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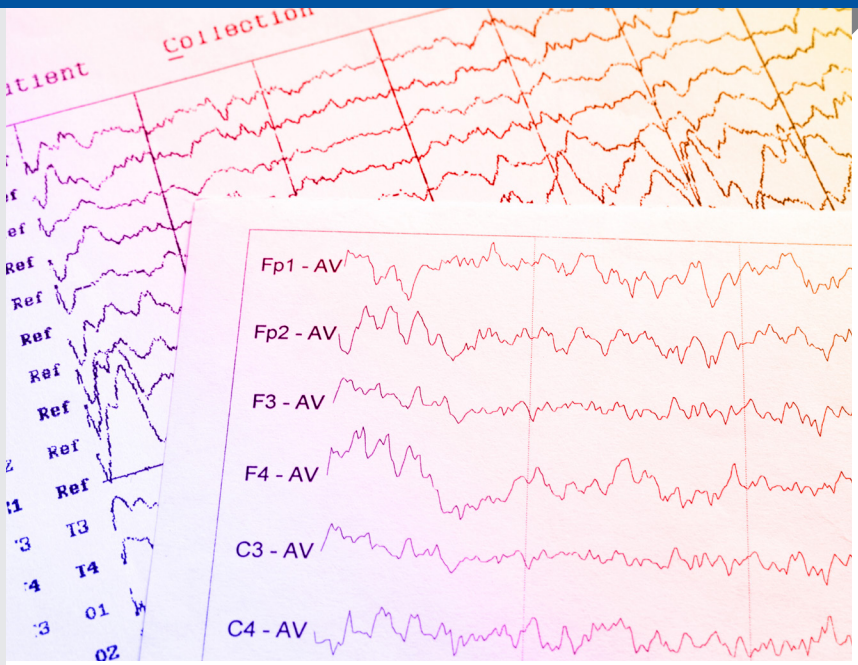
CLINICAL CHALLENGES:

- **What are the typical and atypical presentations of status epilepticus?**
- **How should the patient workup be conducted to determine whether there is a reversible cause of the seizures?**
- **What are the recommendations and cautions for first-, second-, and third-line medications for seizures in the ED?**



Emergency Department Management of Patients With Status Epilepticus

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Prior to beginning this activity, see "CME Information" on page 2.

Abstract

Status epilepticus is a neurological emergency requiring prompt intervention by emergency clinicians, as delays can lead to significant morbidity and mortality. Etiologies include acute causes such as electrolyte imbalance, infection, drugs, and acute strokes, as well as chronic causes such as remote brain injury, progressive epilepsies, and brain tumors. This issue presents evidence for an algorithmic approach to status epilepticus, from managing underlying causes and administering initial benzodiazepines, to second-line antiseizure agents, and escalating to intravenous anesthetics for refractory cases. Disposition for patients in status epilepticus includes inpatient care tailored to the patient's clinical needs, and appropriate follow-up.

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Case Presentations

CASE 1

A 65-year-old man presents to the emergency department via EMS, with ongoing tonic-clonic movement of the right face, arm, and leg for the past 25 minutes…

- EMS administered oxygen and 10 mg intramuscular midazolam, without resolution of symptoms. The patient was placed on a monitor, and IV access was obtained.
- Initial vital signs are: temperature, 37.3°C; heart rate, 120 beats/min; blood pressure, 157/90 mm Hg; and oxygen saturation, 98% on 4 L nasal cannula. A point-of-care glucose level is 81 mg/dL.
- After administration of 4 mg IV lorazepam, he stops seizing. You send initial blood work, including CBC, comprehensive metabolic profile, ethanol level, acetaminophen/salicylate level, and lactate, to the laboratory. His wife arrives and provides history that the patient is receiving radiation and chemotherapy for glioblastoma multiforme of the left temporal lobe.
- After 1 hour, the patient is still not responding to questioning or painful stimulus, and his oxygen requirement worsens. He has slight twitching movements of the right face and mouth every 2 minutes.
- You consider whether the patient could still be seizing and, if so, what the best next course of action should be...

CASE 2

A 25-year-old woman presents with her family to the ED with acute onset of paranoid ideation, lateral nystagmus, and stereotypic repetitive "pill rolling" motor activity…

- Her vital signs include: temperature, 37.6°C; heart rate, 110 beats/min; blood pressure, 140/80 mm Hg; and oxygen saturation, 99%.
- In speaking with her family, you note that she has a past psychiatric history that includes episodes of "poor impulse control" and "outbursts of violent behavior toward family members."
- You consider whether she should be triaged to psychiatry or if something else might be going on…

Introduction

Status epilepticus (SE) is a neurological emergency that requires prompt recognition and treatment in the emergency department (ED). A common theme in neurology is that "time is brain," and in SE, underrecognition and delays in treatment can lead to increased morbidity and mortality. SE that persists despite first-line and second-line treatments often necessitates intubation and administration of anesthetic infusions. While timely treatment of SE is essential, accurately distinguishing it from mimics such as syncope, intoxication, locked-in syndrome, and nonepileptic seizures is important to ensure appropriate therapy. This issue of *Emergency Medicine Practice* presents an approach to managing ED patients with SE, incorporating current evidence and algorithms set forth by the American Epilepsy Society, the Neurocritical Care Society, and the International League Against Epilepsy.

Critical Appraisal of the Literature

A literature search was conducted using PubMed, the Cochrane Library of Systematic Reviews, and Scopus, with search terms including *status epilepticus, status epilepticus trials, status epilepticus management, status epilepticus outcomes,* and *non-convulsive status epilepticus*. Relevant studies were drawn from peer-reviewed journals, clinical trials, meta-analyses, and systematic reviews published over the last 2 decades.

A total of 75 articles were reviewed, with a focus on randomized controlled trials, large observational studies, and systematic reviews. Guidelines from the International League Against Epilepsy,[1] the Neurocritical Care Society,[2] and the American Epilepsy Society[3] were examined. These guidelines provide evidence-based recommendations and practice summaries. Beginning in 2019, 3 major randomized controlled trials—EcLiPSE, ConSEPT, and ESETT—have provided crucial data on the efficacy and safety of phenytoin (or fosphenytoin), levetiracetam, and sodium valproate for the treatment of convulsive SE in both children and adults.[4] EcLiPSE and ConSEPT were pediatric open-label multicenter trials comparing levetiracetam with phenytoin for established convulsive SE. These studies have provided class I evidence on the effectiveness of levetiracetam, phenytoin, and sodium valproate to stop seizures, and they highlight the importance of prospective studies that accurately document the timing of onset and cessation of SE. Nevertheless, no single drug or combination of drugs has been shown to terminate impending or established SE in all patients. A major limitation of the literature is the variability in study designs of different treatment regimens, underscoring the need for standardized protocols for direct comparisons.

Etiology and Pathophysiology

Definitions

SE is the most extreme form of a seizure disorder, and is associated with up to 30% morbidity and mortality in adults."[3] Historically, SE was defined as seizure activity ongoing for more than 30 minutes or 2 or more sequential seizures without full recovery of consciousness in between seizure events.[3] This definition was chosen because irreversible neuronal injury has been shown to occur after 30 minutes of continuous seizure. However, SE treatment protocols have used a 5-minute period for treatment initiation because, after this time, the likelihood of seizure cessation without pharmacologic intervention decreases.[3] Today, the Neurocritical Care Society and the International League Against Epilepsy recognize this important time period and define SE as a seizure lasting for more than 5 minutes or recurrent seizure activity without recovery between seizures.[1,2]

In 2015, the International League Against Epilepsy Task Force introduced a new classification system for SE that is structured around 4 axes: semiology, etiology, electroencephalogram (EEG) findings, and age.[1] **(See Table 1.)** SE is categorized into different clinical forms, with 2 key criteria distinguishing them: (1) SE with prominent motor symptoms (including all convulsive forms) and (2) nonconvulsive forms.[1] **(See Table 2 and Table 3, page 5.)** Although the underlying cause of SE is often the most important determinant of outcome, distinguishing between convulsive and nonconvulsive forms is important, as the latter generally has lower mortality.

