

Review

Management of status epilepticus in adults. Position paper of the Italian League against Epilepsy

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ARTICLE INFO

Article history:

Received 29 August 2019

Revised 30 September 2019

Accepted 30 October 2019

Available online xxxx

Keywords:

Status epilepticus

Epilepsy

Treatment

Antiepileptic drugs

Position paper

Italian League against Epilepsy

ABSTRACT

Since the publication of the Italian League Against Epilepsy guidelines for the treatment of status epilepticus in 2006, advances in the field have ushered in improvements in the therapeutic arsenal. The present position paper provides neurologists, epileptologists, neurointensive care specialists, and emergency physicians with updated recommendations for the treatment of adult patients with status epilepticus. The aim is to standardize treatment recommendations in the care of this patient population.

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1. Introduction

Since the publication of the Italian League against Epilepsy (Lega Italiana Contro l'Epilessia, LICE) guidelines for the treatment of status epilepticus (SE) in 2006 [1], advances in this field have ushered in improvements in the therapeutic arsenal. Two distinct entities are now distinguished: the prehospital

stage and super-refractory SE (SRSE). There is concern, however, that the use of medications newly introduced into clinical practice sometimes relies on low or very low evidence. The reasons are various: insufficient statistical power of randomized controlled trials (RCTs) with heterogeneous selection criteria and patient classification, unclear description of electroencephalogram (EEG) patterns before, during, and after pharmacological intervention, and discrepancies in the use of study products [2]. Furthermore, outcome and follow-up duration differ across clinical studies. These limitations are even more evident for trials conducted in refractory SE (RSE) and SRSE. Finally, small case series report treatment with drugs that are not part of the conventional therapeutic strategy for SE [3,4].

So-called nonconvulsive SE poses further therapeutic challenges, given the wide spectrum of clinical conditions and lack

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of robust evidence supporting aggressive treatment. Therapeutic uncertainties have been only partly addressed by the recent introduction of a new definition and classification of SE [5]. In the present work, time to intervention (T1) and maximum time to seizure control (T2) are differentiated according to seizure semiology. This difference provides the rationale for different treatment algorithms, which are often based on the clinical experience of single authors. This position paper of the Italian League against Epilepsy is addressed to neurologists, epileptologists, neurointensive care specialists, and emergency physicians. It provides recommendations for the treatment of adult patients with SE. The aim is to standardize treatment in the care of this patient population.

2. Methods

A systematic literature search of the MEDLINE database was performed; articles on the treatment of SE in adults published in English between January 2005 and March 2018 were retrieved using the search terms “status epilepticus AND treatment” and “status epilepticus AND randomized clinical trial”. All articles reporting the results of therapeutic studies were evaluated, including RCTs, open trials, prospective studies, meta-analyses of RCTs, as well as retrospective studies and case reports on the treatment of SRSE. The most relevant trials published before 2005, which had been evaluated and included in the previous Italian League against Epilepsy guidelines [1], were also included. Studies were evaluated according to evidence criteria from the American Academy of Neurology [6], which are presented in a reduced and modified version in *Appendix 1* (Supplementary Material); evidence for recommendations is graded A > B > C > U.

This document was submitted to the LICE Executive Committee for approval and published on the LICE website.

3. General interventions

3.1. Prehospital management of status epilepticus

The recommendations for the management of epileptic seizures apply equally to the prehospital management of SE to ensure cardiorespiratory stability and to prevent or minimize the risk of injuries. Calling for urgent hospital transportation should always be considered if it is the patient's first seizure episode and if the first pharmacological intervention has not brought clear improvement.

3.2. Hospital management of status epilepticus

3.2.1. Initial stage

- Evaluate and stabilize cardiocirculatory function
- Ensure airway patency and administer oxygen
- Order fast blood glucose test; if indicated, administer intravenous (IV) glucose (preceded by intramuscular (IM) thiamine 100 mg in patients with suspected chronic alcohol abuse)
- Ensure venous access
- Order blood tests for: complete blood count, erythrocyte sedimentation rate, C-reactive protein, coagulation tests, creatine kinase, liver and renal function, plasma electrolytes (including calcium and magnesium, sodium and potassium)
- Consider toxicological screen and drug level monitoring of antiepileptic drugs in patients under antiepileptic treatment
- Monitor and treat acidosis when appropriate.

