

Epilepsy Emergencies: Diagnosis and Management

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KEYWORDS

- Epilepsy • Seizures • Status epilepticus • Coma
- Intensive care unit • Nonconvulsive seizures • Critical care

Emergencies in epilepsy may be encountered in the home, en route to a nearby hospital, in the emergency department (ED), in the hospital, or in an intensive care unit (ICU). Adequate and effective treatment delivered in a timely fashion is crucial to the successful management of these patients. This review addresses the diagnosis and management of acute seizures, status epilepticus, refractory status epilepticus, and seizures in the critically ill.

DEFINITIONS AND EPIDEMIOLOGY

Acute seizures (Szs) are the most common epilepsy emergency and comprise 1 million, or 1%, of all ED visits.¹ Szs are formally defined as transient occurrences of signs or symptoms related to abnormal synchronous neuronal activity.² The manifestations of Szs are protean. While in the acute setting, most Szs are identified by motor symptoms (especially clonic jerking, termed convulsive seizures [CSz]), it should be recognized that the majority of Szs in adults do not have prominent motor activity. If acute alteration of awareness occurs, these are known as complex partial seizures. For patients with impaired consciousness to begin with, Szs without prominent motor

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activity are typically referred to as nonconvulsive seizures (NCSzs). Typical seizures in ambulatory patients are self-limited and last less than 3 minutes.³

The annual incidence of Szzs ranges from 70 to 100 in 100,000.⁴ The annual cost of prehospital and ED care alone has been estimated at \$1 billion.⁵ More than half of patients with a first Sz will go on to have another. The occurrence of 2 or more unprovoked Szzs constitutes a diagnosis of epilepsy.

When Szzs are prolonged or recurrent without a return to baseline, they are referred to as status epilepticus (SE); the best studied form is convulsive SE (CSE). Most studies of SE use 30 minutes to define "prolonged," a classic distinction based on animal models of neuronal injury that originated with Gastaut.⁶ Clinically, Szzs do become self-sustaining with increased mortality when they last longer than 30 minutes,⁷ but Szzs lasting just 10 minutes are significantly more likely to extend into SE.⁸ Further, despite clear guidelines that early treatment leads to better outcomes,⁹ almost 60% of patients experience a delay of more than 30 minutes to treatment in hospitals.¹⁰ Therefore, most neurologists use an operational definition of any Sz lasting more than 5 minutes, or 2 or more Szzs between which the patient does not return to baseline, to facilitate more timely and therefore more effective treatment.¹¹ For practical purposes, SE should be diagnosed in "any patient that is still seizing."¹²

The definition of nonconvulsive status epilepticus (NCSE) has been more elusive. Electroencephalography (EEG) is required. The most common definitions include 30 to 60 minutes of impaired consciousness in conjunction with some form of Sz activity on EEG.¹³ The electrophysiologic definition of NCSE is beyond the scope of this article, but one definition has been suggested by Chong and Hirsch.¹⁴

SE complicates about 6% of Szzs in the ED.⁵ In the United States, the overall adjusted incidence of SE is 10.3 to 61 in 100,000.¹⁵ Around a quarter are NCSE with a cumulative incidence of up to 14.1 in 100,000, although this is likely underascertained¹³; this means up to 152,000 individuals develop SE yearly¹⁶ at a cost of around \$4 billion.¹⁷ Direct costs are between 60% and 90% higher for those with SE than for similar patients with intracerebral hemorrhage (ICH), myocardial infarction, or congestive heart failure without SE.¹⁷

Of those who develop SE, about a quarter develop refractory status epilepticus (RSE), a condition variably defined as SE wherein there is failure to respond to first-line and second-line antiepileptic drugs (AEDs).¹⁸ Before EEG became a prominent tool in epilepsy emergencies, there were an estimated 2000 to 6000 cases per year; based on prospective data, this number is likely closer to 45,000 cases per year.^{16,18} Up to a third of CSE patients continue to have continuous electrographic Sz activity after convulsive activity stops. When this is accompanied by periodic discharges on the EEG, it has been referred to as "subtle status epilepticus,"¹⁸ or more recently as "status epilepticus terminans," a final stage of SE.¹⁹ About a third of patients with RSE will have recurrence of Szzs within 5 days of tapering an anesthetic medication, a condition referred to as "malignant" SE.²⁰

Szzs and SE are common among patients who are already hospitalized, although large prospective epidemiologic studies are lacking. The majority (about 75% overall in the literature, and up to 92% in one large series²¹) of critically ill patients with Szzs have purely nonconvulsive Szzs that cannot be recognized without continuous EEG monitoring (cEEG) (**Table 1**). Even after excluding those with prior clinical Sz activity or subtle motor signs, 8% of unexplained coma patients will have NCSE.³¹ NCSzs have been documented in 19% of 570 inpatients with altered mental status in whom cEEG was requested.²¹ In the neurologic ICU, 27% to 35% of patients undergoing cEEG will have NCSzs.^{29,34} These statistics reflect a potentially huge number of patients for whom NCSzs or NCSE constitute a frequently delayed or misdiagnosed "brain-threatening emergency."³⁵

Table 1
Prevalence of electrographic seizures and percentages that are clinically unrecognized

Study Population	EEG Type	Design	N	% of Patients with Any Seizures While on cEEG	% of Patients with Purely Nonconvulsive Seizures*	References
Altered consciousness or suspected subclinical seizures anywhere in medical center undergoing urgent routine EEG	Routine	Prospective	198	37	100 (32% had no subtle clinical signs)	Privitera et al ³⁰
Neuro-ICU	cEEG	Retrospective	124	35	74	Jordan ²⁶
Prior convulsive status epilepticus, altered consciousness without clinical seizure activity	cEEG	Prospective	164	48	100 (by definition)	DeLorenzo et al ²⁴
Moderate-to-severe traumatic brain injury, Neuro-ICU	cEEG	Retrospective	94	22	52	Vespa et al ³²
ICU, coma, without evidence of prior current clinical seizures	Routine	Retrospective	236	8	100 (by definition)	Towne et al ³¹
Neuro-ICU with infarct or ICH	cEEG	Prospective	109	19% overall (Lobar ICH: 34% Deep ICH 21%)	79	Vespa et al ³³
All inpatients undergoing nonelective cEEG	cEEG	Retrospective	570	19	92	Claassen et al ²¹
Neuro-ICU	cEEG	Retrospective	105	27	68	Pandian et al ²⁹
Under 18 years old, in an ICU	cEEG	Retrospective	117	44	75	Jette et al ²⁵
ICH	cEEG	Retrospective	102	31	58	Claassen et al ²³
Medical ICU patients without known acute brain injury	cEEG	Retrospective	201	10 (Sepsis: 16%)	67	Oddo et al ²⁸
All inpatients undergoing nonelective cEEG	cEEG	Retrospective	300	28	"Most"	Kilbride et al ²⁷
Pediatric ICU	cEEG	Prospective	100	46	70	Abend et al ²²

* This column refers to the following: Of all patients with seizures on cEEG, what percent of them had purely nonconvulsive seizures (ie, no clinically recognized ones) that could only be recognized with EEG.

Abbreviations: cEEG, continuous electroencephalographic monitoring; ICH, intracerebral hemorrhage; ICU, intensive care unit.

Data from Hirsch LJ. Urgent continuous EEG (cEEG) monitoring leads to changes in treatment in half of cases. Epilepsy Curr 2010;10(4):82-5; and Friedman D, Hirsch LJ. Diagnosing and monitoring seizures in the ICU: the role of continuous EEG for detection and management of seizures in critically ill patients. In: Varelas P, editor. Seizures in critical care: a guide to diagnosis and therapeutics. 2nd edition. New York: Humana Press; 2010. p. 23.

PRESENTATION AND CAUSE

“There are as many types of status as there are types of epileptic seizures”⁶ and accordingly, they are both classified in similar terms (**Table 2**).³⁶ Both SzS and SE may be differentiated by their onset (focal or generalized) as well as the patient’s level of awareness (simple or complex). CSz and CSE are clinically apparent, whereas NCSzs and NCSE may pose a diagnostic dilemma for the clinician (**Table 3**) and have not been adequately defined in terms of Sz subtype.

