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Status epilepticus in adults: a clinically oriented review of etiologies, diagnostic challenges, and therapeutic advances

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Abstract

Status epilepticus (SE) is a neurological emergency associated with a high mortality rate. Collaborative efforts have been made to establish standardized definitions, classifications, and treatment protocols to improve management and reduce mortality. In 2015, the International League Against Epilepsy (ILAE) developed a new definition and classification system for SE, taking into account the pathophysiology of SE and setting time points for treatment decision-making, while considering the variability in seizure semiology.

Timely identification of the underlying cause of SE would facilitate more targeted treatment, as almost half of all SE cases require specific therapy for the underlying cause in addition to providing symptomatic treatment.

A stepwise algorithm for seizure management is proposed, with the initial stage involving the administration of benzodiazepines (BZD), followed by the use of non-sedating anti-seizure medications (ASM) as the second line of treatment. The decision to resort to therapeutic coma is made on a case-by-case basis, as most invasive treatments may not always be the best approach.

This comprehensive review provides an overview of SE and its definition, pathophysiology, diagnostic challenges, and recent treatment advances.

Keywords
Seizures · Emergency · Treatment protocol · Physiopathology · Diagnostics

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Introduction

Status epilepticus (SE) is the second most common neurological emergency following ischemic stroke [1]. Its incidence rate varies among countries, ranging from 4.6 to 41 per 100,000 per year [2]. Mortality rates in adults with SE can reach 30% [2]. The discrepancy in the epidemiological data is partly explained by the great variety of study designs and inclusion criteria. Prompt recognition and urgent treatment are thus necessary to reduce morbidity and mortality [1].

In this updated review, we provide an overview of the SE definition, physiopathology, diagnostic challenges, and recent treatment advances.

Definition

Because of the high mortality rate related to SE and in order to optimize management, concerted efforts have been made to standardize the definition, classification, and treatment protocols [2].

The American Epilepsy Society defined SE as either continuous seizure activity lasting more than 5 min or the occurrence of two or more sequential seizures without complete recovery of consciousness between them [3]. A few years earlier, the Neurocritical Care Society provided a def-

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inition for SE as "ongoing clinical or electrographic activity," specifying that SE is characterized by either "(i) continuous clinical and/or electrographic seizure activity lasting 5 min or more" or "(ii) recurrent seizure activity without recovery between seizures" [4]. The inadequacy of both definitions lies in their failure to account for the various types of SE, such as non-convulsive, focal, and absence seizures. In 2015, the International League Against Epilepsy (ILAE) formed a task force consisting of the Commission on Classification and Terminology and the Commission on Epidemiology to develop a new definition and classification system for SE [5]. As a result, a new definition was proposed stating that SE arises from either the failure of mechanisms responsible for terminating seizures or the activation of mechanisms that lead to abnormally prolonged seizures (after time point t1). This condition can result in long-term consequences (after time point t2), such as neuronal death, neuronal injury, and disruption of neuronal networks, which vary depending on the type and duration of the seizures. This definition considers the pathophysiology of SE and sets the time points for treatment decision-making, with t1 defining the time of treatment initiation and t2 addressing the aggressiveness of the treatment approach required to prevent long-term consequences. The time points (t1 and t2) vary according to the type of seizure ([5]; ◘ **Fig. 1**).

Abbreviations

ASM	Anti-seizure medication
BRV	Brivaracetam
BZD	Benzodiazepines
CLZ	Clonazepam
DZP	Diazepam
EEG	Electroencephalogram
FIRES	Febrile-infection-related epilepsy syndrome
fPHT	Fosphenytoin
GABA	γ-Aminobutyric acid
GAD	Antibodies against glutamate decarboxylase
GCSE	Generalized convulsive status epilepticus
ILAE	International League Against Epilepsy
IM	intramuscular
IV	intravenous
LCM	Lacosamide
LEV	Levetiracetam
LGI1	Leucine-rich glioma-inactivated 1
LZP	Lorazepam
MDZ	Midazolam
NCSE	Non-convulsive status epilepticus
NMDA	*N*-methyl-*d*-aspartate
NORSE	New-onset refractory status epilepticus
PER	Perampanel
RSE	Refractory status epilepticus
SE	Status epilepticus
VPA	Valproate

In the same effort, a novel diagnostic classification system for SE has been suggested, aiming to guide the clinical diagnosis, investigation, and treatment of each patient. According to the ILAE, SE characterization should follow a four-axis approach. The axes include semiology, etiology, electroencephalogram (EEG) correlates, and age ([5]; ◘ **Table 1**). Semiologic assessment and patient age are easily evaluated, while the identification of etiology may require more time. The EEG recordings may not always be available, especially during the initial presentation. Nonetheless, EEG patterns significantly impact treatment and prognosis, so that early testing is recommended. Although some experts propose that determining the "clinical context"— such as SE occurring in individuals with no history of epilepsy or in those with epilepsy, may be more critical than identifying the etiology to facilitate a faster diagnostic evaluation and management [5]—it is important to remember that up to 42% of SE episodes might require a specific treatment targeting its etiology [6].

Pathophysiology

The pathophysiology of SE involves several mechanisms that ultimately lead to neuronal injury and death. Animal studies showed that prolonged convulsive seizures lead to modifications in bodily functions such as significant alterations in blood pressure, heart rate, respiratory performance, electrolyte levels, blood sugar, and body temperature [7, 8]. During the initial phase of convulsive SE, the cerebral blood flow increases, accompanied by tachycardia, higher blood pressure, and dilation of cerebral blood vessels [8]. Although glycemia increases initially, there is a subsequent surge in lactate levels and acidosis due to the greater demand for energy, leading to increased anaerobic metabolism [8]. In non-human primates, compensatory mechanisms gradually fail about 20–40 min after the onset of convulsive SE [8]. This leads to a progressive decline in blood pressure, cerebral perfusion, brain oxygenation, and glycemia. At this point, non-mechanically ventilated primates are at risk of frequent arrhythmias and cardiovascular collapse [8]. According to the literature available on the physiological changes that occur during prolonged seizures and convulsive SE, it appears that humans experience compensatory responses that are comparable to those observed in animal models [9].

In non-human primates, the cortex, cerebellum, and hippocampus are susceptible to lesions caused by prolonged convulsive seizures, which exhibit a similar pattern to that observed in cases of circulatory arrest, systemic hypotension, or hypoglycemia [10]. Although some neuronal damage occurs as a result of physiological dysregulation, injury can also occur in a physiologically stable but seizing brain. The excessive activation of glutamate receptors and subsequent Ca^{2+} influx into the neuron caused by epileptic activity alone can result in neuronal injury and death [11].

