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Modern Treatment of Status Epilepticus in Adults

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Abstract: Status epilepticus is a serious epileptic condition associated with significant morbidity and mortality. It can be divided into four stages: developing (seizures leading up to status epilepticus), established (>5 minutes convulsive status epilepticus, nonconvulsive/focal status epilepticus >10 min), refractory (failure of two adequately dosed antiseizure medications in different drug classes), and super-refractory (persisting despite >24 hours of anesthesia). All seizure types can develop to status epilepticus. Generalized convulsive status epilepticus has the largest potential for brain damage. The drug treatment algorithms for status epilepticus generally go through three stages, starting with benzodiazepines: lorazepam, midazolam, or diazepam as first-line drugs, moving to levetiracetam, valproate or fos-phenytoin as second-line drugs, ending, if necessary, with anesthetics like propofol or midazolam. Lacosamide, topiramate, phenobarbital, brivaracetam, and perampanel are potential alternatives, and pentobarbital is commonly used when long-term anesthesia is needed. Super-refractory status epilepticus is the form that usually causes the most concern.Treatment guidelines for newer treatment alternatives are often based only on case reports and small

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patient series. Such alternatives include ketamine, immunotherapy, ketogenic diet, inhalation anesthetics and hypothermia, and several surgical neurostimulation procedures. This chapter provides an overview of current treatment alternatives, with particular focus on refractory status epilepticus and super-refractory status epilepticus.

Keywords: antiseizure medications; immune therapy; ketamine; non-pharmacological treatment; status epilepticus

INTRODUCTION

Status epilepticus (SE) defined as continuous epileptic activity, is a major medical and neurological emergency requiring immediate treatment to avoid severe morbidity and mortality. All types of epileptic seizures, including focal and absence seizures, can turn into SE, but the most common and serious form of SE is generalized convulsive SE. Persistent epileptic activity, whether generalized or focal, causes excessive stress to both the organism in general and the brain in particular.

According to the previous International League Against Epilepsy (ILAE) definition, SE was defined as 30 minutes of ongoing epileptic activity or a series of seizures without recovery for a period of > 30 minutes. The rationale behind this definition was based on animal studies showing irreversible neuronal injury after long-lasting seizure activity, and it was agreed somewhat arbitrarily on a time limit of 30 minutes (1–3). In 2015, the ILAE proposed a new definition of SE (4) that reduced the time limits to 5 minutes of ongoing seizure activity to diagnose convulsive SE (CSE), and 10 minutes for focal and absence SE (4). Several types of SE with prominent motor phenomena at any time (including CSE) were distinguished from those without (i.e., nonconvulsive SE (NCSE)). The new ILAE definition introduced the concept of two important time points, t1 and t2. The first, t1, is the time point at which the seizure should be regarded as an "abnormally prolonged seizure". The second time point, t2, is the time of ongoing seizure activity beyond which there is a risk of long-term consequences, such as irreversible brain damage and neurological sequelae (4). Evidence for these time points is, however, incomplete. Therefore,these time points should be considered as the best estimates currently available (4) (Table 1).

The incidence of SE varies considerably between studies, from below 10 to above 40 per 100,000 adults per year (5–8). The new definition of SE will invariably lead to a change in incidence. In a population-based study, the incidence of SE was found to be 10% higher when the new definition was applied (5). Mortality in SE varies between 9–37%, highly dependent on etiology and time in SE (9–13). In refractory SE, mortality rate is approximately three times higher than for non-refractory SE (10). Morbidity is high in SE with about 40% of patients having a reduced modified Rankin Scale at hospital discharge (13). There are also indications that focal SE has a negative impact on cognitive function (13–15).

SE can be divided into four stages as follows: (i) developing—seizures leading up to SE; (ii) established—> 5 minutes (CSE, Table 1); (iii) refractory—failure of two adequately dosed antiseizure medications (ASMs) in different drug classes

TABLE 1 Operational dimensions of t1 and t2 for status epilepticus

Type of SE	Operational dimension 1 Time (t1) when a seizure is likely to be prolonged leading to continuous seizure activity	Operational dimension 2 Time (t2) when a seizure may cause long term consequences (including neuronal injury, neuronal death, alteration of neuronal networks and functional deficits)
Tonic-clonic SE	5 min	30 min
Focal SE with impaired consciousness	10 min[a]	>60 min
Absence SE	10-15 min[a]	Unknown

[a]Evidence for the time frame is currently limited and future data may lead to modifications. Operational dimensions with t1 indicating the time that emergency treatment of SE should be started, and t2 indicating the time at which long-term consequences may be expected. Modified from Trinka et al 2015 (4).

(a benzodiazepine + another ASM); (iv) super-refractory—SE persisting despite > 24 hours of anesthesia (4, 16). SE requires immediate treatment to prevent successive brain injury. A series of treatment guidelines and protocols have been published, most of which recommend initial use of benzodiazepines, followed by intravenous ASMs starting with valproate, levetiracetam or, less frequently, fos-phenytoin (fos-PHT), and subsequently induction of anesthesia. Molecular studies indicate that rapid cellular and subcellular changes occur with ongoing SE, such as internalization of GABA-receptors into the cytoplasm of neurons (17) and up-regulation of NMDA-receptors in the synapses after ~30 min (18). Starting treatment early and giving adequate dosages of appropriate medication is therefore a prerequisite for a good outcome. Good diagnostic evaluation of the many possible causes of SE, together with prompt and suitable treatment could prevent development to refractory SE (RSE). This chapter provides a brief overview of non-surgical SE treatment, with major focus on the most severe and resistant form: super-refractory status epilepticus (SRSE). Lack of compliance and forgotten medication are very common cause of SE. Consider starting with a bolus dose of the drug that the patient is already taking.

