (CNS) infection, but may not be required if meningitis is not suspected, particularly in patients with AED non-compliance. If the patient is currently treated with AEDs, a drug level should be checked and history obtained regarding compliance. A comprehensive toxicology screen should be obtained, if there is no clear etiology for SE. Specific toxicology testing should be performed if the history or physical examination suggests a specific toxin. Additional critical care management may apply to those patients with suspected elevated intracranial pressure and/or mass effect.

The treatment of SE, by convention, occurs in stages. Traditionally, these stages have been termed 1st, 2nd, 3rd, and 4th line, which do not reflect the emergent need for SE control. Therefore, these guidelines have revised the traditional SE treatment paradigm to emergent initial therapy, urgent control therapy, and refractory therapy. SE patients refractory to initial therapy may be best treated in experienced, high volume centers.

Definitive control of SE should be established within 60 min of onset. All patients presenting with SE will need emergent initial AED therapy (i.e., 1st line) and urgent control AED therapy (i.e., 2nd line) in addition to AED maintenance therapy, even if SE is immediately controlled. By definition, refractory SE therapy (i.e., 3rd and 4th line) is reserved for those failing the first 2 AEDs administered. If SE is caused by a metabolic disorder (e.g., hypoglycemia), the underlying metabolic disorder should be corrected, in which case maintenance therapy may or may not be necessary.

Outlined below is a heuristic treatment approach for SE. Due to the paucity of controlled clinical trial data regarding the treatment of SE, the writing committee surveyed a select group of international SE experts to supplement the treatment recommendations presented in these guidelines. The specific details of this survey will be published separately. It should be recognized that although the treatment is given in stages, treatment is a continuum and urgent cessation of seizure activity is the goal in each stage.

## Emergent Initial Therapy

Although multiple AEDs have been studied as first line therapy for SE, evidence supports and experts agree that benzodiazepines should be the agent of choice for emergent initial treatment. When skilled health care personnel are available, intravenous (IV) administration is preferred. However, benzodiazepines can be administered via intramuscular (IM), rectal, nasal, or buccal routes when IV therapy is not feasible. For IV therapy, lorazepam is the preferred agent; midazolam is preferred for IM therapy (and can also be given nasally or buccally); and diazepam is preferred for rectal administration (Table 6). Controlled studies have evaluated lorazepam versus diazepam, phenobarbital, phenytoin, and IM midazolam, [19, 30, 83, 84]. IM midazolam was found to be at least as effective as IV lorazepam in prehospitalized patients with SE [84]. While there may be concerns about administering benzodiazepines to non-intubated patients, this may be less relevant in patients diagnosed with non-convulsive status epilepticus in the context of a neurological injury, who may already be intubated or require intubation. Clonazepam has also been studied for the treatment of SE, but it is infrequently used in the United States due to lack of an IV formulation [85, 86].

Supportive treatment should be provided as suggested in Table 5 as rapid administration of benzodiazepines can cause respiratory depression and hypotension. However, in a randomized, controlled trial, respiratory depression was seen less frequently in those treated with benzodiazepines for GCSE than for those who received placebo [19].

Dosing recommendations and considerations of all AED treatment medications are outlined in Table 7. Please note that controlled trials are not available to define the optimal dosage ranges for the treatment of SE; therefore, all AED doses were based on observational data and expert opinion. Doses used in clinical practice may be higher than those listed in the tables and should be titrated according to clinical and EEG findings. Furthermore, infusions with phenytoin and fosphenytoin should occur with cardiac monitoring, due to increased risk for QT prolongation and arrhythmias [170].

## Urgent Control Therapy

Urgent control AED treatment following administration of short acting benzodiazepines is required in all patients who present with SE, unless the immediate cause of SE is known and definitively corrected (e.g., severe hypoglycemia). There are two potential goals of urgent control therapy. For patients who respond to emergent initial therapy and have complete resolution of SE, the goal is rapid attainment of therapeutic levels of an AED and

