Conferences and Reviews

Status Epilepticus
Clinical Features, Pathophysiology, and Treatment

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During the past two decades, substantial progress has been made in the understanding of the clinical features, classification, pathophysiology, central nervous system consequences, and treatment of status epilepticus. The most commonly used drug regimens have advantages and disadvantages, and, in this review, I recommend a protocol for the treatment of status epilepticus. An important concept in the approach to patients in generalized tonic-clonic status epilepticus is that treatment should be administered within a predetermined time frame. Clinical and experimental research indicates that continuous seizure activity for longer than 60 to 90 minutes may result in irreversible brain damage. As our understanding of the basic mechanisms of neuronal function and seizure generation advances, it is expected that more specific and novel approaches to the treatment of status epilepticus will emerge.

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Generalized convulsive (tonic-clonic) status epilepticus is a medical emergency. Unless prompt and appropriate treatment is given, generalized tonic-clonic status epilepticus can lead to profound, life-threatening metabolic and physiologic disturbances. There is also increasing evidence that the repeated seizures that constitute status epilepticus can cause prolonged brain dysfunction and even neuronal death.

Definition and Classification

Status epilepticus can be defined as a state of continuing or recurring seizures in which recovery between attacks is incomplete—that is, a series of seizures without regaining consciousness between attacks. The official definition is that status epilepticus is "a condition characterized by an epileptic seizure that is sufficiently prolonged or repeated at sufficiently brief intervals so as to produce an unvarying and enduring epileptic condition."[1(p72),2] As will be seen later, status epilepticus might be defined pathophysiologically as any seizure activity lasting 30 minutes or longer.

Status epilepticus can occur with any seizure type, and therefore one may speak of generalized tonic-clonic status, absence status, complex partial status, or simple partial (focal) status (Table 1).[3] The only true emergency among these is generalized tonic-clonic status epilepticus, although any type should be terminated as quickly as possible. Aggressive therapy, however, as will be described, has its own risks and therefore must always be weighed against the possible benefits when treating a less than urgent form of this condition.

Epidemiology

It is estimated that about 60,000 cases of generalized tonic-clonic status epilepticus occur in the United States each year.[4] About a third of these cases consist of the first seizure in patients in whom recurrent seizures or epilepsy will develop. Another third of the cases occur in patients with an established diagnosis of epilepsy, and the other third of cases develop in patients without a history of epilepsy.[4]

Status epilepticus occurs most frequently in children but also is frequent in patients older than 60 years. The mortality related to the seizures per se consists of approximately 1% to 2%, whereas the mortality related to the underlying illness causing the status epilepticus is about 10%.[4,5]

Etiology

The reported causes of status epilepticus vary from study to study. They mainly reflect referral patterns within communities and therefore are dependent on the institution at which the study was conducted. Common causes of status

TABLE 1.—*Classification of Status Epilepticus*

Class	*Type*
Generalized convulsive status epilepticus	Tonic-clonic Tonic Clonic Myoclonic
Generalized nonconvulsive status epilepticus	Absence
Simple partial (focal) status epilepticus	Somatomotor—epilepsia partialis continua Sensory—somatosensory, special sensory Aphasic Autonomic
Complex partial status epilepticus	

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ABBREVIATIONS USED IN TEXT

CNS = central nervous system
ECG = electrocardiogram
EEG = electroencephalogram/phic
IV = intravenous

epilepticus include head trauma, tumor, stroke, central nervous system (CNS) infection, drug and alcohol abuse and withdrawal, congenital CNS abnormalities, fever in children, acute systemic and metabolic illnesses, and antiepileptic drug noncompliance in patients with epilepsy. In about 15% to 30% of cases, no cause can be identified, resulting in a diagnosis of idiopathic status epilepticus. A considerable proportion of cases of status epilepticus occur in the context of an acute insult or injury, regardless of whether the patient has a previous history of epilepsy or another neurologic disorder.[4,6,7]

Morbidity and Mortality

Morbidity and mortality from status epilepticus seem to be related to three factors: CNS damage due to the underlying illness or acute insult causing the status epilepticus, CNS damage caused by repetitive electrical discharges of the seizures themselves, and systemic and metabolic factors related to repeated generalized tonic-clonic seizures.[5] Death associated with status epilepticus most often is related to the underlying illness rather than the seizures themselves.

