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Nonconvulsive Status Epilepticus: Overlooked and Undertreated

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Abstract

Nonconvulsive status epilepticus (NCSE) is characterized by persistent change in mental status from baseline lasting more than 5 minutes, generally with epileptiform activity seen on EEG monitoring and subtle or no motor abnormalities. NCSE can be a difficult diagnosis to make in the emergency department setting, but the key to diagnosis is a high index of suspicion coupled with rapid initiation of continuous EEG and early involvement of neurology. Benzodiazepines are the mainstay of first-line therapy, with antiepileptic drugs and anesthetics as second- and third-line therapies, respectively. The few established guidelines on the treatment of NCSE are highly variable, and the objective of this comprehensive review is to create a standardized evidence-based protocol for the diagnosis and treatment of NCSE.

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

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Case Presentations

An 81-year-old woman presents with 1 day of behavioral changes. On examination, she is disoriented, with no focal neurologic findings and no evidence of seizure activity. Her medical history is remarkable for anxiety, arthritis, and hypertension; she has no history of stroke, trauma, or immunocompromise. Her medications include furosemide, lorazepam, and acetaminophen. After an extensive workup in the ED including ECG, CBC, CMP, UA, and brain CT, all of which were normal, she was admitted to the floor. You wonder: Is there something you forgot to consider in your differential diagnosis?

A 35-year-old man with unknown history is brought to the ED following a 10-minute witnessed seizure. EMS administered 4 mg of lorazepam IV and fosphenytoin 1200 PE IVPB, which terminated the seizure; however, the patient remained altered. Brain CT was normal. ECG, CBC, CMP, VBG, UDS, and UA were unremarkable other than an elevated lactate that quickly cleared. You admit him to the ICU, but wonder: Is he is altered because he is postictal? Is it from the lorazepam, or could there be another etiology to consider?

A 42-year-old homeless man with bipolar disorder arrives by EMS after being found on a park bench. He has a temperature of 38.1°C (100.6°F) but otherwise normal vital signs. He smells of alcohol and has abrasions on his hands and face. GCS score is 10, and he is mumbling inappropriate but comprehensible words. Brain CT and cervical spine were normal. Laboratory testing demonstrated elevated BUN, Cr, CPK, and alcohol levels; mild leukocytosis; and normal UA and UDS. When his mental status did not improve, you order a lumbar puncture, but you wonder: Could another test could be diagnostic?

Abbreviations of Types of Status Epilepticus

ASE Absence status epilepticus
CPSE Complex partial status epilepticus
GCSE Generalized convulsive status epilepticus
NCSE Nonconvulsive status epilepticus
sCSE Subtle convulsive status epilepticus
SE Status epilepticus
SPSE Simple partial status epilepticus
SSE Subtle status epilepticus

Introduction

Seizures are classified as *partial* or *generalized*, and they can generate motor, sensory, psychiatric, or autonomic disturbances. A *partial* seizure denotes abnormal neuronal firing within a limited area of 1 brain hemisphere, whereas a *generalized* seizure constitutes abnormal firing diffusely across both hemispheres. Partial seizures are *simple* when they do not involve a change in mental status, and *complex* when consciousness is impaired. Seizures with altered mental status (AMS) but without motor activity are classified as *nonconvulsive seizures*.

Status epilepticus has been traditionally defined as a continuous seizure that lasts > 30 minutes, or multiple seizures in a 30-minute period without return to baseline. This definition was based largely on pathophysiologic observations that long-term consequences, including neuronal injury and death, result from seizures that last > 30 minutes. In practice, individual seizures that last > 5 minutes are prone to persist or recur before full recovery is made and, in all likelihood, represent status epilepticus.[1]

By definition, nonconvulsive status epilepticus (NCSE) presents with a persistent alteration in behavior or consciousness in the absence of convulsive activity, but the range of possible symptoms is broad. **(See Table 1 and Table 2, page 3.)** Although overt convulsions are absent, subtle motor signs such as twitching or blinking, extrapyramidal signs, or myoclonus may be seen.[2] Despite the lack of convulsive activity, NCSE may still result in neuronal injury, making early recognition and treatment critically important.

NCSE is underdiagnosed, especially in patients without antecedent convulsive seizures.[3] Many of these patients are not diagnosed in the emergency department (ED), either due to failure to consider the diagnosis or to lack of access to emergent encephalography (EEG), which confirms NCSE.[4,5] The role of EEG in the ED is evolving, and newer portable technologies are being developed that may increase access and allow rapid confirmation of suspected NCSE.[6]

This issue of *Emergency Medicine Practice* provides an evidence-based review of the diagnosis and management of NCSE. An emphasis is placed on increasing awareness in order to initiate timely therapy and prevent neurologic sequelae.

Classification and Taxonomy of Status Epilepticus

A 2015 report of the International League Against Epilepsy task force proposed a comprehensive classification system of convulsive and nonconvulsive

Table 1. Clinical Features of Nonconvulsive Status Epilepticus[7]

- Altered mental status (82%)
  - Confusion (49%)
  - Coma (22%)
  - Lethargy (21%)
  - Memory loss (8%)
- Speech disturbance (15%)
- Myoclonus (13%)
- Unusual behavior (11%)
- Anxiety, agitation, and delirium (8%)
- Extrapyramidal signs (7%)
- Hallucinations (6%)

forms of status epilepticus that has been largely adopted in the literature. The task force included 4 axes in its taxonomy: (1) semiology (clinical presentation), (2) etiology, (3) EEG correlates, and (4) age.[8] Semiology is perhaps the most helpful to the emergency clinician. In this classification, NCSE is subcategorized by the degree of impaired consciousness, and subcategorized further by clinical and electroencephalographic criteria. NCSE poses a diagnostic challenge to emergency clinicians, largely because the lack of convulsive activity leads to underrecognition, and because its signs and symptoms are nonspecific.

There are 3 general categories of NCSE: (1) partial seizure with preserved consciousness, known as *simple partial status epilepticus* (SPSE); (2) partial seizure with secondary generalization and altered consciousness, known as *complex partial status epilepticus* (CPSE); and (3) primary generalized (no focal origin), known as *absence status epilepticus* (ASE). ASE is sometimes associated with altered consciousness and is difficult to differentiate from CPSE. A fourth category sometimes included with NCSE is known as *subtle convulsive status epilepticus* (sCSE). sCSE is distinct from other forms of NCSE in that it occurs following untreated or undertreated generalized convulsive status epilepticus (GCSE), and it has a notably poor prognosis.[9] In many ways, sCSE is better classified with GCSE than NCSE.

The prevalence of NCSE in the ED is difficult to ascertain due to its varied presentations and delay in diagnosis. An early study found EEG evidence of NCSE in 34% of ED patients presenting with unexplained altered consciousness.[10] A 2013 study by Zehtabchi prospectively assessed ED patients with AMS and found EEG evidence of NCSE in 5%.[11]

Table 2. Clinical Subtypes and Features of Nonconvulsive Status Epilepticus[8,13,14]

NCSE Subtype	ILAE 2015 Definition	Clinical Features	EEG Features	Prognosis
Normal Consciousness				
Simple partial status epilepticus	Focal status epilepticus without impairment of consciousness	• Positive or negative symptomatology with preserved awareness • Can present with hemiparesis, ictal alien hand syndrome, and hemispatial neglect • Sensory, autonomic, or cognitive symptoms, depending on cerebral localization of discharges • Underlying focal epilepsy is common	• Variable findings or normal • Unilateral continuous or waxing and waning rhythmic spike-and-wave or high-voltage slow-wave discharges	Excellent for status itself, but overall prognosis depends on underlying cause
Impaired Consciousness				
Complex partial status epilepticus	Focal status epilepticus with impairment of consciousness	• Symptoms vary by involved area of cortex: ◦ Temporal lobe: fluctuating consciousness, fear, irritability, aggression, automatisms ◦ Frontal lobe type I: unilateral form with affective disinhibition and emotional lability ◦ Frontal lobe type II: bifrontal form with confusion and severe altered mental status	• Generalized slowing and/or suppression • Waxing and waning rhythmic delta activity largely lateralized to 1 side	Good to excellent, but often recurrent
Absence status epilepticus	Generalized NCSE – typical absence status epilepticus	• Prolonged altered mental status • Altered behavior, slow speech, or abnormal movements including regional bilateral (eyelid, perioral, or upper limb) myoclonus • Commonly seen in patients with known epilepsy	• Generalized continuous or waxing and waning 3-4 Hz spike and polyspike slow-wave discharges	Excellent, but may have recurrent attacks
Subtle status epilepticus	NCSE with coma	• Seen after convulsive status • No convulsive activity • May show myoclonus or nystagmus	• Focal, lateralized, or generalized epileptiform discharges • May evolve to a low-voltage pattern with ictal/inter-ictal discharges	Typically poor

Abbreviations: EEG, electroencephalography; ILAE, International League Against Epilepsy; NCSE, nonconvulsive status epilepticus.

However, this study used a 30-minute EEG; it may be speculated that continuous EEG (cEEG) for 24 to 48 hours would increase detection rates.

AMS is the presenting complaint in approximately 5% of ED patients, with 30% found to have a neurologic condition.[12] There is clinical overlap between NCSE and other etiologies of AMS, eg, stroke, traumatic brain injury, and encephalitis, all of which can also precipitate NCSE. Thus, the patient in NCSE is at risk for being misdiagnosed and even erroneously given a psychiatric diagnosis.

The prognosis is equally varied, depending on the subtype of NCSE and etiology of the underlying condition. NCSE in patients with hypoxic-ischemic encephalopathy after cardiac arrest have close to 100% mortality, whereas the morbidity and mortality of ASE is closer to zero. As with many disease states, prognosis in NCSE is related to the underlying condition, as opposed to direct effects of prolonged nonconvulsive seizure activity. This is an area of great controversy in the literature.

Critical Appraisal of the Literature

A review of the English-language literature was performed in PubMed, the Cochrane Database of Systematic Reviews, and MEDLINE®, using the following terms: *nonconvulsive status epilepticus, nonconvulsive status epilepticus,* and *status epilepticus.* A literature search of *status epilepticus* retrieved thousands of articles. However, many of these contained only cursory mention of NCSE. A more limited number of articles were retrieved when *nonconvulsive status* was searched. Of these, references most relevant to adult emergency medicine were reviewed.

Literature surrounding NCSE is limited largely to retrospective studies, case series, and anecdotal reports. Due to the paucity of large trials, information extrapolated from the status epilepticus literature was incorporated, namely large trials that included NCSE as a subset.

There are no consensus statements or clinical guidelines regarding emergency management of NCSE, specifically. There are several guidelines regarding the management of seizures, status epilepticus, and AMS, and to the extent that these guidelines could be extrapolated to NCSE, they were included in the review. Guidelines from the American College of Emergency Physicians (ACEP), the American Epilepsy Society, the American Academy of Neurology, the Society of Critical Care Medicine, and the Neurocritical Care Society were examined.[1,15-19]

By standard criteria and evidence scales, clinical data on NCSE are relatively weak. There are several reasons for this. First, NCSE is uncommon, and rigorous clinical trials are resource-intensive to perform. Second, diagnostic criteria are evolving, and gathering of evidence requires standardization. Third, definitive diagnosis is based on EEG, a modality rarely available on an emergent basis. Finally, advances in understanding of the clinical and EEG features of NCSE call into question data based on prior observational studies of status epilepticus, as well as the body of literature surrounding undifferentiated AMS. When possible, recommendations in this article are evidence-based. Recommendations based on extrapolated status epilepticus consensus statements and accepted practice are noted as such.

Etiology and Pathophysiology

The majority of seizures are self-limited due to endogenous gamma-aminobutyric acid (GABA)-mediated inhibitory pathways.[20] When convulsive activity is prolonged, these pathways are overwhelmed, resulting in the perpetual state of excitation seen in status epilepticus. At the cellular level, increased energy consumption leads the ATP-dependent sodium-potassium pump to fail, and rising extracellular potassium leads to over-excitability and acidosis.[21] GABA receptors are down-regulated, and remaining receptors are conformationally altered, rendering them less responsive to benzodiazepines.[22,23] Additionally, N-methyl-D-aspartate (NMDA) receptors are upregulated, potentiating neuronal excitability. [1,19,24] These derangements form the molecular basis of GCSE.

