

Status Epilepticus

Eliahu S. Feen, MD, Eric M. Bershad, MD, and Jose I. Suarez, MD

Abstract: Status epilepticus (SE) in adults is a state of continuous seizures lasting more than 5 minutes, or rapidly recurrent seizures without regaining consciousness. The overall US and European estimated crude incidence rate of SE ranges from 6.8 to 41/100,000/yr. The etiologies of SE include primary central nervous system pathologies and systemic disorders. The two basic mechanisms involved in the genesis of SE are an excess of excitatory activity and a loss of normal inhibitory neurotransmission. Mortality associated with SE can be as high as 26% for the average adult. Early recognition and treatment are important for improving the chances for a good outcome. The first line of treatment is an intravenous benzodiazepine, with lorazepam being the current preferred agent. All patients with SE who remain with altered awareness 20 to 30 minutes after cessation of clinical seizures should undergo electroencephalographic studies, because up to 20% of patients without clinical evidence of seizures after initial treatment can have nonconvulsive SE.

Key Words: electroencephalogram, mechanical ventilation, respiratory failure, seizures, status epilepticus

Status epilepticus (SE) refers to a state of continuous seizure activity for more than 5 minutes, or rapidly recurrent seizures without regaining consciousness. SE is a medical emergency with a high mortality if poorly treated. Prompt and successful recognition and treatment can improve patient outcome. The type of seizure leading to SE can vary. Generalized convulsive SE involves severe impairment of consciousness (usually coma) together with motor activity involving all limbs or at least one limb on each side of the body. Generalized convulsive SE can represent the secondary spread of focal seizure activity in the brain which began in a discrete

anatomic location. Nonconvulsive SE (NCSE) lacks limb movement but manifests with severe impairment of consciousness. Sometimes patients with NCSE may display subtle physical signs such as lip quivering or eyelid twitching. Complex partial SE has some impairment of consciousness, often associated with repetitive automatisms such as lip smacking or eye fluttering. Partial SE, also termed *epilepsia partialis continua*, usually involves continuous movement of a limb without impairment of consciousness. Generalized convulsive SE carries the worst prognosis and requires the most rapid and effective treatment to avoid devastating and permanent brain injury or death. NCSE can often immediately follow a period of generalized convulsive SE and therefore may carry a similar prognosis. In fact, in the VA cooperative study, 20% of patients with apparently controlled clinical seizures still had persistent electrographic ictal activity.¹ The other forms of SE seem to have a different clinical course and prognosis. The focus of our discussion is generalized SE—either convulsive or nonconvulsive. Because seizure phenomenology quite frequently differs between adults and children, in this review we will primarily examine SE in adults. We will describe the clinical scenario in which SE occurs, the risks associated, the diagnostic approach, and the treatments and prognosis.

Definition

The definition of SE has changed over time. The International League Against Epilepsy categorizes SE into the

Key Points

- Status epilepticus is defined as a state of continuous seizure activity lasting more than 5 minutes, or rapidly recurrent seizures without regaining consciousness.
- Seizures in status epilepticus can present in various forms, including generalized convulsive, generalized nonconvulsive, complex partial, and partial.
- Treatment of status epilepticus should be administered promptly after recognition. The earlier the treatment, the better the outcome.
- Optimal management of status epilepticus requires electroencephalographic monitoring.
- The first-line agent to use for treatment of status epilepticus is an intravenous benzodiazepine. Lorazepam is a preferred drug.

From the Division of Vascular Neurology and Neurocritical Care, Department of Neurology, Baylor College of Medicine, Houston, TX; and Division of Neurocritical Care, Department of Neurology, St. Louis University, St. Louis, MO.

Reprint requests to Jose I. Suarez, MD, Department of Neurology, Baylor College of Medicine, One Baylor Plaza, NB 302, Houston, TX 77030. Email: jisuarez@bcm.tmc.edu

Dr. Bershad has no financial disclosures to declare. Dr. Suarez has received an honorarium from The Medicines Company for his work as a consultant, and has received an honorarium from Bodringer-Ingelheim and Bristol-Myers-Squibb/Sanofi as a speaker. Dr. Feen is on the speaker's bureau for Boehringer-Ingelheim.

Accepted October 16, 2007.

Copyright © 2008 by The Southern Medical Association
0038-4348/0—2000/10100-0400

following subgroups: *epilepsia partialis continua*, supplementary motor area, *aura continua*, *dyscognitive focal* (psychomotor, complex partial), tonic-clonic, absence, myoclonic, tonic, and subtle.² From a practical standpoint, SE can be categorized as convulsive or nonconvulsive.³ In our review, we will refer to the latter definition of SE.

