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Emergency Neurological Life Support: Status Epilepticus

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Abstract Patients with prolonged or rapidly recurring convulsions lasting more than 5 min should be considered to be in status epilepticus (SE) and receive immediate resuscitation. Although there are few randomized clinical trials, available evidence and experience suggest that early and aggressive treatment of SE improves patient outcomes, for which reason this was chosen as an Emergency Neurological Life Support protocol. The current approach to the emergency treatment of SE emphasizes rapid initiation of adequate doses of first line therapy, as well as accelerated second line anticonvulsant drugs and induced coma when these fail, coupled with admission to a unit capable of neurological critical care and electroencephalography monitoring. This protocol will focus on the initial treatment of SE but also review subsequent steps in the protocol once the patient is hospitalized.

Keywords Status epilepticus · Seizures · Anticonvulsant · Pharmacologic coma · EEG monitoring · Protocol

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Introduction

Each year in the United States, emergency departments (EDs) experience an average of one million seizure-related visits based on International Classification of Diseases (ICD)-9 coding. These visits represent approximately 20% of ED visits for neurological problems and 1% of all ED visits [1–3]. Approximately 200,000 US patients per year have prolonged or rapidly recurring convulsions lasting more than 5 min—the defining features of status epilepticus (SE).

The 30-day mortality of patients with generalized convulsive SE ranges from 10 to 27% [4–9]. Prolonged seizures are associated with higher mortality and worse clinical outcomes [7, 8, 10–12]. Adverse effects of SE include both indirect systemic problems arising from the convulsive state (e.g., impaired ventilation, pulmonary aspiration, metabolic aberrations) and direct neuronal cellular injury from excitotoxicity, causing both immediate neuronal loss and delayed programmed cell death.

Rapid control of seizures is fundamental to the emergency treatment of SE (Fig. 1). Earlier termination of SE reduces neuronal injury in animal models of SE, and is associated with improved clinical outcomes in human observational studies. In experimental SE, benzodiazepines are more likely to terminate seizures when given closer to seizure onset and decrease in effectiveness as seizure duration increases. This is most likely related to changes in the neuronal gamma-aminobutyric acid (GABA) receptor subunit composition as a function of time [13]. Rapid seizure cessation may also prevent duration-dependent kindling and adverse cytokine mediated effects in experimental models [14, 15].

The ENLS suggested algorithm for the initial management of SE is shown in Fig. 1. Suggested items to complete

