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What's new in status epilepticus?

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Introduction

Status epilepticus (SE) is essentially an acute, prolonged epileptic crisis, defined by a continuous seizure that lasts 5 min or more. It is the second-most frequent life-threatening neurological emergency after stroke and bears considerable risks of morbidity and mortality [1, 2]. To prevent potentially dismal complications, recent North American and European guidelines strongly advocate timely (immediate to urgent) treatment. At present, the therapeutic arsenal is subdivided into three lines, consisting of the administration of benzodiazepines (first line of treatment), of antiseizure drugs (second line of treatment), and of general anesthetics (third line of treatment) [3, 4]. Despite this relatively simple approach, several uncertainties are associated with the optimal use of specific agents and the best sequence of their administration [2, 5]. Our recommended strategy for treating SE treatment is given in Fig. 1. In subsequent sections of this

article we provide an overview of the most recent clinical findings corroborating this strategy.

Lines of treatment for SE

First line of treatment

In a large multicenter, randomized controlled pre-hospital trial, Silbergleit et al. compared the efficacy of intramuscular (IM) midazolam (MDZ, 10 mg) and intravenous (IV) lorazepam (LZP, 4 mg) therapy in 893 adults and children with convulsive SE [6]. The primary outcome, namely, seizure termination prior to arrival at the hospital, was achieved in 73 % and 63 % of those treated with MDZ and LZP, respectively ($p < 0.001$ for superiority). Need to intubation, recurrent seizures, and safety outcomes were similar among the two treatment groups, and failure to set an IV line was identified as the most likely cause of the difference in the primary outcome.

These findings clearly support the use of IM MDZ as the preferred first-line treatment, at least for convulsive SE, at the doses studied. Whether this approach is superior to the IV administration of LZP at the 0.1 mg/kg dose, which is standard in North America [3], is still unknown.

Second line of treatment

A relatively wide palette of IV antiseizure drugs may be used at this step, including not only the "classical" ones, i.e., phenytoin (PHT), valproate (VPA), and phenobarbital (PB), but also levetiracetam (LEV) and lacosamide (LCM). A few randomized studies have investigated the effectiveness of PHT, VPA, and LEV, but all are flawed by methodological issues (sample size, statistical
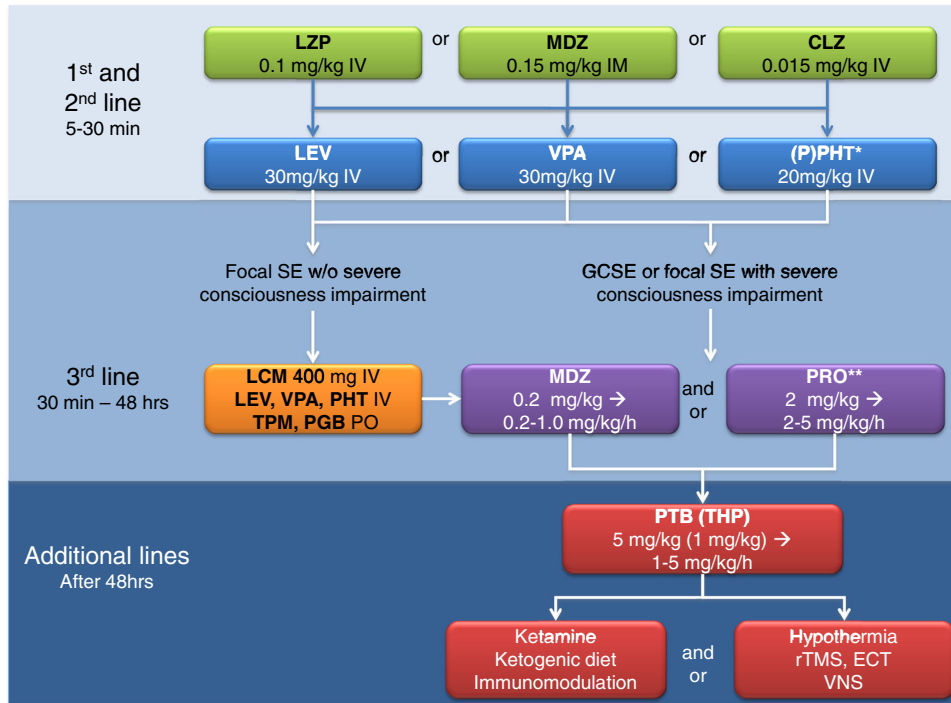
Fig. 1 Flow chart of status epilepticus (*SE*) treatment, with standard dosages and administration routes. The *middle line* (MDZ, VPA) is preferred; alternatives are indicated on the *left* and *right side*. The first line of treatment (benzodiazepines) is shown in *green boxes*; the second line of treatment [intravenous (*IV*) antiepileptic compounds] in *blue boxes*, and the third line of treatment (IV general anesthetics) in *orange* and *lilac boxes*; additional lines are given in *red boxes*. In patients with ongoing SE without severe consciousness impairment, non-sedating antiepileptic agents should be preferred—at least initially—to anesthetic agents (*orange box*). *PO* oral administration, *IM* intramuscular injection. *Single asterisk* Not suitable for some generalized syndromes (including myoclonic or absence seizures), *double asterisks* use in combination with benzodiazepines, but avoid prolonged use without checking creatine kinase, lactate, and triglycerides. *CLZ* clonazepam, *ECT* electro-convulsive treatment, *LCM* lacosamide, *LEV* levetiracetam, *LZP* lorazepam, *MDZ* midazolam, *PGB* pregabalin, *(P)PHT* (phospho-)phenytoin, *PRO* propofol, *PTB* pentobarbital, *THP* thiopental, *rTMS* repetitive transcranial magnetic stimulation, *TPM* topiramate, *VNS* vagus nerve stimulation, *VPA* valproate

