Emergent Treatment of Status Epilepticus

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Definitions and Epidemiology

A single seizure is a significant event during which an electrical discharge in the brain may result in altered awareness often accompanied by motor manifestations. Isolated seizures usually are less than 5 min long and self-limited; however, longer seizures tend not to resolve on their own [1]. Defining status epilepticus (SE) as loss of consciousness or failure to return to baseline as well as other, often tonic-clonic, activity needs to be taken into account. Therefore, the definition of SE as continuous seizure activity or two or more seizures without recovery of consciousness of longer than 30 min in duration seems outdated. Given the non-self-limited nature of seizures longer than 5 min, studies showing that permanent brain injury in SE may occur sooner than 30 min, and recent studies using 5 min as the threshold for SE, SE is now often described as seizure activity lasting 5 min or longer [1, 2].

Subtypes of SE include convulsive SE, epilepsia partialis continua, and nonconvulsive SE (NCSE). Repetitive tonic-clonic movements followed by a post-ictal state occur in convulsive SE. Epilepsia partialis continua is characterized by focal neurologic deficits such as aphasia and motor dysfunction occurring as a result of partial seizures arising from eloquent cortex but in the absence of altered mental status. NCSE is the occurrence of mental status change but without convulsions or outlasting convulsions while electrical seizure activity is ongoing in the brain [2].

SE may also be subdivided based on its response to antiepileptic drugs (AEDs). While refractory SE (RSE) is continuous seizure activity not controlled by first- or second-line AEDs [3], super-refractory SE (SRSE) has been defined in two different ways: SE not controlled by third-line AEDs [4] and SE that continues 24 h or more after anesthesia is given [5].

Annual SE incidence is approximately 12.6/100,000 person-years [6], and 9–43% of patients with SE progress to RSE and 10–20% to SRSE [4, 5]. Seizures or SE may be found in up to 19% of intensive care unit (ICU) patients [7]. This is an important finding as SE in ICU patients is often nonconvulsive. The diagnosis therefore requires a high level of suspicion and a diagnostic electroencephalogram (EEG). Recent studies suggest that SE occurs nearly equally in females and males (11.1/100,000 person-years in females, 11.3/100,000 person-years in males) [6]. Individuals greater than age 50 years (approximately 28.4/100,000 per year) and less than age 10 years (14.3/100,000 per year) seem to be affected most. In addition, more African Americans (13.7/100,000 per year) than whites (6.9/100,000 per year) and other races (7.4/100,000 per year) appear to develop SE [8]. Case fatality rate is approximately 15% though this rate is greater in the elderly (24.9%) and in patients with RSE (33.3%) [6].

SE incidence appears to be increasing over time. In a study evaluating data from US National Hospital Discharge Survey, between 1979 and 2010 the incidence of SE was found to increase from 3.5 to 12.5/100,000 per year but with no significant change in in-hospital mortality [8]. In another recent study that used data from the Centers for Disease Control and Prevention and from the Nationwide Inpatient Sample, SE hospitalizations increased by 56.4% from 1999 (8.9 per 100,000 persons) to 2010 (13.9 per 100,000 persons). Mortality also increased over this same time period, but only by 5.6% (1.8 per 1,000,000 persons to 1.9 per 1,000,000 persons) [9].

Convulsive SE episodes occur 120–180,000 annually in the USA [10], but the incidence of NCSE is not as clear as it cannot be diagnosed without the help of an EEG [11]. The percentage of SE patients progressing to RSE and SRSE is described above. Annual incidence of RSE was found to be 3.4/100,000 in one large study of 395 RSE patients treated in the ICU [12]. As

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expected, prospective studies [13] estimate a lower incidence than ICU retrospective ones [14–16]. However, the exact incidence of SRSE have not yet been delineated, likely due to the low number of patients with this condition and lack of prospective studies [17]. In a recent study that utilized the Finnish Intensive Care Consortium database, 22% of patients with RSE were categorized as having SRSE with an annual incidence estimate of 0.7/100,000 [5].

