STATUS EPILEPTICUS IN CRITICALLY ILL PATIENTS

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ABSTRACT

Status epilepticus (SE) is a common diagnosis in critically ill patients that may bear significant morbidity and mortality. Nowadays it is defined as continuous seizure activity lasting for more than 5 mins and requiring a specific treatment. A generalised convulsive state is a medical emergency burdened by high mortality, especially in the elderly, because repeated seizures swiftly induce significant metabolic and cardiocirculatory derangement. Two different kinds of SE are commonly recognised, depending on the presence of convulsion: convulsive SE and non-convulsive SE, which have different electroencephalographic patterns and require different therapies. In this review we provide an overview of this intriguing issue, focussing on critically ill patients.

Keywords: Status epilepticus (SE), intensive care, seizure.

INTRODUCTION

Status epilepticus (SE) is a common diagnosis in critically ill patients that may bear significant morbidity and mortality. For this reason it is extremely important that it is properly diagnosed and treated. According to the traditional criteria, SE is defined as continuous seizure activity lasting 30 mins or as two or more discrete seizures between which consciousness is not fully regained.[1] Numerous studies have recently revised this definition assuming that seizures lasting more than 5 mins require the same treatment as that used for traditional SE.[2,3] This is because the mechanisms responsible for the seizure's self-termination fail, thus impairing homeostasis of the body and thereby causing the condition to become life-threatening due to the deterioration of various organs and systems as well as from direct damage to the brain cells related to neurotransmitter release.[3] Neuronal injury results from several cellular alterations involving extracellular and intracellular ionic balances, as well as the activation of inflammatory processes and the cell death mechanism.

The opening of the blood—brain barrier during SE has a short-term pro-epileptic effect, causing equilibration of serum electrolytes with cerebrospinal fluid. This results in an increased interstitial space, a lowered extracellular Ca^{2+} concentration, and the facilitation of neuronal excitability.[4] The release of cytokines and neuropeptides with a variety of cytological and chemical reactions affects the brain vascular permeability and determines pro-inflammatory and immune reactions.[5] The most well-known cytokines include interleukin (IL)-6, IL-1β, tumour necrosis factor α, and the activation of the IL-1 Type 1 receptor/Toll-like receptor signal pathway. Seizures trigger neuronal death by an active form of necrosis requiring a mitochondrial death programme and/or the activation of a caspase cascade.[6]

Convulsive Status Epilepticus

Convulsive status epilepticus (CSE) is a condition characterised by epileptic seizures associated with rhythmic contractions of the extremities, tonic–clonic movement of the limbs, altered mental state (coma, lethargy, confusion), and possible focal neurological deficits in the postictal period.

Non-Convulsive Status Epilepticus

Non-convulsive status epilepticus (NCSE) is defined as altered consciousness or behaviour

for 30 mins or more, the absence of overt clinical signs of convulsive activity during that period, and the electroencephalographic (EEG) confirmation of seizures or activity that responds to treatment along with improved consciousness.[7] NCSE is increasingly recognised as a common occurrence in the intensive care unit (ICU) but in coma patients continuous lateralised epileptiform discharges (coma–LED) need to be distinguished from generalised epileptiform discharges (coma-GED), and it is often difficult to understand if the coma is caused by SE or by an underlying brain disorder and thus correlate this with suitable prognosis and therapy.[8]

Refractory Status Epilepticus

SE is defined as refractory when it does not respond to standard therapeutic regimens. Brophy et al.[2] suggest considering patients to be in refractory status epilepticus (RSE) whenever they continue manifesting clinical or EEG signs after an adequate dose of benzodiazepine (BZD) followed by a second anti-epileptic drug (AED) which is deemed effective. The number of AEDs to which patients have not responded that is required for a diagnosis of RSE, and whether or not to consider the duration of the SE from the initiation of treatment for the purpose of classification, remain controversial.