Szs are most commonly unprovoked or from progressive symptomatic causes.³⁷ SE, on the other hand, is most commonly from acute symptomatic etiology.¹⁵ In hospitalized patients, the vast majority of Szs and SE have an acute symptomatic cause (**Box 1** and **Fig. 1**).^{20,38}

MORBIDITY AND MORTALITY

Szs, and particularly SE, are significant sources of morbidity and mortality. For ambulatory patients with a single unprovoked Sz, more than half will go on to develop epilepsy and 3.4% will die over the next 30 days. An acute symptomatic Sz will only herald epilepsy 19% of the time, but 30-day mortality increases to 21%, almost 7 times as high as those with unprovoked Szs.⁴⁸ In the ED, around 1% of patients with Szs will require intubation and 23% are admitted to the hospital.¹

SE will cause an estimated 42,000 deaths each year with a case-fatality rate ranging from 15% to 22%.⁴⁹ Age and etiology are the most consistent determinants; mortality is up to 34% in acute symptomatic SE and is between 38% and 67% in the elderly.⁵⁰ Mortality in SE after an anoxic event approaches 71%.¹⁶ By itself, SE is sufficient to cause serious neuronal damage and mortality; in animals it has been shown that even if the systemic effects of SE are controlled, 30 minutes of SE may cause significant histologic damage.⁵¹ Although the pathophysiology of SE is beyond the scope of this review, some of the broader concepts are represented in **Fig. 2**, and there are several excellent reviews.^{52,55}

For those who survive SE, almost one-quarter will have a deterioration in their functional outcome⁵⁹ and 10% are left needing long-term care.⁴⁶ Around 6% develop an associated chronic encephalopathy.³⁹ 41% will go on to develop epilepsy.⁶⁰

Type	Seizure Classification
Convulsive status epilepticus	Primary generalized Simple partial (SPSE or <i>epilepsia partialis continua</i>) Complex partial (CPSE with motor involvement) Secondarily generalized
Nonconvulsive status epilepticus in the ambulatory population (NCSE-A)	Primary generalized (eg, typical absence) SPSE CPSE Secondarily generalized
Nonconvulsive status epilepticus in the comatose or critically ill (NCSE-C)	Focal Bilateral/generalized
Myoclonic status epilepticus (MSE)	Primary MSE (in primary generalized epilepsy) Secondary MSE (in symptomatic generalized epilepsy) Symptomatic (eg, after cardiac arrest)

Abbreviations: CPSE, complex partial status epilepticus; SPSE, simple partial status epilepticus.

Table 3
Semiological spectrum of nonconvulsive seizures and nonconvulsive status epilepticus

Negative Symptoms	Positive Symptoms	
Anorexia	Agitation/aggression	Laughter
Aphasia/mutism	Automatisms	Nausea/vomiting
Amnesia	Blinking ^a	Nystagmus ^a
Catatonía	Crying	Eye deviation ^a
Coma	Delirium	Perseveration
Confusion	Delusions	Psychosis
Lethargy	Echolalia	Tremulousness
Staring	Facial twitching	Hippus ^a

^a Applicable only to acute symptomatic comatose patients.

Data from Jirsch J, Hirsch LJ. Nonconvulsive seizures: developing a rational approach to the diagnosis and management in the critically ill population. *Clin Neurophysiol* 2007;118:1660–70; and Kaplan PW. Nonconvulsive status epilepticus in the emergency room. *Epilepsia* 1996;37(7):643–50.

There is significant debate over the morbidity and mortality of NCSzs and NCSE (Fig. 3). Studies have yielded inconsistent associations. For instance, generalized NCSE overall is associated with fairly high mortality⁴⁷; yet there is stark contrast between the absence status of primary epilepsy, which leads to no measureable morbidity or mortality, and NCSE in comatose patients, which is associated with mortality rates of 51% to 65%.^{18,24} Kaplan uses mental status as the major determinant of mortality in NCSE; in one study, death occurred in 39% who had severe mental status impairment compared with only 7% with mild impairment.⁶¹ However, the vast majority of severely impaired patients die of their underlying comorbidities, leaving

Box 1

Some medications that lower the seizure threshold

- Analgesics: meperidine, fentanyl, tramadol
- Antiarrhythmics: mexiletine, lidocaine, digoxin
- Antibiotics: β -lactams (benzylpenicillin > semisynthetic penicillin; cefazolin; imipenem), quinolones, isoniazid, antimalarials (primaquine), metronidazole
- Antidepressants, especially bupropion and maprotiline
- AEDs: Phenytoin at supratherapeutic levels, tiagabine
- Baclofen
- Calcineurin inhibitors: cyclosporine, tacrolimus
- Chemotherapeutic agents: alkylating agents (chlorambucin, busulfan), α -interferons
- Neuroleptics, especially clozapine but also phenothiazines
- Lithium
- Multiple sclerosis medications: dalfampridine, 4-aminopyridine, β -interferons
- Radiographic contrast agents (intrathecal and intravenous)
- Theophylline
- Withdrawal from: opiates, alcohol, AEDs (especially benzodiazepines, barbiturates)

Data from Abou Khaled KJ, Hirsch LJ. Updates in the management of seizures and status epilepticus in critically ill patients. *Neurol Clin* 2008;26(2):385–408.

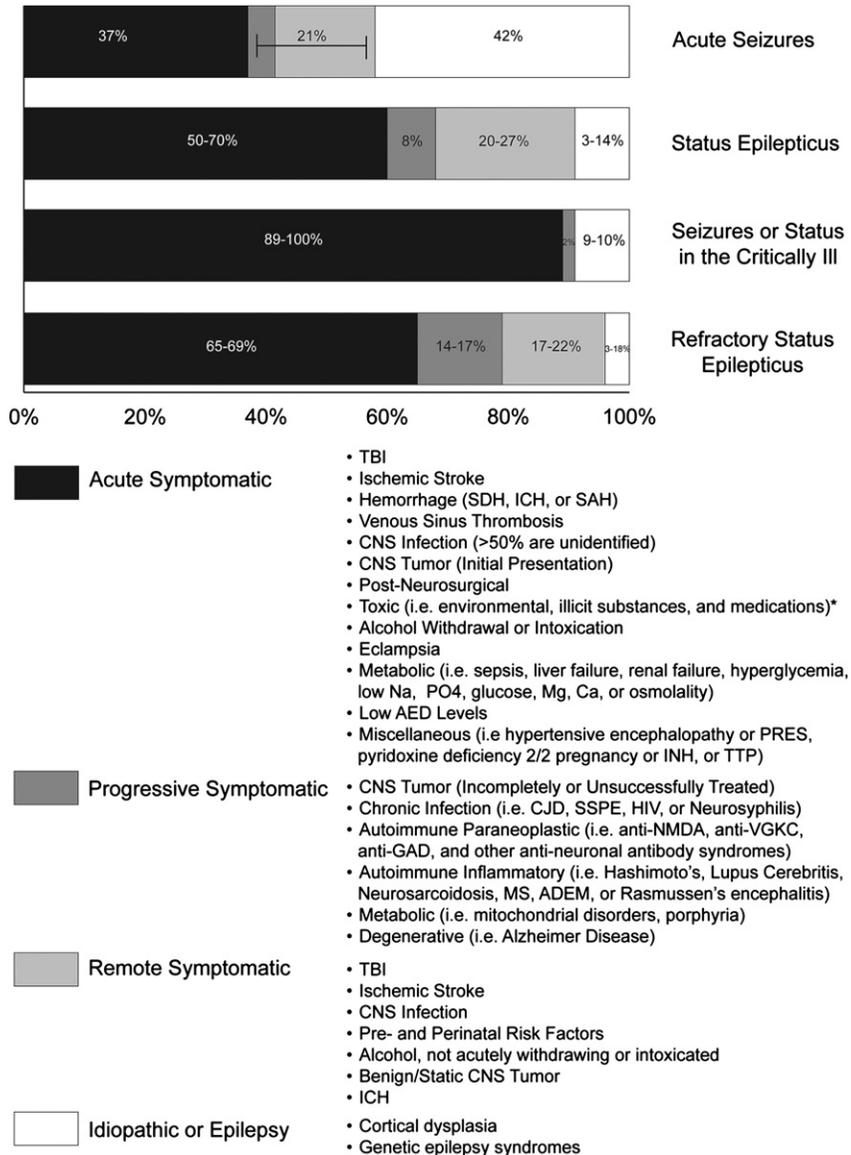


Fig. 1. Causes of seizures and status epilepticus in the United States. ADEM, acute disseminated encephalomyelitis; AED, antiepileptic drug; CJD, Creutzfeldt-Jakob disease; CNS, central nervous system; GAD, glutamic acid decarboxylase; HIV, human immunodeficiency virus; ICH, intracerebral hemorrhage; INH, isoniazid; MS, multiple sclerosis; NMDA, *N*-methyl-*D*-aspartate (receptor); PRES, posterior reversible leukoencephalopathy syndrome; SAH, subarachnoid hemorrhage; SDH, subdural hematoma; SSPE, subacute sclerosing pan-encephalitis; TBI, traumatic brain injury; TTP, thrombotic thrombocytopenic purpura; VGKC, voltage-gated potassium channel. *See [Box 1](#). (Data from Refs. ^{16,20,37-47})