3.2.2. Definite status epilepticus stage (from 20–30 to 60–90 min after treatment start)

- Investigate the cause of SE with diagnostic exams appropriate for the clinical context (computed tomography [CT], magnetic resonance

imaging [MRI], lumbar puncture) and start etiological treatment as soon as possible

- Start EEG monitoring, if not already done, to confirm diagnosis and verify therapy effectiveness (mandatory for diagnosis if nonconvulsive SE is suspected)
- Monitor blood pressure and treat hypotension
- Consider transferring the patient to intensive care for further therapy
- Correct eventual metabolic derangements.

3.2.3. Refractory status epilepticus and super-refractory status epilepticus stage

If generalized motor manifestations are present, drugs usually requiring respiratory assistance are given. This level of care is carried out in an intensive-care setting, which is not discussed in this document. In nonconvulsive SE, the indications at this level of treatment are still debated; therefore, interventions vary from case to case, and management decisions are necessarily left to the discretion of the attending physician. The indication for neurologists to perform EEG monitoring to verify treatment results remains valid also in this setting.

3.2.4. Comments and literature review

Targeted examination is necessary, particularly in the definite, refractory, and super-refractory stages, as not all tests can be performed in all patients. Published evidence for diagnostic workup in children and adults has been reviewed [7,8], but there is no definitive conclusion on indications for the various tests. The investigation of cause is therefore to be tailored to the clinical situation and as quickly as possible since etiology is the main factor influencing prognosis, more so than treatment itself. In brief, successful treatment of the underlying cause is crucial to the outcome [9,10].

4. Pharmacological intervention

See Fig. 1 for summary.

4.1. Prehospital management

• Diazepam (level A)

Route of administration: rectal
Dosing: 0.2–0.5 mg/kg

• Midazolam (level A)

(not approved for this indication in Italy)

Route of administration: intramuscular (IM), oral, or intranasal.

Dosing: 10 mg if body weight > 40 kg, 5 mg if body weight 13–40 kg in a single dose.

4.1.1. Comments and literature review

Until some years ago, rectal diazepam was the only drug prescribed in Italy in this scenario [11,12]. The Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) study [13], however, demonstrated that IM midazolam was at least as efficacious as IV lorazepam and that it can be administered rapidly and easily by paramedics in the prehospital setting. Because absorption times and rates for oral or intranasal midazolam do not significantly differ from IM administration, it is reasonable to recommend the use of IM, oral or intranasal administration of midazolam as a valid alternative to rectal diazepam, especially in adults for obvious ease of administration.

