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Remember the first time you saw a patient seizing? Was it in school, at home, or during your initial training in medicine? Scary, yes? Didn't you think something needs to be done right away?

I remember during my first exposure to seizures in medical school that the neurologist's approach was "What's the hurry? Seizures stop eventually. No need to throw all those drugs with their risk of respiratory depression at a patient." Well, as this review explains, there should be a sense of urgency and treatment should be prompt. Fortunately, we have good and safe drugs when used appropriately and emergency physicians have become expert in the management of acute and prolonged seizures.

This two-part article discusses aspects of seizure assessment and management in the adult patient who presents to the emergency department. The authors have reviewed the literature and "best practice" guidelines to assist you in providing care to your patients. Part 1 covers the assessment of patients, and Part 2 will cover the details of specific medications.

—J. Stephan Stapczynski, MD, FACEP, Editor

Seizures and Status Epilepticus in Adults: Part I

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Introduction

In the 10 years since seizures and status epilepticus have been reviewed in this publication,[1] several new antiepileptic drugs have become available as well as new formulations of older medications. However, the pharmacologic approach to generalized convulsive status epilepticus is little changed. What has changed is the recognition that prompt treatment of status epilepticus is necessary to limit morbidity and mortality. The epidemiologic definition of status epilepticus, that of seizure duration 30 minutes or longer, has no place in the clinical setting. A call for revision of the time factor for generalized convulsive status epilepticus has been sounded. This revised definition for

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adults and older children (5 years and older) urges that treatment be started for generalized convulsive status epilepticus if a single seizure continues for more than 5 minutes, or if there are two or more discrete seizures between which there is incomplete recovery of consciousness.[2] (*See Table 1.*)

It has long been known that status epilepticus causes profound systemic effects such as acidosis, but evidence has emerged that the abnormal, excessive electrical activity itself can cause neuronal damage.[3] Thus status epilepticus may be self-perpetuating and may even predispose patients to further seizures in the distant future.[4]

The literature on treatment of status epilepticus is largely comprised of small case series and case reports. Randomized prospective trials that evidence-based medicine weighs heavily, are notably lacking. This review will focus on seizures and status epilepticus in adults. Seizures in infancy from inborn errors of metabolism or perinatal injury are not discussed, nor are febrile seizures.

Seizures and epilepsy have a large impact on emergency departments. A focused survey of 12 U.S. emergency departments showed that 1.2% of the total patient census during the study period had complaints related to seizures. Seventy percent of these patients utilized the EMS system with the majority of these consuming advanced care resources. New onset seizures constituted about one-quarter of this population. Ethanol withdrawal or low antiepileptic medication was thought to be a factor in about half of the cases. Antiepileptic medication was administered in the ED in the majority of these patients, and one-quarter were admitted to the hospital. Status epilepticus occurred in 6% of the study group. A summary may be found in Table 2.[5]

Pathophysiology

Every person has the capacity to experience seizures with adverse conditions such as sleep deprivation, hypoxia, ingestion of toxic medications, and many other stimuli. Why some individuals develop seizures that are seemingly unprovoked is unknown. The informal concept of a seizure threshold exists with the idea that at some point of environmental stress anyone will have a seizure. Some individuals seemingly have a lower set point of this threshold, or this threshold may vary with medications and other stressors.

The pathophysiology of seizures is multifactorial and incompletely understood. Recent research has turned to focus on failures of inhibition of excessive neuronal firing rather than excitatory mechanisms. Current theory for generalized tonic-clonic seizure pathophysiology is that the seizures start with excitation of susceptible cerebral neurons leading to synchronous discharges of progressively larger groups of connected neurons, eventually affecting a part of the brain that causes clinical signs or symptoms. What triggers the initial events is unknown, but some imbalance of excess excitation and decreased inhibition sustains a seizure.[6] Glutamate is the most common excitatory neurotransmitter and mediates the excess excitation via the n-methyl-D-aspartate (NMDA) subtype receptor. Useful antiepileptic drugs that work by NMDA antagonism have not been developed. On the inhibitory side, gamma-aminobutyric acid (GABA) is an important inhibitory neurotransmitter and is the site of action of many antiepileptic drugs. GABA neurotransmission via activation of the $GABA_{-A}$ subtype receptor prevents excessive neuronal excitation. Many of the antiepileptic drugs including benzodiazepines, barbiturates, and propofol are thought to work through activating $GABA_{-A}$ receptors. Patients may become tolerant to this mechanism of action with the implication that some medications useful for stopping seizures may not be suitable for long-term therapy. Some experimental work suggests that the $GABA_{-A}$ receptors may change in number or sensitivity during the course of status epilepticus; this may imply that medications that might be effective early in the course of status epilepticus might not be effective with prolonged seizures.[7]

Generalized convulsive status epilepticus is characterized by profound physiologic changes with changes of hypoxia, hypotension, hyperkalemia, acidosis, hyperthermia, leukocytosis, CSF pleocytosis, and diminished cerebral blood flow in decompensated status epilepticus.[6] Dividing the physiologic changes into early and late is helpful.[8] In early status epilepticus, blood pressure, cerebral blood flow, and cerebral oxygenation are preserved. Cerebral metabolism is elevated. At some transition time, perhaps around 30 to 60 minutes, adaptive mechanisms fail and

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Table 1. Definition of Generalized Convulsive Status Epilepticus for Adults and Children 5 Years and Older[2]

Continuous seizures lasting ≥ 5 minutes
OR
Two or more discrete seizures with incomplete recovery of consciousness between seizures

Table 2. Facts from the Emergency Medicine Seizure Study Group[5]

- 1.2% of the patient census during the study period had complaints related to seizures
- 70% of these patients utilized the EMS system
- 25% of this population had new onset seizures
- Ethanol withdrawal or low antiepileptic medication was thought to be a factor in about half of the cases.
- Antiepileptic medication was administered in the ED in the majority of these patients
- One-quarter were admitted to the hospital
- 6% of the study group experienced status epilepticus

cerebral blood becomes diminished though brain metabolism is still elevated. There is now a mismatch of metabolic need and substrate supply, and neuronal damage ensues.[6] This physiologic model correlates with the clinical model of need to treat status epilepticus in the early, compensated state.