EARLY-STAGE STATUS EPILEPTICUS

The treatment of SE has been discussed for many years, but no consensus has been reached when it comes to the preferred use of ASM, and especially regarding the use of anesthetics. Many guidelines and protocols have been published (4, 19–27), recommending initial use of benzodiazepines, followed by intravenous ASMs and, subsequently, induction of anesthesia.

All international guidelines recommend the use of benzodiazepines in the early stages of SE (22, 26–28). Which benzodiazepine to use and what is the best route of administration have been discussed for years, but more important is to use a sufficiently high dose of the chosen drug as soon as possible. Lorazepam at a dose of 2-4 mg intravenously (IV) is often advocated as first-line treatment. However, because lorazepam is not listed for use in all countries, diazepam is

often used as a first-line drug, at a dosage of 10-20 mg IV with an infusion rate of 5 mg/min. A few comparative studies and a Cochrane report showed a possible slightly better effect and less need for additional ASMs for lorazepam compared with diazepam (29, 30). However, a more recent systematic review including a meta-analysis of five randomized controlled trials (RCTs) and a total of 656 patients could not find any differences between lorazepam and diazepam regarding effect and side-effects (31). Alternatively, diazepam can be administered rectally and recently also intranasally, an administration route well suited also for children (32). The third drug of choice in early-stage SE is midazolam, at a dosage of 10-20 mg and with buccal, intranasal, or intramuscular administration (33, 34). For prehospital treatment, it is of special interest to note that an intramuscular administration of midazolam was more effective and median time to active treatment was shorter than for IV lorazepam (34). This probably reflects the practical problems with IV administration to a patient with an ongoing seizure outside hospital, an aspect that should be considered when establishing local guidelines for prehospital treatment. Clonazepam 1-3 mg may also be used as an alternative benzodiazepine (35). Generally, the same doses can be administered again after 5 min for all benzodiazepines if the response is inadequate, with individual considerations in the elderly and patients with body weight below 50 kg (10).

ESTABLISHED STATUS EPILEPTICUS

ASMs other than benzodiazepines are the preferred drugs for this stage of SE. The drugs most recommended are valproate, levetiracetam or fos-PHT (36–38).

Valproate

Valproate is most often recommended at dosages of IV 30-40 mg/kg body weight over a period of 10-20 min (36, 39). In the ESETT study, a bolus dose of 40 mg/kg over 10 min was used (37). Initial serum levels drop early as valproate distributes into body fat, so maintenance dosing should be started 30 minutes to 2 hours after IV loading. We have not experienced any difficulties in immediately following up the bolus dose with continuous infusion of 100-200 mg/hour over the next 24 h. Alternatively, maintenance dose of about 5 mg/kg every 6 hours can be used. Following the valproate serum concentration repetitively at this stage is highly recommended.

Levetiracetam

Levetiracetam has been used with increasing frequency in both RSE and SRSE since the first case reports appeared in 2005 (40). Several studies on the effect of levetiracetam have been performed demonstrating an effect ranging from around 50-70% (41–44). An extensive review by Trinka and Dobesberger collecting 156 cases treated with levetiracetam for SE (42) found an overall success rate of 65.4%, confirmed by data from Yasiry and Shorvon describing an efficacy of 68.5% (44). The recently published ESETT study found an efficacy of ~ 50% for the primary outcome of termination of clinical seizures plus improvement in the level of

consciousness by 60 minutes after IV administration of levetiracetam (37). In an earlier study, Eue et al. (45) described a slightly better efficacy of levetiracetam for non-convulsive than generalized convulsive SE, but this has not been confirmed. When it comes to the loading doses of levetiracetam, most recent studies have used 20-30 mg/kg (42, 44, 46). However, the ESETT study employed a loading dose of 60 mg/kg levetiracetam and compared this with respective loading doses of 20 mg/kg for fos-PTH and 40 mg/kg for valproate, all leading to similar results (efficacy in about 50% of cases after 60 min) (37).

Fos-PHT

Fos-PHT is a prodrug of phenytoin with pharmacokinetic bioequivalence (47, 48), and dosage is therefore specified in Phenytoin Equivalents (PE). It is generally recommended to administer fos-PHT IV with a loading dose of 20 mg PE/kg body weight. This is given as an infusion at a rate of 100 mg PE/min (50-150 mg PE/min). A maintenance dose of 5 mg PE/kg body weight is often used, given twice daily, with the first dose typically 6-8 hours after the loading dose. Side-effects of fos-PHT are like those of phenytoin but are usually more moderate (48).

Phenobarbital

Phenobarbital (10 mg/kg iv bolus dose at a max rate of 100 mg/min) is still used as second line treatment for SE in some centres and countries, but because of its depressive effect on respiration it has now been largely replaced by other drugs (49).

Which drug to choose for established status epilepticus, and at what dose?

