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## Management of refractory status epilepticus in adults:

### Still more questions than answers

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### Summary

Refractory status epilepticus (RSE) can be defined as status epilepticus that continues despite treatment with benzodiazepines and one antiepileptic drug. RSE should be treated promptly to prevent morbidity and mortality; however, scarce evidence is available to support the choice of specific treatments. Major independent outcome predictors are age (not modifiable) and etiology (that should be actively targeted). Recent recommendations for adults, relying upon limited evidence, suggest that RSE treatment aggressiveness should be tailored to the clinical situation: to minimize ICU-related complications, focal RSE without major consciousness impairment might initially be approached more conservatively; conversely, early induction of pharmacological coma is advisable in generalized-convulsive forms. At this stage, midazolam, propofol or barbiturates represent the most used alternatives. Several other treatments, such as additional anesthetics, other antiepileptic or immunomodulatory compounds, or non-pharmacological approaches (electroconvulsive treatment, hypothermia), have been used in protracted RSE. Treatment lasting weeks or months may sometimes result in a good outcome, as in selected cases after cerebral anoxia and encephalitis. Well-designed prospective studies of this condition are urgently needed.

### Keywords

treatment; therapy; outcome; prognosis; risk; benzodiazepines; barbiturates; propofol; research

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#### Search strategy and selection criteria

Papers in English, French, and German published between 1966 and May 2011 were searched through PubMed and via cross referencing, using the terms “status epilepticus”, “treatment”, “refractory”, and “therapy”. The final set of papers was selected judging on the quality of each publication and the pertinence for this review.

#### Contributions and conflict of interest

AR performed the literature search; AR and DL interpreted the literature, drafted the manuscript, and the figure. No funding source was involved with the writing of this manuscript. AR received research support from Pfizer, UCB, Eisai, GSK, Sandoz. DL serves on the Scientific Advisory Boards of Neurologix, Inc. and NeuroVista Corporation; he is supported by the NIH (grant...).

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## Introduction

With an annual incidence of 10–40/100,000<sup>1–3</sup>, status epilepticus (SE) is the second most frequent neurological emergency (acute stroke being the first) with a risk of major morbidity or mortality<sup>4</sup>. Regardless of the time frame, SE persisting despite adequate administration of benzodiazepines and at least one antiepileptic drug (AED) is labeled “refractory” (RSE)<sup>5,6</sup>. This occurs in 23%–43% of patients with SE; not surprisingly the only prospective study<sup>6</sup> estimates lower proportions than ICU-based retrospective assessments<sup>7–9</sup>. The occurrence of RSE has been mostly associated with acute, severe and potentially fatal underlying etiologies, such as encephalitis, massive stroke, or rapidly progressive primary brain tumors, and may be accompanied by severe impairment of consciousness<sup>6,7,10</sup>.

Over the last few decades, important advances in basic mechanisms underlying SE and RSE have been achieved, mostly due to seminal animal studies. However, animal data cannot be automatically translated to humans, and to date well-conducted studies on epidemiological, clinical, and therapeutic aspects remain disappointingly, and somewhat surprisingly, scarce. In fact, RSE treatment is not at all evidence-based, despite it being recognized as an important entity in emergency and intensive care settings. The principal aim of this overview is to summarize our current knowledge of RSE in adults, with particular attention to the balance between risks and benefits of different treatment strategies, including rarely used options. Given the substantial differences in pathophysiology and treatment approaches in neonates and infants, our focus is on patients who are two years of age or older. We also identify areas of interest for research, and highlight some major practical difficulties that need to be addressed to design and conduct prospective, clinical studies on this topic.