Electroencephalographic changes have been described that seem to parallel these physiologic changes. A proposed scheme outlines a sequence of motor and EEG changes in generalized convulsive status epilepticus that ranges from distinct motor events with associated EEG changes to paroxysmal EEG changes without associated motor activity.[9] The final step is an electromechanical dissociation of brain from the body identifying a state of abnormal cerebral activity not reflected with convulsions. This is somewhat controversial in that some investigators do not find a stereotypical sequence in electrographic status epilepticus.[10]

Experimental work has demonstrated that the abnormal and excessive electrical activity associated with generalized convulsive status epilepticus is in itself injurious. Experimental status epilepticus causes cortical, cerebellar, and hippocampal damage even when systemic processes such as hypotension, acidosis, and respiratory depression are controlled.[3,4]

Imaging of patients with magnetic resonance imaging (MRI) and magnetic resonance spectroscopy for investigation of seizures has demonstrated changes in the hippocampus within 48 hours of acute symptomatic seizures or status epilepticus.[11] Hippocampal injury is thought to play a major role in epileptogenesis leading to future seizures.

Another line of evidence for neuronal damage is the increase in neuron-specific enolase (NSE) in the serum and the brain that occurs in patients with status epilepticus. NSE is an enzyme important for energy metabolism in the brain, and it is thought to be a marker for central nervous system (CNS) injury. It is elevated in patients with generalized convulsive status epilepticus, complex partial status epilepticus, and subtle or sub-clinical status epilepticus. The highest levels of NSE were found in the patients with subtle status epilepticus and were thought to reflect the severity of neurologic injury in this group.[12]

Clinical Findings

Some historical factors are key to deciding if the patient experienced a seizure, realizing that seizures have many different appearances. For a generalized convulsive seizure, the abrupt onset of loss of consciousness, loss of posture, rhythmic phasic movements of the extremities, followed by a period of confusion is convincing. Type of seizure or movements, number and pattern, duration, presence of incontinence, and associated symptoms should be sought. Possible precipitating factors include noncompliance with prescribed antiepileptic drugs, adverse drug reactions, sleep deprivation, ethanol withdrawal, drug or toxin ingestion, and pregnancy. Other key factors include head trauma, recent headaches, cancer, heart disease, stroke, immunocompromise, or metabolic disturbances.

Some physical examination factors might suggest that the patient has experienced a seizure. Tongue-biting, particularly if lateral, has a high-specificity for convulsions, although absence of tongue-biting has no diagnostic value.[13] Tongue biting with syncope usually involves the tip of the tongue. In one study from an epilepsy monitoring unit, biting of the tip of the tongue or lip suggested psychogenic seizures.[14] Incontinence likewise suggests a generalized seizure, but is present in other conditions and not always found with seizures.

Initial head and eye turning at seizure onset may have localizing value. The forced initial head-turning (versive) indicated seizure onset (verified by EEG) in the contralateral cerebral hemisphere. Later head and eye movements had less localizing value.[15]

The term "post-ictal state" for the patient condition following seizures is in common clinical usage, but remarkably little is written about it. Confusion or unconsciousness following a generalized convulsive seizure is universal; absence of this should raise the consideration of psychogenic seizure. Post-ictal weakness is eponymically known as Todd's paralysis. Again, this is a transient phenomenon. Babinski responses may be present in patients following epileptic seizures; in one study a Babinski response was present post-ictally in 42% of patients following an an epileptic seizure, and in none of the patients following psychogenic seizures.[16] Other physical findings suggestive of non-epileptic seizures are discussed in a later section.

During evaluation of the patient with a seizure, attention must be directed to the possibility of associated injuries from the convulsive movements. One study observed injuries, mainly oral and facial lacerations, in 6% of patients presenting to the ED with a seizure-related complaint, and added the comment that the incidence of minor injuries might be higher but simply were not noted at the initial visit.[5] Orthopedic injuries infrequently reported include posterior shoulder dislocations and femoral neck fractures.[17-19] Vertebral compression fractures of the lumbar and the thoracic vertebrae have been reported with symptomatic spinal canal intrusion.[20]

Table 3. Classification of Clinical Seizure Types

I. PARTIAL ONSET SEIZURES

- **A. Simple Partial Seizure**
  - 1. Motor symptoms
  - 2. Sensory symptoms
  - 3. Special sensory symptoms
  - 4. Other
- **B. Complex Partial Seizure (clouded consciousness)**
  - 1. Partial onset seizure evolving into a complex partial seizure
  - 2. Impairment of consciousness at onset
- **C. Partial Onset Seizure Evolving into a Generalized Seizure**

II. GENERALIZED ONSET SEIZURES

- A. Absence seizures
- B. Myoclonic seizures
- C. Clonic seizures
- D. Tonic seizures
- E. Tonic-clonic seizures
- F. Atonic seizures
- G. Others