NCSE is not a single illness, but a symptom with multiple potential etiologies. In CPSE and SPSE, neuronal networks in the hippocampus and adjacent limbic and neocortical structures experience the same cellular and molecular derangements that lead to self-perpetuating excitation in GCSE.[25] In ASE, by contrast, a global "inhibitory" state occurs via GABA transmission in thalamocortical networks; NMDA-mediated excitotoxicity is not thought to play a role.[2,25-27] This distinction is important, since it impacts pharmacologic management.

Although the subtypes of NCSE share pathophysiology with GCSE to a varying degree, there are 2 important distinctions in NCSE. First, the pathophysiology of the underlying cause is often as clinically significant as the NCSE itself. Medication withdrawal, trauma, infection, and stroke are just a few reported precipitating etiologies of NCSE that may independently contribute to neurotoxicity. Second, much of the morbidity and mortality in GCSE is due to systemic sequelae of prolonged convulsions (lactic acidosis, respiratory failure, rhabdomyolysis, etc), which is generally not relevant in NCSE. Nonetheless, animal experiments and more limited human studies support the hypothesis that sustained excitation may similarly damage neurons involved in excitatory forms of NCSE, but data are far less robust, and results are conflicting.[28-36]

Though it has never been proven that CPSE and

ASE independently lead to brain damage, many experts argue that prompt identification and management of both NCSE and the underlying cause are important to prevent morbidity.[33,37,38]

Although epilepsy is the condition most frequently associated with NCSE, only 50% of patients with NCSE have a prior diagnosis of epilepsy.[39] Most episodes of NCSE in epilepsy are triggered by changes in antiepileptic drug (AED) levels, often caused by drug-drug interactions.[40,41] The emergency clinician should consider NCSE when the patient has suffered structural, toxic, or metabolic insults to the brain. **(See Table 3.)**

Differential Diagnosis

The primary reason that NCSE is underdiagnosed is that it is simply not considered. The only symptom seen consistently in NCSE is AMS, which ranges from mild confusion to obtundation.[42] The differential diagnosis is thus the same as that for any patient with AMS. **(See Table 4.)**

NCSE (SPSE, CPSE, and ASE) can present with any type of psychiatric symptom, including mood disturbance, irritability/impulsivity, delusions, and psychosis.[43] Patients may complain of hallucinations, inappropriate behavior (eg, laughing or crying), or paranoia.[44-46] SPSE can present with isolated fear.[47] CPSE and SPSE are more likely than ASE to mimic all psychiatric conditions, with the exception of catatonia.[48]

Given that NCSE can be diagnosed only by EEG, it is not surprising that many patients go undiagnosed by psychiatrists and emergency clinicians, but certain factors should trigger investigation. Consider NCSE in patients whose psychiatric disease abruptly worsens following reduction or addition of psychotropic or benzodiazepine medication.[49] NCSE should also be in the differential for patients with no psychiatric history who suddenly develop isolated psychiatric symptoms such as delusions or hallucinations. Although hallucinations may be clinically indistinguishable from a primary psychiatric disorder, features that favor NCSE include altered awareness, automatisms, and insight that the hallucinations are not real.[50] NCSE may also present similarly to neurologic diagnoses such as migraine with aura, transient global amnesia, and transient ischemic attacks.[13]

Table 3. Common Etiologies of Nonconvulsive Status Epilepticus

- Traumatic brain injury
- Stroke
  - Ischemic stroke
  - Hemorrhagic stroke
  - Subarachnoid hemorrhage
- Anoxic brain injury
- Medications
  - Intoxication
    - Antibiotics: cephalosporins, penicillins, imipenem, ciprofloxacin
    - Other: ifosfamide, methotrexate, tiagabine, lithium, chloroquine, pseudoephedrine, tramadol
  - Withdrawal
    - Benzodiazepines, baclofen, opioids
- Encephalitis
  - Infectious
  - Autoimmune
  - Creutzfeldt-Jakob disease

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Prehospital Care

Prehospital management of NCSE is primarily supportive unless sCSE is suspected. In these cases, emergency medical services (EMS) should follow status epilepticus protocols and/or contact medical control. Hypoglycemia is a consideration in all patients with AMS or seizures, so point-of-care blood glucose level should be obtained.[16] Patients in NCSE may be unable to give history at the hospital, so the most important role of EMS may be in gathering information from witnesses and family and bringing in patient medications.

Table 4. Differential Diagnosis for Nonconvulsive Status Epilepticus

Neurological
- Postictal state
- Cerebrovascular accident/transient ischemic attack
- Transient global amnesia
- Migraine with aura
- SMART syndrome
- Central nervous system infection
- Concussion

Psychiatric
- Interictal/postictal psychosis
- Psychiatric disorders
- Psychogenic nonepileptic seizures

Other
- Metabolic encephalopathy/hypoglycemia
- Intoxication: lithium, tricyclic antidepressants, alcohol, benzodiazepines, baclofen, opioids
- Withdrawal: alcohol, benzodiazepines, baclofen, opioids
- Neuroleptic malignant syndrome/serotonin syndrome
- Sepsis
- Malingering

Abbreviation: SMART, stroke-like migraine attacks after radiation therapy.

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Emergency Department Evaluation

The first step in diagnosing NCSE is considering the diagnosis. Incorporating information from EMS, family, and the medical record, and performing a thorough physical examination are key to suspecting NCSE and starting therapy expeditiously. **Table 5** lists key history and physical findings.

History

The history is paramount in raising suspicion of NCSE. Age, medical comorbidities, and history of symptom time course are valuable parameters to obtain. Reviewing the medical record and interviewing witnesses (such as EMS and family members) may provide critical information regarding recent events and a reliable indication of the patient's baseline. A thorough history may rule in or out other causes of AMS and/or elicit risk factors for NCSE. One such risk factor is a sudden unexplained departure from baseline, such as the acute onset of psychosis without prior psychiatric history, or an abrupt worsening of a known psychiatric condition, particularly in the context of recent changes to medications.

Background information regarding trauma, infection, or recent illnesses is helpful and may guide management. AED noncompliance is the most common cause for recurrent seizures in the ED and may also precipitate NCSE.[51] A social history of substance abuse may reveal risk factors for alcohol withdrawal and traumatic brain injury, both of which may lead to NCSE.

A prospective case series of patients in whom NCSE was suspected found that remote risk factors for seizures (including previous stroke, tumor, previous neurosurgery, dementia, and meningitis), depressed mental state, and ocular movement abnormalities were all significantly more common in patients with NCSE than in age-matched controls.[42] The combination of remote risk factors for seizure and ocular movement abnormalities was 100% sensitive but only 55% specific for NCSE.[42] Given that NCSE requires EEG for definitive diagnosis, no clinical finding is perfectly specific; however, highly sensitive findings may be used to determine which patients require urgent EEG.

A key historical feature is prior events, especially if they are stereotypic. If the patient or family give a history of past events with the same features, such as a period of psychotic behavior with sudden onset and offset or prolonged periods of blank stare (perhaps with blinking), the diagnosis of NCSE is possible.

Another key to the history is identifying factors that lower seizure threshold, including new medications, infection, drugs and alcohol, trauma, and AED noncompliance. Subtherapeutic AED levels are common, but even well-controlled patients may experience NCSE. The half-life of some AEDs is short, and missing even a single dose can be problematic. Patients with pre-existing epilepsy represent a subset of NCSE with a favorable prognosis.[52,53]

Table 5. Clinical Findings and Risk Factors in Nonconvulsive Status Epilepticus

Suggestive Features

- Preceding convulsion with prolonged postictal confusion
- Altered mental status*: somnolence, subtle changes in cognition/attention, disorientation
- Psychiatric symptoms*: mood (irritable, labile), psychosis, confabulation, bizarre behavior
- Ocular abnormalities: nystagmus, blinking, gaze deviation
- Sensory phenomena: pain, hot/cold sensation, hallucinations (olfactory, gustatory, auditory, visual)
- Subtle motor activity: limb paralysis or myoclonic jerks
- Automatisms: lip smacking, chewing
- Autonomic disturbances: mydriasis, sweating, hypertension, flushing
- Speech disturbance: mutism, stuttering, echolalia, reduced speech

Risk Factors

- History of epilepsy
- Remote/acute brain insult
  - Stroke
  - Traumatic brain injury
  - Tumor
  - Previous neurosurgery
  - Dementia
  - Meningitis
- Elderly (females > males)
- Acute metabolic or septic triggers
- Recent medication changes or antiepileptic drug withdrawal

*Especially if rapid in onset or no prior psychiatric history.

Physical Examination

There are several physical examination findings that may alert the clinician that the patient is in NCSE. The foundation of a thorough examination is a full set of vital signs (including fingerstick glucose) and general appearance of the patient. Fever and/or hypotension can suggest an infectious etiology of AMS, although low-grade fever can also be caused by a seizure. Evidence of head trauma, tongue biting, hyperreflexia, positive Babinski reflex, or incontinence suggest that a convulsive seizure recently occurred.

The neuropsychiatric examination is fundamental. This examination must be systematic, including cranial nerves, motor, sensory, cerebellar, reflexes, and cognition. The cranial nerve examination should include extraocular movements and evaluation of other abnormal eye movement such as nystagmus. The cognitive examination should include orientation, attention (months of the year in reverse), and recall of 5 objects at 1 and 5 minutes. The motor examination should look for evidence of automatisms (ie, repetitive stereotypic movements), which are highly suggestive of ongoing NCSE. Of note,

posterior circulation strokes can cause nonfocal motor weakness with AMS.

Retrospective studies have identified statistically significant association of NCSE with head and eye deviation, nystagmus, focal myoclonus of the face or extremities, and automatisms such as lip smacking, orofacial movements, and hand/arm movements.[54] Numerous cognitive disturbances such as aphasia, perseveration, echolalia, and confabulation have been seen, as have psychic and sensory phenomena.[54]

Diagnostic Studies

Laboratory Studies

Laboratory testing will not diagnose NCSE but can exclude alternative, reversible causes of AMS. Recommended tests include complete blood cell (CBC) count, complete metabolic profile (CMP), pregnancy test in women of childbearing age, serum AED levels (when appropriate), and urine drug screen.[15,55-57]

ACEP has no guideline for NCSE, but guidelines for first-time seizures give Level B recommendations to measure glucose and sodium, and state that urine drug screen can be considered.[15] Although an otherwise healthy adult patient with 1 new-onset seizure and return to baseline does not necessarily need laboratory testing, a patient with suspected NCSE will not be at baseline, and a more conservative approach is warranted.

Neuroimaging

Once stabilized, patients with undifferentiated AMS or those suspected of having NCSE should undergo computed tomography (CT) scan of the brain. A summary statement from a collaboration of ACEP with organizations from neurology, neurosurgery, and neuroradiology recommended that head CT be performed in patients who have had a seizure and have a history of head trauma, malignancy, anticoagulation, or immune compromise, and anyone with fever, persistent headache, new focal neurologic examination, age > 40 years, or focal onset before generalization.[57] The ACEP clinical policy for AMS goes further, recommending CT in any patient with a depressed level of consciousness.[55]

Lumbar Puncture

Lumbar puncture is often performed in patients with unexplained AMS and a negative CT scan. ACEP recommends lumbar puncture in patients who are immunocompromised, or when suspicion for central nervous system infection or subarachnoid hemorrhage persists (Level B).[15,55] White blood cells in the cerebrospinal fluid should be considered to be meningitis until proven otherwise, although pleocytosis is found in 20% to 30% of patients who have had a convulsive seizure.[58-61]

Electroencephalography

An EEG is required to confirm the diagnosis of NCSE. In addition to confirming the diagnosis, EEG may provide prognostic information and is helpful in monitoring response to treatment.[62,63]

EEG interpretation in NCSE is complex, even for experts in the field; however, it plays a critical role in confirming the diagnosis. There are several EEG classification systems used by epileptologists to aid in the diagnosis of NCSE. One systematically developed and validated classification system, known as the *Salzburg criteria*, is sensitive and specific for diagnosing NCSE.[64] Application of the criteria requires expert analysis that may not be available in the ED. Nevertheless, a recent preliminary study showed that, with a brief EEG training module, emergency physicians can improve diagnostic accuracy of detecting seizure activity on EEG.[65]

Of note, CPSE begins with a focal discharge that then becomes secondarily generalized; the EEG is not able to reliably distinguish CPSE from ASE when the patient is actively seizing; thus, an interictal EEG is needed.