In recent years, studies have shown that seizures lasting longer than 60 to 90 minutes may result in neuronal death in patients with generalized tonic-clonic seizures and in those with epilepsia partialis continua.[8-11] Furthermore, prolonged memory deficits have been recorded after complex partial status epilepticus.[12-14] Others have reported that prolonged febrile, and perhaps nonfebrile, seizures occurring between the ages of 6 months and 7 years may result in damage to the hippocampus (hippocampal sclerosis) and thereby contribute to recurrent complex partial seizures of temporal lobe origin.[15-18]

The systemic and metabolic effects of repeated generalized tonic-clonic seizures involve the cardiovascular, respiratory, renal, metabolic, and autonomic nervous systems. Cardiovascular changes in response to status epilepticus include tachycardia or bradycardia, arrhythmias, and hypotension. Respiratory failure may be precipitated by the acute underlying illness or pulmonary edema and may be complicated by antiepileptic drug administration in the treatment of this disorder. Generalized tonic-clonic seizures may rarely result in rhabdomyolysis with resultant myoglobinuria and acute renal failure. Metabolic complications include respiratory and metabolic acidosis, hypoxia, hyperkalemia, hypoglycemia, and pronounced increases in serum levels of prolactin, glucagon, insulin, norepinephrine, epinephrine, growth hormone, and cortisol. Autonomic nervous system effects can include hyperpyrexia, increased sweating, increased tracheobronchial secretions, pupillary dilation or constriction, and cardiovascular complications, as mentioned earlier.[5,7,19-23]

TABLE 2.—*Electroencephalographic Patterns in Status Epilepticus**

Discrete seizures with interictal slowing
Waxing and waning of ictal discharges
Continuous ictal discharges
Continuous ictal discharges punctuated by flat periods
Periodic epileptiform discharges on a flat background

*From Treiman.[29]

Pathophysiology

In considering the pathophysiology of status epilepticus, three general principles have been described:

- Status epilepticus appears to have a distinct natural history and evolution.
- The more prolonged status epilepticus becomes, the more intractable it is to effective treatment.
- The more prolonged the status epilepticus, the more likely it is associated with a poor prognosis.[7,24-26]

Natural History of Status Epilepticus

A number of investigators, studying status epilepticus mainly in animals but also in humans, have described a sequence of events that evolve over a fairly predictable time course. These events can be categorized as electroencephalographic (EEG), motor, and systemic.

Electroencephalographic stages. Treiman and colleagues have described a series of five EEG patterns in status epilepticus (Table 2).[27-29] This sequence of progressive EEG changes has also been described in animal models of status epilepticus provoked by electrical stimulation of the brain.[30,31] In the initial stage, the EEG shows discrete seizures with interictal slowing. As the condition continues, the discrete seizure pattern first begins to wax and wane and then evolves into a stage of continuous ictal discharges. If seizures persist, ictal discharges are interrupted by flat periods in the EEG background, and, in the end stage, paroxysmal bursts of epileptiform discharges arise out of a flat background.

Motor stages. The evolution of motor activity during status epilepticus correlates roughly with that of the EEG. At the start, patients usually undergo discrete seizures that correspond to the discrete episodes of ictal discharges on the EEG. Between seizures there is interictal slowing, and the patient does not recover consciousness. As status epilepticus continues, the seizures may wax and wane and then merge into continuous generalized clonic activity that also is reflected in the EEG. After status epilepticus has persisted for about an hour, motor activity may begin to diminish even though seizure activity continues to be shown on the EEG. In the last stages of status epilepticus, motor activity may actually disappear but the EEG continues to show periodic epileptiform discharges. Treiman and associates speak of an "electromechanical dissociation" between the motor events and the EEG discharges during this stage.[28]