For decades, SE was recognized as a state of continuous seizure activity or rapidly recurrent seizures, without specification of timing. As experimental animal data accrued in relation to permanent brain injury as a function of length of time of seizures, the definition of SE changed to reflect the importance of timing of seizures. Since the late 1980s, practitioners accepted a time frame of 30 minutes.⁴ Animal data demonstrated a precipitous fall in brain oxygenation and the development of cardiovascular instability after 30 minutes of continuous seizure activity. These were associated with permanent parenchymal brain injury.⁵ This concept led many practitioners to believe that there were no ill effects if they waited 30 minutes before pursuing aggressive treatment of SE. However, both animal and human data suggested that after 30 minutes of ongoing seizures, they became self-sustaining and more difficult to treat. As a result, leading specialists in the field recommend using a shorter time interval of 5 minutes.³ There is a biologic basis for the 5-minute time span. Data on seizures in children found that within 5 minutes, 50% of all seizures end spontaneously and by 10 minutes, almost 70% end spontaneously.⁶ Those that continue for 5 minutes or more have a high likelihood of continuing for 30 minutes or longer.⁷ Thus, any continuous seizure period of more than 5 minutes' duration, or recurrent seizures without return of consciousness should be called SE and treated promptly. Prolonged SE, also known as refractory SE, is generally defined as SE that continues either clinically or electrographically after the administration of at least two standard anticonvulsants.⁸

Epidemiology

Based on the reported literature, estimates on the incidence of SE vary. The bulk of the reported epidemiologic data comes from the United States, followed by the United Kingdom, Switzerland, and Germany.⁹ The overall US and European estimated crude incidence rate of SE ranges from 6.8 to 41/100,000/yr.^{9–11} SE accounts for up to 8% (range 1–8%) of US hospital admissions, corresponding to 50,000 to 150,000 patients annually.¹² Estimates of the incidence of SE may underestimate the true incidence as they were based upon older definitions of SE. For patients with known epilepsy, up to 16% will have at least one episode of SE in their lifetime. The incidence of SE in the United States demonstrates a bimodal distribution, with peaks in the youngest (age less than or equal to 4 years of age) and the oldest age ranges (age greater than 60 years of age). Incidence of SE dramatically rises after 60 years of age, with an approximately 60% increase between the ages of 60 and 75.

Risk Factors and Etiologies

The etiologies of SE are myriad. Based on epidemiologic reviews^{10,12} the spectrum of primary pathology of the central nervous system associated with SE includes idiopathic, head injury, neoplasm, stroke (eg, ischemic infarct, subdural hemorrhage, parenchymal intracranial hemorrhage, or subarachnoid hemorrhage), infection (eg, meningitis, encephalitis, abscess, cerebritis), congenital abnormalities, and a history of cerebral palsy/mental retardation. Systemic disorders include generalized cerebral hypoxia (eg, postcardiac arrest), metabolic disturbances (eg, hyponatremia, hypernatremia, hypocalcemia, hypomagnesemia, hypoglycemia, hyperglycemia, and renal or hepatic failure), alcohol-related seizures, drug overdose, systemic infections, and low serum concentration of antiepileptic medications. Cerebrovascular disease—ischemic or hemorrhagic stroke—alone (either as an acute, proximate cause or as a remote cause) may represent almost 50% of cases. Systemic causes are found in up to 20% of cases.

Refractory SE may occur in about 30% of patients with SE, and is associated with increased hospital length of stay and disability.^{8,13} Factors that have been associated with increased incidence of refractory SE include delayed time to treatment, NCSE, focal motor seizures at onset of SE, central nervous system infections, metabolic encephalopathy, and hypoxic-ischemic injury.^{13–15}

Pathophysiology

The pathophysiology of the development of SE is not clearly understood. It is recognized that two fundamental mechanisms are excess excitatory neurotransmission and loss of normal inhibitory neurotransmission. The important role of excitatory neurotransmission comes from reports of cases of prolonged SE developing in the setting of the ingestion of mussels containing toxic amounts of domoic acid, which is a glutamate-like compound. It is well established that glutamate is a prominent excitatory amino acid neurotransmitter.^{16,17} Abundant research has also explored the role of inhibitory circuits in the brain related to the inhibitory neurotransmitter, γ -n-aminobutyric acid (GABA). Basic science research shows that disinhibition of GABA circuits, either pre- or postsynaptic, alters their influence on the development of seizures. Interestingly, persistent seizures lead to conformational changes in the GABA receptor making it less responsive to benzodiazepines, the mainstay of seizure treatment. Seizure activity of up to 30 minutes correlates with the development of resistance to benzodiazepines and even chronic changes in the GABA receptor genetic expression.¹⁸ Human data also support the fact that prolonged SE may be associated with treatment resistance. A recent retrospective review of SE in children found that a treatment delay of more than 30 minutes resulted in a delayed response to the treatment given compared with patients treated early.⁷ Also, an-

imal data and wide clinical experience demonstrates that seizure activity of several minutes leads to acidosis, and prolonged activity (but certainly less than 30 minutes) leads to ominous systemic complications such as hypotension, hyperthermia, and hypoxia.⁵