Nonconvulsive status epilepticus (NCSE) is underrecognized by clinicians due to its lack of overt clinical signs, and there is a need for more studies on diagnostic techniques, treatment options, and outcomes. NCSE often requires EEG for formal diagnosis, and because it may have no motor symptoms or may be suggested only by subtle clinical features such as nystagmus, myoclonus, gaze deviation, or ictal paresis, it is underdiagnosed and requires a high degree of suspicion.[5]

Pathophysiology

SE occurs when the biologic responses that usually terminate seizures fail to function properly. In most seizures, natural inhibitory gamma-aminobutyric acid (GABA) agonist activity, as well as synaptic removal of glutamate by astrocytes, help to terminate seizures shortly after they begin. In SE, these mechanisms are overwhelmed, leading to prolonged seizure activity. During seizures, the excessive release of the excitatory neurotransmitter, glutamate, damages neurons through excitotoxicity. This heightened neuronal activity during SE generates reactive oxygen species, which damages cell membranes and mitochondria, contributing to oxidative stress.[6]

As SE progresses, seizures become increasingly resistant to benzodiazepines, due to the internalization of cell surface $GABA_A$ receptors, the natural binding site of these drugs. With fewer $GABA_A$ receptors to bind to, benzodiazepines become less effective in stimulating the intracellular chloride influx that lowers cell membrane potential and contributes to seizure cessation. Conversely, N-methyl-D-aspartate (NMDA) receptors are upregulated to the neuronal cell surface and excessive calcium influx through NMDA-activated channels leads to the activation of nitric oxide synthase, calpains, and nicotinamide adenine dinucleotide phosphate oxidase, which are enzymes that play key roles in generating seizure-related reactive oxygen species. Calcium also accumulates in mitochondria, leading to decreased adenosine triphosphate production.[6] These mechanisms contribute to making seizures increasingly refractory to first-line agents the longer they continue, increasing the likelihood that escalation to intravenous (IV) anesthetics will be necessary.

Acute and Nonacute Etiologies

Among prognostic factors, etiology is the key determinant of a patient's survival, driving almost 80% of SE-related mortality, long-term cognitive impairments, and risk for chronic epilepsy. **(See Table 4, page 6.)** In 45% of SE cases, addressing the underlying etiology is required to gain control of the seizures, since the management is specific to the underlying disease process. For example, SE due to underlying herpes simplex virus encephalitis requires treatment of the underlying infection.[7] If left untreated, persistent SE can lead to a harmful cycle, worsening the damage caused by the underlying condition.

Table 1. The International League Against Epilepsy Task Force Classifications[1]

Axis 1: Semiology
- With prominent motor symptoms
- Without prominent motor symptoms

Axis 2: Etiology
- Structural
- Metabolic
- Inflammatory
- Toxic
- Infectious
- Genetic
- Unknown (cryptogenic)

Axis 3: Electroencephalogram Findings
- Location
- Name of pattern
- Morphology
- Time-related features
- Modulation
- Effect of antiseizure medication on electroencephalogram

Axis 4: Age
- Neonatal (up to 30 days)
- Infancy (1 mo-2 yr)
- Childhood (2-12 yr)
- Adolescence and adulthood (12-59 yr)
- Elderly (≥60 yr)

Acute Etiologies

Acute SE arises from recent (typically within 7 days) central nervous system (CNS) insults such as head trauma, CNS or systemic infections, cerebrovascular events, toxic or metabolic encephalopathies, and withdrawal from alcohol or drugs.[1] The most common metabolic causes include blood glucose disturbances (eg, hypoglycemia, diabetic hyperosmolar syndrome) and electrolyte imbalances (eg, hyponatremia or hypernatremia, hypercalcemia or hypercalcemia, hypoxemia, or

Table 2. Classifications of Status Epilepticus With Prominent Motor Symptoms[1]

Classification	Comments
A.1 Convulsive SE	
• Generalized convulsive • Focal onset evolving into bilateral convulsive SE • Unknown whether focal or generalized	• Synonymous with tonic-clonic SE • EEG useful in differentiating between focal onset and generalized onset
A.2 Myoclonic SE: Prominent Epileptic Myoclonic Jerks	
• With coma • Without coma	• Seen as myoclonic jerks time-locked with generalized polyspike and wave discharges • Seen in some rare genetic generalized epilepsies and acute hypoxic ischemic injury (poor prognostic factor)
A.3 Focal Motor: Broad Range of Semiologies, Depending on the Cerebral Location of Seizure Origin	
• Repeated focal motor seizures (Jacksonian seizures)	• Focal clonic motor activity that progresses along the homunculus of the affected region
• Epilepsia partialis continua	• Prolonged repetitive focal motor activity restricted to 1 body part, with retained awareness
• Adversive status	• Sustained forced deviation of the head, eyes or body to 1 side
• Oculoclonic status	• Pure oculomotor phenomena of rapid, repetitive, involuntary eye movements • Alteration of consciousness may be present
• Ictal paresis	• Focal inhibitory negative motor phenomenon during ictal phase with paralysis of 1 or more body parts; distinct from a postictal paresis that is a Todd paralysis
A.4 Tonic Status: Rare Presentation Manifesting With Rigid Posturing of Axial and Limb Muscles	
A.5 Hyperkinetic SE	
• Continuous complex, high-amplitude motor activity of the trunk and limbs	• Usually indicates a frontal lobe involvement

Abbreviations: EEG, electroencephalogram; SE, status epilepticus.

Table 3. Classifications of Status Epilepticus Without Prominent Motor Symptoms (Nonconvulsive Status Epilepticus)[1]

Classification	Comments
B.1 Nonconvulsive SE With Coma (Includes "Subtle" SE)	
B.2.a Nonconvulsive SE Without Coma: Generalized	
• Typical absence SE	• Clinically presents as blank staring and impaired awareness
• Atypical absence SE	• Associated with epileptic encephalopathies
• Myoclonic absence SE	• Subtle myoclonic jerks and absences
B.2.b Nonconvulsive SE Without Coma: Focal	
• Categorized depending on the degree of awareness • Associated with features localized to the cerebral focus/ focal lesion - may include automatisms, autonomic, cognitive, sensory symptoms, or speech impairment (aphasic SE), etc	
• Without impaired consciousness	• Aura that may involve sensory, autonomic, visual, gustatory, olfactory, emotional or auditory symptoms
• Aphasic SE	• SE with speech impairment
• With impaired consciousness	• Occurs when the focus of the seizure spreads to involve more cerebral areas and impairs consciousness
B.2.c Unknown Whether Focal or Generalized	
• Autonomic SE	• Vital sign abnormalities, pallor, pupillary changes

Abbreviation: SE, status epilepticus.

hyperammonemia).[8] Acute causes can be more challenging to manage and are often associated with a higher mortality rate. Management in these acute cases is directed toward treating the underlying issue, such as intubation for refractory hypoxia, initiating dialysis for uremia, or administering antibiotics for meningitis.[9]

Nonacute Etiologies

Nonacute etiologies are those in which SE develops more than 7 days after a CNS insult, typically emerging over several months or years. The International League Against Epilepsy's recent classification includes *remote* symptomatic SE and *progressive* symptomatic SE. Patients who experience seizures secondary to nonacute underlying disease may include: (1) patients with underlying epilepsy who experience breakthrough seizures due to nonadherence to antiseizure medications, poor sleep hygiene, or a mild provoking factor; (2) patients withdrawing from alcohol or benzodiazepines; or (3) patients with complications from previous CNS injuries, such as stroke, demyelinating diseases, or autoimmune disorders. Patients with nonacute seizure etiologies are typically treated with targeted antiseizure medications.[9]

Refractory Status Epilepticus

SE that continues despite treatment with benzodiazepines and first-line antiseizure medications is considered *refractory*. When this occurs with no history of epilepsy and no identifiable cause, the term, *new-onset refractory status epilepticus (NORSE)* is used. In half of adult NORSE cases, the cause remains undetermined despite comprehensive workup. Some studies have suggested that many of these cases might be secondary to an occult autoimmune or paraneoplastic encephalitis with unidentified antibodies.[10]

Table 4. Examples of Known Causes of Status Epilepticus

Acute

- Low levels of antiseizure medications in patients with known epilepsy
- Idiopathic generalized epilepsy exacerbated by use of inappropriate antiseizure medications (eg, carbamazepine, phenytoin, vigabatrin)
- Drugs that lower the seizure threshold
- Metabolic issues
- Structural causes
- Inflammatory causes
- Toxins, drugs
- Infection
- Intrinsic conditions in patients with known epilepsy (eg, sleep deprivation)

Remote

- Posttraumatic
- Postencephalitic
- Post stroke

Progressive

- Brain tumor
- Progressive myoclonic epilepsy syndromes
- Dementias and other neurodegenerative conditions

Differential Diagnosis

When considering SE, critical alternative diagnoses such as sudden coma due to catastrophic intracranial hemorrhage, basilar artery occlusion, and hypoglycemia are imperative to rule out, as they lead to devastating consequences if missed. These presentations may be difficult to distinguish from NCSE at first, as they can all present with acute unresponsiveness and coma. **(See Table 5.)**

Syncope may be accompanied by brief jerking movements after the loss of consciousness, but will resolve with the rapid return of normal mentation. These movements typically last only a few seconds and cease once the patient is horizontal.[11] In contrast, generalized tonic-clonic seizures may persist for 30 to 90 seconds.[11,12] Tongue bites, especially when seen along the lateral edge of the tongue, may distinguish seizure from syncope.[11] Additional features that suggest syncope rather than seizure include presyncopal symptoms such as dizziness, lightheadedness, nausea, chest pain and palpitations, as well as a patient's age and a history of cardiovascular disease. Features suggesting seizures include tongue-biting, head-turning, posturing, urinary incontinence, cyanosis, prodromal déjà-vu, and postictal confusion. The complete and immediate return to a fully alert state after a loss of consciousness, without an intervening period of confusion, usually argues against seizures as the most likely problem.

