Review
Journal of Epilepsy Research
pISSN 2233-6249 / eISSN 2233-6257

Diagnosis and Treatment of Status Epilepticus

Sang Kun Lee, MD, PhD

Department of Neurology, Seoul National University College of Medicine, Seoul, Korea

The definition of status epilepticus (SE) was revised recently in accordance with the various evidences of neuronal injury and changes in clinical settings. Currently, the most acceptable duration of continuous seizure activity is 5 minutes. In 2015, the International League Against Epilepsy Task Force, which was convened to develop a definition and classification of SE, presented a new classification based on four axes: 1) semiology, 2) etiology, 3) electroencephalogram (EEG) correlates, and 4) age. The essential element of nonconvulsive SE (NCSE) is the presence of neurological abnormalities induced by a prolonged epileptic process. The definition of refractory SE involves either clinical or electrographic seizures that persist after adequate doses of an initial benzodiazepine and acceptable second-line antiseizure drugs. The use of EEG is critical in the diagnosis and treatment of NCSE. However, there are a wide range of EEG abnormalities in NCSE. Both the Neurocritical Care Society and the American Epilepsy Society have suggested a paradigm for treating convulsive SE (CSE). The first-line treatment of CSE with benzodiazepine is well-established. The second-line treatment comprises intravenous (IV) doses of fosphenytoin (phenytoin), valproate, phenobarbital, levetiracetam, or midazolam. Although fosphenytoin (phenytoin) and valproate are commonly used in NCSE, the effectiveness of antiepileptic drugs (AEDs) on NCSE has not been well studied. New AEDs such as IV levetiracetam and lacosamide can also be used to treat NCSE with fewer side effects and drug-drug interactions. For refractory SE, general anesthesia with IV midazolam, propofol, pentobarbital, or thiopental could be applied. Use of ketamine, megadose phenobarbital therapy, and multiple combinations of various AEDs including high doses of oral AEDs can also be considered. New-onset refractory status epilepticus (NORSE) and its subcategory, febrile infection-related epilepsy syndrome, involve autoimmune processes. AEDs alone are poorly effective in the treatment of SE in autoimmune encephalitis. Immunotherapy such as steroids, immunoglobulin, rituximab, or tocilizumab can be effective. **(2020;10:45-54)**

Key words: Status epilepticus, Classification, Diagnosis, Treatment

Received October 14, 2020
Revised November 10, 2020
Accepted November 24, 2020

Corresponding author:
Sang Kun Lee, MD, PhD
Department of Neurology, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea
Tel. +82-2-2072-2923
Fax. +82-2-3672-7553
E-mail; sangkun2923@gmail.com

Definition and Classification

The classical definition of convulsive status epilepticus (CSE) is continuous seizure activity for at least 30 minutes, or two or more recurrent convulsive seizures with incomplete recovery of consciousness between seizures.[1] Recently, the definition of CSE was revised in accordance with the various evidences of neuronal injury and changes in clinical settings. Currently, the most acceptable duration of continuous seizure activities is 5 minutes.[2,3] In fulfilment of the revised definition and classification of status epilepticus (SE), the 2015 International League Against Epilepsy (ILAE) task force stressed that SE is either the failure of the mechanism responsible for seizure termination or the initiation of a mechanism leading to abnormally prolonged seizures, which can have long-term consequences.[4] The framework of the new classification is based on four axes: 1) semiology, 2) etiology, 3) electroencephalogram (EEG) correlates, and 4) age (Table 1).

The definition of nonconvulsive SE (NCSE) is more controversial. The most common definition is electrographic seizure activity lasting for at least 30 minutes without visible convulsive movement.[5,6] The essential element of the definition of NCSE is that neurological abnormalities are induced by a prolonged period of epileptic activity.[4] The two key components of NCSE classification are absence SE (ASE) and complex partial SE (CPSE) (Table 2).[7] NCSE can also be classified according to the age

Table 1. Classification of status epilepticus by the ILAE task force[4]

Semiology	Presence or absence of prominent motor symptoms	A. Prominent motor symptoms - Convulsive SE - Myoclonic SE - Focal motor status - Tonic status - Hyperkinetic SE
	Degree of impaired consciousness	B. Without prominent motor symptoms - NCSE with coma - NCSE without coma Generalized: Typical or atypical absence status Focal: Without impairment of consciousness (e.g., aura continua) Aphasic status With impairment of consciousness Unknown whether focal or generalized Autonomic SE
Etiology	Known	Acute (e.g., stroke, intoxication, encephalitis, etc.) Remote Progressive SE in defined electroclinical syndrome
	Unknown	Cryptogenic
EEG	Six categories of EEG terminology	Location, pattern, morphology, time-related features, modulation, effect of intervention
Age		Neonatal, infancy, childhood (>2 to 12 years), adolescence and adulthood, elderly ≥60 years

ILAE, International League Against Epilepsy; SE, status epilepticus; NCSE, nonconvulsive status epilepticus; EEG, electroencephalogram.