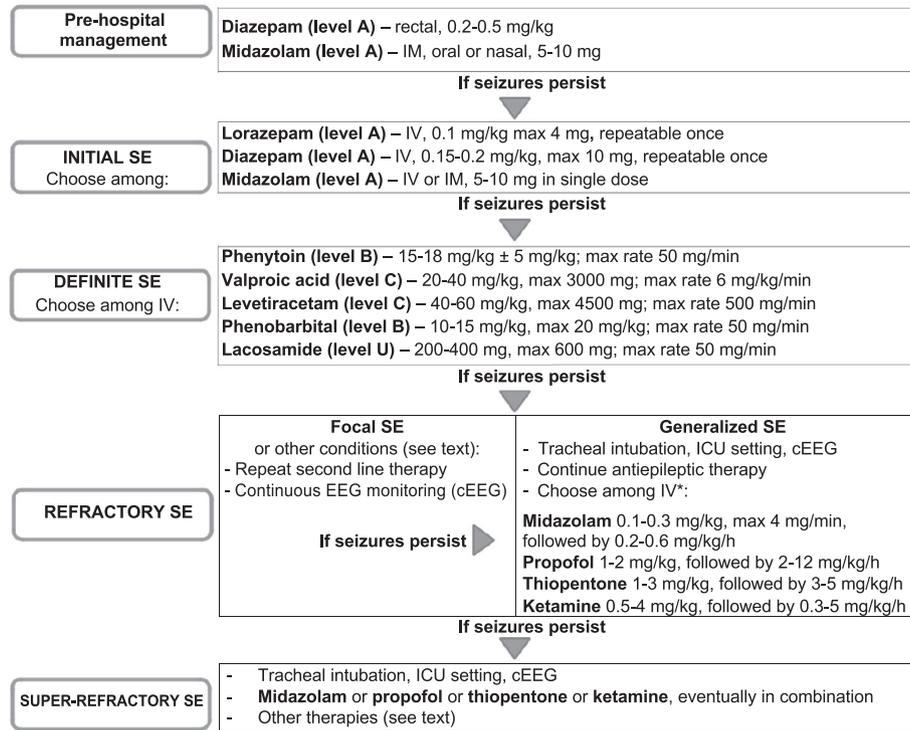


Fig. 1. Workflow for pharmacological intervention. * Titration should aim to suppress seizures or burst suppression. SE: status epilepticus; ICU: intensive care unit; cEEG: continuous EEG.

4.2. Intra-hospital management

4.2.1. Initial status epilepticus stage

• Lorazepam (level A)

Route of administration: IV

Dose: 0.05–0.1 mg/kg max 4 mg, not repeatable more than once

• Diazepam (level A)

Route of administration: IV

Dose: 0.15–0.2 mg/kg, max 10 mg, not repeatable more than once

• Midazolam (level A)

Route of administration: IV or IM

Dose: 10 mg if body weight > 40 kg, 5 mg if body weight 13–40 kg, in a single dose

4.2.1.1. Comments and literature review. The indication to use a benzodiazepine as first-line medication is widely recognized [14]. Some comparative studies [15–17] have demonstrated greater efficacy of lorazepam compared to diazepam, with no differences in mortality rates during the SE episode. In two studies lorazepam [14–18] showed a trend towards higher efficacy in seizure control and lower incidence of side effects compared to diazepam + phenytoin. A recent comparative trial between levetiracetam and lorazepam [19] showed equal probability of success with both drugs, while another trial [18] found no statistical difference either between phenobarbital and diazepam + phenytoin or between phenobarbital and phenytoin. Furthermore, two comparative studies between IV valproate and IV diazepam reported no significant difference in efficacy but a lower risk of hypotension for valproate [20]. In two RCTs, lorazepam and diazepam

were more effective than placebo, although without significant differences in efficacy between the two study drugs [14,21].

In conclusion, first-line therapy of initial SE in a hospital setting relies on the use of injectable benzodiazepines. There is insufficient evidence to prefer IV lorazepam or diazepam or IM midazolam. To date, the use of antiepileptic drugs other than benzodiazepines as first-line therapy is not supported by robust evidence; it may be reconsidered if there are contraindications to benzodiazepines [20,22,23].

4.2.2. Definite status epilepticus stage

Definite SE persists after the administration of first-line treatment with benzodiazepines; therefore, a second line of therapy with IV anti-epileptic drugs is needed. A list of antiepileptic drugs for definite SE is given below.

• Phenytoin (level B)

Dose: 15–18 mg/kg, eventually followed by 5 mg/kg

Max infusion rate: 50 mg/min

Eventual dilution: saline solution

Contraindications: atrioventricular blockade, bradycardia, severe hypotension

Notes:

- Must be infused via separate venous access in a large vein to reduce the risk of phlebitis
- Heart rate and arterial pressure must be monitored during infusion
- IV formulation contains propylene glycol
- Avoid dilution in glucose solution (precipitation of solute).