EPIDEMIOLOGY

SE, and in particular NCSE, has been identified in many studies as a very common nosological entity in ICUs, with a higher incidence in neurological ICUs partly due to medical and metabolic conditions, and partly due to the drugs used that predispose patients to the condition.[9] The incidence of SE in Europe varies from 9.9/100,000 in Switzerland and 10.7/100,000 in Italy[10] to 17.1/100,000 in Germany,[11] with a bimodal distribution involving a high incidence in infants <1 year of age and in the elderly (>60 years of age). In the event of subarachnoid haemorrhage, epileptic seizures are known to be a very common sequela, and some recent scientific evidence shows an underestimated frequency of the non-convulsive type in these patients, especially in those subject to sedation.[12] Even intraparenchymal haemorrhage has proven to be complicated by SE in a high percentage of cases (i.e. 18-21%), due to SE being a factor in midline shift, increased haemorrhaging, and a worsening of the outcome. Ischaemic and haemorrhagic stroke have been shown to be correlated with CSE and NCSE in such a significant percentage of cases as to suggest the early use of EEG monitoring to reveal the presence of periodic lateralised epileptiform discharges, which were followed in a study by Mecarelli et al.,[13] by SE in 70% of cases. To study the incidence of NCSE within the spectrum of SE, some authors have proposed associating prolonged video-EEG recording with standard EEG, reaching a diagnosis of NCSE in 59% of cases studied on the basis of a specific clinical suspicion and in 41% of cases in patients with no clinical evidence. This finding yet again shows the utility of EEG monitoring.[14]

DIAGNOSIS AND ELECTROENCEPHALOGRAPHIC PATTERNS

The initial diagnosis of SE is still based on the clinical assessment of altered motor performance and mental status, but it must inevitably rely on prolonged EEG monitoring in some cases where findings from the first two assessments are not temporally correlated with the EEG findings, both during or after the SE, or in particular forms of SE, such as NCSE. Table 1 shows the characteristic findings for each of the three assessments associated with the different forms of SE. Remarkably, EEG criteria for convulsive SE have been clearly delineated, but a combination of clinical and EEG criteria have to be met for NCSE diagnosis.

Clinical manifestations of SE in the variant of NCSE in patients admitted to intensive care can be blurred due to the underlying condition and drugs administered, such as anaesthetics, muscle relaxants, and anticonvulsants. Furthermore, there are no pathognomonic encephalographic characteristics that precisely identify SE to differentiate it from electrical epiphenomena caused by cerebral dysfunction. In fact, although the significant generalised activity of spike discharges is indicative of severe encephalopathy, this can more often be associated with anoxic phenomena or to NCSE.[8] Furthermore, advanced stages of coma are frequently accompanied by continuous or periodic epileptiform phenomena, considered by some to be the very cause of the severe encephalopathy and the coma. Holtkamp and Meierkord et al.[15] suggested formulating a diagnosis of NCSE only if, in addition to EEG abnormalities, there is clinical evidence of epilepsy

derived from the patient's clinical history or if episodes of epileptic seizures or SE have occurred. In 2010, two further definitions were introduced to attempt to better clarify this complex clinical situation — coma-GED and coma-LED — definable on the basis of the EEG and that can effectively distinguish NCSE from comatose NCSE, as described previously.[8]

Lastly, subtle SE is a form of NCSE that arises from insufficiently treated SE. It may be an unrecognised cause of coma.[16] The distinctive features include a comatose state and the absence of prominent motor features. Nevertheless, there can also be discrete muscle twitching, and EEG tracings mostly show generalised periodic discharges, although lateralised and regional discharges can also occur. The most recent guidelines put forth by the Neurocritical Care Society[2] and by the European Society of Intensive Care Medicine[17] recommend continuous EEG monitoring for comatose patients, patients with intracranial haemorrhage, and patients with recent clinically overt epileptic seizures without normalisation. In particular, continuous EEG monitoring is recommended for at least 48 h for coma patients to assess the presence of NCSE.

NON-EPILEPTIC CONDITIONS THAT MIMIC THE MANIFESTATIONS OF NCSE

A number of conditions can mimic NCSE without there being periodic or rhythmic EEG abnormalities. These include migraine aura, transient global amnesia, transient ischaemic attack, stupor, and dissociative disorders. Pseudostatus epilepticus can present in various forms, such as with bizarre motor features or a simulation of loss or impairment of consciousness without motor features. None of these conditions is accompanied by EEG alterations. In the impossibility of EEG monitoring, 2 mg of intravenous (IV) lorazepam (LZP) can be administered to clarify the diagnosis of NCSE.[15]

There are, however, situations treated in the ICU that can give rise to confusion, both clinically and electroencephalographically with NCSE.

Table 1: Clinical features and electroencephalography (EEG) pattern of convulsive and non-convulsive status epilepticus.