III. UNCLASSIFIABLE SEIZURE TYPES

Table 4. Differential Diagnosis of Seizures in Adults

I. SEIZURES - FROM ABNORMAL, EXCESSIVE NEURONAL DISCHARGES

- A. Unprovoked seizures
- B. Symptomatic or secondary seizures

II. NON-EPILEPTIC SEIZURES - APPEAR TO BE SEIZURES BUT DO NOT RESULT FROM ABNORMAL EXCESSIVE NEURONAL DISCHARGES

- A. Psychogenic seizures (sometimes non-epileptic seizures used synonymously with psychogenic seizures)
- B. Repetitive abnormal posturing
- C. Involuntary movement disorders
- D. Syncope / convulsive syncope
- E. Concussive syncope
- F. Sleep disorders
- G. Migraine disorders

Seizure Types and Epilepsy

Seizures are finite episodes of disturbed cerebral function. Theoretically, any behavior or experience may be produced by this abnormal cortical electrical activity, but patterns occur that allow for a classification of seizures.[21] Physiologically, during seizures cortical neurons have excessive, abnormal, and synchronous electrical discharges. Various behaviors, movements, or sensory experiences are produced by this abnormal cortical activity. Some seizure activity may be apparent to observers or the seizure may be subclinical and inapparent.[22]

Epilepsy may be thought of as a disease with seizures being a symptom of the disease. Seizures provoked by environmental stimuli such as electrolyte abnormalities, toxins, hypoxia, and many other stimuli are considered provoked seizures and do not constitute epilepsy. Epilepsy is defined by spontaneous, recurrent, unprovoked seizures. The complex classification of the epilepsies continues to evolve and is largely outside the scope of emergency medicine practice.[23]

The basic distinction in seizure types is that of partial onset and generalized onset seizures. (*See Table 3.*) Clinically this may be of importance since focal seizure onset may imply focal or structural abnormality of the brain. Partial onset seizure implies that history, observation, or electrographic information indicate that seizure onset is limited to one part of the brain. Partial seizures may be further divided into: simple partial seizures; complex partial seizures; and partial seizures that secondarily become generalized seizures. The term partial implies that the seizures do not cause an alteration in consciousness. The term complex is used to indicate that consciousness is clouded.

Generalized onset seizures represent initial bilateral cortical involvement at seizure onset; most often this is assigned following electroencephalographic analysis. Most seizure types in adults are partial onset seizures with secondary generalization; the generalization occurs too rapidly to be observed in most circumstances but rarely may be seen if the patient has a recurrent seizure in the emergency department. There are several types of generalized onset seizures. Absence or petit mal seizures have a characteristic EEG pattern and are clinically observable as brief staring episodes or arrest in a behavior. Other generalized seizure types include myoclonic, clonic, tonic, and atonic seizures.

Differential Diagnosis of Seizures

There is a reasonably broad differential diagnosis to seizures. The old clinical axiom, "not everything that shakes is epilepsy," is certainly true.[24] A differential diagnosis of seizures in adults is listed in Table 4. A variety of clinical phenomena can simulate the phenotype of a seizure. For generalized convulsive seizures, the key points seem to be abrupt onset, loss of consciousness, motor movements of the extremities, and a period of confusion following the event. This phenotype can be simulated by syncope, from whatever cause, and a variety of other conditions. As the clinician gathers information in the clinical encounter, a probability assessment is formulated using available information as to the likelihood of the event being a seizure or some other process.

Syncope features prominently in the differential diagnosis of seizures. Most cases of syncope are benign and represent simple faints. Often observers assign undue importance to brief movements that accompany syncope, and the patient arrives in the ED being labeled as having had a seizure. "Convulsive syncope," with motor movements accompanying the faint, were frequent in one series observing blood donors. A characteristic pattern has been described with the patient first becoming pale, diaphoretic, and staring. Upward eye-rolling was followed with head and neck extension. Arms were observed to be flexed at the elbow and fists clenched. Brief growling was heard lasting from a few seconds to half a minute. Recovery was prompt but confusion

lasting a few moments was reported as well. A smaller number of patients had 3 to 5 beats of clonic movements and a few had brief and violent myoclonic jerks.[25]

Most causes of syncope are benign and a cause may be inferred from the history. However, recurrent dysrhythmias from a variety of causes including prolonged QT syndrome, Brugada syndrome, and prolonged sinus arrest with resulting syncopal episodes have been reported to lead to a misdiagnosis of epilepsy.[26,27] The role of the emergency physician is to identify and then risk-stratify patients with syncope into those with possible cardiovascular risk and ensure further observation of those patients at risk.[28]

Stiffening and brief posturing of athletes following a head injury has been observed and termed "convulsive concussions." Return to full consciousness is prompt. It is thought that this posturing is not the result of abnormal, excessive cortical electrical activity, and antiepileptic medications or workup for seizures is not recommended.[29,30] Other seizures resulting from trauma, such as early and late-onset, will not be specifically discussed.

Psychogenic or non-epileptic seizures are the preferred terms for events that resemble convulsions but are not from abnormal, synchronous, excess discharges of cortical neurons. The term non-epileptic seizure is used differently throughout the literature and is a source of confusion. Literally this means something that looks like a seizure from that excessive electrical cortical etiology, but is found not to represent the manifestations of abnormal electrical activity. In the larger sense, non-epileptic seizures may include some of the entities discussed above such as simple syncope and convulsive syncope. In practice it is often used in a more restrictive sense as a synonym for psychogenic seizures. Older terms of pseudoseizures and hysterical seizures are discouraged in current practice.

