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# Treatment of Acute Seizures and Status Epilepticus

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**Overt status epilepticus and persistent obtundation after a witnessed clinical seizure are neurologic emergencies. Early recognition and intervention in the electroclinical syndrome of status epilepticus reduces morbidity, although treatment of the underlying etiology is also critical. This review outlines key concepts related to status epilepticus, delineates an approach to the early management of status epilepticus, and highlights novel but practical approaches in the evaluation and treatment of refractory status epilepticus, emphasizing the use of a treatment algorithm. This review is written from the perspective of the intensive care unit clinician, and the approach and opinions expressed stem from clinical experience and review of the current literature. Particular attention is given to an overall approach to the management of convulsive status epilepticus in adults and older children as well as exploring novel approaches and diagnostic tools that may prove useful in difficult-to-control status epilepticus.**

*Key words: acute repetitive seizures; nonconvulsive status epilepticus; refractory status epilepticus; intensive care; infusion therapies; treatment algorithm; novel therapies*

Status epilepticus (SE) is a heterogeneous electroclinical syndrome with diverse causes, inconsistent and dynamic clinical manifestations, and variable clinical course. Conventional teaching dictates that the outcome from SE is largely dependent on the underlying etiology; however, some evidence suggests that SE carries its own morbidity and mortality, independent of the cause. The pathophysiologic changes associated with ongoing seizure activity increasingly point to SE being a dynamic rather than a static process. The clinical course of SE parallels

that of the underlying precipitating disease process but occasionally may prove intractable even when the underlying disease improves, suggesting that SE can “take on a life of its own” and come to dominate the clinical picture. Moreover, SE may arise in patients with chronic epilepsy in the absence of newfound brain injury.

Although SE can be viewed and managed as an entity or disease in itself, somewhat separate from associated medical and surgical comorbidities, in most cases, particularly in the intensive care unit (ICU) setting, SE should be more accurately thought of as a stereotypical electroclinical response to a recent or remote cortical injury or irritation. One potential oversight in the management of SE in the ICU is to equate SE with out-of-control epilepsy and give inadequate consideration to the underlying cause. Ironically, SE occurring in persons with established epilepsy may be easier to control than SE in persons without preexisting epilepsy, possibly owing to earlier recognition of SE and the presence of antiepileptic drugs (AEDs) in these individuals. Furthermore, new onset SE is often due to an acute, active epileptogenic disease process, termed “acute symptomatic” SE, whereas SE in persons with preexisting epilepsy often arises owing to a remote but less acutely active disease process, termed “remote symptomatic.” When SE is viewed as an electroclinical response to brain injury, it follows that a rigorous exploration for the underlying cause is always warranted. This review will outline our approach when confronting SE in adults, paying particular attention to the ICU environment.

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## Epidemiology

Status epilepticus has an incidence of approximately 18.3 to 41 episodes per 100 000 population per annum, amounting to 150 000 new cases per year in the United States [1-5]. This figure largely refers to outpatient, population-based data and may underestimate the true incidence if one considers those cases arising in persons in the hospital. The

reported incidence varies substantially, depending on the definition of SE being used. With recent trends toward a more inclusive definition of SE, the incidence is likely to numerically increase. Furthermore, the incidence refers to clinically apparent episodes of SE, not incorporating the heretofore largely underestimated incidence of nonconvulsive SE. Suffice it to say that SE is quite common, perhaps the second most common acute neurologic emergency after acute vascular accidents.

Many cases of SE will be treated successfully without recourse to intubation and ICU admission. However, many patients admitted in SE need admission to an ICU owing to persistent ictal activity, obtundation secondary to seizures or treatment, or for treatment of the underlying neurologic disease or injury. These patients are prone to seizure recurrence, which may be clinically overt or subtle. Approximately 10% to 15% of patients with chronic epilepsy will experience an episode of SE at some point of their clinical course. Approximately 7% to 10% of patients with chronic epilepsy initially present with an episode of SE. At a health economics level, SE costs approximately \$4 billion per annum in the United States [6]. The annual number of deaths partly or fully attributable to SE has been estimated to be 22 000 in the United States [7].

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## Definitions and Phenomenology

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At first glance, the terms “epileptic seizure” and “epilepsy” ought to be easy to define, but there has been considerable debate about their accurate description. The International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) recently proposed new definitions for both of these clinical phenomena [8]. The proposed definition of an epileptic seizure is a “transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.” This definition underscores the dual clinical and electrographic nature of epileptic seizures. Following on from this, epilepsy is a “disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition.” The definition of epilepsy requires the occurrence of at least 1 epileptic seizure.

Epileptic seizures are either partial (also termed “focal” or “localization-related”) or generalized. A generalized seizure may be generalized at onset (primary generalized) or may have evolved from an initial partial seizure (secondarily generalized). Partial seizures may (*complex* partial seizures) or may not (*simple* partial seizures) impair consciousness,

depending on the extent of cortical involvement, although the distinction of intact from altered consciousness is often difficult. The clinical manifestations exhibited by patients during focal seizures reflect both (1) loss of the normal function subserved by the involved cortex, and (2) superadded manifestations inappropriately generated by the involved cortex, for example, unilateral involuntary motor activity during seizures arising from the motor cortex.

Generalized seizures manifest clinically as tonic, atonic, clonic, tonic-clonic, myoclonic, or absence seizures. Secondarily generalized seizures usually are tonic-clonic in nature. It is often difficult to differentiate primary generalized SE from secondarily generalized SE in the absence of a good account of preceding focal seizures before the episode of SE. Overall, most cases of generalized convulsive SE in adults that require ICU care are ultimately due to focal cortical injury or irritation [1,9]. In general, epilepsy due to focal cortical injury (focal epilepsies) is more difficult to control and manage than idiopathic generalized epilepsy syndromes and hence predominate in the ICU setting.

More than 90% of generalized tonic-clonic seizures (either primary or secondarily generalized) terminate within 2 minutes [10], probably due to the overriding inhibitory cerebral activity that accompanies the initial excitatory hypersynchronous cortical activity. This observation deserves some thought because it tells us something about the nature of SE, where the ictal activity endures. Approximately 7% of seizures will progress into SE [11]. The factors that allow or promote persistent ictal activity resulting in SE rather than self-limiting seizure activity are not well understood. What is evident is that the self-terminating nature of most seizures is lost or overridden in SE. Defining SE has proven more difficult than defining isolated seizures, and any definition of SE needs to highlight this self-perpetuating tendency.

An intuitive approach to defining SE is to declare SE as any seizure activity sufficiently vigorous or prolonged enough to cause neuronal damage; however, this definition is impractical because biomarkers for brain injury are not easily available. Furthermore, similar electroclinical seizure activity will have variable deleterious effects in different patients, depending on confounding clinical and genetic factors such as age, fever, and medication effects. The threshold for induction of neuronal injury can thus vary significantly from patient to patient; for example, classic absence SE is unlikely to lead to significant morbidity, but nonconvulsive seizures in medically ill patients are frequently associated with very significant morbidity and mortality.

The original definition by Gastaut and colleagues in 1964 [12] described SE as “a seizure that persists for a sufficient length of time or is repeated frequently enough to produce a fixed or enduring epileptic condition.” This mechanistic definition has more recently been recast to read “generalized convulsive status epilepticus refers to a condition in which there is a failure of the ‘normal’ factors that serve to terminate a typical generalized tonic-clonic seizure” [13]. Again, the difficulty lies in providing a definition that is not just theoretically insightful and sound but is useful in an emergency department (ED) or ICU situation.

These mechanistic definitions have largely been supplanted by more practical, operational, time-based definitions (particularly applied to convulsive SE) referring to SE as “at least 5 minutes of persistent generalized, convulsive seizure activity or two or more discrete seizures between which there is incomplete recovery of consciousness” [13]. Some experts find the 5-minute definition arbitrary and favor a working definition that SE is persistent seizure activity after sequential administration of appropriate doses of appropriate first- and second-line AEDs. We believe that the 5-minute and 2-drug definitions both convey an appropriate sense of urgency needed to proceed to the next stages of clinical management.

Following on from the distinction between partial and generalized seizures, SE can be either partial or generalized in nature. Partial SE can manifest with preserved (*simple* partial SE) or impaired (*complex* partial SE) consciousness. Generalized SE can manifest as generalized tonic-clonic SE (or convulsive SE), absence SE or myoclonic SE, depending on the predominant seizure type. A nonconvulsive form of generalized SE with subtle or no clinical motor manifestations is increasingly being diagnosed. In fact, nonconvulsive SE may prove to be the most common form of SE encountered in the ICU setting. Figure 1 illustrates the electrographic hallmarks of focal and generalized electrographic seizure activity and also illustrates the typical appearance of 3-Hz spike-and-wave activity.

### Subtle Convulsive or Nonconvulsive Status Epilepticus

Because of the dramatic nature of convulsive SE, prompt recognition by witnesses is universal and treatment is generally initiated in a protocol-driven fashion in most hospital settings; however, the same cannot be said for subtle convulsive SE or nonconvulsive SE. Hereafter, we will use “nonconvulsive

status epilepticus” (NCSE) as a descriptive term denoting cases of SE with little or no clinical signs of ongoing seizure activity apart from obtundation or subtle motor phenomena. Nonconvulsive SE is likely to represent a heterogenous collection of electroclinical states. Nonconvulsive SE is underrecognized, particularly in patients who have abnormal baseline cognitive abilities or multiorgan medical illnesses. In our experience, NCSE is applicable to 3 broad categories of patients: postconvulsive NCSE, benign epileptic NCSE, and acute symptomatic NCSE.

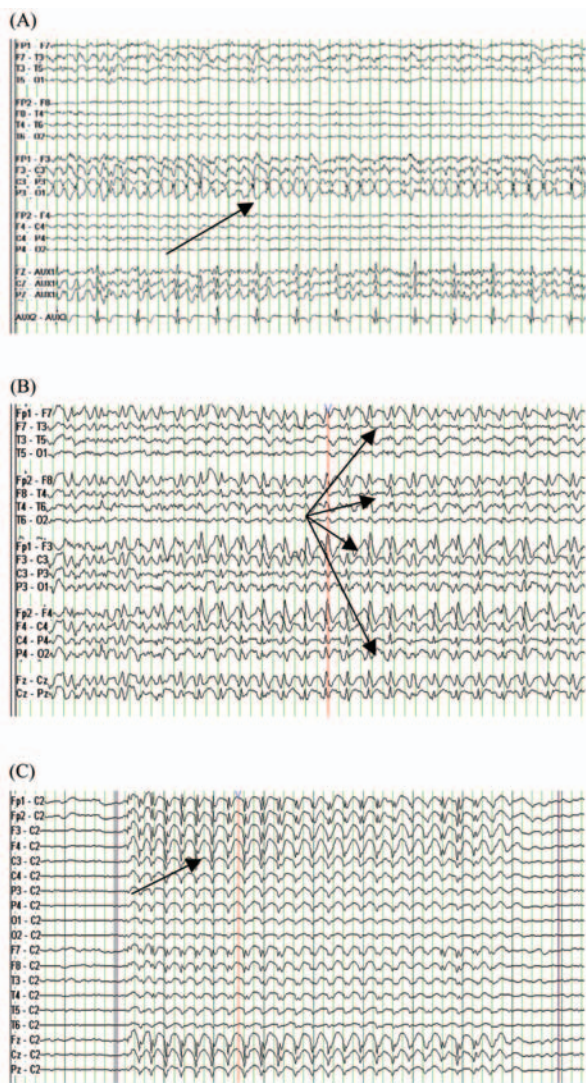
### Postconvulsive Nonconvulsive Status Epilepticus

This category includes patients who have evolved from overt convulsive SE into a state of electro-mechanical dissociation where the epileptiform discharges evident on the electroencephalogram (EEG) are not accompanied by clinical manifestations, other than obtundation or coma [14-16]. Patients with convulsive SE have a 10% to 20% risk of progression into subtle convulsive SE or NCSE, even after apparently successful treatment [16]. This truly epileptic form of NCSE represents the latter stages of convulsive generalized tonic-clonic SE. These patients need to be managed as if still in convulsive SE, using EEG rather than clinical observations as the determinant of response to treatment.

### Benign Epileptic Nonconvulsive Status Epilepticus

The second broad category of NCSE includes those patients in focal or generalized SE where the clinical manifestations are either subtle or not incapacitating. This category encompasses partial SE (with motor, sensory, autonomic or psychic manifestations) and idiopathic absence SE (diagnosed most frequently in children and in the elderly). Essentially, these patients warrant confirmatory EEG, benzodiazepine, and possibly second-line agents but do not typically need ICU care. These patients are otherwise systemically well but are at risk of developing convulsive seizures and convulsive SE.

Patients with idiopathic generalized epilepsy (absence status, spike-wave stupor) that present with NCSE generally have a very good outcome [17,18]. Patients with partial SE typically fare less well because the outcome is etiology-dependent and the SE tends to recur and be more difficult to abolish [19,20].



**Fig 1.** Electroencephalographic (EEG) features of (A) focal electrographic seizure activity in a bipolar longitudinal "double banana" montage, (B) generalized electrographic seizure activity in a bipolar longitudinal "double banana" montage, and (C) classic generalized 3-Hz spike-and-wave EEG activity in a noncephalic (2nd cervical vertebra) referential montage at a sensitivity of 15 uV/mm.