			CLINICAL FEATURES	EEG PATTERN
CONVULSIVE	GENERALISED	*Tonic–clonic seizures*	**Tonic phase:** Sustained powerful muscle contraction, which arrests ventilation **Chronic phase:** Alternating contraction and relaxation (rhythmic jerk), causing a reciprocating movement which could be bilaterally symmetrical or 'running' movements; possible urinary or faecal incontinence, possible morsus	**Tonic phase:** Progressively higher amplitude and lower frequency discharge pattern observed simultaneously in both cortical hemispheres, reaching a maximum of 10 Hz **Chronic phase:** Slow spikes develop progressively into repetitive complexes of high-amplitude spike-and-slow-wave activity
		Myoclonic status	Normal or moderately impaired consciousness and generalised myoclonia (predominantly affects the upper extremities and shows some asymmetry) Anoxic coma	Slowing of background rhythm and high-voltage generalised spike and wave discharges Normal background activity with high amplitude, 5 to 15-Hz rapid bursts of generalised polyspikes synchronous with the myoclonia
	FOCAL	*Epilepsia partialis continua*	Consciousness usually preserved Focal motor clonic seizures without Jacksonian march; lasting for at least 60 mins and often for hours, days, weeks, or even longer; often treatment resistant	Few or no paroxysmal abnormality Irregular 0.5-3 Hz slowing in the frontocentral region with reduction of beta-activity

Table 1 continued.

			CLINICAL FEATURES	EEG PATTERN
NON-CONVULSIVE	GENERALISED	*Typical absence status*	Impaired consciousness; behavioural changes: disorientation, decreased spontaneity, slow speech, hallucinations; rhythmic blinking; slight myoclonic jerking; abrupt onset	2-3 Hz spike-wave discharges Interictal background activity normal
		Late-onset absence status	Impaired consciousness; behavioural changes: disorientation, decreased spontaneity, slow speech, hallucinations; rhythmic blinking; slight myoclonic jerking	Rarely 2-3 spike-wave discharges More frequently 0.5-4 Hz spike-wave discharges
	FOCAL	*Complex partial status epilepticus*	Impaired consciousness; 'epileptic twilight state' with confusion and strange behaviour; oral or manual automatism; gradual development of symptoms	Variable with focal and bilateral spike and spike-waves; surface EEG with good sensitivity
		Subtle status epilepticus	Loss of consciousness; no or subtle movements such as rhythmic twitching of the arms, legs, trunk or facial muscles, tonic eye deviation, or nystagmoid eye jerking	Generalised or lateralised spike or spike-wave discharges Flat periods
	COMATOSE	*Coma with generalised epileptiform discharges (coma-GED)*	Anoxic coma: possible myoclonias and other motor abnormalities disappearing with anaesthesia Impaired consciousness after intoxication, vascular infarcts, cardiopulmonary arrest, infections, space-occupying lesions, and metabolic disorders may present as various degrees of coma	Continuous or periodic generalised spikes and waves with flat periods in between Burst suppression pattern Bilateral triphasic waves with and without spikes EEG pattern tends to mirror the depth of coma
		Coma with lateralised epileptiform discharges (coma-LED)	Focal or lateralising neurologic signs resulting from focal brain lesions (in most cases acutely acquired) or diffuse abnormalities (rarely)	Continuous focal spiking PLEDs (periodic lateralised epileptiform discharges) Bi-PLEDs (bilateral PLEDs) Unilateral burst suppression Unilateral triphasic waves

Post-anoxic encephalopathy often leads to EEG alterations characterised by sharp generalised periodic, single, or grouped discharges, which appear within a flat or slow-activity background; myoclonus can arise from the first day, and is usually sensitive to stimuli. The point of administering an AED in these cases seems purely 'cosmetic' and has no evident benefit for the patient;[15] even so, diminishing myoclonus can simplify treatment for nurses and family. A recent article suggests that in some rare cases, low frequency and non-progressive epileptiform discharges can correspond to NCSE rather than to post-anoxic encephalopathy. In these events, propofol can 'unmask' the underlying state of epilepsy, revealing the absence of biological activity and, therefore, can be used as a 'diagnostic' drug second to BZD.[18]

Table 2: Management of status epilepticus.

Immediate measures (0-5 mins)	Non-invasive or invasive airway protection and oxygenation Vital signs monitoring (O_2 saturation, HR, BP) Fingerstick blood glucose Establish intravenous access Laboratory tests: complete blood count, electrolytes, liver enzymes, arterial blood gases, toxicology screen, serial troponins, AED blood levels Emergent initial AED therapy (if no IV access available, give midazolam IM, PO, or intranasally, or diazepam PR) Fluid resuscitation If serum glucose <60 mg/dl, administer 100 mg thiamine first and then 50% dextrose Call for EEG
Immediate measures (5-15 mins)	Neurological examination Urgent AED therapy for SE control Vasopressor support if needed Continuous EEG monitoring
Urgent measures (15-60 mins)	Urinary catheter Depending on clinical presentation: intracranial pressure monitoring and neurological diagnostic testing (MRI, CT, LP)
RSE measures (20-60 mins after 2nd AED)	RSE therapy if needed EEG continually running for titrating therapy and monitoring AED response

EEG: electroencephalographic; HR: heart rate; BP: blood pressure; AED: anti-epileptic drug; IV: intravenous; IM: intramuscular; PO: oral administration; PR: rectal administration; SE: status epilepticus; MRI: magnetic resonance imaging; CT: computed tomography; LP: lumbar puncture; RSE: refractory status epilepticus.

