Seizures and Status Epilepticus: Diagnosis and Management in the Emergency Department

It's midnight and you are considering going on diversion. A 24-year-old graduate student with no past medical history is brought in by EMS having had a witnessed "seizure" while studying in the library. According to his roommate, he had been pulling a string of "all nighters" studying for midterms and drinking large amounts of coffee in order to stay awake. There are no beds inhouse, the ED is packed, and the CT backed up. The patient looks great and has a normal physical exam, and he wants to go home. While trying to decide if any tests or neuroimaging are needed, the patient has another tonic-clonic event immediately followed by a third event which 10 mg of lorazepam fails to stop. You begin an infusion of 1800 mg of phenytoin and contact the neurologist on call only to find out that he is a headache specialist who has not managed a case of status epilepticus since leaving residency twenty years prior. You keep thinking, "What if I had sent this kid home; would I have been negligent?" More immediate, you wonder, "What am I going to do if phenytoin does not stop the seizure?"

For most of human history, seizures were looked upon differently than most other medical conditions. They manifest clinically as unusual behaviors with attacks occurring suddenly in a dramatic and mysterious fashion; afterwards, patients have no recollection or explanation for what happened. Indeed, their unusual features caused many to believe that it was less of a medical problem and more of a manifestation from another world. Hippocrates, in 400 B.C., referred to it as "the sacred disease," referring to the predominant superstitious view of the condition. Only in recent medical history has electrodiagnostic testing allowed us to understand the pathophysiologic basis of seizures, though there is still much to discover regarding etiology, clinical manifestations, and treatment.

Authors

Peter Shearer, MD
Assistant Professor and Residency Director, Department of Emergency Medicine, Mount Sinai School of Medicine, New York

David Park, MD
Senior Resident, Mount Sinai School of Medicine, Department of Emergency Medicine, New York

Peer Reviewers

Andrew J. Bowman, RN, BSN, CEN, CTRN, CCRN-CMC, BC, CVN-I, NREMT-P
Patient Care Coordinator Education Coordinator Home Hospital Campus Greater Lafayette Health Services, Inc., Lafayette, IN

J. Stephen Huff, MD
Associate Professor of Emergency Medicine and Neurology University of Virginia Health System

CME Objectives

Upon completion of this article, you should be able to:
1. Understand the classification of seizures and distinguish nonconvulsive seizures from convulsive seizures
2. Understand the approach to managing seizures in the prehospital environment
3. Understand the utilization of diagnostic testing in patients who have had a seizure
4. Understand the pharmacologic strategies for managing patients in status epilepticus
5. Understand the advantages and disadvantages of the new generation antiepileptic drugs

Date of original release: August 10, 2006.
Date of most recent review: August 5, 2006.
See "Physician CME Information" on back page.

The challenge for the emergency physician (EP) has three parts:

First, the seizure must be recognized (this is easy when it has a motor component; it's more difficult when it has no motor component) and managed. In the case of status epilepticus, the EP must have an established protocol in place to allow for rapid control.

Second, underlying life threatening conditions must be identified and treated.

Third, the future risk for having seizures must be assessed and, from the ED perspective, proper disposition and follow-up must be arranged in order to minimize potential complications.

This issue of *Emergency Medicine Practice* provides a comprehensive update on seizure diagnosis and management with a focus on clinical situations most commonly encountered in daily practice.

Critical Review Of The Literature

An extensive literature search through the National Library of Medicine's PubMed database (limited to

Chart 1: Resources For Guidelines/Policies Pertinent To Seizure Management

1. American College of Emergency Physicians Clinical Policies Subcommittee on Seizures. Clinical Policy: Critical Issues in the Evaluation and Management of Adult Patients Presenting to the Emergency Department With Seizures. *Ann Emerg Med* 2004;43:605-630
2. Cochrane Review Topics: Epilepsy: http://www.cochrane.org/reviews/en/topics/62.html
3. Treatment of convulsive status epilepticus. Epilepsy Foundation of America. *JAMA* 1993;270:854-859.
4. The neurodiagnostic evaluation of the child with first simple febrile seizure. *AAP*. Pediatrics 1996;97:769-775.
5. The role of phenytoin in the management of alcohol withdrawal syndrome. *Am Soc Addiction Med* 1994/1998
6. Evaluating the first nonfebrile seizure in chilren. AAN. *Neurology* 2000;55:616-623.
7. Role of antiseizure prophylaxis following head injury. BTF / AANS. *J Neurotrauma* 2000;17:549-553.
8. Treatment of the child with a first unprovoked seizure. AAN. *Neurology* 2003;60:166-175
9. Antiepileptic drug prophylaxis in severe traumatic brain injury. *Neurology* 2003;60:10-16

English language) and a review of the pertinent references was performed. The National Guideline Clearinghouse (an initiative of the Agency for Healthcare Research and Quality and the U.S. Department of Health and Human Services) was reviewed to find the most recent guidelines on seizure diagnosis and management. The American College of Emergency Physicians (ACEP) Clinical Policies were reviewed for recommendations and guidelines pertaining to this topic. Chart 1 lists clinical policies/practice guidelines in the literature that are helpful to the acute management of seizures in the ED.

Definitions And Classification

A seizure is a sudden change in behavior characterized by changes in sensory perception or motor activity due to an abnormal firing of neurons. The clinical spectrum of seizures is expansive and includes focal or generalized motor activity, altered mental status, sensory or psychic experiences, and/or autonomic disturbances.

The term epilepsy describes a condition of recurrent unprovoked seizures from known or unknown causes. For example, one who suffers head trauma may have a seizure acutely, but they would not be considered to have epilepsy unless they develop recurring seizures as a sequela of the brain injury.

Ictus refers to the period during which a seizure occurs, and the postictal period refers to the interval after a seizure ends, but before the patient returns to baseline mental status. The postictal state usually resolves within minutes to an hour, but has been known to last several hours.

Seizures are defined by how they are manifested. A generalized seizure occurs when there is abnormal neuronal activity throughout both hemispheres which causes an alteration in mental status. A focal or partial seizure describes abnormal neuronal firing of a limited and confined population of neurons in one hemisphere of the brain. Partial seizures are further divided into simple or complex. A complex partial seizure involves some degree of impaired level of consciousness. This has been referred to in the past as temporal lobe epilepsy though this term is now archaic. The classification of seizure types is presented in **Table 1**.

Approximately 40% of focal seizures remain localized, but the remainder develop secondary generalization. These patients are associated with a

worse outcome than those who experience generalized seizures primarily. The majority of adults who present to the ED with new onset generalized seizures in fact have partial seizures that have generalized. Of note, an "aura" or abnormal sensation prior to generalized seizure is, in reality, a focal seizure event, and is a key part of the history; consequently, the type of aura is useful in seizure focus localization.

Historically, status epilepticus has been defined as 30 minutes of continuous seizure activitiy or sequential seizures without return to normal mental baseline.[1] For a number of reasons, this should not be used as a time frame to guide initial therapy.[2] Prolonged seizures are associated with difficult seizure termination and considerable morbidity and mortality; therefore, treatment should not be delayed. [2, 3, 4] There is evidence that a seizure that does not spontaneously resolve in 5 to 10 minutes is unlikely to resolve quickly. In one prospective childhood study, seizure duration had a bimodal distribution at 3.6 minutes in one group (76% cases), and 31 minutes (24%) in the other.[5] Nonconvulsive status epilepticus (NCSE) refers to continuous seizure activity without predominant motor activity. This should not be confused with subtle status epileptics which refers to generalized convulsive status epilepticus (SE) in which the motor findings have diminished either through high doses of administered medications or from muscular fatigue due to prolonged seizure activity.

Epidemiology

Seizure is a common presentation in the emergency department (ED), representing at least 1% to 2% of all ED visits.[6, 7] Current estimates suggest that 6.6 of 1000 Americans in the general population will present to an ED after a seizure in a given year, accounting for approximately 2.5 million visits a year in the United States.[8, 9] A seizure is often a secondary manifestation of a broad range of etiologies. Generalized convulsive status epilepticus (GCSE) affects from 50,000 to 150,000 patients every year. These patients are critically ill, with mortality estimates ranging from 10 to 40%.[10, 11, 12]

In the US population, the prevalence of active epilepsy is approximately 6 per 1000; one-quarter to one-half of patients with epilepsy continue to have recurrent seizures despite therapy.[13] Even under optimal circumstances, excluding noncompliance and other variables, 5 to 10% of patients have intractable epilepsy despite pharmacologic management.[14]

The incidence of epilepsy matches the underlying etiology. It is high in the first year of life and then decreases throughout childhood, remaining relatively stable and low throughout mid-life. At age 55, the incidence begins to increase, peaking in persons 75 years and older. [15] Partial epilepsies, in particular, increase in the elderly paralleling the increased incidence of degenerative, neoplastic, and vascular pathologies.

Estimates of the incidence of status epilepticus vary widely, and may have changed over the years. A review of a California hospitalization database through the 1990's revealed an overall incidence rate of 6.2 per 100,000 people in the general population, with a decreasing incidence trend through the study

---

Table 1: Classification Of Seizures

Partial Seizures
❑ Simple Partial
  • motor
  • somatosensory
  • autonomic
  • psychic
❑ Complex Partial
  • with focal onset prior to alteration in consciousness
  • without focal onset prior to alteration in consciousness

Generalized Seizures
❑ Primary Generalized Nonconvulsive
  • absence
❑ Primary Generalized Convulsive
  • tonic-clonic
  • clonic
  • tonic
  • myoclonic
  • atonic
❑ Secondary Generalized
  • convulsive
  • nonconvulsive

Status Epilepticus
❑ Convulsive Generalized
  • primary generalized
  • secondary generalized
❑ Convulsive Focal
❑ Nonconvulsive
  • primary generalized (absence)
  • partial with or without secondary generalization (complex partial)

period.[16] In that study, the highest incidence was found in those over the age of 75 (22/100,000). A Virginia study found an overall incidence rate as high as 29 per 100,000.[12]

In one prospective study, over half of patients presenting to the ED in status epilepticus had no prior seizure history.[12] Overall mortality due to status epilepticus ranges from 10 to 40% depending on the study, and seems to be closely related to the underlying etiology.[17, 16, 18, 19, 20] Fatality rates for patients with SE caused by anoxic brain injury and CNS infection is 64% and 32% respectively, but the rate in those with status epilepticus as a primary diagnosis without other identified co-morbidities is only 3.5%.[16] Long term mortality is also increased in patients who experience an episode of status epilepticus, with a 10 year mortality that is 2.8 times that of the general population.[21] In addition to mortality, an additional 5-10% of people experiencing status epilepticus have permanent sequelae, such as a permanent vegetative state or cognitive difficulties.[22]

Prolonged SE is associated with worse outcomes and is thought to be due to both the primary cause of status as well as secondary systemic effects, such as hypoxia, metabolic acidosis, hyperthermia, hypoglycemia which results in dysrhythmias, rhabdomyolysis, pulmonary edema, and DIC.[23] SE is harder to terminate with continued activity.[24, 25] Patients treated within one hour of continuous seizure activity had an 80% likelihood of termination vs. 40 to 50% likelihood in patients in which treatment was initiated after two or more hours.[23]

Pathophysiology

At the molecular level, seizures occur when there is disequilibrium at the neuronal cell membrane, resulting in abnormal and repeated electrical discharges. These discharges may then propagate throughout the brain or may stay limited and localized. The causes of this sort of disequilibrium vary widely and range from physical disruption to metabolic disturbances.

Seizures produce a number of physiologic consequences. During a generalized convulsion, there can be a period of transient apnea and hypoxia. Initially, brain compensatory mechanisms may prevent neuronal injury from seizures, especially hypertension with increased cerebral blood flow. Normal physiological response includes an increase in body temperature, with up to 43% of patients with a generalized convulsion having a transient rise in tempera-ture above 100° F.[26, 27] Glucose levels also increase, and lactic acidosis occurs within 60 seconds of a convulsive event and normalizes within one hour after ictus.[28] A rise in the peripheral white blood cell count without an increase in bands is often seen.

If the seizure persists, at approximately 30 minutes the homeostatic mechanisms begin to deteriorate. Animal models suggest that, even if systemic factors, such as acidosis and hypoxia are controlled, prolonged status epilepticus results in direct neuronal damage from neurotoxic amino acids and calcium influx. There is some evidence that status epilepticus alone may result in cognitive impairment independent of the inciting cause.[29] This becomes particularly relevant when developing a management strategy for nonconvulsive status and is an important area in need of research.

Besides direct neurotoxicity, persistent convulsive seizure activity results in systemic decompensation. Hypoxemia, hypercarbia, hypertension then hypotension, and hyperthermia develop with a decreased brain oxygen tension, mismatch between the sustained increase in oxygen and glucose utilization and a fall in cerebral blood flow, and depletion of brain glucose and oxygen.

The historic definition of status epilepticus using a 30 minute criteria was based on studies in healthy animal models and assumed that compensatory mechanisms remain intact. However, brain compensation requires adequate airway, breathing, circulation, and cerebral blood flow, and there are situations in which compensatory mechanisms may be compromised.[30]

Differential Diagnosis

The differential diagnosis in a seizure patient has two parts. First, the emergency physician must differentiate a true seizure from other causes of transient loss of consciousness and motor activity. Second, once a seizure is confirmed, the task is to identify the primary cause, particularly if it is reversible.

A number of conditions mimic seizures. These include convulsive syncope (with or without cardiac dysrhythmias), decerebrate posturing, psychogenic events, dystonia, and migraine headaches. Patients with strychnine poisoning may develop seizure-like activity yet demonstrate normal mental status. Particularly when faced with a new-onset seizure, pay particular attention to these "mimics" which can masquerade as a seizure.

Convulsive Syncope

Based on observational studies in blood donors, up to 40% of patients who have syncope will have some component of motor activity, most commonly involving tonic extension of the trunk or myoclonic jerks of the extremities.[31] This phenomenon has been observed with patients in a seated position. These events are termed convulsive syncope and usually are not associated with tonic-clonic movements, tongue biting, cyanosis, incontinence, or post-ictal confusion.

Cardiac Dysrhythmias

Syncope due to a cardiac dysrhythmia may result from cerebral hypoperfusion and hypoxia, which results in seizure activity.[32] Prolonged QT syndrome has been reported to be misdiagnosed as a seizure.[33] A careful history may identify preceding cardiac symptoms, such as palpitations, lightheadedness, or diaphoresis. An ECG may be diagnostic, but when it is not clear, a concurrent cardiac workup is indicated.

Abnormal Posturing

Decerebrate posturing has been misdiagnosed as a tonic seizure, resulting in misdiagnosis and delay in life-saving interventions.[34] Tonic seizures are rare in adults and, when they occur, are usually of short duration and associated with upper extremity abduction. Decerebrate posturing is more associated with both upper and lower extremity extension. Tonic posturing has been described in those that have sustained a concussion, and is thought to be a transient dysfunction of the brainstem.[35] Such patients may have experienced significant trauma and warrant prompt neuroimaging and close monitoring.

Migraine

Migraines usually display characteristic symptom patterns associated with a unilateral throbbing headache, photophobia, nausea, and vomiting. However, several migraine variants are associated with transient loss of consciousness or confusion. This makes them difficult to distinguish from complex partial seizures, post-ictal vascular headaches, drop attacks, or TIAs.[36]

Prehospital Concerns

Prehospital management of the seizing patient centers on managing the airway, maintaining oxygenation, obtaining intravenous access, and protecting the patient from injury. The use of a padded tongue blade is contraindicated since it may induce emesis or break a tooth; a nasal trumpet can help maintain the airway when needed.

The majority of seizures are of a short duration and self-limited; thus, little intervention is required. In most cases, pre-hospital personnel will arrive at least five minutes after the onset of seizure activity, such that patients who are still seizing on EMS arrival should be managed as presumed status epilepticus. If a patient is found convulsing or remains confused or unresponsive, paramedics should immediately measure the patient's blood sugar or, if this test is not available, they can empirically administer dextrose (D50).

There have been several studies that have investigated the safety and efficacy of benzodiazepines in the prehospital management of pediatric seizures. In a randomized double-blind out-of-hospital trial, Aldredge et al compared lorazepam, diazepam, and placebo administered intravenously by EMS personnel to patients with seizure activity lasting more than five minutes. The odds ratio for termination of seizure on arrival to ED in the lorazepam group compared to placebo was 4.8. For diazepam, it was 2.3, though this difference between diazepam and lorazepam did not achieve statistical significance. Interestingly, the rates of respiratory and circulatory complications were significantly worse in the placebo group compared to either benzodiazepine group. Not only does this confirm the safety of out-of-hospital benzodiazepine use, but it suggests the danger of untreated and prolonged seizure activity.[22]

When IV access is not immediately available, rectal diazepam is an option.[37, 38] One prospective study reported that there were no significant differences between rectal and intravenous diazepam therapy with regard to SE duration, intubation, or recurrent seizures in the emergency department. These data suggest that prehospital administration of diazepam may shorten the duration of SE in children and simplify the subsequent management.

In a retrospective study on prehospital seizure management in children, rectal diazepam .5 mg/kg, was compared to IM midazolam, .15 mg /kg. Over the four year study period, 2566 children presented with seizures and 107 children were eligible for entry into the study. Of these 107 patients, 62 received diazepam and 45 received midazolam. Both groups were similar in terms of demographics and seizure type. Both drugs were effective in stopping seizures within five minutes of drug administration; however, fewer patients in the midazolam group suffered

apnea.[7] In a study comparing IV diazepam to IM midazolam, Chamberlain et al concluded that IM midazolam is an effective anticonvulsant for children with motor seizures and an important alternative when IV access is not easily available. Vilke et al compared IM to IV midazolam and reported that IV delivery was more effective: 47/49 in the IV group vs 20/25 with IM administration (p less than 0.05). Four patients (three treated IM and one IV) had respiratory compromise necessitating field airway management. In light of the Chamberlain and Vilke studies, some experts recommend IV midazolam as the agent of choice in the prehospital management of seizures.