**Table 6** Treatment recommendations for SE

| Treatment                       | Class/level of evidence | References  |
|---------------------------------|-------------------------|---|
| <b>Emergent treatment</b>       |                         |   |
| Lorazepam                       | Class I, level A        | [19, 30, 52, 83, 87–98]   |
| Midazolam                       | Class I, level A        | [84, 99–108]  |
| Diazepam                        | Class IIa, level A      | [30, 87, 90, 95, 97–105, 107, 109–114]                            |
| Phenytoin/fosphenytoin          | Class IIb, level A      | [30, 87, 94, 115–119]   |
| Phenobarbital                   | Class IIb, level A      | [30, 87, 114]   |
| Valproate sodium                | Class IIb, level A      | [116, 117, 120–122]   |
| Levetiracetam                   | Class IIb, level C      | [119, 123–130]  |
| <b>Urgent treatment</b>         |                         |   |
| Valproate sodium                | Class IIa, level A      | [117, 120–122, 131–136]   |
| Phenytoin/fosphenytoin          | Class IIa, level B      | [30, 87, 97, 107, 114, 115, 117, 119, 132, 133, 137]              |
| Midazolam (continuous infusion) | Class IIb, level B      | [106]   |
| Phenobarbital                   | Class IIb, level C      | [138, 139]  |
| Levetiracetam                   | Class IIb, level C      | [119, 123, 125–127, 129, 133, 140, 141]                           |
| <b>Refractory treatment</b>     |                         |   |
| Midazolam                       | Class IIa, level B      | [28, 106–108, 142–150]  |
| Propofol                        | Class IIb, level B      | [26, 36, 62, 66, 68, 144, 151–155]                                |
| Pentobarbital/thiopental        | Class IIb, level B      | [26, 27, 56, 58, 59, 62, 63, 66, 68, 107, 115, 139, 154, 156–158] |
| Valproate sodium                | Class IIa, level B      | [120, 121, 131, 136, 159–161]                                     |
| Levetiracetam                   | Class IIb, level C      | [37, 66, 125–127, 129, 140, 141, 159, 162–164]                    |
| Phenytoin/fosphenytoin          | Class IIb, level C      | [57, 165]   |
| Lacosamide                      | Class IIb, level C      | [166–168]   |
| Topiramate                      | Class IIb, level C      | [169]   |
| Phenobarbital                   | Class IIb, level C      | [138]   |

continued dosing for maintenance therapy. For patients who fail emergent initial therapy, the goal of urgent control therapy is to stop SE. There is conflicting data and differences in expert opinion about which agent is most effective for urgent control and the choice often varies based on the particular patient scenario. The VA Cooperative Trial was the best attempt to determine optimal SE treatment agent, but many of the newer AEDs were not available at the time of that trial [30]. The preferred top tier agents that are generally used for urgent control of SE are IV fosphenytoin/phenytoin, valproate sodium, phenobarbital, levetiracetam, or continuous infusion midazolam. Of these agents, fosphenytoin may be preferred for most patients with the exception of patients (particularly children) with a history of primary generalized epilepsy, where valproate sodium would be the best choice. One study suggested that IV valproate sodium may have similar efficacy as urgent control therapy when compared to phenytoin [117, 132]. A list of alternative agents that have been reported to be useful as urgent control therapies are also outlined in Table 6. Clinical scenarios may be used on a case-by-case basis to select one of these alternatives for urgent control treatment, but in general the principle of rapid administration of an AED that will quickly reach a

therapeutic level requires selection of an intravenously administered compound. In patients with known epilepsy who have been on an AED before admission, it is reasonable to provide an IV bolus of this AED, if available, prior to initiating an additional agent. This may include additional boluses that will result in higher than normal target concentrations of the AED to achieve the desired therapeutic response (i.e., cessation of seizure activity).

#### Treatment of Refractory SE

In most cases of SE, continuous EEG (cEEG) and/or clinical exam will determine the persistence of SE after both emergent initial and urgent control AED treatments have been given. In this case, the patient has RSE and it is recommended to immediately start additional agents. The main decision point at this step is to consider repeat bolus of the urgent control AED or to immediately initiate additional agents. There is no well defined period of observation that has been determined to be safe, and no data to suggest that watchful waiting is safer than proceeding with more aggressive treatment. Hence, we recommend proceeding with additional treatment immediately, in combination with critical care treatment as described in Table 5.