Diagnosis

A clear description from a witness or direct observation of repetitive convulsive seizures without regaining consciousness, or continuous convulsive activity for more than 5 minutes constitutes SE.³ A seizure may begin focally with rhythmic motor activity on one side of the body, and progress to involve both sides with loss of consciousness. Often after convulsive seizures have persisted for some time, motor activity may cease, yet abnormal electrical activity in the brain will continue. Clinically, this NCSE may present only with coma or have subtle physical manifestations such as quivering or slight myoclonus (small-amplitude jerking) of the muscles of the face, hands, arms, feet, or legs. Sometimes there

may only be slight nystagmus (abnormal jerky eye movements) or subtle blinking in the setting of NCSE.^{19,20} As these subtle motor signs may not be present at all—and coma will be the only sign—an electroencephalogram (EEG) will be necessary to make the diagnosis. In the VA Cooperative Study of the treatment of SE, 20% of patients enrolled had NCSE.¹ In another study, up to 8% of patients in a coma screened with an EEG were found to be in NCSE.²¹ Therefore, any patient presenting in coma warrants EEG monitoring.

Treatment

Once the diagnosis of SE has been made, practitioners must initiate treatment rapidly to improve the chance for a good outcome.^{22–24} Initial treatment in these critically ill patients requires urgent stabilization of the cardiovascular and respiratory systems (Table 1). Similar to other medical emergencies, stabilization begins, of course, with maintenance of a patent airway. As these patients are in a coma, the risk of airway compromise is high, which may lead to aspiration pneumonia. Contrary to popular belief, it is not necessary to “move the tongue out of the way” to avoid “tongue-biting.” However, it is absolutely necessary to ensure proper oxygenation through a stable airway. If a patient requires intubation, one should use rapid-sequence orotracheal intubation (Table 2). Depolarizing neuromuscular blockers, such as succinylcholine, should not be used if at all possible because of an increased risk of fatal hyperkalemia occurring in this patient population with a high incidence of renal impairment or prolonged focal neurologic weakness.²⁵

Medical therapy begins with rapid identification and treatment of reversible underlying causes—namely, hypoglycemia and alcohol withdrawal by infusing glucose and thiamine (Table 1). If serum glucose has not yet been determined, intravenous (IV) or intramuscular (IM) thiamine and a dextrose bolus should be given immediately. Rapid infusion of IV fluids will help to correct hypotension induced by SE and its complications. Laboratory evaluation at this time should

Table 1. Recommended algorithm for treatment of status epilepticus

Immediate treatment of seizures:

- 1) ABCs: secure stable airway, ensure adequate ventilation/oxygenation, and stabilize cardiac perfusion (eg, treat hypotension)
- 2) Establish intravenous access and initiate intravenous fluid resuscitation
- 3) 100 mg thiamine IV and 50 cc of 50% dextrose (D50)
- 4) Initiate rapid diagnostic workup to establish etiology of status epilepticus

Initial treatment:

- 1) Lorazepam 2 mg/min up to total dose of 0.1 mg/kg (alternative: diazepam)
- 2) Phenytoin intravenously (alternative: fosphenytoin; phenobarbital; valproic acid)

For seizures persisting despite initial treatment (refractory status epilepticus):

- 1) ICU admission
- 2) Intubation
- 3) EEG monitoring
- 4) May give extra dose of phenytoin (10 mg/kg)
- 5) May add another anticonvulsant (phenobarbital or valproic acid)
- 6) Propofol infusion to induce anesthesia or possibly burst-suppression (alternatives: midazolam infusion; pentobarbital)

Once seizures are controlled:

- 1) 48 h of induced coma
- 2) Slow taper of anesthetic infusion (and possibly other anticonvulsant medications)
- 3) Optimize other anticonvulsant medications and continue treatment of underlying etiologies and systemic complications

Of the four drug regimens studied for aborting status epilepticus—lorazepam alone, phenobarbital alone, diazepam plus phenytoin, or phenytoin alone, lorazepam was the most effective of these regimens in ending status epilepticus when used as the initial choice of medication.

IV, intravenous.