Etiology

There are a variety of potential causes of SE [1] (see Table 2.1). According to the International League Against Epilepsy, etiology is divided into two groups: (i) known or symptomatic and (ii) unknown or cryptogenic. Subdivisions of the symptomatic group include acute symptomatic, remote symptomatic, and progressive symptomatic [18]. Acute causes may occur more frequently than chronic causes [6]. Importantly, SE mortality can be affected by SE etiology [9].

RSE predictors can include lower level of consciousness, new diagnosis of SE, focal seizures at onset, and NCSE [13, 15]. Low AED levels (or missed doses), metabolic causes, and CNS infections have also been implicated in RSE [19]. RSE was more likely to be associated with encephalitis, and nonrefractory SE with low AED levels in one study [14]. Similarly, another study found that CNS infections were seen in greater frequency in RSE patients compared to patients with nonrefractory SE [20]. The term new-onset RSE (NORSE) has recently emerged to define patients who have prolonged RSE with no readily identifiable cause (though an autoimmune or viral encephalitis etiology may later be found) [21]. Etiology of SRSE may be different from that of SE and RSE [22]. Several studies suggest that encephalitis is a frequent cause of SRSE [23–25].

Table 2.1 Possible causes of SE

Acute Causes
Acute stroke (e.g., ischemic stroke, intracerebral hemorrhage)
Traumatic brain injury
Central nervous system infections
Hypoxic brain injury
Posterior reversible encephalopathy syndrome
Metabolic disorders (e.g., hypoglycemia, abnormal electrolytes)
Drug withdrawal, noncompliance, or toxicity
Autoimmune and paraneoplastic etiologies
Sepsis
Chronic Causes
History of epilepsy
Brain tumor
Preexisting brain pathology (e.g., cortical dysplasia or due to prior trauma or stroke)

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SE Patients: Triage to the Neurointensive Care Unit

Due to the complexities of treatment for SE, RSE, and SRSE, patients in SE benefit from admission to the neurointensive care unit (NCCU) rather than a general ICU. Patients may be triaged to the NCCU in different ways. Most commonly, patients are admitted through the emergency department. In addition, patients are often referred to centers that offer continuous EEG monitoring. Patients may also develop SE after having been admitted for a different reason or for seizures and then subsequently developed symptoms suspicious for SE. There is an absence of literature that discusses the frequency with which these different triage mechanisms occur.

Triage for SE many times begins with dispatch of emergency medical services (EMS), and studies of seizure-related calls to EMS are consistent with seizure patients generally requiring high levels of care [26, 27]. Prehospital management is important – particularly for convulsive SE – until more definitive treatment can occur in the hospital. This includes assessing for and securing the ABCs (airway, breathing, circulation), obtaining history on-scene (e.g., patient's past medical history, physical manifestations, and length of the seizure(s)), preventing injury to the patient, and treating reversible causes of seizures (e.g., hypoglycemia). In addition, EMS may administer first-line therapy (benzodiazepines) [28]. Benzodiazepines have been the most studied medication in the prehospital setting and have been shown to be efficacious. A recent clinical trial showed no benefit to levetiracetam being added to clonazepam in aborting convulsions within 15 min of drug injection in the prehospital setting [29]. Once in the emergency department, patients in SE should have their ABCs reassessed, paying particular attention to the respiratory status of any patients who may have received benzodiazepines prior to arrival. Care should then be guided by the Diagnostic Workup outlined below [28].