In some paramedic systems, patients who are "found down" and seizing are routinely transported to the ED in spinal precautions. One large retrospective study suggests that this may be unnecessary. In a review of 1656 patients with seizures not associated with major trauma, no patient had a concomitant spinal fracture.[39] Regarding level of transport, asymptomatic patients who have had a seizure can be transported by an EMS unit if the transport time is short in that it is unlikely that this group of patients will experience a second event during transport.[40] Patients with a known seizure disorder who experience a "typical" event and are asymptomatic afterwards do not necessarily require transport to the hospital if they are competent to refuse transport. However, medics should advise these patients to contact their primary care provider as soon as possible.

Emergency Department Evaluation

In approaching the seizure patient, the emergency physician is often constrained by the paucity of reliable history and a patient who may be unable to cooperate with the initial examination. The evaluation and management of a seizure can vary significantly depending on whether the seizure is new or recurrent, fully resolved, repeated or continuous, or whether the patient has residual neurological findings. Medical alert bracelets, old medical records, and medication lists or containers can often provide critical clues to assessing these patients.

Clinical History

The first and immediate challenge is determining what happened and the circumstances surrounding the event. Progression and duration of symptoms before, during, and after the seizure will provide important clues towards determining if the event

was truly a seizure or one of the many other mimics. Witnesses and paramedics are valuable resources. Be sure to obtain any history of trauma, either prior to the seizure or during the ictal episode itself, as this may direct management.

Information on symptoms, such as chest pain or palpitations, should be obtained as this may direct the physician toward cardiogenic causes. A headache prior to the onset of seizures is particularly worrisome for intracranial hemorrhage. Other complaints, such as fever, and/or general malaise, may direct the physician toward infectious causes. A careful review of neurological complaints will help direct the physical exam.

A history of prior seizures and prior diagnostic workups is probably the most important part of the past medical history. In patients with epilepsy, any changes in the character of the seizure, such as frequency or clinical features, should be investigated. A history of neurosurgery, especially a shunt or other CNS hardware, may prompt aggressive testing if the patient has concomitant fever or headache. Co-morbid disease may play an important role in the genesis of seizures. A history of renal failure, immune suppression, or recent electrolyte abnormality may drive specific laboratory investigations. Patients with a psychiatric history may have psychogenic seizures but may also suffer hyponatremia from pathologic water intoxication or as an adverse effect of one of their medications. Those with depression or psychosis may be at higher risk for ingestion-related seizures.

Ascertain the use of anti-epileptic drugs (AEDs) and other medications. Noncompliance with anticonvulsants is the most common cause for the ED presentation of recurrent seizures.[12] The use of anticoagulants, such as warfarin, should increase suspicion for intracranial bleeding. Hypoglycemia is the most common metabolic cause of seizures, particularly in diabetics. Suicidal patients may overdose on any medication available to them.

The social history is also important. Alcohol abuse puts the patient at risk for causes for seizure that are not immediately obvious, and alcohol withdrawal is also common. Certain illicit drugs, such as cocaine, phencyclidine, and ecstasy, are known to decrease seizure threshold. Finally, the most common causes of adult onset partial seizures in the developing world are neurocysticercosis[41] and malaria,[42] which should be considered in travelers and immigrants.

Physical Examination

An accurate set of vital signs are the beginning of any physical examination. While a low-grade fever is common immediately after a prolonged convulsion, a persistent high temperature suggests infection or drug reaction. Hypertension with bradycardia may be the result of rising intracranial pressure and impending herniation. Irregular heart rate or carotid bruits may accompany a stroke, which is a common cause of new onset seizures in the elderly.[10] Anticholinergic and sympathomimetic syndromes may suggest a drug-related seizure, which may make a significant difference in management.

If the patient presents actively seizing, observe the specifics of the motor activity. Focal abnormalities, eye deviation, and posturing are signs of an epileptic focus. Pupils are often large during or after a seizure but persistent mydriasis may reflect anticholinergic or sympathomimetic toxicity. Some patients in nonconvulsive status are mistakenly assumed postictal instead of actively seizing. Look for subtle signs, such as "automatisms," repetitive and rhythmic actions such as lip smacking, swallowing, chewing, or fumbling. Automatisms are frequent in complex partial seizures and may be the only indicator of ongoing seizure activity.

The mental status should be carefully documented and observed for change. When possible, recruit persons familiar with the patient. Post-ictal confusion usually resolves over several hours and failure to improve must prompt a search for serious underlying disease, see **Table 2.** In particular, nonconvulsive status epilepticus can present with subtle behavioral changes that can be easily overlooked.

A thorough and complete neurological examination is the key component of the evaluation. Focal deficits may represent an old lesion, new intracranial pathology, or postictal neurologic compromise (Todd's paralysis). In cases of Todd's paralysis that does not quickly resolve, the physician must rule out a new structural lesion. Other physical findings suggestive of a recent seizure include hyperreflexia and extensor plantar responses, both of which should resolve during the immediate post-ictal period.

Check the neck for stiffness and the presence of meningeal signs. Examination of the oropharynx may reveal gingival hyperplasia that is often seen with chronic phenytoin use, oral thrush may suggest that the patient is immunocompromised. A cardiac exam may provide a clue to the etiology of the seizure, such as a irregular heart beat or a mummer, which suggest an embolic or syncopal event. A respiratory exam is a key part of initial stabilization, and crackles or wheezing may indicate aspiration with a reactive airway.

A rash consistent with life-threatening conditions, such as meningococcemia, Rocky Mountain Spotted Fever, or bacterial endocarditis, can provide an early clue and a head start towards appropriate treatment.

Seizures are often associated with injury and the patient must be evaluated for both soft tissue and skeletal trauma. Head trauma and tongue lacerations are frequent. Seizure activity can produce both dislocations and fractures. Posterior shoulder dislocations are extremely rare but, when present, should prompt suspicion that a seizure has occurred.[43] Seizure induced fractures are rare (less than 0.6%) but commonly missed when they do occur.[44] The humerus, thoracic spine, and femur are most commonly involved.

Diagnostic Testing

Laboratory

A number of studies have shown that history and physical examination predict a majority of patients with laboratory abnormalities.[45, 46, 47] Patients in status epilepticus or who have persistent altered mental status, fever, or a new non-focal neurological deficit require additional observation and extensive evaluation and diagnostic testing. Tests include a determination of serum glucose, electrolytes, urea nitrogen, creatinine, magnesium, phosphate, calcium, complete blood count, pregnancy tests in women of childbearing age, anti-epileptic drug levels, liver function tests, and drugs of abuse screening.[48]

A seizure is a physiological stressor, so a thorough understanding of normal lab abnormalities is critical for accurate analysis. If an arterial blood gas analysis (ABG) is obtained in a convulsing patient (and this is not routinely indicated), it may show an anion gap metabolic acidosis, usually secondary to

---

Table 2: Differential Diagnosis Of Altered Mental Status In The Patient Who Has Seized

- Post-ictal state
- Nonconvulsive status or subtle convulsive status
- Hypoglycemia
- CNS infection
- CNS vascular event
- Drug toxicity
- Psychiatric disorder

---

lactic acidosis.[28] The anion gap acidosis should resolve in less than one hour after the seizure ends; persistence beyond this time suggests an underlying abnormality. If the anion gap does not resolve, one should test for ketosis (alcoholic or diabetic) and consider poisoning (methanol, iron, isoniazid, ethylene glycol, salicylates, carbon monoxide or cyanide).

Most of the controversy regarding diagnostic testing involves healthy patients presenting after first-time seizures who return to an alert, normal baseline without focal findings on neurologic exam. If a patient with a new-onset seizure has no significant co-morbid disease and a normal examination (including a normal mental status), the likelihood of an electrolyte disorder is very low. In one prospective study of 136 patients with new onset seizures, only two had electrolyte abnormalities not suspected on the basis of history and physical examination, (both had hypoglycemia).[47] Unexpected hyponatremia has been reported rarely, 1 in 98 in one study[49] and 1 in 247 in another.[50]

Women of childbearing age require a pregnancy test. Pregnancy causes significant physiologic stress and thus can lower the seizure threshold in a patient with an underlying focus. Approximately 25% of patients with new onset seizures in pregnancy are diagnosed with gestational epilepsy, i.e., seizure disorder that occurs only during pregnancy.[51] Identification of pregnancy in a patient with a first time seizure has significant impact on disposition, initiation of therapy, and further testing.

Non-eclamptic pregnant patients with new onset seizures and no co-morbidities, such as drug use or HIV, require a neuroimaging study and an electroencephalogram (EEG). If these tests are normal, it is reasonable to observe the patient without initiating therapy.[51]

There are no good prospective studies in either children or adults at this time to support more in-depth routine laboratory testing, such as serum calcium, magnesium, or phosphate levels, in otherwise healthy patients evaluated in the ED.[51]

Based on a systematic review of the literature, the American College of Emergency Physicians (ACEP) has published a Clinical Policy on the initial approach to patients presenting with a chief complaint of seizure: they do not recommend extensive metabolic testing in patients with a first time seizure who have returned to a normal baseline.[48] The ACEP Clinical Policy recommends that only a serum glucose and sodium level as well as a pregnancy test in women of childbearing age be done on patients who are otherwise healthy adults with a new-onset seizure who return to baseline neurological status. This conclusion has also been reached in a practice parameter published by the American Academy of Neurology on the evaluation of first time seizures in children. [52]

Toxicological Testing

A drug-of-abuse screen and alcohol level are considerations in patients with first time seizures, though there is no evidence that such testing changes outcome.[53, 54, 55] A positive drug of abuse screen does not prove a cause and effect and the patient would still require an EEG and neuroimaging study in order to direct management. Pesola et al reported four cases of cocaine related seizures in 120 patients studied, though not all patients received the same tests nor was a direct correlation demonstrated.[55] Seizure due to alcohol intoxication or withdrawal is a diagnosis of exclusion, as alcoholics are at increased risk for electrolyte abnormalities and traumatic injuries.[56] Testing for drugs of abuse and alcohol is of unknown benefit, but may suggest an etiology and help with future medical and psychiatric management.

Other Laboratory Testing

At times, the emergency physician is faced with a patient who suffered an unexplained loss of consciousness but the lack of witnesses make it hard to determine the etiololgy. Several laboratory tests have been studied, however, no reliable indicator has been found.

Creatine kinase (CK) has been suggested as a possibility based on a retrospective study.[57] However, in another smaller but more rigorous trial (using video EEG recordings) the authors did not find serum CK levels to be useful in differentiating seizures from other causes of loss of consciousness.[58] Elevated CK may indicate rhabdomyolysis in prolonged seizure, so the study may prove to be useful, but not in determining the cause of unexplained loss of consciousness or seizure-like activity.

Electrocardiogram (ECG)

Patients who continue to seize or those suspected of overdose may benefit from cardiac monitoring. An ECG is also an early screen for drug toxicity.[59] Tricyclic cardiotoxicity may manifest as a QRS complex greater than 0.10 seconds or a rightward shift of the terminal 40 ms of the frontal plane QRS complex (a prominent R wave in lead AVR).[60] The ECG also

may identify a prolonged QT, a delta wave, or heart block.

Neuroimaging

While there is agreement that neuroimaging in patients with a first-time non-febrile seizure is indicated, the timing of head computed tomography (CT) is controversial. Three to 41% of patients with first time seizures will have an abnormal head CT.[50] In one retrospective review, 22% of patients with a first-time seizure who had a normal neurological examination had an abnormal head CT scan result.[61]

The question remains whether identifying such abnormalities in the ED has an impact on outcomes for patients with a normal neurologic exam and new onset seizures. This, of course, depends on the outcome measure used. Identifying an intracranial lesion may influence disposition and argues in favor of ED neuroimaging.

In a multidisciplinary collaboration between emergency medicine, neurology, and neuroradiology, an evidence-based clinical policy on neuroimaging of patients with a first time seizure was published in 1996, **Table 3**.[62] It was recommended that a head CT be performed acutely whenever an acute intracranial process is suspected and in patients with a history of acute head trauma,[63] malignancy, immunocompromise,[55] fever, persistent headache, anticoagulation, or a new focal neurologic examination, age over 40,[50] or focal onset with secondary generalization. For all other patients, acute neuroimaging is probably beneficial but not mandatory, and may be deferred if scanning is not immediately available.

Magnetic resonance imaging (MRI) is generally the preferred diagnostic test by neurologists in evaluating first time seizure since it is better than CT in identifying small lesions. MRI is not better than CT for detecting acute hemorrhage. There are no ED based studies that have evaluated MRI. Also, the joint practice guideline discussed previously deferred on making a recommendation regarding emergent MRI.

Lumbar Puncture

No prospective studies suggest the need for routine lumbar puncture in the evaluation of new-onset seizures in patients who are alert, oriented, asymptomatic, and not immunocompromised. Lumbar puncture should be considered in patients with fever, severe headache, or persistently altered mental status.[66, 50, 64] Of note, asymptomatic patients with a history or strong suspicion of immunocompromise should

get a lumbar puncture at some point in their inpatient evaluation. In a prospective cohort, Sempere et al reported on eight HIV patients found to have a CNS infection as a cause of their seizure, two of whom were afebrile with no meningeal signs.[49] No reports of bacterial central nervous system infection presenting as an isolated seizure without fever or an abnormal neurological exam were identified in a MEDLINE search. However, an exception may occur in cases of partially treated meningitis. In children, it has been demonstrated that those who have been taking antibiotics and present with a complaint of seizure may have meningitis even if afebrile; therefore, lumbar puncture should be considered.[65] One retrospective study reported four cases of meningitis in seizure patients with normal physical exams, but none were bacterial: the majority of patients in this study did not receive a lumbar puncture and indications for lumbar

---

Table 3: AAN/ACEP/AANS/ASN Recommendations For Neuroimaging In Emergency Patients Presenting With Seizure (This Policy Is Ten Years Old And Currently Under Revision)

First time seizure:

CT in the ED (guideline): new focal deficit, persistent altered mental status, fever, recent trauma, persistent headache, history of cancer, history of anticoagulation or suspicion of AIDS, fever.

CT in the ED (option): age over 40 years; partial onset seizure.

Arrange CT as outpatient or consider scan in ED if follow-up uncertain (option): Normal exam and no cause identified for the seizure.*

Recurrent seizure in patient with known epilepsy:

CT in the ED (guideline): new focal deficit, persistent altered mental status, fever, recent trauma, persistent headache, history of cancer, history of anticoagulation, suspicion of AIDS.

CT in the ED (option): new seizure pattern or new seizure type, prolongs postictal confusion or worsening mental status.

Arrange CT as outpatient or consider scan in ED if follow-up uncertain (option): no clear cut cause of seizure identified.

* ACEP Clinical Policy on Seizure Management published in 2004 recommends neuroimaging in the ED as a "Level B" recommendation because of issues related to follow up and impact of findings on disposition. However, the Clinical Policy allows for outpatient testing if neuroimaging of the brain is not available in the ED and recommends that the risk of recurrence be discussed with the patient and the patient's primary physician.

puncture were not clear.[66]

A transient CSF pleocytosis of up to 20 WBC/mm³ has been reported in 2 to 23% of patients with seizures.[27, 66] However, the emergency physician is obligated to assume that the presence of white cells in the CSF of a seizing patient represents meningitis until proven otherwise.

Electroencephalography (EEG)

While the EEG is the definitive test for diagnosing a seizure disorder, defining clear indications for obtaining an EEG in the ED has been problematic. It can certainly be helpful in cases where the diagnosis is in doubt, such as acute confusional states and coma.[67, 68] In one series, nonconvulsive status epilepticus (NCSE) was detected in 8% of all patients who present with coma.[69] In addition to making the diagnosis, the EEG can be helpful with monitoring medication effects and recurrence of seizures. The EEG has a role in critical care monitoring of patients with pharmacologically induced sedation, paralysis, coma, and refractory status epilepticus. An EEG should be used to monitor patients who initially had a motor seizure and have persistent altered mental status after the episode. One study found that continued electrical activity occurred in 14% of patients initially treated for GCSE[70] and NCSE was detected in 8% of all comatose patients.[74] In the VA Cooperative trial, performance of early EEG found that continued electrical activity occurred in 25% of patients in whom the seizure was thought to be terminated by bedside observation.[4] Delay in diagnosis of subtle status epilepticus was strongly associated with mortality in one ICU based study.[71]

Management

First Time Seizures With Spontaneous Resolution

The need for hospital admission is obvious in those patients who are clinically ill. The dilemma arises when determining disposition for the patient who returns to a normal baseline after a first-time seizure.

A rational decision regarding whether a patient needs to receive antiepileptic drug (AED) therapy or admission is problematic. The recurrence risk of unprovoked (i.e., epileptic) seizures has been studied rigorously but is, unfortunately, reported in one and five year recurrence rates.[15, 72, 73, 74] Moreover, these studies also exclude patients who had an identifiable cause of their seizure. It is also not clear that AED treatment will lower the risk of recurrence in all subsets of patients who have had a seizure. While an uncontrolled study with a high rate of noncompliance demonstrated a benefit of early initiation of AED treatment,[78] patients with a history of traumatic brain injury have no decrease in seizure recurrence on phenytoin.[75] An extended follow-up study of seizure recurrence found that AED treatment was actually associated with an increased recurrence risk.[15]

The best predictor of seizure recurrence is the causative etiology combined with EEG neuroimaging findings.[78] This information often requires modalities that are not routinely available in the ED. Recurrence rates are lowest (approximately 24% in two years) when no etiology is identified and the EEG is normal. Patients who have structural lesions on CT or patients with focal seizures that generalize secondarily have a risk of recurrence within one year of up to 65%, and are the group of patients that probably benefit from initiating AED therapy.[15, 78] ED-based studies have reported rates of hospital admission, but the decision to admit was not standardized, and the ability of admission to improve outcomes was not studied.[6 50] Only one study investigated the incidence of seizure recurrence within 24 hours of ED presentation.[50] This was a retrospective review of all adult patients admitted to the hospital with a first time seizure during a two-year period. The authors reported a 19% seizure recurrence rate within 24 hours of presentation, decreasing to 9% if those patients with alcohol related events or focal lesions on CT were excluded. However, the applicability of these results is limited because those patients with recurrent seizures were not described well, making it impossible to assess whether recurrence could have been predicted based on physical findings or co-morbid factors. Other than patients who obviously require admission for treatment of a defined illness, there is insufficient evidence to support a recommendation to admit or discharge the patient with no co-morbidities who returns to a normal baseline after a first seizure. The decision must be tailored to the patient, taking into consideration the patient's access to follow-up care. On the other hand, patients with co-morbidities, including age over 60 years, known cardiovascular disease, history of cancer, or history of immunocompromise, should be considered for admission to the hospital.