Table 2. Rapid sequence orotracheal intubation

Steps	Methods/medication
Preoxygenation	Bag mask ventilation Nasopharyngeal airway device Oral airway device Suctioning
Blunting of cough reflex	Lidocaine (IV) 1–1.5 mg/kg
Induction	Etomidate 0.1–0.3 mg/kg Propofol 1–2 mg/kg
Paralysis	Nondepolarizing neuromuscular blockade (eg, vecuronium 0.1 mg/kg)
Endotracheal intubation	Apply cricoid pressure

IV, intravenous.

Table 3. Commonly used medications for control of status epilepticus

Drug	Loading dose	Infusion rate (of loading)	Maintenance dose	Important side effects
Diazepam	0.2–0.5 mg/kg	2–4 mg/min	NA	Respiratory depression, sedation, hypotension
Lorazepam	0.05–0.1 mg/kg	2 mg/min Loading dose may be repeated up to maximum of 0.3 mg/kg	Repeat loading dose or maximum dose every 2–3 h; alternatively, 9–10 mg/h	Respiratory depression, sedation, hypotension
Midazolam	0.05–0.2 mg/kg	Less than 4 mg/min	0.75–10 µg/kg/min	Respiratory depression, sedation, hypotension
Phenytoin	18–20 mg/kg If necessary to control seizures, maximum dose of 30 mg/kg maybe given	50 mg/min (alternatively: 1 mg/kg/min)	5 mg/kg/d	Hypotension, venous irritation, liver dysfunction
Fosphenytoin	18–20 mg/kg of phenytoin equivalent (maximum: 30 mg/kg) It can also be given IM	150 mg/min (alternatively: 3 mg/kg/min)	5 mg/kg/day	Liver dysfunction
Phenobarbital	15–20 mg/kg Additional dosage up to 30 mg/kg	2 mg/kg/min (alternatively: 50–75 mg/min)	1–4 mg/kg/d	Hypotension, sedation, prolonged half-life
Valproic acid	20–40 mg/kg	3–6 mg/kg/min	4–8 mg/kg given q8 hours	Thrombocytopenia, liver dysfunction
Propofol	2–5 mg/kg	Over 5 min	1–15 mg/kg/h	Hypotension, hyperlipidemia, pancreatitis
Pentobarbital	5–12 mg/kg	0.2–0.4 mg/kg/min (alternatively: give loading dose over 1 h)	0.5–1 mg/kg/h	Prolonged hypotension, liver dysfunction, sedation, prolonged half-life (3–5 d)

Chart based upon Refs. 3, and 22–24.

Of the four drug regimens studied for aborting status epilepticus—lorazepam alone, phenobarbital alone, diazepam plus phenytoin, or phenytoin alone, lorazepam was the most effective of these regimens in ending status epilepticus when used as the initial choice of medication.

NA, not applicable.

include determination of serum electrolytes, renal and hepatic function, glucose, acid-base status, anticonvulsant drug concentration, a complete blood count, qualitative and quantitative toxicology screening, and arterial blood gases. A head computed tomography scan should also be obtained once the patient has been stabilized. During this initial period, practitioners should quickly examine the patient looking for signs of systemic disease, trauma, focal signs, or infection. If the latter is suspected (particularly if meningeal signs are present), a lumbar puncture must also be part of the workup after head computed tomography scanning to ensure absence of mass effect.

Immediate control of the seizures is absolutely essential. The first-line agent to use is an IV benzodiazepine.^{26,27} Several drugs are widely available (lorazepam, diazepam, midazolam, and clonazepam), but recent studies support lorazepam as the first-line treatment. The VA SE Cooperative Study compared four drug regimens for aborting SE—lorazepam alone, phenobarbital alone, diazepam plus phenytoin, or phenytoin alone.¹ The study showed that lorazepam was the most effective of these regimens in ending SE when used as the initial choice of medication. In another study of out-

of-hospital treatment of SE, patients treated by emergency medical services with lorazepam had a higher degree of success than with diazepam.²⁸ Both lorazepam and diazepam are rapidly acting, but lorazepam has a longer lasting anticonvulsant effect (12–24 hours, when compared with 15–30 minutes for diazepam)⁴ (Table 3).

If SE persists or the patient has not regained consciousness after initial administration of lorazepam, an IV loading dose of a typical anticonvulsant should be prepared. Phenytoin, fosphenytoin, phenobarbital, and—most recently—valproic acid are the most well-studied and reliable (Table 3). These anticonvulsants take some time to load IV (eg, 30–60 minutes). If IV access is lost or not successfully obtained, fosphenytoin can also be given IM due to its water solubility. However, it is not always necessary to administer a loading dose of a typical anticonvulsant. For instance, if SE resolves and the patient regains consciousness within 5 to 10 minutes after benzodiazepine administration and the cause of SE is clear, one can forgo anticonvulsant treatment. Such is the case in patients with insulin-induced hypoglycemia or alcohol-withdrawal seizures.

