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CURRENT PERSPECTIVES

Treatment of Refractory and Super-refractory Status Epilepticus

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Abstract
Refractory and super-refractory status epilepticus (SE) are serious illnesses with a high risk of morbidity and even fatality. In the setting of refractory generalized convulsive SE (GCSE), there is ample justification to use continuous infusions of highly sedating medications—usually midazolam, pentobarbital, or propofol. Each of these medications has advantages and disadvantages, and the particulars of their use remain controversial. Continuous EEG monitoring is crucial in guiding the management of these critically ill patients: in diagnosis, in detecting relapse, and in adjusting medications. Forms of SE other than GCSE (and its continuation in a "subtle" or nonconvulsive form) should usually be treated far less aggressively, often with nonsedating anti-seizure drugs (ASDs). Management of "non-classic" NCSE in ICUs is very complicated and controversial, and some cases may require aggressive treatment. One of the largest problems in refractory SE (RSE) treatment is withdrawing coma-inducing drugs, as the prolonged ICU courses they prompt often lead to additional complications. In drug withdrawal after control of convulsive SE, nonsedating ASDs can assist; medical management is crucial; and some brief seizures may have to be tolerated. For the most refractory of cases, immunotherapy, ketamine, ketogenic diet, and focal surgery are among several newer or less standard treatments that can be considered. The morbidity and mortality of RSE is substantial, but many patients survive and even return to normal function, so RSE should be treated promptly and as aggressively as the individual patient and type of SE indicate.

Key Words Status epilepticus · refractory status epilepticus · super-refractory status epilepticus · nonconvulsive status epilepticus · treatment · continuous EEG monitoring · highly sedating medications

If status epilepticus (SE) is, as is said in nearly every review article and text, "a life-threatening neurologic emergency," then refractory SE must be much more threatening – but this is not necessarily true for all types of SE. This review concentrates on the treatment of refractory generalized convulsive SE (GCSE), indeed a very serious condition, but it is important to distinguish what type of SE one is attempting to treat at each stage of the illness.

Definitions and Early Treatment

The International League Against Epilepsy states that SE is "a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures (after time point *t1*). It is a condition which can have long-term consequences (after time *t2*), including neuronal death, neuronal injury, and alteration of neuronal networks depending on the type and duration of seizures" [1]. For GCSE, it is generally accepted that the temporal definition (for "*t1*") is met at 5 min—an "operational definition," designed for use in practice [2], i.e., the point at which there is an urgent clinical imperative to treat in order to avoid lasting neuronal damage, neurologic impairment, or death. It is crucial to recognize that the time criteria for other types of SE are debatable, or impossible to determine.

The preferred initial treatment for GCSE is generally agreed upon, first established clearly by the landmark study of Treiman and colleagues, comparing four drugs for the treatment of GCSE [3]. The Neurocritical Care Society recommends beginning with sufficient doses of an intravenous (IV) benzodiazepine (BDZ), the most rapidly-acting medications [4]. With its longer duration of action, lorazepam is usually preferred, at a dose of 0.1 mg/kg [5]. Whether or not this

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interrupts SE, it should almost always be followed by an IV infusion of a longer acting anti-seizure drug (ASD) such as phenytoin, fos-phenytoin, phenobarbital, valproate, lacosamide, or levetiracetam [4–6].

If the first agent is unsuccessful in treating SE, most neurologists go on quickly (within minutes) to a second IV drug, usually choosing from the same list [7]; often, that drug will have been started already. Nevertheless, if the first drug fails, a second ASD succeeds in stopping SE less than 10% of the time (and even less often with subtle or purely electrographic SE) [3]. Therefore, many neurologists move on to IV midazolam (MDZ) quickly [8, 9], sometimes even as the second agent. If first- *and* second-line treatment is unsuccessful, SE is considered refractory (RSE). Older definitions of RSE included seizure durations from unspecified to 30 or 60 min, or even 2 h. Now, however, most neurologists use the term refractory without regard to temporal duration. Rather, RSE is SE that persists despite treatment with an initial IV BDZ and a second, longer-acting IV ASD. It is important to stress that these drugs must be administered promptly and in adequate doses [10–12].

The relative prevalence of RSE varies from 10% to over 30% of all SE, depending on the setting and definitions [10, 11, 13]. Perhaps the most meaningful estimate comes from a prospective study of SE in adults in a tertiary center, finding that 23% of SE became refractory [14].

When GCSE becomes RSE, almost all experts turn to definitive or "aggressive" therapy with continuous intravenous (C-IV) infusions of midazolam, pentobarbital (or often thiopental in Europe), or propofol [4, 5, 15–18], drugs variously referred to as "coma-inducing" or "third line agents." They are also referred to as "anesthetics," although BDZs and barbiturates are not anesthetic at lower doses and often prevent seizures at doses causing no significant sedation (propofol is properly labeled an anesthetic).

These medications may be necessary in refractory GCSE and its nonconvulsive continuation, but not always for other forms of SE. They almost always halt SE, but their major sedating effects prolong treatment, and SE may recur when (as must happen eventually for the patient to recover) this treatment is withdrawn. If those drugs are insufficient to control SE, or SE recurs as they are withdrawn, the course of treatment may become much longer, and this is "super-refractory status epilepticus" (SRSE)—defined as SE "that continues 24 h or more after the onset of anaesthetic therapy, including those cases that recur on the reduction or withdrawal of anasesthesia [18]." About 1/5 of patients with RSE go on to SRSE [19].

