

REVIEW ARTICLES

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Updates on classification and management of status epilepticus

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Abstract

Background: Status epilepticus (SE) is a major medical emergency and requires not only an emergency symptomatic treatment with antiepileptic drugs (AED) but also a rapid identification and treatment of the underlying cause. This narrative review summarizes the most important advances in SE classification and treatment. Data sources included being PubMed / Medline, and tracking references of the relevant studies, reviews and books. SE is now defined as “a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally prolonged seizures (after time point t1). It is a condition, which can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures.” The most effective acute treatments for early SE are the intravenous benzodiazepines (lorazepam, diazepam, and clonazepam) and intramuscular midazolam. In children, oral or intranasal midazolam are useful alternatives. The intravenous antiepileptic drugs (phenytoin, valproate, levetiracetam, phenobarbital and lacosamide) are administered in confirmed SE. Treatment options in refractory SE are intravenous anesthetics; ketamine, magnesium, steroids and other drugs are used in super-refractory SE, showing variable results and outcomes.

Conclusions: Over time, major progress has been made in defining, classifying, and understanding of SE mechanisms. Despite this, the first-line drug management is ineffective in up to 40% of patients with SE. The super-refractory SE treatment is still unknown and no evidence-based data have been found yet. Thus, SE treatment strategies vary substantially from one institution to another due to the lack of data supporting a specific treatment plan.

Key words: status epilepticus, classification, guideline, antiepileptic treatment.

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Introduction

Status epilepticus (SE) is a major neurological and medical emergency that is commonly expressed by a brain injury or systemic changes that lead to cerebral hyperexcitability. The incidence accounts for 61 episodes per 100000 per year, with a total mortality of approximately 20% (range 1.9-40%) [1, 2]. The reported incidence varies considerably depending on the used definition of SE. In addition, the incidence refers to episodes of clinically apparent SE, which do not incorporate the underestimated incidence of nonconvulsive SE. Multiple publications are controversial, with a partial approach to evolution, diagnostic and management criteria. However, there has been considerable development in recent years in understanding the pathophysiology, causes, clinical features, changes in EEG, its prognosis and treatment [3, 4].

Classically, it was defined as a “situation characterized by epileptic seizures long enough or repeated at short intervals to produce a long-lasting epileptic disorder” [5].

Initially, the proposed times ranged from 60 to 30 minutes. However, in terms of the operational definitions, clinicians do not wait for diagnosis confirmation and treatment, since the SE prognosis might worsen over time [6]. This issue has led to a more detailed operational definition [7]: a generalized convulsive SE in adults and children over 5 years of age is defined as “a continuous seizure lasting ≥ 5 min or one or 2 seizures or even more might exhibit an incomplete recovery of consciousness between them”. This time interval was in general accepted by the medical community and used to guide the emergency treatment of generalized convulsive SE. However, other forms of SE were not considered until the last definition, being proposed in 2015 by the SE Working Group of the International League against Epilepsy (ILAE) [8].

According to the new definition approved in 2015, the SE is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally

prolonged seizures (after the time point t1) and which can have long-term consequences (after time point t2), including neuronal death, neural injury, and alteration of neural networks, depending on type and duration of seizures [3, 8]. This definition is conceptual, with two operational dimensions: the first is the duration of the seizure and time point (t1, at 5 min), above which the seizure should be considered as “continuous ictal activity”. The second time point (t2, at 30 min) is the time followed by the risk of long-term consequences [3, 8].

This new definition of SE provides good guidance when the emergency treatment needs to be considered. In general, the time point t1 is the time when treatment should be started, which is within 5 minutes, for generalized tonic-clonic seizures, and over 10 minutes, for focal seizures with or without an altered consciousness. Time point t2 highlights the time when the neuronal damage occurs or self-perpetuation of alteration of neural networks starts, thus indicating that SE should be controlled as quickly as possible; 30 min, in case of generalized tonic-clonic seizures [3, 6]. The proposed time points are based on clinical trials performed on animal models, as well as on clinical researches. These data might vary, thus these specific moments should be considered as the best estimates available now. However, there are no data that have correctly defined all forms of SE, thus the study of these subtypes will allow their incorporation into the definition without changing the basic concept [6].