The most commonly used second-line anticonvulsant medication for treatment of SE in the United States is phenytoin. The VA Cooperative Study demonstrated no statistically significant difference between phenobarbital and phenytoin.¹ However, clinical experience shows that side effects for phenobarbital are worse than for phenytoin, namely, impaired respiratory drive, depression in level of consciousness, hypotension, and prolonged half-life. Data for using valproic acid are limited in SE, but its efficacy maybe as high as 60% in cases refractory to other agents or in cases where other agents cannot be used.²⁹ It is important to realize that the IV loading dose of phenytoin is not 1 g, as is commonly practiced, but 20 mg/kg as indicated in Table 3. In SE refractory to the initial loading dose, an additional 10 mg/kg can be given. This total dose of 30 mg/kg can achieve adequate therapeutic serum levels for over 24 hours.³⁰ Given its lipid solubility, phenytoin will reach maximum cerebral concentration by the end of the infusion time, usually 30 to 45 minutes.³¹ Hypotension is a common side effect from infusion of phenytoin, usually in older patients.²⁹ Slowing the infusion rate can reduce this effect. Alternatively, a chemically altered form of phenytoin, fosphenytoin, is available. Fosphenytoin can be infused at a similar loading dose, more rapidly, and has the advantage in that it can be given IM.³²

If SE persists, an IV load of either phenobarbital or valproic acid should be infused. Phenobarbital is particularly helpful in patients with NCSE¹ and in the elderly in general.³³ Recent data suggests that valproic acid can be used as an alternative to phenytoin and phenobarbital or as an adjunct in refractory SE. Valproic acid has demonstrated efficacy in SE when used as a first agent or even as a third or fourth agent.²⁹ A small randomized pilot study comparing valproic acid or phenytoin in SE patients showed that seizures were aborted in 66% and 42% of valproic acid and phenytoin-treated patients, respectively.³⁴ In addition, in patients with refractory SE, seizures were controlled in 79% of valproic acid-treated patients, but only in 25% of phenytoin-treated patients. Valproic acid can be safely infused as fast as 6 mg/kg/min.³⁵ Until larger randomized studies are undertaken, it is reasonable to use valproic acid for refractory SE, or in patients that can not tolerate phenytoin or phenobarbital.

If SE persists despite the administration of lorazepam or typical anticonvulsants, then continuous infusion of anesthetic agents should be the next step³ (Tables 1 and 3). There is no fixed time to initiate these agents. However, it is common practice to consider them if SE continues for more than 30 minutes after initiation of treatment. Infusion of anesthetics will require intubation and mechanical ventilation. The recommended anesthetic agents include midazolam, propofol, and pentobarbital. Because of its higher risk of prolonged hypotension and longer half-life, pentobarbital is not as commonly used today. We recommend placing a patient into an induced coma for at least 24 to 48 hours with continuous EEG monitoring. The goal of treatment is to stop the electrographic

seizures. This may well be achieved with the initial bolus infusion of the anesthetics. However, in some patients, a deep level of anesthesia to achieve so-called "burst-suppression EEG pattern" maybe necessary. The latter is thought to represent a state of profoundly reduced brain metabolism. After 24 to 48 hours of induced coma, the level of anesthesia is weaned slowly over 12 to 24 hours to determine whether seizure activity recurs. If not, then induced anesthesia can be stopped. Of course, anticonvulsant medications (either IV or enterally) must be continued throughout and their serum concentrations maintained close to their upper limit of normal to help prevent recurrent SE.

Other medications and therapeutic options for patients with refractory SE have been reported only in small case series.^{36–38} Pharmacological treatment with topiramate, levetiracetam, ketamine, lidocaine, and etomidate has been reported with varying success; however further studies are needed to determine safety and efficacy in patients with SE. For instance, ketamine, which was once thought to be neuroprotective, was recently linked to cerebellar degeneration when used in long infusions in refractory SE patients.³⁹ Acute surgical interventions include vagus nerve stimulator and surgical resection of seizure focus.⁴⁰

It is important to optimize a long-term treatment plan concomitantly with the acute treatment of SE. If the patient is known to have epilepsy, it is important to optimize their current regimen, or add other anticonvulsants. If the patient is a de novo case of SE, one can choose between a traditional anticonvulsant such as phenytoin, valproic acid or carbamazepine, or a newer alternative such as oxcarbazepine, levetiracetam, or topiramate.