"**Subtle Generalized GCSE**" Frequently, patients in ICUs (or elsewhere) remain unresponsive after the apparent interruption of generalized convulsions or GCSE. It is often impossible to distinguish whether GCSE has entered a postictal phase or if the lack of recovery is due to continuing SE following inadequate or unsuccessful treatment [20]. Both are possible, and clinical assessment alone (e.g., cessation of motor activity) is inadequate to answer this question. As GCSE becomes prolonged, clinical manifestations become more subtle, often with nystagmus or relatively minimal eyelid or facial or other myoclonic jerking, or even absence of all movement, and patients are usually stuporous or comatose, even as the EEG becomes more discontinuous, but with brief bursts of generalized spikes or generalized periodic discharges, or better-organized continuing seizure activity [21, 22]. When the EEG continues to show electrographic seizure activity even as the visible motor manifestations cease, this becomes a form of electromechanical dissociation, sometimes termed "subtle generalized convulsive' SE, often considered a late stage of continuing GCSE [21]. Some consider these EEG patterns to indicate ongoing SE only if the patient had previous clinical seizures or SE [23]. Subtle SE is important to diagnose and treat promptly as clinically significant SE, albeit nonconvulsive. Most agree that the urgency of treatment continues during the persistent electrographic seizures, at least when preceded by generalized convulsions.

Rationale for Aggressive Treatment

Most seizures cease spontaneously but some progress to longer seizures or SE, with the transition to prolonged seemingly self-sustaining seizures or SE appearing to depend on the relative balance of excitatory and inhibitory electrochemical function at cellular, subcellular, and extracellular levels. Early in SE, there is a marked and progressive impairment of gamma-amino butyric acid (GABA) agonist-mediated inhibitory function [24]. This correlates with a loss of GABA receptors on neuronal surfaces [25], in large part due to progressive internalization or endocytosis of those receptors [26]. Around the same time, there is increasing excitatory activity of glutamate receptors during SE, especially the N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, promoting a hyperexcitable state [27, 28]. As this progresses, seizures appear to become resistant to many ASDs, especially those acting through the GABA system, including BZDs and barbiturates [29]. Those receptors, however, may remain sensitive to other drugs, suggesting potentially useful agents for the treatment of RSE (see ketamine and neurosteroids, below) [30]. These physiologic alterations in neurotransmitter activity occur very early in the course of SE, within minutes, providing an incentive for early escalation to definitive treatment, to avoid such pharmacoresistance [31]. There is also clear evidence experimentally [24, 31] and some clinically [32] that SE becomes harder to interrupt the longer it lasts.

The same excitatory processes appear to be involved in neuronal injury during prolonged SE, with the potential injury depending somewhat on the intensity (or frequency) of the

epileptiform discharges [33]. GCSE also engenders major physiologic changes (including a catecholamine surge and sometimes, cardiac arrhythmias) which may contribute to its potential for morbidity and mortality [34, 35]. These physiologic consequences may in turn have direct harmful effects on the brain—some mediated by excitatory neurotransmitter toxicity, and some via inflammation [36, 37].

Clinically, there are well-detailed cases of severe and permanent neuronal damage, such as hippocampal gliosis and atrophy (some accompanied by neuropsychologic deficits) reasonably attributed to prolonged SE alone [38, 39]. Imaging studies, including CT, MRI, and PET scans, have shown substantial changes in brain tissue with SE, but the clinical implications can be uncertain [40].

It is important to note that the findings above apply primarily to GCSE (and probably to the NCSE that follows GCSE) but not necessarily to most forms of NCSE. Little experimental evidence is available on the long-term consequences of NCSE. Chemical and electrical models for inducing NCSE may damage neurologic tissue independent of the seizures. SE can cause hippocampal edema with subsequent hippocampal atrophy in the same area [41, 42], but most described patients have had earlier GCSE or focal motor SE. Pathologic evidence of severe damage from NCSE is scant; episodes are seldom fatal unless they follow GCSE or are associated with other acute, severe neurologic illness—which makes it difficult to sort out the cause of damage. Similarly, minimal clinical morbidity can be attributed directly to NCSE.

It is a sign of the severity of GCSE that outcome is often measured in fatality rates, but there are also other untoward consequences, including neurologic deficits and long-term disability. Relatively few studies have assessed functional outcome, such as with the modified Rankin Scale (mRS), or how often RSE patients return to a normal life. Functional outcome correlates with the duration of an SE patient's hospital stay, and even more, with that of the ICU stay [43]. A multicenter study of patients admitted to the ICU for RSE indicated that prolonged RSE led to high morbidity and mortality rates, with about 80% of patients having a poor outcome at one-year follow up [43].

Mortality from SE is about 5 to 25% overall, depending on the cause and population studied [44, 45] but substantially higher for RSE and SRSE [10, 13, 46]. In one metaanalysis of treatment of RSE with aggressive therapy, the overall mortality was 48% [13]. SRSE is usually associated with a mortality rate of over 30%, and with over 50% of patients dying or in a vegetative state in cases of "new onset refractory status epilepticus" (NORSE) [46]. Considering both mortality and morbidity, under 1/4 of all SRSE and NORSE patients reported so far have had a good outcome; most survivors had significant residual impairment [46]. Nevertheless, good outcome after RSE and SRSE has been reported in several cases. Some patients return to their baseline conditions even after months in coma [47]. Younger age, absence of structural brain lesions, or multiple medical comorbidities are associated with better outcome [48, 49]. Duration of SE beyond a day or so has not been a reliable predictor of outcome [50], so a decision to withdraw medical care should not be made based on SE duration alone but should rather focus on the underlying etiology, comorbidities, etc. RSE and SRSE are indeed health- and life-threatening, but some patients do well and it is easy to justify aggressive treatment for refractory GCSE.

Implementing "Aggressive Therapy"

Given the evidence for neuronal damage, clinical morbidity and mortality, and the greater difficulty of interrupting SE the longer it continues, there is general agreement that SE must be stopped quickly [4, 9]. Discussion of aggressive therapy for the treatment of RSE and SRSE begins with a review of the "promise and perils" of the drugs used most often in this situation: midazolam, pentobarbital (or in Europe, its "prodrug," thiopental), and propofol (see Table 1).