Psychogenic seizures are a major point in the differential diagnosis of seizures and may present a diagnostic conundrum. In one series, the most common presentation of non-epileptic seizures was unresponsiveness without predominant motor manifestations.[31] Slow, subtle writhing, or in-phase limb movements were the most likely to be mistaken for status epilepticus. This differs from the commonly expected and perhaps easily recognized presentation of out-of-phase limb movements, side-to-side head movements, and pelvic thrusting.[32,33]

Physicians may have difficulty recognizing non-epileptic seizures and at times seem driven to implement treatment protocols without gathering historical information or performing a physical examination that might include some provocative maneuvers. In one study, when presentations of patients later found to have psychogenic seizures were retrospectively reviewed, 74% of patients with psychogenic seizures received anticonvulsants and 12% were thought to be in status epilepticus.[31]

Most recent writings come from video-EEG monitoring literature. Most patients with seizures keep their eyes open; "ictal eye closure" was found to be a reliable discriminator distinguishing non-epileptic seizures from epileptic seizures.[34] The presence of a clenched mouth during a tonic state should suggest psychogenic seizures.[14] The unresponsive patient with spells who consistently deviates eyes away from the approach of the examiner ("alternating eye deviation sign") is reported to be useful in identifying psychogenic seizures,[35] as are "geotropic eye movements," with the eye movements of the patient with non-epileptic seizures being directed toward the ground whether the head is turned to the left or the right.[36] Ictal heart rate increase of $\geq$ 30% over baseline is reported to distinguish epileptic from non-epileptic seizures when the seizures were quiet staring spells.[37] Ictal stuttering in adults was present in 8.5% of patients with non-epileptic (psychogenic) seizures in one series, and not observed in a similar number of patients with epileptic seizures.[38] However, the diagnosis of psychogenic non-epileptic seizures may be quite difficult with one study reporting an average delay of 7.2 years to correct diagnosis.[39]

Patients with prolonged non-epileptic seizures are at risk for iatrogenic complications, notably from the administration of medications to the point of respiratory failure requiring intubation.

Additional Clinical Workup

History and physical examination ideally should direct the depth and tempo of investigation. Obviously, the patient with a possible new-onset seizure who has returned to normal baseline state will differ from a patient with focal deficits, altered mental status, repetitive events, or status epilepticus.

History and physical examination will identify most patients likely to have a laboratory abnormality. Although serum electrolytes and other "routine" laboratory testing is commonly obtained, yield is low in patients with a seizure who have returned to their normal baseline.[40-42] Serum glucose and sodium abnormalities, although uncommon, are the abnormalities most frequently encountered. Screening for stimulant use in emergency department seizure patients has been reported to be of low yield.[43]

If a patient with a seizure has persistent altered mental status or a history of immunocompromise, or other medical co-morbidities, additional workup may indicated. The possibility of a CNS infection becomes more likely in medically complex cases, and sampling of CSF is supported by evidence and emergency medicine clinical policy statement.[42] Testing for pregnancy is recommended for women of childbearing age with a seizure, since pregnancy might alter medication administration.[42]

Elective Testing

The use of prolactin as an adjunct to confirming the diagnosis of epileptic seizures has been discussed for some years, and a recent technology assessment from the American Academy of Neurology evaluated and summarized available information. Elevated serum prolactin level measured 10-20 minutes after a suspected seizure is useful in differentiating a generalized tonic-clonic or complex partial seizure from psychogenic seizures. Prolactin levels designated as abnormally high varied in the reviewed studies and the best cut-off level is not known. Prolactin should return to baseline levels 6 hours after an event. Prolactin elevation is not useful in distinguishing epileptic seizures from syncope.[44]

Serum creatine kinase (CK) is also reported to have some utility in distinguishing seizures from prolonged non-epileptic

seizures. CK was markedly elevated after generalized convulsive status epilepticus and within normal values except for one case with minimally elevated CK with non-epileptic seizures.[45] CK has a delay in rising of at least 3 hours with a peak concentration at more than 36 hours.

Imaging for patients with first-time seizures remains controversial. Current practice patterns often are to obtain a noncontrast cranial CT at the time of the ED visit, and a clinical policy recommends performing neuroimaging after a first seizure if an acute intracranial process is suspected. Specifically, a history of acute head trauma, malignancy, persistent headache, immunocompromise, age older than 40 years, anticoagulation, or focal onset of seizure may suggest the need for imaging promptly.[46] Outcomes data are lacking and little new literature is being generated in this area. MRI is not part of routine practice for new-onset seizures in most U.S. emergency departments. The strategy of deferring noncontrast cranial CT for outpatient MRI to be performed at a later date has not been formally studied.

Symptomatic Seizures and Special Circumstances

A fundamental distinction to be made in the ED is whether the seizure was likely secondary to some identifiable cause, or whether it is of unclear etiology (unprovoked) after initial evaluations.

As discussed above, history and physical examination will help guide this determination. If there is a history of CNS injury or insult that may be the likely etiology of the seizure, treatment of the underlying CNS process will be necessary, if such treatment is available.[47] For example, acute metabolic abnormalities, such as hyponatremia, may be a cause of new onset seizures. Treatment of the underlying cause should be initiated and should be the primary thrust of treatment, and antiepileptic drugs assume a secondary role, if any. Likewise, if an acute CNS infection is the cause of the seizure, this must be identified, and seizure treatment with an antiepileptic drug assumes an adjunctive role to the treatment of the CNS infection.

