Management of Status Epilepticus in Adults
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ABSTRACT
• Objective: To review the management of status epilepticus (SE).
• Methods: Review of the literature.
• Results: SE is a relatively common condition that accounts for 3% to 5% of all emergency department evaluations for seizure disorders and occurs in 2% to 16% of all epilepsy patients. The 3 most common etiologies are low levels of antiepileptic drugs, remote symptomatic etiologies, and cerebrovascular accidents. The majority of SEs are convulsant, but there is growing awareness of non-convulsive SEs, which can be diagnosed only via electroencephalogram. Management, which must be initiated at the earliest possible time, has evolved to incorporate pre-hospital measures and 4 treatment stages, with supportive measures and benzodiazepine administration remaining the mainstay initially and followed by older and newer antiepileptic drugs and anesthetics for resistant cases.
• Conclusion: SE is a neurological emergency that still carries significant mortality and morbidity if not treated immediately and properly.

Key words: status epilepticus; seizures; convulsive status epilepticus; nonconvulsive status epilepticus.

Status epilepticus (SE) is a relatively common condition that accounts for 3% to 5% of all emergency department (ED) evaluations for seizure disorders and occurs in 2% to 16% of all epilepsy patients [1]. It remains a major neurological emergency that, if not properly and timely treated, leads to death or permanent neurological injury. Since most of patients with convulsive SE are admitted to the hospital via the ED and are then transferred to the intensive care unit (ICU), our focus in this review will be on the latter.

Although only a handful prospective, randomized studies have been reported, guidelines on SE have been published in Europe [2] and the US [3,4]. In this paper, we review the evolving definition and types of SE, its incidence, etiology, and pathophysiology, its diagnosis and treatment algorithms, and its outcome. Our goal is to provide the reader with a concise but thorough review of this still lethal neurological emergency.

Definitions
The International Classification of Epileptic Seizures had previously defined SE as any seizure lasting ≥ 30 minutes or intermittent seizures lasting for > 30 min without recovery of consciousness inter-ictally [5,6]. More recently, a duration of 5 or more minutes of (a) continuous seizures or (b) 2 or more discrete seizures with incomplete recovery of consciousness in-between, proposed by Lowenstein [3,7], offers the advantage of incorporating new knowledge. The shortening of the convulsive period to 5 minutes was based on the fact that the majority of tonic-clonic seizures last for only 1 to 2 minutes, that those lasting > 5 minutes do not stop spontaneously [8], that permanent neuronal injury occurs before 30 minutes, and that refractoriness to treatment increases with longer seizure duration [9].

Refractory SE (RSE) has been defined as SE not controlled after adequate doses of an initial benzodiazepine followed by a second acceptable antiepileptic drug (AED) or SE not controlled after the initial parenteral therapy with a minimum number of standard “front-line” AEDs (either 2 or 3) or SE with a minimum duration of seizures that persist despite treatment (eg, at least or 2 hours) [3,10]. Super-refractory SE (SRSE) is defined as SE that continues or recurs 24 hours or more after the onset of anesthetic therapy or recurs on the reduction or withdrawal of anesthesia [11].

Non-convulsive SE (NCSE) is defined as the presence of altered consciousness or behavior for ≥ 30 minutes, the absence of overt clinical signs of convulsive activity during that period, and the electroencephalographic (EEG) confirmation of seizures or activity that responds
to treatment together with improvement of consciousness [12–15]. Two major types of NCSE can be encountered: the one in patients with epileptic encephalopathy/coma and the one in patients with absence or complex partial seizures, who are not usually admitted to ICU and are functional yet impaired. Because of the confusion between these 2 extremes in the NCSE spectrum, working criteria for standardization of reporting, utilizing the frequency of electroencephalographic epileptiform discharges or delta/theta waveforms have been proposed [15]. A recent compendium of 123 cases of NCSE with clinical descriptions and EEG patterns following a syndromic classification approach has also been published [16].

**Types of SE**

Three major categories of SE have been described: generalized convulsive SE (GCSE), focal motor SE (FMSE or epilepsy partialis continua [EPC]) of Kojevnikov, and NCSE. GCSE and FMSE are easily recognized due to overt convulsions. NCSE, however, has a more obscure phenotype and can be subdivided into a spectrum encompassing typical absence and complex partial SE, atypical absence SE and tonic SE (usually in children with learning disabilities), epileptic behavioral disturbance and psychosis, including Balint–like syndrome [17], confusional states or delirium with epileptiform discharges and SE in coma (after significant brain injuries, such as hypoxia-ischemia, most commonly encountered in ICUs) [13,18]. The 2 extremes in this NCSE spectrum have completely different prognoses, with absence SE the most benign and SE in coma the most dismal.

Lastly, SE presents either spontaneously or can be “semi-intentional” iatrogenic, encountered either in the neuro-ICU or epilepsy monitoring unit, when AEDs are withdrawn under continuous EEG recording in order for seizures to emerge and be recorded with surface or intracranial electrodes.

**Incidence of SE**

In a prospective population-based epidemiological study, the incidence of SE was estimated at 41–61/100,000 patients/year. For the US, this translates to 125,000 to 195,000 episodes per year [19].