SE can be considered as the second most common acute neurological emergency after stroke. SE makes up 3.5% of total hospital admissions in developed countries and 11% within the developing countries [9, 10]. Nonconvulsive status epilepticus (NCSE) accounts for approximately 1/3 of all SE cases. Compared to convulsive SE, NCSE has been given less attention, is underdiagnosed and undertreated. NCSE comprises a group of syndromes that have a great diversity in terms of response to anticonvulsant drugs, from practically self-limiting variants to completely refractory forms. The etiology and clinical form of NCSE are strong predictors for the overall prognosis [11].

Status epilepticus classification

The ILAE working group also came up with a new classification that will provide a framework for clinical diagnosis, investigation, and therapeutic approaches for each patient, based on four axes. [3, 8]: (I) semiology, (II) etiology, (III) EEG correlations, and (IV) age. Semiology is thought to be the backbone of this classification. Different clinical forms of SE are differentiated based on two taxonomic criteria: the presence of motor activity and impaired consciousness falling into two major groups: SE with prominent motor symptoms, including all convulsive seizures, and SE without prominent motor symptoms that represent the underlying forms of NCSE (see Table 1).

Axis 1 (semiology) includes different forms of SE, being divided into those with prominent motor manifestations, those without prominent motor manifestations, as well as conditions not determined so far (such as acute confusional states with epileptiform patterns at EEG) [8]. Each group

can be divided again, depending on the degree of the impaired consciousness, which is extremely clinically relevant. NCSE with coma is a life-threatening condition that requires urgent and consistent treatment, while NCSE without coma commonly occurs in the form of absence SE or focal status with impaired consciousness (the previous terms for these conditions were the “psychomotor status” or “partially complex epileptic status”) [3, 8, 12].

Axis 2 (etiology) is divided into two groups: (i) known or symptomatic and (ii) unknown or cryptogenic. The symptomatic group can be subdivided into acute symptomatic, remote symptomatic and progressive symptomatic [3, 6]. SE frequently occurs in the context of genetic epileptic syndromes, however, there are some triggers for the status itself, such as fever, electrolyte disturbances, or other intrinsic factors [13].

Axis 3 of classification includes EEG correlations. In convulsive SE, the clinical presentation is most often clear and with unclear artifacts on EEG, thus the EEG has a low significance. The non-convulsive SE otherwise cannot be often correctly diagnosed without an EEG. In most severe cases of patients with deep coma, only an EEG can reveal the epileptiform or rhythmic discharges that lead to the diagnosis [12, 14].

Table 1

Axis 1 of the classification of SE – semiology [3, 8]

(A) with prominent motor signs
1. Convulsive SE (CSE, synonym: tonic-clonic SE) <ul style="list-style-type: none"> a. Generalized convulsive b. Focal onset evolving into bilateral convulsive SE c. Unknown whether focal or generalized 2. Myoclonic SE (with prominent epileptic myoclonic jerks) <ul style="list-style-type: none"> a. With coma b. Without coma 3. Focal motor <ul style="list-style-type: none"> a. Repeated focal motor seizures (Jacksonian) b. <i>Epilepsia partialis continua</i> (EPC) c. Adversive status d. Oculoclonic status e. Ictal paresis (i.e., focal inhibitory SE) 4. Tonic status 5. Hyperkinetic SE
(B) Without prominent motor symptoms (i.e., NCSE)
1. NCSE with coma (including so-called “subtle” SE) 2. NCSE without coma <ul style="list-style-type: none"> a. Generalized <ul style="list-style-type: none"> i. Typical absence status ii. Atypical absence status iii. Myoclonic absence status b. Focal <ul style="list-style-type: none"> i. Without impairment of consciousness (aura continua, with autonomic, sensory, visual, olfactory, gustatory, emotional/psychic/experiential, or auditory symptoms) ii. Aphasic status iii. With impaired consciousness c. Unknown whether focal or generalized <ul style="list-style-type: none"> i. Autonomic SE