Electroencephalogram

Optimal management of SE requires an EEG. We recommend an initial EEG in all SE patients who have persistence of altered awareness for more than 20 to 30 minutes after the cessation of clinical seizures.⁴¹ In patients with refractory SE, or those who remain in a coma, we recommend continuous video EEG monitoring. The latter provides information as to whether seizures are persistent or recurrent.⁴² In the VA Cooperative Study, about 20% of patients with NCSE would have remained undiagnosed without an EEG.¹ Data from Richmond, Virginia demonstrated that 48% of patients whose convulsive SE was apparently clinically controlled had persistent NCSE when placed on continuous EEG monitoring.⁴³ This is also supported by evidence suggesting that the incidence of NCSE in critically ill patients is high. In a retrospective review of critically ill patients undergoing continuous EEG monitoring, 19% had recurrent seizures detected by the monitoring, of which 92% were nonconvulsive.⁴⁴ Also, a recent review of intracerebral hemorrhage patients placed on continuous EEG monitoring revealed that almost 28% had seizures detected on EEG, of which less than half had any

motor correlate (ie, motor manifestation such as rhythmic jerking which could be appreciated clinically that corresponded to EEG activity showing electrographic seizures).⁴⁵

Prognosis

Both convulsive and NCSE carry a high morbidity and mortality.^{46,47} In the Richmond, Virginia epidemiologic study, overall mortality was 22%, with the adult population specifically suffering a 26% mortality.¹⁰ Extrapolating to the US population at large, somewhat more than 40,000 deaths annually may be attributed to SE.⁴⁸ A retrospective study from two Boston-area hospitals found an overall fatality rate of about 15%.⁴⁹ However, a recent large review of 11,580 US inpatients with convulsive SE admitted from 2000 to 2004 from the National Inpatient Sample with SE reported an in-hospital mortality rate of 3.45%.⁵⁰ The mortality rate in this study is substantially lower than the 20% mortality reported in the Richmond, Virginia VA study. We suspect the relatively low mortality rate found by Koubeissi et al⁵⁰, may reflect underreporting of SE patients to the National Inpatient Sample. Alternatively, recent advances in the management of SE patients may have contributed to reduced mortality.

Predictors of mortality in SE patients include older age, need for mechanical ventilation, female gender, coma, hypoxic-ischemic brain injury, and increased number of comorbidities.^{49,50}

Mortality in NCSE may be even higher, with estimates ranging from 30 to 50% in critically ill patients.^{13,51,52} For instance, data from the VA Cooperative Study demonstrated that the 1-month mortality of convulsive SE patients was 27%, whereas that of the NCSE cohort was 65%.¹ Small series in the literature have shown a mortality rate for complex partial SE of 30%.⁵³ It has also been suggested that the outcome of patients with NCSE correlates strongly with duration of SE and time to diagnosis.⁵⁴ Mortality among patients with NCSE who were diagnosed within 30 minutes was 36%, but when diagnosis was delayed beyond 24 hours, the mortality rose to 75%. Duration of NCSE of less than 10 hours carried a mortality rate of 10%. However, when duration exceeded 20 hours, the mortality rose to 85%.

Long-term morbidity and mortality of patients with SE are also high.⁹ A retrospective review of SE survivors demonstrated that they had a three-fold higher mortality compared with the general population within 10 years after their first episode of SE.⁵⁵ In a small series of patients with complex partial SE, 80% had persistent cognitive impairments (lasting at least 3 months) and 30% also had sensory and/or motor deficits.⁴⁶ In a meta-analysis of studies regarding convulsive SE in children, a recurrence of SE was estimated to be about 20% within 4 years of the first episode, and 70% of recurrences were within the first 2 years.⁵⁶

Conclusion

SE is a medical emergency and is associated with high morbidity and mortality. Continuous convulsive activity for

more than 5 minutes or recurrent seizures without return to consciousness defines SE. Rapid and adequate control of SE, ideally within 30 minutes, will help to lessen the chances of either permanent neurologic injury or increased morbidity and mortality. Stabilization of respiratory and cardiovascular status is the first step. Administration of glucose and thiamine followed by IV benzodiazepines, preferably lorazepam, is the next step. An appropriate search for causes of SE should be concomitant with this initial therapy. Any seizure not immediately controlled within 5 minutes necessitates the immediate IV administration of typical anticonvulsants, preferably phenytoin. When seizure activity persists despite initial measures, patients should be treated with general anesthetics (eg, propofol or midazolam). EEG monitoring, often continuous, is necessary in the management of SE.