SE may occur in the setting of several internal or neurological diseases. In some forms of encephalopathy, of varying aetiology (i.e. metabolic, toxic, or immunologic), the clinical and EEG findings can be similar to those of NCSE, but treatment with BZD does not impact upon the patient's condition, which actually improves with treatment of the base disease. Some authors highlight, for example, the importance of considering anti-neutrophil cytoplasmic antibody (ANCA) dosage in patients with SE of unclear origin, and propose to promptly start adequate immunotherapy in patients with inflammatory changes at brain magnetic resonance imaging (MRI), with or without other systemic signs of ANCA-associated vasculitis.[19] Monoclonal antibody-based B cell depletion may represent a therapeutic alternative for antibody-mediated encephalopathy achieving a good outcome. Other authors have reported, therefore, a case of NCSE induced by acute hypothyroidism in a critically ill patient, and recommended studying the thyroid function in those patients presenting with unexplained SE accompanied with acute anasarca.[20]

NEURONAL AND CLINICAL CONSEQUENCES

A generalised convulsive state is a medical emergency burdened by high mortality, especially in the elderly, because repeated seizures swiftly induce metabolic and cardiocirculatory failure, hyperthermia, cerebral oedema, and potentially irreversible neuron damage. Excessive and prolonged muscular twitching leads to increased creatine kinase and, in the most severe cases, rhabdomyolysis, hyperkalaemia, hypocalcaemia, myoglobinuria, and potential renal failure; metabolic acidosis, caused by depletion of glycogen stores and anaerobic glycolysis, is also frequent. Many patients can develop respiratory acidosis by pulmonary aspiration, diminished respiratory drive, and efficacy of the skeletal-muscle pump. Lastly, a massive amount of circulating catecholamines can cause cardiac arrhythmias, cardiomyopathy (especially Takotsubo), and hyperglycaemia.

Many animal studies have shown how prolonged epileptic seizures, even non-convulsive, can lead to neuron damage. The increase in extracellular glutamate at excitotoxic levels,[21] associated with

an increased lactate/pyruvate ratio, can bring on cellular swelling, increased intracranial pressure, and cellular death, in addition to producing free radicals, inflammation, gliosis, atrophy, and synaptic reorganisation. A recent study also demonstrated that brief seizures result in structural and functional brain alterations, but confirmed that those caused by prolonged seizures are considerably more severe.[22] A number of anecdotal studies using MRI found cerebral acute oedema and chronic atrophy, as well as evidence of neuronal loss on magnetic resonance spectroscopy following NCSE.

Basic research and animal studies are essential to understanding the cellular and molecular mechanism of SE-induced brain pathology and to develop target-specific AEDs for these patients. Duration and frequency of epileptic activity correlates with the extent of neuron damage, so that optimal targeted therapy should provide fast and effective control of the SE and treatment of the accompanying symptoms during the first 6-20 mins.

The duration of SE prior to the initiation of treatment influences its effect, regardless of the type of drug used. The randomised clinical trial on prehospital treatment of SE revealed that the placebo group suffered from unfavourable consequences of prolonged seizure such as acquired neurological deficits or death, confirming that the emergency team have a high chance of administering BZD during the early SE time when the probability of seizure termination with drugs is the highest and neuronal damage is not yet established.[23]

According to many authors,[24] we suggest a time-dependent scale:

- 5-20/30 mins: Early SE (0-5 min interval within which most seizures spontaneously stop; 5-15 min optimum interval for initiation of emergent treatment)
- 20/30-60 mins: Established SE (urgent treatment)
- >60 mins: Refractory SE (refractory treatment)

It is important to underscore that an accumulation of complications is usually encountered in coma patients with SE and it is truly difficult to individuate complications due to persistent seizure activity from those originating from the causative medical disorder or from pharmacological treatments. The cause of SE remains the most important prognostic factor, with alcohol and AED withdrawal having the best outcomes; structural brain injuries such as anoxia-ischaemia, vascular lesions, and brain tumours have the worst prognosis. A prognostic score, the SE severity score (STESS), has been developed to predict survival before initiation of SE treatment (range: 0-6).[25] This score relies on the assessment of age, previous history of seizures, seizure type (simple partial, complex partial, absence of, or myoclonic seizure, generalised tonic–clonic seizure, or NCSE in a coma), and the extent of consciousness impairment.