## Mortality and morbidity

The short-term fatality rates for RSE have been estimated between 16% and 39%<sup>6–9</sup>; when compared to non-refractory SE, mortality after RSE is about three times higher<sup>6,7</sup>. In fact, for the majority of fatalities, death does not occur during persisting SE, but rather after its (sometimes late) resolution, and is generally due to underlying clinical problems<sup>6</sup>. This illustrates the critical prognostic importance of SE etiology: together with age, etiology has been consistently identified as the principal independent outcome predictor<sup>6,11–14</sup>. The classical subdivision between acute-symptomatic vs. remote etiologies, with the former felt to be more dangerous, only partly reflects the prognostic power. Indeed, AED withdrawal is an acute etiology that is often related to good outcome, and primary brain tumors are remote etiologies heralding bad prognosis. Recently, another etiological classification has been suggested, in which “potentially fatal conditions” (implying that these may lead to death if not specifically treated, such as large ischemic stroke or hemorrhage, central nervous infection, severe systemic infection, malignant brain tumor, AIDS with CNS complications, eclampsia, intracranial tumor, and others) have been shown to significantly better predict outcome after SE<sup>6,12</sup>. A longer duration of untreated SE may also render its control more difficult<sup>13</sup>; however, this does not seem to be a robust predictor<sup>11</sup>, and applies mostly to generalized-convulsive forms<sup>12</sup> during the first few hours<sup>15</sup>.

The risk of epilepsy following an incident symptomatic SE event, especially if refractory<sup>7</sup>, is three times higher than after a first symptomatic seizure<sup>16</sup>. The risk of cognitive sequelae appears to depend on the underlying etiology: patients diagnosed with epilepsy, in whom SE is usually due to AED withdrawal or spontaneous fluctuations of the epileptic threshold (etiologies that rarely trigger RSE), do not seem to aggravate their neuropsychological performances after a SE episode<sup>17</sup>. “Functional outcome” appears poorer after RSE<sup>6</sup>, especially generalized-convulsive,<sup>18</sup>. The likelihood of returning to baseline clinical

conditions after RSE is as low as 21%, as opposed to 63% for non-refractory SE. Also the need for admission to acute rehabilitation facilities for surviving patients doubles after RSE (82% vs. 35%)<sup>6</sup>.

## Rationale for early treatment

Given the danger of RSE and the effects of duration on outcome, there is broad consensus on the need for timely and effective pharmacologic treatment<sup>5, 19–22</sup>. In addition, data from the Veteran Affairs Cooperative Study showed that SE treatment becomes less effective as the episode becomes more prolonged: “subtle”, or nonconvulsive SE with coma (a form usually reflecting a longer duration) was controlled by the first medication in 15% of cases compared to 55% in “overt” convulsive SE<sup>23</sup>. Furthermore, a second or third agent was effective in less than 10% of cases in either condition<sup>24</sup>.

Generalized convulsive SE can cause many systemic complications, including cardiac arrhythmias, temperature disturbances, electrolyte and glucose imbalance, rhabdomyolysis, and pulmonary edema<sup>25, 26</sup>. However, apart from rhabdomyolysis, these consequences are also observed in experimental models after inhibition of muscular convulsions<sup>27</sup>. Mechanisms related to refractoriness to treatment have been elucidated in the last few decades. Self-sustained SE in rats, induced by repetitive electrical stimulation of limbic structures, responds to benzodiazepines (a GABA<sub>A</sub> receptor agonist) or phenytoin (a sodium-channel blocker) only if these are administered early (i.e., within the first few minutes). With time, SE becomes progressively resistant to those agents, while antagonists of the N-methyl-D-aspartate (NMDA) receptor, mediating glutamate excitatory inputs, become particularly efficacious in the late phase<sup>28, 29</sup>. This switch of sensitivity to different pharmacological compounds reflects loss of inhibition in ongoing SE<sup>30</sup>, and indeed *in vitro* models show that GABA<sub>A</sub> receptors are internalized into the neuronal cytoplasm<sup>31</sup>. From these observations, it appears that the window for successful pharmacologic intervention using antiepileptic compounds, including benzodiazepines, is relatively limited. On the other hand, there is still no clinical evidence that refractoriness is exclusively accounted for by loss of inhibition. The various etiologies and biological backgrounds encountered in patients suffering from SE are distinct from the controlled and relatively uniform conditions of experiments on rodents, and represent an important limitation to the translation of those findings to humans.