Alcohol-related seizures are a specific sub-group of symptomatic seizures. Traditional teaching is that alcohol-related or alcohol-withdrawal seizures are limited, brief, and require no specific treatment. However, studies of status epilepticus show that a significant proportion of status epilepticus cases are alcohol-related.[48] Additionally, approximately 30% of patients with alcohol-related seizures experience recurrent seizures after presenting to the emergency department.[49,50]

If other causes of seizures have been reasonably excluded, and the diagnosis of alcohol-related seizures seems likely, lorazepam administration is associated with a reduction of risk of recurrence of seizures over the next several hours. The dose of lorazepam studied was 2 mg intravenously.[50] Phenytoin is ineffective in the treatment of alcohol-related seizures.[49]

Many other toxic exposures may cause seizures, notably cocaine and other sympathomimetics, aminophylline, antidepressants, antihistamines, diphenhydramine, and some anti-arrhythmics.[51,52] Specific treatments are beyond the scope of this review. Treatment is generally supportive, with benzodiazepines being the initial antiepileptic drug of choice. Although phenytoin is the second-line agent indicated in the treatment of most causes of seizures, it is usually not efficacious in the management of drug-induced seizures.[52]

Among toxic causes of seizures, isoniazid (INH) overdose deserves special mention because of the specific antidote that it requires—pyridoxine (B6). Metabolic acidosis may be profound with INH overdose. Pyridoxine is reported to decrease seizures and speed resolution of the metabolic acidosis.[53] INH is thought to decrease brain GABA levels, and this decreased inhibition leads to seizures. The specific antidote pyridoxine is administered in an estimated dosage equal to the ingestion, or 5 grams if ingestion amount cannot be estimated.

Seizures with hypertension in advanced pregnancy or in the post-delivery period define eclampsia. Treatment is beyond the scope of this review, but includes magnesium sulfate and may include benzodiazepines. Loading dose of magnesium sulfate is 4-6 grams over 15 minutes with infusions of 1-3 grams per hour. Infusion is adjusted to loss of patellar reflexes. The time-honored definitive treatment is prompt delivery.

First Seizure

After facing the question of diagnosis for a patient with a first unprovoked seizure, the next question arises as to whether to initiate pharmacologic treatment. This has been a topic of ongoing debate, and there are no clear answers. Obviously, some assessment of pre-test probability as to whether this event represented a seizure must be weighed, along with other aspects of the history and physical examination, to arrive at some decision. Recurrence rate after a first unprovoked seizure is cited to vary between 36 and 77%. Of those patients that will have a recurrent seizure, more than 50% will do so within the first 6 months.[54] Factors used by the neurologist to initiate antiepileptic drug treatment include neuroimaging results, EEG, and other factors frequently not available to the emergency physician.[55] Initiating long-term therapy after a single emergency department encounter is not general practice. ACEP Clinical Policies Committee reviewed this topic and concluded that patients with a normal neurologic examination, no medical comorbidities, and no known structural brain disease do not need to be started on an antiepileptic drug in the ED.[42]

Conversation or consultation with a physician involved in follow-up care is ideal regarding the issue of additional evaluation, whether to initiate drug therapy, and, if so, medication selection. Several antiepileptic drugs have been introduced over the past few years. Many of them have fewer side effects than the older antiepileptic drugs but are more expensive. Safety and efficacy trials show similar efficacy but improved tolerability with the newer agents. There is lack of head-to-head comparisons among the medications making any one best treatment regimen unclear. In spite of the fact that most are approved as adjunctive or additional therapy for patients with epilepsy, in practice many are used as monotherapy.[56,57]

Predicting the necessity for admission following a first seizure is the subject of many retrospective studies. Seizure recurrence is typically measured over months to years. Patients with medical comorbidities, focal findings on neurologic examination, history of

CNS injury, or mass lesions on CT certainly will be strongly considered for admission from the ED. Again, most studies looking at this question have been retrospective analyses.[58,59] ACEP Clinical Policies Committee has recently reviewed this topic and concluded that the adult patient with normal neurological examination who has had a new-onset seizure and who has returned to baseline may be discharged from the ED with outpatient follow-up.[42]

Patient with a Recurrent Seizure

The patient with an established seizure disorder who presents to the ED after a seizure may require little further care, if the patient is awake and has returned to baseline mental status. One study showed that in patients presenting to emergency departments who had been prescribed antiepileptic drugs with technically measurable levels, two-thirds were found to be sub-therapeutic.[5] Measuring an antiepileptic drug level seems reasonable if there is a question of compliance with the prescribed regimen. Since many patients are now on antiepileptic drugs that do not have readily obtainable drug levels, the emergency physician is faced with another conundrum. Given that the immediate risk of seizure recurrence in this patient population is simply not known, correct therapy in the ED is often conjectural. If seizure control has been reasonable, continuing medications in the current doses may be reasonable. If the patient admits to medication dosing irregularity, or measurable antiepileptic drug levels are low, giving the first dose of drug while the patient is in the ED seems a reasonable course, given that the rate of seizure recurrence is simply not known.

Several oral loading schemes have been proposed for different medications but the necessity of using a loading dose is far from clear, given the unknown risk of seizure recurrence. Phenytoin can be given orally as a single loading dose at 18 mg/kg with minimal side effects.[60] Carbamazepine rapid oral loading has been studied at a dose of 8 mg/kg, and although therapeutic levels were able to be obtained more than 90% patients, adverse drug reactions (mainly drowsiness and nausea) occurred in the majority of patients.[61] Again, the necessity of giving any loading dose is simply not clear in this patient population.

Status Epilepticus

Status epilepticus may describe any continuing seizure type. The definition of status epilepticus from the textbooks is for research purposes and has no application clinically as a guide to commence treatment. The epidemiologic definition was a continuous seizure lasting 30 minutes or longer, or intermittent seizures lasting for 30 minutes or longer without the patient regaining full consciousness between the seizures. The call to revise the definition of status epilepticus has been announced and revised to a time of 5 minutes or longer of continuous seizures, or two or more seizures without the patient returning to full consciousness between seizures.[2] Any seizure type may be enduring, and it follows that there may be generalized tonic-clonic status epilepticus, complex partial status epilepticus, simple partial status epilepticus, as well status epilepticus from other seizure types.