Taken together, no differences between valproate, levetiracetam or fos-PHT were detected in efficacy or primary safety outcome by drug within each age group (50). However, drug safety should be evaluated carefully for each drug as individual comorbidities may favor or disfavor specific drugs. As an example, valproate should be used with caution in patients with mitochondrial dysfunction or severe liver diseases, although there are no reports of liver failure because of treatment with valproate in the acute phase of SE (51). Fos-PHT might not be the best choice in certain patients with cardiac conduction problems due to its pro-arrhythmogenic side effects (52). Finally, levetiracetam is known to cause behavioural side effects and one should be aware of possible negative consequences in patients with pre-existing behavioural deviations. In most cases, the SE patient is continued on the same drug as used to stop SE. Careful evaluation of which drug to choose after termination of SE should therefore be mandatory already in the early stage of SE treatment. As a precaution, valproate should not be used in pregnant women with SE, although there are no data showing that short-term use of valproate has any negative effect on the fetus, given that valproate is later shifted to another ASM after cessation of SE.

The question of which maximum loading dose to use for second line treatment of SE has not been settled yet. In this respect, it is interesting that the ESETT study (37) utilized a maximum loading dose for patients above 75 kg (4500 mg for

levetiracetam, 1500 mg for fos-PHT and 3000 mg for valproate). Consequently, people with body weight >75 kg received a lower mg/kg dosage than those with body weight <75 kg, but the effect on SE was equal in those above and below body weight of 75 kg (53). This would imply that traditional loading doses may have been higher than necessary. This is also in line with data from Rossetti et al. who found that elevating the loading dose of levetiracetam above 3000 mg was unlikely to provide any additional benefit (54). In an earlier study on valproate treatment in children with SE, the effect was 46% when a bolus dose at 20-30 mg/kg was given, and 73% at bolus dose of 30-40 mg/kg. Paradoxically the effect was again reduced to 40% at bolus doses above 40 mg/kg (55). It therefore seems plausible to use maximum bolus doses of 20 mg/kg for fos-PHT, 40 mg/kg for valproate and 40 to 60 mg/kg for levetiracetam in most adults with body weights up to 75 kg and only increase maximum dose in those with higher body weights after individual considerations.

REFRACTORY STATUS EPILEPTICUS

After failure of two adequately dosed ASMs in different drug classes including a benzodiazepine and one of the above-mentioned drugs (valproate, levetiracetam or fos-PHT), anesthetics should be considered. However, use of anesthesia and thereby therapeutic coma (TC) may also have several negative consequences. A study comparing the use of TC for SE treatment in the US (Harvard) versus Europe (Geneva), showed that TC was much more frequently used in the US. While this did not affect mortality, more extensive TC use increased the length of hospital stay and related costs significantly (56). On the contrary, it was recently found that early induction of TC after unsuccessful first-line treatment was associated with shorter SE duration as well as intensive care unit/hospital stay, than when a second line ASM was applied first (57). Novy and co-workers reported that escalating treatment with a non-sedating ASM terminated refractory SE in more than half their patients (58). In another study where lorazepam was followed sequentially by phenytoin, levetiracetam and valproate, SE was controlled in 92% of cases thereby avoiding TC (59). On the other hand, the risks from using anesthetics must be balanced against the risk of long-lasting seizure activity. The question of when to use TC is therefore not finally settled, but must be discussed on an individual basis, especially for focal and non-convulsive forms of SE (60).

If TC is decided, patients with RSE, independent of generalized or focal/non-convulsive, should be treated with general anesthesia. Recommended anesthetics are propofol, midazolam, or barbiturates, especially pentobarbital. Loading doses and infusion rates vary noticeably in the literature, ranging from 0.5-20 mg/kg/h for barbiturates, 0.1-24 mg/kg/h for propofol, and 0.02-1.8 mg/kg/h for midazolam (36, 38, 47).

Anesthetic drug preferences have been extensively discussed (10, 16, 25, 36, 38, 47), but comparative trials are still lacking. In two systemic reviews, none of the treatments currently available was found to be superior to another (25, 61). Patients with SE based on severe pathological conditions, such as hypoxia, are often treated with barbiturates, as are patients that do not respond to either midazolam or propofol. Complications, such as respiratory depression and hypotension, have been

reported for all three drugs. Therapy failure due to side-effects occurred in 6% of patients who received propofol, versus 3% in barbiturate- and <1% in midazolam-treated patients. Death during therapy was most prevalent in patients receiving barbiturates (19%), versus 8% of propofol- and 2% of midazolam-treated patients. This probably reflects the use of barbiturates in the most severe cases (47).

Generally, propofol or midazolam tend to be the first-line anesthetics, whereas barbiturates are often reserved for SE refractory to these drugs (10). Propofol is advantageous with respect to its short half-life, making frequent neurological exams possible. It should, however, be noted that long-term propofol infusion may lead to propofol infusion syndrome. This is a life-threatening condition, including rhabdomyolysis, cardiac and renal failure, and metabolic acidosis. Propofol treatment should therefore be restricted to 48 h (62). To avoid withdrawal seizures, we recommend that propofol is gradually reduced over 24 h before treatment is stopped. Duration of anesthesia or degree of electrographic suppression is controversial; common practice is to achieve electrographic burst suppression for 24 to 48 h, but the rationale for this is limited. Whether or not burst suppression is necessary can be discussed, but all epileptic activity must be continuously suppressed for a certain period. However, as most hospitals do not have unlimited access (24 h per day) to continuous EEG, burst suppression can be regarded as a practical approach for ascertaining that anesthesia has been sufficient.