Other neurologic conditions, such as Parkinson disease, Guillain-Barré syndrome, polyneuropathy, or stroke, can lead to arrested movement or speech and can sometimes be mistaken for NCSE. The locked-in state, resulting from anterior pontine infarction, can mimic SE by causing paralysis of motor output. Other conditions, such as encephalopathy due to a toxin, drug, or metabolic disturbance (eg, hypo-

Table 5. Differential Diagnosis for Patients With Status Epilepticus

- Intracranial hemorrhage
- Locked-in syndrome
- Hypoglycemia
- Acute hydrocephalus
- Metabolic encephalopathy
- Drug toxicity and withdrawal
- Syncope
- Psychogenic nonepileptic seizures
- Movement disorders such as dyskinesias, severe Parkinson disease, oculogyric crises
- Guillain-Barré syndrome

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glycemia, hyperglycemia, uremia, hyponatremia, or decompensated hypothyroidism [myxedema coma]) may also mimic NCSE.[13] Alcohol intoxication and delirium tremens can cause agitated behavior with confusion and memory impairment similar to NCSE. Hypoglycemia must be evaluated immediately with fingerstick glucose testing (part of the initial assessment after airway, breathing, and circulation), as it can resemble a comatose and NCSE state.

Seizures originate cortically but can spread subcortically and involve the basal ganglia. Patients with basal ganglia involvement during seizures present with ictal dystonic posturing.[14] Characterized by sustained abnormal posture resulting from muscle contractions, ictal dystonic posturing is not to be mistaken for dystonia, an abnormality of tone, which may be induced by medications that block dopamine. Medications such as antipsychotics block dopamine and have been implicated in causing dystonic reactions that can mimic this type of ictal dystonic posturing. Oculogyric crisis, a severe dystonic reaction, involves forced eye deviation along with other symptoms and lasts for 20 to 30 minutes, without loss of consciousness.[15]

Psychogenic Nonepileptic Seizures

Psychogenic nonepileptic seizures (PNES) can be especially challenging to differentiate from true seizures. Many patients with PNES are initially treated as having epileptic seizures when presenting to the ED, which puts a strain on healthcare resources.[16] While tongue-biting and urinary incontinence may suggest true seizures, they are not definitive indicators. The key to differentiation is the history and the characteristics of the event: epileptic seizures are often preceded by an aura, involve rhythmic, involuntary muscle contractions, and typically lead to impaired awareness and possible postictal confusion. In contrast, PNES may include side-to-side head movements, pelvic thrusting, forced eye closure, emotional outbursts, opisthotonic posturing, and subtle tremors. While these features can be suggestive of PNES, their sensitivity is low, and their absence does not rule out an underlying seizure disorder. Video EEG monitoring has identified additional markers that may help differentiate PNES, such as preserved awareness, eye flutter instead of eye opening, modulation of seizure intensity by bystanders, abrupt onset, and absence of a postictal phase.[17] Serum prolactin levels, when drawn shortly after the event, may assist in distinguishing psychogenic seizures, though negative levels do not rule out epilepsy. Other biomarkers such as neuron-specific enolase and creatine kinase have been suggested as potential indicators for psychogenic causes of seizures, but evidence supporting their utility is limited.[18]

Prehospital Care

In the prehospital setting, the initial management of an adult with SE involves 4 key elements: (1) securing the airway, breathing, and circulation; (2) pharmacologic treatment to abort the seizure; (3) preventing additional trauma to the seizing patient; and (4) gathering available medical history from the scene, including medication use, pill bottles, or signs of drug use.

Due to the suppression of the gag reflex during SE, the patient should be placed in the left lateral decubitus position, when possible, to reduce the risk for aspiration. Use of a bite block or oropharyngeal airway is not recommended, as they can obstruct the airway and also lead to hand injuries in responders trying to insert them into a patient's clenched mouth. If an adjunctive airway device is needed, a nasopharyngeal airway should be placed.[19] Respiratory failure is a potential complication of generalized convulsive SE, sometimes due to medications used in its treatment.[2] While data on specific prehospital indications for intubation by advanced cardiovascular life support (ACLS) providers are limited, accepted indications include hypoventilation, recurrent seizures, or altered mental status. The decision for emergency medical services (EMS) providers to intubate the patient in the field should be made collaboratively with medical control centers.[20]

A point-of-care blood sugar measurement should always be performed, as hypoglycemia is a common trigger for seizures and is easily reversible. If low blood sugar is identified, it should be corrected promptly with IV dextrose.

IV access should be obtained to allow for administration of medications and rapid sequence intubation medications, if necessary. Although obtaining IV access may extend on-scene time slightly, it does not significantly delay transport time.[21] If IV access if unobtainable, intramuscular (IM) midazolam should be administered in order to prevent delays in treatment.

After initial stabilization has been performed, assessment begins with information from the caller or bystanders, if available. Any relevant medical history—particularly regarding previous seizures, diabetes, trauma, overdose, or cardiovascular issues—should be obtained. Witness reports regarding the seizure, such as fever, trauma, substance use, onset and duration, eye deviation, incontinence, or specific motor movements, are valuable, although they may not always be accessible.[9]

Benzodiazepines remain the first-line treatment for SE. Despite their respiratory depressant effects, studies have shown that the administration of IM and IV benzodiazepines by prehospital providers is both safe and effective for both adult and pediatric patients.[22] Over time, the methods of benzodiazepine administration and the choice of medications has evolved. Rectal diazepam, initially used since 1989 by

both parents and emergency responders, was particularly effective in pediatric cases;[9] however, given the advent of new and effective United States Food and Drug Administration (FDA)-approved rescue agents, rectal diazepam is no longer recommended for the treatment of SE.

Midazolam has gained popularity in the prehospital setting due to its ease of use via IM, inhalation, or buccal routes. The RAMPART trial demonstrated the use of IM midazolam as an effective alternative to IV administration in the prehospital setting.[22] IM midazolam was more effective than IV lorazepam, terminating seizures in 73% versus 63% of cases ($P < .001$). There was no significant difference in adverse outcomes between the 2 groups.[22] For its simple, fast, and efficacious delivery, the American Epilepsy Society 2016 and Neurocritical Care Society guidelines provide level A recommendations for the use of IM midazolam 10 mg for adults and pediatric populations weighing ≥40 kg, or 5 mg for those weighing between 13 and 40 kg (0.2 mg/kg up to 10 mg) for out-of-hospital SE. As an alternative, there is level B evidence for the use of intranasal midazolam in terminating SE.[2,3] Of note, in a retrospective cohort study by Guterman et al studying different routes of administration of midazolam, intranasal midazolam was noted to be less effective in terminating SE and more likely to require additional rescue therapy compared with IM midazolam. Similarly, when midazolam was administered in doses lower than treatment guidelines (in this study, reported at 4.1% of encounters), additional rescue therapy was required.[23]

Emergency Department Evaluation

In the ED, a thorough reassessment of the patient's airway, breathing, and circulation must be conducted. Particular attention should be given to patients who have received multiple doses of benzodiazepines by EMS providers, as these individuals are at a higher risk for respiratory depression.

History

A detailed medical history should be obtained with a focus on conditions such as prior seizures, current medications, drug use, new focal neurologic deficits, head trauma, and recent infections. The specifics of the seizure event are crucial, including its onset, duration, characteristics, and any associated trauma. The description of the event should include the circumstances leading up to the seizures, the actual ictal behaviors (aura, loss of consciousness, motor vs nonmotor manifestations, focality, duration), and any postictal phenomena. Types of postictal phenomena include depressed mental status, agitation, psychosis, or a temporary weakness in the part of the body involved in the seizure, known as *Todd paralysis*.

Physical Examination

The physical examination should encompass the general appearance of the patient, with particular attention paid to signs of head, face, or oral trauma. An inspection of the tongue for lateral tongue lacerations may help distinguish between syncope and seizures.[11] Cardiopulmonary evaluation and assessment for meningeal signs are also important. Meningeal signs and headache may be masked in the postictal period, and a high level of suspicion should be maintained for possible occult infection.

The neurological examination must include an evaluation of mental status, brainstem reflexes (particularly pupillary response, which may show abnormal rhythmic pupillary dilation and constriction known as *hippus*[24]), abnormal eye movements or gaze deviation, and any focal motor deficits. Due to the global cortical dysfunction during and after seizures, most patients in SE present with depression of mental status (especially those with generalized seizures, focal seizures that secondarily generalize, and NCSE). Lateralizing signs such as focal weakness, focal upper motor neuron signs, and/or gaze deviation in the neurological examination may indicate an underlying focus or brain lesion prompting further evaluation with neuroimaging.

Interestingly, brainstem reflexes after ongoing seizure activity have, in a few animal and human studies, been noted to be suppressed. One study using perfusion imaging noted postictal hypoperfusion in brainstem respiratory centers.[25] Another study highlighted the significant decrease in population firing of neurons in the upper and lower brainstem, leading to decreased arousal and impaired cardiopulmonary function, respectively.[26]

It is important to note that a patient's mental status may be altered both during and after a seizure and, unless a patient has clinical features suggestive of ongoing subtle seizures, it is difficult to differentiate continued subclinical seizures from a prolonged postictal state. Features that suggest prolonged postictal state include a gradual improvement in mental status over the course of several minutes to hours. Nonetheless, further testing is likely to be needed to differentiate the states.

