Review
Clinical review: Status epilepticus

Sarice Bassin*, Teresa L Smith† and Thomas P Bleck‡

*Senior Resident in Neurology, Department of Neurology, University of Virginia, Charlottesville, Virginia, USA
†Neurology Critical Care Fellow and Clinical Instructor of Neurology, Department of Neurology, University of Virginia, Charlottesville, Virginia, USA
‡The Louise Nerancy Eminent Scholar in Neurology and Departments of Neurology, Neurological Surgery, and Internal Medicine Director, Neuroscience Intensive Care Unit, University of Virginia, Charlottesville, Virginia, USA

Correspondence: Teresa L Smith, tls2u@virignia.edu

Published online: 15 March 2002
Available online http://ccforum.com/content/6/2/137

Critical Care 2002, 6:137-142
© 2002 BioMed Central Ltd (Print ISSN 1364-8535; Online ISSN 1466-609X)

Abstract
Status epilepticus (SE) has an annual incidence exceeding 100,000 cases in the United States alone, of which more than 20% result in death. Thus, increased awareness of presentation, etiologies, and treatment of SE is essential in the practice of critical care medicine. This review discusses current definitions of SE, as well as its clinical presentation and classification. The recent literature on epidemiology is reviewed, including morbidity and mortality data. An overview of the systemic pathophysiologic effects of SE is presented. Finally, significant studies on the treatment of acute SE and refractory SE are reviewed, including the use of anticonvulsants, such as benzodiazepines, and other drugs.

Keywords anticonvulsants, benzodiazepine, epidemiology, review, status epilepticus

Status epilepticus (SE) is a medical and neurologic emergency. Given the significant risk of mortality, and the possibility of successful therapeutic intervention, it is essential for all physicians to be able to efficiently identify and treat patients in SE.

Definition
The definition of SE is based on the clinical manifestation, a prolonged seizure or a series of seizures during which the patient has incomplete recovery of consciousness, and duration. The duration parameter is controversial and has created a flux in our definition of SE. In their 1981 definition of SE, the International League Against Epilepsy describes the time elements as “sufficient length” and “frequently enough” [1]. For definition and management purposes, both of these quantifiers are ambiguous.

Elegant animal studies in the 1970s and 1980s revealed significant damage to the brain after 30 minutes of seizure activity, even with control of blood pressure, respiration, and body temperature [2–4]. These studies lent credence to the choice of 30 minutes as a specific time point to define SE. Although seizures can spontaneously remit after 10 to 29 minutes [5], in studies of the natural course of generalized tonic-clonic seizures, it has been well documented that, in humans, most seizures will terminate spontaneously within a few minutes [6]. For this reason, it has been proposed that an operational definition of SE should involve timing much shorter than 30 minutes [7].

The operational definition of SE proposed by Lowenstein, Bleck, and Macdonald is a continuous, generalized, convulsive seizure lasting greater than five minutes (in an adult or child older than five years), or two or more seizures during which the patient does not return to baseline consciousness [7]. Recent treatment studies including the Veterans Administration Cooperative Trial on Treatment of SE and the Pre-Hospital Treatment of SE study have used times of ten and five minutes respectively [8,9]. For treatment purposes, it is more practical to conceptualize SE using these narrower time windows. Shinnar et al. analyzed the duration of new-onset seizure activity in 407 children, and concluded that seizures lasting longer than five to ten minutes were unlikely to stop spontaneously, and should be treated [10].

ASE = acute status epilepticus; EEG = electroencephalograph; GCSE = generalized convulsive status epilepticus; NCSE = nonconvulsive status epilepticus; SE = status epilepticus.
Clinical manifestations and classification

The classification systems used for SE are discrepant throughout the literature. Many schemes have been generated that rely on both clinical and electrographic findings. It is important to note that virtually all seizure types may become prolonged, thereby fulfilling the definition of SE [11]. In an effort to provide a simple overview, a clinical approach will be favored here.