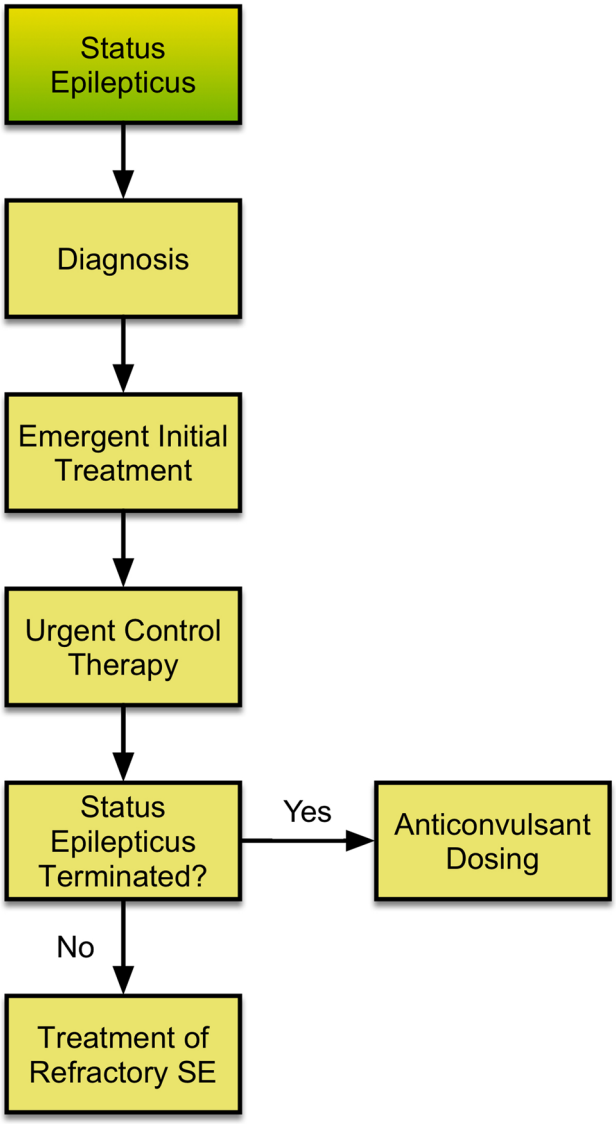

Fig. 1 ENLS status epilepticus protocol

within the first hour of evaluating a patient with SE (to be performed in parallel with treatment) are shown in Table 1. Fingerstick glucose should be checked as soon as possible in all patients with SE of unclear etiology; hypoglycemia is a rapidly treatable cause. Intravenous (IV) access should be obtained when possible, but unless it can be done within minutes, treatment with benzodiazepines can begin in parallel (using intramuscular or rectal delivery). When IV access is obtained, labs should be drawn so that they can be analyzed in parallel with treatment. Head CT should be obtained when either convulsions have been controlled or the airway is secured (if necessary). Finally, for those with continued convulsive SE or suspected SE (i.e., ongoing altered awareness, not recovering or returning to baseline) after intubation, continuous EEG monitoring should be implemented.

Diagnosis

The importance of more rapid treatment of prolonged convulsions is reflected in the current definitions of SE. Outdated definitions of SE required that convulsions persist or recur for greater than 30 min without a return to the pre-seizure neurological baseline. The rationale for this definition has been challenged, and the more useful and clinically relevant duration of greater than 5 min of unrelenting seizure is more appropriate [16, 17].

As in patients with any other critical illness, the diagnostic evaluation of patients with SE is pursued concurrently with treatment and stabilization. However, it is important to ensure that diagnostic testing does not interfere with or delay control of seizures in the ED. The importance of early rapid treatment has been demonstrated by prehospital providers, who have shown that intramuscular (IM) administration of midazolam is more successful in stopping seizures than intravenous (IV) lorazepam; presumably the result of delays in obtaining IV access [18]. This highlights that even the few minutes required for IV access are critical. The prehospital treatment of SE is discussed further below.

The diagnostic evaluation begins in parallel with clinical care (ensuring airway, breathing, and hemodynamics are addressed). Evaluate for hypoglycemia, hypoxia, and hemodynamic instability. Oxygen saturation and cardiac

Table 1 Status epilepticus checklist for the first hour

Checklist
☐ Fingerstick glucose
☐ Obtain IV access
☐ Pulse oximetry, BP monitor, supplemental O_2 and fluid as needed, cardiac monitor
☐ Labs: complete blood count, basic metabolic panel, calcium, magnesium, AED levels
☐ Head CT
☐ Continuous EEG (if available); notify EEG tech if available (as soon as available unless patient returns to pre-status epilepticus baseline)

monitoring are typically initiated during this phase. A neurological evaluation should be performed including a description of ongoing convulsions, automatisms, focal deficits, pupillary changes, and level of arousal.

Once IV access is obtained, blood and serum laboratory evaluation typically includes a complete blood count, basic metabolic panel, and calcium and magnesium determinations. Selected laboratory studies that may be useful in some patients include liver enzymes, cardiac injury markers, toxicology screen, and arterial blood gas determinations. AED levels for specific medications, such as phenytoin/fosphenytoin, valproate, and carbamazepine, may be obtainable on an acute basis and can be helpful to direct management. Approximately two-thirds of patients evaluated in the ED for SE have a history of a prior seizure, and many have either subtherapeutic levels of anti-epileptic drugs (AEDs) or withdrawal from AEDs.