Diagnostic Studies

The diagnosis of convulsive SE is largely clinical and is supported by laboratory testing, imaging studies, and EEG to identify the underlying cause. Initial diagnostic tests in the ED focus on ruling out other potentially life-threatening conditions.

Laboratory Testing

A rapid assessment of serum glucose and electrolyte levels, including calcium and magnesium, is critical.[27] **Table 6** lists laboratory tests commonly ordered in the evaluation of SE, as dictated by the clinical scenario.

Imaging Studies

If increased intracranial pressure or a lesion that could cause herniation is suspected, common practice is to obtain a computed tomography (CT) scan before a lumbar puncture, especially if there is altered mental status or a new focal neurologic deficit.[29] It is recommended by the American College of Emergency Physicians to evaluate these findings with a head CT, without contrast, or magnetic resonance imaging (MRI) of the brain.[27] However, a normal CT scan does not always rule out high intracranial pressure. Any additional signs of high intracranial pressure, such as papilledema on fundoscopic examination or increased optic nerve sheath diameter, should lead to prompt evaluation for cause and subsequent management of the elevated intracranial pressure. Venous sinus imaging via either CT or MR venogram should be considered for patients who may have an increased risk for hypercoagulability, persistent headache, papilledema, recent pregnancy, or oral contraceptive use.

Lumbar Puncture

A lumbar puncture is indicated for patients presenting with signs of meningitis and should also be considered for those who appear to be critically ill, are aged ≤18 months, have had a prolonged febrile seizure, have an incomplete or unknown vaccination history, have new-onset seizures without an obvious cause, or have received antibiotics prior to clinical evaluation. Cerebrospinal fluid (CSF) analysis can help identify infectious, inflammatory, or neoplastic causes. There should be a low threshold to test CSF for infectious causes, given the poor outcomes associated with delays in treatment of bacterial or viral CNS infections. An elevated CSF protein level may be present even when no underlying cause for the seizures is identified. CSF pleocytosis was historically thought to be a result of prolonged seizures, but a retrospective review of 51 patients in a critical care setting concluded that seizures do not directly cause CSF pleocytosis, and further investigation should be undertaken to determine the underlying etiology.[32]

Table 6. Laboratory Testing for Patients in Status Epilepticus

Test	Comments
Fingerstick glucose	• Severe hypoglycemia and hyperglycemia, especially non–ketotic hyperosmolar states, can lead to seizures
Complete blood cell count	• Leukocytosis may indicate an underlying infection, though a transient leukocytosis is typically seen after seizure
Comprehensive metabolic panel, including electrolytes	• Particular attention should be paid to levels of sodium, calcium, magnesium, and phosphorus as etiologies of metabolic disturbance that can cause seizures
Urinalysis	• Evaluates for infection as possible provoking factor
Urine drug screen	• Cocaine, amphetamines, and other stimulants; MDMA; marijuana; and heroin have been associated with seizures
Serum toxicology levels	• Evaluates for intoxication/withdrawal
Blood gas	• Assesses for respiratory acidosis with lactate • Used for evaluation of patients with depressed mental status and hypercarbia
Lactate	• Excess lactate from muscle tissue is a common finding during the first 1-2 hr after a generalized tonic-clonic seizure, but can last longer in status epilepticus. If still elevated 1 hr after the event, recheck to monitor acidosis • Lactate levels of >2.45 mmol/L to distinguish generalized tonic-clonic seizure from syncope and psychogenic nonepileptic seizure; sensitivity, 88%; specificity, 87%[28]
Prolactin	• Measured 10-20 min after a seizure • Sensitivity of 53% and specificity of 93% for diagnosing convulsive status epilepticus[29] • Utility of this test is limited by the narrow window for sample collection, which should occur within 20 min of the seizure
Creatine kinase	• Trend high levels to monitor for rhabdomyolysis and acute kidney injury • Creatine kinase rises during the first 1-12 hr and peaks after 24-72 hr in approximately half of patients with generalized tonic-clonic seizure[30] • Sensitivity of elevated creatine kinase levels in this setting ranged from 14.6%-87.5%; specificity, 85%-100%[31]
Troponin	• Cardiac troponin can be elevated with seizures, especially those with autonomic features • Elevated level should lead to prompt cardiac evaluation, with initiation of electrocardiogram and troponin trending
Antiseizure medication levels	• Typically assessed for medication compliance
Cultures (blood, urine, cerebrospinal fluid)	• Work up for infectious causes
Pregnancy test	• A positive pregnancy test may limit certain antiseizure medications due to risk for teratogenicity

Electroencephalogram Monitoring

EEG monitoring can be helpful when patients do not return to their baseline level of consciousness, if there is concern for ongoing nonconvulsive seizures, or when clinical evaluation is difficult due to sedation or neuromuscular blockade. The ESETT trial was a randomized controlled trial of 475 patients among 58 hospitals that showed that 48% of patients with altered consciousness following SE continued to show nonconvulsive seizures on EEG.[33] Patients who are at high risk for nonconvulsive seizures include those admitted to intensive care units, particularly those receiving neurotoxic medications (eg, cephalosporins, methotrexate, baclofen, lithium, opioids), as well as those with a history of epilepsy, previous generalized tonic-clonic seizures, prior head injury or stroke, or are female sex.[34] For patients with known epilepsy who return to baseline without signs of subclinical seizures, EEG monitoring may not be necessary.

Monitoring for Subclinical Seizures

EEG monitoring for subclinical seizures has some limitations. Data interpretation relies on extensive, manual visual analysis by epileptologists and may not be available at all centers. When continuous EEG is unavailable, intermittent EEGs (usually lasting between 30 and 60 minutes) may still be helpful. One study, however, found this approach missed up to 10% of subclinical seizures.[35] While intermittent EEGs reduce interpretation time, applying and adjusting electrodes can still be resource-demanding for EEG technicians. A potential alternative involves computational analysis and automated seizure detection algorithms, which reduce clinician workload, but are not yet available in most ED settings.[36]

Treatment

Treatment of convulsive SE begins with prompt recognition, hemodynamic support, and immediate administration of medications to achieve seizure control. Rapid initiation of treatment plays a key role in the clinical course and reduction of the morbidity and mortality of SE.[37] An algorithmic approach to treatment should begin with the administration, without delay, of benzodiazepines.[38,39] **Table 7** includes a summary of the first-, second-, and third-line medications for SE.

Benzodiazepine Treatment

Previously, 3 benzodiazepines—lorazepam, midazolam, and diazepam—had been used in initial treatment of SE, but lorazepam has emerged to be the preferred IV agent over diazepam, as studies have shown a higher seizure termination rate with lorazepam compared with diazepam.[40-42] When there is no IV access, IM midazolam is preferred. The RAMPART trial, a double-blind, randomized, noninferiority trial with 893 patients, demonstrated noninferiority of IM midazolam, terminating seizures in 73% of patients compared with 63% who received IV lorazepam in the prehospital setting (P = .001). Furthermore, the frequency of endotracheal intubation and recurrent seizures was not increased in the IM midazolam group.[22]

Currently, the Neurocritical Care Society and American Epilepsy Society guidelines recommend the use of IV lorazepam for treatment of SE at a dose of 0.1 mg/kg, up to 4 mg per dose, with a repeat dose in 5 to 10 minutes if cessation of SE has not occurred.[2,3] For the patient without an IV, the recommended treatment for patients weighing >40 kg is IM midazolam 0.2 mg/kg (max 10 mg). For patients weighing 13 to 40 kg, the initial dose is 5 mg IM.