It is important to remember that therapy failure is probably the result of an insufficient target dose of the anesthetic drug, including dose limitation due to side-effects, rather than choice of drug. We therefore recommend to load the patient fully with the chosen ASM to therapeutic, or even supra-therapeutic, levels when the patient is still in anesthesia to avoid insufficient serum concentrations and seizure breakthrough when anesthesia is tapered off.

SUPER-REFRACTORY STATUS EPILEPTICUS

SRSE is one of the most difficult-to-treat conditions in neurology and life-threatening. Due to a large variation in etiology and clinical presentation (including heterogeneity in age, comorbidity etc.), as well as its rarity, robust clinical studies of SRSE are extremely difficult to perform. One major challenge is the increasing amount of treatment options, both with diverse ASMs but also with a wide range of alternative therapies reported to be helpful in case reports or small patient series. Such reports should be considered cautiously due to the possibility of publication bias. Herein, the treatment of SRSE is discussed under three groups: (i) the use of ASMs other than PHT/fos-PHT, valproate, levetiracetam or phenobarbital, which are used in the earlier phases of SE and commented on above; (iii) other drugs or supplementations given IV, perorally, or through inhalation; and (iii) other non-pharmacologic treatments. In addition to valproate, PHT/fos-PHT, levetiracetam, and phenobarbital, especially lacosamide and topiramate, and even more recently, perampanel and brivaracetam, have gained attention. While lacosamide and brivaracetam can be administered IV, topiramate and perampanel can only be used perorally, hampering its use in SRSE. For all ASMs mentioned here, evidence for their use in SRSE and their effects on SE in general, is very sparse and

should be considered with great caution. Studies also vary markedly regarding etiologies of seizures and SRSE, outcome criteria, and definitions of efficacy. Several studies are not even specific regarding the type of SE.

Lacosamide

To date, lacosamide has been used in a limited number of SE. In their review from 2013, Höfler and Trinka (63) refer to 136 episodes of RSE (50% nonconvulsive status epilepticus, 31% focal status epilepticus, and 19% convulsive status epilepticus) treated with lacosamide. The most frequently used bolus dose used was 200-400 mg IV over 3-5 min. The overall success rate was 56% (76/136). This is very much in line with a recently published systematic review comparing lacosamide (n=115) with phenytoin (n=166) lacking significant differences between the two drugs for either seizure control (57% for lacosamide versus 46% for phenytoin) and for side effects (64). Adverse events of lacosamide are generally mild with dizziness, ataxia, diplopia, headache, and nausea, but one should be aware of possible cardiac effects of the drug. Especially, atrial arrhythmias, AV block, and ventricular tachyarrhythmia may occur with rapid intravenous loading (65, 66). It should therefore be used with caution in patients with underlying proarrhythmic conditions. The exact loading dose to achieve a sufficient serum concentration has been discussed. As mentioned, 200 to 400 mg has been used in most studies, but to be more specific, doses above 9 mg/kg seem to be necessary to swiftly achieve therapeutic serum levels (67). In another study, doses of above 8 mg/kg led to effective drug concentrations of 15-20 µg/ml (68). With a loading dose of 10 mg/kg one would be on the safe side, and this has therefore been suggested (38).

Topiramate

As for lacosamide, data on use of topiramate for RSE, and especially SRSE, are scarce. In one study comprising 35 adults with either generalized or focal SE, topiramate 100 mg x 4-6/day was considered effective in 44% (14/35) after 3 days (69). In another study (70), topiramate was used as an add-on treatment after therapy failure of 1-6 (median 4) previously administered ASMs. It was introduced after a median of 2 (range 2-23) days, for a period of 1-24 (median 3) days. Overall, SRSE was terminated in 71% of patients within 72 h after first topiramate administration, and in 9% of patients within 24 h. In a large study comprising 106 patients with RSE or SRSE, the rate of seizure cessation after topiramate was 27% (71). Topiramate was started at a median of 8.5 days after SE with 100 mg/day and titrated up to 400 mg/day. A possible effect of topiramate was also seen in a small series published in 2017 by Brigo and co-workers (72). As with lacosamide, it seems that there is some evidence that topiramate may be effective and could be considered in very difficult cases.

Newer antiseizure medications

A wide range of other ASMs have been tried to treat SE, and there are ample case reports describing a possible benefit. These include brivaracetam, perampanel, pregabalin, oxcarbazepine, stiripentol, and others.

Brivaracetam is a high-affinity synaptic vesicle glycoprotein 2A ligand that is structurally related to levetiracetam. Due to its more lipophilic characteristics, it may have a quicker penetration across the blood-brain barrier and potentially also a stronger anticonvulsant effect. It would therefore theoretically be a good alternative to levetiracetam in SE. Brivaracetam has been tried in several case reports and small series with promising results, much in line with other ASMs. The largest study so far is an Italian study of 56 cases. Brivaracetam was administered IV as the first drug after benzodiazepine failure in 21% and as second and third (or later used) drug in 38% and 38%, respectively (73). Median loading dose was 100 mg ranging from 50 to 300 mg over 10 to15 min (only 3 min in three cases without complications observed). Brivaracetam was judged effective in 57% which is in line with valproate, levetiracetam and fos-PHT.