Cases of nondisabling focal SE should be dealt with on their own merits where the clinician gauges the risk of ongoing partial SE relative to the risks of coma-inducing therapies in an ICU setting. These cases are difficult, because if one considers them as traditional SE, one feels compelled to terminate the seizure activity. However, despite the more benign appearance of partial SE, it often proves more difficult to terminate using medical therapy than generalized convulsive or NCSE, resulting in significant iatrogenic morbidity. This is particularly true of prolonged focal motor SE, otherwise known as *epilepsia partialis continua* (EPC). An important determinant of the course of management

is consideration of the underlying etiology. As a rule, partial SE due to a solitary structural lesion is more likely to subside with removal of the lesion (if possible) than a course of pharmacologic coma in the ICU.

## Acute Symptomatic Nonconvulsive Status Epilepticus

The third category of NCSE is the least understood. This category encompasses patients who have had few if any recognized clinical seizures beforehand and who present with unexplained obtundation or coma, often in an ICU and often in the setting of significant active comorbidities such as metabolic disarray, hyperglycemia, hypoxia, or sepsis [15,21,22]. The patients with focal cerebral injury are more likely to have focal electrographic seizures on an EEG, whereas those with systemic illness are more likely to have generalized electrographic seizures. Sometimes there is a clear history of significant brain injury, such as acute anoxia due to a cardiac or respiratory arrest. Other patients are recognized because of a highly abnormal EEG (often unexpected) that demonstrates electrographic seizure activity. This category of patient is becoming increasingly recognized in ICUs that have access to continuous EEG monitoring facilities. This electroclinical state is difficult to manage and it has not yet been shown that any intervention alters the clinical outcome. Although these patients typically do not exhibit clinical manifestations during the electrographic seizures or SE [23-25], they may occasionally exhibit stimulus-induced clinical or electrographic seizures, or both [26].

The EEG in acute symptomatic NCSE may reveal discrete, clearly defined electrographic seizures, where it seems justifiable to treat by following the same algorithm as that for convulsive SE until the electrographic seizures are abolished. However, many patients will have equivocal EEG patterns with epochs of activity resembling electrographic seizures. These equivocal patterns overlap with periodic lateralized epileptiform discharges (PLEDs) and generalized triphasic encephalopathic patterns. In this situation, there is generally no "right answer" and each case should be managed based on the clinical situation in conjunction with the EEG pattern. It may be best to view these equivocal EEG patterns as epiphenomena, reflecting the diffuse cortical irritability or injury.

From a clinical perspective, identification of NCSE on clinical grounds is undoubtedly unreliable and necessitates a high index of clinical suspicion to prompt the initiation of EEG monitoring. Another

important clinical aspect of subtle convulsive SE and NCSE in general is that it responds less favorably to treatment than convulsive SE. This is underscored in the study by Treiman et al [27], where among the 134 patients with *subtle* generalized convulsive SE at presentation, the successful termination of seizure activity was much less likely (7.7%-24.2%) compared with the convulsive SE patients.

## Clinical Management of Nonconvulsive Status Epilepticus

Opinions vary on the correct management of NCSE [16,28,29]. As a rule, if NCSE has evolved in a patient with epilepsy or in the setting of an illness known to cause cortical irritation, then it should be treated in the same fashion as convulsive generalized tonic-clonic SE. Hence, patients with primary generalized epilepsy syndromes, incapacitating focal SE, generalized tonic-clonic SE, and subtle convulsive SE in the aftermath of generalized tonic-clonic SE should all be treated promptly using the standard algorithm.

Management of acute symptomatic NCSE is more difficult and less well studied. Frequently, these cases do not have underlying epilepsy and the EEG patterns reflect diffuse cortical network excitability. Clinicians vary in their approach from induction of burst-suppression by infusion therapies to using intermittent IV phenytoin boluses. The underlying etiology often influences the approach—acute symptomatic NCSE occurring in an otherwise-healthy post-operative patient may be treated more aggressively than a patient after a 20-minute out-of-hospital cardiac arrest.

One approach in treating acute symptomatic NCSE manifesting as electrographic seizure activity rather than paroxysmal clinical ictal activity is to administer a bolus of a benzodiazepine, but this is much less useful in the ICU because patients rarely if ever “wake up” after the benzodiazepine trial due to the altered mental state associated with the underlying brain injury. Hence, treatment of ICU patients with NCSE often involves administering an AED infusion using the EEG as a guide to dosing rather than the clinical state of the patient. This approach, however, has not been proven to improve morbidity and mortality in these patients.

Our approach is again to evaluate the case history and EEG and then consider the underlying etiology before committing to a particular regimen. The principal criterion for starting an AED infusion (midazolam, pentobarbital, or propofol) is the presence of definite, discrete, unequivocal electrographic seizures

of sufficient frequency and duration to impair the patient over and above the underlying precipitating comorbidities. This criterion is deliberately nonspecific because each case will have unique characteristics that should govern decision making. For example, a patient whose EEG demonstrates generalized slowing and lateralized rhythmic sharp waves but is known to have underlying significant metabolic dysfunction may be better served by therapeutic-range phenytoin than by more aggressive coma-inducing therapies.

There is no definite evidence that NCSE causes lasting harm [28]; however, studies are confounded by inconsistent definitions of NCSE. The morbidity associated with NCSE was addressed by Shneker and Fountain [30], where they carefully but retrospectively appraised 100 consecutive ICU patients in whom NCSE was detected. The authors reported a mortality of 18% in the group in whom NCSE arose in the setting of significant medical comorbidities and 3% mortality where NCSE was ascribed to preexisting epilepsy. The authors concluded that the mortality attributable to NCSE by itself is 3%, and, similar to convulsive SE, the underlying etiology largely determines the clinical outcome. The authors observed that the level of consciousness evident during NCSE was a useful predictor of outcome. The mortality rate was 39% in patients with severely impaired mental status and 7% in patients who were mildly impaired. The principal message from this study is that NCSE, like convulsive SE, is a heterogeneous syndrome and that outcome is favorable in the setting of a benign etiology but poor in the setting of a malignant etiology.

All these clinical features suggest that NCSE (particularly acute symptomatic) is a very different neurobiologic phenomenon than overt convulsive SE. Presently our understanding of NCSE remains rudimentary, and much work is needed to elucidate which nonconvulsive electroclinical states are merely epiphenomena and which warrant specific intervention with antiseizure medications.

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## Key Concepts

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When managing seizures and SE in the ICU, a number of overriding principles should be borne in mind:

- Clinical seizures may occur in any individual if sufficient provocative factors are present.
- The physician needs to make a distinction between SE arising in a person with preexisting epilepsy and SE arising *de novo* in a medically or surgically ill patient.

- New-onset seizures or de novo SE in the setting of acute illness should be viewed as an electroclinical expression of illness-related cortical irritability or injury.
- A relapse of seizures in the setting of subtherapeutic AED levels in a person with preexisting epilepsy often responds promptly to a bolus dose of the maintenance AED(s); however, SE (particularly convulsive SE) should be treated in the standard fashion.
- Seizures and SE have 2 distinct but varying components—clinical and electrographic; one needs both clinical and EEG information to classify patients.
- Both the clinical and electrographic manifestations of SE have a natural history and evolution within any given patient.
- Morbidity and mortality is high in untreated SE.
- The chance of successful termination of SE with use of a third-line AED after the first- and second-line agents have failed is only about 7%.
- The choice of first- and second-line AEDs is to some extent arbitrary. Current protocols reflect ease of use of specific AEDs rather than their particular therapeutic properties. A more important factor governing successful intervention is the dose of AED given.
- Refractoriness is better predicted by the response to AEDs rather than the duration of SE before the patient received the first AED.
- In an obtunded patient, the EEG is more informative than the clinical examination.
- When evaluating the patient once SE is confirmed, one needs to consider the anatomic location of the seizures. Consideration of the mere presence or absence of seizures can overlook useful lateralizing and localizing information.
- An information-gathering approach that uses multimodal imaging and other diagnostic tools increases the likelihood of understanding the disease process driving the SE.
- Persons in refractory focal status epilepticus are potential candidates for surgical intervention.

The acute occurrence of an epileptic seizure in a patient can lead to a number of potential clinical outcomes, each of which carries a particular mortality and morbidity (Figure 2). The spectrum ranges from a self-limiting single seizure to highly refractory SE.

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### Causes of Status Epilepticus

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Status epilepticus can be caused by a variety of different underlying processes, the unifying aspect of which is cortical irritation or injury. The clinical presentation and semiology (clinical characteristics of

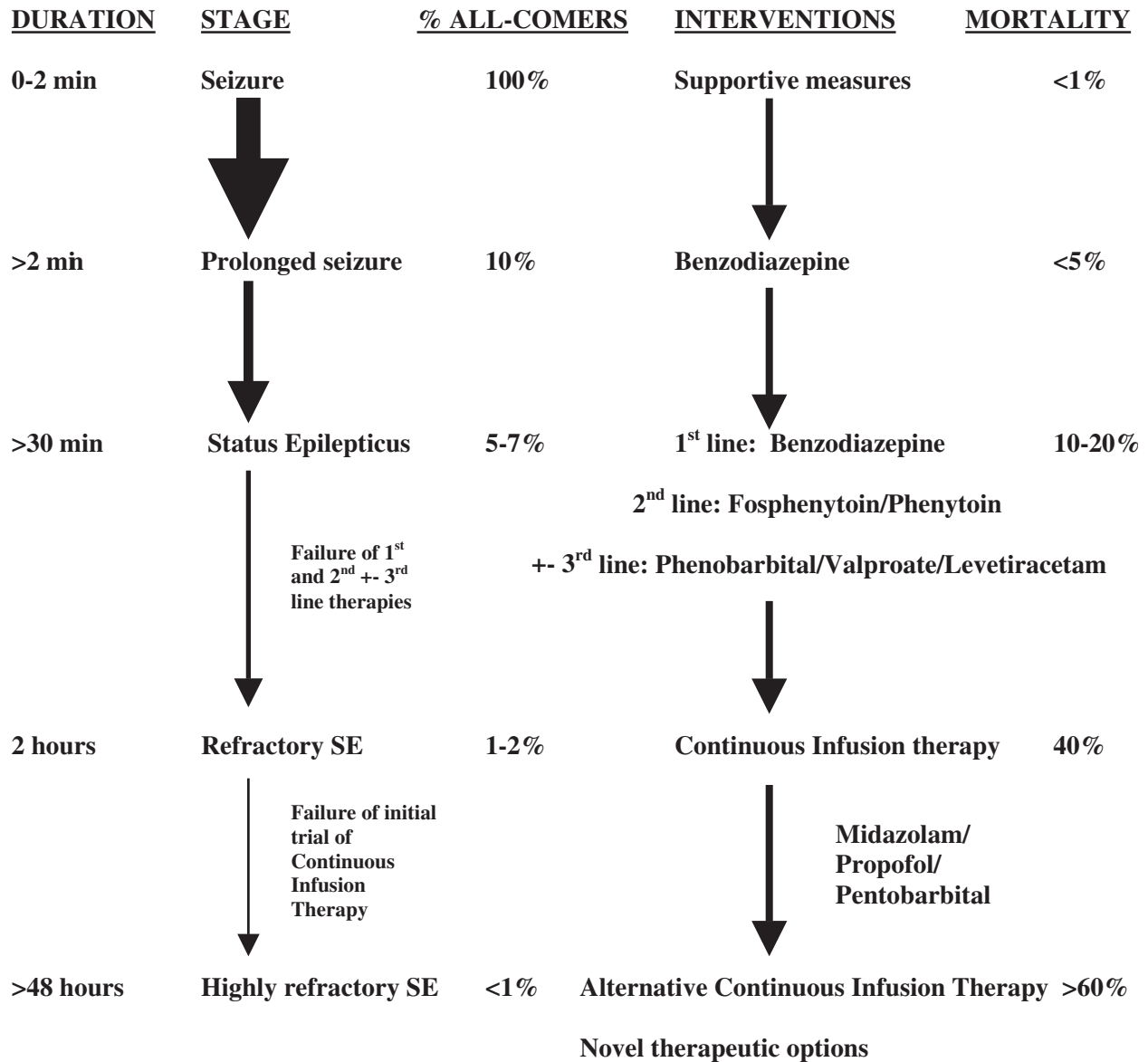
the seizures) typically do not convey accurate information about the underlying cause, although the tempo of the seizure activity often reflects the aggressiveness of the etiology.

Status epilepticus can be categorized as symptomatic, idiopathic, or cryptogenic. The term “symptomatic” indicates that the seizure activity is a secondary phenomenon or a symptom of an underlying disease process. “Idiopathic” denotes a constitutional or genetic predilection to seizure activity or SE, characteristic of idiopathic generalized epilepsy syndromes. “Cryptogenic” refers to seizure activity or SE for which a cause cannot be identified. Most cases of cryptogenic SE are likely to be symptomatic, although the causative lesion cannot be identified with existing technology. Most cases of refractory SE in adults are symptomatic. The underlying brain injury or dysfunction may have occurred temporally distant from the present SE (*remote* symptomatic) or may be recent (*acute* symptomatic). Some authors describe SE associated with an underlying degenerative process such as Alzheimer dementia as *progressive* symptomatic.