References

1. Treiman DM, Meyers PD, Walton NY, et al. A comparison of four treatments for generalized convulsive status epilepticus. *N Engl J Med* 1998;339:792–798.
2. Engel J Jr. Report of the ILAE Classification Core Group. *Epilepsia* 2006;47:1558–1568.
3. Lowenstein DH, Alldredge BK. Status epilepticus. *N Engl J Med* 1998;338:970–976.
4. Treatment of convulsive status epilepticus: recommendations of the Epilepsy Foundation of America's Working Group on Status Epilepticus. *JAMA* 1993;270:854–859.
5. Lothman E. The biochemical basis and pathophysiology of status epilepticus. *Neurology* 1990;40(suppl 2):13–23.
6. Shinnar S, Bert AT, Moshe SL, et al. How long do new-onset seizures in children last? *Ann Neurol* 2001;5:659–664.
7. Eriksson K, Metsaranta P, Huhtala H, et al. Treatment delay and the risk of prolonged status epilepticus. *Neurology* 2005;65:1316–1318.
8. Murthy JMK. Refractory status epilepticus. *Neurol India* 2006;54:354–358.
9. Chin RFM, Neville GBR, Scott RC. A systematic review of the epidemiology of status epilepticus. *Eur J Neurol* 2004;11:800–810.
10. DeLorenzo RJ, Hauser WA, Towne AR, et al. A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. *Neurology* 1996;46:1029–1035.
11. Hesdorffer DC, Logroscino G, Cascino G, et al. Incidence of status epilepticus in Rochester, Minnesota, 1965–1984. *Neurology* 1998;50:735–741.
12. Hauser WA. Status epilepticus: epidemiologic considerations. *Neurology* 1990;40(suppl 2):9–13.
13. Mayer SA, Claassen J, Lokin J, et al. Refractory status epilepticus: frequency, risk factors, and impact on outcome. *Arch Neurol* 2002;59:205–210.
14. Garzon E, Fernandez RM, Sakamoto AC. Analysis of clinical characteristics and risk factors for mortality in human status epilepticus. *Seizure* 2003;12:337–345.
15. Holtkamp M, Buchheim K, Meierkord H. Predictors and prognosis of refractory status epilepticus treated in a neurological intensive care unit. *J Neurol Neurosurg Psychiatry* 2005;76:534–539.
16. Perl TM, Bedard L, Kosatsky T, et al. An outbreak of toxic encephalopathy caused by eating mussels contaminated with domoic acid. *N Engl J Med* 1990;322:1775–1780.
17. Teitelbaum JS, Zatorre RJ, Carpenter S, et al. Neurologic sequelae of