One major reason SE patients may require admission to an ICU is airway protection. A few studies have examined predictors of intubation in patients experiencing seizures in the emergency department. One study was a subanalysis of the RAMPART trial, which was a randomized, double-blind clinical trial comparing intravenous lorazepam to intramuscular midazolam for prehospital SE. Of 1023 enrollments in the trial, 218 (21.3%) intubations occurred. Two hundred four (93.6%) of intubations were performed in the hospital (in an inpatient setting or emergency department) and 14 (6.4%) in the prehospital setting. In addition, 133/218 (61.0%) intubations occurred prior to or within 30 min after emergency department arrival. Patients who were intubated were more likely to be men (26 vs. 21%, $p = 0.047$), older (52 vs. 41 years, $p < 0.001$), having ongoing seizures on arrival to the emergency department (32 vs. 16%, $p < 0.001$), and having received rescue AEDs (29 vs 20%, $p = 0.004$)

[30]. In another study, Sato et al. performed a multivariate analysis revealing that age ≥ 50 years, on-scene heart rate ≥ 120 bpm, and meeting definition of convulsive SE were associated with a higher likelihood of intubation whereas a greater on-scene level of consciousness was associated with a reduced likelihood of intubation [31]. In their study, of 822 patients transported to a tertiary care emergency department due to a convulsive seizure, 59 (7.2%) were intubated; of the 270 patients with SE, 43 (15.9%) required intubation [31].

The importance of noting SE early is emphasized in several studies. One group of authors found a median prehospital delay for SE patients of 2 h 4 min, including delays in calling for emergency services, ambulance arrival, and patient transport to the hospital. Time to diagnosis of SE was significantly shorter in cases diagnosed clinically than in those diagnosed by EEG (median 1 h 50 min vs 13 h 20 min, $p < 0.0001$). This is not surprising, as NCSE requires an EEG for the diagnosis. It is therefore important to look for even the subtlest suggestions of ongoing seizure activity. Median delay of administering the first-, second-, and third-line AEDs (if and when each were necessary) were 35 min, 3 h, and 2 h 55 min, respectively [32]. One study examined prehospital delay in managing SE. For example, in multivariate linear regression analysis, the authors found that focal SE (defined by the authors as SE with normal consciousness) was associated with delayed onset-to-initial treatment time (25.8 h, 95% CI 0.4–60.3, $p = 0.049$), delayed time from onset to SE diagnosis (28.5 h, 95% CI 6.2–53.3, $p = 0.002$), and delayed onset to the administration of third-line AEDs (36.0 h, 95% CI 1.5–69.0, $p = 0.002$). Administering an initial treatment before EMS arrival was associated with long duration from SE onset to the first emergency call (4.0 h, 95% CI 0.7–7.3, $p = 0.024$) and with long duration from SE onset to arrival in the emergency department (4.3 h, 95% CI 1.2–8.8, $p = 0.036$). Initial arrival in a healthcare unit other than a tertiary hospital was associated with a delay in SE diagnosis (8.8 h, 95% CI 1.8–15.4, $p = 0.012$) and delay in administering third-line AEDs (9.8 h, 95% CI 2.6–17.8, $p = 0.019$) [33]. In a recent study regarding the ability of EMS to recognize out-of-hospital SE and association with outcome, 150 SE patients were admitted via EMS. Convulsive SE was recognized in 84.6% of cases while nonconvulsive SE (NCSE) was missed in 63.7% of cases by EMS. NCSE was more likely to be missed in patients who were older, had no seizure history, had a greater STESS score (see Clinical Scores below), and had more possibly fatal etiologies. Accordingly, these patients were also less likely to receive benzodiazepines prior to admission. Independent predictors for not receiving benzodiazepines were greater Glasgow Coma Scale and increasing age. In survivors, delayed recognition of NCSE was independently associated with higher likelihood of not returning to functional baseline (OR 3.83, 95% CI 1.22–11.98, $p = 0.021$) [34]. This is an important finding as it suggests that timely diagnosis and treatment of NCSE can result in a tangible improvement in patient outcomes.