Midazolam The BDZ midazolam (MDZ) acts as an agonist at the GABA-A receptor, penetrating the CNS rapidly, with a fast onset of action, typically in minutes. It is short-acting, with a half-life of 0.8–2.8 h [52], making it ideal for avoiding toxic accumulation. [Caution should be taken in obese patients, in whom accumulation occurs in

Table 1 Highly sedating anti-seizure drugs for the treatment of refractory status epilepticus (adapted from Hocker [51])

Drug	Loading dose	Maintenance infusion rate	Adverse effects
Midazolam	0.2–0.4 mg/kg IV every 5 min until seizures controlled. Maximum dose: 2 mg/kg	0.1–2.0 mg/kg/h	Respiratory depression, hypotension
Propofol	2 mg/kg IV every 5 min until seizures controlled. Maximum dose: 10 mg/kg	30–200 mcg/kg/min Avoid ≥ 80 mcg/kg/min for ≥ 48 h	Hypotension, propofol infusion syndrome
Pentobarbital	5 mg/kg IV up to 50 mg/min every 5 min until seizures are controlled or a maximum loading dose of 15 mg/kg	0.5–5 mg/kg/h	Hypotension, adynamic ileus, respiratory depression, hepatotoxicity, prolonged sedation

adipose tissue, and in those with renal insufficiency.] MDZ infusion can be associated with tachyphylaxis, necessitating gradually higher doses. Hypotension requiring pressors occurs in 30–50% of patients [13, 52]. MDZ is a respiratory depressant, and infusion often requires intubation and mechanical ventilation [52]. In many studies, breakthrough seizures occur more often than with other highly sedating drugs [13, 53]. In a systematic review comparing the efficacy and outcome of highly sedating drugs in 193 RSE patients, 54 were treated with MDZ, 106 with pentobarbital, and 33 with propofol; 20% of patients had seizure recurrence soon after the loading dose [13]. More strikingly, 51% of patients had breakthrough seizures within the first 6 h of MDZ treatment (*vs* 15% on propofol and 12% on pentobarbital) and 63% of patients had withdrawal seizures when tapering MDZ (compared to 46% on propofol and 43% on pentobarbital). Another study [53] compared 100 patients treated with high-dose continuous MDZ infusion to those treated with lower dose MDZ protocols (median maximum doses of 0.4 mg/kg/h, *vs* 0.2 mg/kg/h). With similar baseline patient characteristics, withdrawal seizures within 2 days of MDZ discontinuation were less frequent in the high-dose group (15 *vs* 64%).

Propofol is a potent IV anesthetic that acts as a CNS depressant through direct activation of GABA-A receptors and inhibition of NMDA receptors. Propofol (PRO) has a rapid onset of action and decreases cerebral oxygen utilization quickly, thus reducing intracranial pressure [54]. Hypotension necessitating the use of pressors occurs in 22–55% of patients with PRO infusion [13, 54]. The most worrisome complication is the propofol infusion syndrome (PRIS), a result of toxic effects on mitochondrial and cellular function, causing metabolic acidosis, rhabdomyolysis, renal failure, hypertriglyceridemia, refractory bradycardia, and cardiac failure [55]. In a study of 31 patients treated with PRO, either in combination with other ASDs or alone, the median duration of treatment was 67 h, with a median cumulative dose of 12,850 mg [56]. Three patients had sudden cardiopulmonary arrest; 2 died, and 11 developed PRIS. PRIS may be avoidable by using a protocol limiting its use to 2–3 days at doses not exceeding 80 mcg/kg/min. Should PRIS occur, treatment is supportive and includes discontinuation of PRO along with cardiac, pulmonary, and renal support [57].

Data are limited with regard to efficacy of PRO in RSE. PRO treated RSE successfully in 67% of 31 episodes in one series [58]. In a retrospective study of 18 patients with RSE, breakthrough seizures occurred in 33% of 27 episodes [55]. They were typically treated with an increased infusion rate, repeat boluses of PRO, or bolus doses of another ASD. In only two cases, one with mitochondrial disease, were the breakthrough seizures severe enough to necessitate replacement of PRO with another "aggressive" drug.

Barbiturates Thiopental and its metabolite, pentobarbital (PNT), have strong anti-seizure effects. Their main mechanism of action is by augmenting transmission at the GABA-A receptor. They also lower body temperature and may have neuroprotective effects. In high doses, they can cause a loss of brainstem reflexes and an isoelectric pattern on EEG [59]. Barbiturates are almost always successful in achieving seizure control [13, 60, 61]. Due to their prolonged duration of action, however, the regaining of normal alertness is delayed significantly, so they are not usually first line treatment. Prolonged recovery times and longer duration of mechanical ventilation are due to its zero order kinetics, rapid redistribution, and accumulation [62, 63]. Barbiturates are metabolized by the liver and have many drug-drug interactions. Hypotension requiring pressors occurs in 29–77% of patients treated with barbiturates for RSE [60, 62]. A relatively common adverse effect is an adynamic ileus, occurring in up to 10% of patients, which can lead to bowel ischemia or even perforation [64, 65]. In less than 1% of patients, propylene glycol toxicity can manifest with acidosis [60]. Infrequently, lingual edema develops and can compromise the airway. The latter two complications are treated by stopping the drug [66]. In a retrospective study of 31 patients with SRSE treated with PNT, 90% achieved seizure control, but seizures recurred upon weaning of the drug in 48% [60].

Several questions arise concerning the use of these drugs, in particular: which drug; for how long; how deeply to suppress the clinical seizures; and perhaps most difficult of all, how to taper and discontinue the drugs (assuming they have controlled the SE)—without the patient lapsing back into SE.