Table 2

Salzburg EEG criteria for NCSE [29-31]

Patients without known epileptic encephalopathy:
EDs > 2.5 Hz, or EDs ≤ 2.5 Hz or rhythmic delta/theta activity (>0.5 Hz) and one of the following: EEG and clinical improvement after intravenous AED*, or Subtle clinical ictal phenomena during the EEG patterns mentioned above, or Typical spatiotemporal evolution**
Patients with known epileptic encephalopathy:
Increase in prominence or frequency of the features mentioned above, when compared to baseline with observable change in clinical state Improvement of clinical and EEG features with intravenous AEDs

*If EEG improvement occurs without clinical improvement, or if fluctuation is without definite evolution, this should be considered possible NCSE.

** Incrementing onset (increase in voltage and change in frequency), or evolution in pattern (change in frequency >1 Hz or change in location), or decrementing termination (voltage or frequency).

EDs, epileptiform discharges (spikes, poly spikes, sharp-waves, sharp-and-slow-wave complexes); AEDs: antiepileptic drugs.

Finally, the age should be considered, given that the etiologies are different and there are some age-specific electroclinical syndromes: newborn (<30 days), early childhood (1 month to 2 years), childhood (2–12 years), adolescence-adult (12–59 years), and old age (> 60 years) [3, 6].

Status epilepticus – pathophysiology

The basic SE generating processes can be considered as failure of the normal mechanisms responsible for cessation of the seizures. Reduced inhibition and persistent excessive excitation might produce and sustain further epileptic activity. During a prolonged seizure activity, dynamic changes in gamma-aminobutyric acid A (GABAA) and N-methyl-D-aspartate (NMDA) receptors are observed, these have been termed as “receptor trafficking” [15]. During the excessive neuronal discharges, there is a gradual reduction of GABA-A receptors on the surface of the synaptic membrane with the internalization of receptors in the endocytic vesicles and its subsequent degradation. This process induces the loss of endogenous GABA-ergic inhibition mediator giving rise to sustained epileptic activity [15-17]. The loss of post-synaptic GABA-A receptors is a relevant pathophysiological factor for the onset of progressive drug resistance to drugs, such as benzodiazepines, barbiturates and propofol [18]. In contrast, in continuous epileptic activity, NMDA receptors are progressively transported to the surface of the synaptic membrane, resulting in an increase in the number of excitatory NMDA receptors in the synaptic cleft. This process facilitates neuronal excitability and SE continuity [15]. On the other hand, an increased expression of GABA receptors may be a useful target for pharmacological management in advanced stages of SE [18]. Absence SE and 3 Hz

slow spike-wave discharges are induced by excessive inhibition. This form of SE does not lead to significant neuronal damage.

Brain damage in Status epilepticus

The severity of cerebral hypoxia during convulsive SE is unlikely to cause brain damage [18, 19], though it may trigger some other factors that impair the brain functioning, such as hyperthermia, hypotension, hypoglycemia, and acidosis [19]. These factors are particularly relevant after the compensatory mechanisms have failed [18, 19]. In non-human primates, prolonged seizures lead to lesions in the cortex, cerebellum and hippocampus with a pattern similar to that seen in circulatory arrest, systemic hypotension or hypoglycaemia [18]. A characteristic neuropathology that has been associated with prolonged convulsive SE is hippocampal sclerosis which consists of a loss of neurons in the dentate nucleus and pyramidal layer of the hippocampus with variable gliosis [20].

In 1880, Sommer was the first to describe in detail the hippocampal sclerosis in the brains of epileptic patients [21]. Since then, the controversy over hippocampal sclerosis is considered both a cause and a consequence of SE, which support the existing hypotheses [22]. While the relationship of prolonged seizures to hippocampal sclerosis has well been established in animal models, there is no strong evidence that SE causes hippocampal sclerosis in humans [23]. Therefore, it is likely that hippocampal sclerosis might be both the cause and the consequence of convulsive SE, showing a varied predominance in different clinical scenarios [20].