Diagnostic Workup

General

The following are generally recommended for all patients with suspected SE [1]:

- Vital sign checks
- Laboratory studies, including complete blood count, basic metabolic panel, calcium, magnesium, glucose
- AED levels
- Computed tomography (CT) of the head
- EEG

In addition, other studies may help in investigating the etiology of SE based on individual presentation [1, 35]:

- MRI of the brain
- Lumbar puncture
- Toxicology screen
- Inborn errors of metabolism panel
- Additional imaging, such as single-photon emission CT (SPECT), MR spectroscopy, and positron emission tomography (PET)
- Studies to evaluate for paraneoplastic and autoimmune encephalitis

EEG

EEG is the mainstay of diagnosing SE and is needed to guide management for all forms of SE, and especially in NCSE, which may only be seen by EEG. One study in a general hospital setting found that 19% of patients with SE had NCSE [36]. In one tertiary care center ICU, NCSE was found in 47% of all SE episodes [37]. In a study of 570 ICU patients who underwent continuous EEG for detection of subclinical seizures or unexplained lower level of consciousness, seizures were found in 19%, and 92% of these patients had only nonconvulsive seizures [38]. NCSE was found in 8% of comatose general ICU patients [39], and within the neurological ICU population, 23 of 170 patients (13.5%) had NCSE detected on EEG [40].

Additionally, electrographic seizures may not be seen in the initial hours after continuous EEG is started. While approximately 97% of patients had their first seizure within 24 h of starting continuous EEG in one study [41], another

study demonstrated that, while seizures were detected on continuous EEG in 88% of patients in the first 24 h, longer than 24 h of monitoring was generally required for seizure detection in comatose patients [38].

Imaging

Various imaging modalities may be especially useful in the diagnosis of the underlying cause of a patient's SE and therefore guide its management. It is well-known that CT and MRI can demonstrate focal lesion(s) that, if addressed, impact the course of SE [42]. SPECT can also detect SE foci [42–44], though PET and PET/CT can provide better resolution and the ability to perform quantitative measurements [35, 45].

Management of SE

Initial SE Management

The efficacy of benzodiazepines as the initial treatment of SE has been demonstrated in multiple studies, and they are therefore standard of care [46–50]. Efficacy of other major antiepileptic drugs (AEDs) in SE has also been evaluated. Lorazepam and levetiracetam were similarly efficacious in stopping clinical seizures in a randomized, open label study of 79 convulsive or subtle convulsive SE patients [51]. An improved seizure termination rate was seen with valproic acid in convulsive SE patients randomly assigned to intravenous valproic acid or phenytoin but seizure freedom at 24 h was similar for both medications [52]. Valproic acid and phenytoin equally terminated seizures in a randomized study of 74 patients with SE or acute repetitive seizures (defined as at least two seizures occurring over 5–6 h different from their usual pattern and not categorized as SE) [53]. Another study suggested that phenobarbital more quickly aborts generalized convulsive SE than diazepam and phenytoin combined [54].

While even successful initial treatment with benzodiazepines should always be followed up with longer-term maintenance therapy using AEDs, approximately 40% of patients with convulsive SE do not immediately respond to benzodiazepines and require second-line AEDs to abort seizure activity. In two randomized studies in which second-line therapy was evaluated, intravenous valproic acid and continuous intravenous diazepam were similarly effective [55], and intravenous valproic acid and phenytoin were also similarly effective [56]. In a meta-analysis of studies of benzodiazepine-resistant SE, seizure cessation with either valproate or phenobarbital was greater than with levetiracetam or phenytoin [57]. Notably, the Established Status Epilepticus Trial (ESETT) is an ongoing (though now closed to enrollment for adults) NIH-supported, multicenter, randomized, blinded, comparative effectiveness study of fosphenytoin, valproic acid, or levetiracetam for patients with benzodiazepine-refractory SE [ClinicalTrials.gov Identifier: NCT01960075] [10].

Each subsequently added AED is usually less effective than those used before it. The effectiveness of the first AED in terminating convulsive SE was 55.5%, the second AED 7.0%, and the third AED 2.3% in a randomized controlled trial that compared four different AED regimens (phenytoin, lorazepam, phenobarbital, and diazepam followed by phenytoin) [2, 46]. This suggests that SE becomes more resistant to treatment the longer it continues. Treatment should therefore progress rapidly along a center's treatment algorithm of 2nd, 3rd, 4th, etc. treatment options.