Perampanel is a selective non-competitive AMPA-receptor antagonist, the only one among the available ASMs. The drug seems to be one more alternative in the armamentarium of ASMs to treat SE with its unique mode of action (74). In the largest study so far, 81 patients with different kinds of SE were treated with perampanel after having failed a median of three drugs. Loading doses ranged from 2 to 36 mg followed by median daily doses of 12 mg (75). Thirty-three percentage of cases were judged as responders. Response to perampanel was defined as being clinically and electrographically seizure-free within 72 h of initiation of perampanel if no further drugs were added. No cardiorespiratory adverse events or laboratory abnormalities were noted with perampanel treatment. Personal experience in three cases with 36 mg on day one, 24 mg on day two and 12 mg on day three followed by dose adjustments according to serum concentrations was effective in one SRSE patient (mitochondrial disease) stopping clinical and electroencephalographical seizure activity for >72 h with no observed side effects in any of the patients. Seizures later resumed and the patient died a few weeks later.

However, data are generally limited for both perampanel, brivaracetam, and other "try-and error" ASMs. Such drugs are often only tried in patients that has not responded to more conventional treatment. A further discussion on their role in SRSE treatment is not within the scope of this review. Nevertheless, this demonstrates the urgent need for systematic registration of use of different ASMs on a broader scale to provide information on efficacy and side-effects.

NON-ANTISEIZURE MEDICATIONS USED IN THE TREATMENT OF STATUS EPILEPTICUS

The most promising new treatment strategies for SE, especially SRSE are, in our opinion, ketamine and immunotherapy. Both have been tried in a sufficient number of patients to evaluate their potential role in SRSE treatment.

Ketamine

In the later stages of SE, and with prolonged seizure activity, GABA-A receptors are internalized and sensitivity to GABAergic drugs is reduced. Excitatory synapses show changes in the opposite direction from those of GABA synapses with NMDA receptor subunits being recruited to the synaptic membrane, where they

form additional receptors (76). NMDA receptors may therefore be promising targets for anti-seizure treatment in SRSE. Ketamine is a non-competitive NMDA receptor antagonist and highly efficacious in stopping SE in animals and even with a possible neuroprotective effect (77, 78). Based on these properties, ketamine has been used for SE treatment in humans, but most published data are from single cases or small case series, implying clear limitations as described in detail below; however, the general impression is positive.

Experiences with IV ketamine in the treatment of SRSE have been published in a multicenter study from several hospitals in North America and Europe collecting 60 SRSE episodes in 46 adults and 12 children (79). More than half the patients had new-onset SRSE of unknown origin (NORSE). The main findings were: "permanent control" of SRSE in 57% (34 of 60), defined as no recurrence of SE during the same ICU stay; "likely response" to ketamine in 12%, defined as permanent control of SE within 24 h of initiation of ketamine when ketamine was the last drug added; and "possible response" in 20%, defined as permanent control of SRSE within 24 h of initiation when ketamine was not the last drug added. Taken together, ketamine was considered to have contributed to permanent control in 32% (19 of 60, including seven in which ketamine was the last drug added considered as a "likely response"). Median loading doses used by the participating centres was 1.5 mg/kg, with a maximum of 5 mg/kg, followed by continuous infusion (median 2.75 mg/kg/h; max 10 mg/kg/h).

Another study investigating the effect of ketamine in SRSE in adults consisted of 68 cases collected between 2009 - 2018 from a tertiary epilepsy care centre (80). Seizures were completely controlled in 63% of ketamine recipients; an additional 18% had a greater than 50% reduction in seizures. Average dose of ketamine infusion used in this study was 2.2 mg/kg/h with a median treatment duration of 2 (1-4) days. The same study attested no adverse effects of high-dose ketamine on intracranial pressure; rather the doses used in this study were associated with a decreased need for vasopressor application.

The two abovementioned relatively large studies are supported by previously published minor reports and case series in both adults and children in which doses as high as 7.5 mg/kg/h were used for up to 14 days and were described as effective and safe (81–85). According to one report, even doses up to 10 mg/kg/h for up to 27 days have not been associated with increased complications or mortality (86). Ketamine treatment seems to be effective in cases of both generalized convulsive and focal non-convulsive SE. Data are however insufficient to provide definite therapeutic recommendations regarding the effect of ketamine on different types of SE.

Likewise, optimal loading dose and doses for continuation are not finally settled, but in an ongoing randomised controlled trial in adults (NCT03115489), an IV loading dose of 2.5 mg/kg of ketamine is given followed by a continuous infusion at 3 mg/kg/h with the possibility to increase up to 10 mg/kg/h until burst suppression in EEG. This seems to be a good starting point for further clinical practice.

Side-effects of ketamine are generally few and no increase in mortality rate has been described (79–80), although this can obviously be difficult to evaluate in SRSE. One advantage with ketamine is its cardiovascular effect as a slight vasopressor; one study (83) clearly showed that ketamine improved haemodynamic stability and reduced the need for vasopressor support.