At the level of neurotransmitters, different research groups reported that prolonged seizures or seizure-like activity leads to the internalization and subsequent reduction of γ-aminobutyric acid B (GABA$_A$) receptors in the synapse [9]. The internalization process of GABA$_A$ receptors was shown to be modulated by neuronal activity, with recurrent bursting enhancing it and blockade of neuronal activity reducing it. This internalization was associated with a decreased response to GABA, while inhibition of internalization was linked to an increased response to GABA. Conversely, *N*-methyl-*d*-aspartate (NMDA) receptors were found to accumulate in the synapse during SE. This resulted in a progressive decrease in functionally active GABA$_A$ receptors and an increase in functionally active NMDA receptors in the postsynaptic membrane soon after the onset of SE. These findings might clarify the gradual pharmacoresistance to GABA$_A$ receptor allosteric modulators and the increasing pharmacosensitivity to NMDA

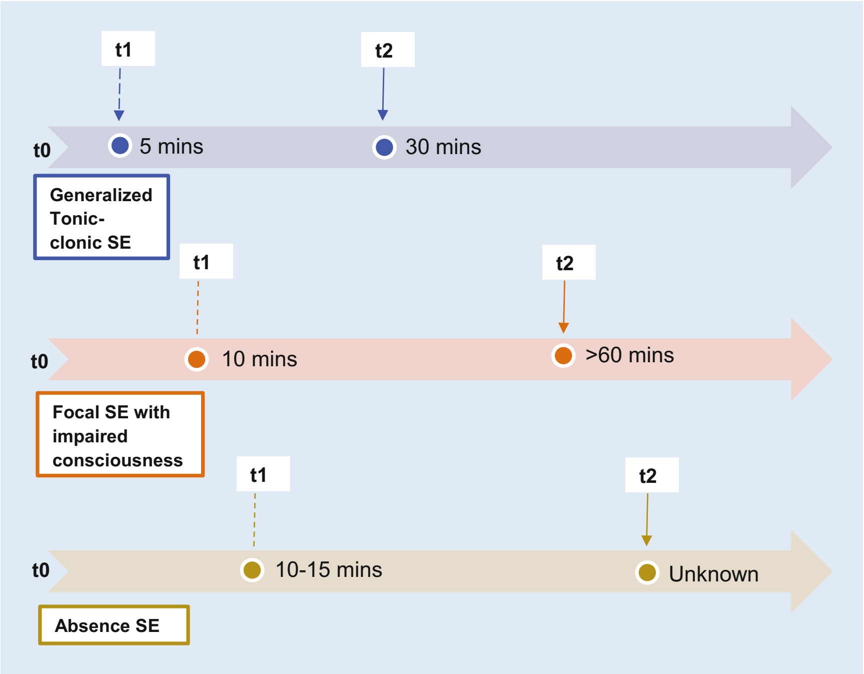

Fig. 1 ▲ Definition of status epilepticus (*SE*) with two operational dimensions according to the 2015 ILAE definition (adapted from Trinka et al., 2015). *t0* Seizure onset; *t1* Operational dimension 1 Time (*t1*), when a seizure is likely to be prolonged leading to continuous seizure activity; *t2* Operational dimension 2 Time (*t2*), when a seizure may cause long term consequences (including neuronal injury, neuronal death, alteration of neuronal networks and functional deficits)

antagonists observed in animal models [9].

Clinical manifestations

The classification of SE can be based on its semiology, duration, and underlying etiology. Since SE is defined basically as a prolonged seizure, there can be as many forms of SE as there are types of seizures. To simplify and emphasize the severe form of SE, the Neurocritical Care Society proposed a classification based on two semiology criteria: the presence or absence of motor symptoms and the retention or impairment of consciousness [4].

Generalized convulsive status epilepticus (GCSE) is characterized by tonic–clonic movements of the extremities and impairment of mental status, such as coma, confusion, or lethargy [4]. Focal neurological deficits can be observed in the postictal period. Convulsive SE makes up 37–70% of all forms of SE [12].

Non-convulsive status epilepticus (NCSE) is characterized by seizure activity detected on an EEG, but without observable prominent motor symptoms. This type of SE is complex since there are several types ranging from an "absence SE" to an "NCSE in coma" complicating a severe brain injury [13]. Furthermore, NCSE might also be seen after uncontrolled GCSE and is common in the intensive care setting [4]. It is important to recognize all NCSE subtypes such as absence, aphasic, autonomic, and subtle SE because each requires a different management approach and might be related to very different outcome. However, they all require the use of EEG for diagnosis.

Patients who fail to respond to standard treatment regimens for SE are considered to have refractory SE (RSE), which involves appropriate doses of an initial benzodiazepine (BZD) followed by an ASM [4].

Super-refractory SE is defined as "status epilepticus that continues 24 h or more after the onset of anesthesia, including those cases in which the status epilepticus recurs on the reduction or withdrawal of anesthesia" [14].

Etiology

While ASM have been widely studied for their ability to stop seizures, it is also crucial to promptly diagnose and address any underlying causes. Various underlying factors, such as alcohol withdrawal or intoxication, infections, severe metabolic disturbances, cerebrovascular events, and brain tumor-related events require immediate and specific treatment beyond ASMs. A timely identification of the underlying cause of seizure activity would facilitate more targeted treatment [6].

Trinka and colleagues proposed in the second axis of the classification system for SE a categorization of the underlying causes, making it easier for physicians from different specialties to communicate with one another [5]. The etiology of SE is divided into two groups: (i) known or symptomatic, and (ii) unknown or cryptogenic.

Within the symptomatic group, the cause can be acute symptomatic, remote symptomatic, or progressive symptomatic, depending on the temporal relationship between the cause and the onset of SE [5, 15]. The known disorder can be caused by a structural, metabolic, inflammatory, infectious, toxic, or genetic factors ([5]; ◘ **Fig. 2**).

Acute symptomatic causes are the leading etiologies, making up approximately 48–63% of all SE. Among these cases, stroke emerges as the leading cause, accounting for 14–22% of SE in adults. Furthermore, in older adults, prior strokes play a significant role as a contributing factor [16].