## Basic principles of SE treatment

The principal aims in treating a patient in SE are to achieve rapid control of seizures and avoid complications. During early stages it is essential to rule out imitators, since the correct diagnosis may be impossible to detect once a patient has been placed under pharmacological coma, potentially leading to dangerous iatrogenic complications. Acute movement disorders, such as focal or segmental dystonias, tremors, and choreatic movements<sup>32</sup> may sometimes present unilaterally in confused patients. At times, clonus in the context of spasticity, which disappears after a passive movement, or shivering in a sedated patient, characterized by high-frequency, rhythmic, proximally located movements, may be mistaken for SE. One particularly challenging group is psychogenic non-epileptic seizures (PNES). As opposed to seizures, these episodes are suggestion-prone, generally not stereotyped, and may occur with or without subjective consciousness impairment. During the ictus, the eyes are often closed, ventilatory drive is maintained, and the episode may present as uncoordinated, discontinuous, and fluctuating in intensity<sup>33</sup>. Importantly, physical injuries may be observed in patients having PNES<sup>34</sup>. A considerable proportion of PNES patients show prolonged seizures that may be misdiagnosed as SE (making up to 50% of patients treated for RSE in a retrospective study), leading to intensive care admissions with considerable risks of

overtreatment<sup>34–36</sup>. Laboratory studies can be helpful in this setting: PNES patients do not have elevated serum lactate, prolactin, or creatine kinase.

The first steps of SE treatment run in parallel with diagnostic procedures. After attending to pulmonary and cardiac function, control of seizures is the top priority and generally follows the intravenous administration of a sequence of three groups of drugs<sup>4, 37, 38</sup> (Figure 1): 1) benzodiazepines aimed at rapid SE control; 2) classical antiepileptic drugs (AED) targeted at early resistant forms and longer-term coverage; and 3) general anesthetics for RSE. Benzodiazepines represent currently the only evidence-based treatment, as shown in three trials and a Cochrane review<sup>23, 39–41</sup>. However, only one trial compared them to other medications: lorazepam resulted statistically better than phenytoin (but not phenobarbital or diazepam combined with phenytoin)<sup>23</sup>. Use of an accepted and available protocol greatly facilitates a smooth interplay between the different care providers (paramedics, neurologists, emergency or ICU team) and probably contributes to a better prognosis<sup>42</sup>.

The overall aggressiveness of treatment depends on the type of SE. Generalized convulsive SE should be treated aggressively given the danger of systemic and neurological injury with ongoing seizures<sup>5, 43</sup>. Conversely, non-convulsive SE without marked impairment of consciousness can usually be treated more conservatively, since its underlying pathophysiology is not associated with the same degree of injury as that of generalized convulsive SE. For example, in patients with idiopathic generalized epilepsy, epileptologists typically treat SE episodes (absence or myoclonic SE) with benzodiazepines and VPA, and do not rely on ICU admissions<sup>44</sup>. The precise criteria for turning to induction of coma for the treatment of complex-focal SE is debated<sup>45–49</sup>, given that the treatment may lead to various complications, such as infections (most patients with mechanical ventilation have pneumonia), metabolic disturbances including medication side effects, ileus, neuropathy, myopathy, thrombosis and embolic events, to cite only the most frequent<sup>50</sup>. It is therefore necessary to balance these risks with the benefit of rapid seizure control. A recently developed and validated clinical SE severity score (STESS) may help to orient early treatment strategy<sup>51, 52</sup>. Including four variables (age, seizure semiology, extent of consciousness impairment, and history of previous seizures, as etiology surrogate), the STESS is readily applicable in emergency settings, relies on straightforward clinical criteria, and has a robust negative predictive value for mortality (i.e., patients with a low score are extremely unlikely to have a fatal outcome). It thus appears reasonable to proceed straight to 3<sup>rd</sup>-line treatment if the 2<sup>nd</sup>-line treatment (which takes at least 20–30 min to be effective) has failed in patients with generalize-convulsive SE<sup>4, 53</sup>. Conversely, at least in some patients, partial RSE without major impairment of consciousness (and therefore a low STESS) may initially be managed without anesthetic compounds for the first 24–36 hours<sup>6</sup>; this approach is also reflected in recent recommendations<sup>5, 22, 37, 38, 54, 55</sup>.

## Choices of anesthetic agents

When elective coma induction is warranted to control RSE, the initial choice is restricted to three groups of compounds<sup>56</sup> (Table 1), whose common characteristic is the modulation of GABA<sub>A</sub> receptors, although each acts on specific sites. Midazolam is a benzodiazepine that is already being used as a 1<sup>st</sup> line treatment. Its half-life, short after single bolus, increases to 6–50 hours after prolonged administration. However, tachyphylaxis often develops within 24–48 hrs<sup>57</sup>, requiring the perfusion dose to be constantly increased to maintain a constant pharmacological action. Midazolam is therefore mostly used initially, or in combination with propofol. No particular problems inherent to its pharmacodynamic or pharmacokinetic properties have been described, and availability of an antidote (flumazenil) represents a theoretical advantage over the other two groups.