Most seizures last only a few moments. One video-EEG study found the mean duration of generalized tonic-clonic seizures was 62 seconds; the investigators urged treatment for any generalized tonic-clonic seizure lasting greater than two minutes.[62] Studies from epilepsy monitoring units support the working definition of status epilepticus as a seizure lasting greater than 10 minutes.[63] In this study of almost 600 monitored patients, it was found that seizure duration differs for the different seizure types, with secondarily generalized tonic-clonic seizures (the most common seizure type in the adult population) lasting longer, on the average, than complex partial seizures and simple partial seizures. The investigators felt that secondarily generalized tonic-clonic seizures lasting longer than 11 minutes were likely to extend into status epilepticus.

A variety of mechanisms are proposed for failure of a seizure to terminate resulting in status epilepticus. Loss of inhibitory influences from the thalamus, impaired GABA transmission, changes in adenosine receptors, intracellular calcium fluxes, and others have been postulated as potentiating the seizure as discussed above.[6,8,63]

Epidemiology of Status Epilepticus

Recent epidemiologic studies on status epilepticus estimate the frequency at 50 cases per year per 100,000 population. This included all seizure types of status epilepticus and studied all age groups. The definition of status epilepticus employed was the older definition using duration of 30 minutes or longer. Status epilepticus occurs more frequently at the extremes of age with the highest incidence in the first year of life. The second highest incidence of status epilepticus occurred in the elderly, which represents the largest group of patients at risk for developing status epilepticus.[64]

The majority of adults and children with status epilepticus did not have a previous history of epilepsy. Status epilepticus occurred in this group in association with other diseases. The elderly had the largest percentage of patients with status epilepticus without a previous history of epilepsy.[64] Roughly a "rule-of-thirds" seems to apply; one-third of status epilepticus occurs in patients as a first unprovoked seizure, one-third in patients with established epilepsy, and one-third in patients at the time of an acute illness.[65] About one-third of patients with afebrile status epilepticus will have recurrence of status epilepticus over a 10-year period. For those patients with a progressive brain disorder, the risk of recurrence was 100%.[66]

A few other interesting facts come from these studies. Over one-half of status epilepticus cases in community hospitals were not brought to the attention of neurologists and were treated by internists, ICU specialists, or "ER personnel."[64] Time to seizure treatment in patients with prolonged seizures showed that less than half of all patients received their first antiepileptic drug within 30 minutes.

Given that the above studies all used the epidemiologic parameter of 30 minutes, what about prolonged seizures that lasted less than 30 minutes? One analysis of status epilepticus patients with prolonged seizures lasting longer than 10 minutes but less than 30 minutes revealed that about half of the seizure

Table 5. Differential Diagnosis of Generalized Convulsive Status Epilepticus

- Non-epileptic seizures (pseudoseizures)
- Repetitive abnormal posturing
- Tetanus
- Neuroleptic malignant syndrome
- Rigors
- Myoclonic jerks
- Tremors
- Hemiballismus
- Involuntary movements

Table 6. Proposed Terminology Status Epilepticus

GENERALIZED STATUS EPILEPTICUS

- Generalized convulsive status epilepticus—overt
- Generalized convulsive status epilepticus—subtle
- ICU status epilepticus
- Electrographic status epilepticus

NONCONVULSIVE STATUS EPILEPTICUS

- Complex partial status epilepticus
- Absence status epilepticus

SIMPLE PARTIAL STATUS EPILEPTICUS WITH MOTOR SYMPTOMS

OTHER ENDURING SEIZURE TYPES

Note: Confusion exists in the terminology. Nonconvulsive status epilepticus has been used in the past to encompass such diverse seizure types as partial complex status epilepticus, absence status epilepticus, epileptic confusional states, as well as generalized convulsive status epilepticus that has evolved a dissociation of the motor convulsions and ongoing electrical activity.

events stopped spontaneously and did not require antiepileptic drugs. The other half of the group responded promptly to antiepileptic drugs. The overall mortality of the group was lower than that of patients with status epilepticus lasting 30 minutes or greater.[67] Other investigators have proposed a classification of generalized convulsive status epilepticus that invokes three phases: impending, established, and subtle.[68]

Differential Diagnosis of Status Epilepticus

Just as there is a differential diagnosis to seizure types, status epilepticus also has a differential diagnosis to consider. (*See Table 5.*) Different types of status epilepticus result in radically different clinical pictures.

A few other clinical conditions simulate generalized convulsive status epilepticus. Decerebrate posturing may superficially resemble seizures. The patient is unconscious, and abnormal motions are occurring, although they may be brief fragments of the typically sustained upper extremity extensor posturing. This has been observed in conditions causing obstructive hydrocephalus[69] as well as subarachnoid hemorrhage.[70] Only case reports and small series exist. It appears that prompt recognition of this abnormal posturing pattern with confirmatory imaging and treatment of the underlying CNS pathophysiology is more appropriate than antiepileptic medications. The key is recognition. The extensor posturing is typical in appearance, may be brief, and is not associated with tonic-clonic movements often seen in generalized seizures. Episodic posturing events with return to consciousness between episodes has been observed.[69] These phenomena may represent or be related to the "cerebellar seizures" described in the distant neurologic literature.[71]

Subtle generalized convulsive status epilepticus and nonconvulsive status epilepticus pose diagnostic challenges. The terminology here is confusing and nonintuitive. Generalized convulsive status epilepticus may present in a more subtle fashion with only fragments of a recognizable seizure, or at times no associated motor movements, requiring EEG for detection. Although often termed a type of nonconvulsive status epilepticus, the term subtle generalized convulsive status epilepticus is preferred to distinguish the clinical syndromes.[72] The term nonconvulsive status epilepticus is perhaps better reserved for those prolonged confusional twilight states of complex partial seizures or absence status epilepticus.(*See Table 6.*)

As EEG monitoring is being employed more frequently in intensive care units (ICU), alerts are being sounded about the presence of electrographic (EEG) seizures being found in many patients. One study initiated EEG monitoring for patients admitted to an ICU after an episode of convulsive status epilepticus; they found persistent EEG evidence of seizures in 48% of their patients and nonconvulsive status epilepticus in 14%.[73] The patients with nonconvulsive status epilepticus were comatose and showed no overt clinical signs of seizure activity. The investigators felt that continuous EEG monitoring is indicated following an episode of convulsive status epilepticus while the patient is unresponsive.