The highest incidence of SE occurs during the first year of life and during the decades beyond 60 years, and is also dependent on the SE subtype. Partial SE occurs in 25% of cases of SE and NCSE accounts for another 4% to 26% [19,20], but the incidence for the latter is considered an underestimate due to the need for continuous EEG monitoring (which is not widely available). For example, NCSE was discovered in no patient with acute stroke [21], 8% of comatose ICU patients [22], 7% of patients with intracerebral hemorrhage [23], 3% to 8% of patients with subarachnoid hemorrhage [24–26], 6% of patients with metastatic cancer [27], and 6% of patients with head trauma [28].

The incidence of RSE and SRSE is also unknown. In a recent retrospective study from a neuro-ICU in a West China hospital, the percentage of non-refractory SE, RSE, and SRSE were 67.3%, 20.4% and 12.2%, respectively [29]. Other retrospective studies have shown that 12% to 43% of SE cases become refractory [30–33] and that approximately 10% to 15% of all cases of hospital-admitted SE will become super-refractory at some point, but no prospective studies have been published.

Risk factors that have been identified for RSE are encephalitis as a cause, severe consciousness impairment, de novo episodes of SE, delay in initiation of treatment, NCSE, and focal motor seizures at onset [30,32,34,35]. In a more recent study from ICU patients in Switzerland and the US, acute SE etiology (traumatic brain injuries, cerebrovascular accidents, meningoencephalitis, brain tumors, surgical brain lesions, exposure to, or withdrawal from, recreational drugs, prescription drugs, alcohol, metabolic disturbances and fever), coma/stupor, and serum albumin < 35 g/L at SE onset were independent predictors for RSE [36].

**Etiology of SE**

The 3 most common etiologies for SE are low levels of antiepileptic drugs (AEDs) in 34% of the cases (usually due to noncompliance), remote symptomatic etiologies (history of neurological insults remote to the first unprovoked SE episode, 24%), and cerebrovascular accidents (ischemic and hemorrhagic strokes, 22%). These are followed by hypoxia (13%) and metabolic disturbances (15%). Because 82% of patients in the remote group have a history of cerebrovascular disease, almost 50% have either acute or remote cerebrovascular disease as etiology of SE [19].

The etiologies of SE can be subdivided into those with clear neurological structural or metabolic pathology and those associated with systemic derangements (usually due to drugs or toxo-metabolic encephalopathies). Table 1 presents a compendium of frequently encountered etiologies of SE. The latter may be encountered in hospitalized
Table 1. Common Etiologies of Status Epilepticus or Seizures in the Emergency Department or Intensive Care Unit (adapted from [84,133])

<table>
<thead>
<tr>
<th>Primary Neurological Pathology</th>
<th>Systemic Derangements</th>
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<tbody>
<tr>
<td>Neurovascular</td>
<td>Hypoxia/ischemia post cardiorespiratory arrest</td>
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<tr>
<td>Ischemic stroke</td>
<td>Drug/substance toxicity</td>
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<tr>
<td>Arteriovenous malformations</td>
<td>Antibiotics</td>
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<tr>
<td>Hemorrhage</td>
<td>Antidepressants</td>
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<tr>
<td>Cerebral sinus thrombosis</td>
<td>Antipsychotics</td>
</tr>
<tr>
<td>Brain tumor</td>
<td>Bronchodilators</td>
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<tr>
<td>Primary</td>
<td>Local anesthetics</td>
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<tr>
<td>Metastatic</td>
<td>Immunosuppressives</td>
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<tr>
<td>Central nervous system infection</td>
<td>Cocaine</td>
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<tr>
<td>Abscess</td>
<td>Amphetamines</td>
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<tr>
<td>Meningitis</td>
<td>Phencyclidine</td>
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<tr>
<td>Encephalitis</td>
<td>Drug/substance withdrawal</td>
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<tr>
<td>Encephalitis (noninfectious)</td>
<td>Barbiturates</td>
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<tr>
<td>Paraneoplastic limbic</td>
<td>Benzodiazepines</td>
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<tr>
<td>NMDA-receptor and other antibodies</td>
<td>Opioids</td>
</tr>
<tr>
<td>Autoimmune limbic</td>
<td>Alcohol</td>
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<tr>
<td>Voltage–gated K+ channel (VGKC/LGII) and other antibodies</td>
<td>Infection – fever – sepsis</td>
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<tr>
<td>Inflammatory disease</td>
<td>Metabolic abnormalities</td>
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<tr>
<td>Vasculitis</td>
<td>Hypophosphatemia</td>
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<tr>
<td>Acute disseminated encephalomyelitis</td>
<td>Hyponatremia</td>
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<tr>
<td>Traumatic brain injury</td>
<td>Hypoglycemia</td>
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<tr>
<td>Contusion</td>
<td>Renal/hepatic dysfunction</td>
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<tr>
<td>Hemorrhage</td>
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<tr>
<td>Blood-brain barrier and autoregulation disruption</td>
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<tr>
<td>Posterior reversible encephalopathy</td>
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<tr>
<td>Hypertensive encephalopathy</td>
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<tr>
<td>Surgical injury (craniotomy)</td>
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<tr>
<td>Primary epilepsy</td>
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<tr>
<td>Primary CNS metabolic disturbance (inherited)</td>
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</table>

or critically ill patients and the former often in outpatients or in the ED.