Refractory SE and Super-refractory SE

RSE management includes controlling seizures, treating seizure etiology, and managing and preventing complications [58]. The degree of background EEG suppression needed to treat RSE is not entirely clear. In a meta-analysis of 193 RSE patients, background EEG suppression was associated with fewer breakthrough seizures versus seizure suppression alone though it was also associated with a greater frequency of hypotension but no difference in mortality [59]. A study including 63 RSE episodes showed that improved functional outcome was associated with seizure suppression versus burst suppression or isoelectric background [58]. In 47 RSE patients, the level of EEG suppression had no effect on outcome [16]. In addition, in 19 patients in RSE and 37 attempts to lift anesthetic coma, it was found that burst suppression ratio (fraction of time spent in burst suppression) and the length of interburst intervals did not predict successful abortion of RSE but that the amount of epileptiform activity within bursts seemed to correlate [60].

RSE is usually treated with continuous anesthetic agents, while progress is assessed with the aid of continuous EEG. These continuous anesthetic agents are typically maintained for 24–48 h before they are weaned to assess for breakthrough seizures, although the optimal duration needed for controlling seizures remains unclear [1]. For 63 episodes of RSE in 54 patients, 11 days was the average duration anesthetic-induced coma was maintained [19].

The four major intravenous anesthetics used for RSE include midazolam, propofol, pentobarbital (thiopental is often used outside the US), and ketamine. Midazolam, propofol, and barbiturates are GABA agonists, and propofol may also act as an NMDA antagonist; ketamine is an NMDA antagonist. All four drugs are primarily metabolized in the liver [4]. It is unclear if the anesthetics with a shorter half-life (midazolam or propofol) should be used before the ones with

a longer half-life (barbiturates). Some algorithms include pentobarbital and ketamine under RSE and others recommend these drugs only for the treatment of SRSE. In one meta-analysis, pentobarbital appeared to be associated with a decreased amount of breakthrough seizures, short-term treatment failure, and changes to another infusion as compared to midazolam and propofol [59]. In RSE cases in which barbiturates were administered, EEG burst or total suppression was achieved more frequently than in RSE cases without the use of this medication [16]. However, barbiturates may be linked to longer hospital stay [16]. In a small randomized trial of propofol versus pentobarbital, time spent being mechanically ventilated was longer in patients treated with pentobarbital, but return to baseline and mortality were similar [61]. One problem with midazolam is that tachyphylaxis can develop, requiring progressively higher doses [58]. On the other hand, propofol infusion syndrome – characterized by bradycardia progressing to asystole, metabolic acidosis, rhabdomyolysis, hyperlipidemia, and enlarged or fatty liver – can be a life-threatening condition typically associated with high doses and long duration of propofol use [62].

Ketamine has recently emerged as an alternative to traditional intravenous anesthetic agents. Unfortunately, knowledge about ketamine and its potential usefulness is limited since it is often added to other continuous infusions [4]. A meta-analysis of 110 adult patients revealed that ketamine may have helped control RSE in about 57% of patients [63]. A review of 95 patients treated with ketamine for RSE or SRSE showed that seizures resolved in 68%, but outcomes were variable: good outcomes were observed in 19 (including discharges to home or rehabilitation), death in 30, and other/unknown deficits in the remaining patients [64]. While the side effects of ketamine for the treatment of SE are not well delineated, concerns include psychiatric symptoms (e.g., hallucinations, delirium, dreams), increased intracranial pressure, increased intraocular pressure, increased secretion of saliva, arrhythmias, respiratory depression, and neurotoxicity [64].

It is important to note that adequate therapy with AEDs must be continued while the patient is being treated with anesthetic agents so that seizure control can be maintained once the patient has been weaned.