Treatment

Therapeutic strategies in NCSE are controversial, due in part to differing prognosis across the subtypes. There are no large prospective, randomized trials or specialty society guidelines regarding pharmacotherapy in NCSE. Thus, management is based on expert consensus, small series and case reports, and extrapolation of the GCSE literature, when appropriate. The most important considerations when determining the therapeutic approach are the NCSE subtype and the underlying etiology.

In 2016, the American Epilepsy Society published a guideline that provides a 4-phase time-dependent treatment algorithm for status epilepticus that has been endorsed by ACEP.[16] Elements of this guideline are applicable to NCSE, particularly sCSE, including the stabilization and initial therapy phases. **(See the Clinical Pathway, page 10.)**

In the stabilization phase (the first 5-20 minutes), priorities include cardiac monitoring, vital signs, fingerstick glucose, establishing intravenous (IV) access, securing the airway when indicated, and maintaining oxygenation and ventilation. In NCSE, as in GCSE, correctable etiologies should be addressed early. If the patient is hypoglycemic, 50 mL of 50% dextrose is administered IV. Thiamine 100 mg IV should be given to malnourished and alcoholic patients.[66] In an altered patient with unexplained fever, empiric antibiotics should not be delayed for CT or lumbar puncture.

Pharmacologic Therapy

It appears that subtypes of NCSE may respond differently to certain medications. The approach to NCSE is generally less aggressive than for GCSE, as the association with neurological morbidity is comparatively less clear (with the exception of sCSE).[53] When suspicion for NCSE is high, empiric pharmacotherapy should be started, though it is ideally deferred until an EEG is obtained (except in sCSE). Additional management is guided by clinical improvement and EEG response. A subtype-specific treatment approach to NCSE is summarized in **Table 6**, and specific pharmacologic agents are detailed in **Table 7, page 9**.

First-Line Treatment

First-line treatment for NCSE is a benzodiazepine. ASE is exceptionally sensitive to these drugs. CPSE is often responsive as well, though response may be delayed and recurrence is common.[68] By contrast, in sCSE, first-line drugs are more likely to fail than succeed, so the need for a second agent should be anticipated and ordered early.[53] Nine randomized controlled trials have addressed the efficacy of initial therapy in status epilepticus, but few have separately analyzed sCSE.[53,70-77] Many trials used older definitions of status epilepticus, limiting confidence in the extrapolation of this data to NCSE under the modern definition.

Lorazepam, diazepam, and midazolam are all effective as first-line agents in NCSE. Lorazepam is the most commonly used and most often-studied agent. Lorazepam has a smaller volume of distribution and a longer duration of action than either diazepam or midazolam, which is advantageous in treating NCSE. A systematic review of 18 studies including 2755 patients with different types of status epilepticus determined that IV lorazepam was superior to diazepam.[78]

In patients without IV access, intramuscular (IM) lorazepam is recommended. Rectal diazepam is a consideration, but has delayed and erratic absorption. The 2012 RAMPART trial demonstrated superiority of IM midazolam in patients without established IV access.[70]

Second-Line Treatment

After administration of a first-line benzodiazepine, treatment with a long-acting AED is often indicated unless the NCSE was caused by a correctable factor

Table 6. Treatment Approach in Nonconvulsive Status Epilepticus, by Subtype[14,67,68]

Subtype	Treatment Strategy	Treatment Response	Prognosis
Absence status epilepticus	• PO or IV benzodiazepine ◦ 4 mg lorazepam IV; repeat in 10 min as needed ◦ If benzodiazepine fails, give PO valproic acid or IV valproate • May consider IV levetiracetam, PO/NGT topiramate, or IV lacosamide in refractory cases (decision made with neurology consultation)	• Excellent	Excellent
Simple partial status epilepticus	• IV benzodiazepine ◦ 4 mg lorazepam IV; repeat in 10 min as needed • Consider IV phenytoin/fosphenytoin, valproate, or levetiracetam for second agent • Treat underlying cause • May consider PO/NGT topiramate or IV lacosamide in refractory cases or as second agent (decision made with neurology consultation)	• Excellent	Good to excellent
Complex partial status epilepticus	• IV benzodiazepine ◦ 4 mg lorazepam IV; repeat in 10 min as needed • Consider IV phenytoin/fosphenytoin, valproate, or levetiracetam for second agent • Treat underlying cause • May consider PO/NGT topiramate or IV levetiracetam in refractory cases or as second agent (decision made with neurology consultation) • In protracted cases or critically ill patients, consider intubation and continuous propofol or midazolam	• Good, but often delayed • Limbic form may be more resistant to benzodiazepine	Good to excellent
Subtle convulsive status epilepticus	• IV benzodiazepine with second agent such as IV phenytoin/fosphenytoin, valproate, or levetiracetam • Intubation and continuous propofol or midazolam as third-line agents • Consider additional agent such as PO/NGT topiramate, IV lacosamide, IV ketamine, or other strategies in conjunction with neurology/intensivist to ensure successful wean • Most patients are managed in the ICU	• Poor • Treatment responsiveness is determined by underlying cause	Poor

Abbreviations: ICU, intensive care unit; IV, intravenous; NGT, nasogastric tube; PO, by mouth.

(eg, hypoglycemia or hyponatremia).[1] In a sense, "second-line" therapy is a misnomer, because most patients with NCSE require a second medication even if the benzodiazepine was successful in termination of the status. The notable exception is with ASE. True ASE is situation-dependent and rapidly responsive to benzodiazepines, so elimination of the precipitating factor and transient benzodiazepine therapy is typically sufficient for control.[68]

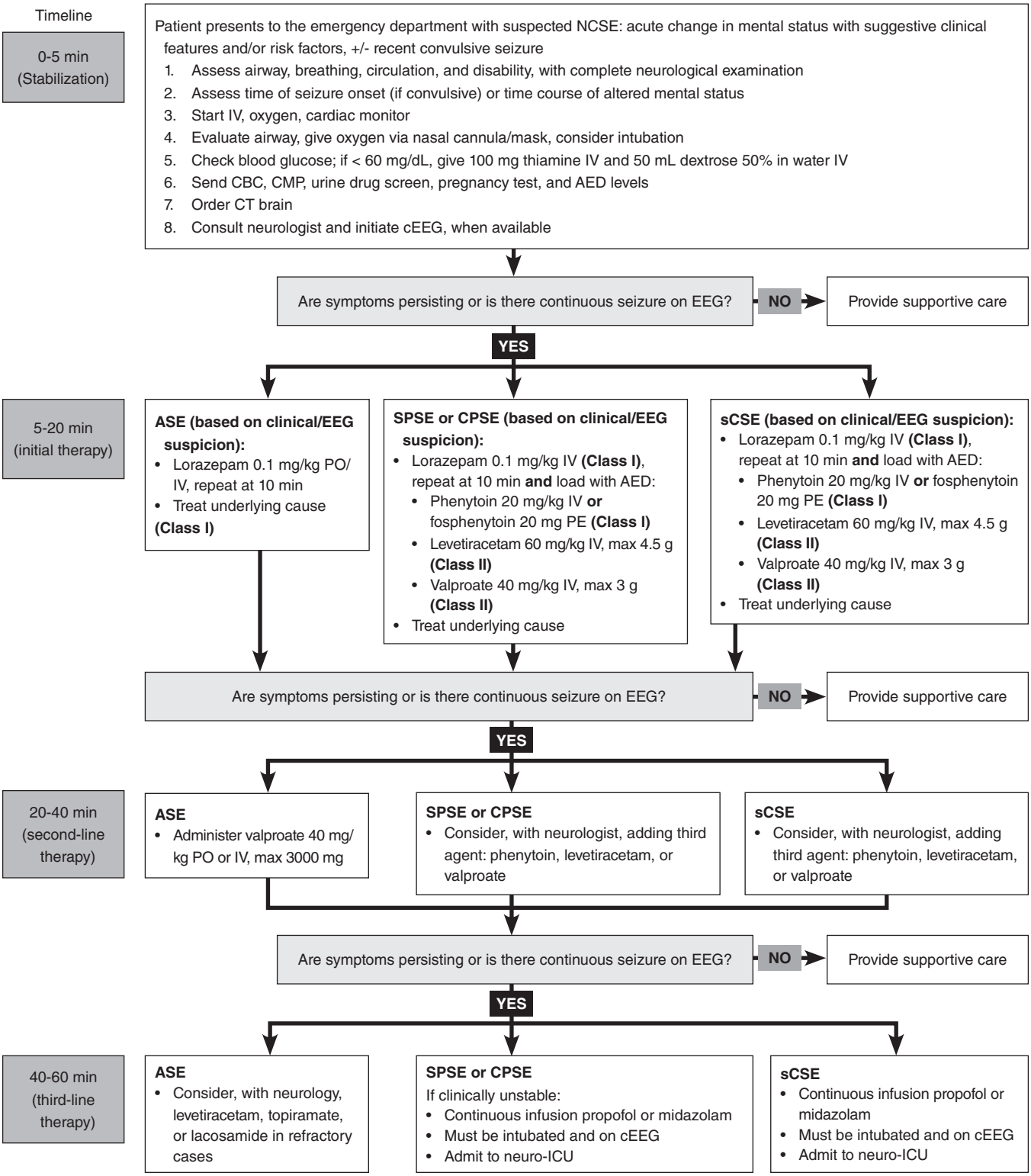
There are far fewer data regarding second-line medications, and no large randomized controlled trials comparing these drugs in NCSE. The most-studied agents include phenytoin, fosphenytoin, valproate, and levetiracetam. Efficacy data are conflicting, and the choice may be guided by clinical parameters. For a patient with epilepsy, it is reason-

Table 7. Pharmacotherapy for Nonconvulsive Status Epilepticus[16,69]

Drug	Dosing	Infusion Rate	Adverse Effects	Considerations
Intermittently Dosed Medications, First Line				
Lorazepam	• 0.1 mg/kg IV up to 4 mg; repeat in 5-10 min	IV push	• Hypotension • Respiratory depression	• Best evidence, most-often used • Long acting
Midazolam	• 0.2 mg/kg IM **or** • Up to 10 mg IV	IV push	• Hypotension • Respiratory depression	• Short duration • Useful if no IV access • Active metabolite, renal elimination
Diazepam	• 0.15 mg/kg IV up to 10 mg; repeat in 5 min • 0.2 mg/kg per rectum, max 20 mg	IV push	• Hypotension • Respiratory depression	• Shorter duration of seizure suppression than lorazepam • Active metabolite
Intermittently Dosed Medications, Second Line				
Phenytoin	• 20 mg/kg IV • May give additional 5-10 mg/kg at 10 min	No faster than 50 mg/min	• Hypotension • Arrhythmia	• Perform cardiac monitoring during loading dose • Low pH may cause phlebitis/necrosis
Fosphenytoin	• 20 mg phenytoin equivalent/kg • May give additional 5 mg/kg at 10 min	No faster than 50 mg/min	• Hypotension • Arrhythmia	• Cardiac monitoring during loading dose • May be given IM
Levetiracetam	• 40-60 mg/kg up to max 4.5 g	Over 15 min	• Rare	• Not hepatically metabolized
Valproate	• 20-40 mg/kg IV	No faster than 10 mg/min	• Rare	• Works well in absence status epilepticus
Phenobarbital	• 20 mg/kg IV • May give additional 5-10 mg/kg at 10 min	50-100 mg/min	• Hypotension • Respiratory depression	• Synergistic respiratory depression with benzodiazepines
Intermittently Dosed Medications, Third Line				
Lacosamide	• 200-400 mg IV	No faster than 200 mg/15 min	• PR prolongation	• Limited experience in status epilepticus
Topiramate	• 200-400 mg PO/NGT	N/A	• Metabolic acidosis	• No IV formulation
Refractory/Continuous Medications (Require Mechanical Ventilation)				
Drug	**Dosing**	**Titration Rate**	**Adverse Effects**	**Considerations**
Midazolam (benzodiazepine)	• 0.05-2 mg/kg/hr	0.05-1 mg/kg every 3-4 hr	• Respiratory depression • Hypotension	• Tachyphylaxis • Short half-life
Pentobarbital (barbiturate)	• 5-15 mg/kg loading dose followed by a continuous infusion at 0.5-5 mg/kg/hr	0.05-1 mg/kg every 12 hr	• Respiratory depression • Hypotension • Cardiac depression • Paralytic ileus • Neurotoxic at high doses	• Half-life 15-60 hr • Theoretically neuroprotective • Must be withdrawn gradually
Propofol (sedative-hypnotic)	• 1-2 mg/kg bolus followed by a continuous infusion of 5-75 mcg/kg/min	Start at 20 mcg/kg/min and titrate by 5-10 mcg/kg/min every 5 min	• Respiratory depression • Hypotension • Propofol-related infusion syndrome	• Short half-life

Abbreviations: IM, intramuscular; IV, intravenous; N/A, not applicable; NGT, nasogastric tube; PO, by mouth.