In general ICUs, metabolic abnormalities can account for 33% of seizures, drug withdrawal for 33%, drug toxicity for 14.5%, and stroke for 9% to 39% [37,38]. In ICUs, sepsis remains a common etiology of electrographic seizures or periodic epileptiform discharges [39,40], and legal or illegal drugs, such as ciprofloxacin, levofloxacin, piperacillin/tazobactam, cefepime and carbapenems [41–43], lithium or theophylline intoxication, vigabatrin, tiagabine or crack/cocaine, are another [18] (especially when their metabolism is altered due to interactions with other drugs or when their excretion is impaired due to hepatic or renal failure).

Beyond these common causes of SE, a workup for rare etiologies should be entertained. In a systematic review of 513 papers on SE, 181 uncommon causes of SE were identified and subdivided into immunologically mediated disorders, mitochondrial diseases, rare infectious disorders, genetic disorders, and drugs or toxins [18,44].

The most recent knowledge in this category is the contribution of paraneoplastic or autoimmune conditions to a large percentage of previously cryptogenic pharmacoresistant seizures or super-refractory SE, most in the context of limbic encephalitis. Many of these patients have never experienced seizures or SE before and a new acronym has been devised for them: new-onset refractory status epilepticus (NORSE), ie, a state of persistent...
seizures with no identifiable etiology in patients without preexisting epilepsy that lasts longer than 24 hour despite optimal therapy [45]. A growing array of autoantibodies against intracellular and surface synaptic neuronal targets has been described in addition to the previous literature of Rasmussen’s encephalitis and Hashimoto’s encephalopathy [46]. The most common autoantibodies associated with seizures and SE include anti-Hu, anti-Ma2, anti-CV2/CRMP5, anti-Ri, ANNA3, anti-amphiphysin, anti-NMDA receptor, anti-LGI1 and CASPR2, anti-GABA-beta, anti-GluR3, anti-mGluR5 and alpha 3 ganglionic acetylcholine receptor [47,48]. The diagnosis frequently remains elusive due to lack of knowledge or absence of widespread availability of serologic testing (with sometimes weeks-long delay for the results to be available), but the response to treatment with removal of tumor, plasmapheresis, or immunomodulation and immunosuppression is often dramatic.

Pathophysiology of SE

Most seizures are self-terminating phenomena lasting from a few seconds to a few minutes [49]. One of the distinguishing characteristics of seizures evolving into SE, however, is the switch to a self-sustaining situation, which is time-dependent. Seizures lasting more than 30 minutes would rarely stop spontaneously compared to 47% of those lasting between 10 to 29 minutes, which are self-resolving [50]. Moreover, in one study no self-limited seizure lasted more than 11 minutes [8].

The self-limiting character of seizures is due to inhibitory circuitry that suppresses their duration and propagation in the brain. Under specific circumstances, however, the inhibitory mechanisms fail and seizures progress to SE, which leads to synaptic reorganization, blood-brain barrier disruption, inflammation, metabolic crisis, more tissue damage, and further seizures. Neuronal injury during SE is the result of increased excitotoxicity [51–53] but also stems from systemic derangements such as hypoxia, acidosis, hypotension, or multiorgan dysfunction [54]. The seminal animal studies by Meldrum have shed a light on the systemic effects: after prolonged bicuculine-induced convulsive SE in baboons, neuronal damage and cell loss was evident in the neocortex, cerebellum and hippocampus. When systemic factors were kept within normal physiological limits (paralyzed and artificially ventilated animals with adequate serum glucose levels), there was decreased but still present neocortical and hippocampal cell damage, but absent cerebellar cell injury [55,56]. These experiments showed more than 40 years ago that the seizure activity per se is responsible for the neuronal damage and the systemic derangements play an additional role.

The direct neuronal injury as a result of the ongoing seizures, the perpetuation of seizures into SE, the resistance to treatment and the refractoriness that ensues have also been elucidated at a molecular level during the last decades. Initially, the g-aminobutyric acid (GABA) inhibitory circuits may be deficient and this is the reason why benzodiazepines or barbiturates, which work through GABAergic receptor agonism, are very effective during this early period. As time passes however, GABA receptors undergo a significant shift in their ability to respond to benzodiazepines [57,58]. This is due to changes in receptor presence at the inhibitory synapse, a phenomenon that has been called “receptor trafficking” by Arancibia and Kittler in 2009 [59]. There are differences in the type of GABA_\text{A} receptors found synaptically and extrasynaptically. GABA_\text{A} receptors containing the \gamma subunit are located synaptically and mediate phasic inhibition. Conversely, the \delta subunit-containing GABA_\text{A} receptors are located exclusively extrasynaptically and mediate tonic inhibition [60,61]. Smith and Kittler described the highly dynamic state of receptor presence on the surface of axons and explained how receptors move laterally from extrasynaptic sites to the synapse and then out of it to be internalized and either recycled to the surface or degraded [62]. This “receptor trafficking” intensifies during SE, and the overall effect becomes a reduction in the number of functional GABA_\text{A} receptors in the synapses. As GABA is the principle inhibitory transmitter, this reduction in GABAergic activity may be an important reason for seizures to become persistent.