Table 2. Simple classification of status epilepticus

Generalized NCSE	
ASE	Atypical ASE
Typical ASE *De novo* ASE	
Partial SE	
CPSE	Simple partial SE
Frontal CPSE Temporal CPSE CPSE originated from other lobes	Epilepsia partialis continua
Subtle SE	

NCSE, nonconvulsive status epilepticus; SE, status epilepticus; ASE, absence status epilepticus; CPSE, complex partial status epilepticus.

of onset (Table 3).[8] ASE is a type of NCSE in which continuous or recurrent generalized epileptiform discharges are associated with a varying degree of consciousness impairment.[4,9] It is most commonly diagnosed in patients with known idiopathic generalized epilepsy. However, it may also be the first presentation of epilepsy. *De novo* ASE occurs in middle-aged or elderly patients without a history of epilepsy and is precipitated by systemic factors with a toxic or metabolic basis. The commonest age of these patients is in the sixth decade. Sometimes, high-dose psychotropic drugs or sudden psychotropic drug withdrawal are related to this phenomenon. In these cases, *de novo* ASE can be categorized as an acute symptomatic seizure.[10,11] NCSE with bilateral ictal discharges often presents asymmetricity. Some of these cases may represent CPSE of frontal lobe origin (ASE with focal features) and it may not be appropriate to describe them as ASE. Atypical ASE is observed in patients with symptomatic or cryptogenic generalized epilepsy such as Lennox-Gastaut syndrome.[12] CPSE can be described as having abnormalities of consciousness with or without behavioral change with lateralized epileptiform discharges.[13] The change of consciousness ranges from impairment of higher cortical function to frank coma. It is also characterized by seizures involving long-lasting stupor, staring, and unresponsiveness. This is sometimes accompanied by automatisms or focal motor phenomena, such as eye twitching.[7]

Table 3. Classification of NCSE according to age

NCSE in the neonatal and infantile epilepsy syndromes	
West syndrome	SMEI
Ohtahara syndrome	NCSE in other forms
NCSE occurring only in childhood	
Panayiotpoulos syndrome	ESES
NCSE in other forms of childhood epileptic encephalopathy	Landau-Kleffner syndrome
NCSE occurring in both childhood and adult life	
With epileptic encephalopathy	Without epileptic encephalopathy
NCSE in Lennox-Gastaut syndrome	Typical absence status epilepticus
Atypical absence status epilepticus	Complex partial status epilepticus
Tonic status epilepticus	Limbic
Other forms of NCSE with learning disability or cerebral development	Non-limbic
	NCSE in postictal phase of tonic-clonic seizures
	Subtle status epilepticus
	Aura continua

NCSE, nonconvulsive status epilepticus; SMEI, severe myoclonic epilepsy in infancy; ESES, electrical status epilepticus in sleep.

The definition of refractory SE (RSE) involves either clinical or electrographic seizures that persist after adequate doses of an initial benzodiazepine (BZD) and acceptable second-line antiseizure medication.[14] Super-refractory SE (SRSE) is seizures continuing to recur 24 hours or more after the onset of anesthetic therapy.[15] Subtle SE is the end stage of prolonged generalized tonic-clonic seizures (GTCS).[16,17] Clinical features include focal or multifocal myoclonic movements, coma, periodic lateralized epileptiform discharges (PLEDs) with low voltage background, or continuous, rapid generalized epileptiform discharges with occasional flat periods. With advancing disease, these flat periods become longer. As an advanced stage of convulsive SE, the prognosis is poor. There is a controversy whether subtle SE should be regarded as a type of NCSE.

Clinical Manifestation and Diagnosis

The clinical manifestation of CSE is overt. However, the diagnosis of NCSE is sometimes difficult and may be dependent on some important clues.[8,18] NCSE may be followed by GTCS or CSE. Some stuporous patients show subtle signs such as twitching, blinking, and nystagmus. If otherwise unexplained stupor or confusion is observed, especially in older people, a diagnosis of NCSE should be considered. Sometimes, a history of seizures and a new medical or surgical stress can also provide clues to the diagnosis of NCSE. Some stroke patients show inappropriate altered mentality not fully explained by the lesion. This condition is called "stroke plus," which suggests that its symptoms were compromised with NCSE symptoms.

The criteria for the diagnosis of NCSE are controversial.[19,20] NCSE can be summarized as a diminished level of consciousness or other neurologic deficit associated with epileptiform EEG of typical discrete seizures or continuous discharges. The response to antiepileptic drugs (AEDs) can be included in the diagnostic criteria. However, many NCSEs are refractory to AEDs both on EEG and on clinical presentation. Typical ASE has been described as an epileptic twilight state or spike-wave stupor. Three-quarters of patients are younger than 20 years of age. The onset is abrupt, without warning, and is sometimes associated with perioral or eyelid myoclonia, or limb myoclonus. Patients may be unaware of their environment with ambulatory automatism, poor communication, and variable amnesia. However, the clinical manifestations of atypical ASE present with fluctuating confusion with tonic, clonic, or sometimes focal-onset seizures. EEGs show bilateral asymmetric discharges of <3 Hz.[9]

CPSE is also known as prolonged epileptic fugue or prolonged epileptic twilight status.[21-23] The change in consciousness ranges from mild clouding to unresponsive coma. There may be recurrent complex partial seizures with incomplete clearing between events or more continuous seizure activity and obtundation. CPSE may be associated with a twilight state with amnestic reactivity, complex reactive automatism, occasional alimentary automatism, perseverative gesticulation, and vocalizations. While symptoms of CPSE and ASE overlap considerably, some semiological differences may provide clues to the correct diagnosis. The cyclicity of semiology and the presence of fear, anxiety, irritability, aggression, and complex automatism favor the diagnosis of CPSE. Lip smacking, lateralized automatism, eye devia-

tion, and nystagmus are also usually associated with CPSE. However, total unresponsiveness, speech arrest, cyclic behavior, and stereotypic nonlateralized automatism may also be present in both CPSE and ASE.[9,24] The categorization based on the clinical characteristics of patients such as the level of consciousness and ability to ambulate may sometimes be helpful to decide the urgency or the best types of drug to treat SE (Fig. 1).