Clinical Pathway for Management of Nonconvulsive Status Epilepticus[19]



- Acceptable alternatives to lorazepam include midazolam and diazepam.
- Alcohol-associated NCSE: Give 100 mg thiamine IV.
- History of epilepsy: Check AED levels and load patient's prescribed AED.
- Intubation: Status epilepticus < 15-20 min is not a contraindication to succinylcholine.

Abbreviations: AED, antiepileptic drug; ASE, absence status epilepticus; CBC, complete blood cell (count); cEEG, continuous EEG; CMP, complete metabolic panel; CPSE, complex partial status epilepticus; CT, computed tomography; EEG, electroencephalography; ICU, intensive care unit; NCSE, nonconvulsive status epilepticus; PE, phenytoin equivalent; PO, by mouth; sCSE, subtle convulsive status epilepticus; SPSE, simple partial status epilepticus.

For Class of Evidence definitions, see page 11.

able to choose an IV formulation of their prescribed AED when levels are subtherapeutic.

The Veterans Affairs (VA) Cooperative Study was a large randomized controlled trial comparing first-, second-, and third-line agents in status epilepticus (which included patients with sCSE). A much smaller margin of efficacy was achieved with all second-line agents, emphasizing the tendency for medications to become less effective as seizures persist. Agents studied included lorazepam, phenytoin, phenobarbital, and diazepam in different combinations, but there was no statistically significant difference between second-line agents.[53]

The combination of a benzodiazepine and valproic acid has been shown to successfully treat and prevent recurrences of ASE.[79,80] Phenytoin and valproate are effective in ASE in the elderly and in SPSE and nonlimbic CPSE when benzodiazepines fail; limbic CPSE and sCSE respond poorly.[67] Some authors have suggested that phenytoin may worsen ASE.[81,82]

Levetiracetam has shown promise as a second-line agent, but data are conflicting. Both SPSE and limbic CPSE have shown response.[83,84] However, in a multicenter randomized controlled trial of IV levetiracetam (2.5 g) added to clonazepam (1 mg) in prehospital treatment of status epilepticus, levetiracetam did not confer additional benefit.[85]

Newer broad-spectrum AEDs such as lacosamide and topiramate are sometimes used as second- and third-line agents.[86-88] These drugs are relatively safe, with few drug-drug interactions. A large multicenter prospective noninterventional study of status epilepticus (of which 18.5% of patients had NCSE) found that IV lacosamide was 77.6% effective.[87] A 2013 review of all reported cases of lacosamide noted overall efficacy of 56%; however, this included many cases of convulsive status epilepticus.[89] A more recent review suggested that, taking into account efficacy and side-effect profiles, the combination of valproate and lacosamide may be superior to phenytoin and levetiracetam in the treatment of NCSE.[90] Results have also been supportive of topiramate; however, topiramate is not available in IV form.[88]

There is insufficient evidence that any particular second-line agent is superior overall, and it is unlikely that a single agent is the correct second-line choice in every case of NCSE. The ongoing Established Status Epilepticus Treatment Trial (ESETT) may bring us closer to the answer.[91] In the meantime, decisions regarding second-line therapy should, whenever possible, involve the consultant neurologist and take into account the subtype of NCSE, the underlying precipitant, and the clinical status of the patient.

Third-Line Treatment

If the benzodiazepine and AED are ineffective, a third AED is unlikely to terminate status epilepticus. The VA study showed that second-line drug therapy was successful 7% of the time, and third-line agents were successful in only 2.3% of patients.[53]

At this stage, it is increasingly important to weigh the risks of continued NCSE against the side effects of additional medication. For critically ill patients with refractory GCSE (eg, significant autonomic instability or respiratory failure), this stage of treatment involves preparation for intubation and continuous infusion of a seizure-suppressing anesthetic. This approach is applicable to sCSE and certain cases of CPSE, but is almost never appropriate in ASE, where patients are typically less ill and morbidity from continued NCSE is presumed to be very low. Clinical monitoring for NCSE after rapid sequence intubation and paralysis is impossible; thus, cEEG is required. However, in emergent cases, securing the airway should not be delayed while waiting for EEG. These patients should be transferred to the intensive care unit.

The agents most often studied for continuous infusion are midazolam, propofol, and pentobarbital. There are insufficient data to suggest a superior agent.[92,93] A systematic review determined that the failure rate of pentobarbitone (8%) was lower than that of midazolam or propofol (23%);[94] however,

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
- Nonrandomized or retrospective studies: historic, cohort, or case control studies
- Less robust randomized controlled trials
- 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

pentobarbitone was associated with a higher risk of severe hypotension, and mortality was high (48%) regardless of the drug used. In practice, propofol and midazolam are preferred and more commonly used.[67,68]

Propofol is an attractive option for emergency physicians and intensivists who are typically comfortable with its use, though it is known to cause hypotension and, rarely, the more ominous propofol infusion syndrome, which is marked by hepatotoxicity and metabolic acidosis with rhabdomyolysis and cardiac failure.[95] Midazolam may cause less hypotension; however, because the patient has failed benzodiazepine therapy, it may be preferable to add an agent with a different mechanism of action.[1,94] All continuously infused anesthetics require assisted ventilation and may require vasopressors for associated hypotension.

Special Populations

Patients Abusing Alcohol

Up to 40% of seizures presenting to the ED can be attributed to alcohol abuse, either by excess intake or withdrawal. Alcohol withdrawal has been reported in 15% to 24% of patients with GCSE, but it may also play a role in NCSE.[96] Alcoholics are also at increased risk for falls, and more prone to traumatic brain injury-related seizures, as alcohol use lowers the seizure threshold. Finally, alcohol abuse can cause metabolic disorders such as hypoglycemia and hyponatremia and deficiencies in vitamins and electrolytes, which can predispose patients to seizure. These conditions should be rapidly assessed and corrected.

Alcohol withdrawal syndrome occurs 6 to 48 hours after decreased intake, and can last up to 7 days, although it should be noted that the history may be inaccurate.[97] Although simple alcohol withdrawal syndrome seizures may not mandate neuroimaging, all patients with status epilepticus or a first-time alcohol-related seizure warrant neuroimaging. A retrospective review of 259 patients with alcohol-related seizures found a clinically significant brain lesion on CT imaging in 6% of the subjects.[98]

Chronic alcoholism is associated with neuropsychiatric conditions including delirium tremens, alcoholic hallucinosis, and Wernicke encephalopathy. Increasingly, alcohol is being recognized as a precipitant of NCSE.[40] One group found that a history of alcohol abuse was frequently associated with de novo ASE.[49] Additionally, cases of ASE precipitated by alcohol withdrawal have been reported, where patients presented with a protracted course of confusion and cognitive abnormalities.[99]

Researchers in the 1980s first described a disorder in alcoholics that was characterized by confusion, lethargy, transient motor deficits, and EEG abnormalities.[100] The authors named the condition *subacute encephalopathy with seizures in alcoholics*, or *SESA syndrome*. The diagnostic criteria for SESA syndrome have recently been modified, and it is now recognized to include focal NCSE in alcoholics who manifest transient neurologic deficits and characteristic EEG abnormalities.[68] Prognosis is generally good, although chronic AED therapy may be required to prevent recurrence.[68] Increased awareness of this syndrome should trigger expedited EEG in the alcoholic patient presenting with new unexplained neurologic findings.

The treatment for alcohol withdrawal seizure is lorazepam. The treatment for alcohol withdrawal is a benzodiazepine, with one not showing superiority over another. Phenytoin has no role in alcohol withdrawal syndrome seizure termination and preventing recurrent seizures. There are no studies comparing second- and third-line agents in alcohol-related NCSE, so treatment should proceed using the pathway for the NCSE subtype, taking into account alcohol withdrawal management algorithms.

Adjunctive IV thiamine should be given empirically. Thiamine deficiency is common in this population, and Wernicke encephalopathy has extensive clinical overlap with NCSE. Thiamine is inexpensive, well tolerated, and effective in treating Wernicke encephalopathy, and is unlikely to complicate treatment of status epilepticus.[101] By contrast, alcohol-related deficiencies such as magnesium and potassium should be confirmed rather than treated empirically.

Elderly Patients

The elderly are particularly susceptible to NCSE, and paradoxically more difficult to diagnose and manage.[102,103] Higher susceptibility may be due to polypharmacy and a higher incidence of cerebrovascular disease and other focal cerebral diseases that form a substrate for NCSE.[104] Diagnosis is frequently delayed,[102] presumably because changes in mental status may be mistakenly attributed to chronic illnesses, medications, or age-related cognitive decline.[105] Morbidity and mortality are comparatively higher for elderly patients with NCSE.[106]

Researchers have attempted to determine whether NCSE has unique features in elderly patients. Multiple groups have noted that NCSE in the elderly is far more common in women.[49,107-110] One group found that, in patients aged ≥ 60 years presenting with AMS of unknown etiology, female gender, rapid onset (< 24 hours), and lack of response to commands were statistically more frequent in the NCSE subset when compared to the patients with nonepileptic confusion.[106] Another study found that elderly patients with NCSE are less likely to have a history of epilepsy.[111]

Management of NCSE in the elderly poses a

challenge, as older patients are more susceptible to side effects of AED therapy (eg, respiratory/cardiac depression and sedation) and more likely to be taking other medications that lead to dangerous drug interactions.[112] Some authors suggest that most of the morbidity and mortality seen in elderly patients with NCSE is related to underlying comorbidities, and a conservative approach is warranted.[26,112] However, studies have shown that the elderly can be safely and effectively treated,[113] and experts have offered modified dosing protocols for AED therapy in older patients.[105] Failure to treat NCSE promptly could lead to aspiration pneumonia, falls, and impaired quality of life. Therefore, treatment of NCSE in the elderly is warranted and important, albeit with a cautious approach that employs modified dosing and care to avoid drug-drug interactions.

Controversies and Cutting Edge

Bedside Electroencephalography

EEG is the gold standard for diagnosis of NCSE, and its role in the ED is evolving. The sensitivity of EEG increases when it is performed continuously, up to 48 hours.[114] However cEEG is time- and resource-intensive, and there is controversy about which patients benefit most. Traditionally, cEEG has been recommended when GCSE is refractory to first- and second-line AEDs, as many of these patients require intubation with neuromuscular blockade, which may mask signs of continued seizure activity.[114]

Current American and European guidelines call for targeted use of cEEG in ICU populations with GCSE in order to detect NCSE transformation;[116] however, NCSE is increasingly being recognized in patients without preceding convulsive activity and in patients who are not critically ill. In these patients, diagnosis is often delayed. The American Clinical Neurophysiology Society published a consensus statement in 2015 that included expanded recommended indications for cEEG in the diagnosis of NCSE.[117] **(See Table 8.)** This guideline is explicitly for ICU patients; however, many of the criteria apply to ED patients as well.