Prolonged convulsions with impaired consciousness constitutes generalized convulsive SE (GCSE). Although a patient with convulsions is easily recognized, some patients who have been in GCSE may progress to have minimal or no apparent motor activity but still show seizures on an electroencephalograph (EEG) [12]. The clinician must be aware of this situation, because aggressive treatment for this group is just as important as it is for the obviously convulsing patient [13].

Prolonged focal seizures, such as isolated hand jerking, associated with intact consciousness, comprises simple partial SE. Some authors conceptualize this entity as a separate category, while others include it as a subtype of NCSE [16].

Etiologies

The causes of SE are varied. Table 1 shows the etiologies of SE in an urban hospital-based population [16]. Although the data on causes of status, reported by DeLorenzo (Table 2), show some correspondence, there are discrepancies such as the higher proportion of cerebrovascular disease, anoxia, and hypoxia [17]. These data sets include only the adult population. In children, up to 51% are secondary to infectious etiologies [16].

Epidemiology, morbidity, and mortality

There have been two recent, prospective, population-based epidemiologic studies of SE. The EPICAR (a population-based survey of SE in the French-speaking part of Switzerland) study from Switzerland showed an incidence of about 10 cases per 100,000 people annually [18]. The population in this study, however, was principally white, and cases of anoxic encephalopathies were excluded. In the prospective population-based study conducted at the Medical College of Virginia, the incidence of SE was found to be 41 cases per 100,000 people [17] (Fig. 1). This would translate to over 100,000 cases of SE within the United States annually [19].

Reports on the mortality of SE range from a few percent to over 50% [20]. The Richmond group found a mortality rate of 22% (corresponding to 22,000–42,000 deaths per year in

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Table 1

| Etiology                  | Percent of cases |
|---------------------------|------------------|
| AED non-compliance        | 26               |
| Alcohol related           | 24               |
| Drug toxicity             | 10               |
| CNS infection             | 8                |
| Cerebral tumor            | 6                |
| Trauma                    | 5                |
| Refractory epilepsy       | 5                |
| Stroke                    | 4                |
| Metabolic abnormalities   | 4                |
| Cardiac arrest            | 4                |
| Idiopathic                | 5                |

AED, anti-epileptic drugs; CNS, central nervous system. Data adapted from Neurology [16].

Table 2

| Etiology                        | Percent of Cases |
|---------------------------------|------------------|
| Withdrawal of anticonvulsants    | 25               |
| Cerebrovascular disease         | 23               |
| Remote symptomatic              | 19               |
| Alcohol withdrawal              | 15               |
| Metabolic disorders             | 13               |
| Hypoxia                         | 12               |
| Infectious disorders            | 8                |
| Tumors                          | 5                |
| Anoxia                          | 4                |
| Trauma                          | 3                |
| Hemorrhage                      | 2                |
| Drug overdose                   | 2                |
| Idiopathic                      | 4                |

Data adapted from Churchill Livingstone [17].
the US) with the primary predictors of poor outcome being anoxia, prolonged seizure (greater than one hour in duration), and advanced age (Fig. 1) [21]. Mortality in the Swiss group was lower (7.6%), which is most likely to be secondary to the exclusion of anoxic encephalopathies [18].

**Pathophysiology of SE**

As a result of sympathetic overdrive, the body responds to GCSE with both systemic and cerebral effects, whereas, to NCSE, systemic effects are more limited. Systemic effects of GCSE are summarized in Table 3. In the initial phase of GCSE, blood pressure, glucose, and lactate increase, and pH decreases. After this initial phase, at approximately 30 minutes, a second phase begins. During this second phase, blood pressure and glucose normalize (sometimes decreasing even further), lactate normalizes, and respiratory compromise and hyperthermia ensue [22].

In both animal models and humans, GCSE has been shown to result in damage to the brain [3,22,23]. The reasons for this damage have not been completely elucidated; however, several contributing factors are believed to exist. Some of the systemic manifestations described in Table 3 can play a contributory role. Meldrum *et al.* showed that hyperthermia causes damage to the hippocampus and cortex [24]. Additionally, it has also been shown that reduction of temperature results in shorter duration of SE and less damage [25]. Initially during SE, there is increased cerebral blood flow to meet the elevated demands; however, as the cerebral blood flow falls, there is a mismatch between blood supply and the utilization of oxygen and glucose, resulting in a lower energy state and metabolic–substrate mismatch [22]. It is important to note that in experiments where systemic factors are controlled, there is still damage to the brain [2,24].