The use of the EEG is critical in the diagnosis and treatment of NCSE. However, there are a wide range of EEG abnormalities in NCSE. Sometimes less-prominent semirhythmic slowing is the only EEG finding in NCSE. Some EEG findings are more suggestive of NCSE, while others are less suggestive (Fig. 2).[19,20,25,26] The typical finding is focal or generalized spike-and-slow activity that usually waxes and wanes at a frequency of >2 Hz. Localized rhythmic delta and theta activity are also frequently found. While triphasic waves are the marker of metabolic encephalopathy, they also indicate the presence of NCSE.[27] The response of triphasic waves to BZD may be helpful in the differential diagnosis between metabolic encephalopathy and NCSE. However, triphasic waves can be suppressed by BZD, even in metabolic encephalopathy. PLEDs on EEG classically suggest an acute destructive brain lesion. Triphasic waves can also be caused by the ictal rhythm itself. PLEDs are periodic epileptiform discharges, usually at a frequency of <1 Hz, often every 1-2 seconds, some with intervals up to 10 seconds. Nine out of 10 patients have clinical seiz-

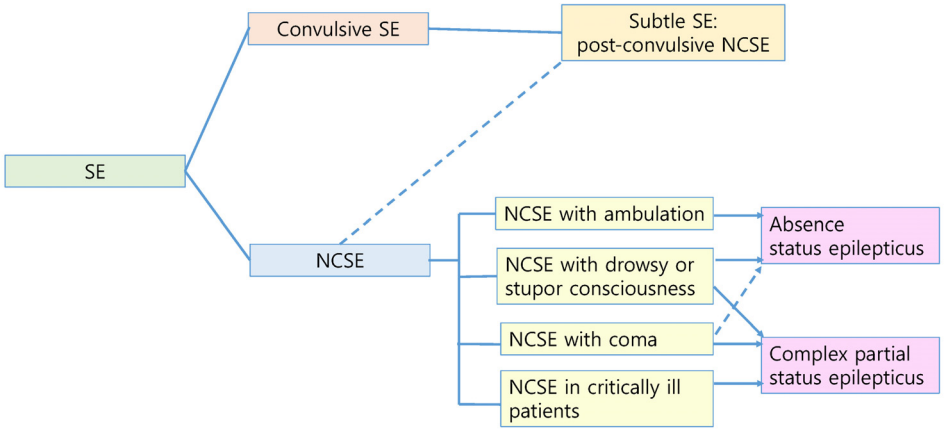

Figure 1. Categorization of SE according to the patient's status, such as level of consciousness and ability to ambulate. SE, status epilepticus; NCSE, nonconvulsive status epilepticus.

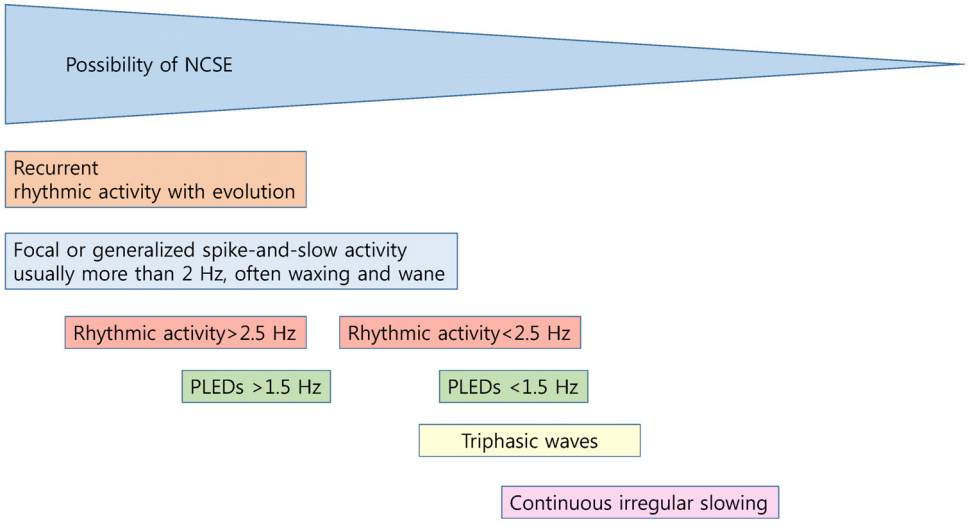

Figure 2. EEG of NCSE showing the increasing possibility of NCSE when approaching the left end. NCSE, nonconvulsive status epilepticus; EEG, electroencephalogram; PLED, periodic lateralized epileptiform discharge.