Systemic and metabolic stages. A number of metabolic and systemic effects have been reported during status epilepticus and have been divided into two phases. The first phase usually lasts about 30 minutes and is associated with an increase in blood pressure with each seizure, an increase in serum lactate and serum glucose levels, and a decrease in serum pH resulting in acidosis. As the transition into the second phase at about 30 minutes occurs, the blood pressure tends to return to normal—the patient may even become hypotensive—and no longer responds with an increase with each seizure. Serum pH and lactate values also return to

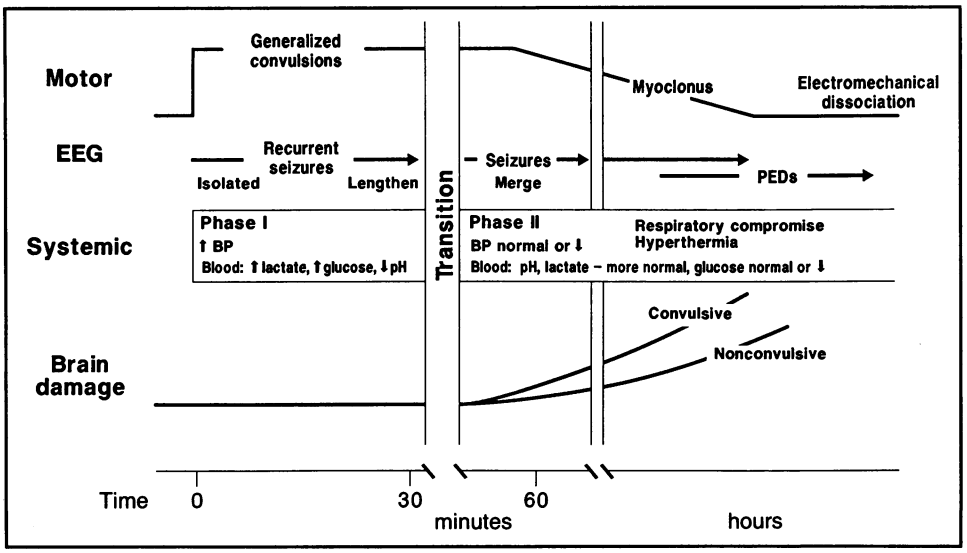

Figure 1.—The diagram shows the evolution of pathophysiologic changes during status epilepticus (adapted with permission from Lothman[25]). BP = blood pressure, EEG = electroencephalographic, PEDs = periodic epileptiform discharges

normal, and the glucose level may become normal or low. As status epilepticus progresses through a second transition period after about 60 minutes, respiratory compromise and hyperthermia occur and the degree of status epilepticus-induced brain damage increases.[8,10,19]

Figure 1 summarizes the pathophysiologic changes in diagrammatic form.[25] This information was obtained from studies using both primates and rodents as well as more limited information from human studies.

Central Nervous System Consequences of Prolonged Status Epilepticus

As mentioned, clinical experience indicates that the longer status epilepticus continues, the more difficult it is to treat and the poorer the prognosis. These observations have been verified in studies of animals. There appears to be a critical "transition period" of 30 to 60 minutes for the duration of status epilepticus. After this period of time, the seizures become more refractory to treatment, and the likelihood of prolonged or even permanent brain damage is greater.

Work with animals has shown that prolonged seizures in primates result in damage in five areas of the brain. These include layers 3, 5, and 6 of the cerebral cortex, the cerebellum, the hippocampus, certain thalamic nuclei, and the amygdaloid body.[8,10] If, however, the animals are protected against the systemic and metabolic effects of status epilepticus by artificial respiratory support and paralyzation, damage involves mainly the hippocampus with partial sparing of the other areas.[9,10,32] This observation has been verified using similar techniques in several species of animals. It appears likely, therefore, that prolonged seizures can cause at least hippocampal damage, especially if the seizures are generalized tonic-clonic. Some degree of CNS damage can occur, however, even if the seizures are nonconvulsive in nature.[10,32-41]