**Table 7** Intermittent drug dosing in SE

| Drug             | Initial dosing   | Administration rates and alternative dosing recommendations  | Serious adverse effects  | Considerations   |
|------------------|--|--|--|--|
| Diazepam         | 0.15 mg/kg IV up to 10 mg per dose, may repeat in 5 min  | Up to 5 mg/min (IVP)<br>Peds: 2–5 years, 0.5 mg/kg (PR); 6–11 years, 0.3 mg/kg (PR); greater than 12 years, 0.2 mg/kg (PR) | Hypotension<br>Respiratory depression                                | Rapid redistribution (short duration), active metabolite, IV contains propylene glycol                                     |
| Lorazepam        | 0.1 mg/kg IV up to 4 mg per dose, may repeat in 5–10 min | Up to 2 mg/min (IVP)   | Hypotension<br>Respiratory depression                                | Dilute 1:1 with saline<br>IV contains propylene glycol   |
| Midazolam        | 0.2 mg/kg IM up to maximum of 10 mg                      | Peds: 10 mg IM (>40 kg); 5 mg IM (13–40 kg); 0.2 mg/kg (intranasal); 0.5 mg/kg (buccal)                                    | Respiratory depression<br>Hypotension                                | Active metabolite, renal elimination, rapid redistribution (short duration)  |
| Fosphenytoin     | 20 mg PE/kg IV, may give additional 5 mg/kg              | Up to 150 mg PE/kg; may give additional dose 10 min after loading infusion<br>Peds: up to 3 mg/kg/min                      | Hypotension<br>Arrhythmias   | Compatible in saline, dextrose, and lactated ringers solutions   |
| Lacosamide       | 200–400 mg IV  | 200 mg IV over 15 min<br>No pediatric dosing established   | PR prolongation<br>Hypotension                                       | Minimal drug interactions<br>Limited experience in treatment of SE   |
| Levetiracetam    | 1,000–3,000 mg IV<br>Peds: 20–60 mg/kg IV                | 2–5 mg/kg/min IV   |  | Minimal drug interactions<br>Not hepatically metabolized   |
| Phenobarbital    | 20 mg/kg IV, may give an additional 5–10 mg/kg           | 50–100 mg/min IV, may give additional dose 10 min after loading infusion   | Hypotension<br>Respiratory depression                                | IV contains propylene glycol   |
| Phenytoin        | 20 mg/kg IV, may give an additional 5–10 mg/kg           | Up to 50 mg/min IV; may give additional dose 10 min after loading infusion<br>Peds: up to 1 mg/kg/min                      | Arrhythmias<br>Hypotension<br>Purple glove syndrome                  | Only compatible in saline<br>IV contains propylene glycol  |
| Topiramate       | 200–400 mg NG/PO   | 300–1,600 mg/day orally (divided 2–4 times daily)<br>No pediatric dosing established                                       | Metabolic acidosis   | No IV formulation available  |
| Valproate sodium | 20–40 mg/kg IV, may give an additional 20 mg/kg          | 3–6 mg/kg/min, may give additional dose 10 min after loading infusion<br>Peds: 1.5–3 mg/kg/min                             | Hyperammonemia<br>Pancreatitis<br>Thrombocytopenia<br>Hepatotoxicity | Use with caution in patients with traumatic head injury; may be a preferred agent in patients with glioblastoma multiforme |

*IM* intramuscular; *IV* intravenous; *IVP* intravenous push; *min* minute; *NG* nasogastric; *PE* phenytoin equivalents; *PEDs* pediatric; *PO* by mouth; *PR* rectal administration; *PRIS* propofol related infusion syndrome

At this stage after attempts to control the SE with bolus intermittent therapy fails, treatment recommendations are to use continuous infusion AEDs to suppress seizures. However, the use of valproate sodium, levetiracetam, and phenytoin/fosphenytoin in intermittent boluses may also be considered if they have not previously been administered, particularly for patients with NCSE who are hemodynamically stable and have not required intubation. Bolus doses of the AED chosen for continuous infusion should be given

and can be repeated for breakthrough SE, in addition to starting the continuous infusion. If the first continuous infusion or AED chosen for RSE fails, then switching to a different continuous infusion or starting another agent from the list above is recommended.

The AEDs most often recommended for use as a continuous infusion are midazolam, propofol, and pentobarbital; in some countries, thiopental will also be used. Dosing considerations for these agents are discussed in