However, this is not all. Additional mechanisms leading to refractoriness include the following:

(a) Excessive relocation of N-methyl-D-aspartate (NMDA) type glutamate receptors to the cell surface after 1 hour of SE, leading to increase of miniature excitatory NMDA currents and NMDA neurotransmission, with potentiation of glutamate excitotoxicity [53,63]

(b) Increased brain expression of drug efflux transporters, such as P-glycoprotein at the blood-brain barrier, which may reduce concentrations of AEDs at their brain targets [64]
(c) Up- and down-regulation of specific ATP-gated ion channels (P2X receptors) inducing altered response to ATP release [65]

(d) Change in the extracellular ionic environment (for example, the normally inhibitory GABA_A receptor-mediated currents may become excitatory with changes in extracellular chloride concentrations) [66]

(e) Mitochondrial insufficiency or failure, which would lead to cell necrosis and apoptosis [67]

(f) Inflammatory processes, with opening of the blood-brain barrier (BBB) contributing to perpetuation of seizures [44]. The underlying mechanism is a maladaptive response of the astrocytes to the BBB damage, leading to activation of the innate immune system and disturbed homeostasis of the extracellular potassium and glutamate [68].

(g) Large-scale changes in gene expression within the affected brain regions; these are regulated by micro-RNAs, influencing protein levels playing a role in excitability, neuronal death and neuroinflammation [69].

All of these pathophysiologic derangements may become targets for future antiepileptic treatments.

Although the direct and indirect injury from ongoing convulsive SE is not in doubt, the significance of NCSE or the ictal-interictal continuum on inflicting additional injury has been more controversial. Recent data, however, do not support a benign process in these situations. It has been shown lately that nonconvulsive seizures lead to physiologic changes in the brain, including elevated intracranial pressure, changes in the brain metabolism, and delayed increase in cerebral blood flow [25]. In addition, using microdialysis, elevated lactate/puruvate ratio, indicating metabolic crisis, has been shown during periods of nonconvulsive seizures or periodic discharges [70]. Similarly, high-frequency periodic discharges lead to inadequate increase in cerebral blood flow and tissue hypoxia [71], and lateralized periodic discharges, lateralized rhythmic delta activity, and generalized periodic discharges are associated with seizures [72].

**Diagnosis of SE**

The diagnosis of SE is primarily clinical and encompasses motor phenomena and alteration of mental status. Focal-onset convulsions can remain focal, follow a Jacksonian march, or immediately generalize to involve the whole body with loss of consciousness. Most of the time, this secondary generalization can only be appreciated during EEG recording. In addition, mental status alteration can differentiate simple partial SE (no change in mental status) from complex partial SE (disturbed sensorium).

The presence or absence of motor phenomena and loss of consciousness do not necessarily correlate with the EEG activity during or after SE. For example, persistent electrographic seizures or NCSE after control of convulsive SE have been demonstrated with continuous EEG [73]. Conversely, altered mental status is also a poor clinical differentiator, since 87% of patients successfully treated for convulsive SE and 100% treated for NCSE remained comatose 12 hours following the initiation of therapy [20]. In addition, only 27% of motor, seizure-like phenomena in the ICU were proven to be seizures in a retrospective study [74]. Psychogenic nonepileptic attacks, occurring in between 3.8% and 9.5% of ICU patients presenting with seizures [74,75], is another situation that may lead to confusion, inappropriate intubation, and ICU admission. Strange phenomena, such as fasciobrachial seizures (brief facial grimacing and ipsilateral arm posturing) many times preceding the onset of amnesia, confusion, or temporal lobe seizures have been described in patients who have non-paraneoplastic limbic encephalitis associated with voltage-gated potassium channel (VGKC) antibodies, especially against the leucine-rich glioma inactivated-1 (LGI1) protein [76,77]. Without a continuous video EEG, these phenomena may not be captured or appreciated. Therefore, EEG monitoring is an important tool for the evaluation of these patients and criteria for its use have been published [78]. The EEG criteria for convulsive SE have been clearly delineated, but for NCSE a mix of clinical and EEG criteria should be met [14,15,79].

In addition to clinical observation and EEG, there has been interest lately in multimodality monitoring of acutely brain-injured patients for seizures or SE using electrocorticography or mini depth electrode placement, partial brain tissue oxygen tension, cerebral blood flow, and microdialysis in addition to scalp EEG. Although preliminary and limited in few academic centers, this approach has produced interesting findings. For example, in a study from Columbia University, 38% of 48 patients with subarachnoid hemorrhage and multimodality monitoring had intracortical seizures, while only 8% of them had surface seizures, all nonconvulsive [25]. In another study, 68% of seizures and 23% of periodic discharges...
were only captured on the depth electrodes and were missed on the surface ones [71]. Therefore, detection of SE may change in the future with use of more sensitive techniques than scalp EEG.

**Treatment**

Significant practice variations exist in the management of SE even among academic centers in the US [80] despite the fact that the goals of treatment are concrete. These include (1) emergent medical management, (2) termination of seizures, (3) prevention of recurrence of seizures, and (4) prevention or treatment of complications.