It has also been shown that spontaneous recurring seizures occur in animals as a chronic sequela to an episode of status epilepticus.[37,42,43] This may mimic the aforementioned phenomenon in humans whereby an episode of prolonged seizure (febrile or nonfebrile) between the ages of 6 months and 7 years may produce hippocampal sclerosis, which in turn may be associated with spontaneous complex partial seizures in later life.[15-18]

The mechanism of neuronal damage during prolonged status epilepticus may be related to reduced inhibition through the γ-aminobutyric acid system, enhanced glutaminergic excitatory transmission, and calcium-mediated cell damage.[10,25,39,40,44]

Initial Treatment of Patients in Generalized Tonic-Clonic Status Epilepticus

From the various pathophysiologic mechanisms described earlier, it should now be clear that time is of the essence in the treatment of status epilepticus. Thus, it seems desirable that every facility should have a predetermined protocol for the treatment of status epilepticus that includes a time frame (Table 3). First, patients should be assessed for signs of cardiorespiratory compromise, hyperthermia, focal neurologic signs, head trauma, or CNS infection, and their seizures should be observed to ascertain that they are in status epilepticus. Baseline laboratory studies should be done, including antiepileptic drug levels, serum levels of electrolytes, glucose, calcium, magnesium, creatinine, and urea nitrogen, a complete blood count, metabolic screen, and drug and toxicology screens. Arterial blood gases should be measured to assess baseline oxygen saturation and pH. If needed, an oral airway should be inserted and oxygen administered. An intravenous (IV) infusion should be started with a saline solution. Thiamine, 100 mg IV, should be administered, and this should be followed by 50 ml of a 50% glucose solution by IV push. Cardiopulmonary resuscitating equipment should always be at the bedside of a patient in status epilepticus in case of a sudden deterioration.

Drug Therapy for Status Epilepticus

Common Drug Regimens

Although much has been written about status epilepticus and its treatment over the years, few well-controlled, prospective, randomized drug trials have been undertaken of this condition.[45-47] The three most commonly used drug regimens for the treatment of status epilepticus include the use of phenytoin alone, a benzodiazepine plus phenytoin, and phenobarbital alone. Each of these will be reviewed briefly and a specific protocol recommended.

TABLE 3.—*Treatment of Status Epilepticus*

Time Frame	*Procedure*
0–5 min	Assess cardiorespiratory function, take history, and perform neurologic and physical examination; draw blood specimens for antiepileptic drug levels, glucose, BUN, creatinine, calcium, magnesium, electrolytes, complete blood count, metabolic screen, drug screen, and arterial blood gases; insert oral airway and administer oxygen if needed
6–9 min	Start IV infusion with saline solution; administer 25 grams glucose and B vitamins
10–45 min	Infuse lorazepam, 0.1 mg/kg (4 to 8 mg), at <2 mg/min
	Also begin infusion of phenytoin, 20 mg/kg, at a rate of 25 mg/min; this may take 20 to 40 min; monitor ECG, respirations, and blood pressure
	If seizures persist, give additional phenytoin, 5 mg/kg, at same rate, and, if needed, another 5 mg/kg until a maximum of 30 mg/kg has been given
46–60 min	If seizures persist, intubate and give phenobarbital, 20 mg/kg, at <100 mg/min IV
1 hour	If seizures persist, pentobarbital coma or general anesthesia should be started

BUN = blood urea nitrogen, ECG = electrocardiogram, IV = intravenous

Phenytoin (Dilantin) only. The main advantages of using phenytoin in the treatment of status epilepticus are its proven effectiveness in controlling seizures, its relatively long half-life, and its lack of significant CNS depression. Disadvantages include its cardiovascular side effects if given too rapidly (arrhythmia, hypotension), the time required to give an average loading dose (20 to 40 minutes), its relative ineffectiveness in suppressing focal seizures, the possibility of local tissue irritation, and its tendency to crystallize in the IV line. When using phenytoin, blood pressure and the electrocardiogram (ECG) should be monitored and the drug must be given in a saline solution. Phenytoin must *not* be given in a glucose-containing IV solution.[48-52]