Overall, a significant proportion of patients diagnosed with SE have a prior history of epilepsy, ranging from 30% to 44% [17]. Also, SE may occur in individuals who have previously been diagnosed with epilepsy or in those who experience it as their first symptom (sometimes called "de novo SE"). Among adults with a history of epilepsy, the primary cause of SE is typically low levels of ASM.

In most cases of SE, the underlying cause can be determined. However, there is a subset of cases, roughly 5%, where the cause cannot be identified despite a comprehensive work-up [6]. This category is now referred to as "cryptogenic SE" in the updated ILAE classification system.

Table 1 Most common etiologies of SE in adults (adapted from Outin et al., 2020)

SE in patients with known epilepsy	
ASM related (non-compliance)	16–35%
Unprovoked seizure	15%
Alcohol or BZD withdrawal	5–20%
Brain tumor	14%
Cerebrovascular disease (remote or acute)	8–14%
Metabolic or toxic	4–15%
Systemic infection	5–7%
Traumatic brain injury sequelae	5%
CNS infection	3%
De novo SE	
Cerebrovascular disease (remote or acute)	32%
Brain tumor	3–18% (5%)
Drug intoxication	5–20%
Unknown etiology	5–10%
Alcohol or BZD withdrawal	6–10%
Metabolic or toxic	6–10%
Traumatic brain injury (acute phase)	7%
CNS infection	5–9%
Inflammatory disease (Including autoimmune)	6%
Undetermined cause	5%
Systemic infection	2%
Neurodegenerative disease	2%

ASM anti-seizure medications, *BZD* benzodiazepines *CNS* central nervous system, *SE* status epilepticus

The term “unknown origin” or “cryptogenic” is used in its original sense of having an unknown cause, without presuming it to be symptomatic or genetic [5]. The terms “idiopathic” or “genetic” are not applicable to the underlying etiology of SE because even in genetic epilepsy syndromes, the cause of SE may not be the same as the disease. Metabolic, toxic, or intrinsic factors (such as sleep deprivation) can trigger SE in these syndromes [5, 15].

The term “new-onset refractory status epilepticus” (NORSE) was coined to describe a group of patients who share certain commonalities and yet are often found to have varying etiologies. A multidisciplinary team of experts came together to develop a clear definition for NORSE: “a clinical presentation, not a specific diagnosis, in a patient without active epilepsy or other pre-existing relevant neurological disorder, with a new onset of RSE without a clear acute or active structural, toxic, or metabolic cause” [18]. Febrile-infection-related epilepsy syndrome (FIRES) is a type of NORSE that is characterized by a febrile infection that occurred between 2 weeks to 24 h before the onset of RSE. This febrile infection may or may not be present during the onset of SE [19].

Recently, a systematic review and meta-analysis examining the etiology and mortality of NORSE was published. The study revealed that cryptogenic causes were responsible for 49.9% of cases, while autoimmune factors accounted for 36.2%, making it the second most prevalent cause [20]. Approximately 10% of NORSE cases are caused by infections, with viruses being the most commonly implicated pathogen, depending on the region’s endemic agents. The onset of NORSE can be attributed to genetic and congenital disorders, along with toxic, vascular, and degenerative conditions that have also been reported [21]. The overall mortality rate was recorded at 22%. Frequently employed treatments encompassed the administration of ASM (with a median of 5), general anesthesia, as well as immunotherapies such as corticosteroids, intravenous immunoglobulin, and plasma exchange. The average duration of intensive care unit stay was recorded as 33.4 days, and upon discharge, approximately 52% of patients were diagnosed with epilepsy. Neurocognitive impairment emerged as a prevalent consequence of NORSE [20].

Diagnosis of SE

It has been shown that 42.5% of SE cases require specific treatment for the underlying cause, in addition to stopping seizures and providing symptomatic treatment [6]. It is crucial to quickly identify the underlying cause of SE. Sometimes, a thorough evaluation may be necessary, especially in cases of SE occurring in patients with “de novo” SE [22].

Approximately half of SE cases occur in patients with epilepsy, while the other half are new-onset cases [6]. It is essential to determine whether the patient has a history of epilepsy or not, and thus a comprehensive medical history and a complete neurological examination are imperative. Focal abnormalities may suggest a structural brain lesion. Vital signs and a general physical examination, including a skin examination, may be informative in revealing indirect signs of drug intoxication, injection sites (toxic), or purpura [23].

It is necessary to perform brain imaging for all patients and conduct basic laboratory tests to rule out major acid-base disturbances, electrolyte imbalances, acute organ failure, and intoxications [22]. Whenever possible, magnetic resonance imaging (MRI) should be favored over other imaging techniques as it is more sensitive in diagnosing certain underlying causes. In some cases, MRI can provide physiopathological insights, such as detecting evidence of ictal or postcritical neuronal damage [24]. In such cases, there are usually visible T2 hyperintensities involving the cortex (especially in the hippocampus), adjacent white matter, basal ganglia, thalamus (pulvinar), corpus callosum, and cerebellum, indicating vasogenic and sometimes cytotoxic edema [25]. In patients with a known history of epilepsy and rapid and favorable evolution, brain imaging might not be required.

In patients with epilepsy who experience occasional breakthrough seizures and for whom no other underlying cause for their SE has been identified through medical history, basic laboratory investigations, and neuroimaging, a lumbar puncture might be considered [22]. In patients presenting with de novo SE, the threshold for performing a lumbar puncture should be set even lower. Additionally, any patient with a suppressed immune system or exhibiting antecedent infectious symptoms or language difficulties, such as fever or hypothermia, should undergo cerebrospinal fluid (CSF) analysis to rule out central nervous system infection [22].