Table 2.2 Alternative therapies used in RSE and SRSE

Therapy	Additional information
Neurosurgery	Consider if a seizure focus can be found in a noneloquent brain region [3]. Includes corpus callosotomy; focal, lobar, or multilobar resection; hemispherectomy; and multiple subpial transections with or without focal resection [65]. Of 23 patients undergoing surgery for RSE, 78.3% were seizure-free during a follow-up period of 4 months to 5 years [65].
Repetitive transcranial magnetic stimulation	Intracranial electrical current provided in a noninvasive manner In 21 SE and RSE patients, rTMS was associated with seizure control or reduction in 71.4%, though seizures recurred in 73.3% who had initially responded [66].
Electroconvulsive therapy	In 19 patients who underwent electroconvulsive therapy for RSE, seizure reduction or control occurred in 57.9% [67] Adverse events included 3 patients who had transient amnesia or lethargy [67].
Hypothermia	Several case reports suggested a possible benefit from hypothermia in RSE [68] A recent study in which 270 mechanically ventilated ICU patients in convulsive SE were randomly assigned to standard care alone or standard care plus hypothermia (32–34°C for 24 h) did not find better outcomes in the patients treated with hypothermia [69].
Immunomodulatory agents	Includes plasma exchange, intravenous immunoglobulins, steroids, adrenocorticotropic hormone, rituximab, and cyclophosphamide [3, 70, 71] These could be considered in SE cases suspected to be caused by an immunological process (such as anti-NMDA receptor encephalitis) after infection has been excluded [3, 70, 71].
Ketogenic diet	In 5 SRSE patients who underwent the ketogenic diet after not responding to multiple AEDs, seizure frequency decreased to half at a median of 8 days [72]. After 1 month on the ketogenic diet, seizure reduction for all patients was at least 75%, and 60% of patients were seizure free and the rest suffered nondisabling partial seizures at last follow-up (1–16 months after initiating the diet) [72]. In a prospective multicenter phase I/II study of adult SRSE patients treated with the ketogenic diet, SRSE resolved in 78.6% who completed treatment with the diet at a median of 5 days [73]. Side effects include metabolic acidosis, hyponatremia, hyperlipidemia, hypoglycemia, gastroesophageal reflux, constipation, weight loss, aspiration pneumonia [72, 73].
Allopregnanolone	Neuroactive steroid positive allosteric modulator of $GABA_A$ receptors that has demonstrated success in reducing seizure activity in animal models and in a phase I/II single arm trial [74, 75]. However, there was no difference between the allopregnanolone and placebo arms in treating SRSE in a phase III, randomized, double-blind, placebo-controlled trial [76].
Others	Intravenous magnesium, inhalational anesthetic agents, vagal nerve stimulation, deep brain stimulation, and classical music have been tried [1, 3, 58].

Finally, several other approaches have been used in RSE and SRSE (Table 2.2). The evidence supporting these treatment strategies is often sparse or contradictory.

Table 2.3 Suggested initial SE treatment algorithm

Check vital signs
Evaluate airway, consider intubation
Check finger stick blood glucose
Check laboratories (basic metabolic profile, toxicology screen, AED levels)
Administer 1st AED (usually a benzodiazepine)
Administer 2nd AED if SE continues (see Table 2.2)
Start diagnostic workup concurrently with emergency treatment (e.g., EEG, CT head, lumbar puncture)

Adapted from Brophy et al. [1] with permission

SE Pharmacology

Algorithms have been proposed for managing SE, such as the one described in Table 2.3. Table 2.4 includes second-line AEDs used to treat SE, and Table 2.5 describes continuous infusions used to treat RSE, including dosing and side effects.