The etiology of SE varies according to whether case ascertainment occurs in the community or in a hospital setting and whether the epidemiologic data are acquired retrospectively or prospectively. The most informative prospective urban population-based epidemiologic study of SE was reported by DeLorenzo and colleagues [1,7]. Although there has not been a prospective ICU-based epidemiologic study on SE, the causes of new-found SE in the ICU setting are likely to be similar but vary in proportion, with a greater number of cases due to traumatic brain injury, central nervous system infection, and new vascular insults [31]. Table 1 gives an approximate breakdown of the causes of SE in adults and older children that one could expect from all-comers in an urban ED, most of whom will not need ICU care.

A recent retrospective ICU-based study highlighted certain risk factors for the development of SE [31]. Of 83 episodes of SE managed in an ICU, 50 arose de novo from newly acquired cerebral injury. Approximately 40% to 50% of SE arose in patients without a history of epilepsy, which has been noted in other studies [32]. Patients in refractory SE, defined as SE which does not respond to appropriate doses of appropriate first- and second-line therapy, are more likely to have underlying encephalitis, be associated with hyponatremia, exhibit cerebrospinal fluid (CSF) pleocytosis, and be febrile [31].

Direct brain injury or irritation accounts for most causes of SE, but there are well-recognized systemic



**Fig 2.** Possible clinical outcomes from a single seizure.

causes, including hyponatremia [33], hypoxia/ischemia, narcotic withdrawal [34], alcohol and drug toxicity [35], and ingestion of proconvulsant medications including  $\beta$ -lactam antibiotics (penicillins and cephalosporins), certain antidepressants (bupropion), certain antipsychotics (clozapine), bronchodilators, and immunosuppressives. Precipitous withdrawal from barbiturates, benzodiazepines, and opiates can lead to the development of or exacerbation of seizures, particularly in those with preexisting epilepsy. Certain illicit drugs clearly are associated with seizures and SE, both acutely and on withdrawal, including cocaine and amphetamines.

Apparently mild or restricted electrolyte or metabolic disturbance, including hypophosphatemia,

hyponatremia, hypoglycemia, liver dysfunction, renal impairment, hypo-osmolality, hypomagnesemia, and hypocalcemia can be implicated in seizure provocation, particularly in the inpatient population.

Overall, the causes of SE can be categorized as acute symptomatic (52%-72%), remote symptomatic (20%-31%), and idiopathic/cryptogenic (3%-15%) [5].

### Detection of Status Epilepticus

When first observed, patients in convulsive SE are generally found to be unresponsive, obtunded, and exhibit repetitive truncal and limb movements, which may be tonic or clonic. In those patients with prolonged



**Table 1.** Etiology of Status Epilepticus

Cause	Approximate % of Total
AED noncompliance/insufficient dosing	20
Old brain injury	15
Acute vascular injury	15
Alcohol-related	10
Metabolic/electrolyte disturbances	10
Unknown/cryptogenic	10
CNS infection	5
Cerebral tumor	5
Acute trauma	5
Drug toxicity	<5
Global hypoxic injury	<5
Idiopathic epilepsy	<5

AED = antiepileptic drug; CNS = central nervous system.

clinical seizure activity, the movements gradually become subtle and eventually are restricted to brief facial, periorbital, and limb twitches [16,25]. Sometimes, no clinical movements are evident; hence, differentiation of subtle nonconvulsive SE from other causes of obtundation based on clinical signs can be fraught with difficulty. Recognition of SE can be even more difficult in the ICU, where patients frequently have coexisting reasons for unresponsiveness. Furthermore, ICU patients are often paralyzed for ventilation and do not exhibit motor signs of seizure activity. Finally, it must be remembered that motor manifestations of seizure activity simply reflects involvement of the motor areas of cerebral cortex. Patients can have seizure activity or SE arising from nonmotor areas, resulting in altered mental status without motor manifestations.

These factors conspire to make seizures and SE difficult to detect by clinical assessment alone, although one can identify "at-risk" patients by the likelihood of their underlying illness to cause cerebral cortical injury with consequent seizures. The unreliability of clinical detection of seizures in the ICU is confirmed in recent studies where ICU patients were screened for seizures by EEG monitoring [23,29,36]. Towne et al [29] reported an 8% incidence of NCSE among 236 comatose patients with no clinical evidence of seizure activity.

A larger study by Claassen et al [23] reported the EEG findings in 570 patients, 89% of whom were in an ICU, who underwent continuous EEG monitoring. Electrographic seizure activity was evident in 110 patients, and only 9 exhibited convulsive motor activity. The risk factors associated with detection of electrographic seizure activity included coma (odds ratio [OR], 7.7; 95% confidence interval (CI),

4.2-14.2), age younger than 18 (OR 6.7; 95% CI, 2.8-16.2), preexisting epilepsy (OR, 2.7; 95% CI, 1.3-5.5), and witnessed convulsive seizures before EEG monitoring (OR 2.4; 95% CI, 1.4-4.3). Overall, 77% of the patients who ultimately exhibited electrographic seizure activity did so within 6 hours of the onset of EEG monitoring, suggesting that EEG monitoring can be an efficient and effective screening measure. However, 5% of noncomatose and 20% of comatose patients needed more than 24 hours of monitoring to detect electrographic seizure activity.

These studies provide compelling evidence for a greater role for EEG monitoring in the detection of seizures and SE in the ICU, although the impact of treatment of heretofore-undetected electrographic seizures is unknown. Provision of a 24-hour EEG monitoring service is logistically difficult, even for large urban centers. Training of ICU personnel in the initiation of EEG recording may be the only effective means of providing on-call EEG monitoring.

Certain scenarios should prompt initiation of on-site EEG monitoring or transfer to an institution where continuous EEG monitoring is available. Broadly speaking, the principal indication for EEG monitoring in the ICU is the suspicion of NCSE, although other indications are also important (see Table 2).

## Pathophysiology of Status Epilepticus

It is important to appreciate that SE is not an all-or-nothing phenomenon with unvarying manifestations. Many lines of evidence show that SE evolves clinically, mechanistically, and electrographically. This dynamic quality mandates a dynamic approach, the outcomes from which can be better understood if one is aware of the maladaptive tissue responses to the seizure activity. The physiologic effects can be arbitrarily divided into overlapping early biochemical changes and later anatomic and functional changes.

Within minutes of ictal onset, the persistent neuronal depolarization within the seizing cortical region is associated with a gradual but profound shift in local homeostasis and neuronal integrity manifesting as ionic fluxes, activation of second messenger systems, altered gene expression with consequent altered protein production, nerve fiber arborization, synaptic reorganization, and ultimately, irreversible cell damage and loss [37-39]. It is likely that self-terminating seizures have physiologic effects that differ, both qualitatively and quantitatively, from self-perpetuating seizure activity. With persisting ictal activity, these complex changes conspire to render the ictal region intrinsically more

**Table 2.** Indications for Continuous Electroencephalographic Monitoring in the Intensive Care Unit

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- History of nonconvulsive status epilepticus
  - Unexplained persistent obtundation or coma in any setting
  - Unanticipated delay in recovery from anesthesia or surgery
  - Delayed recovery after witnessed convulsive seizure
  - Obtundation with subtle clinical signs: oculomotor abnormalities or subtle motor twitching (facial, limbs)
  - Suspected non-epileptic status ("pseudostatus")
  - Monitoring of depth of anesthesia (burst-suppression interval)
  - Delayed recovery after initial treatment of seizure
- 

epileptogenic and increasingly refractory to interventions aimed at terminating the seizure activity. Later structural cortical consequences of SE include mossy fiber sprouting, synaptic reorganization, cell loss, gliosis, and eventually, increased susceptibility to further seizures and loss of normal tissue function. These enduring physical changes within the already damaged cortical region may serve as a substrate for the persistent epilepsy frequently seen after episodes of SE.

At a physiologic level, Lothman [40] described 2 phases of SE, termed phase I (compensated) or phase II (uncompensated) SE. Phase I is characterized by increased cerebral metabolic demand compensated for by increased cerebral blood flow, increased anaerobic respiration, and increased cardiovascular parameters. Phase II evolves when cerebral autoregulation breaks down as cerebral blood flow falls in association with systemic hypotension and autonomic dysfunction. Subsequent cerebral edema, hypoxia, and cardiac dysfunction contribute to the high mortality associated with severe, prolonged SE [41].

Seizure activity will ordinarily activate cortical inhibitory mechanisms, principally through  $\gamma$ -aminobutyric acid (GABA)-mediated mechanisms, with termination of ictal activity. Benzodiazepines, the usual first-line intervention in SE, are GABA-agonists. In SE, there is evidence for failure of GABA-mediated inhibition of ictal activity, which leads to a shift toward excitatory glutamatergic activation of neurons through N-methyl-D-aspartate (NMDA) receptors [42,43]. This may explain the observation that duration of seizure activity partially governs the response to the first-line AED [44].

Resistance to AEDs develops in parallel with ongoing seizure activity and partly explains why medications used to control chronic epilepsy are often ineffective against SE. These dynamic changes in therapeutic responsiveness are complex and stem from pharmacokinetic, pharmacodynamic, and pharmacogenomic factors, which may be unique to the individual person in SE. Other mechanisms for failure of initial therapies include activation of putative

"drug-resistance" genes during SE by ill-understood mechanisms [45]. Given the dynamic changes within the ictal cortical region, it is not surprising that therapeutic efficacy often wanes with increasing duration of ictal activity. Some authors propose a mechanistic approach to the management of the latter stages of SE based on the predominant mechanism of epileptogenesis, for example, use of NMDA-antagonists [46-48].

In parallel with the clinical and neurobiologic evolution of SE, characteristic electrographic stages have been described. Treiman et al [14] suggest that a number of identifiable EEG patterns evolve in a predictable sequence during the course of generalized convulsive SE in humans. These include (1) discrete seizures, (2) merging seizures with waxing and waning amplitude and frequency of EEG rhythms, (3) continuous ictal activity, (4) continuous ictal activity punctuated by low-voltage flat periods, and (5) periodic epileptiform discharges on an attenuated background.

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### Initial Management of Status Epilepticus

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The initial management of status epilepticus begins in the community. Ideally, all caregivers and relatives of patients with epilepsy should be trained in dealing with their family member's habitual seizures. Not infrequently, patients (particularly children) with chronic epilepsy report a crescendo increase in the frequency or severity of their habitual seizures before the onset of SE itself. This premonitory phase presents a critical window of opportunity for preventing episodes of SE. A 1- to 3-day course of regular benzodiazepine therapy, such as oral lorazepam, will often abort the impending SE.

In the community, brief seizures with quick recovery generally do not warrant further immediate treatment. However, more prolonged or repetitive seizures require intervention with AEDs. In the home setting, where vascular access is not available, rectal, or enteral (eg, gastrostomy tube) diazepam [49] or buccal midazolam (in children) [50] can be

used where convulsive seizure activity persists beyond what is typical for a patient or when convulsive seizure activity is sustained for more than 2 minutes.

In the hospital setting, the early ED management involves lateral positioning of the patient to avoid injury and aspiration, maintaining a patent airway, oxygen supplementation, and correction of any immediately reversible precipitants, particularly hypoglycemia. Parenteral thiamine (100 mg) should be administered before a glucose bolus is given if alcohol abuse or poor nutrition is suspected; pyridoxine is a consideration in neonates. Where vascular access is available, the traditional initial management of prolonged convulsive seizures similarly begins with administration of a benzodiazepine.

The rationale for the use of benzodiazepines as first-line AED therapy was consolidated by the most informative clinical trial performed to date examining the optimal initial management of convulsive SE [27]. This trial was conducted in a hospital and compared 4 different treatment arms: diazepam (0.15 mg/kg), followed by phenytoin (18 mg/kg), lorazepam alone (0.1 mg/kg), phenobarbital alone (15 mg/kg), and phenytoin alone (18 mg/kg). In 384 patients with overt convulsive activity, lorazepam terminated the seizure activity in 64.9%, phenobarbital in 58.2%, diazepam plus phenytoin in 55.8%, and phenytoin in 43.6%. An intention-to-treat analysis found no significant difference among treatment groups in patients with overt convulsive SE ( $P = .12$ ), except that lorazepam alone was significantly more effective than phenytoin alone. Furthermore, the treatments did not differ with respect to seizure recurrence during the initial 12-hour study period, the incidence of adverse reactions, or the clinical outcome at 30 days.

Thus, as a first-line treatment for convulsive SE, administration of lorazepam alone, phenobarbital alone, or diazepam plus phenytoin were equally effective. In clinical practice, lorazepam alone is easier and faster to use and hence has become well established as a first agent given to patients in SE of any type. Lorazepam is thought to be more favorable than diazepam because it has a longer therapeutic effect and a lower risk of venous thrombophlebitis and respiratory suppression, particularly in children [51-53]. Alternative benzodiazepines include diazepam (buccal, intramuscular, parenteral), midazolam (buccal, intranasal, parenteral, intramuscular), and clonazepam (intravenous [IV]) although absorption from intramuscular injection is probably too slow for emergency treatment of seizures and SE.