**Table 8** RSE dosing recommendations

| Drug          | Initial dose  | Continuous infusion dosing recommendations-titrated to EEG   | Serious adverse effects  | Considerations  |
|---------------|---|--|--|---|
| Midazolam     | 0.2 mg/kg; administer at an infusion rate of 2 mg/min                                       | 0.05–2 mg/kg/hr CI<br>Breakthrough SE: 0.1–0.2 mg/kg bolus, increase CI rate by 0.05–0.1 mg/kg/hr every 3–4 h  | Respiratory depression<br>Hypotension  | Tachyphylaxis occurs after prolonged use<br>Active metabolite, renally eliminated, rapid redistribution (short duration), does NOT contain propylene glycol |
| Pentobarbital | 5–15 mg/kg, may give additional 5–10 mg/kg; administer at an infusion rate $\leq$ 50 mg/min | 0.5–5 mg/kg/h CI<br>Breakthrough SE: 5 mg/kg bolus, increase CI rate by 0.5–1 mg/kg/h every 12 h   | Hypotension<br>Respiratory depression<br>Cardiac depression<br>Paralytic ileus<br>At high doses, complete loss of neurological function  | Requires mechanical ventilation<br>IV contains propylene glycol   |
| Propofol      | Start at 20 mcg/kg/min, with 1–2 mg/kg loading dose   | 30–200 mcg/kg/min CI<br>Use caution when administering high doses ( $>$ 80 mcg/kg/min) for extended periods of time (i.e., $>$ 48 h)<br>Peds: Use caution with doses $>$ 65 mcg/kg/min; contraindicated in young children<br>Breakthrough SE: Increase CI rate by 5–10 mcg/kg/min every 5 min or 1 mg/kg bolus plus CI titration | Hypotension (especially with loading dose in critically ill patients)<br>Respiratory depression<br>Cardiac failure<br>Rhabdomyolysis<br>Metabolic acidosis<br>Renal failure (PRIS) | Requires mechanical ventilation<br>Must adjust daily caloric intake (1.1 kcal/ml)   |
| Thiopental    | 2–7 mg/kg, administer at an infusion rate $\leq$ 50 mg/min                                  | 0.5–5 mg/kg/h CI<br>Breakthrough SE: 1–2 mg/kg bolus, increase CI rate by 0.5–1 mg/kg/h every 12 h   | Hypotension<br>Respiratory depression<br>Cardiac depression  | Requires mechanical ventilation<br>Metabolized to pentobarbital   |

CI continuous infusion; EEG electroencephalogram; h hour; IM intramuscular; IV intravenous; IVP intravenous push; min minute; PRIS propofol related infusion syndrome

Table 8. At present, there are insufficient data to suggest whether midazolam, propofol, or pentobarbital is the preferred agent [3, 171]. Propofol is an option but its safety profile needs to be considered as it can cause propofol infusion syndrome. Of the two other compounds, midazolam may cause less hypotension as it does not contain the solvent propylene glycol and may be preferred in selected clinical situations. Pentobarbital may have a higher rate of successfully controlling RSE acutely than midazolam, but may have more adverse effects [63]. Use of continuous infusion AEDs frequently requires assisted ventilation and cardiovascular monitoring. Vasopressor agents may be required due to hypotension and cardiopulmonary depression related to these agents [172].

#### *Intensity and Duration of RSE Treatment*

There are currently no data to support a standardized regimen for the intensity and duration of treatment for RSE.

The intensity of treatment is usually dictated by cEEG findings, with the goal of treatment being cessation of electrographic seizures or burst suppression. Limited data suggest that the EEG background activity does not predict seizure control [27, 156]. It is recommended that cEEG findings, not serum drug levels, guide therapy.

The optimal duration of maintaining electrographic seizure control in patients with RSE is not known since there are few data to indicate what duration of treatment is needed to maintain control. Customarily, electrographic seizure control is maintained for 24–48 h, followed by gradual withdrawal of the continuous infusion AED. Patients may have recurrent RSE upon initial withdrawal of the continuous infusion AED, requiring a return to prior or higher doses of the continuous infusion AED for an additional period of time, with or without the addition of another agent.

As a corollary, there is no defined duration of electrographic seizure control or “number of trials” of electrographic seizure control after which care is considered futile. Available

**Table 9** Alternative therapies for RSE

|                                   | Number of articles related to treatment of RSE | Case series $n \geq 3$ | Comments   | References |
|-----------------------------------|--|------------------------|--|------------|
| <b>Pharmacological</b>            |  |                        |  |            |
| Ketamine                          | 9  | 2                      | Intravenous drip, potential neurotoxicity            | [178, 179] |
| Corticosteroids                   | 16   | 2                      | Rasmussen's encephalitis, Hashimoto's encephalopathy | [180, 181] |
| Inhaled anesthetics               | 19   | 2                      | High complication rate/morbidity                     | [182, 183] |
| Immunomodulation (IVIg or PE)     | 3  | 1                      | Rasmussen's encephalitis, EPC                        | [181]      |
| <b>Non-pharmacological</b>        |  |                        |  |            |
| Vagus nerve stimulation           | 8  | 2                      | Catastrophic epilepsy in infants                     | [184, 185] |
| Ketogenic diet                    | 20   | 3                      | Landau-Kleffner syndrome, pediatrics                 | [186–188]  |
| Hypothermia                       | 4  | 2                      | Single or small case series only                     | [189, 190] |
| Electroconvulsive therapy         | 5  | 1                      | Single or small case series only                     | [191]      |
| Transcranial magnetic stimulation | 9  | 1                      | EPC in most cases                                    | [192]      |
| Surgical management               | 13   | 4                      | Most often used and successful in pediatrics         | [193–196]  |

*EPC* epilepsy partialis continua

reports suggest that patients can be effectively treated for RSE for weeks to months after which a full functional recovery may occur. [40, 64, 65, 68, 173] Therefore, the cumulative duration of treatment with continuous infusion AEDs does not appear to be indicative of long term prognosis.