Choice of Drug There is insufficient comparative evidence available to recommend one of these drugs over another, so drug selection is based on the advantages and side effect profile of each, with consideration of each patient's comorbidities and possible complications of the therapies. In one metaanalysis, PNT had a lower incidence of short-term treatment failure, breakthrough seizures, and need for another drug—but a higher incidence of hypotension [13]. That study found PNT more effective for seizure control but associated with more adverse effects, without improved outcome, compared to use of MDZ or PRO. A global survey of RSE treatment found MDZ the most widely used initial sedating ASD, at 59%, followed by PRO (32%) and barbiturates (8%) [67]. Many neurologists start with IV MDZ, sometimes followed by a day or two of PRO if MDZ seems insufficient, then resorting to PNT if MDZ and PRO are inadequate or if seizures or SE recur upon their tapering.

The optimal duration of aggressive treatment has also not been studied sufficiently. Many neurologists recommend suppressing and ensuring the absence of electrographic (and of course, clinical) seizures for 12 to 24 h, some longer [4] with MDZ, PRO or PNT, followed by a gradual taper of

those medications, with concurrent EEG monitoring [4, 5, 18, 51, 68, 69]. Several MDZ trials have been shorter [13]. Shorvon recommended that "anesthetic" treatment should be continued for at least for 24 h after seizures have ceased, then tapering those medications gradually, with continued C-EEG monitoring [5, 18].

The optimal electroclinical goal of treatment [simple cessation of seizures; both clinical and electrographic seizure control; or a certain degree of suppression of cerebral activity as assessed on EEG—often to a burst suppression pattern] has also never been studied well prospectively. It remains unclear what is best [62]. One retrospective study (using PNT alone) raised the possibility that more prolonged seizure and EEG suppression could be beneficial [70]. Another found no difference in outcome depending on the depth of EEG suppression [71]. In a metaanalysis, patients treated with the goal of EEG background suppression (mostly with PNT) had a 4% likelihood of breakthrough seizures *vs* 53% for patients treated to control clinical and electrographic seizures only (mostly with MDZ or PRO) [13]. Still, patients treated with EEG background suppression had a 76% likelihood of significant hypotension, *vs* 29% for those treated to suppress seizures only. Whatever the depth of suppression, mortality was 48%, always attributed to the severity of the underlying illness causing SE. This controversy in EEG endpoints for SE treatment is reflected in recent guidelines, which do not endorse specific EEG background suppression goals [4, 68, 69].

EEG Monitoring During Aggressive Treatment

SE persists in a nonconvulsive form in 14–20% of patients after cessation of clinically evident seizures [72], and clinical signs of SE are nonspecific, subtle, or nonexistent. Of 164 patients who had apparent control of clinical SE in one series, 42% had continued epileptiform discharges, and 14% were in NCSE [72]. In the VA Cooperative study, just 17% of patients with overt GCSE (and none with "subtle" GCSE) regained normal alertness within 12 h of treatment [3]. Failure to recover may be explained by the electrographic persistence of (nonconvulsive) seizure activity—which most epileptologists consider a continuation of GCSE and warranting urgent treatment.

For ICU patients with diminished responsiveness (even those not treated for RSE) NCSE is remarkably common [72–74], especially if there were earlier generalized convulsions [22, 75, 76]. In patients with coma of all causes (without any clinical sign of seizures), 8% had NCSE in another series [73]. Still, the patients at highest risk for unrecognized, ongoing NCSE are those who were in GCSE and were thought to have been treated successfully—but were not!

In patients with persistently impaired mental status, EEG alone can distinguish those in drug-induced coma, from those who are post-ictal, and from those with continued nonconvulsive seizures [71]. Several recent guidelines and consensus statements highlight the critical role of continuous EEG (C-EEG) monitoring during prolonged treatment for SE patients in the ICU [4, 68, 69].

During prolonged IV infusions of ASDs, C-EEG is essential to assess the effectiveness of treatment; for detection and recognition of recurrent (usually nonconvulsive) seizures and SE; and in managing their re-treatment [4, 68, 69]. Such relapse is not rare, especially in the first 24 h [72]; it also occurs in up to 69% of patients as C-IV ASDs are tapered [75]. In a retrospective study of RSE treatment, nonconvulsive seizures were found in 18% of patients within the first 6 h of IV MDZ infusion, and breakthrough seizures occurred in 56% of patients later; they were clinically undetectable (i.e. purely electrographic) in 89% [75]. Electrographic seizures recorded on EEG during treatment predict relapse of clinical seizures and SE [77] and a worsened outcome, and should be avoided if possible. They usually warrant increased ASD treatment. Isolated epileptiform discharges, however, do not appear to necessitate vigorous treatment [70].

Practice C-EEG recording should be initiated as soon as possible after the diagnosis of SE, optimally within 1 h [4]. During treatment, the EEG should be reviewed immediately, and then periodically until SE has been controlled or a burst-suppression record is induced [4, 68, 69]. Once seizures are suppressed, less frequent review may be sufficient; persisting seizures require more intensive monitoring. Optimally, the EEG monitoring should be performed and reviewed from the time aggressive therapy is started until seizures stop and the patient has returned to normal consciousness, or at least until all seizures are controlled for 24 h [4, 68, 69].