• Valproic acid (level C)

(not approved for this indication in Italy)

Dose: 20–40 mg/kg, max dose 3000 mg

Max infusion rate: 6 mg/kg/min

Eventual dilution: saline or glucose solution

Contraindications: liver impairment, mitochondrial diseases, liver porphyria

Notes:

- Risk of liver and pancreas toxicity
- May cause thrombocytopenia and impair platelet aggregation (use with caution in patients with intracranial bleeding).

• Levetiracetam (level C)

(not approved for this indication in Italy)

Dose: 40–60 mg/kg, max dose 4500 mg

Max infusion rate: 500 mg/min

Eventual dilution: saline or glucose solution

Contraindications: severe renal failure

Notes:

- Has no cardiovascular side effects and low probability of worsening level of consciousness
- No pharmacokinetic interactions
- Dosing has to be adjusted according to severity of renal failure
- Is dialyzed: dialysis every 4 h, administer additional dose of 250–500 mg.

• Phenobarbital (level B)

Dose: 10–15 mg/kg, max dose 20 mg/kg.

Max infusion rate: 50 mg/min

Eventual dilution: saline solution

Contraindications: porphyria, liver failure, severe heart disease, severe respiratory depression

Notes:

- Requires continuous cardiorespiratory monitoring
- IV formulation contains propylene glycol.

• Lacosamide (level U)

(not approved for this indication in Italy)

Dose: 200–400 mg in a single dose, max dose 600 mg

Max infusion rate: 50 mg/min

Eventual dilution: saline or glucose solution

Contraindications: II–III grade atrioventricular blockade

Notes:

- Particularly when used at doses >400 mg, monitor heart function if concurrent administration of drugs prolonging PR interval
- No pharmacokinetic interactions.

Details on trials (RCTs + open studies) assessing the role of second-line antiepileptic drugs for the treatment of SE in adults are reported in Appendix 2 (Supplementary Material).

4.2.2.1. Comments and literature review. Previous of Italian League against Epilepsy (2006) guidelines [1] recommended phenytoin and phenobarbital as first-choice drugs for the treatment of SE in adults. Based on most recent studies, other drugs may reasonably be used for treating definite SE. There is quite robust evidence supporting valproic

acid and levetiracetam, and the tolerability profile of these drugs is good [24].

In a systematic review with meta-analysis published in 2014, Yasiry and Shorvon [2] analyzed 27 studies reporting efficacy outcomes in patients with definite SE treated with these five drugs as second-line therapy. Despite multiple sources of clinical and methodological heterogeneity across the studies (study design, population demographics, dosing schedule, infusion rate, clinical characteristics, outcome measurement), the following results were reported:

- **Phenytoin:** 8 studies including 294 episodes of definite SE. Average efficacy (SE cessation): 50%
- **Valproic acid:** 9 studies including 251 episodes of definite SE (not only adults). Average efficacy: 75%
- **Phenobarbital:** 3 studies including 43 episodes of definite SE (not only adults). Average efficacy: 73%
- **Levetiracetam:** 10 studies including 206 episodes of definite SE. Average efficacy: 68%
- **Lacosamide:** meta-analysis was not possible because at the time of publication only 4 patients were treated in RCT with lacosamide as second-line therapy. A subsequent RCT reported 33 episodes of definite SE with an average efficacy of 63.6% [25].

Although the review did not include a meta-analysis [2] on lacosamide, recently published evidence suggests a possible therapeutic role for this drug in definite SE, both convulsive and nonconvulsive [26–29]. An observational study by Lang et al. [27] reported SE cessation in 77% of patients receiving lacosamide. In a study by Moreno Morales et al. [28], lacosamide was used in different phases of SE (from first-line to fourth-line drug), with EEG resolution of SE achieved in 69.6% of convulsive and in 46.6% of nonconvulsive SE. Finally, in a recent RCT, Misra et al. [25] found no significant difference in efficacy between valproate and lacosamide (1-hour seizure cessation rate 63.6% with lacosamide vs. 69.7% with valproate); however, the study was underpowered to detect a statistically significant and a clinically relevant difference between the two drugs. The correct loading dose proposed for lacosamide is still debated, as higher doses have not always been reported to be more effective [30–32].