TREATMENT

The main goal is to stop epileptic activity from both a clinical and an EEG standpoint. The initial treatment strategy involves the management of airways, ventilation and haemodynamics, initial pharmacological treatment of the seizure, analyses to investigate the trigger of the SE, and treatment of the identified cause (Table 2). The guidelines published in 2012 by the Neurocritical Care Society divide the therapeutic strategy into three phases: emergent initial AED therapy, urgent control AED therapy (in association with anti-epileptic maintenance therapy, even if the SE is immediately controlled), and potentially refractory therapy (reserved for SE failing to respond to the first two AEDs administered). The most recent guidelines from the USA and Europe on initial therapy (Emergent Initial Therapy) advocate the use of BZD, preferably IV, although intramuscular and rectal administration is possible. LZP is preferred for IV therapy, whereas midazolam is indicated for intramuscular administration (although it can also be administered intravenously, nasally, or orally) and diazepam for rectal administration (also available in IV form). Clonazepam is not frequently used. Controlled studies defining the exact dosages of SE treatment are not available. Although all reported dosages are derived from observational studies, they are widely used, as the dosage is based on numerous well-controlled clinical studies (Table 3).

The second step is to initiate control therapy of the SE (urgent control therapy), unless the trigger is resolved and if the seizure appears to have ended. For patients whose SE has been resolved, the aim is to reach therapeutic levels of an AED and to continue the maintenance therapy; for ongoing SE, the aim is to stop the seizures. The agents generally used are phenytoin/IV fosphenytoin,

valproic acid, phenobarbital, levetiracetam, or continuous infusion of midazolam; IV fosphenytoin is generally the drug of choice, except in patients with pre-existing epilepsy in whom use of sodium valproate is favoured. Serum levels of phenytoin and fosphenytoin should be carefully monitored due to their nonlinear and saturable kinetics, resulting in highly variable concentrations.

Table 3: Status epilepticus (SE) and refractory status epilepticus (RSE) pharmacological treatment.

DRUG	MECHANISMS OF ACTION	INITIAL DOSE & ALTERNATIVE DOSING	DOSAGES	RSE INITIAL DOSE	RSE CI TITRATED WITH EEG
DIAZEPAM Emergency treatment	Enhancement of GABA-ergic transmission (bond with $GABA_A$ receptor and increase of Cl^- conductance due to increase of channel opening frequency)	0.15 mg/kg IV up to 10 mg may repeat in 5' (*NCS-EFNS*) 0.1 mg/kg IV, may repeat in 10' (*LICE*)	Up to 5 mg/min		
FOSPHENYTOIN Emergency treatment Urgent treatment Refractory treatment	Extension of voltage-dependent Na+ channel refractory period	20 mg PE/kg IV, may give additional 5 mg/kg (*NCS*)	Up to 150 mg PE/min; may give an additional dose 10 mins after loading infusion (*NCS*)		
ISOFLURANE Refractory treatment	Inhibition of NMDA receptor Enhancement of GABA-ergic transmission (bond with $GABA_A$ receptor and increase of Cl^- conductance)			0.8-2 vol % (*LICE*)	Titrate with EEG
LIDOCAINE Refractory treatment	Inhibition of voltage-dependent Na+ channel			1.5-2 mg/kg bolus, may repeat only once (*LICE* - alternative treatment)	Up to 50 mg/min
LORAZEPAM Emergency treatment	Enhancement of GABA-ergic transission (bond with $GABA_A$ receptor and increase of Cl^- conductance due to increase of channel opening frequency)	0.1 mg/kg IV up to 4 mg may repeat in 5-10' (*NCS-EFNS*) 0.05-0.1 mg/kg IV, may repeat in 10' (*LICE*)	Up to 2 mg/min (IVP)		
MIDAZOLAM Emergency treatment Urgent treatment Refractory treatment	Enhancement of GABA-ergic transmission (bond with $GABA_A$ receptor and increase of Cl^- conductance due to increase of channel opening frequency)	0.2 mg/kg IM up to 10 mg (*NCS*) 5-10 mg IM or 5-10 mg rectal may repeat only once; 0.1-0.3 mg/kg IV bolus, up to 4 mg/min; 10 mg PO (the only formulation officially recommended in Italy for epilepsy treatment) (*LICE*)		RSE: 0.2 mg/kg at 2 mg/min (*NCS*) RSE/subtle SE: 0.2 mg/kg bolus (*EFNS*)	RSE: 0.05-2 mg/kg/h CI Breakthrough SE: 0.2 mg/kg bolus, increase CI rate by 0.05-0.1 mg/kg/h every 3-4 h (*NCS*) RSE/subtle SE: 0.05-0.4 mg/kg/h CI (*EFNS*) RSE: 0.05-0.4 mg/kg/h (*LICE*)

Table 3 continued.