- domoic acid intoxication due to the ingestion of contaminated mussels. *N Engl J Med* 1990;322:1781–1787.
18. Jones-Davis DM, Macdonald RL. GABA_A receptor function and pharmacology in epilepsy and status epilepticus. *Curr Opin Pharmacol* 2003; 3:12–18.
19. Lowenstein DH, Aminoff MJ. Clinical and EEG features of status epilepticus in comatose patients. *Neurology* 1992;42:100–114.
20. Simon RP, Aminoff MJ. Electrographic status epilepticus in fatal anoxic coma. *Ann Neurol* 1986;20:351–355.
21. Towne AR, Waterhouse EJ, Boggs JG, et al. Prevalence of nonconvulsive status epilepticus in comatose patients. *Neurology* 2000;54:340–345.
22. Hirsch LJ, Claassen J. The current state of treatment of status epilepticus. *Curr Neurol Neurosci Rep* 2002;2:345–356.
23. Lowenstein DH. Treatment options for status epilepticus. *Curr Opin Pharmacol* 2005;5:334–339.
24. Gullapalli D, Bleck TP. Status epilepticus, in Suarez JI (ed): *Critical Care Neurology and Neurosurgery*. Totowa, Humana Press, 2004.
25. Cooperman LH. Succinylcholine-induced hyperkalemia in neuromuscular disease. *JAMA* 1970;213:1867–1871.
26. Leppik IE, Derivan AT, Homan W, et al. Double-blind study of lorazepam and diazepam in status epilepticus. *JAMA* 1983;249:1452–1454.
27. Shaner DM, McCurdy SA, Herring MO, et al. Treatment of status epilepticus: a prospective comparison of diazepam and phenytoin versus phenobarbital and optional phenytoin. *Neurology* 1988;38:202–207.
28. Alldredge BK, Gelb AM, Isaacs SM, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. *N Engl J Med* 2001;345:631–637. Erratum in *N Engl J Med* 2001;345:1860.
29. Limdi NA, Shimp AV, Faught E, et al. Efficacy of rapid IV administration of valproic acid for status epilepticus. *Neurology* 2005;64:353–355.
30. Cranford RE, Leppik IE, Patrick B, et al. Intravenous phenytoin: clinical and pharmacokinetic aspects. *Neurology* 1978;28:874–880.
31. Wilder BJ, Ramsay RE, Willmore LJ, et al. Efficacy of intravenous phenytoin in the treatment of status epilepticus: kinetics of central nervous system penetration. *Ann Neurol* 1977;1:511–518.
32. Leppik IE, Boucher BA, Wilder BJ, et al. Pharmacokinetics and safety of phenytoin prodrug given IV or IM in patients. *Neurology* 1990;40: 456–460.
33. Treiman DM, Walker MC. Treatment of seizure emergencies: convulsive and non-convulsive status epilepticus. *Epilepsy Res* 2006;68S:S77–S82.
34. Misra UK, Kalita J, Patel R. Sodium valproate vs phenytoin in status epilepticus: a pilot study. *Neurology* 2006;67:340–342.
35. Hodges BM, Mazur JE. Intravenous valproate in status epilepticus. *Ann Pharmacother* 2001;35:1465–1470.
36. Patel NC, Landan IR, Levin J, et al. The use of levetiracetam in refractory status epilepticus. *Seizure* 2006;15:137–141.
37. Rosetti AO, Bromfield EB. Levetiracetam in the treatment of status epilepticus in adults: a study of 13 episodes. *Eur Neurol* 2005;54:34–38.
38. Towne AR, Garnett LK, Waterhouse EJ, et al. The use of topiramate in refractory status epilepticus. *Neurology* 2003;60:332–334.
39. Ubogu EE, Sagar SM, Lerner AJ, et al. Ketamine for refractory status epilepticus: a case of possible ketamine-induced neurotoxicity. *Epilepsy Behav* 2003;4:70–75.
40. Patwardhan RV, Dellabadia J Jr, Rashidi M, et al. Control of refractory status epilepticus precipitated by anticonvulsant withdrawal using left vagal nerve stimulation: a case report. *Surg Neurol* 2005;64:170–173.
41. Hirsch LJ, Arif H. Status epilepticus. *Continuum Lifelong Learning Neurol* 2007;13:121–151.
42. Hirsch LJ. Continuous EEG monitoring in the intensive care unit: an overview. *J Clin Neurophysiol* 2004;21:332–340.
43. DeLorenzo RJ, Waterhouse EJ, Towne AR, et al. Persistent nonconvulsive status epilepticus after the control of convulsive status epilepticus. *Epilepsia* 1998;39:833–840.
44. Claassen J, Mayer SA, Kowalski RG, et al. Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. *Neurology* 2004;62:1743–1748.
45. Vespa PM, O'Phelan K, Shah M, et al. Acute seizures after intracerebral hemorrhage: a factoring progressive midline shift and outcome. *Neurology* 2003;60:1441–1446.
46. Ballenger CE, King DW, Gallagher BB. Partial complex status epilepticus. *Neurology* 1983;33:1545–1552.
47. Guberman A, Cantu-Reyna G, Stuss D, et al. Nonconvulsive generalized status epilepticus: clinical features, neuropsychological testing, and long-term follow-up. *Neurology* 1986;36:1284–1291.
48. DeLorenzo RJ, Pellock JM, Towne AR, et al. Epidemiology of status epilepticus. *J Clin Neurophysiol* 1995;12:316–325.
49. Rossetti AO, Hurwitz S, Logroscino G, et al. Prognosis of status epilepticus: role of aetiology, age, and consciousness impairment at presentation. *J Neurol Neurosurg Psychiatry* 2006;77:611–615.
50. Koubeissi M, Alshekhlee A. In-hospital mortality of generalized convulsive status epilepticus: a large US sample. *Neurology* 2007;69:886–893.
51. Litt B, Wityk RJ, Hertz SH, et al. Nonconvulsive status epilepticus in the critically ill elderly. *Epilepsia* 1998;39:1194–1202.
52. Shneker BF, Fountain NB. Assessment of acute morbidity and mortality in nonconvulsive status epilepticus. *Neurology* 2003;61:1066–1073.
53. Krumholz A, Sung GY, Fisher RS, et al. Complex partial status epilepticus accompanied by serious morbidity and mortality. *Neurology* 1995; 45:1499–1504.
54. Young GB, Jordan KG, Doig GS. An assessment of nonconvulsive seizures in the intensive care unit using continuous EEG monitoring: an investigation of variables associated with mortality. *Neurology* 1996;47: 83–89.
55. Logroscino G, Hesdorffer DC, Cascino GD, et al. Long-term mortality after a first episode of status epilepticus. *Neurology* 2002;58:537–541.
56. Raspall-Chaure M, Chin RFM, Neville BG, et al. Outcome of paediatric convulsive status epilepticus: a systematic review. *Lancet Neurol* 2006; 5:769–779.