There is no set standard for whether a patient should be started on an antiepileptic drug after a first time seizure in the ED. The decision to initiate an AED in the ED for a first-time seizure varies depending upon the patient, physician, and local practices. This decision is best made in conjunction

with the patient's primary care provider or neurologist and should include the estimated risk for seizure recurrence.

Patients With A Known History Of Seizure Disorder

Patients with a known seizure disorder, who have a "typical" event while on medications and who return to baseline mental status need only a serum anticonvulsant level (if appropriate). Exceptions to this include those with underlying disease, such as diabetes, that could result in a metabolic derangement. In such patients, it is important to investigate for precipitants, such as infections or new medications. If the seizure represented a change in the patients stable seizure pattern (more frequent or recurrent), the physician needs to look for a reason, e.g., an underlying infection. Any consideration to changing AED regimens should only be made in conjunction with the patient's primary care provider or neurologist.

Noncompliance and low AED levels in the ED are frequently encountered problems and the emergency physician must decide how to best increase serum levels to the therapeutic range. Current recommendations for the management of epilepsy emphasize monotherapy, see **Table 4**, page 12. This often means increasing a single drug to the point of seizure control or clinical toxicity.[76] Serum drug levels are used only to guide therapy and must be interpreted in the context of the patient's clinical status. In addition, drug levels may vary depending on the patient's dosing schedule. For example, single dosing of phenytoin may result in a peak serum level that is two to three times that of the trough.[77]

For a patient who has a seizure due to a low serum concentration of phenytoin, oral administration of phenytoin is an appealing option given the problems associated with parenteral administration. There has been hesitation to use this strategy due to a study in 1987 that demonstrated that only 60% of patients loaded with 18 mg/kg were therapeutic after 6 to10 hours.[78] Since then, two well designed studies have demonstrated that oral loading (19 mg/kg in men and 23 mg/kg in women) is both safe (patients should be watched for ataxia and dizziness) and provides therapeutic serum levels by four hours in almost all patients.[79, 80] Some EPs still prefer parenteral loading of phenytoin or fosphenytoin to ensure an adequate serum level on discharge.

Management Of Status Epilepticus

Stabilization

Generalized convulsive status epilepticus (GCSE) is a medical emergency with mortality, associated with duration of the event. Mortality estimates range from 10 to 40%, and are related to the underlying etiology. For example, refractory GCSE associated with bacterial meningitis has higher mortality than GCSE due to AED or alcohol withdrawal. Early termination of SE is of the highest priority, since prolonged seizure activity is associated with difficult seizure termination, morbidity, and mortality.[12, 81, 82] Early termination also allows rapid diagnostic evaluation and early initiation of appropriate therapy for the underlying cause. Interestingly, mortality rates of partial and GCSE were not significantly different, perhaps indicating that combination of focal brain injury and partial status epilepticus contributed to the high mortality.[88]

In general, the patients that are most often recognized in the ED to be in status epilepticus are those with GCSE. These may be primary generalized or secondary generalized, but, for the purpose of stabilization, treatment, and work-up, they are approached the same. It is important to remember that, after initiation of treatment with benzodiazepines and as the muscles fatigue, the full tonic-clonic movements may be attenuated and thus subtler in their clinical presentation (subtle SE).

In true emergency medicine fashion, the emergency physician must approach SE from multiple directions at once. Consider the treatable etiologies, see **Table 5**, page 13. Protect the airway and ensure oxygenation and obtain intravenous access and diagnostic studies, while initiating pharmacologic interventions and planning the diagnostic work-up. Intravenous access is best secured with a non-dextrose solution since dextrose will precipitate phenytoin if administered concurrently (fosphenytoin can be safely administered with dextrose solutions). The goal of therapy is to control seizure activity before neuronal injury occurs. Neuronal injury occurs between 20 minutes and one hour in experimental SE, despite adequate oxygenation and ventilation.

Patients in status should be monitored by continuous pulse oximetry to detect seizure-related hypoxia. If, at any time, breathing appears compromised, rapid sequence intubation is recommended using lidocaine (as a pretreatment drug), an induction agent, followed by paralysis with a short acting agent, such as succinylcholine. A sedative agent is

not often needed because the patient should have received high dose benzodiazepines by this time. While measures should be taken to minimize raising the intracranial pressure, these considerations should not delay securing the airway.

Long acting paralyzing agents are contraindicated unless bedside EEG monitoring becomes available. Prolonged pharmacologic paralysis can mask persistent electrical status of the brain, lulling the physician into a false sense of security. While vecuronium may render the body quiescent, the untreated electrical status may cause further damage to the brain.[83] This is thought to be due to the release of excitatory amino acids and to calcium influx. A bedside serum glucose should be obtained early, and IV dextrose should be given if the level is low: 50 cc of 50% dextrose intravenously in adults or 2 mL/kg of 25% dextrose in children (excluding neonates) is the standard dose. Thiamine 100 mg, is recommended with dextrose boluses in patients who either appear malnourished or abuse alcohol.

When infection is suspected, consider early (empiric) antibiotics, since obtaining a head CT and performing a lumbar puncture may be delayed pending patient stabilization. Likewise, prompt administration of activated charcoal 1 gm/kg is a consideration in cases of suspected acute overdose, though this is controversial and should only be done after securing the airway.

A non-contrast head computed tomogram (CT) is recommended for all patients without a prior history of seizure once they have been stabilized. If the seizures cannot be controlled after aggressive use of AEDs, a short acting paralytic can be used to expedite a non-contrast head CT in order to exclude surgically reversible etiologies, such as an epidural hemorrhage. Rocuronium (1 mg/kg) is favored due its short duration of action. Longer acting paralytic

---

Table 4: Recommendations for the evaluation and management of adults presenting to the ED with seizures. From the ACEP Clinical Policies Committee and the Clinical Policies Subcommittee on Seizures.

Clinical question	Recommendation	Level of recommendation
What laboratory tests are indicated in the healthy adult with new-onset seizure who has returned to baseline neurologic status?	1. Serum glucose and serum sodium. 2. Pregnancy test in women of child-bearing age. 3. Perform a LP (after head CT) on immunocompromised patients.	Level B
Which patients with new-onset seizure and return to baseline neurologic status require a head CT in the ED?	1. When feasible, perform neuroimaging of the brain in the ED on patients with a first time seizure. This can be deferred to the outpatient setting when reliable follow-up is available for otherwise healthy patients.	Level B
Which patients with new-onset seizure and return to baseline neurologic status need to be admitted to the hospital and/or started on an AED?	1. Patients with a normal neurologic exam can be discharged from the ED. 2. Patients with no co-morbidities, no structural brain disease, and a normal neurologic exam do not need to start an AED in the ED.	Level C
What are effective phenytoin of fosphenytoin dosing strategies for preventing seizure recurrence in patients with a seizure and subtherapeutic phenytoin levels?	1. Administer IV or PO phenytoin of an IV or IM dose of fosphenytoin.	Level C

Which agent(s) should be administered to a patient in SE who continues to seize after maximum benzodiazepine and phenytoin dosing?	1. Administer one of the following:
	   a. "high dose" phenytoin
	   b. continuous midazolam infusion
	   c. continuous propofol infusion
	   d. continuous pentobarbital infusion
	   e. Phenobarbital
	   f. IV valproic acid loading
		Level C

agents should be avoided due to the danger of masking epileptic activity.

While an EEG is not typically necessary in status epilepticus for initial diagnosis, it plays an important role in monitoring patients after treatment, particularly in refractory status epilepticus. Recurrent seizures after initial control are common, and undetected persistent epileptic activity has been documented in a number of studies.[74, 75, 84] An emergency EEG is indicated in unexplained altered awareness (to exclude NCSE), neuromuscular paralysis for SE, high-dose suppressive therapy for refractory SE, or when there is no improvement or return to baseline mental status after controlling overt convulsive movements (to exclude NCSE).[75, 90]

Traditionally, therapy of SE has been divided into first-, second-, and third-line therapies. A more practical way to categorize these is as medications that are used upon initial presentation which include benzodiazepines, phenytoin, and valproic acid. After that, if the seizure continues, it should be considered "refractory" GCSE and a protocol for the administration of high doses (anesthetic levels) of midazolam, pentobarbital, or propofol must be given.

Table 5: Etiologies Of Secondary Seizures

Partial Seizures
❑ Tumors
❑ Vascular event
  • Subarachnoid hemorrhage
  • Subdural hemorrhage
  • Epidural hemorrhage
  • Stroke
  • Vasculitis
❑ Infection
  • Meningitis
  • Encephalitis
  • Abscess
❑ Metabolic
  • Hypoglycemia1
  • Hyponatremia2
  • Hypomagnesemia3
  • Hypocalcemia
❑ Toxic: consider the following in overdose:
  • Cocaine and sympathomimetics
  • Tricyclic antidepressants
  • Anticholinergics
  • Theophylline
  • Isoniazid
❑ Eclampsia

 1. The most common metabolic cause of seizures
 2. A rare cause of seizures except in infants less than 6
    months
 3. Rarely an isolated cause of seizures; possibly facilitates seizures, especially in malnourished patients
    e.g., alcoholics

The pharmacologic treatment of status epilepticus has changed in the past 20 years with increasing evidence supporting the use of benzodiazepines and less on phenobarbital. In addition, fosphenytoin and intravenous valproic acid have become available in the US and are developing roles in many protocols.

Benzodiazepines

Early and aggressive therapy with benzodiazepines has confirmed benefit in the management of status epilepticus.[3, 85] IV lorazepam has been shown to be equally effective at terminating seizures to phenobarbital and superior to using phenytoin alone.[4]

Intravenous benzodiazepines remain the first drugs of choice for status epilepticus. Lorazepam is generally preferred up to a dose of 0.1 mg/kg given at 2 mg/min. Lorazepam and diazepam (0.2 mg/kg IV given at 5 mg/min) are equally effective at terminating the initial seizure. However, lorazepam has a smaller volume of distribution, and thus the anticonvulsant activity of lorazepam lasts up to twelve hours while that of diazepam only lasts for 20 minutes.[86] In a metanalysis, the Cochrane Database found that IV lorazepam was superior to IV diazepam for cessation of seizure and preventing recurrence/continuation of seizure requiring an additional drug or anesthesia.[87] IV midazolam is less extensively studied, but a number of small studies seem to show a trend toward superior efficacy and decreased incidence of adverse outcomes compared to lorazepam[88] and diazepam.[89]

In a patient with no intravenous access, the options are IM lorazepam or midazolam or rectal diazepam. Of these, IM midazolam is probably the best option.[112] This drug is water soluble, nonirritating, and rapidly absorbed. At least one trial has shown that it as effective as IV diazepam with no additional adverse outcomes.[111] Rectal diazepam is another alternative for the patient with no intravenous access; the recommended dose in adults is 30 mg.[3, 90, 91] It can be given per rectum either using the standard intravenous form, or as a gel formulated for this purpose (Diastat™). In a systemic review of available data, rectal diazepam is recommended when monitoring is not available.[93]

Phenytoin

In the ED setting, phenytoin has been used as a first line drug in status epilepticus since 1956 due to it's availability in parenteral preparation and because it can rapidly achieve therapeutic levels. It is limited

by the rate at which it can be delivered, as well as known adverse effects.

Phenytoin slows the recovery of voltage activated sodium channels thus decreasing repetitive action potentials in neurons. This effect on the myocardium can also lead to QT prolongation and arrhythmias. This is very rare, but cardiac monitoring is still recommended during infusion.[92] A more common effect is hypotension which occurs 3.5% of the time. Its incidence is directly related to the total dose and the rate of infusion.[93, 94]

The recommended dose of phenytoin is 20 mg/kg administered in a non-glucose solution. For a 70 kg person this would be much higher than the common "one gram" often given in practice. Based on observational studies and consensus, a second dose of 10 mg/kg is recommended for patients who continue to seize.[22, 95, 96] The infusion rate is limited to 50 mg/min in order to avoid hypotension caused by the propylene glycol diluent.   The infusion rate should be no faster than 25 mg/min in patients with cardiac disease to minimize the risk of hypotension as well as the direct cardiac effects of phenytoin which can lead to bradycardia and heart blocks.

Due to specific properties of phenytoin, administration is a non-trivial consideration.[99, 100] To maintain phenytoin soluble, it is formulated in solution with a pH of 12, making it extremely toxic to the vascular walls and soft tissue. It must be given through a large and well-secured vein, a potential challenge in some actively seizing patients. Infusion can cause distal limb edema, discoloration, and ischemia. Extravasation can be disastrous for the patient, resulting in extensive necrosis (i.e., 'the purple glove' syndrome).[97, 98, 99]

Because of its side effects, cardiac monitoring is necessary during phenytoin infusions. Reports of sudden cardiac death in patients receiving the intravenous form of the drug were most likely the result of rapid infusion of propylene glycol and/or ethanol, the vehicle used for phenytoin.[100, 101, 102] Other, relatively minor side effects include confusion and ataxia, both of which usually resolve with supportive care.

Fosphenytoin is a parenteral phenytoin precursor with an added phosphoryl group that has the same pharmacological activity as phenytoin in the treatment of seizures.[113] Fosphenytoin has the advantage of being more water soluble and having a lower pH (8.6-9) than phenytoin, obviating the need for the propylene glycol vehicle. These characteristics make

it preferable to phenytoin in a number of ways.[103] When IV access is not available, fosphenytoin can be given IM with rapid achievement of therapeutic serum drug levels within one hour and within 30 minutes in 40% of patients.[104, 105, 106, 107]

For dosing ease, fosphenytoin is measured in phenytoin equivalents (PE) and can be infused at a rate up to 150 mg PE/min. [108] The manufacturer still recommends cardiac and blood pressure monitoring because hypotension, though rare, does occur. The lower pH decreases vascular irritation and decreases tissue toxicity allowing for IM administration with rapid bioavailability. The conversion half-life is 8 to 15 minutes. [113, 109] Fosphenytoin reaches a peak serum level within approximately one hour of intramuscular administration and at six minutes after intravenous loading.

The best therapeutic study on GCSE management is the VA Cooperative Study.[4] This was a head-to-head trial comparing four treatment arms: diazepam (0.15 mg/kg) followed by phenytoin (18 mg/kg), lorazepam alone (0.1 mg/kg), phenytoin alone (18 mg/kg), and phenobarbital alone (15 mg/kg). This well designed, randomized, double blind study found no outcome difference between the four treatments; however, lorazepam was the easiest to administer and the authors recommended it as the first line agent in GCSE management. Because of the high seizure recurrence rate in patients treated with diazepam, phenytoin should always be administered after diazepam; this is not necessarily the case when lorazepam is used and depends on the underlying etiology of the seizure.

Valproic Acid
Valproic acid is unique among older antiepileptic drugs because it is effective in treating all forms of seizures, including absence, partial, and primary generalized. Its mechanism is similar to phenytoin and carbamazepine in that it prolongs recovery of voltage activated sodium channels from inactivation. The drug has recently become available in the US in IV form,[110] although experience in status epilepticus is limited to small studies in adults and pediatrics which show an efficacy rate of 42 to 80%.[111, 112] The recommended loading dose for valproic acid is 15-20 mg/kg at a rate of 3-6 mg/kg/min, although more rapid bolus infusions have been safely administered.[113, 114, 115, 116]

Valproate has some promise due to its generally excellent safety profile.[120, 121, 117] It is generally well tol-

erated with mild side effects. The notable exception is hepatotoxicity, which usually develops with chronic use over the first six months of therapy. There is also an incidence of an occasional rare fatal idiosyncratic hepatoxicity in 1/49,000 adults and 1/800 children.[123, 118] Therefore, the drug is contraindicated in patients with hepatic dysfunction.

Further study is needed, but parenteral valproate is an alternative in cases where benzodiazepine or phenytoin use is limited by hypotension or hypersensitivity, as well as in patients who are in status as a result of valproic acid withdrawal.

Phenobarbital

Introduced in 1912, Phenobarbital is the oldest antiepileptic drug still in use. It is notable as being the only barbiturate that possesses anticonvulsant properties at sub-hypnotic doses. It has been advocated in the past as a first line intervention, but has fallen out of favor today. Phenobarbital works on the GABA receptor similar to the mechanism of benzodiazepines and has generally shown the same efficacy as a first line agent in the combination of diazepam and phenytoin[119] or with lorazepam alone.[4]

The main drawback of phenobarbital is its potential to induce profound respiratory depression and hypotension from its vasodilatatory and cardio-depressant effects. The respiratory depressant effects are compounded when used - as it typically is - after treatment with benzodiazepine. It also has a long half-life, which can make complications and titration difficult to manage.[25] It is therefore generally held as a second line antiepileptic drug due to significant side effects. Many reserve this drug for patients who continue to seize despite benzodiazepine and phenytoin loading.[125]

Phenobarbital is dosed at 20 mg/kg administered at 100 mg/min. For refractory GCSE, it can be given in even higher doses of up to 30 mg/kg or more. However, in such doses, it is likely to cause hypotension and suppress respirations particularly during rapid infusion or co-existing benzodiazepine.

Refractory GCSE: Current literature supports the use of continuous IV midazolam, anesthetic barbiturates (pentobarbital), or propofol in the management of refractory status epilepticus. Inhalational anesthetics do not have a well-defined role and can be considered along with other potentially useful, but less well studied medications, such as lidocaine, chloral hydrate, adenosine, and etomidate.