DRUG	MECHANISMS OF ACTION	INITIAL DOSE & ALTERNATIVE DOSING	DOSAGES	RSE INITIAL DOSE	RSE CI TITRATED WITH EEG
PENTOBARBITAL Refractory treatment	Enhancement of GABA-ergic transmission (bond with GABAA receptor and increase of Cl^- conductance due to increase of channel opening time)			RSE: 5-15 mg/kg IV, may give additional 5-10 mg/kg; infusion rate ≤50 mg/min (*NCS*)	RSE: 0.5-5 mg/kg/h CI Breakthrough SE: 5 mg/kg bolus, increase CI rate by 0.5-1 mg/kg/h every 12 h (*NCS*)
PHENOBARBITAL Emergency treatment Urgent treatment Refractory treatment	Enhancement of GABA-ergic transmission (bond with GABAA receptor and increase of Cl^- conductance due to increase of channel opening time)	20 mg/kg IV, may give an additonal 5-10 mg/kg (*NCS*) 10-20 mg/kg (*LICE* - alternative treatment)	50-100 mg/min IV, may give additonal dose 10 mins after loading infusion (*NCS*) 50-75 mg/min IV (*LICE* - alternative treatment)	RCPSE: 20 mg/kg IV (*EFNS*)	RCPSE: 50 mg/min IV (*EFNS*)
PHENYTOIN Emergency treatment Urgent treatment Refractory treatment	Extension of voltage-dependent Na+ channel refractory period	20 mg/kg IV, may give an additonal 5-10 mg/kg (*NCS*) 18 mg/kg IV (*EFNS*) In patients already treated with benzodiazepines 15-18 mg/kg IV, may give an additonal 5 mg/kg (*LICE*)	Up to 50 mg/min IV; may give additonal dose 10 mins after loading infusion (*NCS*)		
PROPOFOL Refractory treatment	Enhancement of GABA-ergic transmission (bond with GABAA receptor and increase of Cl^- conductance due to increase of channel opening time) Block of voltage-dependent Na+ channel			RSE: start at 20 µg/kg/min, with 1-2 mg/kg loading dose (*NCS*) RSE/subtle SE: start with 2-3 mg/kg bolus, then 1-2 mg/kg boluses until seizure control (*EFNS*) RSE: 2-5 mg/kg bolus (*LICE*)	RSE: 30-200 µg/kg/min Breakthrough SE: Increase CI rate by 5-10 µg/kg/min every 5 mins or 1 mg/kg bolus plus CI titration (*NCS*) RSE/subtle SE: 4-10 mg/kg/h CI (*EFNS*) RSE: 5 mg/kg/h CI for at least an hour (*LICE*)
THIOPENTAL Refractory treatment	Enhancement of GABA-ergic transmission (bond with GABAA receptor and increase of Cl^- conductance)			RSE: 2-7 mg/kg, ≤50 mg/min (*NCS*) RSE/subtle SE: 3-5 mg/kg bolus, 1-2 mg/kg every 2-3 mins until control (*EFNS*) RSE: 5-7 mg/kg/20' then 50 mg every 2-3 mins for "suppression burst" (*LICE*)	0.5-5 mg/kg/h CI Breakthrough SE: 1-2 mg/kg bolus, increase CI rate by 0.5-1 mg/kg/h every 12 h (*NCS*) 3.7 mg/kg/h CI (*EFNS*) 3-5 mg/kg/h CI (*LICE*)

Table 3 continued.

DRUG	MECHANISMS OF ACTION	INITIAL DOSE & ALTERNATIVE DOSING	DOSAGES	RSE INITIAL DOSE	RSE CI TITRATED WITH EEG
TOPIRAMATE Refractory treatment	Enhancement of GABA-ergic transmission Inhibition of excitatory transmission (action on kainate and AMPA receptor) Inhibition of carbonic anhydrase			200-400 mg NG/PO (*NCS*)	300-1,600 mg/day orally (divided 2-4 times daily) (*NCS*)
SODIUM VALPROATE Emergency treatment Urgent treatment Refractory treatment	Increase of PIP3 levels in the brain Inhibition of voltage-dependent Na+ channel Inhibition of voltage-dependent Ca^{2+} channel Alteration of GABA turnover resulting in inhibition of GABA catabolism	20-40 mg/kg IV, may give an additional 20 mg/kg (*NCS*) 15-30 mg/kg IV (*LICE* - alternative treatment)	3-6 mg/kg/min, may give additional dose 10 mins after loading infusion (*NCS*) 1-2 mg/kg/h CI (*LICE* - alternative treatment)	RCPSE: 25-45 mg/kg IV (*EFNS*)	RCPSE: Up to 6 mg/kg/min (*EFNS*)