Propofol displays a short half-life, allowing rapid titration and withdrawal. Besides modulating GABA<sub>A</sub> receptors, it acts on sodium and calcium channels, and possibly on NMDA receptors<sup>58</sup>. Due to its administration as an oil emulsion, it may induce the so-called “propofol infusion syndrome” (PRIS), a syndrome of potentially fatal cardiovascular collapse with lactic acidosis, hypertriglyceridaemia and rhabdomyolysis. PRIS is due to impairment of mitochondrial activity and free fatty acid utilization, with resulting mismatch between energy needs and utilization; catecholamines and glucocorticoids may represent facilitating factors<sup>59</sup>. Mainly described in young children (thus representing a relative contraindication in this age group) and patients with brain trauma, PRIS has also been reported in patients treated for RSE<sup>60</sup>. A recent retrospective series estimated the incidence of PRIS in RSE as 7% (fatal) and 38% (non-fatal)<sup>61</sup>. However, these proportions are in sharp contrast with other retrospective<sup>62</sup> and prospective studies<sup>63, 64</sup> reporting incidences of 0%–7%, and may represent a selection bias. Nevertheless, prolonged perfusions (more than 48 hours over 5 mg/kg/h) should be avoided, and repetitive checks of serum lactate are mandatory for an early detection of this complication<sup>59</sup>. Concomitant benzodiazepines could lower the needed propofol dose<sup>62</sup>, possibly reducing the PRIS risk.

The anesthetic barbiturate thiopental, or its metabolite pentobarbital, represents the oldest compounds used in this setting. In addition to GABA<sub>A</sub> modulation, barbiturates show an NMDA-antagonist action *in vitro*, which might be of interest considering RSE pathophysiology<sup>65</sup>. They have a long half-life (up to 36 hours) after continuous administration, owing to a considerable tendency to accumulate in adipose tissue. This may become challenging especially in older patients with pre-existent cardiovascular problems.

A meta-analysis of the use of barbiturates, propofol, or midazolam in RSE completed a decade ago, mostly based on retrospective and heterogeneous case series, did not reveal any significant difference in short-term mortality, although some variations were noted in both immediate efficacy (favoring barbiturates) and tolerability (favoring midazolam and propofol)<sup>66</sup>. Another single-center retrospective analysis failed to show any outcome difference among different anesthetics, used alone or in combination<sup>9</sup>. Recently, a multicenter randomized, unblinded trial assessing propofol and barbiturates in RSE, interrupted because of insufficient recruitment, found that patients receiving barbiturates had a markedly longer need for mechanical ventilation, while long-term outcome and complications were comparable<sup>64</sup>. In spite of the increasing elimination half-life of midazolam after prolonged infusion, this compound virtually never induces a complete suppression of cerebral activity for several days, as do barbiturates. Thus, despite lack of strong evidence (and also in view of the availability of a pharmacological antidote flumazenil), midazolam seems to represent the safest compound in this setting, but often needs to be combined with propofol to obtain seizure control. Propofol has the advantage of a short half-life, which allows for a rapid clinical assessment upon weaning. However, the risk of PRIS requires very careful metabolic monitoring, and the drug should not be used in young children. Barbiturates should probably be reserved for RSE cases refractory to the other anesthetics in view of its prolonged elimination.

## EEG targets

An EEG should be used to monitor the effects of anesthetics when treating RSE. A potentially interesting alternative may be the bispectral index (BIS)<sup>67</sup>, an automated, amplitude integrated measure of a two-channel EEG derivation (that includes a burst-suppression ratio), frequently used by anesthesiologists in the operation room to monitor anesthesia depth; this, however, should not routinely replace EEG with a comprehensive scalp coverage if the latter is available, as the difference between pharmacological induced burst-suppression and “seizure suppression” patterns may be difficult to assess. The optimal

extent of EEG suppression (i.e., seizure suppression, burst-suppression pattern, flat recording) has not been addressed in prospective studies, and retrospective observations do not clearly favor any of these options<sup>9, 68</sup>. The same uncertainty applies to the optimal length and tapering of anesthetic treatment. In light of our current knowledge, an initial course of midazolam anesthesia targeting EEG burst-suppression with an interburst interval of about 10 sec. for 24 hours, followed by progressive tapering over 6–12 hours under EEG control, seems to represent a reasonable option. Propofol and, subsequently, barbiturates may be used thereafter. Since triphasic waves are often seen during the anesthetic tapering, it is important not to “chase” every sharply contoured EEG transient, and rather concentrate on definite seizure patterns<sup>69, 70</sup>.