The interpretation of the CSF analysis results may be subject to debate, especially in the presence of moderate pleocytosis. Pleocytosis and an increased concentration of lactate and albumin CSF/serum ratio in the CSF are sometimes described in the postictal phase in the absence of any infectious or vascular pathology. However, this pleocytosis remains moderate

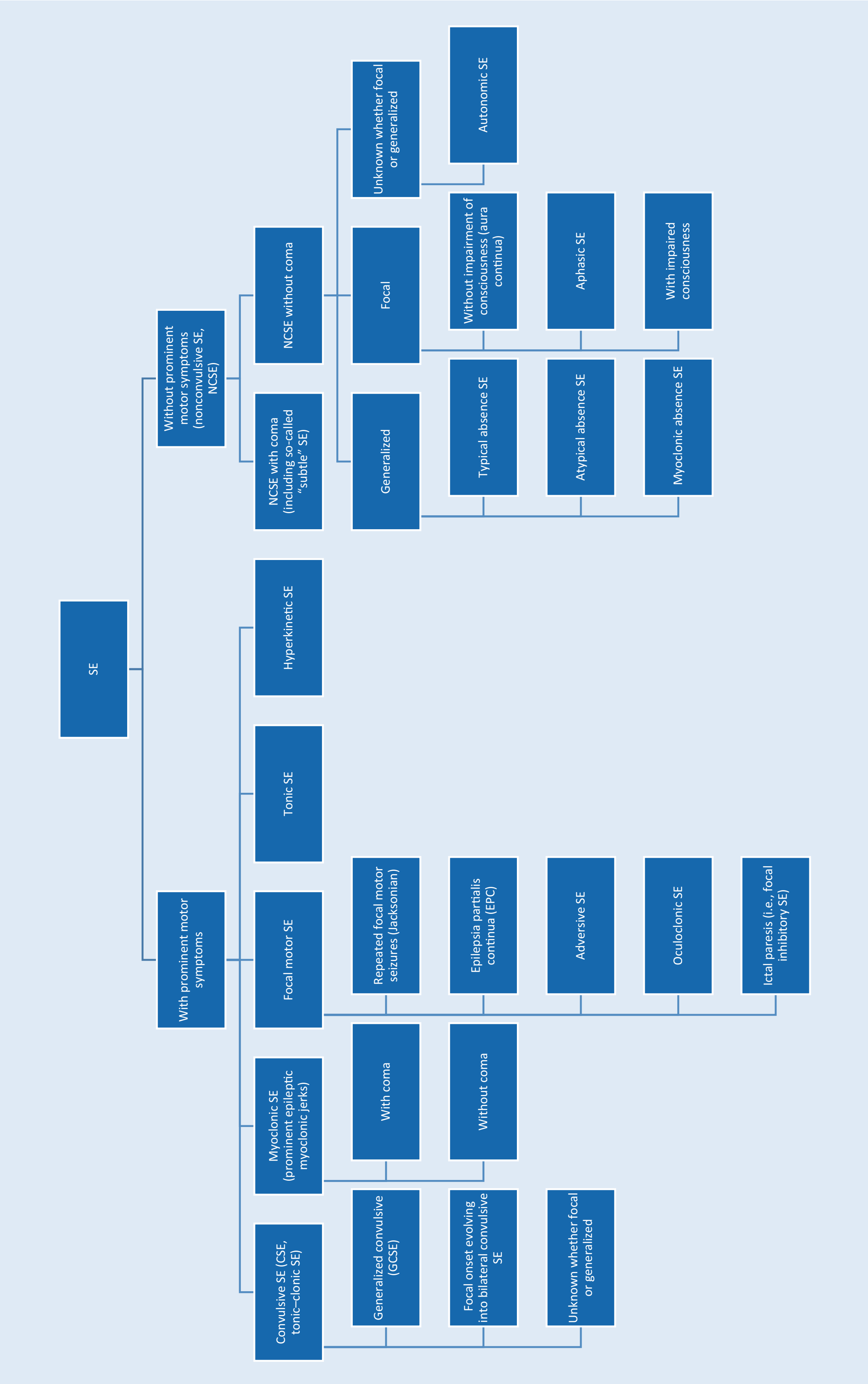
SE
With prominent motor symptoms
Convulsive SE (CSE, tonic–clonic SE)
Generalized convulsive (GCSE)
Focal onset evolving into bilateral convulsive SE
Unknown whether focal or generalized
Myoclonic SE (prominent epileptic myoclonic jerks)
With coma
Without coma
Focal motor SE
Repeated focal motor seizures (Jacksonian)
Epilepsia partialis continua (EPC)
Adversive SE
Oculoclonic SE
Ictal paresis (i.e., focal inhibitory SE)
Tonic SE
Hyperkinetic SE
Without prominent motor symptoms (nonconvulsive SE, NCSE)
NCSE with coma (including so-called "subtle" SE)
NCSE without coma
Generalized
Typical absence SE
Atypical absence SE
Myoclonic absence SE
Focal
Without impairment of consciousness (aura continua)
Aphasic SE
With impaired consciousness
Unknown whether focal or generalized
Autonomic SE

Fig. 2 ◀ Clinical classification of status epilepticus (*SE*; adapted from Trinka et al., 2015)

Table 2 Proposed investigation (laboratory and CSF) in cases of new-onset refractory status epilepticus (adapted from Outin et al., 2020)

Blood test	
General	Complete blood count
	Glycemia
	Liver and kidney function test
	Electrolytes (Na+, K+, Ca++ total and ionized, Mg++)
	ASM trough level
Auto-immune	Intracellular anti-neuronal auto-antibodies: anti-Hu, Yo, Ri, CV2 (CRMP5), Ma2, amphiphysin, GAD65, PCA-2, Tr, SOX1, titin, recoverin
	Surface antineuronal auto-antibodies: Anti-NMDAR, AMPAR, GABAbR, LGI-1, CASPR2, DPPX: Updating antibody panels on a regular basis is crucial to keep up with the latest discoveries of new antibodies
	Systemic auto-immune disease: Antinuclear antibodies (ANA/cytoplasmic), ANCA, rheumatoid factor, anti-SSA, anti-SSB, anti-phospholipids (lupus anti-coagulant, anti-β2-microglobulin et anti-cardiolipin), anti-thyroid peroxidase (TPO) and thyroglobulin, anti-transglutaminase, Angiotensin conversion enzyme
Infectious	Viral: HSV1 and 2, VZV, CMV, EBV, HHV6, enterovirus, measles, rubella, Influenza A and B, HIV, JCV, flavivirus (tick-borne encephalitis), hepatitis C
	Bacterial:: Lyme, Syphilis, *Mycoplasma pneumoniae* (±PCR), Chlamydia (±PCR)
	Parasites: Toxoplasmosis (±PCR), blood smear (malaria)
	Fungal: *Cryptococcus neoformans* antigen
	Adapt Serologies to patient's travel history: consider West Nile virus (V), Japanese encephalitis V, St. Louis encephalitis V, eastern equine encephalomyelitis V, western equine encephalomyelitis V, malaria, etc.
Others	Porphyria
	Lactate, pyruvate, and mitochondrial mutation genes: MELAS, MERRF and POLG1
	Heavy metal testing
CSF	
General	Cell count, glucose, protein, oligoclonal bands
	Gram staining
	Cytology
	India ink
Auto-immune	Intracellular anti-neuronal auto-antibodies and surface antineuronal auto-antibodies: Updating antibody panels on a regular basis is crucial to keep up with the latest discoveries of new antibodies
Infectious	PCR: HSV 1 and 2, VZV, CMV, EBV, HHV6, enterovirus, measles, rubella, Influenza A and B, HIV, JCV
	PCR: AFB sputum test, *Listeria monocytogenes, Mycoplasma pneumoniae*
	Lyme antibodies
	Cryptococcus neoformans antigen
Others	Lactate/pyruvate ration (mitochondrial disease suspicion)

(< 25 elements/mm^3), rare (6% of patients), early (< 24 h), and is not influenced by the duration or type of seizure [26].