A potential neurotoxic effect of ketamine, especially in the developing brain, has been discussed, but ketamine has also been associated with neuroprotective actions (78, 84). The unconfirmed risk of neurotoxicity must thus be balanced against the severity of SRSE and the possibility of serious brain damage due to the SRSE.

Immunotherapy

The first report of epilepsy due to brain inflammation dates back to 1958 when the Canadian neurosurgeon Theodore Brown Rasmussen from Montreal Neurological Institute described a few children with intractable focal seizures, progressive hemiparesis, and one-sided inflammatory changes in the brain (87). Since then, evidence has accrued that brain inflammation is involved in both ictogenesis, the consequence of single seizures, and in epileptogenesis (88–90). In recent years, a wide range of autoantibodies have been identified in relation to severe forms of epilepsy, like FIRES, NORSE and Rasmussens encephalitis, and autoantibodies against the NMDA receptor, leucine-rich glioma-inactivated I (LGI1) complex (a protein associated with the voltage-gated potassium channel VGKC), and other autoantibodies against VGKC, VGCC, GAD, GABA etc. have been found| (90). When assessing a patient with SRSE, autoantibodies should now be measured routinely, and immune therapy considered early. However, lack of RCTs or larger (empirical) studies challenge the choice of immunotherapy. Steroids, intravenous immunoglobulins, plasma exchange/ plasmapheresis, rituximab, efalizumab, natalizumab, tofacitinib, azathioprine, cyclophosphamide, anakinra and other therapies have been tried (25, 90–93). These drugs are often used in different combinations and in combination with other therapies. In FIRES for example, the combination of anakinra and ketogenic diet has recently been suggested (94).

In our clinic, high-dose steroid therapy, intravenous immunoglobulins, and rituximab are most often considered first. Also, anakinra, an interleukin-1 receptor antagonist is another promising drug with possible antiseizure (95–97) as well as antiepileptogenic effect (98). RCTs designed to study immunotherapy in presumed autoimmune epilepsy are urgently needed to provide more valuable information and, at best, guidelines.

Neurosteroids

A promising new antiseizure drug, brexanolone, has recently been tested in SRSE. The active substance of brexanolone is allopregnanolone, a naturally occurring neurosteroid and progesterone metabolite. Progesterone and its metabolites are well known to have strong neuroactive properties decreasing brain excitability with allopregnanolone being the most potent (99). Allopregnanolone is a positive allosteric modulator of the GABAA receptor (100–102) and acts on a broad range of GABAA receptor isoforms including an extrasynaptic GABAA receptor (103).

Several minor studies showed very promising results in SE, and in a study of 25 patients with superrefractory cases, brexanolone was effective in 73%. No serious side effects were observed (104).

These encouraging results gave rise to the multicenter study SAGE-547 (https://clinicaltrials.gov/ct2/show/NCT02477618 [accessed on 21 December 2021]). SAGE-547 is a randomized, double-blinded, placebo-controlled trial designed to evaluate the efficacy and safety of SAGE-547 (brexanolone) administered as continuous IV infusion in patients with SRSE. In this study, brexanolone infusion was given for 6 days. Patients were classified as responders when all third-line agents could be weaned off (and remained off for≥24 hours) before the infusion (drug or placebo) was stopped. 122 study sites participated, and 132 patients were included, of which 66 received placebo and 67 brexanolone. Seizure freedom was found in 43.9% in the group receiving brexanolone in addition to standard treatment (29 of 53 that completed) versus 42.4% in the group receiving standard treatment with placebo as add-on (28 of 50 that completed).

This result is apparently disappointing and challenges present concepts of drug development and testing also for other treatment options for RSE and SRSE. Many currently available treatment alternatives, both pharmacological and non-pharmacological ones, are based on promising results described in case reports, small case series, or open studies that cannot be confirmed in a properly designed randomized, double blinded, placebo-controlled trial as demonstrated in this case. The SAGE-547 results underline the urgent need for larger studies, due to the rarity of RSE and SRSE probably only achievable as multicenter RCT studies, and through the establishment of national and international registries.

OTHER TREATMENT OPTIONS

A broad spectrum of alternative therapies has been suggested and tried to treat SE. For all these therapies generally only case reports and small case series exist while systematic comparative trials are lacking. Publication bias should therefore be regarded as high. Hypothermia, magnesium infusion, pyridoxine infusion (highly effective in cases of inborn error of pyridoxine metabolism, also found as responsible for SE in rare cases in adults), lidocaine infusion, ketogenic diet, nerve stimulation (vagal, trigeminal, deep brain), resective neurosurgery, electroconvulsive therapy (ECT), cerebrospinal fluid drainage, and many others have been tried and may be beneficial in individual cases. The numerous therapeutic possibilities are summarized in multiple review articles (10, 25, 105–110).

Magnesium infusion

Magnesium has a potential role in SE as it blocks the NMDA receptor and has an antiepileptic effect in experimental models (111). Magnesium is the drug of choice when treating seizures in eclampsia and has been found effective in a very few case studies in patients with mitochondrial disease, porphyria, and even in a case with myoclonic SE (106). There is no consensus regarding dose, but a serum level up to 1.7 mmol/l has been suggested (16, 60, 112).