#### *Transition From Continuous Infusion RSE Treatment to Maintenance AED Therapy*

There are no data to guide transition from continuous infusion treatment to intermittent maintenance therapy following resolution of RSE. In general, maintenance AEDs are given in doses sufficient to maintain therapeutic concentrations during and after weaning of the continuous infusion. Therapeutic concentrations may exceed published target concentrations for many AEDs and dosing should be individualized to achieve seizure control and minimize adverse effects. The success of the maintenance regimen is predicated by many clinical features, including EEG pattern, cause of SE, concurrent systemic disease, and drug–drug interaction profiles. Patients exposed to prolonged pentobarbital (or prolonged infusions) are at risk for withdrawal seizures as pentobarbital (drug) concentrations fall, which may precipitate recurrent RSE. High dose phenobarbital sometimes requiring concentrations > 100 mcg/ml may be used if necessary to avoid this complication, but data are lacking to permit formal endorsement of this strategy [138, 174].

#### *Alternative Therapies for Refractory SE*

Aggressive treatment should be continued in all situations until the physician determines therapy is successful or futile. Patients with RSE in whom it is appropriate to use

prolonged therapy include young patients with a healthy pre-morbid state, self-limited disease processes, and absence of intracranial lesions suggesting a poor prognosis (e.g., cortical laminar necrosis) [175–177].

While there are many anecdotal case reports regarding novel interventions to treat RSE, there currently are no randomized trials or compelling evidence to support early initiation of these interventions. Table 9 lists alternative agents and summarizes the available data regarding their use. Practitioners should be aware of these options and consider their use based on the individual clinical situation.

Emerging therapies include ketamine and hypothermia; however, there are limited data on the safety and effectiveness of these treatments for RSE. Therefore, it is recommended to reserve these therapies for patients who do not respond to RSE AED treatment and consider transfer of the patient if they are not being managed by an ICU team that specialize in the treatment of SE and/or cannot provide cEEG monitoring.

#### Special Circumstances

##### *Anoxic Brain Injury*

The prognosis of SE after a hypoxic or anoxic insult has traditionally been considered as poor, particularly for patients that develop myoclonic SE. However, the recent inclusion of hypothermia following cardiac arrest in the advanced cardiac life support (ACLS) guidelines may alter this prognosis [197–201]. Additional data are needed to assess the role of hypothermia in improving prognosis in those patients who exhibit these symptoms following hypoxic injury. Seizures and myoclonus in the setting of

anoxia is controversial and a comprehensive discussion of this is beyond the scope of these guidelines.

### Pregnancy

There is not an increased risk of SE during pregnancy [202]. There are no data regarding the use of AEDs for SE during pregnancy. Good fetal outcome is dependent upon rapid seizure control in the mother [203]. During pregnancy, the volume of distribution and clearance of many drugs are typically increased and this should be taken into consideration when dosing AEDs. Vitamin B6 levels may be low during pregnancy and should be evaluated. Lorazepam and fosphenytoin are recommended as emergent initial therapy and urgent control therapy [204]. However, there are known risks of birth defects with first trimester exposure to AEDs, particularly valproate sodium, phenobarbital, and phenytoin. Data from recent pregnancy registries suggest less risk with exposure to some of the newer AEDs [205]. Therefore, levetiracetam should be considered for SE. Eclampsia must be considered in patients with SE during pregnancy and delivering the fetus is the best therapy in this situation. For pregnant women with seizures and eclampsia, magnesium sulfate is superior to antiepileptic medications, such as phenytoin [206], but additional AEDs may be needed. If medical therapy is chosen, continuous fetal heart monitoring, stand-by obstetric assistance, and pediatric ICU help should be provided to assure the safety of both mother and child.

### Pediatric SE

There is no evidence that children respond differently to AED treatment than adults. However, pharmacokinetic differences, risk of adverse events (e.g., propofol infusion syndrome) and syndrome specific treatment should be considered to optimize therapy for SE. Young children with epilepsy who develop SE should receive IV pyridoxine in case they have pyridoxine dependent seizures [207]. Concern exists for possible hepatotoxicity when using valproate sodium in younger children (<2 years of age), especially those with a metabolic or mitochondrial disorder. There have been several pediatric series that have used diazepam as a continuous infusion with doses ranging from 0.01 to 0.03 mcg/kg/min to control RSE, but this is not a widely used current practice [142, 160, 208].