It is imperative to obtain an EEG at the earliest opportunity. The EEG plays a crucial role in determining the treatment options, aggressiveness, and prognosis. Also, certain types of SE can only be accurately diagnosed through EEG evaluation [5]. In convulsive forms of SE, the EEG is often affected by movement and muscle artifacts, making its interpretation difficult. However, in the case of NCSE, where clinical signs are often subtle and nonspecific, the EEG becomes essential for accurate diagnosis [5, 27].

In the case of NORSE, a thorough investigation (◘ **Table 2**) is necessary. The most frequently encountered etiologies are nonparaneoplastic autoimmune pathologies (19%) and paraneoplastic autoimmune pathologies (18%) associated with various synaptic or intraneuronal autoantibodies [21].

Antibodies directed against neuronal cell surface antigens are inherently pathogenic. This category includes antibodies that bind, for example, to NMDA receptor, leucine-rich glioma-inactivated 1 (LGI1), and GABA$_B$ receptor [28]. The mechanisms underlying seizure generation remain partially elusive, but research suggests that anti-NMDA receptor antibodies have the potential to trigger receptor internalization, anti-LGI1 antibodies may cause disturbances in synaptic protein localization, and antibodies against GABA$_B$ receptor can serve as antagonists for neurotransmitters [28].

Antibodies against glutamate decarboxylase (GAD), as well as classic onconeural antibodies that target intracellular neural antigens, such as antibodies against Hu, Yo, Ri, Ma2, SRY-box transcription factor 1 (SOX1), and amphiphysin, have varying degrees of association with different types of tumors. Unlike antibodies that bind to neuronal cell surface antigens, onconeural antibodies are believed to primarily reflect the epiphenomenon of the underlying immune cascade, in which cellular immunity, specifically cytotoxic T cell infiltration and granzyme B-mediated damage, may play the leading role [28, 29]. Although autoimmune and inflammatory etiologies have received a lot of attention recently, it is important to remember that they represent only 2.5% of SE overall [30]. It is thus important to look for it in the right clinical context.

Rare mitochondrial diseases, such as MELAS, MERRF, or POLG1, may initially present as a de novo SE in adults [23].

Given the variety of underlying causes of SE, the use of a diagnostic guide may be useful. The SEEIT (Status Epilepticus Etiology Identification Tool) questionnaire has been developed for use at the patient's bedside in an emergency setting [6]. The SEEIT questionnaire was evaluated in a cohort of 212 cases of all types of SE in adults. Based solely on information available in the emergency department, it was able to correctly identify the underlying cause in

88.7% of cases (kappa coefficient of 0.88). Additionally, the results were reproducible in 83.3% of cases (kappa coefficient of 0.81) among physicians with different levels of training and specialties.

Treatment

The principle of "time is brain" holds utmost significance when dealing with convulsive SE. Quick administration of symptomatic treatment (seizures control) is imperative and may need to be escalated to anesthetics to avert severe metabolic disorders and long-lasting effects beyond time point t2 [4].

The basis for the recommended staged treatment approach lies in the pathomechanisms of SE characterized by the malfunctioning of GABA-ergic neurotransmission and the overactivity of glutamatergic signaling. The treatment plan suggests that BZDs should be administered immediately after diagnosing SE as a first-line treatment via intravenous (IV) or alternative routes, followed by IV non-sedating ASM [19, 31]. The primary treatment in advanced stages is the use of anesthetic drugs to induce a therapeutic coma [31]. Furthermore, critical care management along with other therapeutic options, such as immune therapies and dietary interventions, offer crucial supplementary treatments [32].

First stage: benzodiazepine

Typically, BZDs are the first-line treatment in the initial phase of SE due to their rapid onset, effectiveness, and tolerance [33]. Even though all BZDs work as allosteric regulators at the inhibitory gamma-aminobutyric acid $GABA_A$ receptor, the diverse agents possess unique pharmacokinetic and pharmacodynamic characteristics, leading to varying effectiveness profiles [33]. Clonazepam (CLZ), diazepam (DZP), lorazepam (LZP), and midazolam (MDZ) are the conventional BZDs, differing mainly in the routes of administration and the duration of their effects [33].

If IV therapy is not feasible, BZDs can be administered via intramuscular (IM), oral, rectal, nasal, or buccal routes [33]. Various controlled studies have been conducted to compare the effectiveness of different BZDs in treating SE. According to the RAMPART study, IM MDZ (10 mg in adults and 4 mg in children) was found to be as effective as IV LZP (0.1 mg/kg) in managing SE among prehospitalized patients [34]. A Cochrane meta-analysis has concluded that LZP is more effective than DZP [35]. Among the BZDs, LZP is the preferred choice for IV therapy, MDZ for IM therapy, and DZP for rectal administration [4].

Because there is no IV formulation available, CLZ is not commonly used in the United States [4]. However, in one study, CLZ appeared to be an effective alternative option to LZP and MDZ as the initial treatment option for SE [36]. In this study, it was observed that LZP was associated with a higher probability of refractoriness and an increased requirement for additional ASM to manage SE compared to CLZ, most likely due to the underdosing of LZP. However, the effectiveness of CLZ and MDZ appeared to be similar [36]. Further evidence supporting the use of CLZ has emerged from the SAMUKeppra study. The study evaluated the effectiveness of CLZ alone versus a combination of CLZ and levetiracetam in terminating seizures within a 15-min timeframe. It was observed that CLZ alone was able to abort 80% of seizures, and there was no added benefit observed when Keppra was added to the treatment [37].

Underdosing of BZDs during the initial stage is a prevalent occurrence that has a correlation with the subsequent development of RSE, increased use of second-line ASM, and longer stays in intensive care [38].