An area of expanding research is excitotoxic-induced cell injury, an important cause of damage to neurons [26]. The damage to neurons is based on a complex interplay of multiple

### Table 3

An overview of the systemic effects of status epilepticus

| System          | Effects                                                                 |
|-----------------|--------------------------------------------------------------------------|
| Lungs           | Due to both metabolic and respiratory acidosis, the pH of arterial blood gases (ABG) is often found to be below normal in SE. Aminoff and Simon found that 59/80 (84%) of the patients with useable ABG information had pHs below 7.35 [43]. They suggest that the aberrations in pH may not be of clinical significance or of prognostic value. In animal studies, pulmonary vascular pressure has been found to be elevated in SE [44] and may contribute to pulmonary edema [45]. |
| Heart           | The sympathetic overdrive can cause tachycardia. In a study by Boggs, potentially fatal arrhythmias were reported in 58% of the patients [46]. In a recent study, Boggs *et al.* completed hemodynamic monitoring in SE patients 24 hours prior to their death, and found that there were two distinct groups with disparate cardiac manifestations [47]. In the group with a lower proportion of previously discovered atherosclerotic disease (ASHD), there was acute cardiac decline without a significant drop in mean arterial pressure (MAP) or heart rate (HR). The second group, 90% of whom had a history of multiple risk factors for ASHD, showed a gradual decrease in MAP and HR prior to death. |
| Muscle          | As a result of continued seizure activity, conversion to anaerobic metabolism contributes to lactic acidosis [3]. |
| Blood chemistries | De-margination of neutrophils occurs with the stress of seizing. In patients without underlying infection, elevated white blood cell counts (above the upper laboratory limit) were present in as many as 63% in one study [43]. |
| Vital signs     | Blood pressure The initial phase of SE results in an increased systemic blood pressure with an increase in peripheral vascular resistance [43]. As the status becomes prolonged, the blood pressure will normalize or even begin to fall with resultant hypotension. |
|                 | Temperature As the seizure progresses, the body’s core temperature elevates. Aminoff and Simon looked at the temperature of 90 patients in SE. Of these, only 8 had temperatures below 98°F, only 3 had fever secondary to known infection, and over 40 had temperatures above 100.5°F, (with two of the temperatures up to 107°F) [43]. |
|                 | Respiratory rate The patient in SE often has a transient change in respiratory rate and tidal volume [22]. |
factors. Significant to this process is the inhibition of γ-aminobutyric acid (a principle inhibitory neurotransmitter), and the excessive action of glutamate (an excitatory neurotransmitter). Additionally, apoptosis is likely to play a role in cell death during SE. Given the probability of cerebral injury, it is imperative for the clinician to recognize and treat SE expeditiously.

**Treatment of acute status epilepticus**

**Basic life support**

Airway, breathing, and circulation should be established immediately. Intravenous access, while sometimes difficult to achieve in an actively seizing patient, should be obtained. Glucose should be given empirically along with thiamine in alcoholic or otherwise malnourished patients. Laboratory studies should include basic chemistry, blood glucose, anticonvulsant levels, blood and urine toxicologic screen, complete blood count, and urine analysis for evidence of infection. The treatment of SE, however, should not be delayed while these tests are pending.

**Benzodiazepines**

Benzodiazepines, usually either diazepam or lorazepam, remain the first-line control for acute SE (ASE). No significant difference has been found between the rate of seizure control when lorazepam has been compared with either diazepam alone [27] or diazepam plus phenytoin [8]. However, lorazepam is believed to bind more tightly to receptors in the brain and therefore has a longer duration of action and less risk of recurrent seizures [28]. All benzodiazepines carry the risk of respiratory depression and hypotension, and therefore the clinician should be prepared to intubate or give pressors if necessary. Diazepam is given at a dose of 10–20 mg; lorazepam is given in 2 mg increments at approximately three-minutes intervals. If seizures have not terminated after 8 mg of lorazepam, another agent should be started.