Inhalation anesthetics

Inhalation anesthetics have been tried in several small studies, with isoflurane usually being the preferred drug. Although isoflurane suppresses seizure activity while the drug is applied, recurrence rate is high and complications probably frequent (16). In a small study including 7 patients, all 7 developed hypotension, 5/7 infections, 3/7 paralytic ileus, and 2/7 deep vein thrombosis (113), but mortality and long-term morbidity were considered as related to the underlying disease and duration of RSE, rather than to isoflurane. A review comprising 13 studies with a total of 82 SE episodes treated with isoflurane draws a different picture attesting fewer and milder complications, with hypotension as the most frequent side effect (108). Given the high recurrence rate after cessation of inhalation anesthetics, but also possible complications, and practical and logistical challenges with long-term use, this therapy approach should be limited to highly selected cases. Despite this, several national guidelines including the newly published guidelines from the German neurological society (27) mention inhalation anesthetics as a possibility in highly refractory cases.

Ketogenic diet

Data on treatment of RSE/SRSE with ketogenic diet are sparse, but several small uncontrolled case series have indicated a favourable outcome in both children (114, 115) and adults (116, 117). The effect usually seems to occur after 2-5 days. In a multicenter study including 15 adult patients, ketogenic diet was started in patients with SRSE with ketosis state reached on average after two days, and successfully stopped SRSE in 11 patients (73%) (117). This is in line with another study comprising 16 children (median age 8 yrs.) in which the diet was effective in 9 cases (56%) (118). With the relatively rapid onset of action, ketogenic diet can be tried, but, if not effective, should be withdrawn 3-5 days after ketosis is reached. Ketogenic diet may affect serum concentrations of ASMs (119) and may also influence certain forms of intensive care treatment. Notably, ketogenic diet is contraindicated in patients with hepatic failure, acute pancreatitis, or metabolic acidosis (109). It is also recommended not to combine ketogenic diet with propofol, since it increases the risk for fatal propofol related infusion syndrome (120). However, more studies and clinical experience on use and safety of ketogenic diet in SE is needed to make more concrete therapy recommendations. So far, no randomized trials or controlled trials are available.

Hypothermia

Hypothermia exerts anti-epileptic and neuroprotective effects in experimental SE and has also been used in the treatment of SRSE in humans. Data are sparse and very few cases have been properly described (107). The usual recommendation is hypothermia to around 31-35 °C, but even lower body temperatures have been tried. The frequency of complications is high and general anesthesia is always required when hypothermia is established (121). One multicenter RCT exists on the efficacy of hypothermia as add-on therapy in critically ill and ventilated patients with convulsive SE (target temperature 32–34 °C for 24 h) (122). In this

study, hypothermia seemed to reduce the number of patients progressing to EEG-verified SE but did not improve clinical outcome at three months post SE. Common adverse effects included deep vein thrombosis, coagulopathy, increased risk for infection, and hemodynamic alterations including bradycardia and hypotension (121, 122).

Electroconvulsive therapy

There are no general recommendations on the use of Electroconvulsive therapy (ECT) in SRSE. However, several case reports, small series, and reviews on ECT treatment in SE are available (123-127). In a review by Lambrecq and colleagues a favourable outcome was reported including cessation of SRSE in 80% and full recovery in 27% of patients (123). More recently, a case series of 6 patients receiving ECT lead to termination of SRSE in all cases (126). However, up to 12 ECT sessions were required posing a challenge to evaluation of the effect of ECT *per se*. ECT is stated as one out of several treatment options for SRSE in the newly published guidelines by the German Neurological Society (27). There are, however, several practical and ethical considerations when treating patients with ECT for SRSE. Notably, a reduction of anesthesia is required to assure recurrence of seizures, and only analgesia is given. Usually, ECT is applied in multiple series, necessitating frequent changes in the anesthesia level. Therefore, a rigorous ethical discussion should be conducted before ECT is performed in patients with SRSE, and this procedure should, in our opinion, be regarded as last resort.

Electrical or magnetic stimulation

Case reports and small case series on the use of vagus nerve stimulation (VNS), trigeminal stimulation (TNS), deep brain stimulation, and transcranial magnetic stimulation have been published, but the data are scarce, and no firm conclusions can be drawn (127). In our own limited experience, treatment with VNS and 2 cases of TNS proved unsuccessful, contrasting the case reports in the literature describing a positive effect. Systematic larger studies evaluating the effect of these treatment options are needed.

CONCLUSION

Most cases of established SE are treatable. However, much more challenging is the treatment of RSE/SRSE in which about 25% of cases are not controlled despite extensive treatment (25). Certain requirements should be fulfilled to avoid that established SE develops to RSE/SRSE. First, it is vital to start treatment rapidly with benzodiazepines immediately followed by levetiracetam, valproate or fosPHT. Second, these drugs must be given in sufficient doses. Our strategy plan for SE treatment is given in Table 2.

Furthermore, it is essential to quickly try to identify the underlying cause of SE, and to detect possible factors that may have triggered the current SE episode. Treatment should then be directed towards these factors, the pathological cause (if detectable) and, naturally, neuronal hyperactivity. Triggering factors and causes

TABLE 2 Flow-chart for treatment of status epilepticus, Stage 1-5

Stage 1

ABC – airway, breathing, circulation

Unknown patient:
1. Consider hypoglycemia – give glucose 50 ml, 50%
2. Consider alcohol related seizures – give thiamine 200 mg i.v. (can be dissolved in 100 ml NaCl). Give thiamine before glucose
3. Avoid hyperthermia

Discuss: Etiology and triggering factors. Intoxication/drugs?