Non-sedative ASM

In around one third of patients, BZDs may not be effective in treating seizures. Therefore, urgent administration of ASM is necessary in all individuals with SE, except if the cause of SE is identified and definitively treated. If patients respond well to initial therapy and SE is fully resolved, the objective is to quickly reach therapeutic levels of ASM and continue administering maintenance therapy to avoid seizures recurrence [4].

Anti-seizure medications such as phenytoin (PHT) or fosphenytoin (fPHT), valproate (VPA), and levetiracetam (LEV) have been utilized for several years. However, there has been a lack of comparative solid data and guidelines were mainly based on cohort or observational studies. In 2019, the ESETT trial established that fPHT (20 mg/kg), VPA (40 mg/kg), and LEV (60 mg/kg) were equally effective in controlling SE. They were successful in approximately 50% of patients with BZD-refractory SE [39].

A meta-analysis of five randomized trials established that there was no significant difference in seizure cessation between second-line therapies (surface under the cumulative ranking curve: PHT 55.6, VPA 59.9, LEV 53.7, lacosamide [LCM] 34.5, fPHT 46.2). Both LCM and VPA ranked highest for safety, although limited data made it challenging to draw firm conclusions about LCM [40]. In a small randomized study that focused on repetitive seizures in coma detected on continuous EEG, IV LCM 400 mg and fPHT 20 mg/kg were found to be equally effective in controlling seizures and had similar side effects [41]. Recently, the use of off-label LCM has demonstrated success in multiple reports of SE and RSE [4, 40–42].

Newly approved ASM, such as brivaracetam (BRV) and perampanel (PER), may present potential benefits in the management of SE. However, additional research is necessary to establish the exact role of these new ASMs in SE management protocols [43].

In summary, LEV (60 mg/kg), VPA (40 mg/kg), and fPHT (20 mg/kg) have solid evidence of efficacy (although ca. 50% of cases). Other fast-acting ASM such as LCM and BRV might also be used.

Therapeutic coma

The management of refractory GCSE is well-established. If initial ASMs fail to control seizures, the appropriate course of action is to administer BDZs, propofol, or pentobarbital, as required [4]. Similarly, if NCSE occurs following a GCSE, and initial ASMs are ineffective, it is advisable to pursue highly active treatment [44]. After tracheal intubation, it is crucial to resort to pharmacologically induced coma with IV anesthetics not only to protect the airways but also to prevent potentially harmful systemic metabolic repercussions [4]. The use of therapeutic coma as a routine treatment remains debated. Several observational studies have suggested that therapeutic coma may be independently associated with increased mortality rates and a significant prolongation of hospital stay, without any observable benefits on patient survival. [43] Therefore, in cases where there is no history of convulsions or when seizure activity is exclusively non-convulsive, adding non-sedating ASMs may be considered as an alternative less aggressive treatment option [45].

According to a retrospective study, there was no observed correlation between the most commonly prescribed general anesthetics (MDZ, propofol, and thiopental) and patient clinical outcomes [46]. In a retrospective study comparing MDZ and thiopental, the equivalence in efficacy was proven; however, thiopental was associated with a higher risk of hypotension, infections, leukopenia, and hyponatremia [47]. Generally, MDZ even at doses exceeding 1 mg/kg/h and propofol particularly at infusion rates below 5 mg/kg/h are safe. Therefore, it may be prudent to initiate treatment for patients with RSE with MDZ (with or without propofol) before considering the use of barbiturates for those with super-RSE [48, 49].

During therapeutic coma, EEG monitoring is critical and mandatory. The EEG target can be categorized into three levels of increasing electrical suppression: (i) seizure suppression only, (ii) burst suppression, or (iii) complete suppression [4]. Previous research suggested that patients who achieved complete EEG suppression had a lower risk of relapse of SE [50]. However, more recent evaluations have indicated that patients who were treated without targeting burst suppression or complete suppression fared better [51]. In a very recent study, > 50% of EEG suppression was achieved in one fifth of 147 RSE cases. However, reaching this level of sedation was not associated with persistent seizure termination or survival. This, once again, suggests caution in adopting deeply sedative strategies [52]. Given this uncertainty, and since the degree of EEG suppression may serve as a surrogate for medication dosage and lead to iatrogenic complications, it is reasonable to conclude, with the limited available evidence, that seizure suppression is a better option than burst suppression or complete EEG suppression [53].

A recent study found that a longer duration of EEG burst suppression was associated with a higher likelihood of successful weaning [54]. After maintaining the desired EEG target for 24–48 h, a gradual reduction of the anesthetic agent is recommended, typically over a 6- to 12-h period, while monitoring the EEG for any signs of seizure recurrence [4]. It is important to note that during the weaning process, de novo periodic discharges with a periodicity of 1–4 Hz and triphasic appearance may appear on the EEG, but these are not indicative of epileptic activity and tend to resolve spontaneously [55].

In conclusion, therapeutic coma is a valid option in selected situations. A reasonable initial approach would be to aim for "seizure suppression" for 24–48 h by utilizing a combination of MDZ (0.2–0.4 mg/kg) and propofol (2 g/kg). It is important to note that continuous EEG monitoring should be implemented during this process.

Practical conclusion

- **Status epilepticus (SE) is a common neurological emergency with a significant mortality rate. Consensus on its definition led to an individualization of the timeline for treatment for each type of SE.**
- **Currently, SE is viewed as a manifestation of brain dysfunction rather than a distinct disease entity, highlighting the need for a thorough search for the underlying etiology.**
- **The etiology is determined in 50% of cases as de novo refractory SE, while the other half remains unknown, leading to the introduction of entities such as new-onset refractory SE and febrile-infection-related epilepsy syndrome.**
- **Treatment guidelines include a stepwise algorithm for SE. The first stage involves benzodiazepines, followed by anti-seizure medication (ASM) in the majority of cases. Resorting to therapeutic coma is decided on a case-by-case basis.**
- **Further research is required to evaluate newer drugs, particularly those with intravascular forms, in order to expand future treatment options.**