How to Tell If Seizures or SE Have Recurred Very often, it is not at all trivial or obvious to determine whether seizures have recurred. EEG patterns are extremely varied, and there are myriad rhythmic and epileptiform sharp waves on EEGs, including many forms of periodic discharges; some of these indicate ongoing seizures [78], but what EEG features constitute a seizure is complicated. The diagnosis of recurrent seizures or ongoing NCSE on EEG relies on the determination by a clinical neurophysiologist that certain patterns are "ictal" in nature (i.e., signifying an ongoing epileptic seizure), but there is substantial controversy regarding which EEG patterns are indicative of seizures. A committee of the American Clinical Neurophysiology (ACNS) proposed criteria for diagnosing seizures on EEG [79, 80]—and if persistent enough, NCSE [80, 81] (see Table 2). Nevertheless, even experts have difficulty applying such criteria consistently [82], and controversy abounds in this field. Criteria similar to those from ACNS were published by a consortium meeting in Austria [83]. Both sets of criteria have good specificity for nonconvulsive seizures and NCSE and assist greatly in their

Table 2 American Clinical Neurophysiology Society Research Criteria for Nonconvulsive Seizures [and, if > 30 min, Nonconvulsive Status Epilepticus]

(1)	Repetitive generalized or focal spikes, poly-spikes, sharp waves, spike-and-wave or sharp-and-slow wave complexes, or other rhythmic waveforms at > 2.5/s, lasting longer than 10 s, or
(2)	The same waveforms as above, with discharges < 2.5/s, but with …..
(a)	Clear clinical ictal phenomena, such as facial twitching, nystagmus, or limb myoclonus.
(b)	An unequivocal evolution of the rhythmic pattern, including increase or decrease in frequency (by > 1 Hz), change in discharge morphology, or in location (gradual spread of rhythmic activity into or out of a region involving at least 2 electrodes). Changes in discharge amplitude or "sharpness" alone are not sufficient, or
(c)	Rhythmic delta waves at > 1/s, with the additional criterion of unequivocal clinical improvement, or improvement on EEG [such as resolution of epileptiform discharges and reappearance of previously-absent normal background rhythms and reactivity] or both, following quickly after acute administration of rapid- acting ASDs, typically BZDs. (Resolution of discharges leaving a slow background alone, without clinical improvement, would not suffice.)

Adapted from Chong and Hirsch [80], Young and colleagues [81]

diagnosis, but they were designed as research guides, and sensitivity can be a problem [79, 84]. Some patients whose EEGs do not meet those criteria are very likely still having seizures [85]. Clinical judgment is still crucial in diagnosis.

When tapering highly sedating medication, it is very important to have one or more (and sometimes several) non-sedating medications on board—although this is not always given sufficient consideration (e.g., stopping IV MDZ when it has been the only treatment). An older study found that having both PB and DPH on board, rather than DPH alone, was far more likely to be successful when tapering PNT [77].

Treatment of Relapse There have been no randomized controlled trials evaluating the treatment of recurrent seizures or SE after aggressive treatment of RSE in the ICU, or elsewhere. Treatment decisions are generally extrapolated from trials of GCSE treatment or tailored to the perceived urgency and morbidity of the seizures and SE encountered in the ICU [86, 87]. When SE recurs, clinically or electrographically, most neurologists intensify treatment, sometimes by re-starting or increasing the dose of MDZ, PNT or PRO; sometimes using these infusions for longer; adding more non-sedating drugs or effecting higher levels of prior ASDs; and continuing aggressive therapy another 24 h before attempting another taper [4, 18, 88]. Alternatively, some might try non-sedating drugs first, resorting to aggressive therapy if they fail. All this re-treatment can lead to a long ICU course, and it may be necessary to tolerate occasional brief seizures to help get the patient out of the ICU sooner (below).

Complications of Aggressive Treatment for Refractory Status Epilepticus

Prolonged treatment of SE with heavily sedating drugs such as MDZ, PNT, or PRO can result in hypotension or prolonged mechanical ventilation and is associated with worsened outcomes—usually attributed to the severe underlying illnesses causing SE [13, 20]. Etiology of SE is overwhelmingly the most important prognostic factor. Short-term mortality is highest when SE results from acute insults, especially strokes, infection or anoxia [44, 89]. Patients with multiple medical problems, including sepsis, fare poorly, while those with SE due to tumors, trauma, alcohol abuse or other drugs have an intermediate or lower mortality [44]. The most favorable etiology is epilepsy itself with some exacerbating factor (e.g., reduced ASDs, fever, sleep deprivation, or an intercurrent illness) prompting the SE [44]. Presentation in coma (*vs* stupor or confusion) confers a poor prognosis [90], but this may also be related to the severity of the etiology. Although etiology is key, one study found that death following SE appeared un-related to etiology in about 10% and may have been caused by complications of the treatments or of prolonged ICU stays in coma [91].

Complications of MDZ, PNT, and PRO, and of the prolonged ICU course they prompt, may also contribute to morbidity and mortality [91, 92]. Some recent studies have found an independent risk of poor outcome associated with use of C-IV highly-sedating or "anesthetic" drugs, even when controlling for the type of SE, level of consciousness, and severity of SE [92, 93], although others have not found this [94]. Control for SE severity was often by use of the well-validated Severity of Status Epilepticus Score (STESS) [95], but it is very difficult to control for the refractoriness of the SE that led the clinicians to choose aggressive treatment (not necessarily identical to the severity of the illness). Also, some studies included patients with absence and complex partial SE (CPSE), which most neurologists would hesitate to treat with these drugs [admittedly, some cases may have been labeled "absence" when they had generalized EEG discharges but without a primary generalized epilepsy syndrome, and some, CPSE when they had a focal onset but progressed to convulsions or generalized seizures]. Most epileptologists still consider aggressive therapy

necessary in the treatment of highly refractory GCSE in the ICU, including for the NCSE or "subtle" GCSE that follows GCSE [4, 18].

Most patients who die in ICUs while being treated aggressively for RSE die because of the life-threatening etiologies of the RSE [13, 60] or from systemic complications linked to the ICU stay [13, 43, 45]. In a paper raising concern for the association of aggressive therapy with poor outcome, 19 patients with RSE treated with these drugs died, 5 in SE, 11 from infections, and 2 from multiorgan failure [92]. In a large recent series, 53% of 78 patients with prolonged RSE died, with a median ICU stay of 28 days; 63% of deaths were from multiorgan failure (even as SE had resolved in half). After a year, only 15% had good outcome (by mRS scores of 0 to 3) [43]. Of course, the use of aggressive therapy and the prolonged ICU course and complications could be consequences of the refractoriness of the SE. It is hard to know which factor is primary.