In conclusion, phenytoin, phenobarbital, valproate, levetiracetam, and lacosamide appear to be effective in the treatment of definite SE, with no clear indication for the preferred use of one drug over another.

4.2.3. Refractory status epilepticus (RSE) stage

Refractory SE does not respond to treatment with benzodiazepines and at least one antiepileptic drug considered suitable for treating definite SE and used at an appropriate dosage. For RSE, recommendations are based on signs and symptoms, distinguishing between convulsive and nonconvulsive RSE.

4.2.3.1. Refractory tonic-clonic convulsive status epilepticus stage. Refractory SE is characterized by tonic-clonic movements of all four limbs. An operative definition of SE by LICE does not foresee a temporal limit but rather defines RSE only according to the lack of response to second-line antiepileptic drug therapy. It should be noted that the drugs that may be used in this stage have an insufficient level of evidence (level U).

• Midazolam (level U):

Dose: Bolus 0.2 mg/kg at max rate of 4 mg/min (may be repeated), then continuous infusion at 0.1–2 mg/kg/h.

Notes:

- Has a rapid action and good safety profile
- May be associated with tachyphylaxis, with risk of seizure recurrence

- Risk of accumulation in the obese and the elderly and in patients with renal failure
- Should be titrated until seizure cessation based on EEG monitoring. When used in monotherapy, an EEG suppression burst pattern is difficult to obtain. When deeper anesthesia is needed, it is common practice to associate midazolam with propofol
- Is the most widely studied anesthetic drug, with a lower risk of side or toxic effects than thiopental. High doses (0.4 mg/kg/h) have the same safety profile as lower doses (0.2 mg/kg/h), with reduced seizure recurrence and lower mortality rates [33].

• Propofol (level U)

(not approved for this indication in Italy)

Dose: bolus 1–2 mg/kg (may be repeated), followed by continuous infusion at 2–12 mg/kg/h (caution warranted when >5 mg/kg/h).

Notes:

- Short-acting anesthetic with excellent pharmacokinetics, rapid action, and very short half life
- May lead to cardiorespiratory depression, involuntary movements, and risk of propofol infusion syndrome (PRIS), especially with prolonged use (cardiotoxicity, lactic acidosis, hypertriglyceridemia, and rhabdomyolysis). Carefully evaluate concomitant use of vasoconstrictors, steroids, and carbonic anhydrase inhibitors if prolonged infusion (>24–48 h), daily monitoring of pH, creatine kinase, and blood lactate levels may allow early diagnosis of PRIS [34,35]
- Combination of propofol and midazolam in continuous infusion may lower the required dose, improving the side-effect profile with equal effectiveness.

• Thiopental (level U)

(not approved for this indication in Italy)

Dose: bolus 1–3 mg/kg (may be repeated), followed by continuous infusion at 3–5 mg/kg/h.

Notes:

- Is a GABA-A agonist
- Has a strong antiepileptic action, reduces intracranial pressure, and lowers body temperature
- Causes severe respiratory and cardiocirculatory depression, is prone to accumulation, prolonging recovery time and duration of intubation after drug weaning [36]
- Carries risk for paralytic ileus, immunosuppression, lingual edema, and hypernatremia; is a CYP-P450 inducer.

• Ketamine (level U)

(not approved for this indication in Italy)

Dose: bolus 0.5–4 mg/kg, then infusion at 0.3–5 mg/kg/h.

Notes:

- Is an N-methyl-D-aspartate (NMDA) receptor antagonist
- Does not cause cardiorespiratory depression but has sympathomimetic action
- May induce tachycardia and other arrhythmias, including asystole [37]; may trigger arterial hypertension and increase intracranial pressure
- Experience with its use has considerably increased in the last 5 years, with at least 200 adult cases reported in retrospective

case series. In patients with compromised hemodynamics (particularly arterial hypotension), the use of ketamine may allow suspension of vasopressor treatment (up to 80% in a retrospective series) [38]. Furthermore, in a pediatric study, sedation with ketamine alone obviated the need for endotracheal intubation [39]

- Rarely used as monotherapy, it is usually combined with continuous infusion of another anesthetic drug.