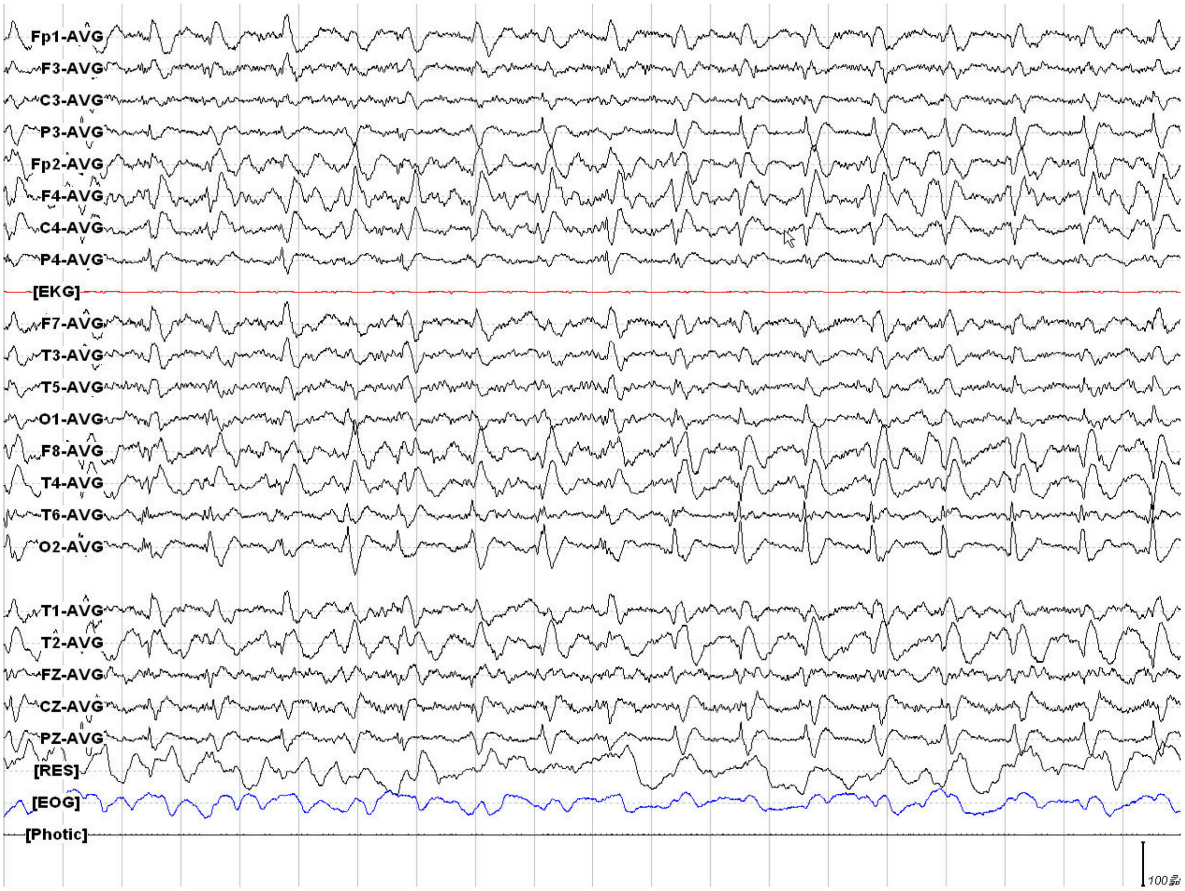

Figure 3. Example of periodic lateralized epileptiform discharges. See the periodic sharp waves at the frequency of 1 Hz in the right posterior area.

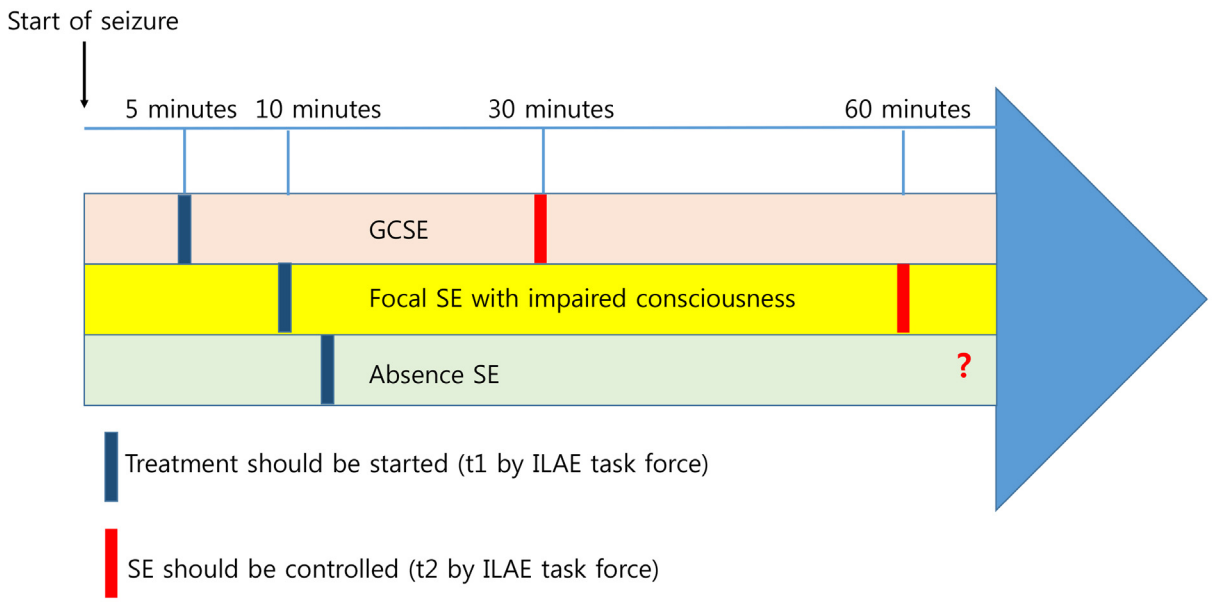

Figure 4. Acceptable time of initial treatment for various SE types recommended by the ILAE task force.[4] GCSE, generalized convulsive status epilepticus; SE, status epilepticus; ILAE, International League Against Epilepsy.

ures, usually a few days before the EEG is taken, and two-thirds had some form of SE before the appearance of PLEDs.[28,29] They may not have a manifestation of seizures at the time. Notably, more rapid periodic discharges are typically seen in acute clinical seizures (>1 Hz or >1.5 Hz) although there is no absolute frequency criterion (Fig. 3).

Various conditions can mimic NCSE:[13,30] e.g., neurologic disorders, such as mitochondrial encephalopathy, transient global amnesia, posttraumatic amnesia, complex migraine, and vascular disorders; toxic and metabolic conditions, such as toxic and metabolic encephalopathy, alcohol withdrawal symptoms, hypo- or hyperglycemia, neuroleptic malignant syndrome, serotonin syndrome; and various drug intoxication and psychiatric conditions, such as psychiatric nonepileptic seizures.