Although most of the specialized literature on the neuropathology of brain lesions in SE refers to seizures, there is evidence that non-seizures also might cause brain damage. When prolonged seizures are induced in paralyzed and artificially ventilated non-human primates, the neuronal injury is less severe, especially in cerebellum. Epileptic activity alone leads to neuronal damage and neuronal death, mainly due to excessive activation of glutamate receptors and subsequent influx of Ca^{2+} into the neuron [24]. Although the epileptic mechanisms are fully understood in animals, the additional impact over the etiology in humans is still uncertain.

Status epilepticus diagnosis

The diagnosis of SE is based on the EEG. The recording of epileptiform changes, which correspond to the motor clinical manifestations in convulsive SE is the main diagnostic criteria in this clinical form [25]. Moreover, if the diagnosis of convulsive SE is usually not difficult to confirm, then in nonconvulsive SE the EEG has a decisive role, whereas the lack of motor clinical manifestations is the main impediment in this regard. Over the years, a number of researches have been published that have tried to standardize and develop the criteria for diagnosing NCSE [26-28].

The ILAE Working Group recommends describing EEG correlations in a SE patient by using the following descriptors: paternal name, morphology, location, time-related characteristics, modulation, and effect of intervention, as well as by using the terminology recently proposed by the

American Clinical Neurophysiology Society and “Salzburg EEG criteria for NCSE” (Table 2) [14, 29-32], as a practical diagnostic guide. Thus, based on the peculiarities of EEG, the researchers proposed to develop a diagnostic decision, based on the NCSE type (electroclinical classification) and the presumed etiological factor [33]. Subsequently, a reduction in the rate of false diagnosis of NCSE was reported due to the implementation of this score [31]. Therefore, different EEG patterns in coma and the diagnosis of NCSE in these cases were difficult to differentiate for a while, however, this dilemma was solved later [14]. Conventional and quantitative methods in the diagnosis of major emergency cases have also been studied and proposed [34]. However, according to Lettinger’s data [35], the so-called Salzburg criteria for diagnosing NCSE, proposed by Beniczky and his workteam [33], show a sensitivity of 75% in short recordings up to 97.7% in long-term EEG recordings (up to 74 hours), with a specificity of 89.6% [35] and are an important tool in diagnostic and therapeutic decisions in these patients.

Status epilepticus treatment

The management of SE and its pharmacological treatment is another area of limited evidence derived from high-quality randomized controlled trials, appropriately selected to inform clinical practice. However, there has been clear progress in understanding the pathomechanisms, which have led to more effective treatment strategies [3]. The therapeutic principle “Time is the brain” might be applied not only to stroke, but also to SE, since the prognosis of SE worsens with the duration of increasing convulsive activity [36, 37]. Indeed, prompt SE confirmation and early treatment is associated with lower morbidity and mortality, fewer drugs required for inpatients, and a decreased seizure duration [38]. Fortunately, SE responds to relatively simple treatment, but when simple interventions fail, refractory SE requires a more aggressive treatment to prevent complications. However, there is a limited interest in the industry to develop new treatments to prevent refractory status. However, the latest ILAE definition has led to standard action protocols, which have been adapted to time points t1 and t2 [6].

The most recent reviews focus on SE pharmacotherapy, but the general measures of any neurological emergency are just as important (airway maintenance, oxygen therapy $\text{SaO}_2 > 95\%$, stabilization of vital signs: blood pressure, temperature, and glycemia). Other measures include intravenous glucose and thiamine as required, emergency measurement of antiepileptic drugs, electrolytes, and magnesium, a complete haematological screening and liver and kidney function [39, 40]. In addition, it is essential to carry out a thorough search of the simultaneous etiology, because an early etiological treatment is highly important for the subsequent prognosis [3, 6, 39].