The need for neuroimaging should be determined for each individual but is generally warranted in patients who do not return to a normal level of consciousness, have new focal neurological findings, or have new onset SE without an otherwise obvious identifiable etiology. Non-contrast computed tomography (CT) of the brain will identify most immediate threats and is the most typical initial imaging study obtained in the ED. Chest X-rays and electrocardiograms should also be obtained selectively based on clinical suspicion. A lumbar puncture should be performed in febrile patients and when there is suspicion of central nervous system infection or subarachnoid hemorrhage, preferably after obtaining the CT scan.

As noted in sections on hospital treatment below, electroencephalography (EEG) is necessary to identify non-convulsive SE [19] in patients who do not return to a normal level of consciousness. EEG may also guide therapy in these patients and provide other diagnostic information.

Non-epileptic spells simulating SE ("pseudostatus") occur mainly in patients with genuine seizure disorders and may be difficult to differentiate from SE. These may represent volitional behavioral problems or non-volitional somatization disorders. Indicators suggestive of non-epileptic spells include preserved consciousness or purposeful movements, poorly coordinated thrashing, back arching, eyes held shut, head rolling, and pelvic thrusting.

In pediatrics, common causes of SE include febrile seizures, central nervous system infections, and underlying genetic or metabolic disorders, especially in the infant and the younger child.

Emergent Initial Treatment of Status Epilepticus

Prehospital: Treatments Administered Before Hospital Admission

The initial minutes after seizure onset offer the most effective opportunity for pharmacological termination of SE seizures. Emergency medical services (EMS) delivery of benzodiazepines results in a higher rate of cessation of seizures prior to arrival in the ED than compared to placebo with a trend toward better outcomes [9]. In addition, IM administration of midazolam was at least as good as IV administration of lorazepam in terminating SE [20]. This has advantages as midazolam does not need refrigeration and the administration of an IM drug is significantly easier and quicker than obtaining IV access for administration.

Prehospital management begins with ABCs. Airway adjuncts and/or supplemental oxygen may be needed. For those with weak pulses or hypotension, establishing an IV or intraosseous (IO) line should should be prioritized to allow for correction of hypotension with fluid resuscitation. A rapid fingerstick glucose should be checked; hypoglycemia is an emergency and a readily correctable cause of SE. If such testing is not available, empiric D50W and thiamine IV can be given empirically when hypoglycemia is suspected (for example, in a known diabetic).

The most important next step is early time to initiating benzodiazepines (emergent initial therapy). Unless IV access will be immediately available, consider beginning with IM or PR medications; in adults, IM midazolam 10 mg or PR diazepam 20 mg; in children, IM midazolam 5–10 mg. IV access can then be attempted while evaluating the effectiveness of initial therapy. However, when IV access is rapidly available, lorazepam 4 mg IV (in adults, or clonazepam 1 mg IV) or 0.1 mg/kg IV (in children) should be considered. Patients did not benefit from prehospital add-on therapy with levetiracetam IV [21].

Respiratory depression can occur both following SE and in untreated SE; therefore, prehospital providers should be prepared to treat this irrespective of benzodiazepine use or dosing. Benzodiazepine doses recommended for SE are relatively higher than those used for many other indications and may contribute to respiratory depression. However, concern for this should not prevent appropriate therapy; continued seizures are more likely to cause respiratory problems than are side effects of the benzodiazepines [9].

In pediatrics, weight based dosing is often considered ideal for many medications. However, in this emergency circumstance, there is a risk of dose calculation error and has not been proven superior.

While lorazepam is highly effective, it needs to be refrigerated or restocked frequently, raising logistical

challenges for EMS systems. Some may find that diazepam and midazolam are preferable alternatives to stock.