Another study assessed EEG patterns in comatose patients admitted to an ICU with altered mental status. Coma was from multiple causes and included patients with anoxic insults, strokes, tumors, infections, and metabolic disturbances. They also found that 8% of these comatose patients had electrographic findings consistent with status epilepticus, without associated motor movements.[74]

Confusional states may represent partial complex seizures. A cautionary note has been sounded urging caution for recognizing this type of nonconvulsive status epilepticus. These prolonged confusional states may be unrecognized in the ED and inpatient units.[75]

Generalized Convulsive Status Epilepticus

There are many more articles listing schema on treatment of status epilepticus than there are randomized, prospective trials to guide best therapy. Many of the articles are written from the perspective of the consultant, hospitalist, or intensivist, and do not accurately reflect emergency medicine practice.

There is general agreement on a few points. Of the different types of status epilepticus, generalized convulsive status epilepti-

cus should be treated aggressively. There is agreement that once the diagnosis of generalized convulsive status epilepticus is established, then prompt steps should be initiated to terminate the seizures. There is general agreement that the definition of 30 minutes of continuous generalized convulsions to trigger treatment interventions is not currently appropriate, if indeed those time limits were ever followed in the clinical arena. There is general agreement that benzodiazepines are the drug class of choice for initial treatment of generalized convulsive status epilepticus.

Hampering the clinician is the inability in most cases to predict response and outcomes from treatment. Are the seizures secondary to an acute CNS insult such as stroke, tumor, or infection, in which case treatment of the seizures may be resistant to antiepileptic drug administration, or are the seizures ethanol-related or related to antiepileptic medication malcompliance, and the prognosis is favorable that the seizures will be easily controlled? Retrospective review of cases may reveal management steps that simply were not clear at the bedside at the initial moments of patient care.

The time constraints that many of the treatment plans outline are arbitrary and are not evidence-based. Pedantic guidelines stating that certain actions should occur with a certain number of minutes must be relegated to opinion. The underlying principle should be that once the diagnosis of generalized convulsive status epilepticus is established—and that will be a bedside diagnosis—then prompt actions should be initiated. The terms STAT and ASAP become prominent in directing care.

ABCs

As every practitioner knows, there is often no clear indication as to when a patient should be intubated. This can certainly hold true with the patient who has had a seizure. Most often this is a self-limited event, and the patient is in that poorly defined transient state referred to as "post-ictal," with every expectation that consciousness will improve over the next several moments. For the patient with active convulsions, oxygenation is generally preserved until a later decompensated state.

Oxygen supplementation is commonly recommended. Patients typically have spontaneous respirations although they may be sonorous. An airway adjunct such as a soft nasopharyngeal tube may relieve the partial airway obstruction as the patient continues to arouse.

Intravenous access should be established and a rapid blood glucose determination performed. Hypoglycemia should be treated with intravenous dextrose. If the patient is at risk for developing Wernicke encephalopathy due to chronic alcoholism or malnutrition, then intravenous thiamine should also be given. A common teaching in emergency medicine is that thiamine should be given before glucose infusion to prevent the development of Wernicke encephalopathy. A careful review of the published literature on this topic found no evidence to support this necessity of this sequence.[76] The association is important and thiamine should be given to malnourished and alcoholic patients who receive glucose infusions, but there is reason to delay the administration of glucose to a symptomatic hypoglycemic patient (e.g., with coma or seizures) while awaiting thiamine.

Should endotracheal intubation be deemed desirable in management, the emergency physician should proceed in the usual manner. There are no studies to guide practice in a different direction. A few caveats seem prudent. For induction, an agent with proven anticonvulsant properties should be considered. Choices include midazolam and propofol. A paralytic agent may not be necessary in some patients following administration of an induction agent.

Regarding neuromuscular blockade for intubation, a few caveats are in order. It bears noting that there are no studies to guide recommendations. Obviously, neuromuscular blockade will halt the motor convulsions but will do nothing for the cortical electrical seizure activity. Succinylcholine is usually the agent of choice for RSI because of rapid onset and relatively rapid resolution of action.[77] Longer-acting neuromuscular paralytic agents should be avoided, since the ability to judge ongoing motor activity will be lost and EEG monitoring will then be necessary to exclude any ongoing electrographic status epilepticus. One of the theoretic risks of succinylcholine administration is hyperkalemia. There is one reported case of fatal hyperkalemia in a patient with suspected seizures who received succinylcholine; however, the medical history of this is complex and included prolonged immobilization.[78] In patients at risk for hyperkalemia, another agent might be considered, and rocuronium is recommended in one review.[79]

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Physician CME Questions

91. In a study of emergency department patients, the Emergency Medicine Seizure Study Group found that status epilepticus occurred in about what percent of patients presenting to the ED with seizure-related complaints?
    A. 60%
    B. 40%
    C. 20%
    D. 6%

92. The most common seizure type in adults is:
    A. partial onset seizure.
    B. generalized onset seizure.
    C. partial onset seizure with secondary generalization.
    D. complex partial seizure.

93. The preferred term for events that appear to be generalized seizures but are of psychogenic origin is:
    A. hysterical seizure.
    B. pseudoseizure.
    C. malingering seizure.
    D. psychogenic seizure.