## Other pharmacological approaches (summarized in Table 2)

Numerous anecdotal case reports and small series describe treatment options for RSE that does not respond to the first intravenous anesthetic agents; due to the lack of comparative data their absolute value is difficult to assess. Other anesthetics may be used sequentially in patients suffering from very long-lasting RSE, in alternation or combination with midazolam, propofol, or barbiturates. Inhalational anesthetics, which act, in part, on GABA<sub>A</sub> receptors appear to be effective in aborting RSE, but the effects seem to be transient, and their administration requires the use of appropriate gas recovery systems (not typically found outside of the operating room). Two small case series describe the use of isoflurane with an end-tidal concentration of 1.2% – 5% for up to 55 days. Several patients required vasopressors, paralytic ileus occurred in some, and the high fatality rates (43%–67%) reflect the difficult long-term control and the impact of the underlying disease<sup>71, 72</sup>. Furthermore, one recent report of isoflurane in RSE raised questions about CNS toxicity, especially in thalamic and cerebellar regions<sup>73</sup>. The intravenous anesthetic agent ketamine has also been tried in RSE, given its properties as an NMDA receptor antagonist and favorable hemodynamic profiles. There are only a few reports on the use of ketamine in this setting, describing dosages up to 7.5 mg/kg/h for several days, and the outcomes have been mixed<sup>74–77</sup>. However, given that the indiscriminate blockade of both extrasynaptic and intrasynaptic NMDA receptors may be the basis of ketamine’s neurotoxicity<sup>78</sup>, it has thus been suggested that ketamine should always be combined with GABAergic drugs<sup>79, 80</sup>, also because of a possible synergistic effect<sup>81</sup>.

Several other non-sedating pharmacological approaches are available and may be used intravenously or orally (through the nasogastric tube) as add-on compounds to optimize RSE control. Topiramate<sup>82, 83</sup>, pregabalin<sup>84</sup>, levetiracetam<sup>85</sup>, and lacosamide<sup>86</sup> (the latter two are increasingly prescribed also as 2<sup>nd</sup> line), have different and potentially synergistic pharmacodynamic actions. Lidocaine modulates sodium channels. Initial boluses up to 5 mg/kg and perfusions of up to 6 mg/kg/hr have been described<sup>87</sup>, but serum levels above 5mg/l may induce seizures<sup>88</sup>. Interestingly, it may even prove successful in phenytoin-refractory patients. A retrospective survey on 37 children in RSE showed a response to lidocaine in 36%, and no major adverse events; mortality was not reported<sup>88</sup>. Verapamil may inhibit multidrug transporters that can lower AED availability in the brain<sup>89</sup>. Few case reports on its use in humans are available, but it appears safe (with cardiac monitoring) up to dosages of 360mg/day<sup>90, 91</sup>. Magnesium, which is responsible for blockade of the NMDA receptor, has been mentioned anecdotally in RSE, but with unconvincing results even at serum levels of 14 mmol/l<sup>92, 93</sup>, apart from a recent report on two patients with mitochondrial encephalopathy<sup>94</sup>. Of note, high doses may induce neuromuscular blockade that may mask clinical seizures. The use of the ketogenic diet in RSE is relatively recent and possibly promising both in children and adults<sup>95–97</sup>. The diet can be administered through a nasogastric tube and should induce ketonuria; this approach may display its effect within a few days.

Since ultra-refractory RSE seems to represent the consequence of immunological processes in many instances<sup>10, 98–100</sup>, immunomodulatory treatment is often prescribed in this setting<sup>43, 93</sup>. Steroids, ACTH, plasma exchanges, or intravenous immunoglobulins may be used alone or in sequential combination after the formal exclusion of infectious etiologies.