The main purpose of treatment is to immediately stop both clinical convulsive activity and electrographic ictal activity. The initial treatment strategy includes simultaneous assessment and management of the airways, respiration rate and circulation (aimed to provide intravenous access,

O_2 administration, and airway safety as needed), immediate treatment with AED drugs (benzodiazepines), screening for the main cause of SE, and immediate treatment of life-threatening causes of SE (e.g. meningitis, intracranial mass injury) [39, 40]. Once SE is under control and the vital signs are stable, specific diagnostic examinations should be performed. These diagnostic investigations are selected based on the patient’s medical history and physical examination. Not every diagnostic test is necessary for every patient. For example, a lumbar puncture is generally necessary if there is any suspicion of central nervous system infection but may be unnecessary in suspected meningitis, especially in patients with AED noncompliance [39]. If the patient is currently being treated with antiepileptic drugs (AED), the serum AED levels should be checked, and compliance history should be obtained. A comprehensive toxicology profile should be performed if there is no clear etiology for SE. Specific toxicological testing should be carried out if history or physical examination suggests a specific toxin.

By the late 1980s there were large variations in patient stabilization procedures, laboratory measures, and the sequence of drugs in SE management [41]. In 1993, the Epilepsy Foundation of America organized a working group on SE. They published guidelines and a treatment protocol [42], which was based on the literature and expert opinions. Some of the key treatment principles included within this guide are still valid. All treatment protocols recognize a step-by-step approach to treatment with different drugs used in early SE (stage I), established SE (stage II), refractory (stage III) and super-refractory SE (stage IV) and underline the recognition and prompt treatment of persistent convulsive activity at each stage in order to reduce morbidity, mortality and long-term consequences of SE (other than t2) [39, 43]. Therefore, these guidelines have revised the traditional SE treatment paradigm to initial emergency therapy, emergency control therapy and refractory SE therapy. Patients with refractory SE who do not respond to initial therapy and super-refractory SE should be treated in highly experienced centers. All patients with SE will need initial AED emerging therapy (i.e., first line) and emergency control AED therapy (i.e., line 2), in addition to AED maintenance therapy, even if SE has been controlled immediately. According to the definition, refractory SE therapy (i.e. 3rd and 4th line) is administered for those who do not respond to the first 2 antiepileptic drugs.

If the SE is caused by a metabolic disorder (e.g. hypoglycaemia), the underlying metabolic disorder must be corrected, thus the maintenance therapy may not require. It must be considered that, although the treatment includes a series of stages, the treatment itself is an ongoing process, thus the urgent cessation of convulsive activity is the major goal applied to each stage.

Most clinical trials were conducted in the early stages of SE, which was the subject of several trials and critical evaluations in systematic reviews of meta-analyses [44-49] and included in treatment protocols or practical guidelines [39, 43, 50, 51].

Stage 1: early SE. Although several AEDs have been studied as first-line therapy for SE, the evidence and experts agree that benzodiazepines should be the drug of choice for initial treatment. Benzodiazepines can rapidly control SE in about two-thirds of patients [4, 48]. The most commonly first-line treatments are diazepam, midazolam and clonazepam (intravenous lorazepam is not marketed in our country). Although the controlled studies demonstrated the superiority of lorazepam [52, 53], a recent comparative meta-analysis of 5 clinical trials found that there is no difference in efficacy or side effects between lorazepam and intravenous diazepam [54]. Benzodiazepines exert their antiepileptic properties by increasing inhibitory neurotransmission by increasing channel opening and GABA-A receptor frequency, with subsequent increase in chlorine conductance and neuronal hyperpolarization [55, 56]. This first-line treatment should be used as early as possible before point t1 in the SE definition, which means it has a major role in the pre-hospital settings. In this context, the intravenous route may be difficult, and other routes of administration, such as intramuscular [38], intranasal or oral midazolam [57], have proven to be more practical, faster and safer alternatives. The pre-hospital recognition of SE is easy to perform in convulsive SE or that with motor involvement; however, the non-convulsive SE may be more difficult to detect and treat, thus clinical scores should be developed or devices should be used to allow faster detection [6].