ACEP has no official position on cEEG, but does give a Level C recommendation to considering emergent EEG in patients with SSE or suspected NCSE, patients who have received a long-acting paralytic, or patients in a drug-induced coma.[15] EEG availability in the ED is limited, as few departments have access to equipment and personnel trained to interpret findings. Several simplified bedside EEG systems are available, with sensitivities ranging from 40% to 93%.[118] One group has advocated an emergency EEG kit, in a system that would employ a telemedicine epileptologist to interpret the EEG remotely.[119] Other studies suggest EEG training modules for emergency clinicians for the purpose of recognizing NCSE.[120,121] Interpretation of these simplified EEGs requires training on wave patterns indicative of NCSE (ie, rhythmicity, periodicity, spike, and wave), but even with expert interpretation, these modalities have inferior sensitivity, and results must be confirmed with conventional EEG.[118] Further research is needed to explore point-of-care EEG for the evaluation of AMS in the ED.

Additional Treatment Options

Ketamine, an NMDA-receptor antagonist, has been proven in multiple studies to be effective in status epilepticus, and has shown synergy with valproate, diazepam, and propofol.[122-125] As GCSE evolves, the number of NMDA receptors increases, making ketamine theoretically more effective as time passes. In a 2013 multicenter retrospective review, 58 adults received ketamine, and permanent control was achieved in 57% of the patients.[126] A more recent retrospective review of 42 patients with refractory status epilepticus showed a resolution rate of 64%.[127] It is unclear whether this effect would be as pronounced in ASE, in which NMDA receptors are not thought to play a primary role. In a trial that included convulsive and nonconvulsive forms of status epilepticus, the combination of ketamine and propofol effectively controlled NCSE in 9 of 13 patients.[124]

Some evidence suggests a dosing regimen for ketamine of 1 to 3 mg/kg IV bolus followed by continuous infusion of up to 5 mg/kg/hour.[66,122,123,127]

Table 8. Indications for Continuous EEG to Diagnose Nonconvulsive Status Epilepticus in the Critically Ill Patient

- Persistently abnormal mental status following generalized convulsive status epilepticus or other clinically evident seizures.
- Acute supratentorial brain injury with altered mental status.
- Fluctuating mental status or unexplained alteration of mental status without known acute brain injury.
- Generalized periodic discharges, lateralized periodic discharges, or bilateral independent periodic discharges on routine or emergent EEG.
- Requirement for pharmacological paralysis and risk for seizures (eg, therapeutic hypothermia protocols, extracorporeal membrane oxygenation).
- Clinical paroxysmal events suspected to be seizures, to determine if they are ictal or nonictal.

Abbreviation: EEG, electroencephalography.

Susan Herman, Nicholas Abend, Thomas Bleck, et al. Consensus statement on continuous EEG in critically ill adults and children, part I: indications. *Journal of Clinical Neurophysiology*. Volume 32, Issue 2. © 2015 by the American Clinical Neurophysiology Society. With permission of Wolters Kluwer Health, Inc. https://journals.lww.com/clinicalneurophys/fulltext/2015/04000/Consensus_Statement_on_Continuous_EEG_in.1.aspx

Risk Management Pitfalls for Patients With Nonconvulsive Status Epilepticus in the Emergency Department

1. **"I didn't even consider it…"**
   The clinical presentation of NCSE is highly variable. NCSE must remain on the differential of AMS or it will surely be missed, as EEG monitoring is not routine. NCSE can mimic anything from migraines, stroke, toxic ingestions, to psychiatric disorders. The strategy in the ED involves high clinical suspicion and an appropriate differential.

2. **"They can call neurology when the patient gets to the ICU."**
   Definitive diagnosis of NCSE requires an EEG, which may be difficult to obtain in the ED. Involvement of a multidisciplinary team is critical. Neurologists and neurointensivists encounter NCSE more frequently than other specialties, and their early involvement is important in the management of suspected NCSE.

3. **"Benzos didn't work. I was starting a second-line agent, and the nurse came to tell me that the sodium was 118."**
   NCSE represents a final common pathway for numerous pathologies. Seizures can be precipitated by various chemical and metabolic insults, with or without structural central nervous system abnormality. It is important to consider all possible causes and focus medical management on identifying a correctable etiology before escalating therapy (ie, seizures brought on by hypoglycemia, pre-eclampsia, isoniazid overdose, and drug toxicity).

4. **"The ICU resident looked in the chart. The patient has a history of cocaine abuse and traumatic brain injury."**
   Because patients are altered, EMS and caretakers are often the only source of information once the patient arrives to the ED. It is important to take a thorough history of events leading up to arrival at the ED, including EMS interventions, drugs of abuse, home medications, history of seizures, and any witnessed convulsive activity.

5. **"The patient still doesn't have an IV."**
   Obtaining IV access is one of the first steps when a critically ill patient presents to the ED. Always obtain multiple IV access sites and consider intraosseous access if IV access is difficult to obtain. If IV access is delayed, IM midazolam and rectal diazepam are viable options for first-line therapy.

6. **"Everything is back and all the tests are normal, but the patient is still altered. We can't get an EEG. Should we give a benzo?"**
   When NCSE is suspected and EEG is unavailable, consider an early trial of benzodiazepines and observe for clinical improvement. Benzodiazepine efficacy decreases the longer a seizure persists, so the initial agent should be started as quickly as possible; however prior to empiric treatment, coordination with neurology is ideal.

7. **"He didn't respond to lorazepam; let's give something different."**
   4 mg IV lorazepam is the accepted standard dose for emergent treatment of seizures. However, this may be subtherapeutic in an average-sized person, as weight-based dosing is 0.1 mg/kg. Suboptimal dosing can lead to refractory seizures and NCSE.

8. **"If we use rapid sequence intubation, we won't know if he is continuing to seize."**
   Medically induced coma and intubation with neuromuscular blockade carry additional risks that can be anticipated and mitigated with good supportive care. cEEG allows for assessment of continued seizure activity. If EEG is delayed but the airway is in jeopardy, intubation should not be postponed. In the ED, the threshold for intubation must be low, as prolonged seizures carry a high rate of morbidity and mortality.

9. **"His oxygen saturation dropped to 60% during the seizure, and he got hypotensive after intubation, but vitals are normal now. Phew!"**
   Hypoxia and hypotension increase mortality in the setting of brain injury. In patients with suspected NCSE, basic management (airway, breathing, circulation) should proceed simultaneously with other therapy. It is critical to maintain normal oxygenation and perfusion during continuous seizure activity.

10. **"He stopped convulsing, but I'm not sure whether he is still seizing."**
    The only way to truly know whether a patient is in NCSE is to monitor brain activity with cEEG. Failure to initiate cEEG early can lead to delayed recognition of clinical deterioration and diminished efficacy of antiepileptic therapy. Emergency clinicians must advocate at an institutional and specialty level for timely access to cEEG, initiated as soon as possible when the diagnosis of NCSE is considered.

When given in conjunction with propofol, reported infusion rates are in the lower range (25-175 mcg/kg/min), but there are no formal guidelines for "ketofol" in status epilepticus.

When pharmacotherapy has failed, there are anecdotal reports of electroconvulsive therapy, vagal nerve stimulation, or repetitive transcranial magnetic stimulation, but none have been rigorously studied in NCSE.[67]

Disposition

Patients with NCSE have a large spectrum of presentations, ranging from ambulatory and well-appearing to comatose and critically ill. Disposition depends on subtype, comorbidities, and underlying precipitants. Nevertheless, definitive diagnosis of NCSE in many cases requires cEEG with round-the-clock interpretation. The neuro-ICU, when available, is typically the appropriate setting for this level of care.

Summary

NCSE is underdiagnosed in the ED. It is a diagnosis that should be considered in all patients with new-onset AMS, new-onset unusual behavior, and in all patients who have had a seizure and exhibit a prolonged postictal state. Familiarity with NCSE subtypes and the range of possible presentations is critical in order for emergency clinicians to suspect the diagnosis. The 3 main categories of NCSE—ASE, SPSE, and CPSE—have certain distinctive clinical features but also a great degree of overlap. All have a generally good prognosis, provided NCSE is recognized and treated promptly and the underlying cause is addressed. By contrast, sCSE, which often results from untreated GCSE, is not strictly a subtype of NCSE, and has a generally poor prognosis. The diagnosis of NCSE should be pursued and managed while continuing to seek and address the underlying cause. A multidisciplinary approach that includes neurology and critical care specialists is crucial in the management of these patients.

Emergency treatment begins with the basics of resuscitation and stabilization. Workup includes a CMP, CBC, urine drug screen, pregnancy test, AED levels for patients with pre-existing seizure disorders (when appropriate), and a noncontrast head CT. Reversible factors such as hypoxia, hypoglycemia, and electrolyte imbalances should be corrected expeditiously. The emergency clinician should advocate for cEEG initiation as early as possible in the course of the workup, in order to properly assess response to therapy.

IV lorazepam is the gold standard first-line agent; however, except for cases of sCSE, it should be held until a diagnostic EEG is obtained. IM midazolam is an acceptable alternative if IV access is not established. Second-line treatments include phenytoin, fosphenytoin, valproate, and levetiracetam. Patients who are clinically unstable with refractory sCSE may require intubation and medically induced coma with propofol, midazolam, or phenobarbital. Treatment success is measured by signs of neurologic and/or EEG improvement.

Case Conclusions

The 81-year-old woman with AMS was evaluated by a neurologist on the floor. Her EEG showed irregular, rhythmic, generalized 2.0–2.5 Hz sharp-and-slow wave complexes that ceased after 10 mg of IV diazepam. Later, her husband noted that her daily lorazepam had recently been discontinued abruptly due to a change in insurance. The patient was diagnosed with NCSE. NCSE can develop in a patient with or without underlying epilepsy, and should be included in the differential of unexplained AMS, especially in the setting of chronic benzodiazepine use. A high level of suspicion is essential for early diagnosis, but urgent confirmatory EEG is required.[128]

After transfer to the ICU, the 35-year-old man who had a 10-minute witnessed seizure was evaluated by a neurologist and underwent urgent EEG, which showed continuous generalized spike-and-wave and polyspike-and-wave discharges. The patient was given levetiracetam 1500 mg IVPB, which produced marked improvement on EEG and eventual normalization of mental status. His clinical picture and EEG findings confirmed the diagnosis of CPSE. After an uneventful ICU stay, the patient was discharged with oral levetiracetam 1000 mg/day. NCSE should be on the differential diagnosis of any patient with status epilepticus who remains altered after convulsions have ceased. A high level of suspicion and urgent EEG are required to obtain early diagnosis and improve patient outcomes.