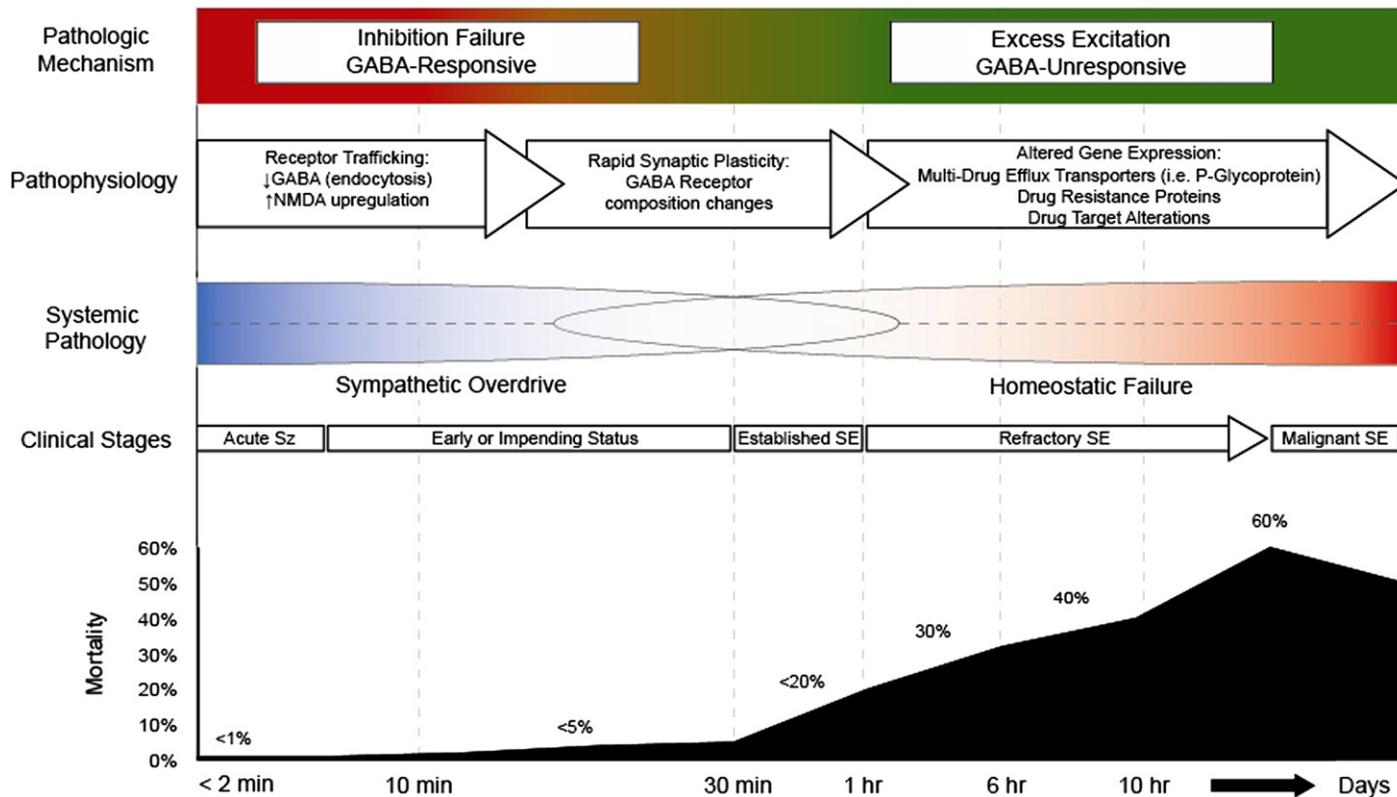


Fig. 2. The pathology of status epilepticus (SE). (Data from Refs. 3,7,16,18,20,46,47,49,52–58)

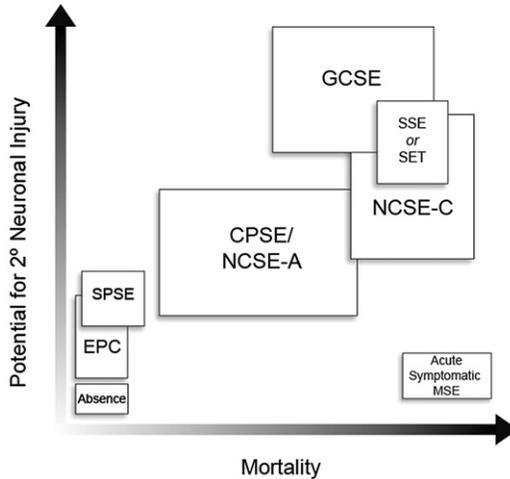


Fig. 3. Mortality and neuronal injury in subtypes of status epilepticus. Absence, absence status epilepticus; CPSE, complex partial status epilepticus; EPC, *epilepsia partialis continua*; GCSE, generalized convulsive status epilepticus; MSE, myoclonic status epilepticus; NCSE-A, nonconvulsive status epilepticus in the ambulatory patient; NCSE-C, nonconvulsive status epilepticus in the comatose or critically ill; SET, status epilepticus terminans; SPSE, simple partial status epilepticus; SSE, subtle status epilepticus.

a question as to the role of NCSE as an independent source of mortality. There are some compelling clinical data suggesting harmful effects of the Sz activity itself, including increased mortality when age and etiology are controlled²⁴; associations between both the delay to diagnosis of NCSE and the duration of NCSE and mortality⁶²; increased glutamate, glycerol, and lactate-pyruvate ratio on cerebral microdialysis⁶³; increased neuron-specific enolase, a biomarker of neuronal damage⁶⁴; increased glutamate, lactate-pyruvate ratio, and intracranial pressure during NCSzs compared with interictal periods within the same patient⁶⁵; increased mass effect and shift on serial brain imaging after ICH³³; and eventual hippocampal atrophy ipsilateral to NCSzs experienced after traumatic brain injury (TBI).⁶⁶

Szs or SE in hospitalized patients is an independent risk factor for morbidity and mortality.^{28,67} In one study of 41 hospitalized patients with SE, death occurred in 61% and only 1 in 5 returned to baseline on discharge.⁴² In 201 medical ICU patients, Szs on cEEG were associated with death or poor outcome in 89% (vs 39% in those without Szs); Szs remained associated with worse outcome even when controlled for age, examination, and organ dysfunction.²⁸ In both medical and surgical ICUs, mortality associated with SE approaches 67%.⁴³ CSE and NCSE also act synergistically with acute brain pathology to worsen outcomes in situations such as stroke,⁶⁸ ICH,³³ subarachnoid hemorrhage (SAH),⁶⁹ and TBI.³² Animal studies suggest this: for example, NCSzs in rat models of acute focal ischemia were associated with increased infarct size and higher mortality,⁷⁰ and a low-dose pilocarpine model of a single episode of NCSE in rats demonstrated permanent histologic, motor, and social behavior changes.⁷¹ It stands to reason that treating Szs and SE quickly and effectively may potentially create better outcomes. Vespa's motto for cEEG monitoring in the ICU setting is: "to detect and protect."⁷²

In the only prospective study of RSE, mortality was 39.3% despite a low percentage requiring intubation,⁷⁵ itself an independent risk factor for mortality in SE.⁷³ Rates of

about 50% are more widely cited. Hospitalization is longer and there is a significant association with deterioration on functional measures⁷⁴; only 20% return to baseline on discharge.⁷⁵

The overall duration of SE may play a role in mortality. Studies stratifying duration^{74,76} found a mortality of 2.7% at less than 30 minutes, 19% at less than 1 hour, 32% at over an hour, and logarithmically up to 6 hours thereafter. However, once RSE has become quite prolonged, duration may no longer be an independent predictor of outcome⁵⁴ even in RSE lasting longer than 7 days.⁴¹

PREHOSPITAL MANAGEMENT AND PRIMARY EVALUATION

An initial evaluation should take place either in the field or immediately on arrival to the ED in conjunction with medication administration (**Box 2**). As with any emergency, strict attention should be paid to the patient's airway, breathing, and circulation (the ABCs).

Treatment that is initiated early is much more likely to be effective¹⁸ and improve outcomes.⁷⁷ Studies have reported that emergency medical services (EMS) may take 15 minutes to get to the ED⁷⁷; only 41% of patients receive treatment before 30 minutes¹⁰; and delays to treatment of up to 50 minutes may occur despite established protocols.⁷⁸ When first-responders (ie, family members, EMS) are able to give medication, Sz time and recurrence decrease and patient outcomes are likely to improve.

Based on 11 randomized controlled studies, diazepam and lorazepam are clearly superior to placebo for stopping Sz's and reducing the incidence of SE.⁷⁹ Their prompt prehospital administration actually leads to significantly decreased rates of intubation⁷⁷ compared with placebo. Intravenous (IV) lorazepam in particular has been shown to be superior to both diazepam alone and phenytoin (PHT) alone as first-line therapy in adults.^{18,77} At times, IV access is not available. A variety of formulations of midazolam (intranasal, buccal, and intramuscular [IM]) have been used in children with prolonged Sz's. Although buccal midazolam has been shown in a prospective randomized controlled trial to be more effective than rectal diazepam in aborting Sz's in children,⁸⁰ the only approved non-IV benzodiazepine for adult patients remains rectal diazepam. A prospective study of adult prehospital IM versus IV benzodiazepine treatment is under analysis as of this review,⁸¹ and the authors offer nasal midazolam,

Box 2

Initial steps in the prehospital management of seizures and status epilepticus

ABCs

Place in left-lateral decubitus position and remove any foreign objects from mouth (ie, dentures); no need for spinal precautions

Pulse oximetry and supplementary oxygen

Suction

Bag-valve mask or secure airway, as indicated

Cardiac monitoring

Insert peripheral intravenous line

Glucometer; if <80 mg/dL, administer 100 mg thiamine followed by 25–50 g dextrose 50%

Benzodiazepine administration based on availability

Data from Michael GE, O'Connor RE. The diagnosis and management of seizures and status epilepticus in the prehospital setting. *Emerg Med Clin North Am* 2011;29(1):29–39.

an effective and preferred route of administration,⁸² to many of their patients at risk for Sz clusters or prolonged Szs to use at home.