Emergency treatment: initial therapy; urgent treatment: SE control therapy (if SE has been controlled with the emergency treatment, the aim is to achieve therapeutic levels of anticonvulsants and establish a maintenance therapy — if SE has not been controlled, the aim is to stop the crisis); refractory treatment: drug treatment indicated for SE unresponsive within 60 mins of emergency and urgent treatment.
$GABA_A$ receptor: γ-aminobutyric acid receptor; NCS: Neurocritical Care Society; EFNS: European Federation of Neurological Societies; LICE: Lega Italiana contro l'Epilessia (Italian League Against Epilepsy); PE: phenytoin equivalent; IV: intravenous; IM: intramuscular; PO: oral administration; CI: continuous infusion; subtle SE: subtle status epilepticus; NMDA receptor: N-methyl-D-aspartate receptor; RSE: refractory status epilepticus; RCPSE: refractory continuous partial status epilepticus; AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NG: nasogastric administration; PIP3: phosphatidylinositol 3,4,5-trisphosphate; CI: chloride; Ca^{2+}channel: calcium channel; IVP: intravenous pyelogram.

Refractory Status Epilepticus

Control of the SE should be achieved within 60 mins using the two treatments mentioned above. If unsuccessful the SE is considered RSE. In this case, it is possible to repeat a bolus of the drug used in the second step, or to start an additional agent,[2] since no data suggest that watchful waiting is safer than initiating more aggressive therapy immediately. If the intermittent bolus therapy fails, it is advisable to use continuous infusion; however, it is recommended to first consider boluses of a drug not previously used (fosphenytoin/phenytoin, levetiracetam, sodium valproate). Bolus doses of the agent used for the continuous infusion should also be started and repeated, in addition to the infusion. If the drug chosen is ineffective it is advisable to use another one from the list (Table 3).

The intensity of the treatment is dictated by the EEG findings, with the aim of obtaining burst suppression. Conversely, definite indications are lacking on what duration of treatment is needed to maintain. As a rule, after 24-48 h the continuous infusion drug dose is gradually weaned; if at this point the patient again shows signs of relapse, the prior or a higher dosage is reinstated for a greater period of time, with or without an additional agent. No data are available indicating how much time should pass before a treatment

is considered useless; some patients need to be treated for weeks or months before recovering. Furthermore, studies defining a standard guideline on discontinuing the continuous infusion and starting the intermittent maintenance treatment with an AED have yet to be conducted.

Alternative Therapy for Refractory Status Epilepticus

The onset of RSE is mediated in part by γ-aminobutyric acid ($GABA_A$) receptor internalisation in a condition of sustained neuroexcitation with consequent loss of response to GABA-ergic drugs.[26] There is also evidence of increased α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and N-methyl-D-aspartate (NMDA) receptor expression on the synaptic membrane, which determines increased sensitivity to excitatory neurotransmitters. Thus, research is aiming to develop drugs acting as excitatory antagonists/inhibitory agonists that may block $GABA_A$ receptor internalisation or increased excitatory receptor expression. Ketamine, by way of its NMDA channel blocking action, has been used on occasion with less than stellar results and with significant side-effects such as psychosis and severe neuron damage.[27]

Recently, in a systematic review of inhaled anaesthetics used to treat RSE, Zeiler et al.[28] individuated isoflurane as an agent that can be used with fair efficacy (Oxford level 4, Grade D) after the failure of other therapies. Hypothermia is now routinely used in several centres around the world for patients with RSE despite an extremely small evidence base, as well as magnesium sulphate infusion.[29] IV pyridoxine is an effective treatment in both rare patients with an inborn error of metabolism of pyridoxine and SE patients with no clear deficit in pyridoxine metabolism.[29] Finally, immunotherapy with steroids, IV immunoglobulins, plasma exchange, or immunosuppressive drugs could constitute an interesting treatment choice in cases of SE associated with immunological disorders, as mentioned above.[29]

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REFERENCES

1. Epilepsy Foundation of America. Treatment of convulsive status epilepticus: Recommendations of the Epilepsy Foundation of America's Working Group on Status Epilepticus. JAMA. 1993;270(7):854-9.