Benzodiazepine plus phenytoin. The main advantage of combination therapy using a benzodiazepine plus phenytoin is that the seizures may be rapidly controlled with the benzodiazepine, followed by the use of phenytoin for its sustained antiepileptic action. Therefore, a benzodiazepine is used to offset the time required to infuse an adequate loading dose of phenytoin. The disadvantage of this combination is that two drugs are used instead of one, which may lead to drug interactions that could result in respiratory depression and hypotension. During the use of a benzodiazepine with phenytoin, blood pressure, respirations, and the ECG should be monitored closely.

In the United States, two benzodiazepine preparations are commonly used in the treatment of status epilepticus. Diazepam became popular in the 1960s because of its rapid onset of anticonvulsant action. Although it acts rapidly, diazepam is quickly redistributed out of the brain and into fat stores.[45,53] Therefore, its antiepileptic action lasts only about 20 to 30 minutes, and repeated doses of diazepam are often necessary if seizures are to remain controlled. This can severely hamper the subsequent treatment of the seizures if status epilepticus is not easily controlled and recurs after the drug redistributes. Lorazepam also has a fairly rapid onset of action but has a much longer effective duration of action, thereby eliminating the need for repeated doses. In fact, some studies indicate that lorazepam may terminate status epilepticus for as long as 12 to 24 hours, allowing more time to institute definitive antiepileptic drug therapy.[46,54,55] For these reasons, if a benzodiazepine is used, lorazepam is probably preferred over diazepam.

Great care must be exercised if a benzodiazepine (especially repeated doses of diazepam) and phenobarbital are used sequentially in the treatment of status epilepticus. Their hypotensive and respiratory depressant actions synergize and may cause abrupt and serious side effects. Therefore, unless absolutely necessary, it is generally recommended that either one or the other of these medications be used without combining them.[47,54,56-61]

Phenobarbital only. The advantages of phenobarbital include its long half-life, its effectiveness in both generalized and focal seizures, and the fact that it can be administered more rapidly than phenytoin. The main disadvantages of phenobarbital include its tendency to depress a patient's level of consciousness, to contribute to respiratory depression, and to interact with benzodiazepines. During the administration of phenobarbital, the patient's blood pressure and respiratory rate should be continuously monitored.[47,52]

Recommended Drug Protocol

Many comprehensive epilepsy centers recommend some variation of the following protocol (Table 3)[5,29,62,63] (also, A. L. Sherwin, MD, Montreal Neurological Institute, oral communication, January 1991). After the initial assessment of a patient and the placement of an IV line, administer lorazepam, 0.1 mg per kg (4 to 8 mg), at a rate of less than 2 mg per minute. Blood pressure, respirations, and ECG should be monitored during this infusion.

If the patient's seizures do not stop with the administration of lorazepam, begin infusing phenytoin, 20 mg per kg, at a rate of 25 mg per minute. This infusion rate will require 20 to 40 minutes to complete but usually will avoid cardiovascular side effects such as hypotension and arrhythmias.[51]

If the seizures persist, an additional phenytoin dose of 5 mg per kg may be administered at the same rate (25 mg per minute). If this is not effective, an additional 5 mg per kg can be infused, bringing the total phenytoin dose to a maximum of 30 mg per kg.[29,54]

If seizures continue, even more aggressive therapy is indicated. Before this is initiated, an endotracheal tube should be inserted, and the patient will obviously need to be under close medical supervision by an intensive care specialist as well as a neurologist. After intubation, administer phenobarbital, 20 mg per kg, at a rate of less than 100 mg per minute.[29,54]