Once the patient has arrived at the treating facility, the focus should remain basic and advanced life support measures, adequate monitoring of cardiopulmonary function, and rapid treatment. SE frequently occurs with systemic manifestations (**Table 4**). In addition, recognition of Szs or SE mandates an evaluation for its cause. An initial evaluation strategy is outlined in the first row of **Fig. 4**.

The value of imaging in the acute evaluation should be balanced against the risks of delaying treatment. Acute symptomatic causes should be urgently evaluated with non-contrast computed tomography in any patient without a known history of epilepsy or with focal findings on examination. EEG is an important tool to evaluate patients in SE. The resolution of clinical symptoms may belie 48% who are still having intermittent NCSzs in the subsequent 24 hours, and 14% still in NCSE after movements stop.²⁴ Similarly, Szs may occur in up to 34% of patients with acute brain injury,³⁴ and often manifests as a decrease in mental status out of proportion to the degree of injury. If the level of consciousness after a convulsive Sz of any duration does not improve by 20 minutes or normalize by 60 minutes, NCSE should be suspected⁸⁹ and an urgent EEG obtained.

Another consideration may include lumbar puncture if there is clinical suspicion for meningoencephalitis or SAH, but only once it is safe to do so and provided there is no delay to treatment of the Szs and possible infection. Empiric antibiotics should include 1 to 2 g ceftriaxone, 1 g vancomycin, and 10 mg/kg acyclovir. For the elderly, the addition of 30 mg/kg ampicillin may be warranted to cover for *Listeria* spp. In addition to cerebrospinal fluid, blood and urine should be concurrently evaluated for organisms.

PRIMARY MANAGEMENT OF SE

Just as in prehospital treatment, the authors' algorithm begins with use of γ -aminobutyric acid A (GABA_A) agonists: benzodiazepines (see **Fig. 4**). While multiple benzodiazepines will abort Szs with similar efficacy, Sz recurrence occurs less frequently with lorazepam than with diazepam owing to its decreased volume of distribution and long-lasting central nervous system (CNS) levels, up to 12 hours.⁹⁰ If diazepam or midazolam are used, a longer-acting maintenance AED, such as PHT or valproate (VPA), should be started concurrently. The response to lorazepam as a first-line agent falls between 59% and 89%.^{18,77,90}

The choice of second-line agent has traditionally been PHT,⁹¹ which works to prolong the recovery of voltage-gated sodium channels (see **Fig. 4**; **Table 5**). PHT is frequently underdosed⁷⁸ and should be based on weight. Complications from PHT include hypotension (27%–58%), respiratory depression (8%–10%), and cardiac arrhythmia (7%).¹⁸ PHT may also impede motor recovery after stroke.¹⁰³ In addition, extravasation of IV PHT and its solvents (including propylene glycol) may cause soft tissue necrosis and/or distal ischemia as part of the “purple-glove syndrome.” The incidence of this complication in one prospective study was 1.7%.¹⁰⁴ A safer but more expensive alternative is a water-soluble diphosphate sodium ester of PHT, fosphenytoin (FosPHT). Although FosPHT is a prodrug and must be converted to PHT, the conversion half-life is roughly 15 minutes, which is offset by faster infusion rates (about triple). Its primary benefit derives from avoiding hypotension and not having to slow down the infusion as often. Cardiac arrhythmia can still occur as FosPHT is converted to PHT,¹⁰⁵ and both cardiac and hemodynamic monitoring should continue for at least 15 minutes after the infusion of the prodrug is complete.

VPA acts on sodium channels, but has effects on calcium channels and GABA_A as well. Two prospective, randomized trials have compared VPA with PHT for patients

Table 4
Systemic manifestations of status epilepticus

System	Effect	Result
Temperature	Increased systemic temperature due to sustained muscle activity; occurs in up to 83%	Neuronal injury, particularly in the cerebellum
Vascular	Blood pressure increases by up to 85 mm Hg systolic in the initial 30 min due to sympathetic overdrive; as cardiac output decreases with increasing mean arterial pressure, sudden loss of homeostatic mechanisms leads to hypotension as SE progresses >30 min	Hypertensive injury due to sympathetic tone followed by loss of perfusion to metabolically sensitive cortex
Cardiac	Potentially fatal cardiac arrhythmias occur in up to 58% Takotsubo cardiomyopathy and contraction band necrosis may occur due to endogenous catecholamines	Increased mortality
Cerebrospinal fluid	Pleocytosis; typically $<10 \times 10^6/L$, up to $80 \times 10^6/L \pm$ mild transient elevation in protein	Misdiagnosis of meningitis or encephalitis
Pulmonary	Elevated minute ventilation and pulmonary hypertension	Pulmonary edema
Other	Acidosis; pH <7.3 in up to 81% Rhabdomyolysis \pm hyperkalemia ^a Hyperglycemia	Refractory hypotension, decreased respiratory drive Renal failure, cardiac arrhythmia Exacerbation of acidosis

^a Depolarizing paralytics (ie, succinylcholine) are relatively contraindicated, as they may result in worsened muscle damage and hyperkalemia, thus facilitating cardiac arrhythmia.

Data from Refs.^{39,55,83–88}

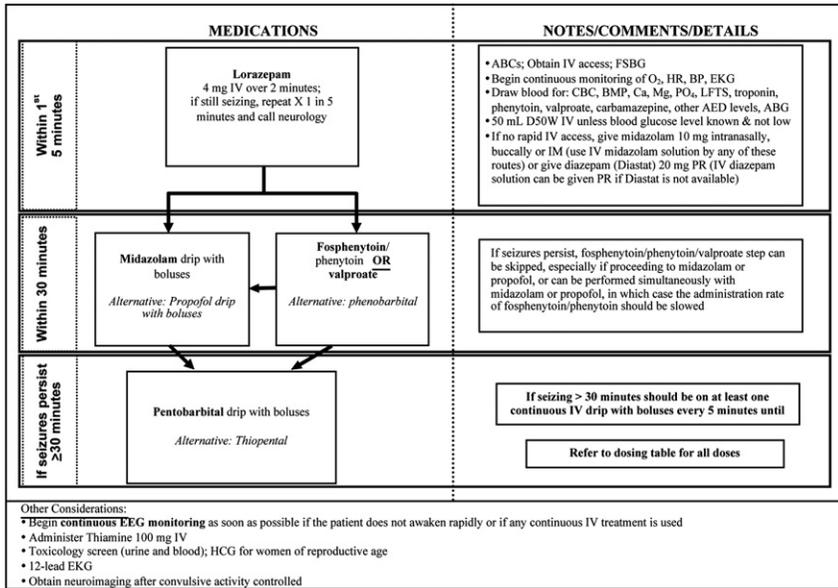


Fig. 4. Convulsive status epilepticus treatment algorithm in adults at Columbia University's Comprehensive Epilepsy Center. ABG, arterial blood gas; AED, antiepileptic drug; BMP, basic metabolic panel; BP, blood pressure; Ca, calcium; CBC, complete blood count; D50W, 50% dextrose in water; EKG, electrocardiogram; FSBG, finger stick blood glucose; HCG, human chorionic gonadotropin; HR, heart rate; IM, intramuscular; IV, intravenous; LFTs, liver function tests; Mg, magnesium; PO₄, phosphorus; PR, per rectum.

with SE. One study randomized 100 patients with SE refractory to diazepam to 20 mg/kg of either VPA or PHT, and found no difference in either efficacy or tolerability.⁹² The second study used VPA (30 mg/kg) or PHT (18 mg/kg) as first-line treatment for SE using a crossover design. VPA was more effective in controlling SE both as the initial drug (66% vs 42%, $P = .046$) and as the second drug after the first had failed (79% vs 25%, $P = .004$).¹⁰⁰ Adverse effects associated with VPA based on studies in other scenarios include hyperammonemia, hepatic dysfunction, pancreatitis, parkinsonism, dose-dependent thrombocytopenia,⁸³ and other potential mechanisms that may lead to impaired coagulation such as lower platelet activation and prolonged thrombin time.¹⁰⁶ Of importance, there are few cardiovascular or mental status effects. One study reported loading doses of up to 32.7 mg/kg in elderly inpatients with no reported hypotension or arrhythmias.¹⁰⁷ This finding makes VPA a particularly attractive AED in the elderly, the critically ill, or those with advanced directives precluding intubation.