At the same time, supportive treatment should be provided, as rapid administration of benzodiazepines may cause respiratory depression and hypotension. Patients who have responded to initial emergency therapy and have a complete resolution of SE should continue dosing for maintenance therapy in order to rapidly achieve the therapeutic levels of AED. Urgent control therapy is to stop SE in patients who do not respond to initial emergency therapy.

Stage 2: established SE. Approximately 40% of patients with generalized convulsive SE are refractory to benzodiazepine treatment [53, 58]. This ongoing convulsive activity is called the established SE (or stage II). In established SE, intravenous antiepileptic drugs (phenytoin, valproic acid, levetiracetam, phenobarbital and lacosamide) are the most commonly used; however, there are no classes of evidence to choose between them. This unsatisfactory condition has several consequences: first of all, most patients are provided off-label treatment.

A meta-analysis comparing the first 4 drugs resulted in higher rates of cessation of seizures with valproic acid (75.7%, 95% CI: 63.7–84.8) and phenobarbital (73.6%; 95% CI: 58.3–84.8) than with levetiracetam (68.5%; 95% CI: 56.2–78.7) or phenytoin (50.2%; 95% CI: 34.2–66.1). Based on this and the favorable tolerability profile of levetiracetam and valproic acid, the authors preferred these drugs to phenytoin / fosphenytoin in established SE [59].

In patients with known epilepsy who have been on an AED prior to admission, case-by-case intravenous bolus administration of AED was given, if available, prior to initiation of an additional agent. This may also include additional

boluses to achieve higher-than-normal target concentrations of AED to achieve the desired therapeutic response (i.e., cessation of seizure activity).

Currently, a large multicenter, randomized, blinded study is being conducted, funded by the National Institute of Health (Established Status Epilepticus Trial), which compares the efficacy of fosphenytoin, valproic acid or levetiracetam in the treatment of patients with benzodiazepine-refractory SE [60]. Unless the results of this study are available, other drugs, such as lacosamide, are also widely used in established and refractory SE, which have been recently reviewed and published [61]. In any case, it is about prioritizing drugs with better tolerance, easy to administer and with few pharmacological interactions (levetiracetam and lacosamide).

It is important to use the correct doses at this stage, as one of the recognized problems for non-response is the use of subtherapeutic AED doses [62]. The recommended doses are presented in table 3.

Table 3

Different doses of drugs used in the second – and third-line-treatment

Drug	Dose
Second-line treatment (AED)	
Valproic acid	30 (20–40) mg/kg on 5–10 min
Phenobarbital	10–20 mg/kg in 15–20 min
Phenytoin	15–20 mg/kg, infusion <50 mg/min
Lacosamide	5–6 mg/kg in 10–15 min
Levetiracetam	60 (30–60) mg/kg, max.4500 mg, in 5–10 min
Third-line treatment (anaesthetics)	
Propofol	Bolus 2 mg/kg; infusion 2–10 mg/kg/h
Midazolam	Bolus 0.1–0.3 mg/kg at –4 mg/min; infusion 0.05–2 mg/kg/h
Ketamine	Bolus: 0.5–3 mg/kg; infusion 1 mg/kg/h – of 10 mg/kg/h
Thiopental	Bolus: 3–5 mg/kg in 3–5 min; repeat bolus 1–2 mg/kg; after 3 min perfusion: 3–7 mg/kg/h

AEDs – antiepileptic drugs, h – hour, kg – kilogram, mg – milligrams.

Regarding lacosamide, a weight-adjusted dose was not considered until recently [63].

Stage 3: refractory SE. 31-43% of patients with established SE seizures are not controlled with antiepileptic drugs [64-66]. In most cases, continuous EEG and / or clinical examination will determine the persistence of SE after initial AED treatment. Refractory SE is considered when two treatment lines have failed (one of which is benzodiazepines) at appropriate doses. Refractory cases are associated with mortality and therefore there is consensus in recommending the use of intravenous anesthetics (midazolam, propofol or barbiturates) as the next line of treatment to control ictal activity. However, there are no data from randomized trials to support the recommended anesthetic, thus medications should be used, based on the experience of each separate hospital.