Phenytoin, perhaps in part for traditional reasons and relative ease of use, is widely used as the next agent if lorazepam proves ineffective; however, the strategy of lorazepam followed by phenytoin has never been compared with other treatments in a well-designed clinical trial. Approximately 40% to 50% of patients who do not respond to initial benzodiazepine therapy will respond to a subsequent 20-mg/kg loading dose of IV phenytoin [54]. Fosphenytoin, a phenytoin pro-drug, is gradually replacing phenytoin owing to its improved safety profile with less risk of severe thrombophlebitis and local tissue necrosis, the possibility of faster administration (IV as well as intramuscular), and compatibility with a wide range of infusion solutions. Other possible second-line AED interventions include a second bolus of benzodiazepine, an IV bolus of sodium valproate, or an IV bolus of phenobarbital, although none of these agents have been studied in a rigorous fashion as an adjunct to lorazepam. Intravenous levetiracetam is a recent addition to the armamentarium of parenteral anti-seizure medications, although it is less well studied.

Irrespective of which agent is chosen as a first- or second-line intervention, it is imperative that adequate doses are given. Fear of precipitating unwanted adverse effects can be allayed by heart rate and blood pressure monitoring and appropriate adjustment of infusion rates. The infusions should begin at 50% of the maximum infusion rate (eg, 25-mg/min phenytoin), followed by gradual titration of infusion rate upward according to the blood pressure response. If the loading dose of phenytoin is administered during a 20-minute period, then the maximal brain concentration of phenytoin will be achieved toward the end of the infusion. Some authors argue for an additional 5- to 10-mg/kg bolus of phenytoin if the levels do not exceed 20  $\mu\text{g/mL}$  after the initial bolus [55].

A critical juncture in the management of SE arrives when SE has not terminated after the administration of both a benzodiazepine and phenytoin/fosphenytoin. The traditional approach is to proceed to a third agent, usually a loading dose of IV phenobarbital. Alternatively, a loading dose of IV valproate or IV levetiracetam may be administered. However, only 7% of patients who have not responded to timely and appropriate doses of first- and second-line AED therapy will then respond to any third-line IV AED [27]. Use of a third-line AED may be justifiable if one is trying to avoid intubation, although many authors favor proceeding directly to continuous infusion therapy at this point.

**Table 3.** Suggested Initial Management (First 30 Minutes) of Status Epilepticus

Stage, time	Interventions	Time, min
0 min	Recognition of status epilepticus (clinical or EEG)	0
0-30 min	Airway/breathing/circulation	0-1
	Suctioning, supplemental oxygen, pulse oximetry	0-1
	Baseline vital signs; capillary glucose level	0-1
	ECG/cardiac telemetry	1-2
	Large bore proximal IV access, baseline labs, IV fluids	1-2
	Administer 100 mg IV thiamine and/or 50 mL bag of 50% dextrose (if needed)	1-3
	Administer 0.1 mg/kg bolus dose of IV lorazepam in equal volume of diluent by slow IV push at ~2 mg/min or in divided stat doses	3-10
	Prepare loading dose (20 mg/kg) of phenytoin or fosphenytoin	
	Begin phenytoin infusion at 25 mg/min or fosphenytoin infusion at 75 mg/min (begin 1 min after end of lorazepam bolus if seizure persists)	5-30
	Titrate phenytoin/fosphenytoin infusion rate up to maximum tolerated rate (~50 mg/min for phenytoin and ~150 mg/min for fosphenytoin) according to BP	
	Regular vital signs especially BP checks (every 2 min)	
	Draw serum phenytoin level approximately 10 min after phenytoin load is completed ± administer extra 5 mg/kg of phenytoin or fosphenytoin (if serum level available)	

EEG = electroencephalogram; ECG = electrocardiogram; IV = intravenous; BP = blood pressure.

Patients who are already taking AED therapy should continue to take maintenance AEDs at the same or higher doses. In patients admitted on phenytoin therapy, a phenytoin level should be drawn before they receive a loading dose of phenytoin; however, administration of a loading dose should not be delayed while waiting for the phenytoin level. Overall, we believe that biochemical phenytoin toxicity (ie, corrected level >20 µg/mL) is less worrisome than ongoing seizure activity associated with inadequate phenytoin dosing. Biochemical therapeutic ranges for the older AEDs are applicable to the outpatient with chronic epilepsy rather than the ED/ICU patient, where the risk versus benefit favors higher AED serum concentrations. Duration of AED treatment in the ICU setting, particularly with continuous infusion therapies, is more predictive of treatment-related complications than serum AED levels.

Specific protocols for the management of SE suggest the sequential administration of a benzodiazepine and a loading dose of phenytoin or fosphenytoin. The critical point made by all authors is that the treatment be instituted early, efficiently, and fully. In reality, all protocols are modified as clinical circumstances and institutional resources dictate. Table 3 outlines the current guidelines on the management of generalized (convulsive and subtle convulsive) SE used at our institution. This protocol is idealized and difficult to implement efficiently in any busy hospital but serves as an algorithm for the initial management of SE. Each step is

open to discussion though the sequence is well established.

Other aspects to the general management of SE include the following:

- *Airway*—If the clinical seizure activity terminates and it is safe to access the oropharynx, a Guedel (or nasopharyngeal) airway may be useful to maintain oropharyngeal patency.
- *Intubation*—Intubation is generally needed during infusion therapies, although patients receiving midazolam may not require intubation. If intubation is necessary but difficult, use temporary non-depolarizing neuromuscular junction blockade for intubation (eg, vecuronium). Otherwise, muscle paralytics are typically not used in the management of SE.
- *Hypertension*—Ensure volume replacement and use vasopressors if needed. Do not treat hypertension unless critical.
- *Hyperglycemia*—Ensure glycemic control because hyperglycemia may exacerbate neuronal injury.
- *Cerebral edema*—Treat hyperventilation with mannitol or steroids, depending on etiology, if evident.
- *Acidosis*—Acidosis usually parallels the degree of anaerobic metabolism and generally resolves with seizure control or intubation with general anesthesia. Boluses of sodium bicarbonate are used exceptionally.
- *Hyperthermia*—Hyperthermia, like hypertension, generally resolves with control of SE, but external cooling, cool peritoneal lavage, or extracorporeal blood cooling may be used if refractory.

- *Rhabdomyolysis*—Rhabdomyolysis is an underappreciated morbidity associated with convulsive SE and should be detected and treated early with saline diuresis, urine alkalization, and if needed, muscle paralysis.
- *Aspiration*—Aspiration should be suspected and screened for in all patients with SE.
- *Maintenance AED therapy*—All patients with de novo SE or epilepsy-related SE need maintenance AED therapy. Ideally, this should be initiated within the first day of admission, irrespective of the clinical course. Once initiated, the maintenance AED regimen can be modified toward the end of the hospital stay.
- *Electroencephalographic monitoring*—Ideally, begin EEG monitoring if patient is not waking up 15 minutes after clinical movements have stopped.

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## Initial Diagnostic Evaluation

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The treating clinician should recognize that the prognosis of SE is largely determined by the underlying cause of the seizure activity and, from the outset, should initiate a diagnostic evaluation in parallel with treating the SE itself. The collateral history from family members or relevant witnesses is invaluable, as is determining the patient's past neurologic history, compliance with AED therapy (if the patient has pre-existing epilepsy), medical history, medication and illicit drug ingestion, and recent ill health. The clinical findings are typically self-evident in convulsive SE with generalized tonic-clonic activity, but the patient should be closely examined for subtle motor and facial/oculomotor signs in suspected NCSE. The extent of the diagnostic evaluation should be dependent on a track record of prior episodes of SE.

Patients with SE in the setting of chronic epilepsy are less likely than patients with de novo SE to have an obscure underlying etiology. In general, patients with new-onset SE should be investigated more extensively than patients with previous episodes of SE, although each case must be considered carefully according to the specific clinical details.

Blood should be drawn from all patients to check values for routine laboratory indicators, glucose level, electrolyte levels (including magnesium, calcium, phosphate), creatine kinase level, anti-seizure medication levels, and toxicology screen in conjunction with urine sampling. Arterial blood sampling is necessary for detection of systemic acidosis due to prolonged anaerobic metabolism associated with vigorous convulsive seizures. If systemic infection is suspected, a septic screen is warranted with particular attention to a lumbar

puncture, preceded by a head computed tomography (CT) scan and careful funduscopy to exclude overtly raised intracranial pressure if the patient is obtunded. A follow-up diagnostic lumbar puncture may be necessary if the SE developed precipitously in the early stages of a systemic or central nervous system illness, where the CSF fluid may initially be nondiagnostic.

Emergency imaging by CT is overused but is important if one is to exclude "neurosurgical" causes for SE, such as tumor and traumatic brain injury. In our experience, the yield from semi-elective planned magnetic resonance imaging (MRI) of the brain is much higher than CT imaging in the ED. Computed tomography imaging should never delay the initiation of first- and second-line AED therapy or impede transfer to an ICU. If intracranial collections (particularly subdural empyema) are suspected, then contrast-enhanced imaging may increase the sensitivity of the CT study. Another imaging tool that may be critical in special circumstances is MR venography where central venous sinus thrombosis is a clinical possibility.

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## Management of Refractory Status Epilepticus

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In practice, refractory SE (RSE) can be defined as SE that does not respond to appropriate doses of appropriate first- and second-line therapy such as IV benzodiazepine and phenytoin/fosphenytoin. The likelihood of progression to RSE in certain patients is largely a reflection of the underlying refractory etiology, although other potential mechanisms of therapeutic resistance include changes in GABA receptor composition [43] and increased expression of drug resistance genes [45].

To date, unfortunately, treatment algorithms in RSE have not been compared in prospective, randomized clinical trials, and the consequent empiricism has led to significant variations in the management of these cases [56-58]. Eriksson et al [59] provide some modest evidence that delay in the institution of first- or second-line therapy may also be a risk factor for development of RSE. Approximately 31% to 44% of all SE patients will evolve into RSE [27,31,32,54]. De novo (first episode) SE has a moderate likelihood (40% to 50%) of becoming refractory [32]. Complex partial, focal motor, and nonconvulsive forms of SE are relatively more likely than convulsive or absence SE to become refractory to first- and second-line therapies, although all forms of SE may become refractory [54].

Although the initial management of SE is relatively well established, the management of RSE is less well established and largely operator-dependent [58].

**Table 4.** Suggested Management of Refractory Status Epilepticus

Time	Interventions
0-30 min	Initial management of status epilepticus (see Table 3)
At ~30 min	Contact EEG laboratory to initiate cEEG monitoring Transfer to ICU (intubate if necessary) Decide on use of (a) 3rd-line IV agent or (b) initiating infusion therapy (see below)
30-60 min	3rd-line IV agent
Onward	Use a 3rd-line IV agent (particularly if reluctant to intubate) <ul style="list-style-type: none"> <li>• administer 20 mg/kg bolus of IV phenobarbital at rate of 75 mg/min, followed by initial maintenance dosing 60 mg TID</li> </ul> OR <ul style="list-style-type: none"> <li>• administer 15-30 mg/kg bolus of sodium valproate at rate of up to 6 mg/kg/min, followed by maintenance dosing 500 mg TID</li> </ul> OR <ul style="list-style-type: none"> <li>• administer 20mg/kg bolus of levetiracetam over 15 minutes, followed by maintenance dosing 1500 mg BID</li> </ul>
>60 min	Initiate EEG monitoring in ICU setting If electrographic seizure activity persists after 3rd-line agent, initiate infusion therapy Infusion therapy After 60 min of clinical or electrographic seizure activity, options include: <ol style="list-style-type: none"> <li>1. Midazolam infusion loading dose: 0.2 mg/kg by slow IV bolus maintenance cIV dose: 0.1-0.4 mg/kg/h, maximum cIV dose: 2.0 mg/kg/h</li> <li>2. Pentobarbital infusion loading dose: 3 mg/kg at 0.2-0.4 mg/kg/min maintenance cIV dose: 0.3-3.0 mg/kg/h maximum cIV dose: 3.0 mg/kg/h</li> <li>3. Propofol infusion loading dose: 1-2 mg/kg at 10 mg/min maintenance cIV dose: 2-10 mg/kg/h maximum cIV dose: 15 mg/kg/h (varies according to institution)</li> </ol> Titrate infusion rate to abolish all clinical and electrographic seizure activity, irrespective of presence or absence of burst-suppression pattern on EEG. Taper (in 25%-50% decrements every 12-24 hours) the midazolam, pentobarbital, or propofol cIV after 12-24 hours, once the therapeutic level of maintenance AED is achieved (ie, corrected phenytoin level, 20-30 µg/mL; phenobarbital level, 35-50 µg/mL; valproate level, 80-120 µg/mL) or the therapeutic dose range is reached (topiramate, 800-1600 mg/d; levetiracetam, 1500-3000 mg/d).

EEG = electroencephalograph; cEEG = continuous electroencephalographic monitoring; ICU = intensive care unit; IV = intravenous; cIV = continuous intravenous infusion; AED = antiepileptic drug.

Current knowledge suggests that the optimal agent for treatment of RSE should have both GABA-ergic and NMDA antagonistic properties, be fast acting, cross the blood-brain barrier, have a short half-life, neuroprotective properties, and a favorable risk profile. In the future, the pharmacogenomic profile of the patient may be another factor in determining the choice of agent for use in SE. At present, no such agent exists. Three classes of medications are currently in use for treatment of RSE: barbiturates, propofol, and benzodiazepines (midazolam). Each has particular advantages and disadvantages.