Emergent Initial Treatment

Emergency Department: Initial Therapy Upon Hospital Arrival

Initial treatment of SE in the ED continues the care initiated by EMS. Airway, breathing, and circulation should be re-evaluated and supportive care continued. Cardiac and oxygen monitoring should be initiated, and fingerstick glucose checked if not already performed. If IV access has not already been obtained, it should be achieved upon arrival in the ED, and laboratory testing should be performed above (Diagnosis). For hospitalized patients, both emergent initial therapy and urgent control therapy should proceed seamlessly.

In patients who continue to convulse after initial benzodiazepine treatment, additional benzodiazepines should be administered after 5–10 min. Therefore, initial ED therapy will typically include IV benzodiazepines if initial EMS therapy has not succeeded. If the patient did not receive benzodiazepines prior to ED arrival and is still seizing, initial dosing should proceed as for prehospital providers (IV benzodiazepines when IV access immediately available, IM or PR benzodiazepines in parallel with IV placement when not). A repeat dose 5–10 min after the first should be given if SE continues.

Benzodiazepines are frequently under-dosed because the labeled 4 mg initial (adult) dosing of lorazepam for SE is greater than the initial dose used for most indications other than seizures in the ED. The same is true in pediatric dosing. Initial treatment failure is, therefore, often a result of using inadequate initial doses of IV benzodiazepines, waiting too long to repeat benzodiazepine doses, and advance to second line agents or general anesthesia and drug-induced coma.

As fingerstick glucose testing is widely and rapidly available in emergency departments, empiric administration of glucose is typically not warranted. However, for suspected or proven hypoglycemia, D50W should be emergently provided.

As emergent treatment continues, the diagnostic workup should proceed in parallel. If a cardiac arrhythmia or myocardial injury is suspected, ECG should be performed when possible. In addition, for patients with respiratory distress or hypoxia, chest X-ray should be performed. Providers should consider potential toxidromes that are associated with seizures:

- Isoniazid (treat with lorazepam followed by pyridoxine 70 mg/kg; max dose 5 gm)
- Tricyclics (evaluate for QRS widening on the EKG, treat with sodium bicarbonate)
- Theophylline
- Cocaine/sympathomimetic agents (treat with lorazepam)
- Alcohol withdrawal (treat with accelerating doses of a benzodiazepine)
- Organophosphates (treat with atropine, midazolam, and pralidoxime)
- Almost any overdose that leads to respiratory or circulatory compromise can cause seizures indirectly.

Status Epilepticus Terminated? Urgent Control Therapy

Seizures have not Stopped, or They Stopped but the Patient will not Awaken

If SE continues after 10–20 min of initial and re-dosing of benzodiazepines, and no correctable underlying etiology is found during this time, the next step will typically be a second line agent. The best choice of second line AEDs for patients with established SE unresponsive to benzodiazepines is uncertain since the second line AEDs have not been adequately compared in randomized controlled trials. Options include phenytoin/fosphenytoin, phenobarbital, valproate sodium, and levetiracetam [4].

Among second line AEDs, the preferred medications in most units have been IV 20 mg/kg of phenytoin or 20 mgPE/kg of fosphenytoin, the latter given at rates of up to 150 mg/min [22–24]. Phenytoin and fosphenytoin are FDA labeled for the treatment of SE in adults. Fosphenytoin is a water-soluble prodrug that is converted to phenytoin by plasma esterases. Phenytoin, but not fosphenytoin, is labeled for SE in children. They act at the sodium channel rather than the gamma-aminobutyric acid (GABA) receptor, and therefore represent a rational choice for treating patients whose seizures do not terminate with the benzodiazepine GABA agonists. Bradycardia and hypotension may occur at high infusion rates with the phenytoins, especially in the elderly or those with significant cardiac disease.

Although phenytoin-related adverse events are usually self-limited, some physicians who treat SE prefer alternative approaches. A small, randomized study suggested that IV valproate sodium may have similar efficacy in SE when compared to phenytoin [22]. Sodium valproate 20–40 mg/kg is given intravenously over 10 min, with an additional 20 mg/kg given over 5 min if the patient is still seizing. Although adverse events were not statistically significantly

different in the randomized study, sodium valproate probably has less cardiopulmonary side effects than phenytoin and may be preferred in patients with hypotension or respiratory distress.