After the lumbar puncture, the 42-year-old homeless man's mental status remained poor. CSF showed only mild leukocytosis, and brain MRI revealed mild chronic involutional changes. EEG demonstrated generalized synchronous polyspike-and-wave discharges bilaterally. A trial of lorazepam led to rapid improvement in EEG and mental status. The patient was diagnosed with NCSE, and transitioned to oral levetiracetam. The differential diagnosis of AMS is broad, and in this case ranges from psychiatric disorder with concomitant drug abuse to posttraumatic amnesia. NCSE is difficult to diagnose in the emergent setting, and other causes of AMS must be systematically ruled out (ie, hypoglycemia, trauma, etc). Although the role of EEG in the ED is uncertain, the test is essential to diagnose NCSE.[66]

Time- and Cost-Effective Strategies

- **Coordinate the choice of neuroimaging.**
  In the acute setting, virtually all patients with new-onset or traumatic seizures receive a brain CT. In the setting of suspected NCSE, the neurologist may prefer MRI, due to its higher sensitivity for subtle structural lesions. Although CT is often faster in the ED, coordinating early with a multidisciplinary team may avoid redundancy, lower costs, and expedite clinical management.
- **Don't wait for confirmed diagnosis in sCSE; start treatment early.**
  The diagnosis of sCSE is rarely confirmed in the ED. If clinical suspicion is high, treatment must be initiated early. Prolonged seizures increase morbidity and mortality.
- **Identify subtherapeutic AED levels.**
  Subtherapeutic AED levels are a common precipitant and an easily correctable cause of seizures and status epilepticus.
- **Identify precipitating factors.**
  Precipitating factors may be the key to suspecting the diagnosis of NCSE, and addressing these factors may lead to termination of status. The key to eliciting these factors is a thorough history with attention to information provided by family and EMS.
- **Suspect the diagnosis in acute-onset altered behavior, especially in the elderly.**
  An acute onset of behavioral change, especially without a prior psychiatric or neurologic diagnosis, may be indicative of NCSE. If the time course corresponds to change in medications or other precipitating factors, the diagnosis of NCSE is further supported.

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 is included in bold type following the references, where available. 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.

1. Brophy GM, Bell R, Claassen J, et al. Guidelines for the evaluation and management of status epilepticus. *Neurocrit Care.* 2012;17(1):3-23. **(Guidelines)**
2. Fountain NB, Lothman EW. Pathophysiology of status epilepticus. *J Clin Neurophysiol*. 1995;12(4):326-342. **(Review)**
3. Shneker BF, Fountain NB. Assessment of acute morbidity and mortality in nonconvulsive status epilepticus. *Neurology.* 2003;61(8):1066-1073. **(Retrospective case series; 100 patients)**
4. Kaplan PW. Nonconvulsive status epilepticus in the emergency room. *Epilepsia.* 1996;37(7):643-650. **(Retrospective case series; 23 patients)**
5. Ziai WC, Schlattman D, Llinas R, et al. Emergent EEG in the emergency department in patients with altered mental states. *Clin Neurophysiol*. 2012;123(5):910-917. **(Single-center prospective cohort intervention study; 82 patients)**
6. Does the Use of Rapid Response EEG Impact Clinical Decision Making (DECIDE). Available at: https://clinicaltrials.gov/ct2/show/NCT03534258. **(Prospective nonrandomized observational multicenter clinical trial)**
7. Hesdorffer DC, Logroscino G, Cascino G, et al. Incidence of status epilepticus in Rochester, Minnesota, 1965-1984. *Neurology*. 1998;50(3):735-741. **(Epidemiological study)**
8. Trinka E, Cock H, Hesdorffer D, et al. A definition and classification of status epilepticus--report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia*. 2015;56(10):1515-1523. **(Review)**
9. Holtkamp M, Meierkord H. Nonconvulsive status epilepticus: a diagnostic and therapeutic challenge in the intensive care setting. *Ther Adv Neurol Disord*. 2011;4(3):169-181. **(Review)**
10. Privitera M, Hoffman M, Moore JL, et al. EEG detection of nontonic-clonic status epilepticus in patients with altered consciousness. *Epilepsy Res*. 1994;18(2):155-166. **(Prospective clinical trial; 198 patients)**
11. Zehtabchi S, Abdel Baki SG, Grant AC. Electroencephalographic findings in consecutive emergency department patients with altered mental status: a preliminary report. *Eur J Emerg Med*. 2013;20(2):126-129. **(Prospective observational study; 50 patients)**
12. Kanich W, Brady WJ, Huff JS, et al. Altered mental status: evaluation and etiology in the ED. *Am J Emerg Med*. 2002;20(7):613-617. **(Prospective cohort study; 317 patients)**
13. Meierkord H, Holtkamp M. Non-convulsive status epilepticus in adults: clinical forms and treatment. *Lancet Neurol*. 2007;6(4):329-339. **(Review)**
14. Kinney MO, Craig JJ, Kaplan PW. Hidden in plain sight: non-convulsive status epilepticus-recognition and management. *Acta Neurol Scand*. 2017;136(4):280-292. **(Review)**
15. Huff JS, Melnick ER, Tomaszewski CA, et al. Clinical policy: critical issues in the evaluation and management of adult patients presenting to the emergency department with seizures. *Ann Emerg Med*. 2014;63(4):437-447. **(Clinical policy)**
16. Glauser T, Shinnar S, Gloss D, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the Guideline Committee of the American Epilepsy Society. *Epilepsy Curr*. 2016;16(1):48-61. **(Guideline)**
17. Harden CL, Hopp J, Ting TY, et al. Practice parameter update: management issues for women with epilepsy--focus on pregnancy (an evidence-based review): obstetrical complications and change in seizure frequency: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. *Neurology*. 2009;73(2):126-132. **(Consensus statement)**
18. Le Roux P, Menon DK, Citerio G, et al. The International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care: a list of recommendations and additional conclusions: a statement for healthcare professionals from the Neurocritical Care Society and the European Society of Intensive Care Medicine. *Neurocrit Care*. 2014;21 Suppl 2:S282-S296. **(Consensus statement)**
19. Meierkord H, Boon P, Engelsen B, et al. EFNS guideline on the management of status epilepticus in adults. *Eur J Neurol*. 2010;17(3):348-355. **(Guideline)**

20. Lado FA, Moshe SL. How do seizures stop? *Epilepsia*. 2008;49(10):1651-1664. **(Review)**
21. Meldrum BS. Concept of activity-induced cell death in epilepsy: historical and contemporary perspectives. *Prog Brain Res.* 2002;135:3-11. **(Review)**
22. Jones-Davis DM, Macdonald RL. GABA(A) receptor function and pharmacology in epilepsy and status epilepticus. *Curr Opin Pharmacol.* 2003;3(1):12-18. **(Review)**
23. Chen JW, Wasterlain CG. Status epilepticus: pathophysiology and management in adults. *Lancet Neurol*. 2006;5(3):246-256. **(Systematic review)**
24. Wasterlain CG, Niquet J, Thompson KW, et al. Seizure-induced neuronal death in the immature brain. *Prog Brain Res*. 2002;135:335-353. **(Review)**
25. Hosford DA. Animal models of nonconvulsive status epilepticus. *J Clin Neurophysiol*. 1999;16(4):306-313. **(Review)**
26. Drislane FW. Evidence against permanent neurologic damage from nonconvulsive status epilepticus. *J Clin Neurophysiol*. 1999;16(4):323-331. **(Review)**
27. Huguenard JR, Prince DA. Clonazepam suppresses GABAB-mediated inhibition in thalamic relay neurons through effects in nucleus reticularis. *J Neurophysiol*. 1994;71(6):2576-2581. **(In vitro animal study; rats)**
28. Meldrum BS, Vigouroux RA, Brierley JB. Systemic factors and epileptic brain damage. Prolonged seizures in paralyzed, artificially ventilated baboons. *Arch Neurol*. 1973;29(2):82-87. **(Review)**
29. Sloviter RS. Decreased hippocampal inhibition and a selective loss of interneurons in experimental epilepsy. *Science.* 1987;235(4784):73-76. **(In vitro animal study)**
30. Young GB, Jordan KG. Do nonconvulsive seizures damage the brain?--Yes. *Arch Neurol*. 1998;55(1):117-119. **(Expert commentary)**
31. Wasterlain CG, Fujikawa DG, Penix L, et al. Pathophysiological mechanisms of brain damage from status epilepticus. *Epilepsia*. 1993;34 Suppl 1:S37-S53. **(Review)**
32. Krumholz A, Sung GY, Fisher RS, et al. Complex partial status epilepticus accompanied by serious morbidity and mortality. *Neurology*. 1995;45(8):1499-1504. **(Case series; 10 patients)**
33. Fujikawa DG, Itabashi HH, Wu A, et al. Status epilepticus-induced neuronal loss in humans without systemic complications or epilepsy. *Epilepsia*. 2000;41(8):981-991. **(Case series; 3 patients)**
34. Parmar H, Lim SH, Tan NC, et al. Acute symptomatic seizures and hippocampus damage: DWI and MRS findings. *Neurology.* 2006;66(11):1732-1735. **(Case series; 12 patients)**
35. Bauer G, Gotwald T, Dobesberger J, et al. Transient and permanent magnetic resonance imaging abnormalities after complex partial status epilepticus. *Epilepsy Behav*. 2006;8(3):666-671. **(Case report)**
36. Vespa PM, McArthur DL, Xu Y, et al. Nonconvulsive seizures after traumatic brain injury are associated with hippocampal atrophy. *Neurology*. 2010;75(9):792-798. **(Prospective case series; 16 patients)**
37. Fernandez-Torre JL. Status epilepticus in idiopathic generalized epilepsy. *Epilepsia*. 2006;47(4):805-806. **(Review)**
38. Ruegg S. Nonconvulsive status epilepticus in adults: types, pathophysiology, epidemiology, etiology, and diagnosis. *Neurology International OPEN*. 2017;01(03):E189-E203. **(Review)**
39. Barry E, Hauser WA. Status epilepticus: the interaction of epilepsy and acute brain disease. *Neurology*. 1993;43(8):1473-1478. **(Prospective cohort; 217 patients)**
40. Kaplan PW. Nonconvulsive status epilepticus. *Semin Neurol*. 1996;16(1):33-40. **(Review)**
41. Patsalos PN, Froscher W, Pisani F, et al. The importance of drug interactions in epilepsy therapy. *Epilepsia*. 2002;43(4):365-385. **(Review)**
42. Husain AM, Horn GJ, Jacobson MP. Non-convulsive status epilepticus: usefulness of clinical features in selecting patients for urgent EEG. *J Neurol Neurosurg Psychiatry*. 2003;74(2):189-191. **(Prospective case series; 48 patients)**
43. Chicharro AV, Kanner KA. Psychiatric manifestations of NCSE. In: Kaplan PW, Drislane FW, eds. *Nonconvulsive Status Epilepticus.* New York, NY: Demos Medical; 2009:203-215. **(Textbook chapter)**
44. Elliott B, Joyce E, Shorvon S. Delusions, illusions and hallucinations in epilepsy: 2. Complex phenomena and psychosis. *Epilepsy Res*. 2009;85(2-3):172-186. **(Review)**
45. Takaya S, Matsumoto R, Namiki C, et al. Frontal nonconvulsive status epilepticus manifesting somatic hallucinations. *J Neurol Sci*. 2005;234(1-2):25-29. **(Case report)**
46. Ng YT, Rekate HL. Coining of a new term, "status gelasticus". *Epilepsia*. 2006;47(3):661-662. **(Case report)**
47. Brigo F, Ferlisi M, Fiaschi A, et al. Fear as the only clinical expression of affective focal status epilepticus. *Epilepsy Behav*. 2011;20(1):107-110. **(Case report)**
48. Kaplan PW. Behavioral manifestations of nonconvulsive status epilepticus. *Epilepsy Behav.* 2002;3(2):122-139. **(Review)**
49. Thomas P, Beaumanoir A, Genton P, et al. 'De novo' absence status of late onset: report of 11 cases. *Neurology*. 1992;42(1):104-110. **(Case series; 11 patients)**
50. Trimble M, Kanner A, Schmitz B. Postictal psychosis. *Epilepsy Behav*. 2010;19(2):159-161. **(Review)**
51. DeLorenzo RJ, Hauser WA, Towne AR, et al. A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. *Neurology*. 1996;46(4):1029-1035. **(Prospective population-based study)**
52. Sutter R, Semmlack S, Kaplan PW. Nonconvulsive status epilepticus in adults - insights into the invisible. *Nat Rev Neurol*. 2016;12(5):281-293. **(Review)**
53. Treiman DM, Meyers PD, Walton NY, et al. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. *N Engl J Med*. 1998;339(12):792-798. **(Randomized double-blind study; 384 patients)**
54. Shorvon S. Clinical forms of status epilepticus. In: Shorvon S, ed. *Status Epilepticus: Its Clinical Features and Treatment in Children and Adults.* New York, NY: Cambridge University Press; 1994:34-138. (**Textbook chapter)**
55. American College of Emergency Physicians. Clinical policy for the initial approach to patients presenting with altered mental status. *Ann Emerg Med*. 1999;33(2):251-281. **(Clinical policy)**
56. Krumholz A, Wiebe S, Gronseth G, et al. Practice parameter: evaluating an apparent unprovoked first seizure in adults (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2007;69(21):1996-2007. **(Practice parameter)**
57. Practice parameter: neuroimaging in the emergency patient presenting with seizure (summary statement). American College of Emergency Physicians, American Academy of Neurology, American Association of Neurological Surgeons, American Society of Neuroradiology. *Ann Emerg Med*. 1996;28(1):114-118. **(Practice parameter)**
58. Devinsky O, Nadi S, Theodore WH, et al. Cerebrospinal fluid pleocytosis following simple, complex partial, and generalized tonic-clonic seizures. *Ann Neurol*. 1988;23(4):402-403. **(Retrospective chart review; 27 patients, 62 specimens)**
59. Prokesch RC, Rimland D, Petrini JL Jr, et al. Cerebrospinal fluid pleocytosis after seizures. *South Med J*. 1983;76(3):322-327. **(Case series; 102 patients)**
60. Rider LG, Thapa PB, Del Beccaro MA, et al. Cerebrospinal fluid analysis in children with seizures. *Pediatr Emerg Care*. 1995;11(4):226-229. **(Retrospective chart review; 212 children)**
61. Barry E HW. Pleocytosis after status epilepticus. *Arch. Neurol*. 1994;51:190-193. **(Retrospective chart review; 138 patients)**