Aggressive therapy may not lead directly to poor outcomes, but a long ICU course puts patients at risk for infectious, hematologic and other medical complications. Whether the highly sedating drugs or medical complications of the long ICU course contributed to the deaths, there is a very strong incentive to expedite the treatment of RSE and get the patient out of the ICU as quickly as possible.

Recommendations We recommend that most patients with RSE and SRSE, including those with "subtle generalized SE" or other NCSE that follows GCSE be treated aggressively with continuous IV infusions of MDZ, PNT or PRO (Table 1). Most other types of RSE, however, should not be so treated—unless the SE is particularly long and refractory and the patient and neurologists accept the possible complications of such treatment. There are several other types of SE and RSE.

Other Types of Refractory Status Epilepticus

Typical absence SE (and *de novo absence SE*) that occurs within absence epilepsy or arising in other primary generalized (genetic) epilepsy syndromes is relatively uncommon and almost always interrupted readily (on EEG and clinically) with increased doses of the patient's earlier ASDs, modest doses of BDZs, or the addition of other non-sedating ASDs, preferably IV, but sometimes effective even orally [96]. Absence SE almost never becomes refractory. It has an excellent prognosis, and aggressive therapies should almost always be avoided [96–98].

The outcome of *complex partial SE* [or now, focal-onset NCSE with dyscognitive features or altered awareness] depends primarily on the etiology; morbidity often derives from the unresponsive state and from complications of the underlying illness rather than from the CPSE itself. Early reports of ("classical") CPSE included relatively few patients; it seldom became refractory, and almost all patients returned to normal or "baseline cognitive function" [99, 100]. One series of 65 patients with "classic" NCSE (mostly CPSE) showed long term morbidity in just one [101]. Some patients had prolonged memory and other cognitive deficits following the NCSE [102, 103], but many of these resolved eventually. Prolonged CPSE has clearly been *associated* with serious morbidity, but most of these patients had significant underlying lesions (e.g., encephalidities or strokes) causing the CPSE and likely contributing substantially to the later deficits [104].

Epilepsia Partialis Continua (EPC) The continued focal jerking of EPC is often refractory to ASDs [105]. Valproate, clonazepam, and levetiracetam are common treatments; topiramate and levetiracetam can be helpful [106]. For the EPC of Rasmussen's encephalitis, intravenous immunoglobulin (IVIG) and plasma exchange are used increasingly [107]. Resective surgery can be curative if the lesion is small enough [108]. Larger resections, corpus callosotomy, and multiple subpial transections can be helpful in selected cases [109, 110]. EPC may also resolve without treatment [104]. EPC can be refractory, and ASDs may help prevent dangerous secondarily generalized convulsions, but especially with preserved consciousness, it should very rarely be treated aggressively.

There are many forms of *myoclonic status epilepticus (MSE)* [111]. Many occur in the primary generalized, "idiopathic" (usually genetic) epilepsy syndromes. Several include prominent eyelid blinking and low amplitude multifocal jerking. A few of these syndromes include generalized convulsions, but some do not cause significant alterations in consciousness [112]. This MSE very seldom becomes refractory, even when including convulsions, and aggressive treatment is almost never needed.

Anoxic MSE is entirely different. Most cases are fatal; therapeutic hypothermia has led to some improved outcome, but after a few days of anoxic coma, the outlook is almost always grim, especially if RSE appears on the EEG then [113–115]. Similarly, the MSE due to medical problems such as major organ failure and metabolic derangements is often associated with coma; the prognosis depends on the underlying medical illness—sometimes reversible [111]. It is very unusual that a patient with this form of MSE should receive "aggressive" treatment. Rather, the treatment should focus on the underlying cause.

Treating for the appropriate type of SE is crucial, so there should be a very careful determination of which type of SE is occurring. GCSE is an obvious diagnosis, but some others are not. This was discussed well in one decision analysis-oriented paper considering different SE types, the probable harm due to that type of SE itself, and their likely courses and outcomes [116]. It concluded that patients with some

types of SE were more likely to benefit from aggressive treatment, and in others, it would be unnecessary (e.g., absence SE) or futile (e.g., anoxic MSE).

The Problem of "Non-classical" NCSE

If diagnostic choices were as simple as GCSE, "subtle GCSE," absence SE, CPSE, or EPC, decisions would be much easier than they are in modern ICUs.

Absence SE and similar generalized forms of NCSE on the one hand, and CPSE or focal-onset NCSE on the other, constitute the "classic" types of NCSE. Most cases of ongoing NCSE diagnosed in ICUs currently, however, are not of these classic types but are rather related to acute medical, neurologic, or traumatic illnesses, sometimes superimposed upon epilepsy syndromes but more often arising anew during the acute illness [117]. Many generalized NCSE syndromes are secondarily generalized (with underlying and sometimes severe lesions) or the result of systemic or metabolic derangements. Those other illnesses may contribute to the reduced responsiveness and in turn, make recognition of NCSE and its clinical significance more difficult. The diagnosis rests heavily on the EEG. These "non-classic" cases are the most common types of NCSE in ICUs now. They are often much harder to treat [74, 81, 118], and some cases (especially those following convulsive seizures) can become refractory and necessitate aggressive treatment.

The morbidity and mortality of this "non-classic" NCSE in the ICU are substantial [119], but it is difficult to dissect out that portion of the long-term harm caused by epileptiform discharges, seizures, or SE from the damage caused by the underlying illness [32, 74]. Nevertheless, the total "seizure burden" (percentage of time in seizures or SE, convulsive or nonconvulsive) correlates well with the degree of clinical deterioration, at least in young children [120], suggesting that NCSE in the ICU should definitely be treated promptly—but if at all possible, with non-sedating drugs. In some cases, aggressive therapy may be necessary, but this is a complicated and difficult decision, depending heavily on the individual patient's condition, including concomitant illnesses, the refractoriness of the SE, and overall clinical situation—not lending itself easily to simple rules.