IV phenobarbital is also FDA labeled for the treatment of SE in both adults and children and remains a reasonable option, but it is now less commonly chosen in adults unless other agents are contraindicated or unavailable. Phenobarbital 20 mg/kg of IV is given at 50–100 mg/min. An additional 5–10 mg/kg may be given after 10 min, if needed. Phenobarbital also acts at the GABA receptor and may be a less rational choice in those who have not responded to benzodiazepines, although there is a paucity of data addressing this topic.

Finally, levetiracetam is often used off-label as a second line agent to treat SE and can be given as a 1–2 g dose IV over 5 min or infused at 2–5 mg/kg/min [25].

At this time or if available before this, consider arranging EEG monitoring. If a patient stops convulsing but does not wake up or does not return to the pre-convulsive state, an EEG should be obtained to detect continuing non-convulsive SE. The reasons for persistent seizures should be established by determining AED levels, neuroimaging, urine toxicology, and any other appropriate testing. The most important cause of persistent stupor after convulsive SE is ongoing electrical seizures (subclinical or electrographic seizures) that can only be detected by EEG monitoring.

Second line AEDs may be less effective, and may sometimes be contraindicated, for urgent treatment in patients with SE that is secondary to intoxication or poisoning. SE known to result from isoniazid or organophosphates should preferentially be treated with specific antidotes. Cardiac effects of tricyclic antidepressant poisoning may be exacerbated by attempting to prevent seizures with some second line anticonvulsants.

Status Epilepticus Terminated?

Seizures have Stopped and the Patient is Following Commands

Urgent control therapy is used to prevent seizure recurrence after SE has been terminated. If seizures have stopped and the patient has awakened, loading doses of antiepileptic medications with longer half-lives should be initiated and can be given either intravenously or orally. A single oral loading dose of phenytoin 20 mg/kg can result in therapeutic levels within 3 h. For those requiring IV loading, fosphenytoin 20 mgPE/kg IV at a rate not exceeding 150 mgPE/min, or sodium valproate 40 mg/kg IV over 10 min with an additional 20 mg/kg over 5 min if still seizing, can be used.

For pediatric patients, load IV fosphenytoin 20 mg/kg IV unless they can reliably take oral medication at this time.

Treatment of Refractory and Super Refractory SE

SE will typically be terminated by the primary and secondary drugs described above. If the seizures have not stopped despite urgent and emergent drug therapy, SE is considered refractory. Intubation, ventilation, and drug-induced coma are typically recommended in these circumstances.

It is not necessary, and is usually not advisable, to delay advanced therapy with repeated trials of alternative second tier AEDs. A short period of time, generally shorter than an hour and perhaps even 30 min, is usually adequate to determine if the above-described conventional approach will be successful.

Endotracheal intubation is necessary to allow induction of coma and should be quickly performed in refractory SE. Because pharmacologic paralysis performed for purposes of intubation and mechanical ventilation will mask ongoing convulsions, it is appropriate to obtain continuous EEG monitoring at this time. This should particularly be done in super refractory SE (if propofol or midazolam infusions do not stop seizure activity).

The agents most commonly used to induce a general anesthetic state of coma are continuous infusions of midazolam or propofol [26–29]. IV midazolam infusions usually are preceded by a loading dose of 0.2 mg/kg at 2 mg/min, with repeated boluses of 0.2–0.4 mg/kg every 5 min until the seizures stop, up to a maximum loading dose of 2 mg/kg. A continuous infusion should then be started at 0.05–2 mg/kg/hr. IV propofol infusions usually include a loading dose of 1–2 mg/kg IV over 3–5 min, with repeated boluses of the same amount every 3–5 min until the seizures stop, up to maximum total loading dose of 10 mg/kg. The propofol infusion should then be maintained at a rate of 30–200 mcg/kg/min. Hypotension may be seen with higher doses.