approach, use as first-line treatment, or particular geographical settings where infectious etiologies clearly predominate), thereby limiting their generalizability. Therefore, non-randomized analyses may still prove informative. In an assessment of 187 adult patients with any SE form, Alvarez et al. focused on the use of LEV, PHT, and VPA as second-line treatment (loaded at 20 mg/kg after treatment with benzodiazepines) [7]. These authors found that after adjustment for the most relevant outcome predictors, LEV failed to control SE more often than VPA [odds ratio (OR) 2.7; 95 % confidence interval (CI) 1.2–6.1] and that PHT was intermediately effective [7]. One caveat to their study is the relatively low dosages of LEV and VPA. A meta-analysis of 22 studies including more than 700 patients, which assessed the likelihood of various antiseizure drugs used in second-line treatment to achieve control of SE, found VPA to have an efficacy of 75.7 % (95 % CI 63.7–84.8 %), LEV 68.5 % (95 % CI 56.2–78.7 %), PB 73.6 % (95 % CI 58.3–84.8 %), and PHT 50.2 % (95 %

CI 34.2–66.1 %) [8]. However, the heterogeneity of the source data and the lack of adjustment for outcome predictors are important limitations to this study. Finally, a retrospective comparison between PHT and LCM (used however as a third drug, following treatment with benzodiazepines and LEV) in 46 adults showed that SE was terminated in 40 % of those administered PHT versus 33 % of those receiving LCM (non-significant difference), with more side effects in the PHT group [9].

At the present time, these findings seem to support the prescription of VPA (which is also a wide-spectrum agent) as the preferred second-line agent. However, a randomized-control trial in this particular setting is urgently needed [10].

Third line of treatment and beyond

General anesthetics are prescribed in refractory SE (RSE), but a randomized trial on 24 adults that was interrupted

due to insufficient recruitment (underscoring the difficulties of studying this entity) did not disclose any clear difference between barbiturates and propofol, apart from a longer intubation time with the former [11]. When RSE persists after the first anesthetic course, alternative treatment options are required. A recent reappraisal of studies on ketamine, an *N*-methyl-D-aspartate (NMDA) antagonist, remind that in terms of pathophysiological considerations, this drug appears to be very promising in treating RSE. In a retrospective, multicenter assessment of 58 adults and children (60 episodes) [12], permanent RSE control was achieved in seven patients (12 %) likely due to the administration of ketamine; intriguingly, as many as four of these patients had postanoxic SE (it is unclear how many survived). No response was observed below infusion dosages of 0.9 mg/kg/h or if the ketamine was introduced into the treatment regimen after more than 8 days since the beginning of SE. In this study, safety concerns lead to discontinuation of the infusion in four (7 %) subjects [12]. Another retrospective series on 11 adults reported RSE termination in all patients with ketamine, seven of them within 1 week of initiating ketamine treatment (2 subsequently died); SE lasted less than 8 days in all patients [13]. There were no side effects.

The ketogenic diet is well known in pediatric epilepsy, but its use in adult SE also appears promising. A multicenter retrospective review of ten patients (7 with encephalitis) showed that despite a very long RSE duration (up to 2 months), acidosis was reached in nine patients, with SE ceasing in all of these latter patients at a median of 3 days thereafter. Two patients died at 6 months [14]. Although potentially flawed by some selection and information bias due to the study design, these observations corroborate the efficacy of both the relatively early use of ketamine in RSE and the ketogenic diet in adults in the intensive care unit (ICU).

Specific prognostic role of antiepileptic treatment

While endotracheal intubation would seem to be clearly indicated in patients with ongoing convulsive RSE, there are no clear data on subjects with RSE forms not accompanied by profound consciousness disturbance; moreover, mechanical ventilation and ICU immobilization are related to potential important medical complications. This lack of data illustrates the daunting tasks faced by the treating physician: to optimize treatment effectiveness and achieve a balance between the desired efficacy (SE control) and minimal side effects [15]. The appropriateness of pharmacological SE treatment, quantified according to existing international recommendations, does not seem to play any significant prognostic role after adjustment for underlying etiology, age, SE severity, and medical comorbidities [16]. Moreover, two recent retrospective studies suggest an association between the use of anesthetics and a risk of mortality {OR 5.6, 95 %CI 2.3–13.8 in 126 patients [17]; relative risk 2.9, 95 % CI 1.5–5.7 in 171 patients [18]}, after attempting to adjust for relevant outcome predictors.

The considerations mentioned here challenge the practice of proceeding automatically to endotracheal intubation in every case of RSE. We suggest that it seems reasonable, in patients with some preserved consciousness, to attempt additional non-sedating agents before considering the use of general anesthesia. The special case of the patient in absence SE virtually never requires intubation. In all situations, the active search for and the treatment of the underlying etiology represent an important mainstay in the treatment of SE [1].

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