2. Brophy GM et al. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care. 2012;17(1): 3-23.

3. Millikan D et al. Emergency treatment of status epilepticus: current thinking. Emerg Med Clin North Am. 2009;27(1):101-13.

4. Kovács R et al. Mechanism underlying blood-brain barrier dysfunction in brain pathology and epileptogenesis: role of astroglia. Epilepsia. 2012;53 Suppl 6:53-9.

5. Yu N et al. Modulation of Immunity and the Inflammatory Response: A New Target for Treating Drug-resistant Epilepsy. Curr Neuropharmacol. 2013;11(1):114-27.

6. Niquet J et al, "Programmed Necrosis After Status Epilepticus," Noebels JL et al. (eds.), Jasper's Basic Mechanisms of the Epilepsies (4th edition) 2012, New York City, NY: Oxford University Press.

7. Sutter R, Kaplan PW. Electroencephalographic criteria for nonconvulsive status epilepticus: synopsis and comprehensive survey. Epilepsia. 2012;53 Suppl 3:1-51.

8. Bauer G, Trinka E. Nonconvulsive status epilepticus and coma. Epilepsia. 2010;51(2):177-90.

9. Maganti R et al. Nonconvulsive status epilepticus. Epilepsy Behav. 2008;12(4):572-86.

10. Vignatelli L et al. Incidence and short-term prognosis of status epilepticus in adults in Bologna, Italy. Epilepsia. 2003;44(7):964-8.

11. Knake S et al. Incidence of status epilepticus in adults in Germany: a prospective, population-based study. Epilepsia. 2001;42(6):714-8.

12. Lindgren C et al. Frequency of non-convulsive seizures and non-convulsive status epilepticus in subarachnoid hemorrhage patients in need of controlled ventilation and sedation. Neurocrit Care. 2012;17(3):367-73.

13. Mecarelli O et al. EEG patterns and epileptic seizures in acute phase stroke. Cerebrovasc Dis. 2011;31(2):191-8.

14. Belcastro V et al. Non-convulsive status epilepticus after ischemic stroke: a hospital-based stroke cohort study. J Neurol. 2014;261(11):2136-42.

15. Holtkamp M, Meierkord H. Nonconvulsive status epilepticus: a diagnostic and therapeutic challenge in the intensive care setting. Ther Adv Neurol Disord. 2011;4(3):169-81.

16. Treiman DM et al. A progressive sequence of electroencephalographic changes during generalized convulsive status epilepticus. Epilepsy Res. 1990;5(1):49-60.

17. Claassen J et al. Recommendations on the use of EEG monitoring in critically ill patients: consensus statement from the neurointensive care section of the ESICM. Intensive Care Med. 2013;39(8):1337-51.

18. Koutroumanidis M et al. "Paradoxical" EEG response to propofol may differentiate post-cardiac arrest non-convulsive status epilepticus from diffuse irreversible cerebral anoxia. Epileptic Disord. 2014;16(4):510-7.

19. Ferlazzo E et al. Positivity to p-ANCA in patients with status epilepticus. BMC Neurol. 2014;14:148.

20. Rocco M et al. Nonconvulsive status epilepticus induced by acute

hypothyroidism in a critically ill patient. Intensive Care Med. 2011;37(3):553-4.

21. Vespa P et al. Increase in extracellular glutamate caused by reduced cerebral perfusion pressure and seizure after human traumatic brain injury: a microdialysis study. J Neurosurg. 1998;89(6):971-82.

22. Cardoso A et al. Seizure-induced structural and functional changes in the rat hippocampal formation: comparison between brief seizures and status epilepticus. Behav Brain Res. 2011;225(2):538-46.

23. Lowenstein DH et al. The prehospital treatment of status epilepticus (PHTSE) study: design and methodology. Control Clin Trials. 2001;22(3):290-309.

24. Raspall-Chaure M et al. The epidemiology of convulsive status epilepticus in children: a critical review. Epilepsia. 2007;48(9):1652-63.

25. Rossetti AO et al. A clinical score for prognosis of status epilepticus in adults. Neurology. 2006;66(11):1736-8.

26. Goodkin HR et al. Impact of receptor changes on treatment of status epilepticus. Epilepsia. 2007;48 Suppl 8:14-5.

27. Mewasingh LD et al. Oral ketamine in paediatric non-convulsive status epilepticus. Seizure. 2003;12(7):483-9.

28. Zeiler FA et al. Modern inhalational anesthetics for refractory status epilepticus. Can J Neurol Sci. 2015;42(2):106-15.

29. Ferlisi M, Shorvon S. The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy. Brain. 2012;135(Pt 8):2314-28.