Two additional AEDs have recently been studied in SE. The first is levetiracetam (LEV), which is a synaptic vesicle (SV2A) ligand and inhibits high-voltage-gated calcium-channel currents. Adverse effects in two case series were limited to mild sedation (often when given close to benzodiazepines), mild nausea, transient asymptomatic thrombocytopenia, and a transient elevation in liver function tests.^{94,99} Response varies: SPSE and CPSE were effectively treated by 1 to 2 g LEV as second-line therapy 60% to 79% of the time.^{93,97} Generalized NCSE or subtle status responded 30% of the time, whereas none of the patients with GCSE in one series responded.⁹⁷ A small study of SE in elderly patients with medical comorbidities reported an 88% EEG response to 1.5 g IV bolus as first-line therapy.¹⁰⁸

Table 5
Common medications in status epilepticus

Medication	Initial Dose	Clearance	Protein Binding	Maintenance	Level	Response
<i>Non-cIV (Without Respiratory Depression, Except Phenobarbital)</i>						
PHT	18–20 mg/kg IV up to 50 mg/min (25 mg/min for the elderly or patients with cardiovascular compromise)	Hepatic	90%	5–7 mg/kg PO/IV div up to TID; caution with tube feedings that decrease absorption	Total: 15–20 µg/mL Free: 1.5–2.5 µg/mL	37%–84%
FosPHT	18–20 PE/kg IV up to 150 mg/min	Same as PHT				
Valproate	20–40 mg/kg IV over 10 min	Hepatic	90%	1000 mg PO/IV q 6 h	80–140 µg/mL	79%–88%
Levetiracetam	2500 mg IV over 15 min (maximum bolus dose: 4 g)	Renal 67%, enzymatic hydrolysis 33%	<10%	2–12 g PO/IV div up to QID	25–60 mg/L	60%–90%
Lacosamide	300 mg IV over 30 min	Hepatic 60%, renal 40%	<15% ^a	200–300 mg PO/IV q 12 h	—	57%–60%
Phenobarbital	20 mg/kg IV up to 60 mg/min	Hepatic 75%, renal 25%	20%–45%	1–3 mg/kg/d PO/IV div BID or TID	20–50 mg/L	Equivalent to PHT/valproate
<i>cIV (With Respiratory Depression)</i>						
Midazolam	0.2 mg/kg IV q 5 min until Sz control or maximum dose 2 mg/kg	Hepatic; active metabolites excreted renally	95%	0.1–2.9 mg/kg/h cIV	—	Acute: 82% 48-h: 37% 7-d: N/A
Propofol	2 mg/kg IV q 5 min until Sz control or maximum dose 10 mg/kg	Hepatic	90%	2–15 mg/kg/h cIV (limited to 5 mg/kg/h for treatment >48 h)	—	Acute: 67%–73% 48-h: 54% 7-d: 43%
Pentobarbital	5 mg/kg IV up to 50 mg/min q 5 min until Sz control	Hepatic	35%–55%	1–10 mg/kg/h cIV	—	Acute: 92% 48-h: 57% 7-d: 22%
Ketamine	1.5 mg/kg IV q 5 min until Sz control or maximum 4.5 mg/kg	Hepatic	45%	1.2–7.5 mg/kg/h cIV	—	Unknown

Abbreviations: BID, Twice per day; cIV, continuous intravenous; div, divide; FosPHT, fosphenytoin; IV, intravenous; N/A, no data available; PE, phenytoin equivalents; PHT, phenytoin; PO, by mouth; q, every; QID, four times per day; Sz, seizure; TID, three times per day.

^a New data suggest LCS may exhibit up to 90% protein binding.

Data from Refs.^{74,92–102}

The second agent is the recently available AED lacosamide (LCS), which enhances the slow inactivation of voltage-dependent sodium channels. Similar to LEV and VPA, there are minimal if any effects on respiratory function, and cardiovascular effects are limited to potential PR interval prolongation. Although data on nonrefractory SE are limited, one case series of 39 patients has been published.⁹⁸ Dose ranges between 200 and 400 mg were given to patients, 85% of whom were in NCSE-A. Almost half of patients needed no further medication when LCS was used, and there were no adverse effects related directly to LCS.

PRIMARY MANAGEMENT OF RSE

Even prolonged RSE lasting months can resolve with good outcome.⁴¹ Despite the incredible challenges of treating RSE and the lack of consensus on how to best to do so, it is crucial to establish a rapid, effective agent in patients who continue to have Sz. As only a minority of patients will respond to a third bolus AED,¹⁸ a continuous IV (cIV) medication should be considered, either midazolam (MDZ) or propofol (PRO) initially (see **Fig. 4**). It should be emphasized that RSE is very often electrographic only, or has subtle clinical correlate, even after “successful” treatment of convulsions^{18,24,74}; transfer to a unit or hospital with cEEG should be considered for the most effective use of these continuous drips.

MDZ is a rapid-acting benzodiazepine. Its major adverse effect is hypotension, often requiring pressors, and respiratory suppression. In addition, tachyphylaxis may occur and there is a theoretical concern of secondary downregulation of GABA receptors from either prolonged benzodiazepine use or SE. Because breakthrough Sz predict Sz recurrence after anesthetic weaning, in the authors’ center MDZ infusion is now used at much higher doses than in the past, up to 2.9 mg/kg/h, 10 times higher than average rates in older studies. Sz suppression is typically maintained for 24 hours followed by slow weaning over 6 to 24 hours while on cEEG to evaluate for Sz recurrence.

PRO is a GABA_A agonist with rapid onset (about 3 minutes) and easy reversibility. In addition, it inhibits *N*-methyl-D-aspartate (NMDA) and modulates calcium influx. Adverse effects include hypotension, respiratory suppression, transient movement disorders that may be misconstrued as Sz,¹⁰² and the propofol infusion syndrome (PIS; **Box 3**). Originally described in children, PIS has been recognized in adults who receive propofol at more than 5 mg/kg/h for longer than 48 h, particularly after head injury.¹⁰⁹ A maximum of 5 mg/kg/h is recommended if PRO is to be maintained for more than 48 hours, and creatine kinase, lactic acid, pH, and triglycerides should be checked daily. To maintain efficacy while reducing the dose, some use an adjunctive “dose-sparing” cIV benzodiazepine.¹⁰² As with MDZ, PRO is typically weaned over 6 to 24 hours.

Box 3

Propofol infusion syndrome: diagnostic criteria greater than 6 hours after initiation of propofol

Creatine kinase >2000 U/L

Triglycerides >500 mg/dL

Progressive lactic acidosis >2.5 mmol/L

+ Bicarbonate <20 mmol/L >6 hours after propofol infusion (not due to sepsis)

Data from Rossetti AO, Milligan TA, Vulliemoz S, et al. A randomized trial for the treatment of refractory status epilepticus. *Neurocrit Care* 2011;14:4–10.

For decades, the preferred anesthetic for ICU treatment of RSE has been barbiturates. In the United States this is typically pentobarbital, which acts on different GABA receptor isoforms than do benzodiazepines. While benzodiazepine-sensitive receptors are internalized in experimental models of SE, barbiturate-sensitive receptors maintain their responsiveness.¹¹⁰ The adverse effects of pentobarbital are principally cardiovascular: cardiac depression, vasodilatation and hypotension, and poikilothermia.

MDZ, PRO, and barbiturates have been compared in a systematic review of 193 patients,⁹⁶ and more recently PRO and barbiturates have been compared in a prospective, randomized controlled trial of 23 patients.¹⁰¹ In the systematic review, pressor-requiring hypotension occurred in about 30% of patients on MDZ, significantly fewer than with pentobarbital (77%). This result was likely related to dosing and goals of treatment: MDZ is typically titrated to Sz control whereas pentobarbital is titrated to background suppression. Related to this, MDZ was associated with significantly more breakthrough Sz's (more than half) compared with PRO (15%) and pentobarbital (12%). However, cEEG was only performed in one-quarter of patients receiving pentobarbital (compared with 80% of those on MDZ), so it remains unclear if the rates of breakthrough Sz's (usually NCSz's) were truly lower. Finally, doses of PRO averaging 3.2 mg/kg/h only succeeded in achieving burst suppression 38% of the time, much less often than with pentobarbital (96%). By contrast, the prospective trial randomized patients to either PRO or barbiturates with the goal of achieving background suppression. Seven-day Sz freedom rates after 36 to 48 hours of suppression-burst were similar between PRO and barbiturates, but patients receiving barbiturates experienced longer mechanical ventilation time than patients receiving PRO.

There does not appear to be any significant difference in mortality between MDZ, PRO, and barbiturates when used for RSE.^{96,101} Mortality also remains the same when only one versus more than one anesthetic is administered.¹¹¹ Therefore, there are no clear guidelines as to which agent should be used first. Also, goals are not clear regarding titration of anesthetics to suppression burst versus Sz freedom, and for how long to do this. On one hand, barbiturate treatment seems to demonstrate significantly more suppression burst and possibly less Sz recurrence,⁹⁶ a predictor of relapse and subsequently mortality.¹¹² On the other hand, there is no clear difference in mortality between patients who achieve suppression burst and those who do not.¹¹¹ At least one organization has formally recommended 24 hours of suppression before medication weaning,¹¹³ but data from a randomized prospective study found an overall Sz-free response rate of only 35% after suppression burst for 36 to 48 hours on cEEG.¹⁰¹ Could longer durations therefore be required to establish efficacy of treatment? Older studies did not incorporate cEEG and therefore data are limited. Sz's can still occur during suppression burst, and even during complete background EEG suppression.