### Summary of Treatment Recommendations

1. The treatment of convulsive SE should occur rapidly and continue sequentially until clinical seizures are halted (*strong recommendation, high quality*).
2. The treatment of SE should occur rapidly and continue sequentially until electrographic seizures are halted (*strong recommendation, moderate quality*).
3. Critical care treatment and monitoring should be started simultaneously with emergent initial therapy and continued until further therapy is considered successful or futile (*strong recommendation, moderate quality*).
4. Treatment options
  - a. Benzodiazepines should be given as emergent initial therapy (*strong recommendation, high quality*).
    - i. Lorazepam is the drug of choice for IV administration (*strong recommendation, moderate quality*).
    - ii. Midazolam is the drug of choice for IM administration (*strong recommendation, moderate quality*).
    - iii. Rectal diazepam can be given when there is no IV access and IM administration of midazolam is contraindicated (*strong recommendation, moderate quality*).
  - b. Urgent control AED therapy recommendations include use of IV fosphenytoin/phenytoin, valproate sodium, or levetiracetam (*strong recommendation, moderate quality*).
  - c. Refractory SE therapy recommendations should consist of continuous infusion AEDs, but vary by the patient's underlying condition (*strong recommendation, low quality*).
  - d. Dosing of continuous infusion AEDs for RSE should be titrated to cessation of electrographic seizures or burst suppression (*strong recommendation, very low quality*).
  - e. A period of 24–48 h of electrographic control is recommended prior to slow withdrawal of continuous infusion AEDs for RSE (*weak recommendation, very low quality*).
  - f. During the transition from continuous infusion AEDs in RSE, it is suggested to use maintenance AEDs and monitor for recurrent seizures by cEEG during the titration period. If the patient is being treated for RSE at a facility without cEEG capabilities, consider transfer to a facility that can offer cEEG monitoring (*strong recommendation, very low quality*).
  - g. Alternative therapies can be considered if cessation of seizures cannot be achieved; however, it is recommended to reserve these therapies for patients who do not respond to RSE AED treatment and consider transfer of the patient if

they are not being managed by an ICU team that specialize in the treatment of SE and/or cannot provide cEEG monitoring (*weak recommendation, very low quality*).

### Continuous EEG Monitoring in SE

The treatment of SE in the ICU usually requires cEEG monitoring to direct treatment. This section will focus on the major considerations for cEEG including indications for, timing and duration, technical specifications, and EEG-defined treatment endpoints.

The indications for cEEG are outlined in Table 10. The guiding principles for these indications are multifactorial. First, SE is often non-convulsive with the clinical findings of coma with or without subtle motor signs such as nystagmus, clonus, or opsoclonus [30, 80, 81]. In addition, non-convulsive seizures and NCSE exist in a high proportion of comatose patients with traumatic brain injury, intracranial hemorrhage, sepsis, cardiac arrest, or CNS infection [25, 82, 209–215]. Patients demonstrating periodic patterns in addition to fluctuating or semi-rhythmic patterns that do not clearly meet EEG criteria for electrographic seizures (known as the ictal-interictal continuum) may be considered for treatment [80, 209, 216]. However, it is controversial whether these patterns cause additional brain injury and if they warrant aggressive antiepileptic therapy. These concerns also exist in children with coma [217] and critical illness [218, 219]. In patients being treated with continuous infusion AEDs, in which most or all convulsive activity resolves, cEEG is the only way to know if treatment is successful. The use of video monitoring in conjunction with cEEG in the ICU may aid EEG interpretation and help assess the presence of clinical behaviors accompanying the ictal EEG. However, no prospective studies have been performed to formally assess

efficacy of adding video to cEEG in the setting of SE in the ICU.

The timing, duration, and essential technical elements for cEEG are also very important considerations in patients with SE. As outlined above, the cumulative duration of SE affects mortality and neurologic outcome, hence delays in starting cEEG should be minimized [51]. cEEG should be initiated within one hour of suspected SE in all patients. The duration of cEEG monitoring should be at least 48 h following acute brain insult in comatose patients [6, 209–211, 220] and 24 h after cessation of electrographic seizures or during the AED weaning trials [6, 63, 210, 220]. EEG electrodes should be placed to sample major regions of the brain, and CT/MRI compatible electrodes may be considered. [209, 214, 221, 222] Due to the complexity of cEEG recordings in patients with NCSE, the person reading the EEG should have specialized training in cEEG interpretation, including the ability to analyze raw EEG as well as quantitative EEG tracings [209, 210, 214, 216]. However, the logistics of having continuous, real-time reading of EEG, especially after hours, have not been studied and this capability is not available at every institution.