If seizures persist, pentobarbital coma or general anesthesia should be initiated because at this point the patient has been in status epilepticus for at least an hour. The risk of prolonged or permanent brain damage is present if status epilepticus is allowed to continue for longer than 60 minutes.[5,29,54,64-69] Pentobarbital coma must be conducted in an intensive care unit with the patient intubated, mechanically

ventilated, and maintained under continuous cardiovascular, respiratory, and EEG monitoring. A loading dose of pentobarbital (5 to 10 mg per kg IV) is given slowly to induce a "burst-suppression" EEG pattern. This EEG pattern is maintained with a continuous IV infusion of pentobarbital (1 to 5 mg per kg per hour). The infusion is slowed or terminated every 2 to 12 hours and reinstated if seizures recur. Such treatment may be required for days to weeks in refractory cases.[5,29,64-69]

Future Developments in the Treatment of Status Epilepticus

To determine the most appropriate therapeutic regimen for the treatment of status epilepticus, a large, prospective, double-blind, multicenter cooperative study was initiated by the Division of Veterans Affairs in June of 1990. This study will include more than 1,100 patients with generalized tonic-clonic status epilepticus and is scheduled to be completed in 1993. Four regimens are being compared. These include phenytoin, 18 mg per kg; diazepam, 0.15 mg per kg, followed by phenytoin, 18 mg per kg; lorazepam, 0.1 mg per kg; and phenobarbital, 15 mg per kg. By 1993, we should have additional information concerning the best treatment regimen for this condition.[70]

It is hoped that more specific therapy for status epilepticus can be devised in the future. Such medications may include antagonists of excitatory amino acid neurotransmitters such as glutamate, specific calcium channel blockers, and agonists of inhibitory neurotransmitters such as γ-aminobutyric acid.[71] In addition, a phenytoin prodrug is under investigation in an attempt to circumvent some of the difficulties experienced with the use of phenytoin as presently formulated.[72,73] Investigations using an IV preparation of valproic acid are also under way.[74,75] Therefore, it can be expected that within the next decade we will not only have established the best drug regimen for the treatment of status epilepticus with currently available medications, but we will also have discovered novel and specific medications to use in the treatment of this serious malady.

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GENERALIZED TONIC-CLONIC STATUS EPILEPTICUS SUGGESTED GUIDELINES FOR INITIAL TREATMENT

Time Frame	Procedure
0-5 minutes	Obtain vital signs, establish airway, administer oxygen if needed. Observe seizures briefly to ascertain that patient is really in status. Draw baseline blood work (CBC, chemistry panel, antiepileptic drug levels--send STAT), draw ABGs (for pO_2 and pH), draw toxicology screen. Quickly assess patient for signs of cardiorespiratory compromise, hyperpyrexia, focal neurologic signs, head trauma, CNS infection, etc. Always have CPR equipment at bedside of a patient in status.
6-9 minutes	Start IV infusion with saline solution. Administer 100 mg thiamine, IV. Administer 50 ml of 50% glucose solution, IV, if blood sugar is low or unobtainable. Do not give glucose if blood sugar is normal or high.
10-45 minutes	Infuse lorazepam (Ativan), 0.1 mg/kg, at 2 mg/min. Begin IV loading dose of fosphenytoin (Cerebyx), 20 mg/kg, at 150 mg/min. Monitor patient's B/P, pulse, EKG, and respirations while giving IV fosphenytoin and lorazepam. Most common side effects: hypotension, arrhythmia, paresthesias, and respiratory depression.
46-60 minutes	If seizures persist, intubate and give phenobarbital, 20 mg/kg, at 100 mg/min. Never use Valium and phenobarbital sequentially in the treatment of status, unless the patient is intubated and in an ICU. Their hypotensive and respiratory depressant actions synergize. Serious and abrupt side effects can occur with these two drugs when given together.
1 hour	If seizures persist, the patient should be placed in a drug induced coma with pentobarbital, a benzodiazepine, or other anesthetic agent to prevent life threatening lactic acidosis, hypoxia, hyperthermia, and permanent seizure-induced neuronal damage. The patient must be in an ICU, and outcome should be monitored and treatment guided by EEG with the goal being suppression of seizure activity on EEG.