There is no consensus on achieving optimal sedation (only ictal activity suppression, burst-suppression pattern or isoelectric pattern). Each anesthetic option has its own considerations (doses are shown in Table 3).

– Propofol may be associated with metabolic acidosis, rhabdomyolysis, renal failure and heart failure. The propofol infusion syndrome is less likely to be treated for less than 48 hours and not more than 5 mg / kg / h.

– Midazolam seems the safest drug at this stage, with the lowest rate of metabolic complications [67, 68].

– Barbiturates are frequently associated with cardiovascular complications, severe immunosuppression, and infections.

In a worldwide research study of 488 episodes of refractory SE, a continuous infusion of midazolam was the most widely used anesthetic (59%), followed by propofol (32%) and barbiturates (8%) [69]. The ongoing use of infusion AEDs often requires assisted ventilation and cardiovascular monitoring. Vasopressor agents may be needed due to hypotension and cardiopulmonary depression related to these agents. Once the sedation is discontinued, the dose is recommended to be gradually reduced over 24 hours if no ictal activity occurs, over 12 hours in case of barbiturates, as well as gradually reduced over the next 12 hours and 24 hours in case of midazolam or propofol.

Another anesthetic that has regained interest is ketamine. It has a significant antagonistic effect on N-methyl-D-aspartate glutamate receptors, which play a key role in the advanced stages of SE [70]. Ketamine is a racemic mixture that contains equal amounts of two enantiomers, (S)- and (R)-ketamine. Ketamine is metabolized by N-demethylation to produce norketamine, a non-competitive NMDA receptor antagonist that may also exhibit enantioselective pharmacological activity. (S)-ketamine has different pharmacodynamic activities and is two to three times stronger as an analgesic agent than (R)-ketamine. (S)-ketamine administered alone has a higher clearance than in the racemic mixture resulting in rapid elimination, shorter duration of action and faster recovery from anesthesia [71]. There are several series and isolated cases that report an efficiency in refractory SE of about 63%, and in particular it seems that the form (S)-ketamine has advantages in terms of better psychomotor recovery than the racemic form [72].

The problem, apart from the lack of clinical data, is that various observational studies have recently shown that the use of anesthetics has been associated with a worse prognosis of SE, in addition to the increase in hospital stay, which leads to some concern about the safety of the use of intravenous anesthetics in the refractory SE approach [73, 74]. For this reason, an individualized approach to sedation should be applied, in case if the ictal activity can leave permanent sequelae (t2) or depending on the type of SE.

There are no data to guide the transition from continuous infusion therapy to intermittent maintenance therapy after resolution of refractory SE. The overall maintenance drugs are given in sufficient doses to maintain therapeutic concentrations during and after the continuous infusion is

discontinued. Therapeutic concentrations may exceed target concentrations for several antiepileptic drugs and dosage should be individualized to control seizures and minimize side effects. The success of the maintenance regimen is predicted by many clinical features, including EEG pattern, cause of SE, concurrent systemic disease, and drug-drug interaction profiles.

The most recent AEDs that have started to be used in this refractory phase of SE are the following:

Lacosamide. The use of lacosamide is based on clinical experience. A review of all 522 SE series cases (486 adults and 36 children) has recently been published, showing an overall efficiency of 57%. The efficacy is the same for both non-convulsive SE and convulsive SE, being higher than in previously used ones [61]. Although its use was first implemented in the refractory phase, it has been updated as the first- or second-line treatment option after benzodiazepines in many healthcare centers due to its speed of action and few side effects.

Perampanel. It exerts its mechanism in the antiepileptic pathway, through AMPA receptors. Unlike ketamine it does not act, even at high doses on NMDA receptors, but it is an uncompetitive antagonist of the alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor [75]. Although the intravenous formula has not been marketed yet, its use via the nasogastric tube has been reported in limited cases of SE, with doses ranging between 4 and 32 mg [6, 64, 76]. The number of patients in these series of cases was quite small (the largest single-center experience with 12 cases), while the patients were too heterogeneous to draw valid conclusions about its efficacy.