Midazolam is a newer benzodiazepine that is associated with a very favorable hemodynamic and pharmacokinetic profile [29]. Its major advantage over lorazepam in the acute setting is that its high water solubility and rapid onset of action when given intramuscularly make this an attractive choice when secure intravenous access is unobtainable [28]. Its use in refractory SE will be discussed below.

**Fosphenytoin**

Traditionally, phenytoin alone at 20 mg/kg intravenous infusion has been considered an appropriate first-line option in the treatment of ASE. We recommend it be only used as a second-line agent after a faster acting benzodiazepine has been tried. Infusion rates are limited to 50 mg/min secondary to the potential side effects of arrhythmia and hypotension.

Conversely, fosphenytoin (a water-soluble phosphate ester prodrug of phenytoin with a neutral pH) can be delivered at 150 phenytoin-equivalent mg/min with essentially no risk of reaction at the infusion site. Because it is water soluble, it does not need a propylene glycol vehicle. It is 100% bioavailable when given either intravenously or intramuscularly, and it is quickly converted by phosphatases to phenytoin once it is in the vascular compartment [30].

In one small study of GCSE, fosphenytoin was associated with a success rate of 93.8% in terminating seizures [31]. Studies have shown that therapeutic plasma concentrations of phenytoin can be achieved more rapidly with fosphenytoin that phenytoin when given at 15–20 mg/kg [31]. This is probably related to three factors: faster rate of infusion; displacement of protein-bound phenytoin; and rapid conversion of prodrug to phenytoin (half-life of 8.1 min) [32]. Although fosphenytoin is a more expensive alternative [33], the cost of treating complications from the use of intravenous phenytoin can be substantially higher [34].

**Barbiturates**

The Veterans Administration Cooperative study showed no significant difference in efficacy between lorazepam (0.1 mg/kg) and phenobarbital (15 mg/kg) [8]. However, it also showed that if a patient did not respond to lorazepam or phenytoin, the response rate to phenobarbital was only 2.1% (unpublished data). We therefore recommend a more definitive treatment strategy for patients that have not responded to one, or at most two, first-line agents.

**Treatment of refractory status epilepticus**

Refractory SE is defined as ongoing seizures despite the use of two first-line agents, usually a benzodiazepine plus either phenytoin or phenobarbital. Definitive therapy often requires doses of medications that cause respiratory suppression and hypotension, so patients should be intubated and transferred to an intensive care unit if this has not already been done. Treiman et al. showed that respiratory suppression requiring mechanical ventilation occurred in 18.9%, and pressor support was needed in 32.6% of patients treated for SE [8]. Patients at this stage of SE require EEG monitoring, since the physical exam is clouded by the use of paralytics for intubation and the potential for electromechanical dissociation.

The traditional goal of therapy has a burst suppression pattern on EEG for 12–24 hours before attempting to taper medications. There are no convincing prospective data to suggest that a burst suppression pattern is required to control or to prevent recurrent seizures [35], thus we recommend seizure suppression as a goal, regardless of the EEG background.

**Pentobarbital**

Pentobarbital, with a loading dose of 5–12 mg/kg followed by an infusion of 1–10 mg/kg, is extremely effective in producing coma and achieving burst suppression on EEG. Maintenance therapy of a longer-acting anticonvulsant is continued during this time in anticipation of reversing coma as soon as clinically feasible. High doses of barbiturates can cause poor chemotaxis of white cells, paralysis of respiratory cilia, and
seizures. Hypotension, hypertriglyceridemia, and worsening of anemia have also been reported with this agent. Two small studies have shown an interesting, but insignificant, increase in mortality among SE patients treated with propofol versus midazolam or high dose barbiturates. Future studies are needed to better elucidate this issue.

Conclusion
As the issue of SE is often faced by practitioners of critical care, it is imperative that SE be recognized and treated as a medical emergency. Given the complex pathophysiology, being able to abort SE will contribute to a decrease in the systemic effects and neurologic injury. First line treatment with benzodiazepines, followed by the other agents discussed above, provide the maximal potential for successful management of SE.

Competing interests
None declared.

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