Pentobarbital (or thiopental in some countries) is an alternative agent for the treatment of refractory SE. It has significant side effects, including hypotension, and a prolonged effective half-life, but it is still a reasonable option when other agents have failed or are contraindicated. Use of a pentobarbital infusion requires close monitoring and should be undertaken in a care environment with appropriate nursing and monitoring resources. IV pentobarbital infusions include a loading dose of 5–15 mg/kg IV at a rate of up to 50 mg/min, with repeated 5–10 mg/kg boluses

Table 2 Treatment of status epilepticus in children

Stage of therapy	Drug
Emergent initial therapy	Lorazepam, IV 0.1 mg/kg, maximum dose 4 mg
Urgent control therapy	fosphenytoin, 20 mg/kg, infuse no faster than 150 mg/min or 3 mg/kg min
Treatment of refractory status epilepticus	phenobarbital 20 mg/kg, infuse at 1 mg/kg min, no faster than 30 to 60 mg/min
	or, start midazolam: midazolam, 0.2 mg/kg, maximum dose 10 mg. If seizures continue for another 5 min, repeat dose at 0.2 mg/kg and start infusion of 0.1 mg/kg h. If seizures continue for another 5 min, administer another 0.2 mg/kg and increase infusion to 0.2 mg/kg h. If seizures continue, repeat midazolam bolus and then start pentobarbital: pentobarbital, 5 mg/kg, followed by infusion of 1 mg/kg h, increase as needed to 3 mg/kg h

Table 3 Status epilepticus communication regarding assessment and referral

Communication
☐ Clinical presentation
☐ Duration of status epilepticus
☐ Relevant past medical history/past surgical history
☐ Prior medications, medications given so far; AED levels if drawn
☐ Neurological examination
☐ Brain imaging/lumbar puncture/other results (if available)

until seizures stop, and then maintenance of 0.5–5 mg/kg/hr.

Sedatives and anesthetics used for treatment of SE may have a number of side effects and will frequently be associated with dose dependent hypotension requiring IV vasopressor support [26]. Hypotension may be more frequently seen with pentobarbital, while prolonged use of propofol is associated with the rare-but-often-fatal propofol related infusion syndrome (PRIS). PRIS is characterized by rhabdomyolysis, metabolic acidosis, cardiac and renal failure [29]. Pentobarbital is used more frequently in children with refractory SE because of this adverse effect with propofol.

IV valproate sodium may be preferentially used for patients with refractory SE who cannot or should not be intubated [30–33]. Valproate sodium is not recommended in children under the age of 2 due to its association with fatal hepatotoxicity. Other potentially useful but unproven therapeutic options in refractory SE include ketamine, lacosamide, and induced mild hypothermia.

In the ED, sedative IV agents will usually be titrated to the cessation of clinical manifestations of convulsive or subtle SE. When continuous EEG monitoring is available, the administration rate can be titrated to the desired electroencephalographic findings, ranging from suppression of frank seizures to burst suppression or a completely suppressed background. Few data are available to identify the optimal treatment level of suppression.

It is appropriate to continue second line AEDs to attain therapeutic serum levels during the treatment of refractory SE, as these are needed to prevent seizure recurrence. Expeditious admission to an intensive care setting, preferably with continuous EEG monitoring, is advisable for patients with refractory SE.

In pediatrics, the agents used are similar, although pentobarbital and midazolam are preferred over propofol because of concerns regarding PRIS [34]. Continuous intravenous infusions in children with refractory SE should follow adult criteria but are often not used until after the failure of three first or second line agents. Because of a rare genetic disorder of pyridoxine (B6) metabolism, it is recommended that children with refractory SE, especially the infant and younger child, receive intravenous B6 (Table 2) early in the course of resuscitation.

Communication

When communicating to an accepting or referring physician about a SE patient, consider including the key elements listed in Table 3.

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