For patients with RSE, following EEG treatment endpoints is crucial since the vast majority of seizures at this point are non-convulsive. Endpoints are controversial and options include burst suppression, complete background suppression or seizure suppression. [27, 66, 223] cEEG defined treatment endpoints are outlined in Table 11.

### Summary of cEEG Recommendations

1. The use of cEEG is usually required for the treatment of SE (*strong recommendation, very low quality*).
2. Continuous EEG monitoring should be initiated within 1 h of SE onset if ongoing seizures are suspected (*strong recommendation, low quality*).

**Table 10** Indications for cEEG in SE

| Indication   | Rationale   | Grade            | Reference         |
|--|---|------------------|-------------------|
| Recent clinical seizure or SE without return to baseline > 10 min        | Ongoing non-convulsive status despite cessation of motor activity 18–50 % | Class I, level B | [30, 54, 80, 81]  |
| Coma, including post-cardiac arrest                                      | Frequent non-convulsive seizures, 20–60 %                                 | Class I, level B | [25, 82, 209–215] |
| Epileptiform activity or periodic discharges on initial 30 min EEG       | Risk of non-convulsive seizures, 40–60 %                                  | Class I, level B | [80, 216]         |
| Intracranial hemorrhage including TBI, SAH, ICH                          | Frequent non-convulsive seizures, 20–35 %                                 | Class I, level B | [209–212, 214]    |
| Suspected non-convulsive seizures in patients with altered mental status | Frequent non-convulsive seizures, 10–30 %                                 | Class I, level B | [25, 211, 213]    |

EEG electroencephalogram; ICH intracranial hypertension; SAH subarachnoid hemorrhage; TBI traumatic brain injury

**Table 11** Continuous EEG treatment endpoints

| EEG defined endpoint                 | Rationale   | Grade              | Reference          |
|--------------------------------------|---|--------------------|--------------------|
| Cessation of non-convulsive seizures | Recurrent non-convulsive seizures result in ongoing brain injury and worsen mortality | Class I, level B   | [51, 216, 223–226] |
| Diffuse beta activity                | Verifies effect of anesthetic agents  | Class IIb, level C | [51, 214, 223]     |
| Burst suppression 8–20 s intervals   | Interruption of synaptic transmission of electrical activity                          | Class IIb, level C | [27, 66, 227]      |
| Complete suppression of EEG          | Interruption of synaptic transmission   | Class IIb, level C | [66, 227]          |

EEG electroencephalography

- The duration of cEEG monitoring should be at least 48 h in comatose patients to evaluate for non-convulsive seizures (*strong recommendation, low quality*).
- The person reading EEG in the ICU setting should have specialized training in cEEG interpretation, including the ability to analyze raw EEG as well as quantitative EEG tracings (*strong recommendation, low quality*).

### Future Directions

There remains a lack of the rigorous scientific evidence needed to create a more comprehensive evidence-based approach to the care of the patient with SE in the neurocritical care unit. The current state of clinical practice couples sparse clinical trial evidence about first- and second-line therapy in adults with expert clinical experience to develop individualized therapeutic approaches based on “trial and error.” Despite today’s challenges, future care of patients with SE can be improved by a multifaceted nationwide and international effort to raise awareness of the dangers of ongoing SE, develop new drugs, develop faster and more reliable diagnostic techniques including advanced monitoring algorithms, create research networks that employ standardized language, and systematically examine outcomes resulting from national clinical pathways or randomized controlled trials. There is growing evidence that SE is a dynamic state and, therefore, untreated or inadequately treated SE results in progressive changes in the EEG patterns, conversion of overt to subtle or even absent motor activity, increasing refractoriness to treatment, and increasingly severe consequences.

Because only two-thirds of patients in SE respond to the first treatment [30] it is increasingly important to understand the underlying pathophysiology of refractoriness to treatment so better interventions can be developed. There is growing evidence that increasing refractoriness to treatment is at least partly the result of progressive impairment of gamma-aminobutyric acid (GABA)-mediated inhibition [228, 229]. Goodkin et al. [228] and Naylor et al. [229]