Management of SE must begin in a prehospital setting by the emergency medical services, because the faster the treatment is offered, the better the response. Several studies have attempted to assess the possibility of aborting SE even prior to the hospital. In a randomized, double-blinded study, lorazepam was 4.8 times and diazepam 2.3 times more effective than placebo in terminating SE on arrival in the ED when given intravenously (IV) by paramedics [81]. The RAMPART study was a double-blind, randomized, non-inferiority trial comparing the efficacy of intramuscular (IM) midazolam (10 mg followed by placebo IV) with that of IM placebo followed by intravenous lorazepam (4 mg) for children and adults in SE treated by paramedics. At the time of arrival in the ED, seizures had ceased without rescue therapy in 73.4% and 63.4%, respectively, favoring midazolam [82].

**Table 2** shows the proposed algorithm for treating SE in the hospital and includes 4 stages (emergent initial measures, urgent control, refractory SE, and super-refractory SE) [3,11,18,83,84].

**Table 2. In-hospital Treatment Algorithm for Convulsive and Non-convulsive Status Epilepticus (modified from [3,18,84,90,115,134])**

<table>
<thead>
<tr>
<th>Stage 1: Emergent Initial Measures</th>
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<tbody>
<tr>
<td>Preserve airway and oxygenation by oxygen face mask or intubation, as needed</td>
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<tr>
<td>Establish IV access. If none, establish intraosseous access.</td>
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<tr>
<td>Measure finger-stick blood glucose. Administer 1 amp of DW 50% IV if &lt; 60 mg/100 mL and 100 mg thiamine IV.</td>
</tr>
<tr>
<td>Order continuous video-EEG to be available during therapy</td>
</tr>
<tr>
<td>Send to the lab: antiepileptic drugs blood levels, electrolytes, complete blood count, liver function tests, arterial blood gases, toxicology screen (urine and blood)</td>
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<tr>
<td>At the same time with the above: Immediate benzodiazepines—IV lorazepam 0.07-0.1 mg/kg or diazepam 0.15-0.25 mg/kg IV. If no IV access, diazepam 20 mg per rectum or midazolam 10 mg IM, buccally or intranasally.</td>
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<tr>
<th>Stage 2: Urgent Control</th>
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<tr>
<td>Phenytoin loading dose 20 mg/kg IV at 50 mg/min or fosphenytoin 20 mg/kg PE (phenytoin equivalents) IV at 150 mg/min</td>
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<tr>
<td>If allergic to phenytoin, valproate 25–40 mg/kg IV load at 3-6 mg/kg/min or levetiracetam 20–60 mg/kg IV (100–500 mg/min; max 4500 mg) or phenobarbital 20 mg/kg IV (rate 50–75 mg/min)</td>
</tr>
<tr>
<td>If seizures continue, phenytoin or fosphenytoin (additional 5 mg/kg to 10 mg/kg or 5 mg/kg PE to 10 mg/kg PE). Goal serum level 20–25 mg/dL. If phenytoin allergy, additional valproate load 20mg/kg IV.</td>
</tr>
<tr>
<td>Continuous video-EEG connected and running</td>
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<tr>
<td>Monitor for hypotension and arrhythmias</td>
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<tr>
<th>Stage 3: Refractory SE</th>
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<tbody>
<tr>
<td>If NCSE and patient not intubated yet, 1 or more of IV phenytoin, valproic acid, levetiracetam, phenobarbital (if not been administered in Stage 2), or IV lacosamide can be tried</td>
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<tr>
<td>Intubation and mechanical ventilation. Avoid hyperventilation.</td>
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<tr>
<td>Propofol 2 mg/kg IV bolus and 150 μg/kg/min to 200 μg/kg/min infusion, ORr</td>
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<tr>
<td>Midazolam 0.2 mg/kg IV bolus, which can be repeated every 5 minutes up to total 2mg/kg, followed by infusion 0.1–0.2 mg/kg/hour</td>
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<tr>
<td>Hemodynamic support by pressors and IV fluid boluses</td>
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<tr>
<td>Continue the infusions for 24 hours if patient not actively seizing on cEEG and then hold them and re-assess</td>
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*continued on page 7*
Emergent Initial Phase

During the emergent initial phase, the goals are protection of the airway, oxygenation, maintenance of blood pressure, exclusion of easily treatable causes (such as hypoglycemia or hyponatremia), and rapid cessation of seizures by administration of first-line AEDs. Benzodiazepines are considered the best first-line AEDs, based on large prospective randomized trials. Lorazepam IV [20], midazolam IM [82] or buccally [85] and diazepam rectally [85] are considered the most effective agents. However, due to the risk for hypoventilation or hypotension, benzodiazepines may be challenged in the future by newer AEDs. In an open-label randomized study of 79 patients with convulsive SE or subtle convulsive SE that compared levetiracetam 20 mg/kg IV over 15 min to lorazepam 0.1 mg/kg over 2–4 min, SE was controlled by levetiracetam in 76.3% and by lorazepam in 75.6% of patients. In patients resistant to the above regimens, lorazepam offered better control than levetiracetam (88.9% vs 70%), but also led more often to mechanical ventilation and hypotension [86]. Endotracheal intubation, however, may not be due to benzodiazepine administration but may occur as a consequence of decreased airway protection from ongoing seizures. In the RAMPART study, actively seizing patients upon ED arrival were twice as likely to be intubated as those with cessation of seizures, and the most common primary reasons reported for intubation were respiratory depression (39%), depressed mental status with or without persistent convulsions (36%), and recurrent convulsions after initial termination (16%) [87].