There is very little empiric data to guide the choice of therapy in an evidence-based fashion. Treatment modality is often based upon expert opinion and available resources (e.g., IV midazolam may be preferred as it is more readily available in the ED than pentobarbital) and the patient's hemodynamic status.[120]
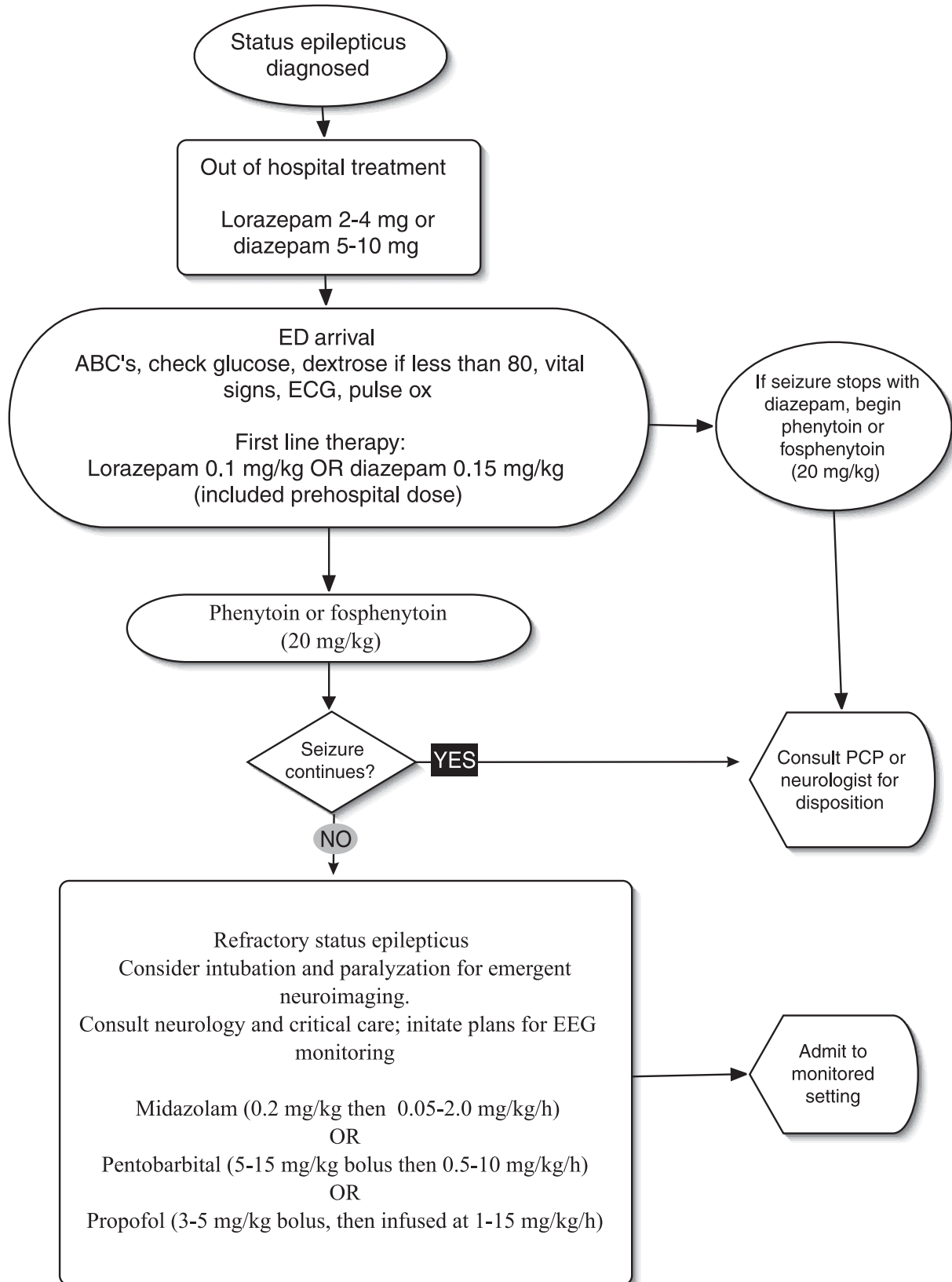
A recent systematic review[98] did not find sufficient evidence to support the superiority of pentobarbital, propofol, or midazolam. Pentobarbital had less treatment failure but caused more hypotension than either propofol or midazolam, but this was based on a total of 28 patients over different study conditions. Midazolam and propofol are medications that are more familiar to most emergency medicine and critical care physicians, and are, therefore, often recommended due to the ease of access and familiarity. None of these drugs have shown clear superiority over the other but it is well known that delays in controlling the seizure lead to worse outcomes.

Continuous benzodiazepine infusion: Even after maximum dosing of lorazepam or diazepam, continuous infusions of midazolam or lorazepan have been reported to be effective in terminating refractory GCSE in small case series. Midazolam is water soluble and continuous infusion allows for high CNS penetration. It has a short duration of action and it is easy to titrate. The loading dose is 0.2 mg/kg, and this is followed by an infusion of 0.05 – 2.0 mg/kg/hour.[121, 122] When compared to propofol or pentobarbital in a meta-analysis for refractory status epilepticus, IV midazolam was effective in 80% of cases. While this was less effective than propofol or pentobarbital, it was also associated with less hypotension than the other two medications.[123] Lorazepam .3 to 9 mg/hour can also be given as a continuous IV infusion; however, there is limited data on its use in status and its long half-life makes withdrawal more difficult.[124]
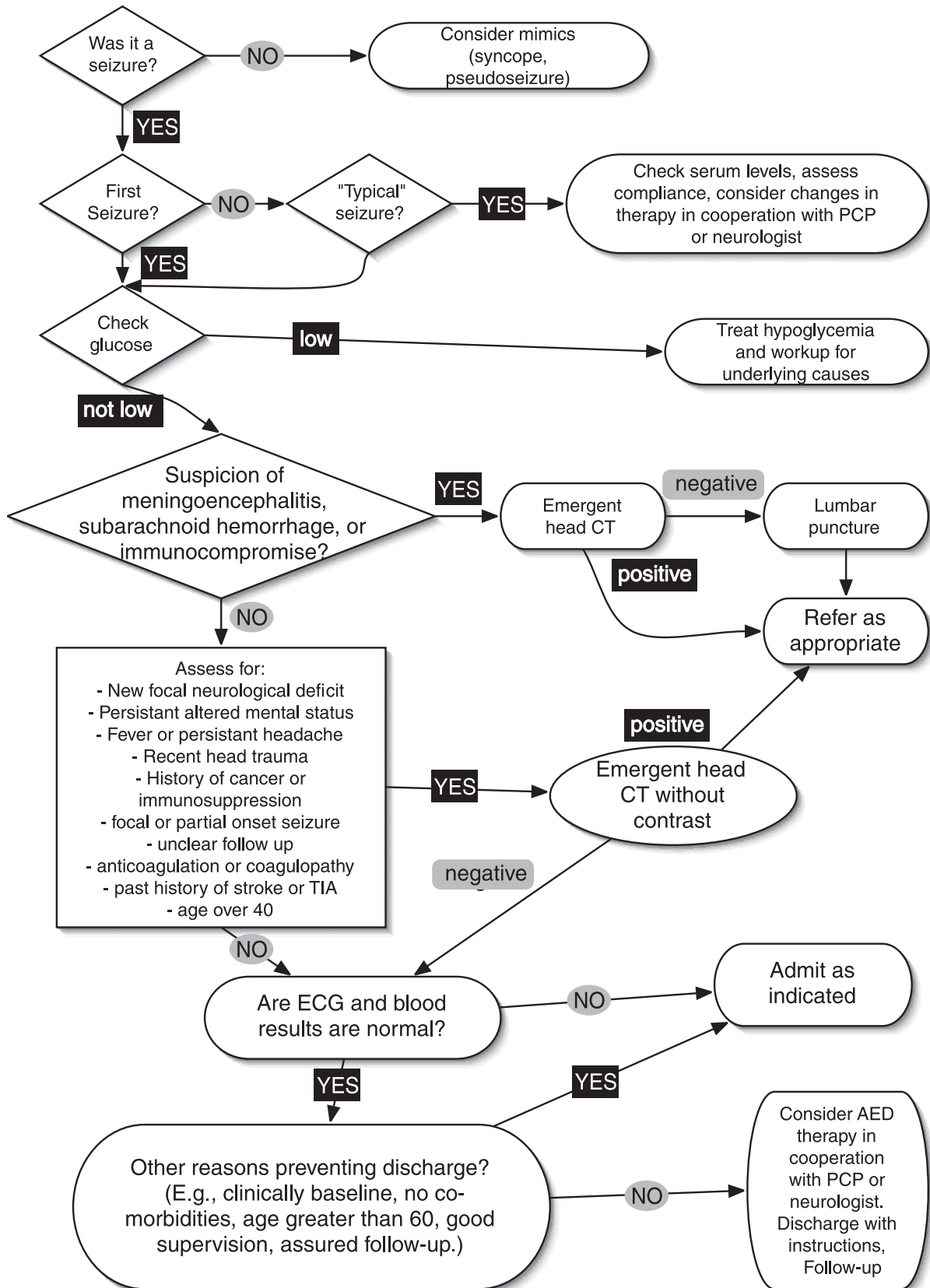
Propofol

Propofol is a global CNS depressant; it acts as a direct GABA agonist as well as an NMDA antagonist. There are limited studies of its efficacy in status epilepticus, but there is evidence that it provides almost immediate suppression of seizure activity after a bolus infusion.[125] It is rapidly metabolized and studies report rapid recovery from the propofol when the infusion is discontinued. Propofol is dosed with a bolus of 3-5 mg/kg followed by a continuous infusion at 30-100 mcg/kg/min.[22, 126] Limiting factors in its long term and high dose use is the "propofol infusion syn-

Clinical Pathway: Status Epilepticus

Status epilepticus diagnosed

↓

Out of hospital treatment

Lorazepam 2-4 mg or
diazepam 5-10 mg

↓

ED arrival
ABC's, check glucose, dextrose if less than 80, vital
signs, ECG, pulse ox

First line therapy:
Lorazepam 0.1 mg/kg OR diazepam 0.15 mg/kg
(included prehospital dose)

→ If seizure stops with
diazepam, begin
phenytoin or
fosphenytoin
(20 mg/kg)

↓

Phenytoin or fosphenytoin
(20 mg/kg)

↓

Seizure continues? —YES→ Consult PCP or
neurologist for
disposition

↓ NO

Refractory status epilepticus
Consider intubation and paralyzation for emergent
neuroimaging.
Consult neurology and critical care; initate plans for EEG
monitoring

Midazolam (0.2 mg/kg then 0.05-2.0 mg/kg/h)
OR
Pentobarbital (5-15 mg/kg bolus then 0.5-10 mg/kg/h)
OR
Propofol (3-5 mg/kg bolus, then infused at 1-15 mg/kg/h)

→ Admit to
monitored
setting

Clinical Pathway: Seizure Not Status Epilepticus

Was it a seizure? —NO→ Consider mimics (syncope, pseudoseizure)

↓ YES

First Seizure? —NO→ **"Typical" seizure?** —YES→ Check serum levels, assess compliance, consider changes in therapy in cooperation with PCP or neurologist

↓ YES

Check glucose —low→ Treat hypoglycemia and workup for underlying causes

↓ not low

Suspicion of meningoencephalitis, subarachnoid hemorrhage, or immunocompromise? —YES→ Emergent head CT —negative→ Lumbar puncture

Emergent head CT —positive→ Refer as appropriate

Lumbar puncture → Refer as appropriate

↓ NO

Assess for:
- New focal neurological deficit
- Persistant altered mental status
- Fever or persistant headache
- Recent head trauma
- History of cancer or immunosuppression
- focal or partial onset seizure
- unclear follow up
- anticoagulation or coagulopathy
- past history of stroke or TIA
- age over 40

—YES→ **Emergent head CT without contrast** —positive→ Refer as appropriate

Emergent head CT without contrast —negative→

↓ NO

Are ECG and blood results are normal? —NO→ Admit as indicated

↓ YES

Other reasons preventing discharge? (E.g., clinically baseline, no co-morbidities, age greater than 60, good supervision, assured follow-up.) —YES→ Admit as indicated

—NO→ Consider AED therapy in cooperation with PCP or neurologist. Discharge with instructions, Follow-up

drome" of hypotension, lipidemia, and metabolic acidosis in both adults and children.[126, 127] Propofol can cause non-seizure jerking movements and even induce seizures, so EEG monitoring should be strongly considered.[128] In one small, retrospective study of IV midazolam and propofol, the mortality was 57% in the propofol group and 17% in the IV midazolam group, though the study had only 14 patients, was not randomized, and did not have the power to demonstrate significance in this difference.[129]

Barbiturates

Pentobarbital and thiopental are much shorter acting than phenobarbital. Thiopental is rapidly metabolized to pentobarbital. Both agents are highly lipid soluble and will accumulate in fat stores, leading to prolonged elimination. In a recent series of 12 ICU patients in status epilepticus, high dose thiopental terminated seizures in all of the patients. However, one-third of the patients needed either dobutamine or norepinephrine to support their mean arterial pressure during therapy. The authors also noted prolonged recovery time from the medication after the seizures had been suppressed.[130]

Thiopental has a less favorable side-effect profile than pentobarbital. It is more lipid soluble and the metabolic pathway can become saturated, leading to an accumulation of thiopental and delays in recovery when stopped. For these reasons, pentobarbital is preferred when a barbiturate is used to manage refractory status.[22] Pentobarbital is dosed with a loading dose of 3 to 5 mg/kg followed by an infusion of 0.5 to 3 mg/kg/hr. Pentobarbital can compromise cardiovascular status, and its use necessitates EEG monitoring since motor activity will be suppressed. Use fluid boluses to treat pentobarbital-induced hypotension and consider dopamine in case of persistent hypotension.[131, 132]

Other agents

Other medications that have been used to treat status epilepticus in case series include lidocaine,[133, 134] chloral hydrate,[135] and etomidate.[136] As of yet, these medications have not been validated for general use and should only be considered when other, more standard, therapies have failed.

Putting it all together: When a patient presents with GCSE, the time to termination of seizure may become dependent upon the time it takes for the physician to chose a drug and for the nurse to administer it. Thus, the ability of an emergency department to provide the rapid resources needed to treat status epilepticus depends upon development of a pre-arranged treatment algorithm, see Clinical Pathway on page 16. Pre-selection of medications for first-line use and those for refractory status epilepticus use will prevent delays when patients present. With a lack of strong evidence to select a preferred treatment for refractory status epilepticus, individual departments may make choices in conjunction with their neurology and critical care services, based upon drug availability and upon nursing familiarity with the given drugs.

Treatment in the prehospital arena begins with either IV lorazepam or diazepam. Upon presentation to the ED, continued seizure treatment begins with the stabilization of airway and vital functions. Initial medication choice is IV lorazepam (0.1 mg/kg), IV midazolam (0.2 mg/kg) or diazepam (0.15 mg/kg), taking into account the dose of the medication given in the field. If diazepam terminates the seizure, it should be followed by phenytoin or fosphenytoin (20 mg/kg or 20 PE/kg, respectively). If a benzodiazepine does not terminate seizure activity, phenytoin or fosphenytoin should be given with consideration to a second half load in refractory cases. Intravenous valproic acid might be considered if the patient is known to have been on valproic acid in the past.

If seizure activity continues, the patient is considered to be in refractory status epilepticus. Management choices include infusions of a benzodiazepine, propofol, and pentobarbital.

Nonconvulsive Status Epilepticus

Nonconvulsive status epilepticus (NCS), like convulsive status epilepticus, is a state of continuous or intermittent seizure activity lasting more than thirty minutes without a return to baseline function. Nonconvulsive status can be either a primary generalized process (absence status) or secondary generalized (complex partial status). The hallmark of NCS is altered mental status and, unless it is suspected, the diagnosis is easily missed. The literature is rife with patients who present with altered mental status and were initially labeled as having psychiatric problems. Only later was the NCS recognized, either by EEG or a subsequent convulsion.[137, 138, 139, 140, 141] Though the distinction is not clear in the literature, NCS in general should be distinguished from subtle generalized convulsive status epilepticus, which is the end stage of GCSE, associated with anoxic brain injury, and has a very poor prognosis.[4]

Epidemiology of NCS: NCS has been reported in all age groups and can be the first manifestation of a seizure disorder. Absence status has been associated with benzodiazepine withdrawal,[142] use of psychotropic drugs, metabolic disorders, and chronic alcoholism. A history of a seizure disorder, especially when the patient's symptoms are temporally related to a convulsive event, is a red flag that needs to be pursued. Prolonged "postictal periods," persisting aphasic, somatosensory, or psychic findings after ictus all suggest possible ongoing epileptogenic activity. Automatisms, abnormal eye movements, persistent twitches, or blinking provide clues to non-convulsive status. When NCS is suspected, the definitive test is an EEG.[143]

Treatment: When presented with a patient thought to be in NCS, EEG confirmation is indicated. Benzodiazepines are generally effective in terminating the seizure, though they do not provide long term control. The literature is unclear as to the urgency of controlling NCS, although there is evidence that ongoing neuronal firing does result in neuronal injury.[144] A neurology consultation should be obtained to determine long-term therapy.

Special Situations

Alcohol Withdrawal Seizures (AWS)

Of special concern to any emergency physician is the relation of alcohol to seizures. Twenty to 40% of seizure patients presenting to an ED will have their seizures related to alcohol abuse, and alcohol is reported as a causative factor in 15 to 24% of patients with status epilepticus.[25, 145] Diagnostic yield for CT after first alcohol related seizure is high, mainly because patients who overuse alcohol have a high incidence of structural intracranial lesions, such as subdural hematomas or other intracranial hemorrhages.[218, 146]

Alcohol may act in one of several ways to produce seizures in patients with or without underlying foci: (1) by its partial or absolute withdrawal after a period of chronic intake, (2) by an acute alcohol-related metabolic brain disorder (e.g., hypoglycemia, hyponatremia), (3) by creating a situation leading to cerebral trauma, or (4) by precipitating seizures in patients with idiopathic or posttraumatic epilepsy. Moreover, alcoholics are more susceptible to other disorders associated with seizures, including cerebral infarct, cerebral trauma and subarachnoid hemorrhage, neurosyphilis, acquired immunodeficiency syndrome (AIDS), brain abscess, and meningitis.[147 148]

Seizures occur in approximately 10% of patients who withdraw from alcohol. Alcohol abuse also increases the risk of having a seizure or developing a seizure disorder independent of withdrawal.[56] AWS usually occur between 6 and 48 hours after cessation of drinking. AWS are usually generalized events that can be multiple but rarely persist past twelve hours from onset. The patient may or may not have other signs of alcohol withdrawal, such as tachycardia, confusion, or tremors to predict that they will develop a seizure.