MAINTENANCE THERAPY IN RSE

In RSE, maintenance AEDs facilitate continued Sz control after weaning from cIV medications. Agent(s) used in the initial treatment of SE should be maximized and continued, but additional AEDs are commonly required (see **Table 5**). PHT can be used IV or transitioned to oral administration. For patients receiving continuous tube feedings, dosing should remain IV to avoid a dramatic (up to 71%) decrease in absorption of PHT.¹¹⁴ Daily total and free levels should be monitored. PHT is highly protein bound and hepatically cleared, thus free levels may be quite elevated in the setting of low protein binding or when using other highly protein-bound medications such as VPA or benzodiazepines. In critically ill patients on PHT plus full doses of VPA, the free PHT level is usually close to 3 times the expected level, that is, it is close to

30% of the total PHT rather than the usual 10%. In these patients, a total PHT level of 8 to 10 $\mu\text{g/mL}$ will provide a high-therapeutic free level of 2.4 to 3.0 $\mu\text{g/mL}$. In some centers, free levels may take longer to report than total levels; if there is a predictable relationship between the two over several consecutive days of steady dosing, the total level may be used reliably.

VPA, like PHT, is highly protein bound and hepatically cleared. However, it is a cytochrome P450 inhibitor rather than inducer. Another interaction of particular concern has been the interaction between VPA and meropenem, and probably carbapenems as a class, which are widely used for resistant gram-negative infections. These antibiotics may dramatically reduce VPA levels, due to a variety of mechanisms involving decreased glucuronidation and increased renal excretion.¹¹⁵

LEV is only minimally protein bound and is cleared mostly by the kidneys. The significance of levels is not well established. Similarly, LCS is purported to have minimal protein binding, although a recent study demonstrated that perhaps 90% is protein bound.¹¹⁶ LCS is both hepatically and renally cleared. Specifically for RSE, an uncontrolled, unblinded study reported that LCS has a response rate of 20%⁹⁸; all 4 cases of refractory partial status responded to doses of 100 mg or less despite NCSE lasting up to 50 hours.¹¹⁷ The authors' algorithm includes LEV and LCS as later add-on medication unless there are contraindications to PHT and VPA.

Phenobarbital, a barbiturate, may be used as a bolus for second-line or third-line treatment. Adverse reactions include respiratory depression, impaired mental status, hypotension, and rash. Like PHT, phenobarbital may affect motor recovery after stroke.¹⁰³ Phenobarbital can be useful in patients requiring cIV barbiturates, as phenobarbital reduces the risk of relapse even if levels are subtherapeutic.¹¹² It remains a reasonable alternative for the early treatment of SE, as it was not statistically inferior to lorazepam in the VA Cooperative study and did not have greater acute adverse events.¹⁸ Because of hypotension, prolonged sedation, the need to load it fairly slowly, and its strong induction of P450 enzymes, the authors prefer other agents, but include phenobarbital as an option for select patients only.

Any oral agent may be used, such as topiramate (TPM), gabapentin (GPN), pregabalin (PGB), oxcarbazepine, or carbamazepine (CBZ). Two of these agents, PGB and TPM, have been studied in this setting. PGB was used in mostly partial RSE in 11 patients.¹¹⁸ After a median of 5 days of RSE, 150 to 600 mg of PGB was given enterally in divided doses with Sz cessation within 24 hours in 5 patients for a response rate of 45%. TPM exhibits a variety of actions that may be helpful in SE including sodium-channel inhibition, GABA potentiation, high-voltage-gated calcium-channel inhibition, and antagonism of excitatory transmission. Rapid titration of up to 1600 mg/d (a very high dose) may be useful in treating RSE based on one series of 6 patients, although this has yet to be confirmed in further studies.¹¹⁹ Animal studies suggest TPM may have neuroprotective properties, and may act synergistically with NMDA antagonists.¹²⁰ When using TPM, it should be kept in mind that it is a carbonic anhydrase inhibitor and may exacerbate acidosis. The authors avoid the use of TPM while using propofol, as it theoretically may exacerbate the acidosis associated with PIS. In addition, cases have been reported of acute hepatic failure associated with the use of TPM in combination with VPA.¹²¹

ALTERNATIVE MANAGEMENT OF RSE

As described, failure of an anesthetic agent or Sz recurrence after its withdrawal has been termed "malignant" status.²⁰ The authors might revise this definition as Sz recurrence at any time after a period of at least 24 hours of suppression burst on cEEG plus

trials of at least 3 AEDs titrated to appropriate serum levels. Alternative strategies may need to be considered in these patients.

Ketamine is an NMDA antagonist that has been used by anesthesiologists for decades. In experimental models of prolonged SE, ketamine has been found to be less effective early, but is increasingly effective as Szs become self-sustained.¹²² This process is the reverse of that of GABA agonists (including benzodiazepines and barbiturates), likely a result of internalization of GABA receptors during SE. Thus, glutamate blockade becomes more effective than GABA agonism in later stages of SE (see **Fig. 2**). In addition, because excitatory amino acid mediated toxicity is thought to underlie neuronal injury in SE, NMDA antagonism may be neuroprotective.⁴⁹ Animal models have suggested a synergistic effect when ketamine is used together with benzodiazepines in SE.¹²³ These models have also demonstrated potential ketamine toxicity, and a single anecdotal human case of cerebellar atrophy allegedly due to prolonged (72 hours) ketamine use in SE has been reported.¹²⁴

Despite the theoretical benefits of ketamine and its short-term efficacy in aborting Szs, very few studies support its use. At the authors' center ketamine is used in conjunction with MDZ, often in the instance that maximal MDZ cIV has not resulted in Sz control on cEEG. It is also used as a bridge when tapering off of cIV barbiturates to limit withdrawal-associated Sz recurrence. Increased cardiovascular output, including tachycardia and hypertension, is both an adverse effect and a strength of ketamine, in contrast to the hypotension induced by other anesthetic agents used for treating RSE. Dissociative effects such as hallucinations or psychosis occur at sub-anesthetic dosing in awake patients, but are not a problem in this setting. Caution should be exercised prior to infusion in patients with elevated intracranial pressure; cardiovascular disease including hypertension; myocardial ischemia, or congestive heart failure; autonomic dysregulation; and TBI.

Inhaled anesthetics have been used with some success, but are impractical and have not demonstrated sustained benefit after cessation. Mirsattari and colleagues¹²⁵ reported a case series of isoflurane and desflurane in patients with RSE at end-tidal concentrations of 1.2% to 5%. Suppression burst was initiated within minutes and was maintained for a median period of 11 days while maintenance AEDs were optimized. Four of the 7 patients included in the study survived with good outcomes. Adverse effects included hypotension, along with ICU-associated problems such as atelectasis and ileus. With prolonged use of more than 30 days, thalamic and cerebellar hyperintensities on T2-weighted magnetic resonance imaging (MRI) may occur, indicating potentially reversible neurotoxicity.¹²⁶

Lidocaine is a nonanesthetic class IB antiarrhythmic agent that has been used in cardiology for many years. It works by blocking sodium-channel conduction, attenuating depolarization, and decreasing automaticity. In addition, lidocaine has been used as a nonsedating, rapidly acting agent in SE. The largest prospective study comprised 36 chronic obstructive pulmonary disease patients with SE¹²⁷ in whom lidocaine given at cardiac doses led to immediate Sz cessation in almost three-quarters. Szs recurred quickly in more than half. Initial bolus is 1 to 3 mg/kg, and an infusion of up to 4 mg/kg/h is recommended to prevent recurrence.¹²⁸ Caution should be exercised in using lidocaine in patients with hepatic disease and the elderly, although it is noted that doses typically associated with hypotension or myocardial depression are about twice as high, and those associated with induction of Szs are about 3 times as high.¹²⁸

Magnesium (Mg) is an important component of the NMDA receptor, effectively blocking transmission at membrane resting potential. Mg repletion may saturate NMDA receptors to restore tonic blockade. Its use is largely anecdotal in adults

with the exception of eclampsia, in which it is the treatment of choice. The mechanism of action in eclampsia, however, is likely related to endothelial stabilization and therefore the treatment of the underlying condition, not the SzS directly. One recent study found Mg to be effective in 2 young adults with mitochondrial disease (POLG1 mutation).¹²⁹ Given the ever-growing spectrum of juvenile-onset and adult-onset presentations of mitochondrial disease, Mg should be considered in patients with cryptogenic RSE. Typical loading doses are 2 to 4 g IV, but optimal serum levels are not established.