Brivaracetam. It is available on the market as intravenous form and therefore considered potentially usable in SE. To date, only 2 series have been published with a total of 17 patients, showing a variable efficacy [77, 78].

Stage 4: Super-refractory SE. Super-refractory SE is considered when SE continues, even though the anesthetic treatment has been initiated in high doses or when it resumes within the first 24 hours after the anesthetic withdrawal. At this stage, there are no data from clinical trials that have shown effective treatment and several options are described [68, 79], some of which have been published as isolated clinical cases.

Pharmacological therapies:

- Intravenous anesthetics (thiopental / pentobarbital, midazolam, propofol, and ketamine). It is usually the first-line option administered in SE patients to restart or increase sedation again.
- Inhalation anesthetics.
- Other AEDs: topiramate, lacosamide, pregabalin, levetiracetam and brivaracetam.
- Magnesium sulphate.
- Pyridoxine.
- Immunotherapy.
- Neurosteroids.

Non-pharmacological therapies:

- Hypothermia.

- Ketogenic diet.
- Surgery.
- Electroconvulsive therapy.
- Drainage of the cerebrospinal fluid.
- Repetitive magnetic stimulation.
- Vagus nerve stimulation.
- Deep brain stimulation.

As regarding the immunotherapy, there is a growing evidence of the role of inflammation in some refractory SEs, as well as in epileptogenesis [80]. In addition, antibodies against neuronal components are more commonly described as the cause of encephalopathy with seizure and refractory and super-refractory SE [81]. In addition, final results of complementary examinations that have confirmed an autoimmune cause might take weeks in these cases and in these serious conditions, especially in newly-onset SE (NORSE, New-Onset Refractory Status Epilepticus). Thus, various studies explain that early use can be beneficial to avoid serious consequences [82, 83]. Therefore, immunotherapy, including glucocorticoids, immunoglobulins, and plasmapheresis, might be an option in various guidelines in the super-refractory phase [39].

On the other hand, glucocorticoids may have additional non-immunological effects, such as changes in the opening of the blood-brain barrier essential for the persistence of epileptic activity and may reverse GABAergic inhibition, in addition to their effects on intracranial pressure [79]. However, when testing these therapies, potential side effects, such as severe infections or metabolic disorders should be considered.

Recently, the potential use of neurosteroids (brexanolone) has been described in super-refractory phase. Despite the name, these are not anti-inflammatory treatments, but they modulate the synaptic and extrasynaptic gamma-aminobutyric type A (GABA-A) receptors (synaptic receptors are internalized in the cell during the super-refractory SE phase, that is why benzodiazepines do not respond; they only bind to the synaptic ones) [84].

Conclusions

Major clinical advances have been made, regarding the new definition and classification of SE, thus providing the clinicians with better guidance on the time of treatment initiation, aggressiveness of treatment, and how to avoid over- or under-treatment of this condition. Furthermore, new small pharmaceutical companies are involved in the development of niche products, such as neurosteroids in super-refractory SE or new alternative routes of administration. An increased interest among physicians regarding SE has alerted them to provide an early and more appropriate treatment, as well as to determine the causes of SE in each individual patient.

Despite these progresses, there are still many issues to solve, starting with identifying the cause-oriented treatment not only to prevent the SE recurrence, but also to protect the brain from the SE impact and the development of epilepsy,

as well as better distinguish the status subtypes. This might be achieved only by a better understanding of the mechanisms of various SE etiology, as well as by reducing the gap between the preclinical knowledge used in treatment of humans.

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Authors' contribution

CM and SG designed the study, conducted the laboratory work, and drafted the first manuscript. SG, CV and CM revised the manuscript and completed the final design. All the authors approved the final version of the manuscript.

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No approval was required for this review study.

Conflict of Interests

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