Urgent Control

If seizures continue, stage 2 medications should be used for benzodiazepine-refractory SE as urgent control treatment. There are some data suggesting better response

<table>
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<th>Table 2. (continued)</th>
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<tr>
<td><strong>Stage 4: Super-refractory SE</strong></td>
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<tr>
<td><strong>Stage 4.1</strong> If seizures and status not controlled by Stage 3 measures:</td>
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<tr>
<td>- Pentobarbital 10 mg/kg IV load at up to 50 mg/min, can be repeated several times until EEG burst-suppression pattern with 20-30 sec suppression goal is achieved. Start at the same time continuous infusion 1 mg/kg/hour and titrate up to 10 mg/kg/hour for same goal, OR</td>
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<tr>
<td>- Thiopental 2-3 mg/kg IV bolus and 0.3 mg/kg/min to 0.4 mg/kg/min infusion, OR</td>
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<tr>
<td>- Ketamine 0.5-4.5 mg/kg bolus IV and 0.9-5 mg/kg/hour infusion</td>
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<tr>
<td>- Isoflurane or desflurane or gabapentin or levetiracetam (in acute intermittent porphyria)</td>
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<tr>
<td><strong>Stage 4.2</strong> Alternative therapies for SRSE (in order from the first to last resort)</td>
</tr>
<tr>
<td>- If seizures continue or recur after emergence from Stage 4.1 treatments:</td>
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<tr>
<td>- Topiramate 2–25 mg/kg/day (children) or up to 300–1600 mg/day (adults) per oro/nasogastric tube</td>
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<td>- Neurosurgical resection of epileptic focus, if one identified</td>
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<td>- Magnesium infusion 4 g bolus IV, 2–6 g/hour infusion</td>
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<td>- Pyridoxine 180–600 mg/day IV or per oro/nasogastric tube for 3 days</td>
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<tr>
<td>- Steroids: methylprednisolone 1 g/day IV for 3 days, followed by prednisone 1 mg/kg/day for 1 week or IVIG 0.4 g/kg/day IV for 5 days, OR</td>
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<tr>
<td>- Plasmapheresis</td>
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<td>- Ketogenic diet 4:1</td>
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<tr>
<td>- Vagal nerve or deep brain stimulation, trigeminal nerve stimulation (TNS) or transcranial magnetic stimulation</td>
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<tr>
<td>- Hypothermia 32°–35°C for &lt; 48 hours</td>
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<td>- Electroconvulsive therapy</td>
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<td><strong>Stage 4.3</strong></td>
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<tr>
<td>After several weaning attempts have failed over a period of weeks or months, consider end-of-life discussion with surrogate decision maker about withdrawal of life support</td>
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rate to valproate after failure to control seizures with phenytoin than to phenytoin after failure of valproate [88]. If available, IV fosphenytoin is preferable to IV phenytoin due to potentially lower risk of side effects. Levetiracetam and phenobarbital IV are also acceptable choices. Levetiracetam can be administered as an off-label loading dose of 20–60 mg/kg IV (although the initial manufacturer was not supporting a “loading” dose; dose of up to 60 mg/kg IV up to 4500 mg maximum has been supported by the latest American Epilepsy Society guidelines [4]). This AED at an initial dose of 2–3 g/day confers an estimated success rate around 70% [89]. In a systematic review of 27 studies (798 cases of convulsive SE) comparing 5 AEDs in the treatment of benzodiazepine-resistant convulsive SE, phenobarbital and valproate had the highest efficacy (73.6% and 75.7%, respectively), followed by levetiracetam (68.5%) and phenytoin (50.2%). Lacosamide studies were excluded from the meta-analysis due to insufficient data [90], but its efficacy has been reported for patients with convulsive and NCSE [91,92]. There is not enough evidence at this point, however, to recommend its routine use for benzodiazepine refractory SE [90].

Refractory SE

When seizures continue despite the use of benzodiazepines and 2nd stage AEDs, SE becomes refractory (stage 3). Treatment of these resistant cases is frequently initiated in the ED and continued in an ICU. Outcomes were not significantly better in patients with SE admitted and managed in a neuro-ICU compared to a general medical ICU in a retrospective study, but the numbers were small (only 27% of SE were admitted to the former) [93] and this may change in the future. Intubation and mechanical ventilation is the first step, if not already present (only 21% of patients in the RAMPART study received endotracheal intubation, with 6.4% in the prehospital setting and 93.6% after admission [87]). Hemodynamic support with pressors or inotropes may be required as most anesthetic agents may decrease the blood pressure. Because of the urgency of controlling the seizures during SE, the potential aspiration risk and the questionable enteral absorption per os administration of additional AEDs is problematic, and IV formulations should be used.