### Non-pharmacological approaches (summarized in Table 3)

Pharmacological treatment may be supported and potentiated by non-pharmacological therapeutic strategies; however, the latter mostly represent *ultima ratio* approaches in cases of extremely refractory SE. Similar to the preceding section, the marked variability among the reports in terms of clinical setting (particularly, etiologies and concomitant therapies) greatly limits the generalizability of these treatments.

Resective surgery may represent a valuable option in selected cases when a definite seizure focus generating the RSE episode can be identified in a non-eloquent brain area,<sup>101</sup>. Acute vagal nerve stimulation (VNS) implantation has been suggested to be effective in a few cases<sup>102–104</sup>. While the stimulation was already initiated in the operation room, the intensity was progressively titrated over a few days up to 1.25 mA (with various regimens for the other stimulation parameters); transitory bradycardia/asystole may occur in this setting<sup>102</sup>. Low-frequency (0.5–1 Hz) transcranial magnetic stimulation (TMS) at 90%–100% of the resting motor threshold, at times applied after a short “priming” high frequency stimulation (up to 100 Hz), has been reported to be transiently successful in patients with simple-partial SE<sup>105, 106</sup>, although loss of efficacy after the initial stimulations suggests the need for a repetitive use. Electroconvulsive treatment (ECT) has also been applied in cases of extremely resistant RSE. Patients were mostly exposed to 1–4 daily sessions of induced electrographic seizures over a few consecutive days, resulting in permanent RSE control in some patients<sup>107–109</sup>. The antiseizure mechanism of ECT is essentially unknown.

Brain hypothermia exerts beneficial effects on several pathophysiological axes implicated in acute cerebral injuries. In animal studies of SE, hypothermia has been shown to reduce seizure severity and epileptic discharges, brain edema, and apoptosis<sup>110</sup>. However, clinical observations in RSE are limited. Mild hypothermia (31°–36°C) together with midazolam, ketamine, or thiopental for one to several days has been reported to control RSE, but seizures may recur after rewarming<sup>50, 111–113</sup>. While side-effects (including electrolyte disturbances, coagulation dysfunction, infections, cardiac arrhythmia) are relatively infrequent in patients treated with hypothermia after cardiac arrest<sup>114</sup>, paralytic ileus may represent a challenging complication in patients with SE, especially when barbiturates are co-administered<sup>50</sup>.

Recently, the beneficial effect of classical music has been reported on both electrographic and clinical parameters in a few patients with RSE, evident within hours of exposure<sup>115</sup>. The mechanism of action is entirely unknown.

### When to stop RSE treatment

Although long-lasting RSE generally heralds a poor prognosis, some exactions exists: patients suffering from RSE from several days, weeks, or even months may at times recover with a good functional outcome<sup>15, 100, 116–118</sup>. Certainly in some patients, most often those with an infectious or autoimmune etiology, the underlying disease process subsides after some time, allowing awakening of the patient without repetitive seizures. It appears therefore advisable not to stop supportive treatment, including repetitive courses of anesthetics if needed, just because of protracted treatment duration, if neuroimaging remains normal, apart from minor signs of global atrophy<sup>118</sup>, and no underlying etiology heralding a catastrophic prognosis is identified (e.g., rapidly progressive brain tumors, paraneoplastic



limbic encephalitis with disseminated primary cancer, prion disease). This especially applies to younger patients, who are usually able to tolerate the cardiovascular side effects of long-term anesthesia.

RSE in the setting of cerebral anoxia represents a controversial issue. This entity does not seem to imply an invariably poor outcome. Although recent observations confirm that SE occurring during therapeutic hypothermia and sedation, mostly presenting as a “seizure-suppression” EEG pattern, represents a situation of extreme brain damage and extremely poor outcome<sup>119, 120</sup>, it has been reported that SE arising after rewarming may be treated as SE if the EEG background remains reactive and somatosensory evoked potentials and brainstem reflexes are preserved<sup>121</sup>. In these rare cases, survival with reasonable functional outcome has been reported after administration of AEDs and at times a single-course of anesthetics. Conversely, the outcome remains dismal despite every therapeutic attempt in patients showing severe loss of CNS function and EEG non-reactivity<sup>122</sup>.