The diagnosis of AWS is based on a history of recurrent events temporally related to stopping (or significantly decreasing) alcohol intake. Consequently, a first time withdrawal seizure must be worked-up as any first time seizure and thoroughly evaluated. This includes alcoholics who claim to have had seizures in the past but for whom no documentation of previous seizures or of an appropriate work-up is available. Metabolic disorders, toxic ingestion, infection, and structural abnormalities need to be ruled out by history, physical examination, and diagnostic testing including electrolytes, glucose, and CT scan.[149] An EEG scheduled during follow-up may be considered (but its value is limited) in the patient whose seizures have not been explained.[150]

Once a patient with an AWS is brought to the ED, clinical findings cannot predict who is likely to have a recurrent seizure in the department.[151] There is good evidence to recommend benzodiazepines, even in a patient who is no longer actively seizing. A recent double blind, placebo controlled study of 186 patients showed that 2 mg IV lorazepam decreases the short term recurrence of seizures related to alcohol withdrawal and reduces the need for hospitalization. The number needed to treat in this study to prevent one further withdrawal seizure at six hours was five.[152]

Phenytoin does not have a role in managing either AWS or controlling recurrent alcohol-related seizures in the ED.[151, 153] However, many alcoholics may have an underlying seizure disorder from prior head trauma or other causes. For this reason, phenytoin may play a role in the management of alcoholics who have recurring seizures. Many of these patients will be sporadically taking one or more AEDs. It is difficult, if not impossible, to determine in the ED whether these AEDs were given for an underlying seizure disorder or AWS.

To prevent AWS effectively, detoxification with benzodiazepines should be initiated early because most AWS occur within the first 24 hours after alco-

hol withdrawal. Treatment should be started with the understanding that the patient will be observed for four to six hours and referred to a detoxification/rehabilitation program.

In ideal situations, if the initial physical exam and laboratory tests are normal, patients who remain seizure free and symptom free with no sign of withdrawal after four to six hours of observation may be discharged. Optimal outpatient treatment includes clear guidelines for follow-up and re-evaluation, and the help of a concerned family member or friend (who is not a drinking partner). Ideally, this individual should remain with the patient for one to two days. These criteria may be difficult to meet, and the physician must use discretion in deciding to admit for observation when the patient is at risk of serious injury. The ideal disposition is participation in a detoxification/rehabilitation program.[155]

Toxin Related Seizures
Toxins can alter the balance of the brain equilibrium of excitation-inhibition in a variety of ways to cause seizures. Most drug-induced seizures, particularly those resulting from cocaine and other stimulants, best respond to benzodiazepine therapy.

Cases of refractory status epilepticus pose a particular challenge because the mechanism of status may be different from status from other causes. A number of toxins cause depletion of GABA neurotransmitter, and many of the typical pharmacologic agents act by sensitizing the GABA receptor, making those agents less effective. In these cases, early administration of pyridoxine may be advantageous.

Pyridoxine acts by replenishing the quantities of GABA in the brain, and is initially dosed at 5 grams IV in adults and 70 mg/kg IV in children. In cases of known isoniasid (INH) ingestion, pyridoxime should be given on a gram-for-gram basis. When given and dosed properly, the effect of therapy should be apparent within minutes of administration. Pyridoxine may also be beneficial in hydrazine and other poisoning (theophylline), as well as a number of other metabolic seizure disorders.[154] Pyridoxine is commonly on formulary, but usually not in the quantities required in the management of toxin related seizures.[155, 156, 157] One-third or more of

Cost Effective Strategies in ED Seizure Management

1. Inform patients about generic options.

2. Consider oral phenytoin loading.
Given the lack of evidence that intravenous loading is more effective than oral loading, oral loading is an acceptable strategy and negates the need for IV and cardiac monitoring. The time to reach peak serum AED levels will be slower, four to six hours; however, the risks of side effects – neurologic, cardiac, and tissue related – will be lower. If IV loading is done, it should be done slowing over one hour, not the expedited rate used for managing status epilepticus.

3. Chose the type and timing of neuroimaging carefully.
The ACEP Clinical Policy supports neruoimaging as an outpatient for patients who have had a new onset seizure and have returned to a normal baseline. Neurologist generally prefer an MRI over a CT in evaluating these patients. To avoid redundant testing in select patients with coordinated care, an outpatient MRI would constitute best practice.

4. Limit your laboratory testing.
Extensive metabolic panels are not indicated for uncomplicated first time seizure patients. Patients with a history of seizures who have stopped taking their medication do not necessarily need a level or other lab test; they just need to be restarted on their medication.

5. Keep patients safe.
Though most patients will not have a recurrent seizure in the ED, *be prepared for the rare case!* Keep the bedrails up and use bedrail pads if available. Keep these patients in a place in your ED where they can be watched closely and think twice before allowing them to go unaccompanied to the bathroom!

6. Check the IV site.
When giving a parenteral dose of phenytoin, check the IV site yourself to be sure that it is large enough and has good flow. Ensuring that the vein is secure could save the patient from unnecessary pain and potentially from a necrotizing extravasation.

hospitals do not have adequate stores to treat a single INH overdose. [158]

There are no clear evidence-based guidelines for the management of toxin related seizures; most recommendations are based on case reports and expert opinion. Phenytoin is less effective for most drug-induced seizures than phenobarbital or benzodiazepines.[159] Phenytoin has been shown to be ineffective in many toxin related seizures, and may be potentially harmful in seizures induced by theophylline or cyclic antidepressants.[162] Pentobarbital is an option in these cases. Since the activity at the GABA receptor is less dependent on the presence of adequate normal quantities of GABA, pentobarbital has a theoretical benefit in treating seizures induced by toxins that deplete GABA.[160] Finally, propofol's mechanism of action is different from benzodiazepines and has theoretic benefit due to this different mechanism of action.[161]

Seizure after trauma: The risk of developing a seizure disorder after a traumatic brain injury (TBI) is related to the severity of the injury. The incidence after minor TBI (GCS score greater than 12) is 1.5%, while the incidence increases to 17% after a severe TBI (GCS score less than 9). Although the incidence of post-traumatic seizures in the first week is decreased to less than 4% by the early use of phenytoin, after the first week, there is no statistical difference in seizure incidence whether or not patients are treated. [162] In addition, though the incidence of an early post-traumatic seizure is decreased with AED use, there is no change in outcome. For these reasons, prophylactic antiepileptic drugs are not indicated to prevent late posttraumatic seizures.[163]

Seizures In Pregnancy

Seizures in pregnancy can be classified as one of three types: 1) those that can occur in epileptics who happen to be pregnant, 2) the new onset seizure in a pregnant patient, 3) seizures that are unique to the pregnant state: eclampsia

The most complete prospective observation study of pregnant women with epilepsy is the EURAP Pregnancy Registry. Of 1956 pregnancies, over half were seizure free during the pregnancy; 17.3% of women had an increase in seizure frequency and 15.9% had a decrease in frequency during the pregnancy.[164] In a previous study, a larger increase in seizure frequency was attributed to the discontinuation of AEDs.[165] Other factors that may lower the

seizure threshold in pregnancy include sleep deprivation, nausea, and vomiting.

Epilepsy in pregnancy can affect the total blood levels of AED. The serum concentration tends to go down during the pregnancy due to an increase in hepatic and renal clearance of drug and a pregnancy related increase in the volume of distribution of the drug. [166, 167, 168] This decrease in serum drug level is balanced by the fact that free (unbound) drug levels may actually be increased due to the decrease in concentration of serum proteins that normally occurs in pregnancy.

Pregnant patients with new onset seizures (not ecamptic) should be worked-up as any new onset seizure patient with a metabolic profile and head CT with appropriate abdominal shielding. Precipitating etiologies, such as infections and drug toxicities, should also be investigated. If no source is identified, anticonvulsants should be withheld and the patient referred for close follow-up. In pregnant patients with epilepsy, noncompliance and sleep deprivation are common causes for seizures.

Patients who are actively seizing should be managed as the non-pregnant patient. The risks to the fetus from hypoxia and acidosis are greater than the potential teratogenicity of anticonvulsant medications. Arrange for fetal monitoring during and after a seizure in patients more than 24 weeks gestation.[169]

Eclampsia: Eclampsia is the major consideration in pregnant patients of more than 20-week gestation and up to 23 days postpartum[170, 171] who present with new onset seizures. Magnesium has been demonstrated to be the therapy of choice in the treatment of acute eclamplic seizures and for prevention of recurrent eclampic seizures.[172] A systematic review[173] of four good quality trials involving 823 women found magnesium sulfate to be substantially more effective than phenytoin with regards to recurrence of convulsions and maternal death. Complications, such as respiratory depression and pneumonia, were also less for magnesium than for phenytoin. Magnesium showed a trend towards increased incidence of renal failure when compared to phenytoin; however, this was not statistically significant. Magnesium sulfate was also associated with benefits for the baby, including fewer admissions to the NICU.

In the eclamptic patient, give 4 grams of intravenous magnesium sulfate followed by a 2 gm/h drip (some centers use intramuscular regimens.) Control the patient's blood pressure if very high (SBP greater than 160 and/or DBP greater than 110)

and contact an obstetrician. Agents of choice for blood pressure control according to the American College of Obstetrics and Gynecology (ACOG) and the National High Blood Pressure Education Program: Working Group Report on High Blood Pressure in Pregnancy[174] in the emergency setting include hydralazine (first line) and labetalol. In resistant cases, nitroprusside may also be used, although fetal cyanide toxicity can occur after even a few hours of therapy.

Psychogenic Nonepileptic Seizures

Psychogenic nonepileptic seizures (pseudoseizures) are characterized by episodes of behavior and/or motor activity that are not the result of abnormal cortical discharges. It is important to note that psychogenic seizures are different from malingering and are grouped with psychoneurological illness (e.g., conversion disorders, somatoform disorders). Psychogenic seizures can be extremely difficult to differentiate from epileptic seizures and, when inappropriately labeled, can result in mismanagement.[175, 176, 177] One review cites a mean time to diagnosis as 7.2 years.[178] Several historical, clinical, and laboratory characteristics of convulsive psychogenic seizures can help the emergency physician make the correct diagnosis.[179]

Epidemiology of psychogenic seizures: The prevalence of psychogenic seizures ranges from 2 to 33 cases in 100,000 persons in the general population.[180] Five to ten percent of the outpatient epileptic population has PNES, compared to 20 to 40% of the inpatient epilepsy population.[181, 182, 183] Confounding the diagnosis is the concurrence of psychogenic seizures with true seizures. Early studies reported that up to 60% of patients with psychogenic seizures had a co-existent neurogenic seizure disorder,[184] although more recent studies using a strict definition of epilepsy report a co-existence rate of approximately 10%.[188, 185] Authors have reported epileptic seizures evolving into nonepileptic events.[186]

Clinical characteristics: Care should be taken when using clinical characteristics to distinguish neurogenic from psychogenic seizures. In a cohort of patients referred by experienced epilepsy neurologists for video-EEG monitoring, misdiagnoses occurred in 24% of cases.[187] Characteristics that are suggestive, but not diagnostic of psychogenic seizures are listed in **Table 6**. Head, extremity, and pelvic thrusting movements are useful in identifying psychogenic seizures, especially if observed in conjunction with each other.[187] Neurogenic seizures tend to have in-phase, synchronous tonic-clonic movement of the extremities. Asynchronous and/or thrashing movements of the extremities are more characteristic of psychogenic seizures. This is not an absolute observation and care must be used in applying these features. In particular, complex motor automatisms, such as thrashing and kicking, without an associated change in mental status or post-ictal period may be seen in supplementary motor seizures of the frontal lobe.[188] Interestingly, both self-injury and urinary incontinence occur in psychogenic seizures and are not helpful in differentiating them from neurogenic events.[189]

Maneuvers: While some cases of psychogenic seizures may be nearly impossible to diagnose in the ED, other cases may be uncovered with simple maneuvers. The simplest involves non-noxious sensory stimulation, such as placing a cotton swab in the nose, passive eye opening, dropping the patient's arm over their face, or corneal stimulation. These simple tests may result in avoidance (the patient's hand never hitting their face) or resistance (forceful eye closing) from a patient having a psychogenic seizure. In one study, 18 out of 18 patients with confirmed psychogenic seizures tested positive to avoidance maneuvers.[190] The geotrophic eye test is performed by turning the patient's head from side to side and observing the eyes: the patient will look away from the examiner, regardless of which way the head is turned.[191] Noxious stimulation, such as a sternal rub, firm pressure on a digit, or an anhydrous ammonia capsule under the patient's nose, may also terminate psychogenic seizures.[192] Patients with psychogenic seizures may terminate in response to verbal suggestion.[193] Many cases do not reveal themselves even with maneuvers, and ultimately require video-EEG monitoring to confirm the diagnosis. The treatment of psychogenic seizures is based on behavioral therapy aimed at identifying stressors, precipitants, and underlying psychiatric disease.[194]

Pediatric Considerations

There are several seizure types that are seen primarily in pediatrics which include absence and febrile seizures. Most patients with epilepsy in childhood are seizure free in adulthood; prognosis depends on the underlying etiology and the response to therapy.[195]

Absence seizures: Primary generalized noncon-

vulsive seizures, also called petit mal or absence seizures, are typically characterized by a sudden onset of unresponsiveness that is not preceded by an aura or succeeded by a postictal period. Absence seizures account for approximately 15% of all cases of childhood epilepsy.[196] They are seen primarily in the young, usually beginning between the ages of 5 and 10 years, and are rare after the mid-teens. The average duration of an absence event is 10 seconds.[197] Atypical absence seizures are events that last longer, have more complex automatisms or associated motor activity, and often have a postictal period. Patients are often not cognizant that the seizure has occurred. These events are the result of bihemispheric neuronal discharges that usually last less than 20 seconds. Though altered consciousness is the hallmark of absence events, at times, absence seizures are associated with clonic motor activity, especially of the eyelids, with automatisms, or with mild motor activity. Diagnosis is made by EEG. The ictal EEG in absence seizures is classically a 3-Hz spike-wave discharge. Absence seizures are, by definition, a generalized process, and the discharge is bilateral without an area of focus. The EEG in atypical absence seizures is less characteristic and can be irregular, with bilateral spike and slow waves. Treatment of choice is ethosuximide unless the child also has motor seizures, in which case valproic acid is recommended.

Febrile Seizures

The major challenge of an emergency physician when presented with a febrile seizure is differentiating simple from complex febrile seizure. By definition, a simple febrile seizure lasts less than 15 minutes, is non-focal, does not have a prolonged postictal period and occurs in a child between six months and five years of age.[198]

Two to four percent of all children will have a simple febrile seizure.[199] Children who have had a febrile seizure have a 25 to 50% chance of having a second event, usually within a year. Children at highest risk for recurrence are those with a first degree relative who has had a febrile seizure, complex first febrile seizure, or age younger that one year when the first event occurred. There is an increased incidence of developing epilepsy in children who have had a simple febrile seizure (2.4% versus a .4% incidence in the general population).[200] Ten to 50% of cases of status epilepticus in children are associated with febrile seizures; status in this group is a consistent predictor of increased risk for subsequent seizures.[201]

Simple febrile seizures are a benign process. When they occur in children older than 18 months who have not been on antibiotics, they do not require any particular diagnostic work-up, even for a first time event.[204] Management focuses on a careful history and physical, and on parental education.

Patients with simple febrile seizures require no special workup or treatment. Reassuring the parents is often the most Herculean task. Nearly half of parents think that their child is dying during the seizure.[202] Such concerns need to be addressed; simply suggesting the child be discharged on acetaminophen is not appropriate.

Children with febrile seizures have no greater

Table 6: Clinical And Historical Features Suggesting A Diagnosis Of Psychogenic Nonepileptic Seizures

Clinical Features
Ability of observer to modify the patient's motor activity
Asynchronous limb movements
Avoidance behavior during seizures
Change in symptomatology, or nonstereotypical seizure patterns
Closed eyes during seizures
Dystonic posturing (including opisthotonos)
Emotional or situational trigger for the seizures
Gradual onset and cessation of seizures
Ictal crying, weeping
If tongue biting is present, usually the tip (not the side) of the tongue
Intermittent or waxing and waning motor activity
Nonphysiologic progression
Pelvic movements (especially forward thrusting)
Prolonged seizures (duration of two to three minutes)
Resisted eyelid opening
Seizures provoked by suggestion
Side-to-side head movements

Historical Features
Associated (often multiple) psychiatric disorders
Flurries of seizures or recurrent pseudo-status epilepticus that lead to multiple emergency department visits or hospitalizations
High seizure frequency
History of sexual or physical abuse
Lack of concern or an excessive or exaggerated emotional response
Multiple unexplained physical symptoms
No history of injury from seizures
No response to antiepileptic drugs or a paradoxical increase in seizures with antiepileptic drug treatment
Personal, family, or professional experience with epilepsy
Seizures that occur only in the presence of others or only when the patient is alone

Adapted from: Alsaadi TM, Marquez AV. Psychogenic nonepileptic seizures. Am Fam Physician. 2005 Sep 1;72(5):849-56.

incidence of bacteremia than febrile children who do not seize.[203] Therefore, management should be guided by general fever protocols. If the child has a source of infection, simply treat it. Electrolytes, calcium, phosphorous, magnesium, blood sugar, CBC, or neuroimaging are not routinely necessary in patients with simple febrile seizures. If the child with an obvious source of infection appears toxic or has a stiff neck, a lumbar puncture must be considered. As many as one third of children with bacterial meningitis have a concurrent infection, such as pneumonia, otitis media, or orbital cellulitis.[204] Patients who experience a complex febrile seizure should get a complete diagnostic work-up, including LP, looking for underlying precipitating etiologies.