Currently in the US, phenytoin, valproic acid, phenobarbital, levetiracetam, lacosamide, diazepam, lorazepam are available in IV formulations. In February 2016, the FDA also approved brivaracetam (which also is available in an IV formulation) and in October of the same year IV carbamazepine. None of these AEDs has an FDA indication for SE, although they are widely used. Parenteral lacosamide has a success rate of 33% to 67.7% (200–400 mg over 3–5 min was the most common bolus dose) depending on its use as second or third AED [94–96]. In lacosamide-naïve patients with RSE on continuous EEG monitoring, the success rate for cessation of SE was 15.7, 25.5, 58.8, and 82.4% by 4, 12, 24, and 48 hours, respectively [97]. Alternatively, topiramate in doses 300–1600 mg/day per oro/nasogastric tube can be considered [98]. In a study of 35 patients with RSE treated with topiramate as an adjunct AED, the response rate was 86% (as the third AED), and remained stable at 67% after administration as the fourth to seventh AED. Overall, RSE was terminated in 71% of patients within 72 hours after first administration of topiramate [99]. Other studies, however, adjusting for co-variates, did not prove topiramate to be effective in RSE [100]. Clobazam, a unique oral 1,5-benzodiazepine with excellent absorption, has been also used in the treatment of RSE. Seventeen patients with RSE (11 with prior epilepsy) were successfully treated with clobazam, which was introduced after a median duration of 4 days and after a median of 3 failed AEDs. Termination of RSE within 24 hours of administration, without addition or modification of concurrent AED and with successful wean of anesthetic infusions, was seen in 13 patients, whereas indeterminate response was seen in another 3. Clobazam was deemed unsuccessful in 1 patient [101]. In another recent report of 70 episodes of RSE, clobazam was used in 24 (34.3%) of them. If clobazam was the last AED added to therapy before RSE termination, the success was attributed to this drug. Based on this definition, clobazam led to 6 episodes (25%) of successful RSE resolution [102]. If primary or metastatic brain tumor is the presumed cause of SE, a combination of IV phenytoin, IV levetiracetam (median dose 3 g/d) and enterically administered pregabalin (median dose 375 mg/day) led to 70% control of SE on average 24 hours after addition of the third AED [103]. However, the major treatment options, which should not be delayed in unresponsive RSE, are propofol or midazolam infusions at high rates and under continuous EEG monitoring. These infusions should be continued for at least 24 hours and then held to reassess the situation. By that time, co-occurrent metabolic derangements and low AED levels from noncompliance should have been corrected. Prolonged and high-dose propofol should be avoided because of the risk for propofol infusion syndrome, especially if pressors/inotropes are co-infused [104].
Super-refractory SE

Should seizures continue or recur, stage 4 options for SRSE are considered [105]. Pentobarbital with shorter half-life is favored to phenobarbital. The main disadvantages of barbiturates are compromised neuro-exam (which has to be assessed frequently), cardiovascular depression and hypotension, respiratory depression with need for full ventilator support, cough suppression with increased risk for atelectasis and pneumonia, immunosuppression increasing the risk for infection or sepsis, immobility increasing the risk for thromboembolism and ileus mandating parenteral nutrition [106,107]. The depth and duration of the EEG suppression that must be achieved by barbiturates is unknown. Some experts recommend instead of burst-suppression pattern complete suppression or “flat record” because of better seizure control and fewer relapses [108]. Moreover, patients with more prolonged barbiturate treatment (> 96 hours) and those receiving phenobarbital at the time of pentobarbital taper are less likely to relapse [109]. European guidelines recommend titration of propofol and barbiturate to EEG burst-suppression, and midazolam to seizure suppression, maintained for at least 24 h [2]. In recent reviews, it was found that barbiturates control refractory and super-refractory SE in 64% of patients and are ineffective in only 5% [11,110].

If SE continues or recurs after emergence from barbiturate coma, ketamine may be an option [11,83]. Ketamine offers the advantage of NMDA receptor antagonism, which may be important in the late phase of SE and lacks cardiodepressant or hypotensive properties. Early [111] or late [112] use of ketamine has been reported in small case series with various success rates. In a recent multicenter retrospective study from North America and Europe, evaluating 58 patients with 60 RSE, ketamine was likely responsible for seizure control in 12% and possibly responsible in an additional 20%. No responses were observed when infusion rate was lower than 0.9 mg/kg/h or when ketamine was introduced 8 days or more after onset of SE or after failure of seven or more drugs [113].

If all these measures have failed, stage 4.2 treatment options are available (Table 2), but these are mostly based on small case series and expert opinions (except for the recent hypothermia study). Pyridoxine hydrochloride in an IV or enteral form at a dose of 100–300 mg/day for few days can be used in stage 4 or earlier stages, as it is a cofactor in the synthesis of the inhibitory neurotransmitter GABA [114]. There are no strong data for its effectiveness, but it can be used as a cheap and safe alternative [115]. Magnesium has been successfully used in 2 girls with juvenile Alper’s syndrome [116] and is the treatment of choice for eclamptic seizures. Ketogenic diet may also be an option for these patients [117]. Resection of the epileptic focus after mapping with intracranial EEG electrodes may be highly effective but cannot be used in many patients due to lack of focus or eloquence location [83,106,115]. Use of steroids, plasmapheresis or IVIG, followed by immunosuppression can be tried, but one should balance risks and benefits. These immunosuppressive or immunomodulating treatments should be especially considered in patients with NORSE or suspected autoimmune or paraneoplastic encephalitides, where AEDs usually have no effect [46]. These therapies though often precede the diagnosis, since it takes time for the autoantibody panel results to return and the treating physician has to make a decision to blindly start treatment for SRSE.