94. Which is the largest population group at risk for developing status epilepticus?
    A. Infants
    B. Children
    C. Young adults
    D. The elderly

95. Which of the following is/are part of the new revised definition of status epilepticus?
    A. A seizure lasting 30 minutes or longer
    B. Two or more discrete seizures without a full return to consciousness between seizures
    C. A generalized seizure lasting longer than 5 minutes
    D. B and C

96. Which of the following statements regarding measurement of serum prolactin in patients with possible seizures is *false*?
    A. Serum prolactin is elevated 10-20 minutes after a generalized seizure
    B. An elevated serum prolactin can differentiate seizure from syncope
    C. Serum prolactin levels stay elevated for 1-2 days after seizure
    D. Serum prolactin levels cannot differentiate a generalized seizure from a psychogenic seizure

97. Which class of medications is the consensus drug of choice for initial pharmacologic treatment of generalized convulsive status epilepticus?
    A. Benzodiazepines
    B. Phenytoins
    C. Propofol
    D. Barbiturates

98. Which clinical finding supports the diagnosis of psychogenic seizure?
    A. biting the side of the tongue
    B. biting the tip of the tongue
    C. closing of the eyes

D. urinary incontinence

99. Which of the following toxicologic causes of seizures has a specific antidote?
    A. Amitriptyline
    B. Isoniazid (INH)
    C. Theophylline
    D. Cocaine

100. In a patient with an established seizure disorder who presents to the emergency after a recurrent seizure, approximately what percentage will have sub-therapeutic anticonvulsant levels?
    A. 30%
    B. 50%
    C. 65%
    D. 85%

Emergency Medicine Reports
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To help physicians:

- quickly recognize or increase index of suspicion for specific conditions;
- understand the epidemiology, etiology, pathophysiology, and clinical features of the entity discussed;
- apply state-of-the-art diagnostic and therapeutic techniques (including the implications of pharmaceutical therapy discussed) to patients with the particular medical problems discussed;
- understand the differential diagnosis of the entity discussed;
- understand both likely and rare complications that may occur.

CME Answer Key

91. D; 92. C; 93. D; 94. D; 95. D; 96. B; 97. A; 98. B; 99. B; 100. C

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i. Total *(Sum of 15g, and h.*	4436	4506
Percent Paid and/or Requested Circulation *(15c divided by 15g times 100)*	98%	98%

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PS Form **3526**, September 1999 *(Reverse)*

Emergency Medicine Reports®
The Practical Journal for Emergency Physicians

ED Infection Control

CDC Handwashing Recommendations

According to the CDC, handwashing is recommended:

• After touching blood, bodily fluids, secretions, and contaminated items, whether or not gloves are worn;
• Between patient contacts
• Before eating
• After using the restroom

Infection Control Strategies for MRSA

- Hand hygiene. This has been shown to decrease nosocomial infections in multiple reports.
- Detection of asymptomatic colonization by surveillance cultures, generally from the nares, but also from open wounds. Active surveillance cultures may be particularly beneficial for patients in intensive care, burn, or oncology units, or those undergoing bone marrow transplant.
- Contact precautions, including private rooms, possibly cohorting colonized or infected patients when private rooms are scarce, and use of gowns and gloves for all patient contact.
- Decontamination of the environment: disinfecting bed rails, tables in close proximity to the patient.
- Eradication of MRSA carriage: intranasal mupirocin 2-3 times a days for three to five days, 4% chlorhexidine baths.
- Possibly, judicious use of antibiotic drugs.

Guidelines for Use of Vancomycin

- Treatment of serious infections caused by beta-lactam-resistant gram-positive microorganisms.
- Treatment of infections caused by gram-positive organisms in patients with serious allergies to beta-lactams.
- Treatment of antibiotic-associated colitis unresponsive to metronidazole.
- Prophylaxis for endocarditis following high-risk procedures as recommended by the American Heart Association.
- Prophylaxis for major surgical procedures involving implantation of prosthetic materials or devices at institutions with high rates of MRSA infections.

ED Situations in which Vancomycin Use Should Be Discouraged

- Routine surgical prophylaxis other than in a patient who has a life-threatening allergy to beta-lactam antibiotics.
- Empiric antimicrobial therapy for a febrile neutropenic patient, unless there is evidence that the patient has an infection caused by gram-positive organisms (as at the site of an inflamed Hickman catheter) and the presence of MRSA in the hospital is substantial.
- Treatment in response to a single blood culture positive for coagulase-negative staphylococcus (where contamination of the blood culture is likely).
- Primary treatment of antibiotic-associated colitis.
- Treatment for beta-lactam sensitive gram-positive infections in patients with renal failure.
- Use of vancomycin solution for topical irrigation.
- Local prophylaxis for infection or colonization of indwelling central or peripheral intravascular catheters.

Recommendations for the Use of Emergency Departments in Outbreaks of Influenza

- All healthcare workers, including ancillary staff, nurses, and EMS personnel, should be immunized against influenza.
- Rapid screening, identification, and infection control intervention should be implemented in the ED.
- The practice of boarding in-patients in the ED should be ended, with a view to distributing admitted ill influenza patients together in the hallways of the ED.
- Regional protocols should be developed and implemented to monitor in-patient and ED capacity, as well as ambulance diversion status.
- Require hospitals and communities severely affected by influenza to postpone elective admissions until the crisis abates.
- Provide federal and state funding to compensate hospitals and EDs for unreimbursed costs incurred during a public health challenge.

Supplement to *Emergency Medicine Reports*, October 15, 2007: "Infection Control and the Emergency Department." *Author:* **Jonathan M. Glauser, MD**, Department of Emergency Medicine, Cleveland Clinic Foundation, Cleveland, OH.