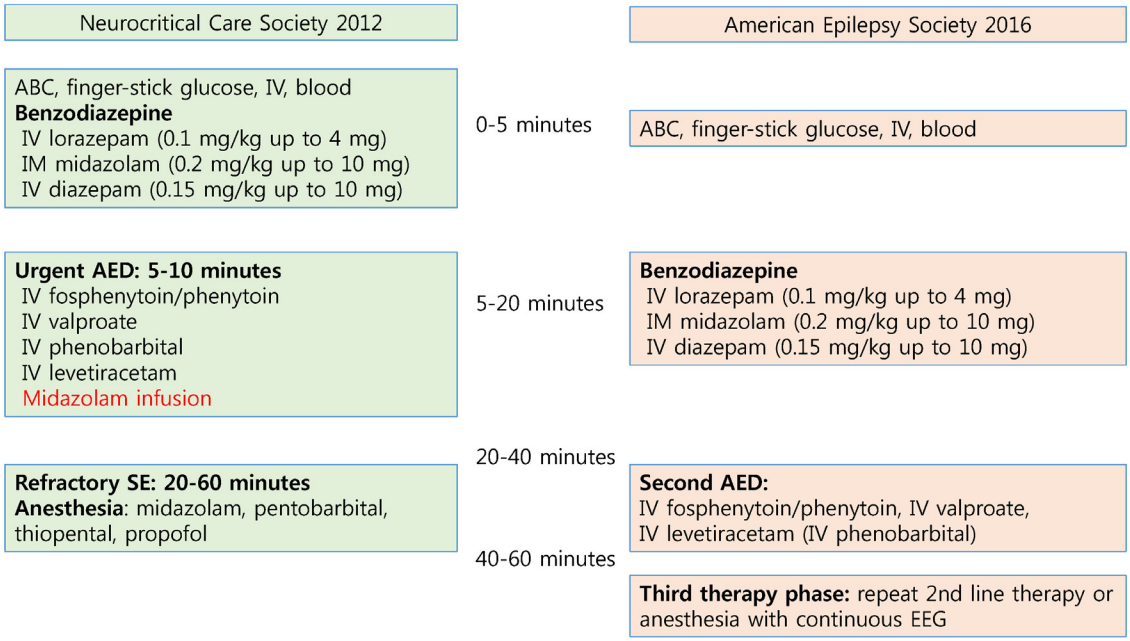

Figure 5. Treatment algorithm for convulsive status epilepticus by the Neurocritical Care Society and the American Epilepsy Society.[31,32] ABC, airway, breathing, circulation; IV, intravenous; AED, antiepileptic drug; SE, status epilepticus; IM, intramuscular; EEG, electroencephalogram.

Table 4. Recommended dose of AEDs in CSE

Drugs	Neurocritical Care Society	American Epilepsy Society
Lorazepam	0.1 mg/kg up to 4 mg	0.1 mg/kg up to 4 mg
Midazolam	0.2 mg/kg up to 10 mg	10 mg if >40 Kg
Midazolam continuous infusion	0.2 mg/kg; infusion rate 2 mg/min	
Diazepam	0.15 mg/kg up to 10 mg	0.15-0.2 mg/kg up to 10 mg
Fosphenytoin/phenytoin	20 mg/kg phenytoin equivalent	20 mg/kg phenytoin equivalent up to 1,500 mg
Valproate	20-40 mg/kg	40 mg/kg up to 3,000 mg
Phenobarbital	20 mg/kg	15 mg/kg
Levetiracetam	1,000-3,000 mg	60 mg/kg up to 4,500 mg
Pentobarbital	5-15 mg (5-10 mg additional dose); infusion rate ≤50 mg/min	
Propofol	1-2 mg/kg; infusion rate 20 mcg/kg/min	
Thiopental	2-7 mg/kg; infusion rate ≤50 mg/min	

AED, antiepileptic drug; CSE, convulsive status epilepticus.

Treatment

Although clear features have not been identified, especially in NCSE, much experimental evidence indicates that irreversible brain damage arises after prolonged seizures. As a result, the 2015 ILAE task force recommended the 5-minute time point for the start of treatment (Fig. 4).[4]

Treatment of CSE

Both the Neurocritical Care Society and the American Epilepsy Society (AES) have suggested a paradigm to treat CSE (Fig. 5, Table 4).[31,32] These two paradigms share almost identical frameworks that recommend similar AEDs with only slight differences in the administered dose. The AES recommends a time difference in dosing based on evidence derived from real-world situations.

The first-line treatment of CSE with BZD is well-established. The second-line treatment comprises intravenous (IV) fosphenytoin (phenytoin), valproate, phenobarbital, levetiracetam, or midazolam. Several studies have compared the efficacy of various AEDs in this situation (Table 5).[33-38] IV lorazepam was superior to IV phenytoin for the control of CSE in a randomized controlled trial.[33] IV lorazepam and diazepam showed equal efficacy,[34] although lorazepam was favored because of its prolonged binding to GABA receptors. Midazolam was superior to lorazepam in one study, probably because of the shorter injection time of midazolam.[35] IV levetiracetam was equally effective as IV lorazepam. Meta-analysis showed that IV valproate, phenobarbital, and levetiracetam were superior to IV phenytoin.[36,37] Children, adults, and older adults with established SE respond similarly to phenytoin, valproate, and levetiracetam (about 50%) in prospective randomized controlled trials. Levetiracetam and fosphenytoin were equally effective in the prevention of recurrent seizures after the control of CSE.[38] Midazolam given via the intranasal, buccal, or intramuscular route may be as safe and effective as IV or rectal diazepam in terminating early-onset SE in children and potentially in adults.[39]

Treatment of NCSE

There is no universal consensus about how aggressively to treat NCSE. The etiology of NCSE is the most important prognostic factor in this disease.[40] As a result, it is difficult to assess the effect of NCSE alone on neuronal damage in human subjects. However, there is much evidence in animal models of neuronal damage in prolonged NCSE.[41,42] The treatment paradigm is similar to CSE. In addition, when or how to apply anesthetic treatment of refractory NCSE is controversial.