All patients in whom there is a possibility of refractory, ongoing seizure activity (manifesting clinically or confirmed electrographically) need to be

cared for in an ICU by staff proficient in the management of SE [23]. These patients need long-term EEG monitoring and typically need intubation. Although the management of early SE should be familiar to all frontline medical personnel, the care of patients in RSE should ideally be undertaken by those with experience in the ICU management of SE and with immediate access to expertise in EEG monitoring and interpretation. Hence, after recognition of SE and subsequent treatment with IV benzodiazepine and phenytoin or fosphenytoin, the clinician in charge should seek transfer to an ICU, ideally where continuous EEG monitoring is available. Our overall approach to the management of difficult-to-terminate seizure activity is outlined in Table 4.

All patients receiving continuous infusions for the management of SE should be in an ICU and should have continuous EEG monitoring. Intermittent "snapshot" EEGs may be satisfactory once the patient reaches a status quo where a given infusion rate leads to seizure abolition; however, titration of infusion rates is best done using continuous EEG guidance. It is important for the clinicians to regularly review the EEG (3 times per day) and, ideally, be familiar with the original ictal EEG pattern characteristic of that patient, particularly when faced with deciding the significance of equivocal or difficult EEG findings. Staff members should highlight and communicate the recent EEG findings to other relevant carers. Repeated interaction with an epileptologist or neurophysiologist will aid in the interpretation of the video-EEG when difficulties arise.

The traditional end point for dosing continuous infusion therapy with propofol, midazolam, and pentobarbital is induction of a burst-suppression pattern where bursts of activity are separated by 10- to 15-second periods of EEG attenuation or flattening. It is likely that seizure-suppression (ie, suppression of electrographic seizures, irrespective of whether the EEG enters a burst-suppression pattern) is a better end point than burst-suppression where coma-inducing infusions are used. Although often strived for, burst-suppression on continuous EEG monitoring has not been shown to improve clinical outcome [32,60]. Moreover, a patient whose EEG reveals a burst-suppression pattern may still exhibit electrographic seizure activity, and it must be remembered that suppression of the EEG does not necessarily equate with termination of seizures. However, until more sensitive means of neurophysiologic or biomonitors (ie, microdialysis), become available, scalp-derived EEG remains the most reliable and practical method for the monitoring of patients in SE.

The choice of coma-inducing agent(s) for continuous infusion therapy is often determined by physician preferences and the particular aspects of a clinical case, particularly the presence of hypotension. Barbiturates generally lead to a longer hospital stay because the prolonged clearance leads to a longer recovery from iatrogenic coma. Some authors avoid propofol in children because of an increased risk of the propofol infusion syndrome.

The clinician should view the use of IV infusions as temporary respite from seizure activity. It is critical to ensure that the patient is placed and maintained on appropriate doses of maintenance AEDs given enterally or as intermittent IV boluses that will, hopefully, prevent a return to SE when the infusion(s) have been withdrawn. Intravenous administration of AEDs should be used rather than enteral

administration if gastrointestinal motility and absorption is impaired. In general, high-normal or supra-therapeutic concentrations of maintenance AEDs should be maintained; for example, corrected phenytoin level, 20 to 30  $\mu\text{g}/\text{mL}$ ; phenobarbital level, 35 to 50  $\mu\text{g}/\text{mL}$ ; and valproate level, 80 to 120  $\mu\text{g}/\text{mL}$ . In the absence of established therapeutic concentration ranges, newer oral agents should be maintained on full adult doses of these agents; for example, topiramate, 800 to 1600 mg/d, and levetiracetam, 3000 to 4000 mg/d.

There are currently no prospectively acquired data to support the use of one particular infusion regimen over another. What is clear, however, is that each of these agents can be associated with particular morbidities and thus should be used in a goal-oriented fashion rather than indefinitely. The infusions should be tapered gradually at fixed time points, usually every 12 to 24 hours. This can be done in a staged manner where the dose is reduced by 25% to 50%, followed by a period of observation, followed by further tapering of the infusion, and so on. If one particular infusion regimen fails, as evidenced by a return of clinical or electrographic seizures on discontinuation or reduction of the infusion, then that particular regimen should be abandoned, although the agent may be used in a combination regimen thereafter.

Another useful strategy in managing a case of RSE is to taper and temporarily discontinue the infusion therapy. This allows a fresh look at the EEG without the confounding effects of the IV infusions and allows differentiation between the persistence of sustained electroclinical SE and intermittent non-sustained electroclinical or electrographic seizures, which may not necessarily need treatment with continuous IV AED therapy.

In conjunction with ongoing treatment of the SE, the clinician should be satisfied that he or she recognizes the underlying etiology. An unclear etiology should prompt systematic investigations including MRI, CSF analysis, screening for infections (particularly if the patient is immunocompromised), paraneoplastic markers, antithyroid antibodies, porphyria screen, and screens for toxins and illicit drugs. Particular effort should go into planning good quality neuroimaging studies, including consideration of particular sequences and techniques, for example, gadolinium administration, coronal views, MR venography, diffusion maps, and gradient-echo sequences. Careful planning with an experienced neuroradiologist will greatly enhance the information gleaned from imaging, which may clarify the underlying etiology. If an etiology remains obscure, consideration should be given to rare or unusual causes of RSE or recurrent SE, which are listed in Table 5.

**Table 5.** Rare or Under-recognized Causes of Status Epilepticus

Structural	Occult cortical dysplasias and malformations of cortical development
Genetic	Mitochondrial disorders, porphyria
Systemic inflammatory disease	Neurosarcoidosis, systemic lupus erythematosus
CNS inflammatory disease	Rasmussen encephalitis, primary angiitis of the CNS, Hashimoto encephalopathy, ADEM, multiple sclerosis
Infections	Neurosyphilis, prion diseases, Bartonella, rabies, emerging forms of viral encephalitis
Illicit drugs	Cocaine, amphetamine derivatives, heroin, PCP, Ecstasy (MDMA)
Oncologic causes	Paraneoplastic limbic encephalitis
Toxic causes	Domoic acid and marine toxins, other causes of toxic leukoencephalopathy
Iatrogenic causes	Lithium toxicity, theophyllines, isoniazid (consider giving vitamin B <sub>6</sub> ), insulin, lidocaine, certain psychotropic agents, beta-lactam antibiotics, meperidine, cyclosporine, tiagabine, baclofen
Metabolic	Hypocalcemia, hypomagnesemia, hypoglycemia from insulinoma, nonketotic hyperglycemia
Vascular	Central venous sinus thrombosis, antiphospholipid syndrome

CNS = central nervous system; ADEM = acute disseminated encephalomyelitis; PCP = phencyclidine; MDMA = 3,4-methylenedioxy-N-methylamphetamine.

### Antiseizure Medications Used in Status Epilepticus

A limited number of AEDs are used in the management of SE. These medications overlap with the AEDs used in chronic epilepsy, although the dose escalation is more rapid and the desired serum concentrations are higher when patients are in SE. The treating clinician should be familiar with dosing regimens and potential adverse effects associated with each of the commonly used AEDs. The key aspects of the commonly used AEDs are outlined here.

#### Benzodiazepines

The benzodiazepines are a family of medications whose mode of action is primarily agonistic at GABA receptors, which exert inhibitory effects on neurons. At high concentrations, benzodiazepines limit sustained repetitive neuronal firing in a manner similar to that of carbamazepine and phenytoin. These agents are generally easy to administer by oral and parenteral routes, although new formulations administrable by the rectal, intranasal, and buccal routes are being developed and used, particularly diazepam and midazolam. Owing to their relative ease of use, the agents have become the first-line treatment for SE of any type. The principal adverse effects are sedation and respiratory suppression. When persistently administered, tachyphylaxis becomes a significant problem.

Within the family of benzodiazepines, various agents differ from each other, mainly by pharmacokinetic properties. In the hospital setting, the most

commonly used benzodiazepines are diazepam, lorazepam, and midazolam.

#### Diazepam

Diazepam is highly protein-bound (99%). Although the half-life of the metabolite of diazepam is 20 to 40 hours, when administered IV, diazepam is rapidly redistributed into body fat away from the brain, leading to a short therapeutic effect of 15 to 20 minutes. Diazepam may be associated with a higher risk of ventilatory suppression requiring intubation among children.

#### Lorazepam

Lorazepam has a slower onset of action of about 5 minutes but a longer duration of action (4-14 hours) primarily due to retention in brain tissue. Hence, although diazepam has a quicker mode of onset, its effect is curtailed by rapid redistribution, whereas lorazepam has a slower onset of action but more durable clinical effect. This has led to replacement of diazepam with lorazepam as a first-line agent in treatment of seizures and SE.

#### Midazolam

Effective parenteral benzodiazepine therapy can be implemented by administering serial boluses or infusions of diazepam or lorazepam, but in the ICU setting, midazolam has gained popularity as the benzodiazepine of choice owing to its relatively short elimination half-life of 1.8 to 6.4 hours, relatively benign side-effect profile, and reported effectiveness [61]. Elimination takes place via hepatic metabolism of midazolam to hydroxylated metabolites that are conjugated and excreted in the urine. Midazolam is very effective for suppression of



seizure activity and is generally very well tolerated. However, the main difficulty with use of midazolam is tachyphylaxis, which becomes a problem within 48 hours of initiation.

## Phenytoin

Phenytoin remains the traditional second-line AED, after the benzodiazepines. Phenytoin has the advantages of relative ease of use, familiarity among clinicians, cheap cost, long duration of action, and the ability to rapidly load the patient in the ED or ICU. The disadvantages of phenytoin include hypotension, drug rashes, eosinophilia, irritative thrombophlebitis, purple-hand syndrome if extravasation occurs, and unstable serum concentrations caused by zero-order kinetics, which may be particularly problematic in the setting of renal dysfunction or illness-associated hypoalbuminemia.

Phenytoin is a potent inducer of the P450 system, leading to increased metabolism of some concurrently prescribed medications. The half-life of phenytoin varies according to the serum concentration, typically about 24 hours at therapeutic concentrations. Phenytoin is extensively bound to albumin and the concentration of free, unbound phenytoin (the active agent) varies with albumin levels. The true "corrected" concentration (C) of phenytoin (in  $\mu\text{g/mL}$ ) can be calculated by the Sheiner-Tozer equation as follows:

$$C_{\text{CORRECTED}} = C_{\text{MEASURED}} / [(0.2 \times \text{serum albumin}) + 0.1]$$

In the setting of renal impairment with creatinine clearance of less than 10 mL/min, the adjusted level is:

$$C_{\text{CORRECTED}} = C_{\text{MEASURED}} / [(0.1 \times \text{serum albumin}) + 0.1]$$

In the setting of SE, clinicians should aim to maintain the patient's phenytoin concentration at 15 to 25  $\mu\text{g/mL}$ . A 20-mg/kg loading dose will typically lead to a plasma concentration of more than 20  $\mu\text{g/mL}$  for the next 24 hours. Obtaining the level of free phenytoin is the best way to assay phenytoin concentrations, although this is not rapidly available in many institutions.

## Fosphenytoin

Fosphenytoin is a dose-equivalent pro-drug of phenytoin used IV as an alternative to phenytoin. Its advantages are that it can be given more rapidly than phenytoin (up to 150 mg/min IV) because it is water soluble and less likely to cause problematic

hypotension, has a neutral pH in solution, and consequently leads to fewer injection site reactions. Like phenytoin, IV administration requires electrocardiographic monitoring. Fosphenytoin can also be given intramuscularly, but absorption is too slow by this route for treatment of SE. The use of fosphenytoin has been hampered by its expense, although it is generally safer than phenytoin to use.

## Barbiturates

Barbiturates bind to specific sites on GABA-regulated ion channels. This leads to increased channel open times resulting in an increased influx of chloride ions into neurons with resultant enhanced hyperpolarization of the postsynaptic neuron. Barbiturates are classified according to duration of action. Long-acting agents include phenobarbital, short-acting agents include pentobarbital, and ultra-short-acting agents include thiopental and methohexital.

### Phenobarbital

Phenobarbital, also known as phenobarbitone, is the traditional agent of choice after phenytoin, has proven ineffective in the setting of SE. However, the role of IV phenobarbital in SE is diminishing because of the recognition that a third-line AED rarely terminates SE. Phenobarbital requires less dilution, can be given as a slow IV push over 10 minutes, and can be quick to control seizures [62]. Phenobarbital is sedating although not sufficient to induce a burst-suppression EEG pattern when a 20 mg/kg loading dose is administered. Many patients need intubation after a loading dose.

Phenobarbital has a very long half-life of 3 to 7 days and accumulates in tissues; hence, patients often require a long waking-up period after significant doses are administered. Many clinicians now favor directly proceeding to continuous infusion therapy rather than using a third-line AED such as phenobarbital. However, phenobarbital is still useful in SE treatment where rapid access to an ICU is not available and when weaning a patient off continuous infusion therapy. Phenobarbital rarely causes idiosyncratic reactions, but rashes, hepatic dysfunction, and aplastic anaemia have been reported.