Underdosing of benzodiazepines leads to poor response, lower likelihood of termination of SE, and increased likelihood that greater levels of sedation will be required for seizure control.[43,44] IV diazepam may also be administered, as an alternative, at a dose of 0.15 to 0.2 mg/kg, up to 10 mg and repeated once, though this is a class II recommendation.[2] When benzodiazepines are unavailable, IV phenobarbital at a dose of 15 to 20 mg/kg may be used.[2,3]

Table 7. Medications for Status Epilepticus[2,3]

Agent	Route	Dosage
First-Line Agents		
Lorazepam	IV	• 0.1 mg/kg; max 4 mg/dose • May repeat once
Midazolam	IM	• Weight 13-40 kg: 5 mg • Weight >40 kg: 0.2 mg/kg, max 10 mg • May repeat once
Diazepam	PR	0.2-0.5 mg/kg, up to 20 mg, 1 time
Second-Line Agents		
Levetiracetam	IV	• 60 mg/kg; max 4.5 g
Valproate sodium	IV	• 40 mg/kg; max 3 g
Fosphenytoin	IV	• 20 mg PE/kg; max 1.5 g
Phenobarbital	IV	• 15-20 mg/kg; max 2 g
Lacosamide	IV	• 200-400 mg
Third-Line Agents		
Midazolam	Infusion	Load with 0.2 mg/kg and infuse at 0.05-2 mg/kg/hr, with repeat bolus of 0.1-0.2 mg/kg if breakthrough seizure
Propofol	Infusion	Load with 1-2 mg/kg and infuse at 30-200 mcg/kg/min
Pentobarbital	Infusion	Load with 5-15 mg/kg and infuse at 0.5-5 mg/kg/hr
Thiopental	Infusion	Load with 2-7 mg/kg and infuse at 0.5-5 mg/kg/hr
Ketamine	Infusion	Load with 0.5-3 mg/kg and infuse at 0.1-5 mg/kg/hr

Medications for Benzodiazepine-Refractory Convulsive Status Epilepticus

According to Neurocritical Care Society and American Epilepsy Society guidelines, when first-line benzodiazepine treatment fails to terminate a seizure, it is recommended to proceed to a non–benzodiazepine antiseizure medication within 5 to 10 minutes.[2] Several non–benzodiazepine antiseizure medications have been studied in the treatment of SE, including fosphenytoin/phenytoin, valproate sodium, levetiracetam, lacosamide, and phenobarbital. ESETT studied the efficacy and safety of levetiracetam IV 60 mg/kg, fosphenytoin IV 20 mg PE/kg, and valproate sodium IV 40 mg/kg in the management of SE and found no major differences in time to cessation of seizure at 60 min between the 3 medications. Adverse events were also similar among the the 3 medications, and SE stopped in approximately 50% of patients in each treatment group.[45] Given their similar efficacy, the antiseizure medication treatment should be tailored to the patient's specific characteristics and comorbidities.

Currently, 4 medications are recommended for benzodiazepine-refractory convulsive SE. These include fosphenytoin/phenytoin IV 20 mg PE/kg, up to 1.5 g; valproate sodium IV 40 mg/kg, up to 3 g; levetiracetam IV 60 mg/kg, up to 4.5 g. If these 3 options are unavailable, phenobarbital IV 15 to 20 mg/kg, up to 2 g can be administered.[2,3,29]

Lacosamide

Recently, lacosamide has emerged as a possible adjunct to currently recommended treatment for SE. Though not FDA-approved for SE, its use has been described in cases where further control is needed after benzodiazepine and antiseizure medication administration and before escalation to anesthetic agents. There are mixed data on its efficacy. One trial comparing the efficacy and safety of lacosamide and fosphenytoin in NCSE demonstrated noninferiority between the 2 agents.[46] Another case report of 9 patients receiving lacosamide in refractory SE demonstrated no cessation of seizure activity.[47] In 2017, a systematic review and meta-analysis of 522 SE cases (32% focal motor SE, 17% generalized SE, 50% NCSE) in 486 adults and 36 minors, by Strzelczyk et al, demonstrated an overall lacosamide efficacy of 57%, though timing of administration varied significantly, from hours to days after onset of SE.[48] A 2014 meta-analysis of 27 studies and 798 cases of convulsive SE by Yasiry et al compared the relative effectiveness of antiseizure medications.[49] Due to a paucity of literature, lacosamide was excluded in the study; however, important findings were noted for levetiracetam, valproate, and phenytoin.

Levetiracetam, Valproate, and Phenytoin

The Yasiry et al meta-analysis noted important findings for levetiracetam, valproate, and phenytoin.[49] Regarding levetiracetam, there were very few drug-drug interactions or adverse side effects. Similarly, valproate was well-tolerated, even with larger doses and rates of infusion, though hyperammonemia remained a concern in high-risk populations. Phenytoin's side-effect profile, including cardiac arrhythmia, hypotension, and infusion site reactions, made it a less favorable option.[49]

Second-Line Antiseizure Medications Summary

Based on these comparative reviews, one may consider the use of lacosamide subsequent to other first-line antiseizure medications but before escalation to IV anesthetic medications (eg, propofol, thiopental, pentobarbital), though this is not yet standard of care. When using these medications, it is important to be aware of the side-effect profile of each drug and use with caution.[2,50] **(See Table 8.)**

Management of Refractory and Super-Refractory Status Epilepticus

For patients with refractory SE, treatment recommendations include adding another non–benzodiazepine antiseizure medication or proceeding directly to the initiation of anesthetic anticonvulsants.[39,51] At every stage, the goal of treatment is cessation of clinical and electrographic seizures.

Midazolam and propofol are commonly used infusion agents, though there are no large randomized controlled trials that demonstrate a clear superiority between the agents in patients with refractory and

Table 8. Side-Effect Profiles of Second-Line Antiseizure Medications[50]

Second-Line Therapy	Side Effects	Patient Conditions Requiring Caution for Use
Levetiracetam	Psychiatric symptoms, drowsiness	Mood disorders
Valproic acid	Thrombocytopenia/neutropenia, drowsiness, tremors, teratogenicity	Thrombocytopenia, hepatotoxicity, hyperammonemia, pancreatitis, child-bearing age in females
Phenytoin, fosphenytoin	Cardiac arrhythmia, Stevens-Johnson syndrome, hypotension, purple glove syndrome (phenytoin)	Hepatic dysfunction, hypotension
Lacosamide	Cardiac arrhythmia, PR prolongation	Cardiovascular disease (PR prolongation)
Phenobarbital	Respiratory depression, hypotension	Hypotension

super-refractory SE.[52] One retrospective cohort study found comparable outcomes in efficacy and complications. In this study, patients initially managed with propofol infusions were more likely to require the addition of a second anesthetic infusion compared with those on midazolam infusions, although the difference was marginal.[53] The Neurocritical Care Society recommends a midazolam bolus of 0.2 mg/kg IV followed by continuous infusion of 0.05 to 2 mg/kg/hr or propofol bolus 1 to 2 mg/kg IV followed by continuous infusion at 30 to 200 mcg/kg/min.[4]

Ketamine at 0.5 to 3 mg/kg IV followed by a continuous infusion of 0.1 to 5 mg/kg/hr may be used for patients who do not respond to midazolam or propofol infusions and require further seizure control, although some case reports recommend a trial of ketamine prior to other IV anesthetics for possible avoidance of endotracheal intubation.[2,54-56]

Although the clinical signs of SE may disappear with treatment, patients may still harbor NCSE, and a high index of suspicion should be maintained even after the patient's convulsive activity has ceased. Continuous EEG monitoring is crucial to confirm NCSE, and subtle features may increase concern and warrant additional treatment.[57]

Regarding PNES, antiseizure medications will not be effective, and supportive care is ultimately the treatment. However, if there is uncertainty about the diagnosis of psychogenic SE, and SE remains high on the differential, the patient should be treated as having SE until it can be effectively ruled out.

Special Populations

Substance-Induced Status Epilepticus

SE may be secondary to intoxication or withdrawal of recreational or prescription drugs. Nine percent of SE cases are substance-induced and have been described in the setting of drug intoxication with antidepressants, stimulants, antihistamines, tramadol, and isoniazid, among others.[58] If isoniazid toxicity is suspected, pyridoxine should be given in addition to standard treatment. Phenytoin is not recommended for patients with drug-induced SE, as it has been shown in experimental studies and case reports to be ineffective in terminating drug-induced seizures. Reasons cited for this include phenytoin's selective activity on voltage-gated sodium channels, which may not be enough to terminate seizures caused by drugs that cause more diffuse effects on the CNS.[59,60]

Pregnant Patients

A 2024 survey of 95 neurointensivists and neurologists by Swor et al found that seizure is the most common major neurologic complication in pregnancy.[61] SE may occur in pregnancy as the result of pre-existing epilepsy or it can emerge as a new diagnosis. In the former, pregnancy causes hormonal changes that affect the levels of antiseizure medications in the blood, often causing subtherapeutic levels and breakthrough seizure, which may ultimately progress to SE.[62] In newly diagnosed patients, there should be an investigation for a primary underlying etiology driving SE, such as posterior reversible encephalopathy syndrome, reversible cerebral vasoconstriction syndrome, eclampsia, or cortical venous thrombosis.[63] Obstetric team consult should be obtained promptly for all pregnant patients presenting with seizures.