While there are some studies that show that AED therapy for simple febrile seizures reduces recurrance,[205] since simple febrile seizures are a benign entity, the risks of AEDs make preventive therapy unwarranted.[206]

Non-Febrile Seizures

The evaluation of non-febrile seizures, complex seizures, and febrile seizure outside of the usual age group, in essence, parallels the discussion presented on adults in the preceding sections. If the seizure was exertional, consider the possibility of convulsive syncope secondary to a cardiac arrhythmia. In children, this could be due to a prolonged QT syndrome or hypertrophic cardiomyopathy. During the evaluation, be attentive to the stigmata of the phakomatoses (hereditary disease characterized by tumors in multiple tissues) such café au lait spots (tuberous sclerosis) or fleshy bumps (neurofibromatosis). Both of these may result in seizures secondary to CNS tumors. Checking a bedside glucose is especially important in children of all ages, while hyponatremia is a more frequent cause of seizures in infants than in other age groups.[207] A toxicology screen for drugs of abuse may be valuable when cocaine could be the culprit.[208]

Status Epilepticus In Children

The treatment of status seizures in children is similar to that of adults. Interosseous access is an alternative when intravenous access is not secured. While rectal diazepam has long been used as an alternative to parenteral administration in children, buccal midazolam may be equally effective (and more palatable).[209][210] Intranasal midazolam (0.2 mg/kg) has been reported to have equal efficacy with IV diazepam (0.3 mg/kg) for prolonged febrile seizures.[211]

Both phenytoin and phenobarbital are often effective in pediatric status if a bolus administration of a benzodiazepine fails. However, as in adults, continuous infusion of benzodiazepines have been reported as successful. Infection has been reported as a more common cause of status in children than in adults.[10] Therefore, many physicians will empirically cover such children with broad-spectrum antibiotics, usually ceftriaxone (or the combination of ceftriaxone and amoxicillin in neonates). The routine use of empiric acyclovir to treat presumed herpes encephalitis in the neonate remains unstudied.

Controversies And Cutting Edge

Neuroimaging In Patients With Alcohol Related Seizures

The term alcohol related seizure refers to either seizure due to alcohol intoxication or its withdrawal. The diagnosis should be made only after work up for other causes of the seizure have been exhausted as this group of patients is more prone to traumatic abnormalities. A 1988 Denver study reported head CT results in 259 patients with a first alcohol-related convulsion. A "clinically significant" lesion was found in 16 (6.2%) patients, seven of whom were alert and had non-focal neurological exams and no history of trauma. Nearly 4% of patients had CT findings that changed clinical management (e.g., subdural hematoma, aneurysm, subarachnoid hemorrhage, and neurocysticercosis). In these patients, the history and physical examination did not predict the CT abnormality. This study emphasizes the importance of avoiding labeling an alcoholic with a first time seizure as having an alcohol withdrawal seizure; it also emphasizes that alcohol is a co-morbidity that drives the need for ED neuroimaging.[212]

Neuroimaging In Patients With Cocaine Related Seizures

There is one study that suggests that patients who experience a new onset cocaine-related generalized seizure do not require neuroimaging, as long as they do not have a severe headache, recover promptly, and have a normal postictal examination.[213] This study only included 35 patients who had both a cocaine related seizure and a head CT and was not part of the formal derivation of a decision rule. In general, cocaine users are at a significantly increased risk of intracranial hemorrhage, as well as trauma

and other risk factors; therefore, care must be applied when applying this evidence to clinical practice.

EEG In The ED

An EEG is used to help stratify patients regarding risk of seizure recurrence; thus, it is an important test in deciding who needs to be started on an AED. In addition, as discussed above, the EEG helps to identify those patients who are in nonconvulsive status epilepticus. The controversy is when and where an EEG needs to be done; the corollary is, what is the impact of delay in making an EEG based diagnosis? A survey of medical directors in accredited North American EEG laboratories revealed that a majority of facilities required neurologic consultation or other specialized consultation before emergent EEG could be obtained. Furthermore, though many labs claimed to provide "emergent" EEG, there was an average response time of approximately three hours from the time the test was requested, with a range up to 24 hours.[214] A multicenter survey revealed that EEG was rarely performed in EDs.[7]

EEG interpretation is also a specialized field within the specialty of neurology, so it is reasonable to get an EEG only when there is someone available to interpret it. This, along with the generally limited availability of EEG in the ED, makes it reasonable to obtain a neurological consultation prior to considering obtaining an EEG. As of yet, there is no clear recommendation for ordering an EEG in the ED, and its use will be heavily dependent on local practice patterns and technical availability of personnel and equipment. The ACEP Clinical Policy only states that the EEG be "considered" for suspected NCSE and subtle SE, as well as in those patients who have received a long-acting paralytic or are in pharmacological coma.

New Anti-epileptic Drugs

Table 7: The New Generation Anti-Epileptic Drugs

Felbamate (Felbatol®): Approved in 1993 for the adjunctive treatment of partial seizures in adults and Lennox-Gastaut syndrome in children and adults; mechanism of action is not known. The postulated mechanism of action is due to NMDA receptor interaction. Concurrent administration increases serum concentrations of phenytoin, phenobarbital, and valproic acid, and will decrease serum concentrations of carbamazepine. It is associated with aplastic anemia and hepatic failure – currently, use is restricted.

Gabapentin (Neurontin®): Mechanism of action thought to be related to GABA agonist and binding to specific voltage-sensitive calcium channels. Used as an adjunct or partial seizures with or without secondary generalization. It is not metabolized and is excreted unchanged by the kidneys. Adverse reactions are generally mild. It is devoid of any significant drug interactions.

Levetiracetam (Keppra®): Levetiracetam was approved in 1999 for the treatment of partial seizures with or without secondary generalization. Its precise mechanism of action is unknown. It is renally excreted and has no known clinically significant drug interactions; it has mild adverse effects.

Topiramate (Topiramax®): Approved for refractory partial seizures in adults. It enhances the inhibitor effect of GABA, blocks sodium channels, and antagonizes kainate/AMPA receptor subtype of the glutamate receptor. Adverse reactions are generally mild. Topiramate may reduce the effectivenss of oral contraceptives, increase phenytoin concentrations, and decrease serum digoxin and valproic acid concentrations.

Tiagabine (Gabitril®): Approved for partial seizures. Inhibits the reuptake of GABA by binding to recognition sites associated with the GABA uptake carrier. Adverse reactions are generally mild. It does not appear to affect the serum concentrations of other drugs.

Zonisamide (Zonegran®): Adjunct treatment for partial seizures in adults. Mechanism of action is thought to involve the blockade of sodium and T-type calcium channels. Acute psychosis reported in 2% of patients. Other side effects include decreased sweating, hyperthermia, and renal calculi. It may affect phenytoin and carbamazepine levels.

Lamotrigine (Lamictal®): Adjunct treatment for refractory partial seizures and Lennox-Gastaut syndrome. Mechanism of action may involve the inhibition of glutamate release by inhibition of voltage-sensitive sodium channels. Lamotrigine carries an FDA black box warning for the development of life-threatening rashes. The risk is increased with concomitant administration of valproic acid. The metabolism of lamotrigine is enhanced by carbamazepine, phenobarbital, and phenytoin and reduced by valproic acid.

Oxcarbazepine (Trileptal®): Approved for monotherapy and adjunct therapy for patients with partial seizures. Mechanism of action similar to carbamazepine through GABA receptors but less induction of hepatic enzymes. May cause a dose-related hyponatremia.

A number of new AEDs have been added to the armamentarium available for managing seizures. In the majority of cases, the decision to use these medications should be made in conjunction with the physician who will assume care for the patient. The advantage of these drugs are that, in general, they have a better safety profile than the traditional AEDs, phenytoin, carbamazepine, Phenobarbital, ethosuximide, and valproic acid. The disadvantage is that they tend to be significantly more expensive. **Table 7** lists some of the new AEDs; note that some are not protein bound and are renally excreted, making them preferred agents in patients who have liver disease and/or are on other drugs that are protein bound. Of the new AEDs, only levotiracetam has an intravenous formulation (not yet FDA approved) which may have benefit when rapid loading is required; however, there are no studies at this time supporting its use in status epilepticus.

Disposition

Disposition from the ED must take into consideration the patient's social situation, resources, and compliance. Patients are not ready for discharge until they have returned to their baseline mental status. Patients who have had a first time seizure but have a completely normal neurologic exam and no underlying medical problems do not usually require admission, especially if good follow-up can be provided. Known seizure patients with low AED levels are usually safe for discharge home once they have been loaded with their AED. Those with adequate AED levels and breakthrough seizures are usually safe for discharge after discussion with their physician or neurologist and a period of observation from four to six hours.

All patients who have had a seizure must be advised not to drive and to avoid placing themselves or others in potentially dangerous situations until assessed by their physician. All states have laws regulating driving and epilepsy though only six states have mandatory reporting requirements.[215]

If possible, family members should be instructed how to handle the patient if another seizure occurs. Emphasis should be on safe positioning; the myth of forcing an object, such as a spoon, into the patient's mouth to keep them from "swallowing their tongue" should be explicitily addressed since such action may result in more harm than good.

Case Conclusion

The 24-year-old student seized for 35 minutes. Fortunately, the status terminated after 10 mg of lorazepam and 1800 mg of phenytoin; in preparation for refractory status, a propofol infusion was set up. A CT of his head showed a previously undiagnosed glioblastoma and the patient was admitted to the Neurosurgery Service.

Regarding the question whether you would have been negligent had the patient been sent home for an out patient work-up, the literature and ACEP's Clinical Policy on Seizures would have supported this strategy and would not support initiating AED therapy.[48] Predicting seizure recurrence is based on the patient's age, history, and physical exam, and findings on neuroimaging and EEG. His age and normal physical exam predicted a low risk of recurrence; the ACEP Clinical Policy and the ACEP/AAN Practice Guideline on Neuroimaging after first time seizures would also support an outpatient evaluation (with the caveat that one could be arranged).[67] In this patient's case, sleep deprivation and stimulant use most likely uncovered his seizure focus; had he been sent home, a well documented neurologic exam, clinical decision making, and discharge instructions would be critical to any medico-legal defense of your care.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study, will be included in bold type following the reference, where available.

1. Working Group on Status Epilepticus: Treatment of convulsive status epilepticus: Recommendations of the Epilepsy Foundations of America's Working Group on Status Epilepticus. JAMA 1993;270:854-9.
2. Lowenstein DH, Bleck, T, Macdonald RL. It's time to revise the definition of status epilepticus. Epilepsia, 1999; 40:120-122.
3. Alldredge BK, Gelb AM, Isaacs M ea: A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. N Engl J Med 2001;345:631-637.
4. Treiman DM, Meyers PD, Walton NY, et al. for the Veterans Affairs Status Epilepticus Cooperative Study Group. A comparison of four treatments for generalized convulsive status epilepticus. NEJM 1998;339:792-8.
5. Shinnar S, Berg AT, Moshe SL, Shinnar R. How long do new-onset seizures in children last? Ann Neurol 2001;49:659-664.
6. Krumholz A, Grufferman S, Orr S, Stern B, Seizures and seizure care in an emergency department, Epilepsia 1989; 30:175-181. Retrospective review over 6 months. 200 cases / 29,000 ED visits
7. Huff JS, Morris DL, Kothari RU et al., Emergency department

7. management of patients with seizures: a multicenter study. Medical Interface. Acad Emerg Med 8 (2001), pp. 622–628.

8. Hauser WA and Kurland LT, The epidemiology of epilepsy in Rochester, Minnesota, 1935 through 1967. Epilepsia 16 (1975), pp. 1–66

9. McCaig, LF and Burt CW, "National Hospital Ambulatory Medical Care Survey: 2001 Emergency Department Summary: 2001,"Advance Data From Vital and Health Statistics; No. 335,: National Center for Health Statistics, Hyattsville, Md. (2003); U.S. General Accounting Office, Hospital Emergency Departments: Crowded Conditions Vary Among Hospitals and Communities (GAO-03-460), Washington, D.C. (March 2003).

10. DeLorenzo RJ, Towne AR, Pellock JM et al., Status epilepticus in children, adults, and the elderly. Epilepsia 33 Suppl 4 (1992), pp. S15–25.

11. Coeytaux A, Jallon P, Galobardes B, et al. Incidence of status epilepticus in French-speaking Switzerland (EPISTAR). Neurology 2000;55:693-7.

12. DeLorenzo RJ, Hauser WA, Towne AR, et al. A prospective, population based epidemiologic study of status epilepticus in Richmond, Virginia. Neurology 1996;46:1029-35

13. Semah F, Picot M, Adam C, et al. Is the underlying cause of epilepsy a major prognostic factor for recurrence. Neurology 1998; 51: 1256-1262. Cross sectional, observational hospital based study. 2200 patients

14. Hauser W, The natural history of drug resistant epilepsy: epidemiologic considerations. Epilespia 1992; suppl 5:25-28. Review

15. Hauser W, Rich S, Annegers J, Anderson E. Seizure recurrence after a first unprovoked seizure: An extended follow-up. Neurology 1990; 40:1163-1170. Prospective cohort. 208 patients

16. Wu YW, Shek DW, Garcia PA, Zhao S, Johnston SC. Incidence and mortality of generalized convulsive status epilepticus in California. Neurology 2002;58:1070-1-76.

17. Delorenzo R, Lacrix J, Gauthier D. Admissions to a pediatric intensive care unit for status epilepticus: A 10-year experience. Crit Care Med 1994; 22:827-832. Retrospective descriptive study. 147 patients

18. Knake S, Rosenow, F, Vescovi M, et al. Incidence if Status Epilepticus in Adults in Germany: A Prospective, Population-Based Study, Epilepsia 2001;42:714-8.

19. Vignatelli L, Caterina T, D'Alessandro R, Incidence and Short-term Prognosis of Status Epilepticus in Adults in Bologna, Italy, Epilepsia 2003;44:964-68.

20. Hesdorffer DC, Logroscino G, Cascino G, Annegers JF, Hauser WA. Incidence of status epilepticus in Rochester, Minnesota, 1965–1984. Neurology 1998; 50: 735–741.

21. Logroscino G, Hesdorffer DC, Cascino GD, et al. Long-term mortality after a first episode of status epilepticus. Neurology, 2002;58:537-41.

22. Lowenstein DH, Aldredge BK, Status Epilepticus, New Engl J Med 1998;338:970-6.

23. Jagoda A, Riggio S, Refractory status epilepticus in adults. Ann Emerg Med, 1993;22:1337-48.

24. Walton NY, Treiman DM. Response of status epilepticus induced by lithium and pilocarpine to treatment with diazepam. Exo Neurol 7998;101:267-75.

25. Lowenstein DH, Alldredge BK. Status epilepticus in an urban hospital in the 1980s. Neurology 1993;43:483-8.

26. Wachtel T, Steele G, Day J. Natural history of fever following seizure. Arch Intern Med. 1987; 147:1153-1155. Retrospective. 93 patients.

27. Aminoff M, Simon R. Status epilepticus: causes, clinical features and consequences in 98 patients. Am J Med 1980; 69:657-666.

28. Orringer C, Eustace J, Wunsch C, et al, Natural history of lactic acidosis after grand-mal seizures. New Engl J Med 1977; 297:796-799. Prospective convenience sample. 8 patients)

29. Dodrill C, Wilensky A. Intellectual impairment as an outcome of status epilepticus. Neurology 1990; 40 (suppl 2): 23-27. Prospective study. 143 adults

30. Lothman E. The biochemical basis and pathophysiology of status epilepticus. Neurology 1990; 40 (suppl 2):13-23. Review)

31. Lin J. Convulsive syncope in blood donors. Ann Neurol 1982; 11:525-528. Prospective cohort. 84 patients

32. Linzer M, Grubb B, Simon H, Ramakrishnan L, Bromfield E, Estes N. Cardiovascular causes of loss of consciousness in patients with presumed epilepsy: a cause of increased sudden death rate in people with epilepsy. Am J Med 1994; 96:146-154. Case series. 12 patients

33. Bell MR. Kozak RJ. Seizures and the long-QT syndrome. Annals of Emergency Medicine. 28:556-60, 1996

34. Haines S. Decerebrate posturing misinterpreted as seizure activity, Am J Emerg Med 1988; 6:173-177. Case series, 4 patients

35. McCrory PR. Berkovic SF. Video analysis of acute motor and convulsive manifestations in sport-related concussion. Neurology. 54:1488-91, 2000. Retrospective analysis of a prospective cohort. 234 cases.

36. Marks D, Ehrenberg B. Migraine related seizures in adults with epilepsy with EEG correlation. Neurology 1993; 43:2476-2483. Prospective cohort. 395 patients

37. Dieckmann R. Rectal diazepam for prehospital pediatric status epilepticus. Ann Emerg Med 1994; 23:216-224. Retrospective review. 31 patients

38. Alldredge B, Wall D, Ferriero D. Effect of prehospital treatment on the outcome of status epilepticus in children. Pediatr Neurol 1995; 12:213-216. Retrospective review. 45 patients,

39. McArthur CL 3rd. Rooke CT. Are spinal precautions necessary in all seizure patients?. Am J Emerg Med 1995; 13:512-3. Retrospective. 1656 patients

40. Abarbanell N. Prehospital seizure management: Triage criteria for the advanced life support rescue team. Am J Emerg Med 1993; 11:210-214. Retrospective. 230 patients.

41. Shandera WX. White AC Jr. Chen JC. Diaz P. Armstrong R. Neurocysticercosis in Houston, Texas. A report of 112 cases. Medicine. 73:37-52, 1994. Case series

42. Kanu I, Anyanwu EC, Nwachukwu NC, Ehiri JE, Merrick J. Clinical microbiological aspects of epileptic seizures in the tropical countries with specific focus on Nigeria. Scientific World Journal. 2005 May 13;5:401-9.

43. Pear B. Bilateral posterior fracture dislocation of the shoulder: An uncommon complication of a convulsive seizure. New Engl J Med 1970; 283:135-136. Case report.

44. Finelli P, Cardi J. Seizures as a cause of fracture. Neurology 1989; 39:858-860. Retrospective. 2800 patients. McCullen G, Brown C. Seizure-induced thoracic burst fractures: A case report. Spine 1994; 19:77-79. Case report and review

45. Eisner RF, Turnbull TL, Howes DS, Gold IW. Efficacy of a "standard" seizure workup in the emergency department. Ann Emerg Med. 1986; 15:33-39.