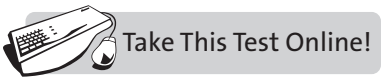
62. Jaitly R, Sgro JA, Towne AR, et al. Prognostic value of EEG monitoring after status epilepticus: a prospective adult study. *J Clin Neurophysiol*. 1997;14(4):326-334. **(Case series; 180 patients)**
63. Nei M, Lee JM, Shanker VL, et al. The EEG and prognosis in status epilepticus. *Epilepsia*. 1999;40(2):157-163. **(Case series; 50 patients)**
64. Leitinger M, Beniczky S, Rohracher A, et al. Salzburg consensus criteria for non-convulsive status epilepticus--approach to clinical application. *Epilepsy Behav*. 2015;49:158-163. **(Retrospective case control study; 100 patients)**
65. Chari G, Yadav K, Nishijima D, et al. Improving the ability of ED physicians to identify subclinical/electrographic seizures on EEG after a brief training module. *Intl J Emerg Med.* 2019;12(1):11. **(Randomized controlled trial; 30 emergency physicians at 3 institutions)**
66. Shah AM, Vashi A, Jagoda A. Review article: convulsive and non-convulsive status epilepticus: an emergency medicine perspective. *Emerg Med Australas*. 2009;21(5):352-366. **(Review)**
67. Sutter R, Ruegg S, Kaplan PW. Epidemiology, diagnosis, and management of nonconvulsive status epilepticus: opening Pandora's box. *Neurol Clin Pract.* 2012;2(4):275-286. **(Review)**
68. Fernandez-Torre JL, Kaplan PW, Hernandez-Hernandez MA. New understanding of nonconvulsive status epilepticus in adults: treatments and challenges. *Expert Rev Neurother*. 2015;15(12):1455-1473. **(Review)**
69. Lawson T, Yeager S. Status epilepticus in adults: a review of diagnosis and treatment. *Crit Care Nurse*. 2016;36(2):62-73. **(Review)**
70. Silbergleit R, Durkalski V, Lowenstein D, et al. Intramuscular versus intravenous therapy for prehospital status epilepticus. *N Engl J Med*. 2012;366(7):591-600. **(Randomized control trial; 893 patients)**
71. Alldredge BK, Gelb AM, Isaacs SM, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. *N Engl J Med*. 2001;345(9):631-637. **(Randomized, double-blind clinical trial; 205 patients)**
72. Leppik IE, Derivan AT, Homan RW, et al. Double-blind study of lorazepam and diazepam in status epilepticus. *JAMA*. 1983;249(11):1452-1454. **(Randomized controlled trial; 78 patients)**
73. Gilad R, Izkovitz N, Dabby R, et al. Treatment of status epilepticus and acute repetitive seizures with I.V. valproic acid vs phenytoin. *Acta Neurol Scand*. 2008;118(5):296-300. **(Prospective clinical trial; 74 patients)**
74. Misra UK, Kalita J, Patel R. Sodium valproate vs phenytoin in status epilepticus: a pilot study. *Neurology*. 2006;67(2):340-342. **(Randomized controlled trial; 82 patients)**
75. Remy C, Jourdil N, Villemain D, et al. Intrarectal diazepam in epileptic adults. *Epilepsia*. 1992;33(2):353-358. **(Prospective randomized study; 39 patients)**
76. Shaner DM, McCurdy SA, Herring MO, et al. Treatment of status epilepticus: a prospective comparison of diazepam and phenytoin versus phenobarbital and optional phenytoin. *Neurology*. 1988;38(2):202-207. **(Randomized clinical trial; 36 patients)**
77. Misra UK, Kalita J, Maurya PK. Levetiracetam versus lorazepam in status epilepticus: a randomized, open labeled pilot study. *J Neurol*. 2012;259(4):645-648. **(Randomized open-label pilot study; 79 patients)**
78. Prasad M, Krishnan PR, Sequeira R, et al. Anticonvulsant therapy for status epilepticus. *Cochrane Database Syst Rev.* 2014;10(9):CD003723. **(Cochrane review; 18 studies, 2755 participants)**
79. Kaplan PW. Intravenous valproate treatment of generalised nonconvulsive status epilepticus. *Clin Eectroencephalogr.* 1999;30(1):1-4. **(Case report)**
80. Berkovic SF, Andermann F, Guberman A, et al. Valproate prevents the recurrence of absence status. *Neurology*. 1989;39(10):1294-1297. **(Clinical trial; 25 patients)**
81. Thomas P, Valton L, Genton P. Absence and myoclonic status epilepticus precipitated by antiepileptic drugs in idiopathic generalized epilepsy. *Brain*. 2006;129(Pt 5):1281-1292. **(Case series; 14 patients)**
82. Osorio I, Reed RC, Peltzer JN. Refractory idiopathic absence status epilepticus: a probable paradoxical effect of phenytoin and carbamazepine. *Epilepsia* 2000;41(7): 887-894. **(Retrospective chart review)**
83. Eue S, Grumbt M, Muller M, et al. Two years of experience in the treatment of status epilepticus with intravenous levetiracetam. *Epilepsy Behav*. 2009;15(4):467-469. **(Retrospective review; 43 patients)**
84. Rupprecht S, Franke K, Fitzek S, et al. Levetiracetam as a treatment option in non-convulsive status epilepticus. *Epilepsy Res*. 2007;73(3):238-244. **(Retrospective chart review; 8 patients)**
85. Navarro V, Dagron C, Elie C, et al. Prehospital treatment with levetiracetam plus clonazepam or placebo plus clonazepam in status epilepticus (SAMUKeppra): a randomised, double-blind, phase 3 trial. *Lancet Neurol*. 2016;15(1):47-55. **(Randomized clinical trial; 107 patients)**
86. Albers JM, Moddel G, Dittrich R, et al. Intravenous lacosamide--an effective add-on treatment of refractory status epilepticus. *Seizure*. 2011;20(5):428-430. **(Case series; 7 patients)**
87. Lang N, Lange M, Schmitt FC, et al. Intravenous lacosamide in clinical practice-Results from an independent registry. *Seizure*. 2016;39:5-9. **(Prospective observational study; 119 patients)**
88. Hottinger A, Sutter R, Marsch S, et al. Topiramate as an adjunctive treatment in patients with refractory status epilepticus: an observational cohort study. *CNS Drugs*. 2012;26(9):761-772. **(Observational cohort study; 268 patients)**
89. Hofler J, Trinka E. Lacosamide as a new treatment option in status epilepticus. *Epilepsia*. 2013;54(3):393-404. **(Review)**
90. Wasim M, Husain AM. Nonconvulsive seizure control in the intensive care unit. *Curr Treat Options Neurol*. 2015;17(3):340. **(Review)**
91. Bleck T, Cock H, Chamberlain J, et al. The established status epilepticus trial 2013. *Epilepsia*. 2013;54 Suppl 6:89-92. **(Multicenter randomized double-blind clinical trial; proposed sample size, 795 patients)**
92. Rossetti AO, Lowenstein DH. Management of refractory status epilepticus in adults: still more questions than answers. *Lancet Neurol*. 2011;10(10):922-930. **(Review)**
93. Rossetti AO. Which anesthetic should be used in the treatment of refractory status epilepticus? *Epilepsia*. 2007;48 Suppl 8:52-55. **(Review)**
94. Claassen J, Hirsch LJ, Emerson RG, et al. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. *Epilepsia*. 2002;43(2):146-153. **(Systematic review)**
95. Roberts RJ, Barletta JF, Fong JJ, et al. Incidence of propofol-related infusion syndrome in critically ill adults: a prospective, multicenter study. *Crit Care*. 2009;13(5):R169. **(Prospective review; 1017 patients)**
96. Teran F, Harper-Kirksey K, Jagoda A. Clinical decision making in seizures and status epilepticus. *Emerg Med Pract.* 2015;17(1):1-24. **(Review)**
97. McMicken D, Liss JL. Alcohol-related seizures. *Emerg Med Clin North Am*. 2011;29(1):117-124. **(Review)**
98. Earnest MP, Feldman H , Marx JA, et al, Intracranial lesions shown by CT scans in 259 cases of first alcohol-related seizures. *Neurology*. 1988;38(10):1561-1565. **(Retrospective review; 259 patients)**
99. Fernandez-Torre JL, Martinez-Martinez M. Non-convulsive status epilepticus as an unrecognized cause of acute confusion in alcoholics. *Eur J Neurol*. 2007;14(8):e14-e15. **(Case report)**