In general, any pregnant patient presenting with seizures should receive magnesium empirically while further history and collateral information are obtained. If magnesium fails to terminate SE, benzodiazepines are typically also administered.[2,61,64] Neurocritical Care Society guidelines recommend lorazepam and fosphenytoin as emergent initial therapy and urgent control therapy, respectively, for seizures in pregnant patients; however, given their teratogenic effects in the first trimester of pregnancy, they also recommend caution with fosphenytoin/phenytoin, as well as valproate sodium.[2] Based on data from recent pregnancy registries suggesting less risk with newer antiseizure medications, levetiracetam should be considered for SE in the pregnant patient.[2] Though there are conflicting data about the safety of these medications in pregnancy, most of the studies examined the fetal effects of chronic exposure rather than brief exposure to the agent.[63,64]

If first-line therapy is insufficient, second-line agents include phenytoin, lacosamide, levetiracetam, and phenobarbital. One proposal calls for the use of levetiracetam or phenytoin and valproic acid only if other medications have failed.[64] This protocol excludes lacosamide due to a lack of data on maternal and fetal outcomes. A 2024 survey of 95 neurologists and neurointensivists reported that, in the setting of pregnancy, 89% of respondents preferred levetiracetam as a first-line agent (after administration of benzodiazepine), followed by lacosamide if an additional agent was needed.[61] The treatment of refractory and super-refractory SE involves anesthetic agents, similar to nonpregnant patients, with preferred choices among clinicians being midazolam followed by propofol and thiopental, as well as consideration for early delivery.[64,65]

If new-onset SE is caused by eclampsia, the primary treatment is administration of magnesium sulfate and delivery. Magnesium is administered as a loading dose of magnesium sulfate 4 to 6 grams IV over 15 to 20 minutes, followed by a continuous infusion of 1 to 2 g/hr.[64]

Pediatric Patients

For pediatric patients, benzodiazepines remain the first-line emergent initial therapy of choice. The benzodiazepine recommendations for pediatric patients are the same as for adults, with no recommen-

Case Conclusions

CASE 1

For the 65-year-old man with glioblastoma who presented to the ED via EMS with ongoing tonic-clonic movement of the right face, arm, and leg…

Lorazepam seemed to control the seizures, but 1 hour post administration, he was still not responding, and you suspected that he was in subtle convulsive SE. A bedside EEG was performed and confirmed your suspicion. The patient was loaded with levetiracetam 60 mg/kg IV, but his mental status remained depressed, his respiratory drive deteriorated, and the EEG continued to show uncontrolled seizure activity. Because the patient was in refractory SE, you intubated him, started a propofol infusion, and admitted him to the ICU, where continuous EEG monitoring showed burst wave suppression. In the ICU, the infusion was down-titrated after a period of seizure cessation that was shown clinically and on EEG. A lumbar puncture was performed to rule out infectious causes. Ultimately, an MRI brain scan with and without contrast was performed to assess the progression of his glioblastoma and radiation necrosis/scarring.

CASE 2

For the 25-year-old woman with a psychiatric history who presented with acute onset of paranoid ideation…

Your differential diagnosis included drug overdose, brainstem stroke, metabolic encephalopathy, and nonconvulsive seizures. Her initial workup of fingerstick glucose, CBC, CMP, electrolytes, urine toxicology, pregnancy screen, and lactate were all normal. CT scan of the head was normal, followed by a normal CT angiogram. Because of this young adult's acute onset of psychiatric manifestions, nystagmus, and other repetitive motor activity, your suspicions were raised for autoimmune encephalitis. You treated her with 4 mg IV lorazepam, which resulted in normalization of her mental status and resolution of her physical findings. After video monitoring in the epilepsy unit, a diagnosis of NCSE was made and confirmed.

dation for one over another. Recommended first-line benzodiazepines are IM midazolam (5 mg for weight 13-40 kg or 10 mg for weight >40 kg); IV lorazepam (0.1 mg/kg, max 4 mg); or IV diazepam (0.15-0.2 mg/kg, max 10 mg). Rectal, buccal, and intranasal formulations of benzodiazepines have level B evidence for their use and are probably effective for stopping SE.

The pathophysiology of SE and its effects on receptors are not different between pediatric patients and adults,[3] so when benzodiazepines fail, pediatric treatment should follow the same pathway as that for adults. In fact, the ESETT trial included both children and adults when assessing efficacy of levetiracetam, valproate, and phenytoin.[45] For young children with a history of epilepsy who develop SE, IV pyridoxine should be given in case they have pyridoxine-dependent epilepsy.[2,3] Though rare (with an incidence range of 1:20,000 to 1:276,000 and 1:783,000), pyridoxine-dependent epilepsy should be considered in the pediatric patient, typically aged <18 months, with intractable seizures that do not respond to conventional anticonvulsants.[66,67]

5 Things That Will Change Your Practice

1. An algorithm-based approach for the treatment of SE will allow for prompt treatment with less delay.
2. Avoid underdosing of benzodiazepines. Underdosing does not decrease the risk for respiratory compromise and may increase risk for respiratory decompensation.
3. For patients with a suspected etiology of toxic ingestion, consider an alternative second-line agent for termination of seizure activity, and avoid phenytoin.
4. When the postictal period is prolonged, consider whether the patient is experiencing ongoing subtle convulsive SE or NCSE. A portable EEG may be able to help diagnose this if conventional EEG is not readily available.
5. To reduce the likelihood of intubation in patients with refractory SE, a trial of ketamine prior to the use of propofol or midazolam should be considered.[54-56]

Controversies and Cutting Edge

Ketamine for Refractory Status Epilepticus

One area of controversy involves the use of ketamine as an initial IV anesthetic for terminating SE or as an adjunct to other anesthetics such as midazolam or propofol. Given that ketamine acts as an NMDA receptor antagonist, it seems reasonable that its use would be effective in counteracting the increased NMDA receptor activation seen in SE, thus terminating it. Literature on this topic is limited to case reports, case series, and reviews, most of which demonstrate that ketamine is more effective when administered earlier in the course of refractory SE and super-refractory SE, with its efficacy dropping from 64% to 32% by 3 days.[68] Another important finding in these case series is avoidance of endotracheal intubation.[56] There are no published randomized controlled trials on this topic, and a randomized controlled trial aimed at evaluating the efficacy of ketamine versus other anesthetic agents in treating refractory SE in children was terminated due to insufficient number of patients for recruitment.[69] This continues to be an area of controversy that requires more investigation. To avoid the need for intubation in patients with refractory SE, a trial of ketamine prior to the use of propofol or midazolam should be considered.

Ganaxolone

Ganaxolone, a synthetic neuroactive steroid with activity at both synaptic and extrasynaptic $GABA_A$ receptors, was FDA-approved in an oral suspension in 2022. An IV formulation of ganaloxone is under investigation for treatment of refractory SE. In a phase 2 trial, 17 patients received ganaxolone after failure of benzodiazepine and antiseizure medication but before initiation of IV anesthetics. Among the patients receiving ganaxolone, median time to SE cessation was 5 minutes, and none of the treatment patients required escalation to IV anesthetics within 24 hours of receiving the drug. This medication shows promise in reducing morbidity and mortality associated with refractory and super-refractory SE.[70] A phase 3 trial is currently underway.

Risk Management Pitfalls in Managing Status Epilepticus in the Emergency Department

1. **"The patient isn't having any abnormal movements, so he's not seizing anymore."** Not all SE is convulsive SE. For any patient with altered mental status, NCSE should be included in the differential diagnosis. In 14% of cases of SE, NCSE persisted on EEG after convulsions stopped.[72] Furthermore, NCSE commonly presents with altered mental status and coma. Continuous EEG monitoring is crucial in further elucidating whether the patient remains in SE.

2. **"We gave 2 mg of lorazepam, so the seizure should stop."** Underdosing benzodiazepines is a common problem, leading to inadequate treatment and a lower likelihood of seizure cessation. The first-line treatment recommended by the Neurocritical Care Society and the American Epilepsy Society is for administration of 0.1 mg/kg of lorazepam IV up to 4 mg, repeated once, with maximum dose of 8 mg.

3. **"The point-of-care EEG showed no seizures, so we didn't need formal EEG monitoring."** Whether or not a patient's convulsions cease, continued management with EEG monitoring should be undertaken. Point-of-care EEGs, if available, can be helpful in ruling out NCSE but are still limited compared with traditional EEG testing.

4. **"The patient has a history of epilepsy, so the seizures must be due to nonadherence. No further workup is required."** Though a history of epilepsy is a risk factor for SE, a workup should still be undertaken to ensure there are no underlying etiologies driving the SE. Several conditions, such as infection, sleep deprivation, drug use, pregnancy, stress, and new medications (eg, oral contraceptives) lower the seizure threshold in these patients, which may lead to the development of breakthrough seizures and SE. Prompt identification of those underlying conditions may assist in management of SE.

5. **"The patient in SE is pregnant and has an elevated blood pressure, so we should give a benzodiazepine to stop the seizures."** Prompt involvement of the obstetrics team for pregnant patients is crucial to ensuring appropriate diagnosis and management. In these patients, one should consider eclampsia as the diagnosis and administer IV magnesium for treatment of seizures. If IV magnesium fails to abort the seizure, benzodiazepines should be given.