### Thiopental/Pentobarbital

The commonly used barbiturates for coma in refractory SE are thiopental (used in Europe), or its metabolite pentobarbital (used in North America). These agents are very potent antiseizure medications but are hampered by cardiovascular depression and hypotension. Pentobarbital has a very protracted clearance, with a half-life of 144 hours,

leading to accumulation in tissues. The use of barbiturate infusion therapies has become less popular among clinicians with the advent of the shorter-acting agents propofol and midazolam. That said, there is a perception that barbiturate therapy is the most potent and effective of the infusion therapies [23]. Their main action is also agonistic at GABA<sub>A</sub> receptors, with possible action also on Ca<sup>2+</sup> channels. Both thiopental and pentobarbital are NMDA antagonists *in vitro*. Barbiturates are known to cause poikilothermia and there is also some evidence that barbiturates exert immunologic effects [63].

## Sodium Valproate

Sodium valproate is a very effective, traditional broad-spectrum antiseizure medication in which there has been a resurgence of interest owing to the availability of an IV formulation. This role of sodium valproate in SE has yet to be determined. It is frequently used when there is a contraindication to the use of phenytoin/fosphenytoin or if the treating clinician is hoping to avoid the use of pharmacologic coma in the ICU. There is some evidence that intravenous valproate may be as effective as phenytoin in the initial management of SE [64]. Sodium valproate is reported to be safe when administered rapidly as an infusion in medically unstable patients [65,66]. A loading dose of sodium valproate of 20 to 30 mg/kg yields an average serum concentration of 132.6 µg/mL (range, 64–204 µg/mL). One report of the use of sodium valproate involved administration of loading doses of up to 78 mg/kg [67] at rates of up to 500 mg/min.

In the context of SE, recognized adverse effects include hyperammonemia pancreatitis, (1:250 patients treated), hepatic dysfunction and thrombocytopenia. A significant obstacle to the use of valproate in medically complex patients or RSE is the drug–drug interactions (sodium valproate is a P450 enzyme system inhibitor) associated with valproate, particularly with other AEDs.

Preexisting thrombocytopenia precludes use of sodium valproate, particularly in patients with intracranial hemorrhages and collections. Hyperammonemia is a common and under-recognized adverse effect of sodium valproate. Sodium valproate is contraindicated in patients with urea cycle disorders, such as ornithine transcarbamylase deficiency, and mitochondrial disorders. Ideally, all patients starting sodium valproate in the setting of SE should have an arterial ammonia level checked before therapy is initiated, but certainly within 24 hours and at regular intervals thereafter. This is especially true in patients with underlying hepatic dysfunction.

Sodium valproate has a half-life of 12 to 20 hours and is 80% to 90% protein bound. Serum valproate concentrations are notoriously variable in patients taking valproate, often for unclear reasons. The quoted therapeutic range is 50 to 120 mg/L. In the setting of SE, the clinician should strive for a concentration of at least 80 mg/L, usually requiring a daily maintenance dose of 500 mg (or more) by IV route every 8 hours for the average 70-kg patient.

## Propofol

Propofol is an ultra–short-acting, nondissociative IV anesthetic agent that was first used for procedural sedation. The principal antiseizure mechanism of action is as an agonist on GABA<sub>A</sub> receptors, but modulation of Ca<sup>2+</sup> and Na<sup>+</sup> channels has also been described [68]. Its effect on NMDA glutamate receptors is unclear. Propofol is hydrophobic and is prepared as a milky white emulsion containing soybean oil, egg lecithin, and glycerol. It is highly lipophilic, with a physiologic volume of distribution of 600 L.

Because of its short half-life of 3 minutes, it must be used in a continuous IV infusion for long-duration sedation. Propofol is only available in an IV formulation. An IV injection of a therapeutic dose of propofol produces hypnosis rapidly, with minimal excitation, usually within 40 seconds. As with other rapidly acting IV anesthetic agents, the half-time of the blood–brain equilibration is approximately 1 to 3 minutes, and this accounts for the rapid induction of anesthesia.

The pharmacodynamic properties of propofol are dependent on the therapeutic blood propofol concentrations. Steady-state propofol blood concentrations are generally proportional to infusion rates, especially within an individual patient. Undesirable side effects such as cardiorespiratory depression are likely to occur at higher blood concentrations that result from bolus dosing or a rapid increase in infusion rate. After an IV bolus dose, there is rapid equilibration between the plasma and the highly perfused tissue of the brain, thus accounting for the rapid onset of anesthesia. Plasma levels initially decline rapidly as a result of rapid distribution and high metabolic clearance. Distribution accounts for about half of this decline after a bolus of propofol.

The principal concern associated with use of propofol is that of the development of the *propofol infusion syndrome*, a rare but often fatal syndrome first described in critically ill children. The main features of the syndrome consist of cardiac failure, rhabdomyolysis, severe metabolic acidosis, and renal failure. Propofol infusion syndrome typically occurs in the setting of high infusion doses over long periods of

time in patients who are otherwise very ill. A recent comprehensive evaluation of use of propofol in a busy adult ICU suggested that this syndrome is detectable by monitoring plasma triglyceride levels and serum creatinine kinase concentrations. Vigilant ICU clinicians can thus be alerted early in the development of this preventable syndrome [69].

Some evidence suggests that propofol may not be as safe as midazolam in very ill patients [70,71]. One study found that propofol was associated with a 56% mortality rate in patients with Acute Physiology and Chronic Health Evaluation (APACHE) scores exceeding 20, whereas patients treated with midazolam had a 17% mortality rate [70].

### Carbamazepine, Oxcarbazepine, Topiramate, and Levetiracetam

These antiseizure medications are often added to the acute AED regimen with the intention of providing adequate maintenance AED coverage to prevent SE recurrence when infusion therapy is withdrawn. In the setting of SE, these medications are generally titrated quickly up to dose ranges considered high in the outpatient setting.

- Carbamazepine is a traditional AED used in the management of chronic epilepsy. The use of carbamazepine in SE is primarily as a maintenance antiseizure medication, important when coma-inducing infusions are withdrawn. A parenteral formulation is not yet available. Typical daily doses in the setting of SE are up to 1600 mg/d.
- Oxcarbazepine is used in the same way as carbamazepine. A parenteral formulation is not yet available. Typical daily doses are up to 2400 mg/d.
- Topiramate is a new AED that has been reported to be effective when administered enterally in the setting of SE [72]. Topiramate can be administered by nasogastric tube or rectally, is generally well tolerated except for mild sedation, and can be quickly titrated to dose ranges of up to 1600 mg/d.
- Levetiracetam is a new AED that has gained popularity in the setting of ICU care. Levetiracetam can now be administered parenterally as well as by nasogastric tube. Typical daily doses of levetiracetam in the setting of SE are up to 5000 mg/d. There are some preliminary reports on the use of levetiracetam in the setting of SE both as an IV agent and as a maintenance AED given by nasogastric tube [73-75]. The main advantage of levetiracetam in the setting of acute seizures and SE is the ease of administration, rapid titration, easy transition to use as a maintenance AED, and few drug-drug interactions. However, although this AED is

increasing in popularity, there are limited data on its efficacy in SE in humans.

### Other AEDs

The list of other maintenance AEDs is growing and includes lamotrigine, gabapentin, zonisamide, pregabalin, felbamate, methsuximide, ethosuximide, acetazolamide, primidone, tiagabine, and vigabatrin. Although used in chronic epilepsy, these agents are rarely used in SE owing to slow titration or lack of evidence for clinical efficacy in the setting of SE. Felbamate had promise as a maintenance AED but has been associated with development of aplastic anemia in adults.

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### Novel Therapeutic Approaches in Highly Refractory Status Epilepticus

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Given that the best predictor of clinical outcome from SE is the underlying etiology, then it seems likely that the most effective way to terminate RSE is to successfully treat the underlying cause. Hence, it is important to treat any *active* underlying disease processes in conjunction with treatment of the SE itself. However, many causes of SE are actually static or remote from the active episode of SE, such as an old stroke. Treatment of the SE should be the focus of one's efforts in these cases.

So what does a clinician do when a patient remains in SE despite pharmacologic suppression of seizures by coma-inducing agents? When confronted with a patient with persistent, highly refractory SE despite apparently appropriate management, we recommend the following steps:

- Reevaluate the case and be satisfied that the underlying cause has been identified, particularly metabolic, inflammatory, infectious, or iatrogenic causes.
- Ensure that imaging studies, using MRI, positron emission tomography (PET), and single-photon emission computed tomography (SPECT), if available, have been conducted appropriately and studied adequately. These frequently reveal a causal structural lesion.
- Be certain that the electrographic seizure activity is abolished while the patient is receiving infusion therapy. The presence of a burst-suppression pattern on EEG does not equate to abolition of all seizure activity: the bursts may in fact be electrographic seizures. Study the bursts carefully and compare them with the characteristic electrographic seizures evident at the onset of EEG recording, before infusion therapy.

- Ensure that adequate levels of maintenance AEDs are being used to increase the success of an elective wean from infusion therapy.
- If an infusion therapy does not work, then another should be tried. There is little prospective evidence that one agent (from midazolam, propofol, or pentobarbital) is more effective or safer than another, although some retrospective data suggest that pentobarbital is more effective (but more likely to induce hypotension) than either propofol or midazolam [76]. If a given infusion therapy regimen does not terminate SE after the initial 12- to 24-hour period, then it is unlikely to be successful after a 48- or 72-hour period. The regimen should be changed, and the underlying etiology should be identified and treated.

If the patient continues to seize despite appropriate trials of appropriate regimens and the underlying etiology has been managed appropriately, then other novel therapeutic measures can be considered. It must be noted that use of these novel treatment strategies is based on anecdotal cases or small case series rather than prospective clinical trials.

Lastly, at times, when EEG activity is equivocal or difficult to interpret, it is not unreasonable to temporarily discontinue infusion therapies to allow clarification of the current clinical and EEG status. This is sometimes the only way to be sure that the patient is still in SE. This is likely to be less risky than prolonged trials of unnecessary treatment.

## Surgical Intervention

Although rarely undertaken, surgery is a plausible option where electrographic SE remains focal, particularly if there is evidence of a candidate causal structural lesion. The very high morbidity and mortality rates associated with RSE argue for a role for surgical intervention where that SE is focal and particularly where the SE is related to a clearly delineated focal cortical lesion or region. Evidence suggests that patients are unlikely to respond to a re-trial of any particular medical intervention if the intervention failed on the initial trial [55,70,77,78]. Hence, by working through a therapeutic algorithm on a day-by-day basis, one can identify possible surgical candidates.

Surgical resection of epileptogenic foci has gained widespread acceptance as a valid therapeutic intervention in chronic epilepsy. The general criteria for surgery in patients with epilepsy are (1) the epilepsy is medically refractory, (2) the epilepsy is disabling, (3) the focal epileptogenic region can

be identified, (4) the focal epileptogenic region can be removed without risk of a cognitive, motor, or sensory deficit, and (5) removal of the epileptogenic region has a reasonable expectation of complete or nearly complete abolition of further seizures.

The same criteria can be extended to the acute setting of refractory focal SE. In the acute setting, however, consideration of postoperative deficits and the prospect of long-term seizure freedom should be weighed against the risks associated with ongoing focal SE. The likelihood of successful intervention is related to identification of a causative candidate structural lesion or functional epileptogenic region and the timing of surgical resection. Identification of a structural lesion or functional region requires correlation of EEG findings with structural (usually MR) and functional (usually PET or SPECT) imaging. This often requires an aggressive approach to imaging, with repeated studies during the course of SE and use of optimal imaging techniques.

The timing of surgical intervention is critical to the likelihood of success for a number of reasons. Historically, surgical intervention for refractory SE is undertaken as a last-ditch effort to terminate the SE, typically after at least a month in the ICU. These patients are more likely to have suboptimal outcomes because they usually have undergone prolonged medical therapy and their SE may have evolved into a broader secondarily generalized electroclinical form of SE where the chance of success of surgical removal of a focal cortical region decreases.

There have been a number of reports of successful treatment of refractory focal SE by surgical removal of an underlying structural lesion, particularly in the pediatric population [79]. Surgery generally involves removal of the structural lesion (lesionectomy) or brain region in which the lesion is embedded (partial or complete lobectomy) [80].

## Multiple Continuous Infusion Therapy

In general, if a single-agent infusion therapy is not effective on the first trial, it generally remains ineffective thereafter. It is not known whether combinations of these infusions are more effective or safer. If hypotension is a major problem, then the infusion rate of pentobarbital can be lessened if midazolam is commenced. Moreover, the different modes of action may enhance the chance of terminating SE. It is worth re-emphasizing that continuous infusion therapy simply provides temporary abolition of SE. Optimization of maintenance AED therapy is at least as important as the choice of infusion therapy.

## Ketamine

Ketamine is a potent NMDA antagonist that has been used in some institutions in the setting of RSE. It is administered as a loading dose of 2 mg/kg, followed by an infusion of 10 to 50 µg/kg/min. Limited data are available on the use of this infusion therapy in humans, although its use in RSE has theoretic advantages. In established SE, there is evidence that excessive NMDA excitatory receptor-mediated transmission is an important mechanism of persistent neuronal firing. This may explain the ineffectiveness of GABA agonists in the latter stages of SE. Ketamine is used in the same fashion as other coma-inducing agents; that is, IV bolus, followed by maintenance infusion. The evidence for efficacy of ketamine is largely anecdotal [47,81].