46. Powers RD. Serum chemistry abnormalities in adult patients with seizures. Ann Emerg Med. 1985;14:416-420. Retrospective review. 181 patients

47. Turnbull TL, Vandenhoek TL, Howes DS, Eisner RF. Utility of laboratory studies in the emergency department patient with a new-onset seizure. Ann Emerg Med. 1990;19:373-7.

48. American College of Emergency Physicians. Clinical Policy: Critical Issues in the evaluation and managementof adult patients presenting to the emergency department with seizures. Ann Emerg Med. 2004;43(5):605-625.

49. Sempere AP, Villaverde FJ, Martinez-Menendez B, et al. First seizure in adults: a prospective study from the emergency department. Acta Neurol Scand. 1992;86:134-8.

50. Tardy B, Lafond P, Convers P. Adult first generalized seizure: etiology, biological tests, EEG, CT scan, in an ED. Amer J Emerg Med. 1995; 13:1-5. Retrospective review. 247 patients.

51. Knight AH, Rhind EG. Epilepsy and pregnancy: a study of 153 pregnancies in 59 patients. Epilepsia. 1975;16:99-110.

52. American Academy of Neurology. Practice parameter: Evaluating a first nonfebrile seizure in children. Neurol. 2000;55:616-623.

53. Olson KR. Seizures associated with poisoning and drug overdose. Amer J Emerg Med. 1994;12:392-395.

54. Dhuna A, Pascual-Leone A, Langendorf F, et al. Epileptogenic properties of cocaine in humans. Neurotoxicology. 1991;12:621-626.

55. Pesola GR. Westfal RE. New-onset generalized seizures in patients with AIDS presenting to an emergency department. Acad Emerg Med. 1998;5:905-911.

56. Ng S, Hauser W, Brust J, et al. Alcohol consumption and withdrawal in new-onset seizures. N Engl J Med. 1988;319:666-673.

57. Libman MD. Potvin L. Coupal L. Grover SA. Seizure vs. syncope: Measuring serum creatine kinase in the emergency department. J Gen Int Med 1991; 6:408-12, 1991

58. Wyllie E, Lueders H, Pippenger C, VanLente F. Postictal serum creatine kinase in the diagnosis of seizure disorders. Arch Neurol 1985; 42:123-126. 189 events

59. Boehnert M, Lovejoy F. Value of the QRS duration versus the serum drug level in predicting seizures and ventricular arrhythmias after an acute overdose of tricyclic antidepressants. New Engl J Med 1985; 313:474-479. Prospective cohort. 49 patients

60. Wolfe T, Caravan E, Rollins D. Terminal 40-ms frontal plane QRS axis as a marker for tricyclic antidepressant overdose. Ann Emerg Med 1989; 18:348-351. Retrospective cohort. 48 patients

61. Henneman P, DeRoos F, Lewis R. Determining the need for admission in patients with new-onset seizures. Ann Emerg Med 1994; 24:1108-1114. Retrospective. 294 patients

62. American College of Emergency Physicians, American Academy of Neurology, American Association of Neurological Surgeons, American Society of Neuroradiology. Practice Parameter: Neuro-imaging in the emergency patient presenting with seizure (Summary Statement). Ann Emerg Med 1996; 27:114-118. Evidence based practice guideline).

63. Lee ST, Lui TN. Early seizures after mild closed head injury. J Neurosurg. 1992;76:435-439.

64. Green SM, Rothrock SG, Clem KJ, et al. Can seizures be the sole manifestation of meningitis in febrile children? Pediatrics. 1993;92:527-34.

65. Rosenberg NM. Seizures associated with meningitis. Pediatr Emerg Care. 1992;8:67-9.

66. Rider L, Thapa P, Del Beccaro M, et al. Cerebrospinal fluid analysis in children with seizures. Ped Emerg Care 1995; 11:226-229. Prospective convenience sample. 212 patients

67. Kaplan PW. Nonconvulsive status epilepticus in the emergency room. Epilepsia 37 (1996), pp. 643–650.

68. Guberman A, Cantu-Reyna G, Stuss D et al., Nonconvulsive generalized status epilepticus: clinical features, neuropsychological testing, and long-term follow-up. Neurology 36 (1986), pp. 1284–1291.

69. Towne AR, Waterhouse EJ, Boggs JG, Garnett LK, Brown AJ, Smith JR Jr, DeLorenzo RJ. Prevalence of nonconvuslive status epilepticus in comatose patients. Neurology 2000;54:340-345.

70. DeLorenzo RJ, Waterhouse EJ, Towne AR, Boggs JG, Ko D, DeLorenzo GA, Brown A, Garnett L. Persistent nonconvulsive status epilepticus after the control of generalized convulsive status epilepticus. Epilepsia 1998;39:833-840.

71. Young GB, Jordan KG and Doig GS, An assessment of nonconvulsive seizures in the intensive care unit using continuous EEG monitoring: an investigation of variables associated with mortality. Neurology 47 (1996), pp. 83–89.

72. Annegers JF, Shirts SB, Hauser WA, Kurland LT. Risk of recurrence after an initial unprovoked seizure. Epilepsia. 1986; 27:43-50.

73. Berg AT, Shinnar S. The risk of seizure recurrence following a first unprovoked seizure: a quantitative review. Neurology. 1991;41:965-972.

74. First Seizure Trial Group (FIR.S.T. Group). Randomized clinical trial on the efficacy of antiepileptic drugs in reducing the risk of relapse after a first unprovoked tonic-clonic seizure. Neurology. 1993;43:478-483.

75. Temkin NR, Dikman SS, Wilensky AJ, et al. A randomized, double blind study of phenytoin for the prevention of post-traumatic seizures. New Engl J Med. 1990; 323:497-502.

76. French J. The long-term therapeutic management of epilepsy. Ann Int Med 1994; 120:411-422. Review

77. Brown T, Pincus J. Phenytoin (Dilantin) and other hydantoins. In: Brown T, Feldman R, (eds), Epilepsy. Little, Brown, and Co. Boston. 1983; 175-189. Review

78. Osborn H, Zisfein J, Sparano R. Single dose oral phenytoin loading. Ann Emerg Med 1987; 16:407-412. Convenience cohort. 51 patients

79. Ratanakorn D, Kaojarern S, Phuapradit P, Mokkhavesa C.

80. Single oral loading dose of phenytoin: a pharmacokinetic study. J Neurological Sci 1997; 147:89-92. Prospective, two groups: 19 volunteers, 14 seizure patients

80. Mayden C, Kruger A, Muller F, et al. Acute oral loading of carbamazepine-CR and phenytoin in a double blind randomized study of patients at risk of seizures. Epilepsia 1994; 35:189-193. Double blind. 48 adults

81. Simon RP: Physiologic consequences of status epilepticus. Epilepsia. 1985;26(Suppl 1):S58-S66.

82. Boggs JG, Marmarou A, Agnew JP, Morton LD, Towne AR, et al: Hemodynamic monitoring prior to and at time of death in status epilepticus. Epilepsy Res. 1998;31:199-209.

83. Meldrum B, Vigouroux R, Brierley J. Systemic factors and epileptic brain damage. Arch Neurol 1973; 29:82-87. Animal study. 8 baboons

84. Privitera MD, Strawsurg RH. Electroencephalographic monitoring in the emergency department. Emergency Medical Clinics NA 1994;12:1089-1101.

85. Leppik IE, Derivan AT, Homan RW, et al. Double-blind study of lorazepam and diazepam in status epilepticus. JAMA 1983;249:1452-4.

86. Treiman D, Pharmacokinetics and clinical use of benzodiazepines in the management of status epilepticus. Epilepsia 1989; 30:4-10. Review 47 studies; 1455 patients

87. Prasad K, Al-Roomi K, Krishnan PR, Sequeira R. Anticonvulsant therapy for status epilepticus. The Cochrane Database of Systematic Reviews 2005, Issue 4. Art. No.: CD003723. DOI: 10.1002/14651858.CD003723.pub2.

88. McCormick EM, Lieh-lai M, Knazik S, Negro M. A prospective comparison of midazolam and lorazepam in the initial treatment of status epilepticus in the pediatric patient. Epilepsia 1999;40(7):160.

89. Singhi S, Murthy A, Singhi P, Jayashree M. Continuous midazolam versus diazepam infusion for refractory convulsive status epilepticus. Journal of Child Neurology 2002;17:106-10.

90. Dreifuss FE. Rosman NP. Cloyd JC, et al. A comparison of rectal diazepam gel and placebo for acute repetitive seizures. N Engl J Med 1998; 338:1869-75. Randomized Controlled Trial. 125 children

91. Pellock JM, Mitchell WG, Cloyd JC. Diastat (diazepam rectal gel) in the treatment of acute repetitive seizures in adults. Epilepsia 1998;39(6):126.

92. Manno EM, New management strategies in the treatment of status epilepticus, Mayo Clin Proc. 2003;78:508-18

93. Donovan P. Phenytoin administration by constant intravenous infusion: Selective rates of administration. Ann Emerg Med 1991; 20:139-142.

94. Earnest M, Marx J, Drury L. Complications of intravenous phenytoin for acute treatment of seizures. JAMA 1983; 249:762-765.

95. Browne T. The pharmacokinetics of agents used to treat status epilepticus. Neurology 1990;40:28-32.

96. Osorio I, Reed R, Treatment of refractory generalized tonic clonic status epilepticus with pentobarbital anesthesia after high dose phenytoin. Epilepsia 1989; 30:464-471. Case series. 13 patients).

97. Kilarski DJ, Buchanan C, Von Behren L. Soft-tissue damage associated with intravenous phenytoin. N Engl J Med 1984;3111:1186-7

98. O'Brien TJ, Cascino GD, So EL, Hanna DR. Incidence and clinical consequence of the purple glove syndrome in patients receiving intravenous phenytoin therapy. Neurology 1998;51:1034-9

99. Burneo JG, Anandan JV, Brakley GL. A prospective study of the incidence of the purple glove syndrome. Epilepsia 2001;42:1156-9

100. Gellerman GL, Martinez C: Fatal ventricular fibrillation following intravenous sodium diphenylhydantoin therapy. JAMA 1967; 200:161-2. Case Report.

101. Unger AH, Sklaroff HJ: Fatalities following intravenous use of sodium diphenylhydantoin for cardiac arrhythmias. JAMA 1967; 200:159-160. Case Report.

102. Zoneraich S, Zoneraich O, Siegel J: Sudden death following intravenous sodium diphenylhydantoin. Am Heart J 1976; 91:375-7. Case report.

103. Wilder BJ (ed). The use of parental antiepileptic drugs and

the role for Fosphenytoin. Neurology 1996; 46:S1-S28. Review

104. Appleton RE, Sweeney A, Choonara I, Robson J, Molyneux E. Lorazepam versus diazepam in the acute treatment of epileptic seizures and status epilepticus. Develpmental Medicine and Child Neurology 1995;37

105. Chamberlain JM, Altieri MA, Futterman C et al.. A prospective, randomized study comparing intramuscular midazolam with intravenous diazepam for the treatment of seizures in children. Pediatr Emerg Care 1997;13:92-4.

106. Towne AR, DeLorenzo RJ. Use of intramuscular midazolam for status epilepticus. J Emerg Med. 1999;17:323-8

107. Fischer JH, Patel TV, Fischer PA. Fosphenytoin: clinical pharmacokinetics and comparative advantages in the acute treatment of seizures. Clin Pharmacokinet 2003;42:33-58.

108. Leppik I, Boucher R, Wilder B, et al. Phenytoin pro-drug: Preclinical and clinical studies. Epilepsia 1989 (suppl 2); 30:S22-S26. Open label non-blinded. 25 volunteers

109. Browne TR, Kugler AR, Eldon MA. Pharmacology and pharmacokinetics of fosphenytoin. Neurology 1996;46(6 Suppl 1):S3-S7

110. Devinsky O, Leppik I, Willmore LJ, et al. Safety of intravenous valproate. Ann Neurol. 1995;38:670-4

111. Giroud M, Gras D, Escousse A, Dumas R, Venaud G. Use of injectable valproic acid in status epilepticus. Drug Investigation 1993;5:154-159. (23 patients)

112. Hovinga CA, Chicella MF, Rose DF, Eades SK, Dalton JT, Phelps SJ. Use of intravenous valproate in three pediatric patients with nonconvulsive or convulsive status epilepticus. Ann Pharmacother. 1999;33:579-584

113. Venkataraman V, Wheless JW. Safety of rapid intravenous infusion of valproate loading doses in epilepsy patients. Epilepsy Res 1999;35:147-153.

114. Limdi NA, Faught E: The safety of rapid valproic acid infusion. Epilepsia 2000;41:1342-1345.

115. Sinha S, Naritoku DK: Intravenous valproate is well tolerated in unstable patients with status epilepticus. Neurology 2000;55:722-724.

116. Naritoku DK. Mueed S. Intravenous loading of valproate for epilepsy. Clinical Neuropharm 1999; 22:102-6. Review

117. Raskind JY, El-Chaar GM. The role of carnitine supplementation during valproic acid therapy. Ann Pharmacother 2000;34:630-638.

118. Powell-Jackson PR, Tredger JM, Williams K. Hepatotoxicity to sodium valproate: a review. Gut 1984;25:673-687.

119. Shaner DM, McCurdy SA, Herring MO, Gabor AJ. Treatment of status epilepticus: a prospective comparison of diazepam and phenytoin versus phenobarbital and optional phenytoin, Neurology 1988;38:202-7.

120. Marik PE, Varon J. The Management of Status Epilepticus. Chest. 2004;126:582-591.

121. Parent J, Lowenstein D. Treatment of refractory generalized status epilepticus with continuous infusion of midazolam. Neurology 1994; 44:1837-1840. Retrospective case series. 4 patients

122. Kumar A, Bleck TP. Intravenous midazolam for the treatment of refractory status epilepticus. Crit Care Med 1992;20:483-8.

123. Claassen J, Hirsch LJ, Emerson RG, Mayer SA. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. Epilepsia 2002; 43: 146-153.

124. Labar D, Ali A, Root J. High-dose intravenous lorazepam for the treatment of refractory status epilepticus. Neurology 1994; 44:1400-1403. Case series. 9 patients

125. Brown LA, Levin GM. Role of propofol in refractory status epilepticus. Annals of Pharmacotherapy, 1998;32:1053-59.

126. Cannon ML, Glazier SS, Bauman LA. Metabolic acidosis, rhabdomyolysis, and cardiovascular collapse after prolonged propofol infusion. J Neurosurg 2001;95:1053-56.

127. Bray RJ. Propofol infusion syndrome in children. Paediatr Anaesth 1998;8:491-9.

128. Makela JP, Livanainen M, Pieninkeroinen IP. Seizures associated with propofol anesthesia. Epilepsia 1993;34:832-5.

129. Praasad A, Worrall BB, Bertram EH, Bleck TP. Propofol and midazolam in the treatment of Refractory Status Epilepticus. Epilepsia, 2001;42:380-6.

130. Parviainen I, Uusaro a, Kalviainen R, et at. High-dose thiopental in the treatment of refractory status epilepticus in

131. Osorio, Van Ness P. Pentobarbital and EEG burst suppression in treatment of status epilepticus refractory to benzodiazepines and phenytoin. Epilepsia 1990; 31:61-67. Case series. 7 cases

132. Lowenstein D, Aminoff M, Simon R. Barbiturate anesthesia in the treatment of status epilepticus: Clinical experience with 14 patients. Neurology 1988; 38:395-400. Case series. 14 patients

133. Walker L, Slovis C. Lidocaine in the treatment of status epilepticus. Acad Emerg Med 1997; 4:918-922 (evidence based review)

134. Pascual J, Sedano M, Polo J. Intravenous lidocaine for status epilepticus. Epilepsia 1988; 29:584-589 (case series, 8 patients)

135. Lampl Y, Eshel Y, Gilad R, et al. Chloral hydrate in intractable status epilepticus. Ann Emerg Med 1990; 19:674-676 (case series 5 patients)

136. Yeoman P, Hutchinson A, Byrne A, et al. Etomidate infusions for the control of refractory status epilepticus. Intensive Care Med 1989; 15:255-259 (8 patients)

137. Krumholz A, Sung G, Fisher R, et al. Complex partial status epilepticus accompanied by serious morbidity and mortality. Neurology 1995; 45:1499-1504. Case series. 10 patients;

138. Lee S, Nonconvulsive status epilepticus: ictal confusion in later life. Arch Neurol 1985;42:778-781. Case series 11 patients;

139. Ellis J, Lee S. Acute prolonged confusion in later life as an ictal state. Epilepsia 1978;19:119-127. Case series. 6 patients

140. Thompson S, Greenhouse A, Petit mal status in adults. Ann Intern Med 1968;68:1271-1278. Case series. 4 patients;

141. Tomson T, Lindbom U, Nilsson B, Nonconvulsive status epilepticus in adults: thirty-two consecutive patients from a general hospital population. Epilepsia 1992;33:829-835. Case series. 32 patients

142. Thomas P, Beaumanoir A, Genton P, et al, 'De novo' absence status of late onset: report of 11 cases. Neurology 1992;42:104-110. Case series. 11 patients

143. Cascino G, Non-convulsive status epilepticus in adults and children, Epilepsia 1993;34(suppl 1):S21-S28. Review

144. DeGiorgio C, Gott P, Rabinowicz A, et al. Neuron-specific enolase, a marker of acute neuronal injury, is increased in complex partial status epilepticus. Epilepsia 1998; 37:606-609. Prospective cohort. 8 patients

145. Rathlev N, D'Onofrio G, Fish S, et al. The lack of efficacy of phenytoin in the prevention of recurrent alcohol-related seizures. Ann Emerg Med 1994; 23:513-518. Prospective, randomized, double blind study. 147 patients.

146. Schoenenberger RA and Heim SM. Indication for computed tomography of the brain in patients with first uncomplicated generalised seizure. BMJ; 1994 309:986-989

147. Brust JC. Acute neurologic complications of drug and alcohol abuse. Neurologic Clinics; 1998: 16:503-519

148. Lacy JR et al: Brain infarction and hemorrhage in young and middle-aged adults. West J Med 1984:141:329.

149. McMicken D, Freedland E. Alcohol-related seizures: Pathophysiology, differential diagnosis, evaluation, and treatment. Emerg Med Clin No Amer 1994; 12:1057-1080. Review.