4.2.3.2. Comments and literature review. There is no evidence supporting a specific anesthetic agent over another owing to the rarity of this condition and the difficulty of performing randomized trials in this setting [36]; the choice of a drug will depend on patient characteristics, availability of medications, experience, and preference of the attending physician. Continuous infusion of anesthetic drugs should be preferentially initiated under continuous EEG monitoring, since convulsive SE often evolves into nonconvulsive SE in critical patients [40]. Most experts agree that anesthetic therapy should be titrated until cessation of all electric seizure activity and/or achievement of a burst-suppression pattern. It is not yet clear whether achieving burst suppression or isoelectric EEG may always prove beneficial compared to electrical seizure control [41,42]. As this pattern can be obtained only with higher dosages of anesthetics, and the side effects of anesthetic agents have an impact on outcome [43], the need to sedate the patient at such a level must be carefully evaluated. When needed, continuous infusion of anesthetic drugs should be maintained for 24 to 48 h; in selected cases, a shorter period of 12 h may be considered [44]. The anesthetic drug should then be tapered over the next few hours: a common approach is to halve the infusion rate every 1–2 h, adapting the rate to the patient's electroclinical condition. If seizures relapse, possible options are reintroduction of the anesthetic drug at equal or higher dose, combination with a second agent, and switching to a different anesthetic. After a relapse, it is common practice to increase the duration of the following anesthesia cycle [45]. Treatment with antiepileptic drugs should be continued at adequate doses; early change of underlying antiepileptic drugs should not be done during this phase, while changes in antiepileptic therapy may be considered in prolonged RSE [37]. Antiepileptic drugs with GABA-ergic mechanism of action may become ineffective because of internalization of GABA-A receptors on the synaptic membrane [46], while drugs acting on NMDA and AMPA receptors may prove more effective in this stage [47]. Propylene glycol is used as excipient in IV preparations of lorazepam, phenobarbital, diazepam, phenytoin, and thiopental [48]: tissue toxicity may arise if extravasation occurs at the infusion site, and other side effects can occur after prolonged infusion especially at high doses (e.g., hypotension, bradycardia, T- and QRS-wave abnormalities at electrocardiogram (ECG), arrhythmias, cardiac arrest, blood hyperosmolality, lactic acidosis, or hemolysis).

In conclusion, given the lack of robust data, the choice among drugs should be made on a case-by-case basis. Midazolam is probably to be preferred as first-choice in most patients, either as monotherapy or combined with propofol. Ketamine may also be useful in earlier phases, particularly if arterial hypotension is present. Because of its unfavorable safety and tolerability profile, we suggest reserving the use of thiopental for severe cases of RSE.

Refractory SE with or without myoclonus in patients with postanoxic encephalopathy can carry a dismal prognosis – particularly if the N20 component of somatosensory evoked potentials is absent at 72 h after SE onset, which is not modifiable by therapy [49]. Aggressive SE treatment is not always indicated in patients with postanoxic myoclonic RSE.

4.2.3.3. Nonconvulsive RSE stage. This RSE manifests without prominent motor manifestations. Since third-line therapy with anesthetic drugs is associated with significant side effects and complications, aggressive treatment should be reserved for situations in which the ongoing SE is a higher risk than the treatment itself. Some recent observational

studies have suggested that third-line treatment could even worsen patient outcome [43,50–52]; furthermore, scientific evidence on timing and entity of neuronal damage secondary to seizures is limited and mostly refers to convulsive SE [53–58]. The intensity of treatment should be decided on a case-by-case basis.

An alternative, less aggressive option is sequential use of different second-line antiepileptic drugs. Other more recent IV antiepileptic drugs have been used in this stage in recent years, although the evidence level is very poor. One of the latest antiepileptic drugs available in IV formulation is brivaracetam, which acts as a selective high-affinity ligand of the synaptic vesicle protein (SV2A). Its use in the treatment of SE has been described in various case series [59]: in the largest study, it was effective in 23/43 (54%) patients at a median loading dose of 100 mg [60]. As the evidence for this therapy is still extremely scarce, in our opinion it should be reserved for cases where more validated treatments have failed.