The reported adverse effects relate to its use as an analgesic, where hallucinations and other transient psychotic sequelae are reported. Ketamine is associated with cardiovascular stimulation and a rise in arterial pressure and heart rate and should be used with caution in patients with systemic or intracranial hypertension. Cerebellar damage has also been reported after longer-term use [82].

## Lidocaine Infusion

There are a number of reports of successful use of lidocaine in the setting of RSE [83]. This agent should not be used in patients with coexisting sinoatrial disorders, all grades of atrioventricular block, or severe myocardial depression.

## Inhalation Anesthetics

Inhalational anesthetics are used for the induction and maintenance of anesthesia. There have been several case reports of successful use of inhalation anesthetics in the setting of RSE [84]. These include isoflurane and desflurane [85]. These agents have not been rigorously tested in a clinical trial.

## Paraldehyde

Paraldehyde was an important therapy in the past but is now rarely used because of difficulties in administration and associated unwanted adverse effects.

## Direct Brain Stimulation

Although surface and deep brain stimulation devices are being developed for use in focal and generalized epilepsies, their use has not been reported in humans in the setting of SE.

## Transcranial Magnetic Stimulation

Transcranial magnetic stimulation has similarly been evaluated in animal models of focal SE but has not yet been reported to be helpful in human SE.

## Electroconvulsive Therapy

Owing to its potent anticonvulsant actions, electroconvulsive therapy has been proposed as an intervention for SE [86]. It may seem illogical to administer a proconvulsive stimulus in SE, but the after-coming inhibitory state after a convulsion induced by electroconvulsive therapy may, in theory, be beneficial to patients in SE. Electroconvulsive therapy has not been evaluated in a rigorous fashion by clinical trial. In our experience, it has not been helpful in the management of refractory SE.

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## Diagnostic Tools in Refractory Status Epilepticus

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The principle advances in diagnostic techniques in the setting of difficult-to-control SE have been digital EEG recording and novel imaging approaches. These diagnostic modalities in conjunction with established investigations (CSF analysis, AED levels) allow greater insight into the etiology and progression of SE in patients, particularly those who have become refractory.

Digital EEG has made continuous EEG monitoring with video much less cumbersome compared with paper EEG. Continuous digital EEG monitoring allows for easier data acquisition, reformatting, storage, and application of seizure-screening software tools such as event detection and spectral analysis. Continuous video recording in conjunction with EEG facilitates interpretation, principally by facilitating artifact rejection and assessing the clinical correlation of paroxysmal EEG activity or events.

Imaging plays a role in the management of SE at 2 levels. Most patients initially undergo imaging, typically with CT, in the ED or en route to an ICU.

This initial imaging is generally done to exclude neurosurgical causes for seizures, such as mass lesions and traumatic injury, and to gauge the safety of a planned lumbar puncture. Overall, CT imaging has a limited further role in the specific management of SE.

In RSE, careful planning of appropriate structural and functional imaging can maximize the information obtained with respect to the cause of the SE and the degree of progression. Before clinicians interpret such imaging, however, they need to be familiar with potential peri-ictal changes frequently seen in patients with prolonged seizure activity that are related to the ictal activity itself. These peri-ictal changes should not be interpreted as structural lesions, although they often correlate neuroanatomically with an underlying structural lesion. Table 6 lists recognized peri-ictal changes evident on imaging studies in some patients with SE or vigorous electroclinical seizures.

These peri-ictal structural changes are best seen on MRI. Peri-ictal findings can be categorized as local or remote according to their proximity to the site of maximal ictal EEG activity. Many of the findings described are reversible and do not necessarily equate with neuronal loss, although the factors that determine their occurrence and persistence are incompletely understood. It is likely that the remote diencephalic, corpus callosal (splenium), and contralateral cerebellar changes arise as a consequence of abnormal reverberating para-ictal activity in circuits involving these structures [87].

Local peri-ictal findings that may be present include a swollen cortical ribbon with loss of grey-white matter differentiation. Increased T2 signal intensity due to edema occurs in areas of cortex and adjacent subcortical white matter. The local T2-weighted changes may be associated with MRI evidence of restricted diffusion, which are bright on diffusion-weighted imaging and dark on apparent diffusion coefficient maps, suggesting that they represent cytotoxic rather than vasogenic edema. Whereas in acute ischemia, diffusion-weighted images reveal restricted diffusion before any abnormality of the T2 signal becomes apparent, in ongoing SE, diffusion-weighted images and T2 signal changes appear to occur roughly synchronously. Restricted diffusion has commonly been identified as a marker of irreversible ischemic injury, but recent studies suggest that in some situations, decreased diffusion associated with seizures is reversible without the subsequent appearance of tissue injury.

Another important finding to recognize is the occasional occurrence of migratory T2 and lesions

**Table 6.** Peri-ictal Imaging Findings

Local	Remote
Mass effect	Posterior leukoencephalopathy
Hippocampal swelling	Unilateral/bilateral diencephalic lesions
Focal cortical lesions	Splenium abnormalities
Migratory lesions	Cerebellar diaschisis
Blood-brain barrier breakdown	
Local increased vascularity	
Restricted diffusion	

on diffusion-weighted imaging, appearing in remote cortical areas, distant from the original or principal seizure focus (in focal SE). It is important to recognize that these local findings, at times quite dramatic, are often reversible, at least in the early stages of SE.

Perhaps even more informative are the various peri-ictal findings evident on functional neuroimaging techniques. Both ictal SPECT, which uses technetium Tc 99-hexamethyl-propyleneamine-oxime as a marker of local cerebral perfusion, and fluorodeoxyglucose (FDG)-PET, which uses fluorodeoxyglucose-18 as a marker for cortical glucose utilization, can provide valuable data in focal seizures. Ictal SPECT may be used to localize the seizure focus in focal epilepsy. Imaging with FDG-PET often demonstrates peri-ictal focal hypermetabolism in SE of focal origin.

In our view, the most informative use of EEG structural and function imaging modalities involves co-registration of data sets from each of these diagnostic modalities. This is critical if any surgical intervention is planned, but we have also found this approach invaluable in the assessment of nonlesional SE where a structural focus for the seizures is not evident.

## Outcomes

Factors that are thought to contribute to the morbidity and mortality associated with SE are underlying etiology, the age of the patient, and possibly, the duration of the SE. Secondary factors that likely contribute to the outcome from SE include sepsis, anoxia, duration of infusion therapy, and comorbid ICU-related medical complications. Data from 2 recent ICU-based studies of SE [31,32], along with previous data [1,4,9,54,88-92], can be used to summarize the clinical sequelae of a bout of SE (see Table 7).

**Table 7.** Morbidity and Mortality of Status Epilepticus

Variable	Nonrefractory SE	Refractory SE
Duration of seizure activity, h	2.4	92
Seizure recurrence, <sup>a</sup> %	6.5	45.4
Duration of stay, d		
Intensive care unit	2.0	16.5
Hospital	10-11.1	25.3-30
Mortality, %		
Inpatient	8.0-8.6	16.7-23.0
30-day		7.0-44
Discharge home without assistance, %	50	31
Development of epilepsy, %	22.2-42.0	87.5

SE = status epilepticus.

<sup>a</sup>Within 24 hours of apparent termination of SE.

Inpatient mortality is linked to potentially fatal etiologies, increasing age, and severely impaired consciousness when first evaluated [32]. Not surprisingly, the list of potentially fatal etiologies is identical to the list of causes of RSE. As expected, patients with underlying anoxic brain injury, vascular lesions, tumors, and infections fare worse than patients whose SE was provoked by alcohol, drug withdrawal, or noncompliance with AED therapy. Although intuitively one would expect that abundance of data that SE results in neuronal injury, it has been difficult to separate the morbidity associated with the underlying cause of the SE from injury due to the SE itself. Despite these constraints, there is some evidence that SE per se carries a 3% mortality rate [93]. Animal studies suggest that SE is associated with significant neuronal injury [94,95].

There are numerous reports of progressive imaging findings in patients who have experienced an episode of SE [96-98]. These reports typically describe progressive hippocampal damage manifesting as atrophy, gliosis, and destruction of cortical architecture. Rare neuropathologic case reports have described neuropathologic changes associated with SE in humans [97,99]. This correlates with neuronal loss within the hippocampus, especially in the CA1 and CA4 regions, as well as neuronal loss in more diffuse brain regions [99,100].

One consistent long-term adverse outcome related to SE is progression to chronic epilepsy, seen in up to 90% [2,3,9,31,32]. The risk that enduring epilepsy will develop is approximately 4 times greater after a bout of SE than after a single seizure. Although one would expect significant cognitive decline after an episode of SE, this has been a less consistent finding in the few and largely retrospective studies that have examined this question [101-103].

The mortality rates for SE, which are not uniform across age groups, are about 40% for patients aged

older than 60 years and exceed 60% for those aged older than 80 [104,105]. Patients with short-duration SE, lasting less than 1 hour, have a lower mortality of 2.7% compared with the 32% mortality rate in those with longer-duration SE that lasts more than 1 hour [106]. This 1-hour demarcation may be a crude temporal dividing line between responsive and refractory SE. Increased complications are evident where SE persists for longer than 4 hours [105]. It must be noted that any study that includes patients with postanoxic SE skews mortality rates toward the high end. Finally, NCSE was associated in 1 study with an overall 18% mortality rate, although the patients who died had a greater burden of medical comorbidities [30]. As with convulsive SE, the attributable morbidity and mortality associated with NCSE are difficult to quantify, but it seems clear that NCSE is not a favorable prognostic factor in the ICU.

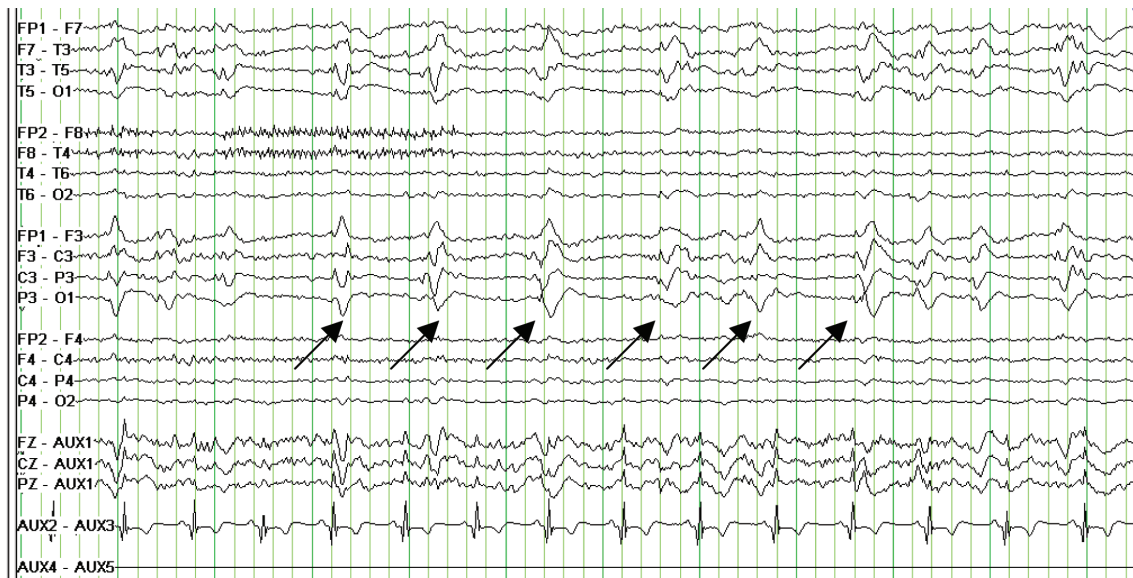
Despite the high morbidity associated with RSE, there are numerous reports of survival even after very prolonged hospital courses for SE, particularly in children. As a rule, however, many patients will have persistent refractory epilepsy and functional deficits [107,108]. Particularly alarming but less well recognized is that approximately 40% of patients who survive the first 30 days after a first episode of SE die within the next 10 years [109]. The combined short- and long-term mortality associated with SE accounts for the estimated 22 000 deaths associated with SE per annum in the United States [7].

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### Problem Areas in Intensive Care Unit Management of Status Epilepticus

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The management of SE is frequently difficult. "Status epilepticus" is not a single entity but is a heterogenous collection of electroclinical syndromes with wide



**Fig 3.** The electroencephalographic characteristics of periodic lateralized epileptiform discharges—regular, constant periodicity of the discharges occurring at once per second or less.

ranging etiologies, some benign and some malignant, and with varied clinical outcomes. Despite the variable manifestations and evolution, SE is often treated by the same management algorithm within the same institution. This one-size-fits-all approach is based on solid evidence, particularly in the early stages of SE. However, a number of specific management problems arise in patients with SE, particularly when refractory, that are not easily dealt with in an algorithmic fashion and can be difficult to resolve.

### Significance of Periodic Lateralized Epileptiform Discharges

With the advent of continuous EEG monitoring, the clinician will frequently encounter rhythmic or repetitive EEG patterns that do not have a paroxysmal clinical correlate. These most common patterns include periodic lateralized epileptiform discharges (PLEDs) and stimulus-related discharges such as stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDS). When the EEGs in these patients are reviewed, it is important to recognize that although sensitive to summated cortical activity, the EEG is still a relatively crude 2-dimensional mode of demonstrating complex cortical activities. Thus, benign and malignant neurophysiologic processes may be similarly represented without etiologic or prognostic distinction. Like seizures and SE, PLEDs are neurophysiologic markers of cortical injury and disturbance.