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Declarations

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References

1. Rossetti AO, Lowenstein DH (2011) Management of refractory status epilepticus in adults: still more questions than answers. Lancet Neurol 10(10):922–930
2. Ascoli M, Ferlazzo E, Gasparini S, Mastroianni G, Citraro R, Roberti R et al (2021) Epidemiology and outcomes of status epilepticus. Int J Gen Med 14:2965–2973
3. Glauser T, Shinnar S, Gloss D, Alldredge B, Arya R, Bainbridge J et al (2016) Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the guideline committee of the American Epilepsy Society. Epilepsy Curr 16(1):48–61
4. Brophy GM, Bell R, Claassen J, Alldredge B, Bleck TP, Glauser T et al (2012) Guidelines for the evaluation and management of status epilepticus. Neurocrit Care 17(1):3–23
5. Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S et al (2015) A definition and classification of status epilepticus—Report of the ILAE task force on classification of status epilepticus. Epilepsia 56(10):1515–1523
6. Alvarez V, Westover MB, Drislane FW, Dworetzky BA, Curley D, Lee JW et al (2014) Evaluation of a clinical

tool for early etiology identification in status epilepticus. Epilepsia 55(12):2059–2068
7. Wasterlain CG, Fujikawa DG, Penix L, Sankar R (1993) Pathophysiological mechanisms of brain damage from status epilepticus. Epilepsia 34(s1):S37–S53
8. Meldrum BS, Horton RW (1973) Physiology of status epilepticus in primates. Arch Neurol 28(1):1–9
9. Fernández IS, Goodkin HP, Scott RC (2019) Pathophysiology of convulsive status epilepticus. Seizure 68:16–21
10. Meldrum BS, Brierley JB (1973) Prolonged epileptic seizures in primates: Ischemic cell change and its relation to ictal physiological events. Arch Neurol 28(1):10–17
11. Lipton SA, Rosenberg PA (1994) Excitatory amino acids as a final common pathway for neurologic disorders. N Engl J Med 330(9):613–622
12. Trinka E, Höfler J, Zerbs A (2012) Causes of status epilepticus. Epilepsia 53(s4):127–138
13. Meierkord H, Holtkamp M (2007) Non-convulsive status epilepticus in adults: clinical forms and treatment. Lancet Neurol 6(4):329–339
14. Shorvon S, Ferlisi M (2012) The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy. Brain 135(8):2314–2328
15. Eugen T, Reetta K (2017) 25 years of advances in the definition, classification and treatment of status epilepticus. Seizure 44:65–73
16. Knake S, Rosenow F, Vescovi M, Oertel WH, Mueller HH, Wirbatz A et al (2001) Incidence of status epilepticus in adults in Germany: a prospective, population-based study. Epilepsia 42(6):714–718
17. Neligan A, Shorvon SD (2010) Frequency and prognosis of convulsive status epilepticus of different causes: a systematic review. Arch Neurol 67(8):931–940
18. Leitinger M, Trinka E, Giovannini G, Zimmermann G, Florea C, Rohracher A et al (2019) Epidemiology of status epilepticus in adults: a population-based study on incidence, causes, and outcomes. Epilepsia 60(1):53–62
19. Hirsch LJ, Gaspard N, van Baalen A, Nabbout R, Demeret S, Loddenkemper T et al (2018) Proposed consensus definitions for new-onset refractory status epilepticus (NORSE), febrile infection-related epilepsy syndrome (FIRES), and related conditions. Epilepsia 59(4):739–744
20. Tharmaraja T, Ho JSY, Neligan A, Rajakulendran S (2023) The etiology and mortality of new-onset refractory status epilepticus (NORSE) in adults: a systematic review and meta-analysis. Epilepsia 64(5):1113–1124
21. Gaspard N, Foreman BP, Alvarez V, Cabrera Kang C, Probasco JC, Jongeling AC et al (2015) New-onset refractory status epilepticus: etiology, clinical features, and outcome. Neurology 85(18):1604–1613
22. Hocker SE (2015) Status Epilepticus. Continuum 21(5):1362–1383
23. Outin H, Guèye P, Alvarez V, Auvin S, Clair B, Convers P et al (2020) Prise en charge des états de mal épileptiques en préhospitalier, en structure d'urgence et en réanimation dans les 48 premières heures (à l'exclusion du nouveau-né et du nourrisson). Méd Intensive Réanim 29(3):135–172
24. Mendes A, Sampaio L (2016) Brain magnetic resonance in status epilepticus: a focused review. Seizure 38:63–67

Zusammenfassung

Status epilepticus bei Erwachsenen: klinisch orientierte Übersichtsarbeit zu Ätiologie, diagnostischen Herausforderungen und therapeutischen Fortschritten

Ein Status epilepticus (SE) stellt einen neurologischen Notfall dar, der mit einer hohen Mortalitätsrate einhergeht. Es wurden gemeinsame Anstrengungen unternommen, um standardisierte Definitionen, Klassifikationen und Behandlungsschemata zu etablieren und so die Versorgung zu verbessern sowie die Mortalität zu vermindern. Im Jahr 2015 entwickelte die International League Against Epilepsy (ILAE) eine neue Definition und ein neues Klassifikationssystem für den SE, dabei wurden die Pathophysiologie des SE berücksichtigt und Zeitpunkte für die Entscheidungsfindung hinsichtlich der Behandlung festgelegt – unter Beachtung der Variabilität der Anfallssemiologie. Die frühzeitige Erkennung des zugrunde liegenden Auslösers des SE würde eine gezieltere Therapie erleichtern, da fast die Hälfte aller SE-Fälle zusätzlich zur symptomatischen Behandlung eine spezifische Therapie des zugrunde liegenden Auslösers erfordert. Ein Stufenalgorithmus zur Anfallsbehandlung wird vorgestellt, dabei ist der Einsatz von Benzodiazepinen (BZD) Teil des Initialstadiums, dem folgt die Anwendung nichtsedierender anfallssuppressiver Medikamente (ASM) als Zweitlinientherapie. Die Entscheidung zum Rückgriff auf ein therapeutisches Koma wird von Fall zu Fall getroffen, denn die meisten invasiven Therapien stellen nicht immer die beste Lösung dar. In der vorliegenden umfassenden Übersichtsarbeit wird ein Überblick über den SE gegeben, dabei werden die Definition, Pathophysiologie, die diagnostischen Herausforderungen sowie aktuelle Therapiefortschritte erörtert.