Thrombolysis for Patients With Todd Paralysis

An area of uncertainty around SE involves administration of thrombolysis in patients with a Todd paralysis (a subsequent focal paralysis). Focal paralysis may be confusing on presentation, as strokes may present with seizures at onset, making it unclear whether a patient's focal deficit is secondary to seizure activity alone or seizure activity in the setting of stroke. For patients in whom stroke is considered the likely diagnosis, thrombolytics are recommended as long as no other contraindications are present. While this may raise concern for increased complication rates, the complication rates in stroke mimics are low, at 0.4%.[71]

Emerging Technologies for Electroencephalogram Monitoring

Technologies are being developed to reduce the time and resources needed for EEG application and interpretation. These include simplified placement of electrodes and caps and bands that serve as screening tools to help determine whether patients require conventional EEG monitoring.[74] This type of "point-of-care EEG" or "spot EEG" could be particularly beneficial in settings with limited access to standard EEG equipment, despite its limitations and variability on sensitivity and accuracy of screening. The DECIDE multicenter observational clinical study was a prospective study in 5 academic hospital ICUs throughout the United States that studied a type of "spot EEG" and reported improved sensitivity, specificity, and confidence in physician diagnosis.[74] Much of this literature is industry-sponsored and more data on its utility are needed. Although these reduced-montage approaches have improved the rate and access to EEG, the false-positive rate with rapid EEG and seizure prediction algorithms remains high.[75] Further research and technological advancements are necessary, particularly in the development of accessible, cost-effective EEG monitoring that can be deployed in a broader range of clinical settings.

6. **"The patient has renal failure, so I should reduce the loading dose of levetiracetam."** If a patient is in SE and has renal failure with no contraindications to other medications, other antiseizure medications in the algorithm may be used. If levetiracetam is being used, the loading dose should not be reduced. Subsequent maintenance dosing should be corrected for renal function.

7. **"We successfully treated the seizures, so the patient does not need a higher level of care."** Most, if not all patients, will require some form of inpatient monitoring. If a patient is no longer seizing and they do not meet critical care unit requirements, admission to an inpatient neurology service for further workup of the cause of their SE is appropriate.

8. **"The patient is in NCSE, so I don't need to be as aggressive treating it as with convulsive SE."** NCSE is a medical emergency similar to convulsive SE that should be treated to avoid brain damage. If a point-of-care EEG demonstrates that the patient is in NCSE, it should be treated promptly and effectively. In one study, patients with NCSE treated within 10 hours had 10% mortality as opposed to those who remained in NCSE for at least 20 hours, where mortality was 85%.[73]

9. **"The patient's seizures stopped after I administered a benzodiazepine. They don't need any more medications."** All patients with SE should receive both a benzodiazepine and a first-line antiseizure medication unless the immediate cause of SE has been identified and is definitively corrected, as in metabolic abnormalities. Benzodiazepines are short-acting and, to ensure adequate treatment of SE and prevention of return of seizures, a longer-acting antiseizure medication will provide sustained control and ensure seizure suppression.

10. **"The patient's saturations are in the low 90s, so I will give a lower dose of benzodiazepine to protect their airway."** Underdosing of benzodiazepine can occur due to concern for respiratory failure; however, this leads to a poor response and lower likelihood of seizure cessation and increases the risk for respiratory failure, because prolonged seizures cause more profound respiratory compromise than does treatment-dose benzodiazepine.[40] It is important to give treatment-dose benzodiazepine as a first-line treatment for SE.

Disposition

If a patient's SE has aborted with first- and/or second-line agents and there is slow but gradually improving return to baseline, they should be admitted to an inpatient neurology service for further workup and management. A brief period of observation should ensue to confirm that there is no further seizure activity before discharge.

Patients who are in refractory or super-refractory SE who are on IV anesthetic agents need to be admitted to an intensive care unit (preferentially a neurointensive care unit, when available), where continued titration of anesthetic agents can be provided. If there is high suspicion for ongoing seizures or NCSE and EEG monitoring is not immediately available, consideration should be given to transferring the patient to a center with EEG capability.

Summary

SE is a neurological emergency that requires prompt recognition and initiation of treatment, which should ideally begin before the patient reaches the hospital. Differentiating SE from mimics such as syncope, intoxication, locked-in syndrome, and non–epileptic seizures is important to ensure correct therapy is delivered. Etiologies may include pre-existing epilepsy, toxidromes, metabolic abnormalities, and CNS insults. Prolonged seizures lead to molecular changes that can increase the refractoriness of seizures and lead to a feedback loop in which benzodiazepines become less effective over time.

Prompt treatment should be initiated with adequate dosing of benzodiazepines. If SE persists, antiseizure medications, which include levetiracetam, valproate, and fosphenytoin, should be administered. SE that does not terminate after first-line therapy is administered often requires intubation and the rapid initiation of anesthetic infusions. Point-of-care EEG systems are being developed to help frontline providers identify SE earlier. When these systems are available, they may assist in ruling out SE in moderate to high-risk patients. In most cases, patients should be admitted to an ICU where continuous EEG monitoring is available.

Time- and Cost-Effective Strategies

- Ensure that adequate treatment doses of benzodiazepines are administered. Providing adequate dosing decreases the risk for progression to refractory and super-refractory SE, thus saving time and decreasing costs that may be associated with invasive procedures and initiation of IV anesthetics.
- Immediate collection of blood work to rule out immediate causes of seizures and SE, such as hypoglycemia or hyperglycemia, can save time and be less costly, once the driving cause is addressed. Treat any metabolic disturbances, infections, or other triggers as soon as possible. If SE is being driven by one of these underlying conditions, prompt treatment of the underlying etiology may prevent recurrence and decrease prolonged seizure activity, thus decreasing the need for further escalation of medications.

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 will be included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the authors, are noted by an asterisk (*) next to the number of the reference.

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Clinical Pathway for Management of Patients With Status Epilepticus in the Emergency Department

Click here or scan for interactive pathway

Patient presents with seizure-like activity

- Place on monitor
- Check airway, breathing, circulation
- Establish IV access

Seizure >5 minutes or 2+ seizures with no return to baseline between seizures?

NO

- Work up for underlying causes of breakthrough or first-time seizure
- Obtain neurology consult
- Monitor for ongoing seizure activity

YES

First-line: Administer treatment-dose benzodiazepine (AES Level A)
If IV access obtained:
- IV lorazepam, 0.1 mg/kg up to 4 mg, may repeat once **(NCS: Class I, Level A; AES Level A)**

If no IV access:
- IM midazolam, weight 13-40 kg: 5 mg; weight >40 kg: 0.2 mg/kg, max 10 mg; may repeat once **(NCS: Class I, Level A; AES Level A)**
- PR diazepam, 0.2-0.5 mg/kg up to 20 mg once **(NCS: Class IIa, Level A; AES Level B)**

Seizure persisting?

NO

- Work up for underlying causes
- Obtain neurology consult
- Disposition: inpatient neurology service

YES

Second-line: Administer antiseizure medication (no preferred agent among the 3, AES Level U)
- IV levetiracetam, 60 mg/kg up to max 4.5 g **(NCS: Class IIb, Level C; AES Level U)**
- IV valproate sodium, 40 mg/kg up to max 3 g **(NCS: Class IIa, Level A; AES Level B)**
- IV fosphenytoin, 20 mg PE/kg up to max 1.5 g **(NCS: Class IIa, Level B; AES Level U)**

If none of the above are available:
- IV phenobarbital, 15-20 mg/kg up to max 2 g **(NCS: Class IIb, Level C; AES Level B)**

If seizures do not abort and patient is in refractory SE, guidelines recommend:
- Repeat step with medication above not previously used
- IV lacosamide, 200-400 mg **(NCS: Class IIb, Level C)**
- IV medications as below

Seizure persisting?

NO

- Perform EEG as soon as possible to rule out nonconvulsive SE
- Disposition: inpatient neurology vs intensive care unit, pending stability

YES

Third-line: Patients at this stage should be intubated if not already done, and continuous EEG monitoring should be pursued. At this stage, there is no clear evidence to choose 1 agent over another. Options for treatment include:
- Midazolam infusion: load with 0.2 mg/kg and infuse at 0.05-2 mg/kg/hr with repeat bolus of 0.1-0.2 mg/kg if breakthrough seizure **(NCS: Class IIa, Level B; AES Level U)**
- Propofol infusion: load with 1-2 mg/kg and infuse at 30-200 mcg/kg/min **(NCS: Class IIb, Level B; AES Level U)**
- Pentobarbital infusion: load with 5-15 mg/kg and infuse at 0.5-5 mg/kg/hr (**NCS: Class IIb, Level B; AES Level U)**
- Thiopental: load with 2-7 mg/kg and infuse at 0.5-5 mg/kg/hr **(NCS: Class IIb, Level B; AES Level U)**

Agents limited to use only when additional seizure control is required:
- Ketamine: load with 0.5-3 mg/kg and infuse at 0.1-5 mg/kg/hr **(Class Indeterminate)**

Abbreviations: AES, American Epilepsy Society; EEG, electroencephalogram; IM, intramuscular; IV, intravenous; NCS, Neurocritical Care Society; PR, per rectum; SE, status epilepticus.