independently reported internalization of GABA receptors under conditions of sustained excitability [230, 231]. Goodkin et al. [230, 231] subsequently reported that GABA receptor internalization is specific to receptors containing beta 2/3 and gamma 2 subunits. The result of such internalization appears to be less responsiveness to GABAergic drugs during sustained SE. There is also evidence for increased numbers of  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and *N*-methyl-D-aspartic acid (NMDA) receptors at the synaptic membrane [229]. These changes result in increased sensitivity to excitatory neurotransmitters. These observations suggest several lines of attack for possible development of new drugs for refractory SE, including identification of excitatory antagonists, other inhibitory agonists, and drugs that may block the internalization of GABA receptors or the externalization of excitatory receptors. NMDA channel blockers, such as ketamine, have been used occasionally in refractory SE, but success has been variable and NMDA channel blockers have the potential for adverse behavioral effects, such as the development of psychosis or possibly even neuronal loss. Competitive NMDA antagonists that bind to the glutamine receptor may be more effective at shutting down excitation, but some of these compounds do not readily cross the blood brain barrier [232], although during SE the blood brain barrier may break down and allow access of otherwise restricted drugs [233]. NMDA receptor antagonists have been studied in the treatment of experimental SE, but use of competitive NMDA receptor antagonists has not been reported in human SE. There are no reports of drugs that inhibit the internalization of GABA receptors or externalization of excitatory receptors. The role of other neuroprotective compounds remains to be evaluated.

Another mechanism that may play a role in onset of seizures and evolution to SE is cortical spreading depolarizations (CSD) [234]. CSDs are mass depolarizations of neurons that arise spontaneously from injury foci, cause suppression of spontaneous activity, and propagate through gray matter at 1–5 mm/min. Use of continuous electrocorticography (ECoG) in surgical patients with intracranial hypertension, subarachnoid hemorrhage, traumatic brain injury, and malignant hemispheric stroke have shown that

CSD (1) occurs commonly in patients with acquired brain injury, (2) can recur for up to 2 weeks after injury, (3) can lead to secondary neuronal injury, and (4) often presents in a status-like pattern of repetitive depolarization waves lasting hours to days [235–238]. Importantly, electrographic seizures in ECoG recordings occur mainly in patients who also exhibit the more common CSD [239]. In these patients, seizure patterns interact with CSD both spatially and temporally, with CSD occurring either before or after prolonged seizures. These activities appear to be different manifestations of hyperexcitability, and recursive influences (either facilitatory or inhibitory) are likely and deserve further study. The time course of electrophysiologic dysfunction as evidenced by ECoG argues in favor of more prolonged EEG monitoring, although the relationship of ECoG to EEG findings also requires further study [240].

In addition to the development of more effective drugs, management of SE will also improve with development of faster and more reliable diagnostic techniques. The current state-of-the-art in diagnosis of SE is to visually inspect the raw EEG and make a diagnosis of SE because the EEG “looks like SE.” Obviously, the accuracy of such a pronouncement is dependent on the experience of the electroencephalographer. Treiman et al. [241] described a sequence of progressive EEG changes during GCSE. While these patterns have proven useful in the study of experimental SE, there are several issues that remain problematic. In what these investigators called “SE EEG Stage III,” marked by continuous ictal discharges, the morphological pattern frequently is very difficult to differentiate from the EEG of metabolic encephalopathy, especially when the pattern is one of rhythmic generalized triphasic waves. Also, there is not universal agreement that SE EEG Stage V (periodic epileptiform discharges on a relatively flat background) is truly an ictal pattern rather than a reflection of widespread neuronal damage. Lastly, one study of SE was not able to verify that this sequence actually occurs with any reliability in humans [242]. What is needed is an independent measure of “ictal-ness” or independent measure of which EEG patterns are associated with ongoing neuronal injury and thus warrant aggressive treatment. Markers such as serum prolactin [243] and neuron-specific enolase [244] lack sufficient specificity to serve as independent markers of SE. There are preliminary reports of the use of non-linear dynamic analysis of the EEG to identify unique characteristics of SE that are currently under development and that may prove useful in SE diagnosis [245]. Such techniques may also prove useful in ICU monitoring of patients in SE. The development of high speed algorithms (utilizing quantitative EEG analysis) for EEG diagnosis of SE with a high degree of both sensitivity and specificity should make the rapid diagnosis of SE possible, even in remote areas without immediate access to

experienced electroencephalographers, and thus allow earlier initiation of treatment and enhanced probability of success.

A key first step to testing new drugs and new diagnostics would be acceptance of standardized EEG terminology across a network of cooperating medical centers. Such terminology has been proposed but requires widespread adoption since ambiguity in terminology hampers collaborative efforts [246]. A consortium of centers specializing in cEEG monitoring of critically ill patients is currently developing a multicenter database utilizing the proposed standardized EEG terminology to further explore relationships between various EEG patterns, seizures and outcomes. An NIH-sponsored workshop on SE terminology and operational definitions would also provide an important foundation for the subsequent development of either clinical pathways or randomized controlled trials. Only in this organized fashion can important advances (from the lab or the bedside) be rigorously tested to determine their true value.

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