Although fosphenytoin (phenytoin) and valproate are commonly used in NCSE,[43] the effectiveness of AEDs on NCSE has not been well studied. New AEDs such as IV levetiracetam and lacosamide can also be used to treat NCSE with fewer side effects and fewer drug-drug interactions. The efficacy of lacosamide (usually 200-400 mg, IV) to treat SE has been assessed by systemic review[43] and was found to be 61% for CSE and 57% for NCSE. The effectiveness of lacosamide to treat recurrent electrographic nonconvulsive seizure was compared with fosphenytoin (IV lacosamide 400 mg vs. fosphenytoin 20 mg; phenytoin equivalent/kg). This was a noninferiority, prospective, multicenter, randomized controlled trial that found lacosamide to be superior to fosphenytoin (63.3% vs. 50%) in preventing seizure re-

Table 5. AED comparison in the treatment of CSE

Study	AEDs	Results (efficacy)
US Department of VA cooperative study:[33] RCT	IV lorazepam 0.1 mg/kg vs. IV phenytoin	Lorazepam > phenytoin
Leppik et al.[34] (double blind study)	IV diazepam 10 mg vs. IV lorazepam 4 mg	Equal efficacy (diazepam 76% vs. lorazepam 89%)
RAMPART[35]	10 mg midazolam vs. 4 mg lorazepam	Midazolam > lorazepam (probably rate dependent)
Yasiry and Shorvon[36] (meta-analysis)	IV valproate, IV phenobarbital, IV levetiracetam, IV phenytoin (BZD refractory CSE)	VPA (75.7%), phenobarbital (73.6%), levetiracetam (68.5%) > phenytoin (50%)
ESETT (ongoing):[37] prospective RCT	Phenyoint, vlaporate, levetiracetam (BZD refractory CSE)	
Nakamura et al.[38]	Recurred seizure after control of SE by BZD: levetiracetam vs. fosphenytoin	Equal efficacy

AED, antiepileptic drugs; CSE, convulsive status epilepticus; RCT, randomized controlled trial; IV, intravenous; BZD, benzodiazepine; VPA, valproic acid; SE, status epilepticus.

currence (p=0.02).[44]

Treatment of RSE and SRSE

For RSE, general anesthesia with IV midazolam, propofol, pentobarbital, or thiopental is recommended (Fig. 6). Continuous EEG monitoring is mandatory. When RSE is not controlled after 24-hour use of anesthesia, other options are available. Ketamine,[45] megadose phenobarbital[46] therapy, and multiple combinations of various AEDs including high-dose oral AEDs can be considered.[47-49] Oral AEDs such as topiramate, oxcarbazepine, and perampanel can also be used with a loading or high dose (Table 6).

The effect of BZD or other GABA agonists to control RSE is limited because GABA receptor internalization occurs[50,51] after repeated seizures or continuous SE, which makes it impossible for GABA agonists to reach their receptors. High-dose phenobarbital may clear this hurdle. The advantage of megadose phenobarbital therapy is that less respiratory depression occurs compared with other anesthetic

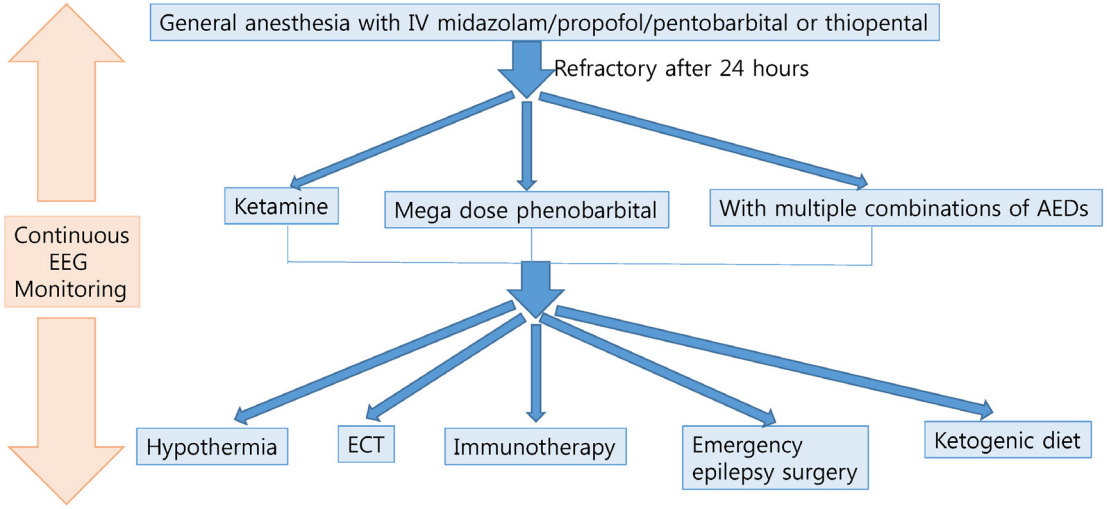

Figure 6. Suggested treatment algorithm for refractory status epilepticus and super-refractory status epilepticus. IV, intravenous; EEG, electroencephalogram; AED, antiepileptic drugs; ECT, electroconvulsive therapy.

Table 6. Oral antiepileptic drugs used in status epilepticus

AEDs	Loading dose	Peak level after a single dose
Topiramate	400-800 mg	1.5-2 hours
Oxcarbazepine (MHD)	30 mg/kg	5-6 hours (therapeutic range within 2 hours)
Perampanel	4-32 mg	0.25-2 hours

AED, antiepileptic drugs; MHD, monohydroxy derivatives.

Table 7. Other treatment options

Method	Consideration
Ketamine	Early use may have better prognosis
Isoflurane	No sustained effect
Ketogenic diet	Difficult compliance
Hypothermia	Coagulation disorders
Electroconvulsive therapy	
Mega dose phenobarbital	
Epilepsy surgery: focal resection	

therapy; therefore, it is suitable for long term use. Other special methods can also be considered for SRSEs that are resistant to these treatments, including application of hypothermia; electroconvulsive therapy; ketogenic diet; and emergency epilepsy surgery (Table 7).