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1. **Which of the following is most suggestive of seizure rather than syncope?**
   a. Brief clonic or myoclonic jerks that cease when the patient is horizontal
   b. Lateral tongue laceration
   c. Prodrome of lightheadedness, dizziness, and dimming vision
   d. Loss of consciousness, with eyes closed, lasting a few seconds

2. **A patient with a history of psychogenic nonepileptic seizures presents to the ED after being found down in their urine. Per emergency medical services (EMS), the patient just had an altercation with a friend and subsequently collapsed, with shaking movements for 3 minutes, which were not recorded or described to EMS. On your evaluation, the patient is sleepy but arousable with tactile stimulus and able to state their name. There is dried blood on their lips, and you notice a lateral tongue bite. There are no abnormal movements noted. A prolactin level is negative. What is the best next course of action?**
   a. Observe for return to baseline and subsequently discharge, as this patient suffered a nonepileptic seizure.
   b. Load with 60 mg/kg levetiracetam IV due to concern for nonconvulsive status epilepticus (NCSE).
   c. Administer benzodiazepines for concern for status epilepticus (SE) and intubate for airway protection.
   d. Work up for underlying causes of seizures, including blood work, urine toxicology, head imaging, and electroencephalogram (EEG).

3. **Which of the following medications is most appropriate for an adult patient with active seizure activity and no intravenous (IV) access?**
   a. Intramuscular (IM) lorazepam
   b. IM midazolam
   c. Rectal midazolam
   d. Rectal diazepam

4. **Which of the following laboratory tests is most important in the initial evaluation of SE?**
   a. Serum glucose and electrolytes
   b. Serum prolactin
   c. Blood and urine cultures
   d. EEG

5. **All of the following patients should undergo further EEG monitoring EXCEPT:**
   a. A patient with a history of refractory seizures presenting with a single breakthrough seizure after several days of poor sleep; no further seizure activity now, with return to baseline.
   b. A patient previously in convulsive SE, now intubated.
   c. A patient with 2 seizures, now status post benzodiazepines, with poor mental status with very slow improvement.
   d. A patient with end-stage renal disease with blood urea nitrogen level 100 mg/dL, altered mental status, and frequent myoclonic jerks.

6. **A patient arrives at the ED in SE. They have a past medical history of thrombocytopenia. They have been treated with lorazepam 4 mg twice but have continued seizure activity. What second-line agent should be used with caution in this patient?**
   a. Valproic acid
   b. Levetiracetam
   c. Fosphenytoin
   d. Phenobarbital

7. **Which medication is appropriately matched with its side effect?**
   a. Phenobarbital/hypertension
   b. Valproic acid/psychiatric symptoms
   c. Levetiracetam/tremors
   d. Lacosamide/cardiac arrhythmia

8. **You are treating a patient with SE in the ED. The patient's convulsive SE aborts after being given valproic acid but she has persistently poor mental status. What is the best next step in management for this patient?**
   a. Monitor for return to baseline in the ED
   b. Admit to a neurology floor
   c. Intubate and admit to intensive care unit for EEG monitoring
   d. Empirically treat with second- and third-line treatments

9. **A patient presents to the ED with ongoing seizure activity. The patient is 37 weeks pregnant, with a blood pressure of 170/105 mm Hg. What is the treatment of choice for this patient?**
   a. IV lorazepam
   b. IM midazolam
   c. IV levetiracetam
   d. IV magnesium sulfate

10. **Prior to arrival to the ED, a patient experienced a seizure lasting >5 minutes. The seizure ceased after IM midazolam was administered. The patient has nearly recovered to their baseline neurologic status. What is their appropriate disposition?**
   a. To home
   b. Continued monitoring in ED for full return to baseline, with neurology consultation
   c. Admission to neurology service
   d. Admission to ICU

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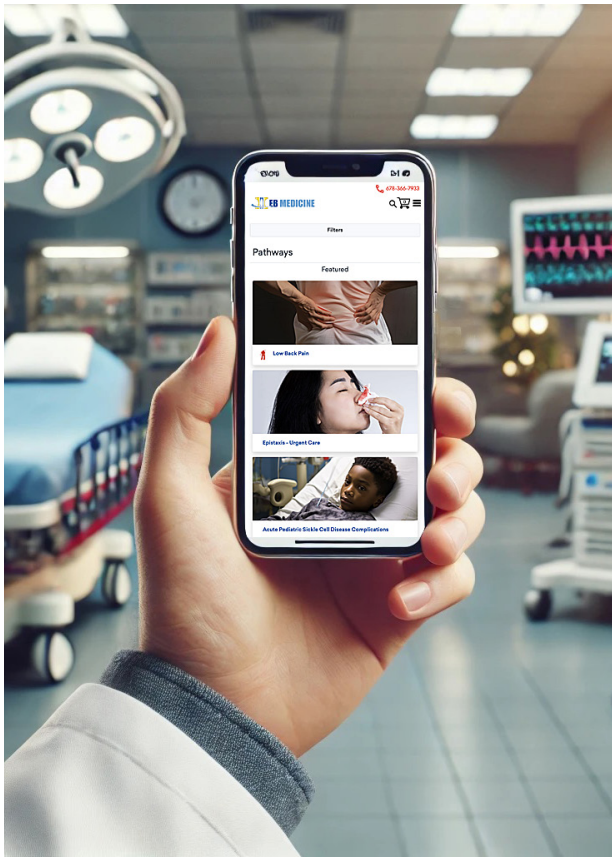

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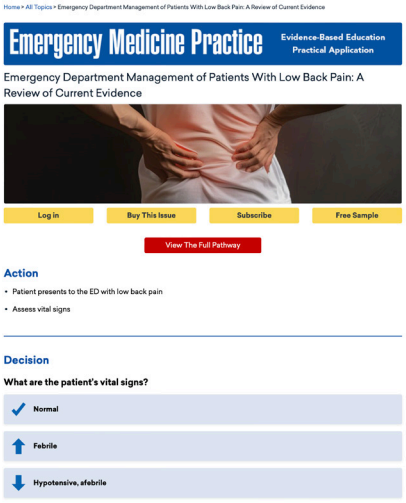

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QUICK READ

Points & Pearls

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Emergency Department Management of Patients With Status Epilepticus

Points

- Status epilepticus (SE) is the most extreme form of a seizure disorder and is associated with up to 30% morbidity and mortality in adults.[3]
- Irreversible neuronal injury has been shown to occur after 30 minutes of continuous seizure.[3]
- SE is categorized by 2 criteria: (1) with prominent motor symptoms, and (2) nonconvulsive forms.[1] **Tables 2 and 3** outline the classifications.
- The Neurocritical Care Society and the International League Against Epilepsy define SE as a seizure lasting for more than 5 minutes or recurrent seizure activity without recovery between seizures.[1,2]
- Hypoglycemia is a common trigger for seizures, and point-of-care blood sugar measurement should be performed.
- In 45% of SE cases, addressing the underlying etiology is required to gain control of seizures.[7]
- Acute etiologies include central nervous system (CNS) trauma or infection, cardiovascular events, toxic/metabolic encephalopathies, withdrawal, and electrolyte abnormalities.[1] **See Table 4.**
- Nonacute etiologies include withdrawal from alcohol or benzodiazepines, complications from previous CNS injuries (eg, stroke, demyelinating diseases, or autoimmune disorders) or, for epilepsy patents, experiencing a provoking factor or nonadherence to antiseizure medication.
- Elements of the history and physical examination, including specifics of the seizure event, such as onset, duration, and characteristics, are crucial in determining the cause.
- The differential diagnosis for SE is broad, and includes life-threatening diagnoses such as intracranial hemorrhage, as well as conditions such as syncope, movement disorders, or Guillain-Barré syndrome. **See Table 5.**
- Psychogenic nonepileptic seizures (PNES) can be difficult to differentiate from true seizures. Evidence of utility from biomarkers is limited.[18] Key to differentiation are the history and characteristics of the event.

Pearls

- Underdosing of first-line benzodiazepines leads to a lower likelihood of termination of SE, and an increased likelihood that greater levels of sedation will be required for seizure control.[44,45] **See Table 7** for dosages of first-, second-, and third-line medications for SE.
- Second-line treatment should be tailored to the patient's specific characteristics and comorbidities.[2,3,29] **See Table 8.**
- Electroencephalogram (EEG) monitoring is helpful when a patient does not return to baseline level of consciousness, there is concern for nonconvulsive status epilepticus (NCSE), or when a patient is sedated.[33]
- NCSE is underdiagnosed, as it may be present after clinical signs of SE have ceased.
- Postictal phenomena include depressed mental status, agitation, psychosis, or temporary weakness in the body part involved in the seizure (Todd paralysis.) Meningeal signs and headache may be masked; maintain suspicion for occult infection or NCSE.
- Prolonged postictal state may last minutes to hours; further testing is likely to be needed to distinguish from continued subclinical seizures.

- The patient's clinical scenario will dictate the laboratory testing that is required. **See Table 6.**
- In the case of a patient with altered mental status, new focal neurologic deficit, and suspicion for increased intracranial pressure/herniation, CT is usually performed before lumbar puncture.[29]
- Poor outcomes are associated with delays in treatment of CNS infections. Lumbar puncture is indicated for patients with seizures when signs of infection are present.
- Intermittent EEGs may be helpful but may miss up to 10% of subclinical seizures.[35]
- For pregnant patients, prompt involvement of the obstetrics team is crucial to ensure appropriate management.