Some refer to these patients as in electrographic status epilepticus (ESE) [22]. Others refer to it as "status epilepticus in coma," but not all patients with ongoing electrographic seizures are comatose. Some label these patients with severe medical illness as having "epileptic encephalopathies"—indicating that the underlying disease causing the discharges is key, and that the epileptic component is not primary and may not respond to ASDs. That term, however, is probably best reserved for childhood conditions such as those associated with Electrical Status Epilepticus of Sleep [121, 122].

More Recommendations For very sick ICU patients (and for all), the treatment should be appropriate for the type of SE encountered. For less-threatening types of SE, non-sedating ASDs should be the mainstay of treatment, even when the SE is refractory, perhaps especially when there have been no definite generalized convulsions during the course of illness, i.e., the RSE has been entirely nonconvulsive, as far as can be determined. Nevertheless, there are some cases of prolonged and refractory "non-classic" NCSE (and rarely, particularly debilitating EPC) for which the clinician may choose more aggressive treatment. In these cases, one must consider the refractoriness of the SE, the patient's overall medical condition, co-morbidities, and prognosis, and the possible complications of treatment. These are difficult decisions for difficult cases.

There are two main situations in which "non-aggressive" treatment or non-sedating ASDs are particularly important components of the treatment of RSE: for most SE in forms other than GCSE (or its "subtle" continuation) and in adding ASDs to facilitate tapering highly sedating or "aggressive "therapy later in the ICU course.

Non-sedating Drugs in the Treatment of RSE

For patients with RSE who have never had a definite convulsion, there should be a vigorous attempt to interrupt and keep seizures suppressed with one or more non-sedating ASDs. Among the many choices are IV phenytoin, fos-phenytoin, phenobarbital, valproate, lacosamide, or levetiracetam; enteral (usually by nasogastric or other feeding tube) topiramate, carbamazepine and other standard ASDs without IV formulation; and various forms of stimulation, diet, and even surgery. Avoidance of intubation (or later, to facilitate weaning from mechanical ventilation) should be a priority.

The recommended loading dose for IV phenytoin or fosphenytoin [in "phenytoin equivalents"] is 18–20 mg/kg for adults and 15 mg/kg in the elderly (> 65 years), although up to 50% more medication may be helpful in many cases, without major toxicity [123]. Phenytoin is not sedating, but hypotension (28–50%) and cardiac arrhythmias (2%) may complicate treatment; patients over the age of 50 years and those with prior cardiac disease are at higher risk for cardiovascular complications [124]. Fosphenytoin is a water-soluble precursor transformed rapidly to phenytoin. Advantages are a faster rate of infusion, up to 150 mg/min, and a better local (at least for the "purple glove" syndrome) tolerability [125]. Better cardiopulmonary tolerability is not certain.

Valproic acid (VPA) is a non-sedating ASD, often helpful for patients with SE. Rapid IV infusions (up to 40 mg/kg/min) are generally tolerated well [126]. IV VPA in patients with SE had good cardiovascular and respiratory

tolerability and a low incidence of adverse effects (< 10%), the most frequent being dizziness, thrombocytopenia, and mild hypotension—which was independent of infusion rates [127]. A report summarizing 30 studies of IV VPA in a total of 860 patients showed an overall response rate in interrupting SE of 71% [127]. The most commonly used effective dose was 15–45 mg/kg as a bolus (6–10 mg/kg/min) followed by 1–3 mg/kg/h infusion [126]. The most concerning adverse effects include an acute encephalopathy, often related to hepatic abnormalities or hyperammonemia [128, 129]. Some reports suggest that VPA may be superior to phenytoin in the early treatment of (non-refractory) SE [130].

Phenobarbital (PB) like other barbiturates enhances inhibitory neurotransmission by binding to a specific barbiturate site on the GABA-A receptor [131] but may antagonize AMPA receptors [132]. PB has over 95% bioavailability, 48–54% protein binding, a half-life of 72–144 h, and is metabolized by the liver [133]. To date, there are limited reports on treatment with PB in RSE. Enteral PB absorption is rapid, reaching a therapeutic range in 30 min [134]. In a case series of RSE 6 patients treated adjunctively with enteral PB, 50% reached complete control, with partial control in the remaining 50%, usually within one hour [135]. One study evaluated "mega-dose" PB (≥ 10 mg/kg, enteral or parenteral) for treatment of SRSE in 10 patients following continuous IV sedating treatment [136]. Initial control of SRSE was reached in 8 of 10 patients, but 2 had withdrawal seizures and 1 died of septic shock, so therapy was considered successful in just 50%. PB has frequent complications, including hemodynamic instability, respiratory depression, immunosuppression, and reduced gastrointestinal motility, which can limit the duration and dose of its use [137]. At high serum concentrations, PB can suppress brainstem reflexes [132].

Lacosamide (LAC) is used commonly for the treatment of focal epilepsies [138]. In a review of 19 studies, a total of 136 episodes of RSE were treated with LAC [139]. Presentations were with focal (31%), nonconvulsive (50%) or convulsive (19%) SE in various phases. The most frequent bolus dose was 400 mg, followed by a total daily dose of 200–400 mg, with an overall success rate in 76 of 136 patients (56%). Adverse effects included mild sedation, and less frequently, hypotension and allergic skin reactions. LAC can cause a dose-dependent prolongation of the PR interval and a (reversible) AV conduction block, so caution should be maintained, especially when treating patients with cardiac and renal risk factors [140, 141].

Levetiracetam (LEV) is a well-tolerated ASD, without drug interactions, efficacious against many seizure types including established SE [142, 143]. A randomized, open-label study compared its use with that of IV lorazepam in 79 patients with early SE [144]. The two drugs were equally effective in halting clinical seizures within 10 min of administration, but there was a significantly higher rate of respiratory failure requiring artificial ventilation in patients receiving lorazepam, suggesting an advantage for LEV in early-stage SE. The Neurocritical Care Society recommended an initial IV loading dose of 1000 to 3000 mg [4]. Adverse effects are few, most often sedation and rarely thrombocytopenia [145].