The definition of PLEDs remains critical when trying to ascribe significance to this electrographic entity. Irrespective of the definition used, lateralized epileptiform discharges are typically evident in the setting of focal, acute brain injury or insult. The traditional definition [110] of PLEDs highlighted the regular, constant periodicity of the discharges occurring every 0.5-2.0 seconds. Periodic lateralized epileptiform discharges do not wax and wane in frequency, but remain relatively constant (see Figure 3). In our view, epileptiform discharges that wax and wane (ie, are not periodic) should be thought of as interictal epileptiform discharges, and that traditional PLEDs are less epileptogenic than frequent, waxing and waning epileptiform discharges.

These are relative distinctions, however, because both electrographic patterns are symptomatic of underlying cortical injury, from which substrate seizures can arise. These distinctions are often not very helpful when one is at the bedside determining if a particular EEG pattern represents seizure activity. Generally speaking, we will not treat the EEG pattern per se after a single viewing. Recognition of PLEDs will prompt us to continue EEG monitoring to make a determination of whether the PLEDs are interictal or ictal in a given patient. Our overall approach is to make a judgment based on the evolution of the EEG—comparing with EEGs done in the past, if available—in conjunction with the clinical details. Comparison of the current EEG activity with any previous unequivocal ictal EEG activity is often the most useful way of ascribing significance to





**Fig 4.** Metabolic encephalopathy with characteristic “triphasic” morphology, in a longitudinal bipolar “double banana” montage. Examples of triphasic waves are highlighted.

PLEDs or repetitive epileptiform discharges. It often requires review of at least an hour of EEG to determine if a particular pattern is likely to be truly ictal.

Unwavering constant PLEDs persisting for hours are less likely to represent true seizure activity. Electrographic seizure activity typically tends to wax and wane in a crescendo-decrescendo manner because the cerebral cortex is generally not capable of generating energy-expending hypersynchronous ictal activity indefinitely but rather tends to generate seizures in a stop-and-start fashion. The exception to this rule may be electrographic SE of sleep (ESES) and *epilepsia partialis continua*, where ictal activity can persist for long periods of time.

If available, functional imaging using SPECT or PET can be helpful to assess the significance of PLEDs. A hotspot (focus of increased blood flow or increased glucose uptake) on a SPECT or PET study during active PLED activity is suggestive of significant ongoing seizure activity, particularly if the hotspot is not evident on a repeat study when the PLEDs are suppressed by infusion therapy.

A number of studies have examined the outcomes of patients with EEGs exhibiting (presumably) new-onset PLEDs in the setting of acute neurologic illness. Snodgrass et al [111] reported that 90% of such patients had 1 or more seizures during hospitalization and 60% to 70% had an episode of SE. Walsh and Brenner [112] reported that 41% of patients whose EEGs demonstrated PLEDs died within 2 months. The limitations of these studies of PLEDs are that they were largely

retrospective and used varied definitions of PLEDs. Furthermore, it is likely that the true incidence of PLEDs is underestimated, but only those patients who had EEGs as a result of the development of acute symptomatic seizures or altered mental status were discovered to have PLEDs.

*Nonconvulsive status epilepticus versus encephalopathy.* When trying to decide if a generalized periodic or rhythmic EEG pattern is due to NCSE or to a metabolic encephalopathy, it is important to factor in the clinical aspects and evolution of the patient, particularly changes in metabolic parameters. As such, there is no reliable method of distinguishing NCSE from an encephalopathic EEG. Our belief is that the triphasic EEG pattern that arises in the setting of metabolic disarray is neurophysiologically similar to NCSE that arises in very ill ICU patients (see Figure 4), and both of these patterns reflect diffuse cortical excitability.

*Electroencephalographic artifact.* The use of concurrent video recording will help to determine if the EEG abnormalities are artifactual or have an associated clinical correlate. This is particularly important with the wide array of artifacts seen in the ICU environment.

*Paroxysmal clinical behaviors.* Many ICU patients will exhibit episodic behaviors of unclear significance. This should prompt the performance of an EEG, to exclude seizures, though other causes should be

considered. In general, if clinical movements are nonpatterned or nonspecific, then one should perform an EEG rather than assume that the movements are seizures. Other behaviors that mimic seizures in the ICU include agitation due to pain or partial awareness, transient ischemic attacks, delirium, nonepileptic myoclonus, hemiballism, brainstem-mediated posturing, motor manifestations of brain herniation, nonepileptic seizures or pseudostatus, and transient neurologic symptoms associated with cerebral amyloid angiopathy.

*Nonepileptic seizures.* It is not unheard of for patients with nonepileptic seizures to present so realistically that intubation and anesthesia are initiated. This is a very forgivable mistake, and generally speaking, clinicians should err on the side of caution when dealing with atypical clinical presentations. It is important to obtain video EEG monitoring early in the course of management to avoid inappropriate and potentially harmful management.

*Nonconvulsive status epilepticus.* There will be an increasing awareness of NCSE because of more proactive use of continuous EEG monitoring. As mentioned above, although NCSE is clearly not a good prognostic sign in an ICU patient, it is not clear whether the NCSE is an epiphenomenon in these patients or whether it carries attributable morbidity and mortality. It is not clear whether intervention for the NCSE itself confers benefit to the patient.

*Partial (focal) status epilepticus.* Generally speaking, most cases of SE should be treated promptly and aggressively. The most common cause of focal SE is stroke: seizures develop in 5% to 9% of acute stroke patients and SE develops in 20% of these [113]. However, caution should be taken when managing some patients in focal SE, particularly when consciousness is preserved. The textbook example is that of simple focal motor SE or *Epilepsia partialis continua*. *Epilepsia partialis continua* and other forms of focal SE where consciousness is preserved are often tolerated by the patient and are sometimes very refractory to AED therapy, including infusion therapies. *Epilepsia partialis continua* often persists for weeks but is less likely to lead to widespread cerebral damage. The appropriate approach to the management of these cases is often dictated by the underlying etiology and often does not involve pharmacologic coma in an ICU. *Epilepsia partialis continua* may respond to correcting reversible causes of encephalopathy, for example, hyperosmolar nonketotic hyperglycemia.

*When to stop treating highly refractive status epilepticus.* In our estimation, the prognosis of the underlying etiology determines the duration and intensity of extended (weeks to months) highly refractory SE. There are reports of good clinical outcomes from very prolonged (>1 month) episodes of highly refractory SE. However, if the underlying etiology causing the SE carries a grave prognosis (eg, glioblastoma multiforme), then a less aggressive approach of clearly defined duration, agreed on by family members, is appropriate.

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## Postanoxic Status Epilepticus

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Postanoxic SE is a specific electroclinical state resulting from diffuse cortical damage. Electrographically, the postanoxic state varies in severity from electrocerebral silence to diffuse nonreactive alpha and theta-range activity (“alpha coma” and “theta coma”) to an intrinsic burst-suppression pattern to frequent generalized epileptiform discharges. The EEG findings may reflect the activity of the residual islands of viable cerebral cortex, which are sometimes capable of generating background activity or epileptiform discharges.

Irrespective of the EEG findings, the patient may or may not exhibit myoclonus. Such myoclonic status that arises in patients after an anoxic insult is usually transient (evolving into motionless coma) and invariably has a dismal outcome [114-117]. The presence of myoclonus may confer a worse prognosis than electrographic SE without clinical manifestations. The myoclonus is often very dramatic and distressing for caregivers and family members and in association with an “active” EEG, one feels compelled to institute treatment.

We view such measures as being palliative, although it is critical to establish that the original brain injury was anoxic rather than due to a potentially reversible cause such as a lithium overdose. A reasonable course of action is to institute a clearly defined course (24-48 hours) of IV propofol or midazolam sufficient to abolish the myoclonus and to suppress the EEG. This can be performed in conjunction with other interventions such as head-cooling and administering neuroprotective agents.

During this period, useful prognostic information can be obtained by ancillary tests and serial clinical evaluations such as MRI brain imaging, SPECT imaging, and somatosensory evoked potentials [117]. This prognostic information along with the clinical state of the patient after the infusion therapy, in consultation with family members, will dictate subsequent clinical management. It is critically

important to determine that the cause of the coma was due to an anoxic event, because some causes of myoclonic SE carry a favorable prognosis, such as myoclonic SE seen in primary generalized epilepsy and lithium toxicity or after respiratory arrest. Overall, we rely on the clinical history (circumstances of cardiorespiratory arrest) and prognostic markers to a much greater extent than the EEG or the presence or absence of myoclonus to guide what we relay to the family and our clinical management of the case.

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## Potential Mistakes in the Management of Status Epilepticus

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Potential errors in the management of SE do not revolve around the nuances of choosing fifth- or sixth-line agents in RSE but relate to the early recognition and prompt use of appropriate doses of appropriate first- and second-line AEDs. Potential mistakes that can occur in the ED setting include assuming that the seizure activity has terminated when overt convulsive activity has stopped but the patient remains obtunded, failure to administer appropriate loading doses of AEDs in proportion to the patient's weight, and failure to recognize nonepileptic seizures or pseudostatus. In general, one cannot overtreat SE in the acute setting. A more problematic error is undertreatment of SE, because delay in treatment will lead to an increasingly refractory situation.

Potential errors in an ICU setting include the mislabeling of paroxysmal clinical behaviors as seizures, underutilization of diagnostic EEG monitoring, lack of recognition of NCSE or metabolic encephalopathy, failure to initiate adequate amounts of maintenance AED therapy, and inappropriate delay in switching from an ineffective treatment regimen (manifesting as ongoing seizure activity on EEG monitoring) to another regimen. Overall, once a treatment regimen at appropriate doses is deemed to be ineffective then another regimen should be instituted promptly. Reinstating a regimen that has already failed delays potentially successful interventions. Finally, potential mistakes in the diagnostic evaluation of patients with SE include misinterpreting perictal imaging findings as structural lesions and an inadequate search for an underlying etiology.

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## Future

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In the future, as our understanding of the biologic evolution of SE increases, novel agents will undoubtedly emerge. To rigorously evaluate these

interventions in SE, the nomenclature used to describe the various forms of SE and electrographic patterns needs to be unified and clearly defined. This is particularly important when studying a heterogeneous syndrome. However, given the dynamic and protean nature of SE, it is unlikely that a single "magic bullet" will prove effective. Just as our approach to acute stroke has changed in the last decade, a similar shift in attitude and emphasis toward early recognition and intervention in SE is needed.

In overt convulsive SE, treatment in the field by paramedical personnel may be effective at terminating SE at the potential expense of overtreating some seizures that would have self-terminated. In the ED setting, use of prefilled syringes with weight-appropriate doses of lorazepam (akin to prefilled syringes used in cardiac resuscitation) may reduce the time to first-line treatment. Another advance in the early management of SE is the recent development of EEG caps that allow easier initiation and recording of EEG, critical in the early recognition of nonconvulsive SE and pseudostatus. In the ICU setting, the principal advance is the advent of continuous digital format EEG monitoring allied to surveillance software technology that will allow automatic detection of seizures. Other forms of monitoring, such as microdialysis, may offer very useful diagnostic information in the ICU setting, particularly when faced with equivocal EEG patterns such as PLEDs and NCSE.

The diagnostic workup of patients in SE is likely to include functional and metabolic imaging such as PET, SPECT, and MR spectroscopy as well as novel structural imaging modalities and applications. The therapeutic role of the newer AEDs and newer parenteral formulations of existing AEDs remains to be determined. The use of other treatment modalities such as surgery and neurostimulation devices may increase with the increasing recognition of heretofore poorly recognized structural lesions such as dysplasias increasingly detected by high resolution MRI in the setting of SE.

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## Conclusions

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The initial management of SE is now well established, but the management of advanced or refractory SE remains a difficult proposition. However, advances in our understanding of SE as well as both diagnostic and monitoring tools offer the prospect of better clinical outcomes in the future. Early recognition and intervention in SE is far more likely to succeed than any delayed intervention. Ensuring an appropriate dose of a first- and second-line antiseizure

medication is more important than which specific agent is chosen. The morbidity of administering excessive amounts of first- or second-line antiseizure medications is far less than the morbidity of enduring seizure activity or the adverse effects associated with prolonged treatment of SE in an ICU setting.

The ICU management of refractory SE is still largely operator-dependent. There is a pressing need for a prospective multicenter trial to determine the best of the currently available strategies for the management of refractory SE. All ED, neurology, and ICU personnel should be well versed in the initial management of SE. It behooves paramedic personnel, neurologists, and clinicians in the ED and ICU to collectively develop and implement a practical treatment algorithm applicable to their institution for the comprehensive management of SE, beginning in the community and ending in the ICU. Neurologists are ideally placed to manage SE, particularly those with a knowledge of EEG, and should be consulted early.

Because of the high morbidity and mortality associated with SE, physicians and staff must be aggressive in the management of SE. It is imperative to follow a designated therapeutic algorithm and progress to the next step in the algorithm if the current intervention is proving ineffective. Finally, surgery should be considered a potential therapeutic option in refractory focal SE.

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