Immunotherapy

Autoimmune processes have a vital role to play in SE. For example, some viral infections of the central nervous system can result in SE. Furthermore, the etiology of a recent increase in the number of SE cases can be explained by autoimmune encephalitis.[52] Two special circumstances of SE are closely aligned with autoimmune processes.[53-55] New-onset refractory SE (NORSE) is a clinical presentation that occurs in patients without active epilepsy or other preexisting relevant neurological disorder and no clear acute or active structural, toxic or metabolic disorder. Febrile infection-related epilepsy syndrome is a subcategory of NORSE. In both cases, a preceding febrile infection starts between 2 weeks and 24 hours before the onset of RSE. Other features suggesting an autoimmune etiology include acute or subacute onset, a history of preceding infection or trauma, the presence of anti-GABA A receptor antibodies, and a progressive course not responding to standard AEDs, but responsive to immunotherapy.

AEDs alone are largely ineffective in the treatment of SE in autoimmune encephalitis. Immunotherapy such as steroid, immunoglobulin, rituximab, or tocilizumab can be effective. In one study of six patients, NORSE was treated, without recurrence with one or two doses of tocilizumab with a median interval of 3 days from initiation.[56]

References

1. Treatment of convulsive status epilepticus. Recommendations of the epilepsy foundation of America's working group on status epilepticus. *JAMA* 1993;270:854-9.
2. Lowenstein DH, Bleck T, Macdonald RL. It's time to revise the definition of status epilepticus. *Epilepsia* 1999;40:120-2.
3. Brophy GM, Bell R, Classen J, et al. Guidelines for the evaluation and management of status epilepticus. *Neurocrit Care* 2012;17:3-23.
4. Trinka E, Cock H, Hesdorffer D, et al. A definition and classification of status epilepticus--report of the ILAE task force on classification of status epilepticus. *Epilepsia* 2015;56:1515-23.
5. Walker M, Cross H, Smith S, et al. Nonconvulsive status epilepticus: Epilepsy Research Foundation workshop reports. *Epileptic Disord* 2005; 7:253-96.
6. Husain AM. Treatment of recurrent electrographic nonconvulsive seizures (TRENdS) study. *Epilepsia* 2013;54 Suppl 6:84-8.
7. Kaplan PW. Clinical presentations of nonconvulsive status epilepticus. In: Drislane FW, Kaplan PW, eds. *Status epilepticus: a clinical perspective*. 2nd ed. New York: Springer Nature, 2018;241-58.
8. Drislane FW. Presentation, evaluation, and treatment of nonconvulsive status epilepticus. *Epilepsy Behav* 2000;1:301-14.
9. Thomas P, Zifkin B, Andermann F. Absence status. In: Wasterlain CG, Treiman DM, eds. *Status epilepticus: mechanisms and management*. Cambridge: MIT Press, 2006;91-108.
10. Thomas P, Andermann F. Absence status in elderly patients is most often situation-related. In: Malfosse A, Genton P, Hirsch E, Marescaux C, Broglin D, Bernasconi R, eds. *Idiopathic generalized epilepsies: clinical, experimental and genetic aspects*. UK ed. London: John Libbey, 1994; 95-109.
11. Thomas P, Beaumanoir A, Genton P, Dolisi C, Chatel M. 'De novo' absence status of late onset: report of 11 cases. *Neurology* 1992;42:104-10.
12. Thomas P, Zifkin B, Migneco O, Lebrun C, Darcourt J, Andermann F. Nonconvulsive status epilepticus of frontal origin. *Neurology* 1999;52: 1174-83.
13. Kaplan PW. Behavioral manifestations of nonconvulsive status epilepticus. *Epilepsy Behav* 2002;3:122-39.
14. Bleck TP. Refractory status epilepticus. *Curr Opin Crit Care* 2005;11:117-20.
15. Shorvon S, Ferlisi M. The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. *Brain* 2011;134(Pt 10):2802-18.
16. Rai S, Drislane FW. Treatment of refractory and super-refractory status epilepticus. *Neurotherapeutics* 2018;15:697-712.
17. Meierkord H, Boon P, Engelsen B, et al. EFNS guideline on the management of status epilepticus in adults. *Eur J Neurol* 2010;17:348-55.
18. Shorvon S. What is nonconvulsive status epilepticus, and what are its subtypes? *Epilepsia* 2007;48 Suppl 8:35-8.
19. Herman ST. The electroencephalogram of nonconvulsive status epilepticus. In: Kaplan PW, Drislane FW, eds. *Nonconvulsive Status Epilepticus*. New York: Demos Medical Publishing, 2009;41-62.
20. Young GB, Jordan KG, Doig GS. An assessment of nonconvulsive seizures in the intensive care unit using continuous EEG monitoring: an investigation of variables associated with mortality. *Neurology* 1996;47:83-9.
21. Mikati MA, Lee WL, DeLong GR. Protracted epileptiform encephalopathy: an unusual form of partial complex status epilepticus. *Epilepsia* 1985; 26:563-71.
22. Markand ON, Wheeler GL, Pollack SL. Complex partial status epilepticus (psychomotor status). *Neurology* 1978;28:189-96.
23. Ballenger CE 3rd, King DW, Gallagher BB. Partial complex status epilepticus. *Neurology* 1983;33:1545-52.
24. Thomas P, Zifkin B, Andermann F. Simple and complex partial status epilepticus. In: Wasterlain CG, Treiman DM, eds. *Status Epilepticus: Mechanisms and Management*. Cambridge: MIT Press, 2006;69-90.
25. Chong DJ, Hirsch LJ. Which EEG patterns warrant treatment in the critically ill? Reviewing the evidence for treatment of periodic epileptiform dis-