Adjunctive medications may be useful; coadministration of benzodiazepines with PRO or ketamine has already been discussed. Pathologic studies have implicated drug efflux transporters such as P-glycoprotein (Pgp) in the refractory nature of prolonged RSE.¹³⁰ Verapamil, a calcium-channel antagonist and Pgp inhibitor, was used in one patient with recurrent SzS after prolonged RSE.¹³¹ A dosage of 120 mg/d, roughly half the starting dose for cardiovascular indications, significantly reduced the burden of the patient's nocturnal SzS over the course of 2 weeks while levels of PHT and phenobarbital remained essentially constant. However, a recent animal study found no benefit of calcium-channel blockers for phenobarbital-resistant recurrent SzS, and 3 of the 11 animals actually developed Sz clusters.¹³² Animal studies have also recently hinted at the use of HMG-CoA reductase inhibitors, or statins, in long-lasting SE.¹³³ Lovastatin decreased the expression of proinflammatory cytokine mRNA and body temperature in rats, which may provide neuroprotection. In addition, erythropoietin (EPO), a cytokine hormone with receptors located widely within the CNS, has been studied in low-dose pilocarpine rat models of SE. When administered after SE, EPO reduced blood-brain barrier disruption, decreased neuronal cell death, and attenuated microglial activation. Clinically, spontaneous recurrent SzS were less frequent during prolonged monitoring (>1 month).¹³⁴ Further studies will be required to test these agents for use in humans with SE.

There is a variety of nonpharmacologic interventions for RSE including hypothermia, electroconvulsive therapy (ECT), the ketogenic diet, and music therapy. Hypothermia, typically used in cardiac arrest patients, has been used for RSE in a small case series,¹³⁵ based on animal data¹³⁶ that suggests hypothermia has anticonvulsant and neuroprotective properties. Four patients refractory to MDZ and barbiturates received endovascular cooling to 31° to 33°C. cIV anesthetics were weaned, and after a 24-hour Sz-free period, 0.5°C rewarming every 4 hours to 36.5°C took place. RSE was stopped in all patients; 2 of the 4 remained Sz free. Adverse effects were prominent and included shivering, acidosis, coagulopathy, thrombosis (ie, deep vein thrombosis, pulmonary embolism), cardiac arrhythmia, and immunosuppression. Although these risks might be mitigated by a short duration of cooling, controlled studies are needed. ECT presumably increases endogenous anticonvulsant signaling pathways and induces a refractory period that aborts SE. One case series and review¹³⁷ suggests weaning all maintenance AEDs while on an anesthetic titrated to suppression burst followed by sessions of ECT for 3 to 8 days. If SzS recur, suppression can be resumed along with maintenance medications; however, 70% of the cases reported in the literature remained Sz free. Lastly, music has been reported to abort SE. Miranda and colleagues¹³⁸ have now reported two cases of RSE that spontaneously aborted within hours of continuously played classical music from Mozart and Bach.

The ketogenic diet (KD) is a carbohydrate-restricted diet with high fat content that induces ketosis and suppresses SzS. KD is typically used in children. In the ambulatory pediatric population, KD has been shown in a randomized controlled trial to effectively treat daily SzS (>90% reduction in Sz frequency in 7% vs 0% of controls and >50% reduction in Sz frequency in 38% vs 6% of controls).¹³⁹ Recently, KD

has been used in two adult cases of RSE.¹⁴⁰ In both, KetoCal 4:1 tube feedings were gradually introduced to patients with malignant RSE. Ketosis was achieved in 8 to 10 days coincident with Sz control. There are a variety of adverse effects including hypoglycemia, gastrointestinal upset, and acidosis; long-term effects are not well reported, but include renal stones and growth delay. With the use of KD a nutritional specialist should be involved, a urinalysis should be checked for ketones daily, and serum β -hydroxybutyrate should be checked weekly.

Data on the effectiveness of epilepsy surgery for RSE are limited and are mostly from pediatric populations. Nonetheless, surgery may be considered in select patients with malignant RSE with evidence of one main Sz focus. One case series documented resection and multiple subpial transections in one patient with focal status and callosotomy in two patients with multifocal status, all with resolution of SE.¹⁴¹ The patient with focal status continued to have "occasional brief partial seizures," one of the patients with multifocal status remained Sz free for 2 years, and the other had monthly Sz with one recurrence of treatable SE. A more recent case reported resection in one patient with focal status who remained Sz free at 16 months postsurgery.¹⁴² Some investigators advocate for 2 weeks of failed treatment as a justification for surgery.¹⁴³ However, concordance is crucial for accurate localization, and MRI demonstrating focal restricted diffusion, ictal single-photon emission computed tomography (SPECT),¹⁴¹ ictal ¹⁸F-fluorodeoxyglucose positron emission tomography (PET),¹⁴² or electrocorticography^{141,142} may all be helpful. As RSE becomes malignant, physicians should consider acquiring data early so that surgical options become available. Other strategies that need further evaluation include vagus nerve stimulation and deep brain stimulation. The latter has been successfully used in intractable epilepsy to good effect,¹⁴⁴ but has been evaluated only in animal models of SE.¹⁴⁵

RSE caused by CNS "infection" infrequently yields a proven pathogen.⁴⁰ A variety of autoimmune or paraneoplastic disorders may be implicated, although the incidence is unknown. It is reasonable, then, to consider steroids, adrenocorticotropic hormone, intravenous immunoglobulin, and/or plasma exchange to treat cryptogenic RSE in conjunction with other AEDs. It is even postulated that systemic exposure of brain tissue through damaged blood-brain barrier associated with prolonged Sz may induce a "secondary immune-mediated encephalitis,"¹⁴⁶ further justification for empiric immunomodulatory therapy in RSE.

TREATMENT CONSIDERATIONS IN THE COMATOSE OR CRITICALLY ILL

Szs and SE in the critically ill are largely nonconvulsive. As opposed to NCSE in the ambulatory population, the typical presentation of NCSE in the comatose or critically ill is nonlocalizing coma.¹⁴⁷ Despite more widely available cEEG, diagnosis is frequently delayed: by 24 hours in 16% of patients in the neuro-ICU,⁶² by 48 hours in the medical ICU, and by 72 hours in the surgical ICU.⁴³ Routine EEG (20–60 minutes) will miss at least half of patients who are having NCSzs. In noncomatose patients, 24 hours of cEEG will identify up to 95% of patients with NCSzs. In comatose patients, only 80% will be diagnosed by 24 hours. Therefore, a full 48 hours of cEEG should be used in comatose patients to increase the sensitivity of NCSz detection to almost 90%.²¹

The critically ill will often do poorly regardless of the presence or absence of Sz. However, in multivariate analyses, NCSE,^{18,24} delays to treatment,⁶² duration of Sz,^{24,62} and coma⁵⁴ portend worse prognosis. In the elderly, there is some retrospective evidence for increased mortality and longer hospitalization with IV benzodiazepine treatment,¹⁴⁸ but others suggest there were not adequate controls of dosage and

timing in the study, and that “lack of clinical prudence [rather] than an inherent danger from the benzodiazepines” played a role.³⁵

Complicating the diagnosis and management of Szs and SE in the critically ill are so-called boundary conditions,¹³ whereby the EEG may appear potentially ictal yet does not strictly fulfill criteria for definite NCSzs or NCSE. In ambulatory patients, much of the differentiation between ictal and nonictal can be made based on mental status. In the critically ill, on the other hand, these conditions occur in the context of coma. Chong and Hirsch¹⁴ provide a thorough review of patterns such as lateralized periodic discharges (LPDs), generalized periodic discharges (GPDs), and their potential clinical significance.

It is clear that LPDs are highly associated with Szs¹⁴⁹ and they may also be associated with worse outcomes after SE.^{150,151} The authors' recent analysis of 200 patients with GPDs and a matched control group showed that GPDs are associated with NCSzs and NCSE but do not appear to be associated with worse outcome after thorough adjustment for age, neurologic examination, and etiology.¹⁵² One subset of GPDs, triphasic waves, are seen in metabolic encephalopathy and degenerative diseases, but cannot be reliably distinguished from generalized epileptiform discharges or NCSE in a given individual based on EEG alone.^{153,154} It should be noted that LPDs are occasionally ictal without question, for instance when they are associated with time-locked jerking on the contralateral side¹⁴ or with aphasia that resolves along with the LPDs in response to AED.¹⁵⁵ At times, LPDs are associated with increased glucose metabolism on PET or increased cerebral blood flow on SPECT.¹⁴ The authors view these periodic patterns as part of an ictal-interictal continuum, in an attempt to avoid the false dichotomy of interictal versus ictal EEG patterns in encephalopathic patients. Ongoing efforts are being made to define and therefore facilitate study of these and other confusing EEG phenomena.¹⁵⁶

When there is reasonable suspicion for NCSE, an urgent EEG is indicated. A lack of rapid clinical response to an AED does not help rule out NCSE. In the VA Cooperative Study, 100% of the patients with subtle SE remained comatose 12 hours after treatment.¹⁸ In another study, more than half of nonanoxic patients with NCSE in the ICU improved in alertness after treatment with AEDs, but the response was almost never immediate, sometimes only minimal, and not always sustained.⁴³ Yet if EEG is not available or the EEG findings lie along the ictal-interictal continuum, it may be useful to perform a trial of a rapid-acting AED at the bedside to evaluate for clinical improvement (**Box 4**). A major restriction of empiric AED trials in possible NCSE in the critically ill or comatose is that many EEG patterns resolve, leaving a comatose patient with diffuse slowing. Resolution of an abnormal pattern does not represent proof of its epileptic nature; for example, in patients believed to have pure metabolic encephalopathy without Szs, triphasic waves resolve with benzodiazepines as well.¹⁵³

In the ICU most patients do not have a history of epilepsy, and new Szs may be the presenting symptom of a new cerebral insult.⁴⁵ For patients in whom the EEG is equivocal or clearly ictal, an assessment for acute brain injury (stroke, hemorrhage) or new systemic syndrome (hepatic failure, renal failure, sepsis), medication review, and consideration of lumbar puncture may be appropriate as treatment is initiated.³⁵ In patients with periodic discharges, equivocal patterns or only brief intermittent NCSzs, the authors generally try to avoid coma-inducing doses of medications, and typically start with IV PHT, VPA, or LEV, and possibly LCS.