4.2.4. Super-refractory SE (SRSE) stage

Super-refractory SE is defined as SE persisting despite adequate third-level anesthetic drug therapy for at least 24 h or recurring after its suspension [45]. All drugs used in this stage have an insufficient level of evidence (level U) and are not approved for this indication in Italy. As the quality of the evidence supporting the use of these drugs is very low and is based on single case reports and small case series, we list these options with details for clinical guidance.

- **Lidocaine**
- **Inhalant anesthetic drugs (isoflurane and desflurane)**
- **Topiramate** (administered enterally with a loading dose of 300–800 mg, followed by a daily dose of 400–1000 mg in 2–3 doses) [61]
- **Perampanel** (administered enterally with a loading dose from 2 to 32 mg) [62]
- **Other drugs: pregabalin, clobazam.** In addition to these, the use of oxcarbazepine, rectal carbamazepine, rufinamide, stiripentol, paraldehyde, clomethiazole, etomidate has been reported [44,45].
- **Magnesium**
- **Corticosteroids and immunomodulating therapies** (IV methylprednisolone, possibly followed by oral prednisone, plasmapheresis, immunoglobulins, cyclophosphamide, and rituximab in selected cases): apart from treatment of cases of autoimmune etiology, as demonstrated in clinical and instrumental studies, inflammation may be relevant for seizure persistence [63,64], also in seronegative cases [65]. When autoimmune encephalitis is part of a paraneoplastic syndrome, rapid and aggressive treatment of the primary neoplasm is necessary [66].
- **Ketogenic diet:** initially used in children in the context of FIRES (*febrile infection-related epilepsy syndrome*) [67], its use has been attempted also in adults [68,69]; metabolic acidosis and hypertriglyceridemia are common side effects.
- **Hypothermia**
- **Neurosurgery:** may be considered in symptomatic SRSE with a lesion that might benefit from surgery [70]: high success rates were reported in 22 cases of urgent surgery (cortical or lobar resection, functional hemispherectomy, callosotomy, multiple subpial transection, often in combination) for focal-onset SRSE [69].
- **Vagal and trigeminal stimulation, transcranial magnetic stimulation, deep brain stimulation, electroconvulsive therapy**
- **Other drugs and nondrug therapies:** some nonantiepileptic drugs have been used in SRSE, e.g., verapamil, pyridoxine, cannabidiol oil, statins. Among the nondrug therapies, two case reports described the use of exposure to classical music [71,72] and one on cerebrospinal fluid drainage [73].

4.2.4.1. *Comments and literature review.* Treatment of SRSE stage currently lacks any solid scientific evidence and relies only on the results

of case reports or small series, with a high risk of publication bias. The mainstay for SRSE therapy remains continuous infusion of anesthetic drugs. Since the available evidence shows that good functional recovery may be possible even in patients with a very prolonged SRSE [74], there is currently no time limit beyond which intensive treatment should be considered, except in cases of unknown etiology [75]. The treatment of etiology remains crucial, as the cause of SE is the major determinant of outcome [9,76].

Declaration of competing interest

Dr. Fabio Minicucci has received personal compensation as scientific advisory board member for UCB and Eisai.

Dr. Stefano Meletti has received personal compensation as scientific advisory board member for UCB and Eisai.

Dr. Oriano Mecarelli has received compensation related to congress attendance and speeches by UCB, Eisai, BIAL, ECUPHARMA, GW.

Dr. Francesco Brigo received travel support from Eisai, LUSOFARMACO, and UCB PHARMA; he acted as consultant for Eisai, LIVANOVA and UCB PHARMA.

Acknowledgments

We thank Marco Vabanesi (Department of Neurology, San Raffaele Hospital, Milan, Italy) for his assistance with writing this position paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.yebeh.2019.106675>.

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