charges and related patterns. *J Clin Neurophsiol* 2005;22:79-91.
26. Kaplan PW. The EEG of status epilepticus. *J Clin Neurophysiol* 2006;23: 221-9.
27. Brigo F, Storti M. Triphasic waves. *Am J Electroneurodiagnostic Technol* 2011;51:16-25.
28. Snodgrass SM, Tsuburaya K, Ajmone-Marsan C. Clinical significance of periodic lateralized epileptiform discharges: relationship with status epilepticus. *J Clin Neurophysiol* 1989;6:159-72.
29. Brenner RP. Is it status? *Epilepsia* 2002;43 Suppl 3:103-13.
30. Navarro V, Fischer C, Convers P. Differential diagnosis of status epilepticus. *Rev Neurol (Paris)* 2009;165:321-7.
31. Brophy GM, Bell R, Claassen J, et al. Guidelines for the evaluation and management of status epilepticus. *Neurocrit Care* 2012;17:3-23.
32. Glauser T, Shinnar S, Gloss D, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the guideline committee of the American Epilepsy Society. *Epilepsy Curr* 2016;16:48-61.
33. Treiman DM. The role of benzodiazepines in the management of status epilepticus. *Neurology* 1990;40(5 Suppl 2):32-42.
34. Leppik IE, Derivan AT, Homan RW, Walker J, Ramsay RE, Patrick B. Double-blind study of lorazepam and diazepam in status epilepticus. *JAMA* 1983;249:1452-4.
35. Silbergleit R, Lowenstein D, Durkalski V, Conwit R; Neurological Emergency Treatment Trials (NETT) Investigators. RAMPART (rapid anticonvulsant medication prior to arrival trial): a double-blind randomized clinical trial of the efficacy of intramuscular midazolam versus intravenous lorazepam in the prehospital treatment of status epilepticus by paramedics. *Epilepsia* 2011;52 Suppl 8:45-7.
36. Yasiry Z, Shorvon SD. The relative effectiveness of five antiepileptic drugs in treatment of benzodiazepine-resistant convulsive status epilepticus: a meta-analysis of published studies. *Seizure* 2014;23:167-74.
37. Chamberlain JM, Kapur J, Shinnar S, et al. Efficacy of levetiracetam, fosphenytoin, and valproate for established status epilepticus by age group (ESETT): a double-blind, responsive-adaptive, randomised controlled trial. *Lancet* 2020;395:1217-24.
38. Nakamura K, Inokuchi R, Daidoji H, et al. Efficacy of levetiracetam versus fosphenytoin for the recurrence of seizures after status epilepticus. *Medicine (Baltimore)* 2017;96:e7206.
39. Brigo F, Nardone R, Tezzon F, Trinka E. Nonintravenous midazolam versus intravenous or rectal diazepam for the treatment of early status epilepticus: a systematic review with meta-analysis. *Epilepsy Behav* 2015; 49:325-36.
40. Power KN, Gramstad A, Gilhus NE, Engelsen BA. Adult nonconvulsive status epilepticus in a clinical setting: semiology, aetiology, treatment and outcome. *Seizure* 2015;24:102-6.
41. Olney JW, Collins RC, Sloviter RS. Excitotoxic mechanisms of epileptic brain damage. *Adv Neurol* 1986;44:857-77.
42. Meldrum BS. Excitotoxicity and selective neuronal loss in epilepsy. *Brain Pathol* 1993;3:405-12.
43. Strzelczyk A, Zöllner JP, Willems LM, et al. Lacosamide in status epilepticus: systematic review of current evidence. *Epilepsia* 2017;58: 933-50.
44. Husain AM, Lee JW, Kolls BJ, et al. Randomized trial of lacosamide versus fosphenytoin for nonconvulsive seizures. *Ann Neurol* 2018;83:1174-85.
45. Rosati A, De Masi S, Guerrini R. Ketamine for refractory status epilepticus: a systematic review. *CNS Drugs* 2018;32:997-1009.
46. Byun JI, Chu K, Sunwoo JS, et al. Mega-dose phenobarbital therapy for super-refractory status epilepticus. *Epileptic Disord* 2015;17:444-52.
47. Kim DW, Gu N, Jang IJ, et al. Efficacy, tolerability, and pharmacokinetics of oxcarbazepine oral loading in patients with epilepsy. *Epilepsia* 2012; 53:e9-12.
48. Fechner A, Hubert K, Jahnke K, et al. Treatment of refractory and super-refractory status epilepticus with topiramate: a cohort study of 106 patients and a review of the literature. *Epilepsia* 2019;60:2448-58.
49. Ho CJ, Lin CH, Lu YT, et al. Perampanel treatment for refractory status epilepticus in a neurological intensive care unit. *Neurocrit Care* 2019; 31:24-9.
50. Walker MC. Pathophysiology of status epilepticus. *Neurosci Lett* 2018; 667:84-91.
51. Arya R, Rotenberg A. Dietary, immunological, surgical, and other emerging treatments for pediatric refractory status epilepticus. *Seizure* 2019; 68:89-96.
52. Spatola M, Novy J, Du Pasquier R, Dalmau J, Rossetti AO. Status epilepticus of inflammatory etiology: a cohort study. *Neurology* 2015;85: 464-70.
53. Sculier C, Gaspard N. New onset refractory status epilepticus (NORSE). *Seizure* 2019;68:72-8.
54. Gaspard N, Hirsch LJ, Sculier C, et al. New-onset refractory status epilepticus (NORSE) and febrile infection-related epilepsy syndrome (FIRES): state of the art and perspectives. *Epilepsia* 2018;59:745-52.
55. Hirsch LJ, Gaspard N, van Baalen A, et al. Proposed consensus definitions for new-onset refractory status epilepticus (NORSE), febrile infection-related epilepsy syndrome (FIRES), and related conditions. *Epilepsia* 2018;59:739-44.
56. Jun JS, Lee ST, Kim R, Chu K, Lee SK. Tocilizumab treatment for new onset refractory status epilepticus. *Ann Neurol* 2018;84:940-5.