100. Niedermeyer E, Freund G, Krumholz A. Subacute encephalopathy with seizures in alcoholics: a clinical-electroencephalographic study. *Clin Electroencephalogr*. 1981;12(3):113-129. **(Case series)**
101. Sechi G, Serra A. Wernicke's encephalopathy: new clinical settings and recent advances in diagnosis and management. *Lancet Neurol*. 2007;6(5):442-455. **(Review)**
102. Sheth RD, Drazkowski JF, Sirven JI, et al. Protracted ictal confusion in elderly patients. *Arch Neurol*. 2006;63(4):529-532. **(Case series; 22 patients)**
103. Rosenow F, Hamer HM, Knake S. The epidemiology of convulsive and nonconvulsive status epilepticus. *Epilepsia*. 2007;48 Suppl 8:82-84. **(Review)**
104. Rohracher A, Reiter DP, Brigo F, et al. Status epilepticus in the elderly-a retrospective study on 120 patients. *Epilepsy Res*. 2016;127:317-323. **(Retrospective case series; 120 patients)**
105. Cheng S. Non-convulsive status epilepticus in the elderly. *Epileptic Disord*. 2014;16(4):385-394. **(Review)**
106. Veran O, Kahane P, Thomas P, et al. De novo epileptic confusion in the elderly: a 1-year prospective study. *Epilepsia.* 2010;51(6):1030-1035. **(Prospective case series; 44 patients)**
107. Dunne JW, Summers QA, Stewart-Wynne EG. Non-convulsive status epilepticus: a prospective study in an adult general hospital. *Q J Med*. 1987;62(238):117-126. **(Prospective case series; 113 patients)**
108. Scholtes FB, Renier WO, Meinardi H. Simple partial status epilepticus: causes, treatment, and outcome in 47 patients. *J Neurol Neurosurg Psychiatry*. 1996;61(1):90-92. **(Retrospective case series; 47 patients)**
109. Stephen LJ, Brodie MJ. Epilepsy in elderly people. *Lancet*. 2000;355(9213):1441-1446. **(Review)**
110. Korn-Lubetzki I, Steiner-Birmanns B, Galperin I, et al. Nonconvulsive status epilepticus in older people: a diagnostic challenge and a treatable condition. *J Am Geriatr Soc.* 2007;55(9):1475-1476. **(Review)**
111. Bottaro FJ, Martinez OA, Pardal MM, et al. Nonconvulsive status epilepticus in the elderly: a case-control study. *Epilepsia*. 2007;48(5):966-972. **(Retrospective case-control study; 53 patients)**
112. Kaplan PW. Assessing the outcomes in patients with nonconvulsive status epilepticus: nonconvulsive status epilepticus is underdiagnosed, potentially overtreated, and confounded by comorbidity. *J Clin Neurophysiol*. 1999;16(4):341-352. **(Review)**
113. Shavit L, Grenader T, Galperin I. Nonconvulsive status epilepticus in elderly a possible diagnostic pitfall. *Eur J Intern Med*. 2012;23(8):701-704. **(Prospective case series; 14 patients)**
114. Sutter R, Fuhr P, Grize L, et al. Continuous video-EEG monitoring increases detection rate of nonconvulsive status epilepticus in the ICU. *Epilepsia*. 2011;52(3):453-457. **(Review)**
115. Bleck TP. Management approaches to prolonged seizures and status epilepticus. *Epilepsia*. 1999;40 Suppl 1:S59-S63. **(Review)**
116. Sutter R. Are we prepared to detect subtle and nonconvulsive status epilepticus in critically ill patients? *J Clin Neurophysiol*. 2016;33(1):25-31. **(Review)**
117. Herman ST, Abend NS, Bleck TP, et al. Consensus statement on continuous EEG in critically ill adults and children, part I: indications. *J Clin Neurophysiol*. 2015;32(2):87-95. **(Consensus statement)**
118. Kuroda Y. Neurocritical care update. *J Intensive Care*. 2016;4:36. **(Review)**
119. Abdel Baki SG, Omurtag A, Fenton AA, et al. The new wave: time to bring EEG to the emergency department. *Int J Emerg Med*. 2011;4:36. **(Review)**
120. Roodsari GS, Chari G, Mera B, et al. Can patients with nonconvulsive seizure be identified in the emergency department? *World J Emerg Med*. 2017;8(3):190-194. **(Restrospective study; 332 patients)**
121. Sergot P, Chari, G., Omurtag, A. Utility of a brief training module on improving emergency physicians' ability to identify non-convulsive seizure on emergent electroencephalography performed in patients with altered mental status. *Ann Emerg Med.* 2015;66(4):S111-S112. **(Prospective study; in progress)**
122. Zeiler FA. Early use of the NMDA receptor antagonist ketamine in refractory and superrefractory status epilepticus. *Crit Care Res Pract*. 2015;2015:831260. **(Literature review)**
123. Fung EL, Fung BB, Subcommittee on the Consensus Statement of the Hong Kong Epilepsy Society. Review and update of the Hong Kong Epilepsy Guideline on status epilepticus. *Hong Kong Med J*. 2017;23(1):67-73. **(Consensus statement)**
124. Sabharwal V, Ramsay E, Martinez R, et al. Propofol-ketamine combination therapy for effective control of super-refractory status epilepticus. *Epilepsy Behav*. 2015;52(Pt A):264-266. **(Retrospective review; 67 patients)**
125. Niquet J, Baldwin R, Suchomelova L, et al. Treatment of experimental status epilepticus with synergistic drug combinations. *Epilepsia*. 2017;58(4):e49-e53. **(Animal study)**
126. Gaspard N, Foreman B, Judd LM, et al. Intravenous ketamine for the treatment of refractory status epilepticus: a retrospective multicenter study. *Epilepsia.* 2013;54(8):1498-1503. **(Retrospective review; 60 patients)**
127. Hofler J, Rohracher A, Kalss G, et al. (S)-ketamine in refractory and super-refractory status epilepticus: a retrospective study. *CNS Drugs*. 2016;30(9):869-876. **(Retrospective review; 42 patients)**
128. Jones RM, Butler JA, Thomas VA, et al. Adherence to treatment in patients with epilepsy: associations with seizure control and illness beliefs. *Seizure.* 2006;15(7):504-508. **(Cross-sectional study; 54 patients)**

Correction

The August 2019 issue of *Emergency Medicine Practice* contained an error in Table 1, page 4. The rivaroxaban (Xarelto®) dosing for venous thromboembolism should have read: "15 mg twice daily for first 21 days, followed by 20 mg **once daily.**" This has been corrected in the online version of the issue. We regret the error.

CME Questions



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1. Regarding the pathophysiology of nonconvulsive status epilepticus (NCSE), which of the following statements is TRUE?
   a. NCSE causes permanent irreversible damage, even when treated.
   b. NCSE often evolves into generalized convulsive status epilepticus (GCSE).
   c. NCSE is more likely than GCSE to cause widespread systemic physiologic changes.
   d. Pathophysiology of NCSE is likely different for different subtypes (absence status epilepticus, complex partial status epilepticus)

2. In patients with epilepsy, the most common etiology of NCSE is:
   a. Antiepileptic drug (AED) noncompliance or subtherapeutic AED levels
   b. Progression of disease
   c. A new focus of epileptiform activity
   d. Trauma

3. A 55-year-old woman with a history of breast cancer presents to the ED following a generalized tonic-clonic seizure. She is confused but alert. Her husband states that she has been complaining of left-sided weakness. On examination, she has full strength and sensation in all 4 extremities. Minimum testing in the ED must include:
   a. CBC, chemistry, urinalysis, fingerstick glucose, and brain CT
   b. CBC, chemistry, urinalysis, fingerstick glucose, brain CT, and lumbar puncture
   c. CBC, chemistry, urinalysis, fingerstick glucose, and electrocardiogram
   d. CBC, chemistry, urinalysis, and fingerstick glucose

4. A 72-year-old man with a history of anxiety and hypertension presents to the ED with changes in behavior. He is otherwise neurologically intact and has normal vital signs. Fingerstick glucose, blood work, and urinalysis are normal. His wife notes that 3 days ago, he abruptly discontinued his alprazolam. An empiric trial of lorazepam in the ED leads to normalization of his mental status. Based on clinical gestalt and response to therapy, the patient is presumptively diagnosed with NCSE. Which additional test would have confirmed the suspected diagnosis?
   a. Brain CT
   b. Lumbar puncture
   c. Electroencephalogram (EEG)
   d. No additional test is needed; response to IV lorazepam is confirmatory

5. Regarding benzodiazepines in NCSE, which of the following statements is TRUE?
   a. Benzodiazepines are first line.
   b. Diazepam is superior to lorazepam.
   c. Benzodiazepines should not be initiated until diagnosis is confirmed.
   d. Efficacy is maintained regardless of duration of NCSE.

6. Which of the following medications is the first choice for empiric therapy of NCSE?
   a. Phenobarbital IV
   b. Diazepam IV
   c. Phenytoin IV
   d. Lorazepam IV

7. An elderly woman with a history of epilepsy presents with altered mental status (AMS). The ED workup is unrevealing, so a neurologist is consulted, and the patient undergoes emergent EEG, which is diagnostic of NCSE. The patient is given IV lorazepam and a dose of IV levetiracetam, which she takes chronically. Her mental status and EEG abnormalities do not improve. Which of the following would be INAPPROPRIATE third-line therapy for this patient?
   a. Etomidate IV
   b. Phenytoin IV
   c. Fosphenytoin IV
   d. Valproate IV

8. **Which of the following statements best describes the principles guiding diagnosis of NCSE?**
   a. Rule out other causes of AMS, maintain a high index of suspicion, consider EEG and empiric therapy early.
   b. Consult neurology on all altered patients, perform MRI and EEG emergently, and consider starting therapy before diagnosis is confirmed.
   c. Rule out other causes of AMS, maintain a high index of suspicion, and start 2 AEDs concurrently.
   d. Encourage prehospital diagnosis and treatment of NCSE in altered patients, consult neurology, and perform lumbar puncture to rule out encephalitis.

9. **A 23-year-old man with unknown medical history is found down by bystanders. He has abrasions to his face, and a broken front tooth. He is awake but mumbling incomprehensibly, and not following commands. GCS score is 9. Trauma evaluation shows no injuries, and lab results, including alcohol level and urine drug screen, are normal. On re-evaluation, his GCS score is 8 and the patient is obtunded. Vital signs are normal. What is the next step in management?**
   a. Stat psychiatry consultation
   b. Rapid sequence intubation and emergent intubation
   c. IV phenytoin
   d. Emergent EEG

10. **Regarding treatment of NCSE in the elderly, which of the following statements is TRUE?**
   a. Elderly patients are less sensitive to benzodiazepines.
   b. Elderly patients with NCSE should be treated more aggressively than younger patients.
   c. Elderly patients may require lower adjusted doses of medications to treat NCSE
   d. NCSE in the elderly usually resolves without treatment.

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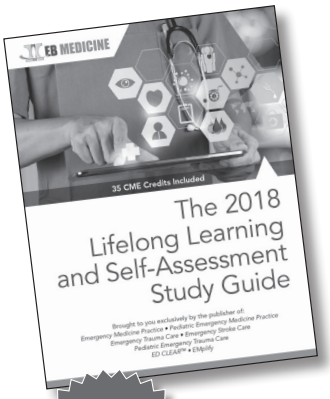

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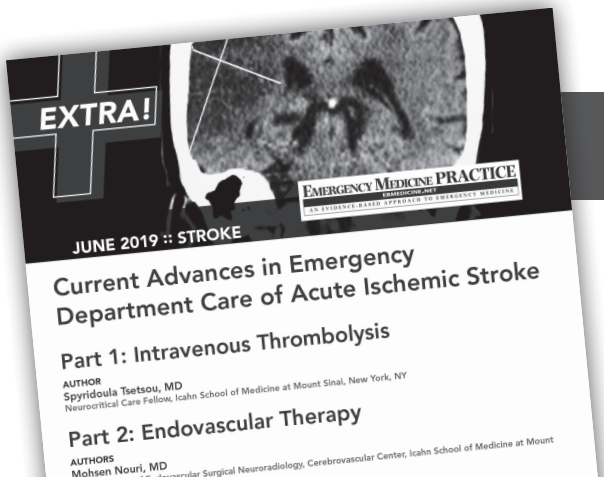

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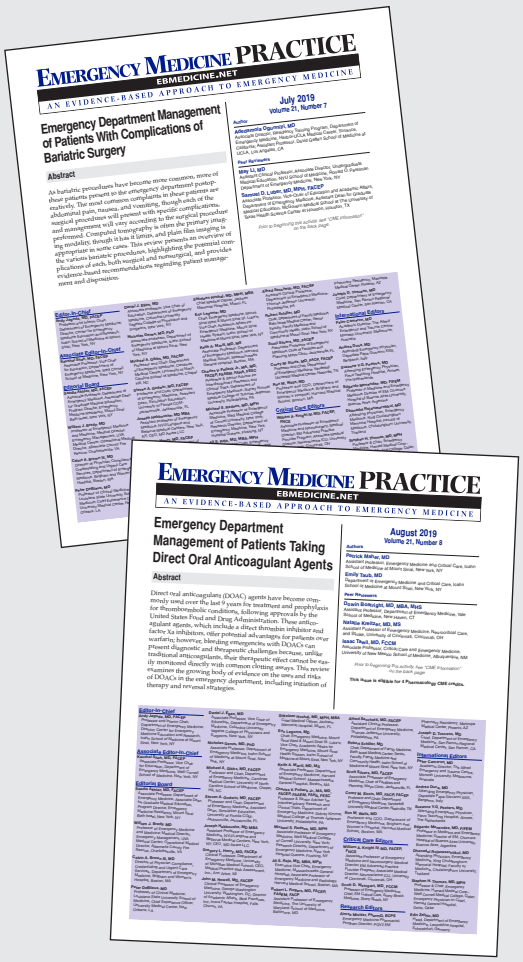

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