Schlüsselwörter
Anfälle · Notfall · Therapieschema · Physiopathologie · Diagnostik

25. Requena M, Sarria-Estrada S, Santamarina E, Quintana M, Sueiras M, Rovira A et al (2019) Peri-ictal magnetic resonance imaging in status epilepticus: temporal relationship and prognostic value in 60 patients. Seizure 71:289–294
26. Tumani H, Jobs C, Brettschneider J, Hoppner AC, Kerling F, Fauser S (2015) Effect of epileptic seizures on the cerebrospinal fluid—A systematic retrospective analysis. Epilepsy Res 114:23–31
27. Bauer G, Trinka E (2010) Nonconvulsive status epilepticus and coma. Epilepsia 51(2):177–190
28. Tan THL, Perucca P, O'Brien TJ, Kwan P, Monif M (2021) Inflammation, ictogenesis, and epileptogenesis: an exploration through human disease. Epilepsia 62(2):303–324
29. Lattanzi S, Leitinger M, Rocchi C, Salvemini S, Matricardi S, Brigo F et al (2022) Unraveling the enigma of new-onset refractory status epilepticus: a systematic review of aetiologies. Eur J Neurol 29(2):626–647
30. Spatola M, Novy J, Pasquier RD, Dalmau J, Rossetti AO (2015) Status epilepticus of inflammatory etiology: a cohort study. Neurology 85(5):464–470
31. Trinka E, Höfler J, Leitinger M, Brigo F (2015) Pharmacotherapy for status epilepticus. Drugs 75:1499–1521
32. Arya R, Rotenberg A (2019) Dietary, immunological, surgical, and other emerging treatments for pediatric refractory status epilepticus. Seizure 68:89–96
33. Kienitz R, Kay L, Beuchat I, Gelhard S, von Brauchitsch S, Mann C et al (2022) Benzodiazepines in the management of seizures and status epilepticus: a review of routes of delivery, pharmacokinetics, efficacy, and tolerability. CNS Drugs 36(9):951–975
34. Silbergleit R, Lowenstein D, Durkalski V, Conwit R (2011) RAMPART (rapid anticonvulsant medication prior to arrival trial): a double-blind randomized clinical trial of the efficacy of IM midazolam versus IV lorazepam in the pre-hospital treatment of status epilepticus by paramedics. Epilepsia 52(Suppl 8):45–47
35. Prasad M, Krishnan PR, Sequeira R, Al-Roomi K (2014) Anticonvulsant therapy for status epilepticus. Cochrane Database Syst Rev 9:CD3723
36. Alvarez V, Lee JW, Drislane FW, Westover MB, Novy J, Dworetzky BA et al (2015) Practice variability and efficacy of clonazepam, lorazepam, and midazolam in status epilepticus: a multicenter comparison. Epilepsia 56(8):1275–1285
37. Navarro V, Dagron C, Elie C, Lamhaut L, Demeret S, Urien S et al (2016) Prehospital treatment with levetiracetam plus clonazepam or placebo plus clonazepam in status epilepticus (SAMUKeppra): a randomised, double-blind, phase 3 trial. Lancet Neurol 15(1):47–55
38. Kellinghaus C, Rossetti AO, Trinka E, Lang N, May TW, Unterberger I et al (2019) Factors predicting cessation of status epilepticus in clinical practice: data from a prospective observational registry (SENSE). Ann Neurol 85(3):421–432
39. Kapur J, Elm J, Chamberlain JM, Barsan W, Cloyd J, Lowenstein D et al (2019) Randomized trial of three anticonvulsant medications for status epilepticus. N Engl J Med 381(22):2103–2113
40. Brigo F, Del Giovane C, Nardone R, Trinka E, Lattanzi S (2020) Second-line treatments in benzodiazepine-resistant convulsive status epilepticus: an updated network meta-analysis including the ESET trial—What did change? Epilepsy Behav 106:107035
41. Husain AM, Lee JW, Kolls BJ, Hirsch LJ, Halford JJ, Gupta PK et al (2018) Randomized trial of lacosamide versus fosphenytoin for nonconvulsive seizures. Ann Neurol 83(6):1174–1185

42. Misra UK, Dubey D, Kalita J (2017) Comparison of lacosamide versus sodium valproate in status epilepticus: a pilot study. Epilepsy Behav 76:110–113
43. Rossetti AO, Alvarez V (2021) Update on the management of status epilepticus. Curr Opin Neurol 34(2):172
44. Treiman DM, Meyers PD, Walton NY, Collins JF, Colling C, Rowan AJ et al (1998) A comparison of four treatments for generalized convulsive status epilepticus. N Engl J Med 339(12):792–798
45. Rossetti AO, Hirsch LJ, Drislane FW (2019) Nonconvulsive seizures and nonconvulsive status epilepticus in the neuro ICU should or should not be treated aggressively: a debate. Clin Neurophysiol Pract 4:170–177
46. Rossetti AO, Logroscino G, Bromfield EB (2005) Refractory status epilepticus: effect of treatment aggressiveness on prognosis. Arch Neurol 62(11):1698–1702
47. Bellante F, Legros B, Depondt C, Créteur J, Taccone FS, Gaspard N (2016) Midazolam and thiopental for the treatment of refractory status epilepticus: a retrospective comparison of efficacy and safety. J Neurol 263(4):799–806
48. Fernandez A, Lantigua H, Lesch C, Shao B, Foreman B, Schmidt JM et al (2014) High-dose midazolam infusion for refractory status epilepticus. Neurology 82(4):359–365
49. Rossetti AO, Reichhart MD, Schaller MD, Despland PA, Bogousslavsky J (2004) Propofol treatment of refractory status epilepticus: a study of 31 episodes. Epilepsia 45(7):757–763
50. Krishnamurthy KB, Drislane FW (1999) Depth of EEG suppression and outcome in barbiturate anesthetic treatment for refractory status epilepticus. Epilepsia 40(6):759–762
51. Hocker SE, Britton JW, Mandrekar JN, Wijdicks EFM, Rabinstein AA (2013) Predictors of outcome in refractory status epilepticus. JAMA Neurol 70(1):72–77
52. Fisch U, Jünger AL, Baumann SM, Semmlack S, Marchis GMD, Hunziker S et al (2023) Association between induced burst suppression and clinical outcomes in patients with refractory status epilepticus: a 9-year cohort study. Neurology 100(19):e1955–e1966
53. Kroeger D, Amzica F (2007) Hypersensitivity of the anesthesia-induced comatose brain. J Neurosci 27(39):10597–10607
54. Johnson EL, Martinez NC, Ritzl EK (2016) EEG characteristics of successful burst suppression for refractory status epilepticus. Neurocrit Care 25(3):407–414
55. Bhatt AB, Popescu A, Waterhouse E, Abou-Khalil BW (2014) De novo generalized periodic discharges (GPDs) related to anesthetic withdrawal (GRAWs) resolve spontaneously. J Clin Neurophysiol 31(3):194–198