In patients with frequent or periodic epileptiform discharges, cEEG monitoring is recommended for 48 hours, as these patients are more likely to have a delay before recording their first definite Sz.²⁷ The authors advocate a nonsedating AED for Sz prophylaxis for patients with frequent or periodic epileptiform discharges during the acute illness only (typically a couple of weeks) if there have been no definite Szs,

Box 4**Antiepileptic drug trial for diagnosis of suspected nonconvulsive status epilepticus***Indication:*

Rhythmic or periodic focal or generalized epileptiform discharges on EEG with neurologic impairment

Contraindication:

Patients who are heavily sedated/paralyzed

Patients who have a clear reason for their level of consciousness

Monitoring:

EEG, pulse oximetry, blood pressure, electrocardiography, respiratory rate with dedicated nurse

Antiepileptic Drug Trial:

- Sequential small doses of rapidly acting short-duration benzodiazepine such as midazolam 1 mg per dose or nonsedating AED such as levetiracetam, valproate, phenytoin, or lacosamide
- Between doses, repeated clinical and EEG assessment
- Trial is stopped after any of the following
 - Persistent resolution of the EEG pattern (and examination repeated)
 - Definite clinical improvement
 - Respiratory depression, hypotension, or other adverse effect
 - A maximum dose is reached (such as 0.2 mg/kg midazolam, though higher may be needed if on chronic benzodiazepines)

Test is considered positive if there is resolution of the potentially ictal EEG pattern AND either an improvement in the clinical state or the appearance of previously absent normal EEG patterns (eg, posterior-dominant "alpha" rhythm). If EEG improves but patient does not, the result is equivocal.

Adapted from Jirsch J, Hirsch LJ. Nonconvulsive seizures: developing a rational approach to the diagnosis and management in the critically ill population. Clin Neurophysiol 2007;118:1660–70.

clinically or electrographically. If Szs develop, the authors typically treat with an AED for about 3 months, obtain another EEG, and re-assess at that point. There are minimal data to guide these decisions, but extensive experience with TBI, brain tumors, and other scenarios suggests that prolonged prophylactic AEDs in those without clear epilepsy (ie, recurrent unprovoked Szs, which excludes Szs during the acute illness) will not be effective and may cause unnecessary adverse effects.

SPECIAL SITUATIONS: ORGAN FAILURE

In patients with liver failure and Szs or SE, serum levels of hepatically metabolized medications will increase. In addition, decreased protein synthesis may lead to hypoalbuminemia, further increasing serum free (unbound) drug levels. Medications that are not hepatically metabolized and demonstrate minimal protein binding, such as LEV, GPN, or PGB, are easier to use in these settings.

Renal failure causes metabolic disturbances including hyponatremia, acidosis, and hypoalbuminemia. Medications that are renally cleared such as LEV, GPN, PGB, and to a lesser degree phenobarbital and TPM, should be dosed significantly lower and a dose should be given immediately following dialysis. Medications such as TPM and zonisamide have carbonic anhydrase activity, which can precipitate acidosis or

renal calculi in patients with poor renal function. Highly protein-bound medications such as PHT, VPA, benzodiazepines, and possibly LCS¹¹⁶ will experience higher-than-usual unbound levels for a given total serum level, but are only minimally dialyzed because protein-bound drug is not removed during dialysis.

SPECIAL SITUATIONS: ORGAN TRANSPLANTATION

Szs in transplant patients occur frequently in the context of the following: significant metabolic abnormalities, depending on the organ involved; infection or neurotoxicity from medications; and complications from surgery, such as hypoxia (**Table 6**). Liver transplant patients in particular appear to develop Szs 4 to 6 days postoperatively.¹⁵⁷ Abou Khaled and Hirsch⁸³ speculate that the cause may be withdrawal from high endogenous benzodiazepines as the new organ begins functioning. Patients on calcineurin inhibitors such as tacrolimus are at risk for the posterior reversible encephalopathy syndrome (PRES), characterized by Szs and cerebral edema associated with cortical blindness, aphasia, or altered mental status. Other factors implicated in the development of this syndrome include hypertension, hypomagnesemia, and supra-therapeutic immunosuppressant levels.

Medications should not interfere with the new organ; for instance, certain AEDs (PHT, CBZ, and several others) can affect cardiac conduction and should be used judiciously after heart transplant. Similarly, barbiturates can cause myocardial depression. The choice of medication must also navigate the difficult interactions that often occur with transplant medications. Cyclosporine and methylprednisolone are metabolized through the cytochrome P450 pathway, thus inducers such as PHT, CBZ, and phenobarbital may increase clearance and reduce levels, sometimes quite dramatically.

SPECIAL SITUATIONS: PREGNANCY

As in the critically ill, Szs in a pregnant woman should warrant an evaluation for new acute brain injury, as only 15% to 30% of women with epilepsy develop increases in Sz frequency during pregnancy.¹⁵⁸ The reversible vasoconstriction syndrome (sometimes referred to as the Call-Fleming syndrome, or peripartum vasculopathy) may occur at any time during or even several weeks after pregnancy, and relative hypercoagulability increases the incidence of venous thrombosis. In addition, pregnancy-specific systemic illness such as hyperemesis gravidarum, the HELLP

Liver failure	2–33
Renal failure (on hemodialysis)	2–10
Transplant	
Liver	25–30
Kidney	1–31
Heart	2–15
Lung	22–27
Bone marrow	3–12.5
Pancreas	13

Data from Abou Khaled KJ, Hirsch LJ. Updates in the management of seizures and status epilepticus in critically ill patients. *Neurol Clin* 2008;26(2):385–408.

syndrome (hemolysis, elevated liver enzymes, and low platelets), and eclampsia may precipitate Szs. Eclampsia is the most common cause of Szs during pregnancy and may occur during or up to 3 weeks after pregnancy.¹⁵⁸ In patients with hypertension, Mg may be used to treat the underlying endothelial dysfunction in preeclampsia and eclampsia, and thereby help prevent Szs or SE.

A recent study group found that among pregnant women with epilepsy, SE occurred in 1.8% with no maternal mortality and one stillbirth related to CSE.¹⁵⁹ For a pregnant woman in SE, emphasis should be placed on positioning the woman into a left-lateral decubitus position if she is obviously gravid. Thiamine and glucose should be used empirically. Lorazepam should be used as a first-line agent to abort prolonged Szs, followed by Mg. A load of 2 to 4 g Mg may be given IV, but if Sz cessation is not prompt, alternative AEDs should be added according to the standard algorithm. It is important to recognize that unless a woman has previously been on VPA or phenobarbital with good control, it is not recommended to begin and maintain treatment with these medications.¹⁶⁰ In addition, hormone binding and increased renal and hepatic clearance of medications may lead to decreased drug concentrations, which will require close monitoring as Szs are controlled. Theoretical concerns for the fetus are derived from systemic effects of CSE such as hypoxia and lactic acidosis. If RSE develops, medications should be given aggressively as in nonpregnant patients, although boluses of anesthetic medications should perhaps be given somewhat more slowly and with fetal monitoring if possible. An obstetrics team should be closely involved to determine if and when the baby can be delivered to either treat (if eclamptic) or facilitate further treatment.

SUMMARY

Szs and SE are epilepsy emergencies with high morbidity and mortality. Early treatment is crucial, and the identification of an underlying etiology informs both continued treatment and prognosis. Many patients have underdiagnosed NCSzs or NCSE, particularly the comatose or critically ill, as well as those with acute or remote brain injury, prior convulsions, or sepsis. How aggressively to treat is controversial, but timely EEG can be useful for diagnosis, management, optimizing treatment response, and determining prognosis in these patients. Refractory conditions can be quite complicated, with limited evidence-based guidance, but treatment should not be restricted by nihilism even in the most prolonged cases, especially if there is not widespread irreversible brain injury. Further studies are needed to identify faster delivery mechanisms, appropriate monitoring, and more effective treatment in addition to clarifying our basic understanding of how these emergencies occur.

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