## Areas needing research

In contrast to the steadily growing basic-science literature on SE that continues to shed important lights on underlying mechanisms, it is very disappointing to have such little evidence for current approaches to SE treatment, apart from the 1<sup>st</sup> line of benzodiazepines<sup>43</sup>. This is accounted for by the fact that clinical studies represent a daunting task in this setting. There is an urgent need to fill this gap.

Translational strategies bridging animal to human studies, aiming at identifying potential molecular targets for novel treatments, need to be developed, with subsequent proof-of-concept clinical trials to evaluate the clinical efficacy of candidate targets. Given that SE represents a very heterogenous entity, it is unlikely that a single approach identified from animal models will prove decisive. As an example, ketamine unfortunately does not appear to give reliably good results in humans, as opposed to those in animal models. It seems reasonable to think that more than one animal model should be developed to address the multitude of etiologies associated with SE.

Regarding the general approach to treating RSE, it is unclear if other factors beside age and etiology represent independent outcome predictors. For example, pre-existent comorbidities (modifiable)<sup>123</sup>, race (not modifiable)<sup>2</sup>, and hospital settings (modifiable)<sup>124, 125</sup> have received scarce attention to date. Duration of SE, emphasized in some studies<sup>13, 18</sup>, may actually reflect an early selection of SE forms that are intrinsically difficult to treat, rather than a modifiable risk factor. It is unclear to what extent the use of a given SE treatment protocol allows a better prognosis, apart from a recent single study<sup>42</sup>. Also, the optimum sequence and timing of initial SE treatment is essentially unexplored. Apart from these questions, in view of potentially relevant differences in both efficacy<sup>126</sup> and tolerability<sup>64</sup>, well-designed trials assessing medication at the 2<sup>nd</sup> and 3<sup>rd</sup> line levels are clearly needed, as well as controlled assessments on depth and duration of EEG suppression. As described in the recent report of an aborted trial investigating 3<sup>rd</sup> line treatment<sup>64</sup>, these studies have failed up to now mainly because of difficulties in obtaining sufficient funding and the need for a very large number of clinical sites for enrollment. As an example, a 3-armed trial investigating a 2<sup>nd</sup>-line AED would need approximately 1500 enrolled patients in order to detect differences that are potentially clinically relevant. Since a high-volume tertiary center treats an average of 50–70 adults for SE yearly, and at best one-fourth of them will prove eligible for the study, 50 centers would need to recruit for a minimum of two years in order to complete the trial.

## Conclusion

Refractory SE represents a heterogeneous entity which is regularly encountered in every hospital setting. There is a strong consensus about the need for an early, effective treatment to prevent morbidity and mortality. In the first hours, it seems reasonable to tune treatment aggressiveness (pharmacological coma induction) according to the clinical subtypes: while generalized-convulsive SE must be approached aggressively, partial SE and SE related to idiopathic generalized epilepsy (absence and myoclonic forms) can be treated initially with non-sedating agents. Facing long-lasting RSE, which is usually related to particular etiologies, it is mandatory not to stop supportive treatment unless irreversible brain damage is proven. Furthermore, SE etiology is a potentially modifiable outcome predictor that should always be specifically addressed. Finally, multicentric well-designed drug trials are needed in order to improve the current management of RSE.

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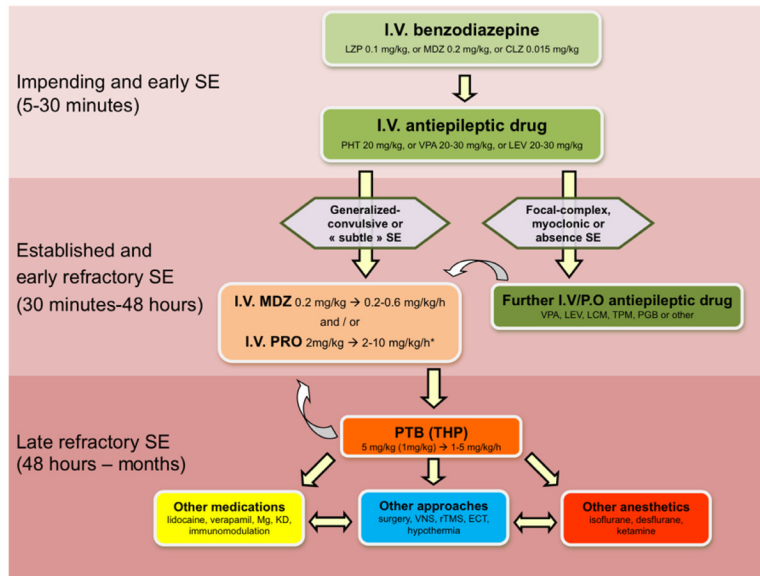
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**Figure 1.**

Flow chart of status epilepticus treatment\*. Increasing refractoriness is illustrated by the background color intensity; the non-sedating agents are green, anesthetics in orange to red, and other options in yellow or white. First-line treatment is light green, second-line darker green, and third line light and darker orange. Other options are given in red, yellow and blue.