150. Sand T, Brathen G, Michler R, et al: Clinical utility of EEG in alcohol-related seizures. Acta Neurol Scand 2002: 105: 18-24.

151. Rathlev N, Ulrich A, Fish S, D'Onofrio G. Clinical characteristics as predictors of recurrent alcohol related seizures. Acad Emerg Med 2000; 7:886-891. Retrospective review. 105 patients)

152. D'Orofrio G, Rathlev N, Ulrich A, et al. Lorazepam for the prevention of recurrent seizures related to alcohol. NEMJ 1999; 340:915-919. Double blind placebo controlled. 229 patients)

153. Chance J. Emergency Department treatment of alcohol withdrawal seizures with phenytoin. Ann Emerg Med 1991; 20:520-522. Prospective, randomized, double blind study. 55 patients).

154. Gospe SM Jr. Pyridoxine-dependent seizures: new genetic and biochemical clues to help with diagnosis and treatment. Curr Opin Neurol. 2006 Apr;19(2):148-53.

155. Miller J, Robinson A, Percy AK. Acute isoniazid poisoning in childhood. Am J Dis Child 1980;134:290-2.

156. Saad SF, el Masry AM, Scott PM. Influence of certain anticonvulsants on the concentration of GABA in the cerebral hemi-

157. Gospe SM Jr, Bell RM. Hospital pharmacy and emergency department availability of parenteral pyridoxine. Pediatr Emerg Care. 2005 Sep;21(9):586-8.

158. Santucci KA. Shah BR. Linakis JG. Acute isoniazid exposures and antidote availability. Pediatr Emerg Care 1999; 15:99-101. Review

159. Kunisaki T, Augenstein L. Drug and toxin induced seizures. Emerg Clin No Amer 1994; 12:1027-1056. Review

160. Rashkin MC, Youngs C, Penovich P. Pentobarbital treatment of refractory status epilepticus. Neurology 1987;37:500-503.

161. Orser BA, Bertlik M, Wang LY, MacDonald JE. Inhibition by propofol (2,6 di-isopropylphenol) of the N-methyl-D-aspartate subtype of glutamate receptor in cultured hippocampal neurones. Br J Pharmacol 1995;116:1761-1768.

162. Annegers J, Hauser W, Coan S, et al. A population-based study of seizures after traumatic brain injuries. NEJM 1998; 338:20-24. Retrospective cohort. 4541 patients, all ages

163. Temkin NR, Haglund MM, Winn HR. Causes, prevention, and treatment of post-traumatic epilepsy. New Horiz. 1995 Aug;3(3):518-22. Review.

164. The EURAP Study Group, Seizure control and treatment in pregnancy: Observations from the EURAP Epilepsy Pregnancy Registry, Neurology 2006;66:356-360.

165. Schmidt D, Janz D, et al. Change of seizure frequency in pregnant epileptic women. J Neurol Neruosurg Psychaitry 1983; 46:751-755.

166. ACOG educational bulletin. Seizure disorders in pregnancy. No. 231, December 1996. Committee on Educational Bulletins of the American College of Obstetricians and Gynecologists. Int J Gynaecol Obstet 1997;56:279-86.

167. Schmidt D, Beck-Mannagetta G, Janz D, Koch S. The effect of pregnancy on the course of epilepsy: a prospective study. In: Janz D, Dam M, Richens A, eds. Epilepsy, pregnancy, and the child. New York: Raven Press, 1982:39-49.

168. Yerby MS, Friel PN, McCormick K, Koerner M, Van Allen M, Leavitt AM, et al. Pharmacokinetics of anticonvulsants in pregnancy: alterations in plasma protein binding. Epilepsy Res 1990;5:223-8.

169. Delgado-Escueta A, Dieter J. Consensus guidelines: Preconception counseling, management, and care of the pregnant woman with epielspy. Neurology 1992;42(suppl 5): 149-160. Consensus

170. Lubarsky SL, Barton JR, Friedman SA, Nasreddine S, Ramaddan MK, Sibai BM. Late postpartum eclampsia revisited. Obstet Gynecol 1994;83:502–5.

171. Chames MC, Livingston JC, Invester TS, Barton JR, Sibai BM. Late postpartum eclampsia: a preventable disease? Am J Obstet Gynecol 2002;186:1174–7.

172. The Eclampsia Trial Collaborative Group. Which anticonvulsant for women with eclampsia? Lancet 1995; 345:1455-1463. Randomized, double blind study. 1680 patients

173. Duley L, Henderson-Smart D. Magnesium sulfate versus phenytoin for eclampsia. (Cochrane Review). In: The Cochrane Library, Issue 3, 2003. Oxford: Update software.

174. National High Blood Pressure Education Program Working Group Report on High Blood Pressure in Pregnancy. Am J Obstet Gynecol. 1990 Nov;163(5 Pt 1):1691-712. Review.

175. Savard G, Andermann F, Teitelbaum J, Lehmann H, Epileptic Munchausen's syndrome: a form of pseudoseizures distinct from hysteria and malingering, Neurology 1988;38:1628-1629. Case report; Krumholz A, Niedermeyer E, Psychogenic seizures: a clinical study with follow-up data, Neurology 1983;33:498-502. Retrospective. 41 patients

176. Howell S, Owen L, Chadwick D, Pseudostatus epilepticus, Quarterly J Med 1989;71:507-519. Review; Leis A, Ross M, Summers A, Psychogenic seizures: ictal characteristics and diagnostic pitfalls, Neurology 1992:42:95-99. Review

177. Levitan M, Bruni J, Repetitive pseudoseizures incorrectly managed as status epilepticus, Can Med Assoc J 1986;134:1029-1031.Case series. 3 patients

178. Reuber M, Elger CE. Psychogenic nonepileptic seizures: review and update. Epilepsy Behav 2003;4:205-16.

179. Leis AA, Ross MA, Summers AK. Psychogenic seizures: ictal characteristics and diagnostic pitfalls. Neurology. 1992 Jan;42(1):95-9.

180. Benbadis SR, Hauser WA. An estimate of the prevalence of psychogenic non-epileptic seizures. Seizure 2000;9:280-1.

181. Gates JR. Epidemiology and classification of non-epileptic events. In: Gates JR, Rowan AJ, eds. Non-epileptic seizures. 2d ed. Boston: Butterworth-Heinemann, 2000:3-14.

182. Benbadis SR, Agrawal V, Tatum WO 4th. How many patients with psychogenic nonepileptic seizures also have epilepsy? Neurology 2001;57:915-7.

183. Scott D, Recognition and diagnostic aspects of non-epileptic seizures, in Riley T, Roy A (eds): Pseudoseizures. Baltimore, Williams and Wilkens Co., 1982. Book chapter

184. Gates J, Ramani V, Whalen S, Loewenson R, Ictal characteristics of pseudoseizures, Arch Neurol 1985;42:1183-1187. Prospective video review. 50 patients

185. Martin R, Burneo JG, Prasad A, Powell T, Faught E, Knowlton R, et al. Frequency of epilepsy in patients with psychogenic seizures monitored by video-EEG. Neurology 2003;61:1791-2.

186. Devinsky O, Gordon E. Epileptic seizures progressing into nonepileptic conversion seizures. Neurology 1998; 51:1293-1296. Case series, 4 patients

187. Alsaadi TM, Thieman C, Shatzel A, Farias S. Video-EEG telemetry can be a crucial tool for neurologists experienced in epilepsy when diagnosing seizure disorders. Seizure 2004;13:32-4.

188. Riggio S, Harner R, Frontal lobe epilepsy, Neuropsych Neuropsychol Behav Neurol 1992;2:283-293. Prospective. 12 patients

189. Peguero E, Abou-Khalil B, Fakhoury T, Mathews G. Self-injury and incontinence in psychogenic seizures. Epilepsia 1995; 36:586-591. Survey. 102 patients

190. Luther J, McNamara J, Carwile S, et al, Pseudoepileptic seizures: methods and video analysis to aid diagnosis, Ann Neurol 1982;12:458-462. Prospective. 18 patients

191. Rosenberry M, The eyes in hysterical states of unconsciousness, J Clin Neuro Ophthalmol 1982;2:259-260. Review

192. Pakalnis A, Drake M, Phillips B, Neuropsychiatric aspects of psychogenic status epilepticus, Neurology 1991;41:1104-1106. Prospective convenience sample. 20 patients

193. Massey E, Riley T, Pseudoseizures: recognition and treatment, Psychsomatics 1980;21:987-997. Review

194. Alsaadi TM, Marquez AV. Psychogenic nonepileptic seizures. Am Fam Physician. 2005 Sep 1;72(5):849-56.

195. Sillanpaa M, Jalava M, Kaleva O, Shinnar S. Long-term prognosis of seizures with onset in childhood. New Eng J Med 1998; 338:1715-1722. Prospective. 220 patients

196. Hauser A. The prevalence and incidence of convulsive disorders in children. Epilepsia 1994; 35(suppl 2):S1-6. Review

197. Penry J, Porter R, Dreifuss F, Simultaneous recording of absence seizures with videotape and electroencephalography: a study of 374 seizures in 48 patients. Brain 1975;98:427-432. Prospective cohort. 48 patients

198. American Academy of Pediatrics. Practice parameter: The neurodiagnostic evaluation of the child with a first simple febrile seizure. Pediatrics 1996; 97:769-775. Evidence based clinical policy

199. Knudsen F. Febrile seizures: Treatment and prognosis. Epilepsia 2000; 41:2-9. Review

200. Annegers J, Hauser A, Shirts S, Kurland L. Factors prognostic of unprovoked seizures after febrile convulsions. New Engl J Med 1987; 316:493-498. Retrospective review of a prospective cohort. 687 patients

201. Maytal J, Shinnar S, Moshe S, Alvarez L. Low morbidity and mortality of status epilepticus in children. Pediatrics 1989; 83:323-331. Retrospective with prospective followup. 97 patients

202. van Stuijvenberg M. de Vos S. Tjiang GC. Steyerberg EW. Derksen-Lubsen G. Moll HA. Parents' fear regarding fever and febrile seizures. Acta Paediatrica 1999; 88:618-22

203. Teach SJ. Geil PA. Incidence of bacteremia, urinary tract infections, and unsuspected bacterial meningitis in children with febrile seizures. Pediatr Emerg Care 1999; 15:9-12. Retrospective review. 243 children

204. Akpede GO. Localized extracranial infections in children with acute bacterial meningitis. Journal of Tropical Pediatrics 1994; 40:231-4

205. Rosman N, colton T, Labazzo C, et al. A controlled trial of diazepam administered during febrile illnesses to prevent recurrence of febrile seizures. New Engl J Med 1993; 329:79-84. Randomized double blind. 406 children

206. American Academy of Pediatrics. Practice parameter: Long term treatment of the child with a simple febrile seizure. Pediatrics 1999; 103:1307-1309. Evidence based clinical policy

207. Farrar HC, Chande VT, Fitzpatrick DF, Shema SJ. Hyponatremia as the cause of seizures in infants: a retrospective analysis of incidence, severity, and clinical predictors. Ann Emerg Med 1995; 26: 42–48.

208. Mott S, Packer R, Soldin S. Neurologic manifestations of cocaine exposure in childhood. Pediatr 1994;93:557-560.

209. Scott RC. Besag FM. Neville BG. Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: a randomized trial Lancet 1999; 353:623-6. Randomized Controlled Trial

210. Holmes GL. Buccal route for benzodiazepines in treatment of seizures. Lancet 1999;353:608-609.

211. Lahat E, Goldman M, Barr J, Bistritzer T, Berkovitch. Comparison of intranasal midazolam with intravenous diazepam for treating febrile seizures in children: prospective randomized study. BMJ 2000;321:83-86.

212. Earnest MP. Feldman H. Marx JA. Harris JA. Biletch M. Sullivan LP. Intracranial lesions shown by CT scans in 259 cases of first alcohol-related seizures. Neurology 1988; 38:1561-5. Retrospective. 259 patients

213. Holland RW, Marx JA. Earnest MP. Ranniger S. Grand mal seizures temporally related to cocaine use: Clinical and diagnostic features Ann Emerg Med 1992;21:772-6

214. Quigg M, Shneker B, Domer P. Current practice in administration and clinical criteria of emergent EEG. J Clin Neurophysiol, 2001;18:162-5.

215. Krumholz A, Fisher R, Lesser R, Hauser A. Driving and epilepsy: A review and reappraisal. JAMA 1991:265:622-626. Review

CMEQuestions

17. Which of the following antiepileptic is the first choice for status epilepticus?
    a. Lorazepam IV
    b. Diazepam IV
    c. Phenytoin IV
    d. Fosphenytoin IV

18. Which of the following needs to be checked prior to discharge for an otherwise healthy adult female with a new onset seizure who has returned to baseline mental status?
    a. Urine toxicology for cocaine
    b. Pregnancy test
    c. Serum chloride
    d. Prolactin level
    e. Lumbar puncture (following head CT)

19. Which of the following is true about fosphenytoin?
    a. It is very lipid soluble and so penetrates the CNS faster than phenytoin
    b. It has cardiac side effects
    c. Because it is not diluted in propylene glycol, it can be given as an IV push
    d. The pH is 12
    e. It is available in generic form

20. Pyridoxine is effective in isoniazid (INH) induced seizures by which mechanism?
    a. it competes for INH binding sites on the GABA receptor
    b. it helps replenish GABA stores depleted by INH

    c. It has sodium channel blocking properties
    d. It up-regulates the GABA A receptor making it more receptive to endogenous GABA

21. Phenytoin or fosphenytoin prevents:
    a. Alcohol withdrawal seizures
    b. Long term development of seizures after traumatic brain injuries
    c. Short term development of seizures after traumatic brain injuries
    d. Chronic pain development with herpes zoster
    e. Short term development of epilepsy after the first presentation with a seizure

22. You have been observing a 53 yo chronic alcoholic in your department for 8 hours. He was originally found on the street intoxicated. Prior to his discharge he has a tonic-clonic seizure lasting 30 seconds followed by a post ictal period of confusion. Which of the following is your next intervention?
    a. Admit the patient to the neurology service for observation
    b. Admit the patient to a monitored bed for impending delirium tremens
    c. Administer 2 mg of lorazepam IV and observe for 6 hours.
    d. Give valium 20mg orally and discharge the patient quickly when he returns to a baseline mental status.
    e. Get a STAT head CT

23. You suspect a 38 yo male in police custody is faking a seizure: which of the following is your best approach?
    a. A low serum prolactin level.
    b. Put him in a dark, quiet room to decrease the attention he is getting
    c. Tell him you know he is faking it and that he won't get fed until he stops acting out.
    d. Observe his gaze as you turn his head side-to-side to see if he avoids eye contact with you

24. Of the following, which is the best way to load a patient who seized due to non-compliance with phenytoin?
    a. oral load with fosphenytoin 20mg/kg
    b. oral load with phenytoin 20mg/kg, divided into 3 divided doses, 4 hours apart
    c. IV load over 10 minutes with phenytoin 20mg/kg
    d. IM load with fosphenytoin 20mg(PE)/kg
    e. all of the above

25. A 62 yo hypertensive woman was found to have a subarachnoid hemorrhage. She has a GCS = 13 and her BP is well controlled. While waiting for an ICU bed, she begins to seize. After receiving 10 mg of IV Lorazepam over 10 minutes, she continues to have less vigorous but present tonic-clonic activity. What is your next course of action?
    a. Intubation, vecuronium and repeat head CT to assess worsening hemorrhage
    b. Start loading phenytoin or fosphenytoin.
    c. Start propofol drip
    d. Start pentobarbital drip

26. **Regarding nonconvulsive status epilepticus, which of the following is true?**
   a. It is rare and relatively benign
   b. It may be the underlying disorder etiology for coma of undetermined etiology
   c. It generally develops after a SE patient continues to seize for more than one hour
   d. This is the term given to a convulsive SE patient after long acting paralytic agents have been given.

27. **Which of the following antiepileptic drugs is renally excreted and does not interfere with drug levels of patients who are on other protein bound medications?**
   a. Phenytoin
   b. Felbamate
   c. Carbamazepine
   d. Levetiracetam

28. **Which of the following is true of simple febrile seizures?**
   a. They are associated with a significant incidence of bacteremia

b. Recurrance should be prevented by placing the patient on Phenobarbital for six months
c. Patients with a first time simple febrile seizure should have a noncontrast head CT as part of their evaluation
d. CSF analysis is not indicated in patients with a first time simple febrile seizure

Class Of Evidence Definitions

Each action in the clinical pathways section of *Emergency Medicine Practice* receives a score based on the following definitions.

Class I
• Always acceptable, safe
• Definitely useful
• Proven in both efficacy and effectiveness

Level of Evidence:
• One or more large prospective studies are present (with rare exceptions)
• High-quality meta-analyses
• Study results consistently positive and compelling

Class II
• Safe, acceptable
• Probably useful

Level of Evidence:
• Generally higher levels of evidence
• Non-randomized or retrospective studies: historic, cohort, or case-control studies
• Less robust RCTs
• Results consistently positive

Class III
• May be acceptable
• Possibly useful
• Considered optional or alternative treatments

Level of Evidence:
• Generally lower or intermediate levels of evidence

• Case series, animal studies, consensus panels
• Occasionally positive results

Indeterminate
• Continuing area of research
• No recommendations until further research

Level of Evidence:
• Evidence not available
• Higher studies in progress
• Results inconsistent, contradictory
• Results not compelling

Significantly modified from: The Emergency Cardiovascular Care Committees of the American Heart Association and representatives from the resuscitation councils of ILCOR: How to Develop Evidence-Based Guidelines for Emergency Cardiac Care: Quality of Evidence and Classes of Recommendations; also: Anonymous. Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part IX. Ensuring effectiveness of community-wide emergency cardiac care. JAMA 1992;268(16):2289-2295.

Physician CME Information

Emergency Medicine Practice is not affiliated with any pharmaceutical firm or medical device manufacturer.