There were some promising data regarding hypothermia use in these desperate situations [118,119] until the HYBERNATUS study, conducted in France, was recently published. In this study, 270 patients with convulsive SE were randomized in to hypothermia (32° to 34°C for 24 hours) in addition to standard care or to standard care alone. A Glasgow Outcome Scale score of 5 (primary outcome) occurred in 49% of patients in the hypothermia group and in 43% in the control group (a nonstatistical difference). Secondary outcomes, including mortality at 90 days, RSE on day 1, SRSE and functional sequelae on day 90 were not different except for the rate of progression to EEG-confirmed SE on the first day, which was lower in the hypothermia group (11% vs. 22% in the controls). Adverse events were more frequent in the hypothermia group than in the control group [120].

Additional anecdotal treatments are presented in Table 2, but their efficacy is questionable.

This staged management approach may change in the future to a more physiologic and rational treatment with polytherapy based on synaptic receptor trafficking during SE [63]. For example, in an animal model of severe SE, combinations of a benzodiazepine with ketamine and valproate, or with ketamine and brivaracetam, were more effective and less toxic than benzodiazepine monotherapy [121]. Allopregnanolone, a metabolite of progesterone, is an endogenous, naturally occurring neuroactive steroid produced in the ovary, the adrenal cortex and the central nervous system. It is a potent positive allosteric modulator of synaptic and extrasynaptic GABA_A receptors with
antiepileptic activity [122]. Neuroactive steroids, such as allopregnanolone, are currently evaluated in SE.

Outcomes
SE still carries significant mortality and morbidity. Distinct variants of SE carry different mortalities, and the range is quite broad: from zero mortality for absence or complex partial SE in ambulatory patients [12], to 19% to 27% 30-day mortality for generalized tonic-clonic SE [20,123] and to 64.7% 30-day mortality for subtle SE [20]. Variables playing an important role in the outcome are the underlying cause (regarded by most authorities the most important variable), the duration of SE (mortality 32% if persistent for > 1 hour vs 2.7% if < 1 hour), the type of SE, the treatment administered, and the age of the patient (children have better outcomes than adults) [123–125]. The etiology of SE still remains the most important prognostic factor, with alcohol and AED-withdrawal/noncompliance having the best outcomes; structural brain injuries, such as anoxia-ischemia, vascular lesions, or brain tumors, have the worst prognosis.

The most resistant cases pose significant dilemmas regarding the length of treatment using barbiturate coma and the potential for acceptable prognosis or the need to withdraw life support. For RSE, for example, in-hospital mortality is 31.7% and 76.2% of patients reach poor functional outcome. Long-term outcomes are also dismal: at 1 year post-discharge, 74% are dead or in a state of unresponsive wakefulness, 16% severely disabled, and only 10% have no or minimal disability [126]. Duration of drug-induced coma, arrhythmias requiring intervention, and pneumonia are associated with poor functional outcome, whereas prolonged mechanical ventilation with mortality and seizure control without burst-suppression or isoelectric EEG are associated with good functional outcome [127,128].

Treatment with barbiturates may contribute to these outcomes, although it is very challenging to prove causality in such a complex and prolonged ICU environment. Some data have shed light towards that direction: in a recent retrospective study of 171 patients with SE, of which 37% were treated with IV anesthetic drugs, there was a higher risk for infections and a 2.9-fold relative risk for death after adjustment for confounders in the group treated with IV anesthetics compared to the group without these agents [129].

The SE Severity Score (STESS, range 0–6) is a prognostic score for survival [130] and can be used as a scaffold for discussions with families and covariate adjustment tool for research. A favorable score of 0–2 has a negative predictive value of 0.97 for survival and likelihood to return to baseline clinical condition in survivors, although an unfavorable score (3–6) had a positive predictive value for death of only 0.39 [131].

The risk for recurrence of afebrile SE in a population-based study in Minnesota has been estimated at 31.7% over a 10-year follow-up period. The risk for recurrence was about 25% regardless of the underlying etiology, except in those patients with SE occurring in the setting of a progressive brain disorder (who had a 100% risk). Female gender, generalized (vs partial) SE and lack of response to the first AED after the initial episode of SE were independent factors for recurrence [132].

Conclusion
Despite the use of better diagnostic tools (continuous video EEG), advances in technology in the ICU, and availability of new AEDs, SE still carries significant mortality and morbidity, which depends mainly on age and etiology. The current treatment is still staged, with supportive measures and benzodiazepine administration remaining the mainstay initially and followed by older and newer AEDs and anesthetics for resistant cases. With the advance of pathophysiologic mechanisms elucidation at a molecular/receptor level, combinations of AEDs may become the foundation of future SE control.

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