\*Great caution is required for valproate in children under 2 years (hepatic toxicity), and propofol in young children (propofol infusion syndrome). In this setting, benzodiazepines, phenytoin and barbiturates represent the most widely used options.

CLZ: clonazepam; ECT: electroconvulsive treatment; KD: ketogenic diet; LCM: lacosamide; LEV: levetiracetam; LZP: lorazepam; MDZ: midazolam; PGB: pregabalin; PHT: phenytoin; PRO: propofol; PTB: pentobarbital; rTMS: repetitive transcranial magnetic stimulation; SE: status epilepticus; THP: thiopental; TPM: topiramate; VNS: vagus nerve stimulation; VPA: valproate.

**Table 1**

Anesthetic agents used in RSE 5, 53, 56

	<b>Loading dose</b>	<b>Maintenance dose</b>	<b>Remarks</b>
<b>Midazolam</b>	0.2 mg/kg	0.2–0.6 mg/kg/h	Increasing doses needed with time
<b>Propofol</b>	2 mg/kg	2–5 (–10) mg/kg/h	Attention to “PRIS”, especially in young children; combine with BDZ
<b>Barbiturates</b>	THP: 1–2 mg/kg PTB: 5 mg/kg	THP: 1–5 mg/kg/h PTB: 1–5 mg/kg/h	Loading with repetitive boluses Long wash-out time

BDZ: benzodiazepines; PRIS: propofol infusion syndrome; PTB: pentobarbital; RSE: refractory status epilepticus; THP: thiopental.

**Table 2**

Other pharmacological and nutritional treatments for RSE (see text for references)

	<b>Advantages</b>	<b>Disadvantages/Remarks</b>
<b>Isoflurane</b> <sup>72</sup>	Fast acting	Possible neurotoxicity Needs close system
<b>Ketamine</b> <sup>74-77</sup>	Anti-NMDA	Possible neurotoxicity, combine with BDZ
<b>Lidocaine</b> <sup>76,77</sup>	May rescue PHT- resistant RSE	Cardiac monitoring needed; possible seizures induction
<b>Verapamil</b> <sup>90,91</sup>	Safe	Not AED action, may optimize availability of AED in CSF
<b>Magnesium</b> <sup>94</sup>	May enhance NMDA blockade	May induce neuromuscular blockade
<b>Ketogenic diet</b> <sup>95,96</sup>	Safe	Need experienced dietologist; check ketonuria
<b>Immunological Treatments</b> <sup>93</sup>	May act causally	Formal exclusion of infection before treatment

AED: antiepileptic drug; BDZ: benzodiazepines; CSF: cerebrospinal fluid; RSE: refractory status epilepticus

**Table 3**

Non-pharmacological options for RSE (see text for references)

	<b>Advantages</b>	<b>Disadvantages/Remarks</b>
<b>Resective surgery</b> <sup>101</sup>	May act causally	Not appropriate in multifocal SE; need of experienced interdisciplinary team; surgical risks
<b>Vagal nerve stimulation</b> <sup>102</sup>	Appropriate for long-term use	Invasive procedure; cardiac arrhythmias rarely reported
<b>Repetitive transcranial magnetic stimulation</b> <sup>106</sup>	Non-invasive procedure	Possible seizure induction; need to sustained treatment
<b>Electroconvulsive treatment</b> <sup>108, 109</sup>	Non-invasive procedure	Need of experienced interdisciplinary team; possible seizure induction
<b>Mild hypothermia</b> <sup>112</sup>	Acts on several pathophysiological mechanisms	Mostly only transitory control; avoid barbiturates (ileus)
<b>Classical music</b> <sup>115</sup>	Pleasant for nursing team	No side effects; scarcely reported

RSE: refractory status epilepticus