↓

Stage 2

Benzodiazepines

Diazepam 10 mg i.v. (can be give rectally) OR
Midazolam 10 mg p.o. (can be given i.m. or intranasally) OR
Lorazepam 2-4 mg i.v.

Individual assessments must be done. Initial diazepam dose often increased up to 20 mg i.v. in adults. All drugs can be given in repeated doses if needed. Consider reducing dose (up to 50%) in the elderly and in patients <50kg

↓

Stage 3

Valproic acid, 40 mg/kg, i.v., infusion rate 10 min (Max dose often set to 3000 mg)
Levetiracetam, 40 mg/kg i.v., infusion rate 10 min (Max dose often set to 4500 mg)
Phenytoin/fos-phenytoin, 20 mg/kg (20 mg/kg PE) i.v. infusion rate 50 to max 150 mg/min

↓

Stage 4

Anesthesia
Propofol, 2-5 mg/kg i.v., infusion 2-5 (10) mg/h. Try to restrict to 48 h treatment, OR
Midazolam 0.2 mg/kg i.v., infusion 0.2-0.6 mg/kg/h
If still not controlled, consider pentobarbital

↓

Continued

TABLE 2 **Flow-chart for treatment of status epilepticus, Stage 1-5 (*Continued*)**

Stage 5 – Super-refractory SE*

Ethics. Discuss continuously how far treatment shall go, must be related to underlying pathology and an evaluation of the prognosis. When should active treatment be ended in the individual case?

Should be tried/discussed

Ketamine (loading dose 2.5 mg/kg (1-3), continuous infusion at 3 mg/kg/h until burst suppression in EEG or up to a maximum dose of 10 mg/kg/h.

Ketogenic diet. Ketosis usually reached within 2-3 days. Evaluate effect after 3-5 days in ketosis. If not effective after 5 days, stop treatment

Immunotherapy; steroids, immunoglobulins, rituximab, anakinra

Inhalation anesthetics (isoflurane) (low evidence, can be discussed)

Alternative ASMs

Lacosamide, 400 mg i.v. followed by 200 mg x 2 until se-concentration measurements

Perampanel, up to 36 mg through ngs, reduce gradually to 12 mg/day after 2 days. Adjustments according to se-concentrations

Brivaracetam, 100-300 mg iv loading dose?

Other treatment alternatives to be discussed in individual case (very low evidence)

Magnesium
Hypothermia
Pyridoxine (May be relevenat also for adults with uncontrolled seizures/SE)
Lidocain
Electroconvulsive treatment (ECT)?

End treatment? Ethical discussions

* No consensus on doses and infusion rates. Suggestions based on literature search and personal experience. Should be discussed individually in each case.

of SE will often be identified as metabolic abnormalities, fever, change of medication, non-compliance, intoxications, and different types of brain insults.

It is important to stop both clinical and subclinical neuronal hyperactivity. Most current rational treatment programs are geared towards this by influencing glutamatergic and GABA-ergic mechanisms. However, SE is based on a complex and yet mostly unclear range of mechanisms reaching far beyond glutamatergic and GABAergic imbalance, including genetic, epigenetic, molecular, and other cellular, intercellular and network alterations. As an example, it has been shown in an experimental epilepsy model using lithium-pilocarpine in rats, SE ceased when scopolamine was administered together with diazepam and phenobarbital (128).

With the complex mechanisms involved, several forms of rational polytherapy should probably be tried out. It is only the combination of diazepam and PHT that has been shown to be effective in humans (type 1 evidence) (129). We recommend that different combinations of therapies should be

tested systematically in both animal models and clinical studies, and that clinical data should be collected in an international database. This would reduce the large number of "try and error treatment" attempts and would also counteract publication bias.

The primary cause of SE should be in greater focus. As an example, we are currently witnessing an increasing number of putative immunological causes for SE, opening for more specific diagnostic tools and more personalized treatment options in the future.

A highly important matter is the discussion of the ethical aspects of SRSE treatment. Treatment facilities dealing with SRSE should discuss ethical issues profoundly and define procedures to aid more streamlined treatment approaches including how many trials to use and when to stop the treatment. This is not an easy task as the origin of SRSE seems to be highly individual and by this makes general guidelines difficult. Some of the ethical questions are: what is right for the patient? What is ethical for family and relatives? What is ethical for other patients also requiring the often limited ICU resources in most hospitals? These considerations and questions have been excellently discussed by Crippen et al (130). One major challenge is to distinguish at an early stage between patients with a good prognosis and potential for a worthy life, versus those patients expecting severe brain damage or death. Presently no clear risk factors or biomarkers are available that are near to allow distinction between these groups. The suggested prognostic scoring systems like, STESS and EMSE do not hold sufficient sensitivity and specificity. This poses a particular challenge to decision-making on an individual basis.

Regarding SRSE, there are probably cases where the cause of the condition is so unique that it is very difficult, or even impossible, to either diagnose, or to treat. Other cases of SRSE, however, probably represent RSE that has been developing and that could, perhaps, have been prevented by better treatment at an earlier stage. This underlines the importance of prompt and appropriate treatment from the moment a patient with SE enters the clinic.

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