Complications of SE

It should be noted that complications may occur in SE. These include cardiac arrhythmias, hypotension, need for intubation, deep vein thrombosis or pulmonary embolus, infections such as pneumonia, critical illness myopathy or neuropathy, and drug rash. Some of these complications may at least in

Table 2.4 Second-line AEDs

Medication	Initial dose	Maintenance dose	Serious adverse effects/notes
Fosphenytoin	20 mg PE/kg IV	Up to 150 mg PE/min	Arrhythmia, hypotension Phenytoin and valproic acid interact [77]
Lacosamide	200–400 mg IV	200 mg IV	PR prolongation, hypotension Minimal drug interactions Has not been used much in SE
Levetiracetam	1000–3000 mg IV	2–5 mg/kg/min IV	Occasional behavioral issues [78] Minimal drug interactions
Phenobarbital	20 mg/kg IV	50–100 mg/min IV	Respiratory depression, hypotension IV form contains propylene glycol
Phenytoin	20 mg/kg IV	Up to 50 mg/min IV	Arrhythmia, hypotension, purple glove syndrome IV form contains propylene glycol Phenytoin and valproic acid interact [77]
Topiramate	200–400 mg PO	300–1600 mg/day PO (divided over 2–4 doses daily)	Metabolic acidosis Not available in IV form
Valproic acid	20–40 mg/kg IV	3–6 mg/kg/min	Gastrointestinal issues (pancreatitis, hepatotoxicity), hyperammonemia, thrombocytopenia Phenytoin and valproic acid interact [77]

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Table 2.5 Continuous infusions for RSE

Medication	Initial dose	Maintenance dose	Serious adverse effects/notes
Isoflurane	Not established	End tidal concentrations 0.8–2% titrated to EEG	Cardiac and respiratory depression Infections
Ketamine	0.5–4.5 mg/kg	Up to 5 mg/kg/h	Hypertension Arrhythmia Pulmonary edema Anaphylaxis
Lidocaine	1.5–2 mg/kg	Up to 3.5 mg/kg/h	Arrhythmia Methemoglobinemia
Midazolam	0.2 mg/kg	0.05–2 mg/kg/h	Respiratory depression Hypotension Tachyphylaxis after long use
Pentobarbital	5–15 mg/kg	0.5–5 mg/kg/h	Cardiac and respiratory depression Hypotension Ileus Loss of neurologic exam at high doses
Propofol	1–2 mg/kg loading dose	30–200 mcg/kg/min	Propofol infusion syndrome Respiratory depression Hypotension
Thiopental	2–7 mg/kg	0.5–5 mg/kg/h	Cardiac and respiratory depression Hypotension

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part be the result of immobility from SE or possibly from induced therapeutic coma. Further, intravenous anesthetic agents and other treatments may cause toxicity and/or immunosuppression [58]. Some complications may result in the death of patients independent of the SE.

In-Hospital Decision-Making

Generally, physicians (including trainees such as residents and fellows) are responsible for making the majority of the decisions regarding SE patients in the NCCU. However, both the epileptologist and pharmacist play important roles as well. The epileptologist provides invaluable information regarding whether SE is ongoing and how SE treatments may or may not have modulated the seizure activity. In the neurocritical care patient population, the analysis of both raw and quantitative EEG data by physicians specialized in interpreting EEG is essential [38, 79]. The pharmacist helps to guide the initiation and continuation of AEDs and also provides information regarding side effects and interactions with other medications patients may be taking (including other AEDs).

Decision-making in the management of SE can be challenging and is definitely a team effort. It is important that physicians and nurses comprehensively and jointly care for the patient with SE [1]. To underscore the importance of this collaborative approach it should be noted that the recent guidelines for the treatment of SE published by the Neurocritical Care Society as well as the American Epilepsy Society both were co-authored by specialists in the fields of epileptology, neurocritical care, and pharmacology [1, 2]. In fact, one of these guidelines specifically indicates that the people who reviewed the studies used in the guideline "consisted of a group of neurologists, neurology nurses, emergency medicine physicians, clinical pharmacists, methodologists, and neurocritical care physicians with experience in status epilepticus and anticonvulsants." [2]

SE Outcomes and Discharge Destinations

Clinical Outcomes

Mortality in patients with SE may be as high as 30% [2]. However, it is not definitively known whether detecting and treating seizures affects outcomes since seizures are often epiphenomena for severe brain injury [7]. Worse discharge outcomes can be seen with the female sex, age > 60 years, smaller hospitals, comorbidities (e.g., hypertension, previous stroke), SE complications (e.g., respiratory failure, sepsis), and etiologies such as post-cardiopulmonary resuscitation [80]. Reduced likelihood of functional deterioration at discharge has been shown to be associated with normal brain imaging and presence of SE on admission [81].

In RSE, mortality rates can reach 16–39% [3]. In a study of 63 RSE episodes, poor outcome at discharge (defined as modified Rankin scale 4–6) was noted in 76.2% and in-hospital mortality in 31.8% of episodes. Mechanical ventilation was required in 90.5% of episodes, and prolonged mechanical ventilation was associated with mortality. Poor functional outcome was associated with greater CSF white blood cell count, days under anesthetic coma, cardiac arrhythmias needing intervention, and pneumonia. Good functional recovery was associated with seizure control without need for deep suppression on EEG (isoelectric or burst-suppression) [19]. Fever was the only independent predictor of outcome after adjusting for acute symptomatic etiology, viral encephalitis etiology, septicemia, and acidosis in another study [20]. In-hospital mortality was 7.4% and mortality at 1 year was 25.4% in 395 RSE patients treated in an ICU. In a multivariate analysis, only Sequential Organ Failure Assessment (SOFA) score was independently associated with in-hospital mortality. Independent predictors of mortality at 1 year were older age, SOFA score, SRSE, and previously not being independent in activities of daily living [12].

Not much is known regarding the outcome of SRSE. Long-term mortality is approximately 30–50% [5, 23, 24]. At 6 months, Glasgow Outcome Scale 4–5 was achieved in 33.3% of SRSE patients, which was significantly worse than in nonrefractory SE patients (79.1%), but similar to RSE patients (57.1%) [24]. In another study, compared to RSE patients, SRSE patients had a longer stay in the neurologic ICU and in the hospital and were also more likely to be functionally dependent at hospital discharge [25].

Prognostic Scores

Scores to predict outcomes in SE are available.

The Status Epilepticus Severity Score (STESS) is based on 4 factors: age, level of consciousness, seizure type, and history of seizures [82]. STESS has been found to be a predictor of survival and ability to achieve baseline clinical condition, and – regardless of whether patients underwent coma induction – patients with favorable STESS scores generally seem to survive [83]. In an external validation study of 171 patients, the score performed better in identifying survivors compared to nonsurvivors [84].

The Epidemiology-Based Mortality Score in Status Epilepticus (EMSE) assigns points based on mortality rates in the literature for factors thought to be predictive for outcome, and includes age, comorbidities, etiology, and EEG findings. This score was found to predict mortality correctly in nearly 90% of cases and to perform superior to STESS [85].

The END-IT score includes the following independent predictors of unfavorable outcome (modified Rankin Scale 3–6) at 3 months after discharge: encephalitis, NCSE (here defined as subtle SE in which myoclonic jerks or nystagmus occur in insufficiently treated convulsive SE), diazepam resistance, imaging abnormalities (unilateral lesions, bilateral lesions, or diffuse cerebral edema), and intubation. Each category is assigned 1 point except for imaging (1 point is given for unilateral lesions, 2 for diffuse cerebral edema or bilateral lesions). A cut-off of 3 or more points provided the best sensitivity and specificity for predicting unfavorable outcomes [86].

Conclusion

SE is a complex condition that requires expert care, preferably provided by a multidisciplinary team in the NCCU. Rapid escalation of treatment with AEDs along an established algorithm should be performed. RSE and SRSE may require treatment with anesthetic agents, which – while they have the potential to abort seizure activity – may introduce significant complications and side effects. Further research is needed to fully evaluate alternative treatments. Prognosis may be tied to the underlying cause and can be estimated with the help of recently developed prognostic scores.

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