Topiramate is a broad-spectrum ASD with several mechanisms of action, including blockade of AMPA receptors [146]. There is no available IV formulation, but it can be administered enterally and has been an efficacious adjunctive treatment for SE in doses ranging from 2 to 25 mg/kg/day in children, and up to 1600 mg/day in adults [147], leading to clinical seizure cessation in 62 of 95 patients (65%), summed over several studies [148, 149]. Metabolic acidosis was the most frequent side effect.

Carbamazepine (CBZ) is an established treatment for focal epilepsy in adults, but no parenteral formulation is available [150]. In one small series, rectal CBZ syrup appeared to help prevent relapse in patients whose cluster of seizures in GCSE had been halted earlier [151].

Expediting the ICU Phase of Treatment

Although aggressive treatment with MDZ, PNT, or PRO almost always succeeds in controlling RSE and keeping it under control, the course may be long, especially if there are several relapses. C-EEG monitoring can help guide treatment, tapering of medications, detection of relapse, and avoiding under- or over-treatment. Recurrent RSE must be stopped, but often with some restraint and an attempt to avoid or taper highly sedating medications, because the long ICU course also has its dangers. The key to improving outcome in the highly refractory cases may be the expeditious but careful withdrawal of highly sedating medications after control of SE in the ICU, without precipitating relapse of the SE. Non-sedating drugs may be valuable beneficial as add-on, adjunctive treatment in these cases.

As noted above, recurrent seizures should be treated, but it may be better to tolerate occasional electrographic or even clinical seizures, especially if they are brief and infrequent (as is tolerated with non-ICU patients and for outpatients with discrete seizures), than to keep patients in the ICU for repeated or additional aggressive therapy—and several more days. Balancing the risk of clinical relapse of SE against the risks of longer ICU stays and possible infection, hematologic complications, etc. is an important goal (and problem) in the management of RSE and SRSE (see Table 3).

Table 3 Expediting ICU stays for patients with "Super Duper" refractory status epilepticus

Consider new treatment: immunotherapy, ketamine, surgery, ketogenic diet, various types of stimulation.
Consider prolonged phenobarbital/lorazepam—covered withdrawal of highly sedating drugs (can be tapered out of ICU, or even out of hospital).
Try non-sedating ASDs first when treatment must be intensified, e.g., for relapses.
Assure adequate doses of concomitant non-sedating ASDs (two or more) when tapering highly sedating drugs.
Surveillance for and management of infection, hematologic problems, organ failure.
Tolerate a few seizures per day, especially if nonconvulsive, or focal, or brief (under a few minutes each); not generalized convulsions.
Do not increase treatment for isolated or non-rapid periodic epileptiform discharges.

Late Stage or "Super Duper" Refractory Status Epilepticus

"Aggressive" and other treatments are usually successful in treating all but the most refractory SE. For some SRSE patients, however, it may become clear after several (?5 to 7) days [perhaps after failure of the second attempt to withdraw highly sedating drugs], that the course is not going well and will be especially prolonged. When SRSE relapses each time aggressive therapy is withdrawn, the dangers of a prolonged ICU course may rival those of the RSE or its treatments, and it may be necessary to change plans and institute some new and different interventions. While some cases of RSE prove refractory to all treatments [137], alternatives should probably be considered at this point. Numerous other treatments have been tried, ranging from lidocaine or felbamate, to ECT, to inhaled anesthetics. The evidence supporting (or not supporting) use of nearly all of these treatments is discussed expertly in a recent review by Holtkamp [152]. There is a staggering array of choices. Among the most commonly chosen options are immunotherapy, ketamine, and a moderately prolonged taper of phenobarbital after it replaces the (other) highly sedating drugs.

Immunosuppressive Therapy: Encephalitis and Autoimmune Disorders After a few days of aggressive therapy for RSE, immunotherapy is often considered. Indeed, if the presentation suggests a recognizable autoimmune (AI) syndrome, it should be begun at the onset. Many of the most refractory cases of SE seem to occur in young adults who present with new-onset refractory SE (NORSE) which often appears to have an inflammatory or AI etiology [153, 154]. Although this review concentrates almost exclusively on adults, a very similar syndrome of "febrile infection-related epilepsy syndrome" (FIRES) is reported in children [155].

Clinical clues that an RSE patient has one of these AI syndromes include a subacute onset (over days to weeks), high seizure frequency, seizure variability or multifocality, ASD resistance, history of cancer, and personal or family history of AI disease [156]. Others are gradual cognitive impairment, neuropsychiatric symptoms, multilevel nervous system involvement, or a new-onset movement disorder. The detection of neural-specific autoantibodies in serum or cerebrospinal fluid (CSF) can help to establish the diagnosis. Testing abnormalities suggesting one of these illnesses include evidence of inflammation on MRI (e.g., mesial temporal T2-weighted or FLAIR hyperintensities), on FDG-PET, or in the CSF (e.g., pleocytosis, elevated protein, or oligoclonal bands) [157].

NMDA-receptor encephalitis was first described in young women with ovarian teratomas [158] but can occur in patients without tumors, including men and children [159]. The classic presentation is with a viral-like prodrome followed by psychiatric disturbances and often, oro-lingual-facial dyskinesias, seizures, and later, central hypoventilation, autonomic dysfunction, and coma [159]. One study of C-EEG use in 23 patients with NMDAR encephalitis found that 60% had electrographic seizures without clinical correlate and 30% had a unique EEG "signature" called "extreme delta brushes" [160].

Voltage-gated potassium channels (VGKCs) modulate neuronal excitability, axonal conduction, and neurotransmitter release in the central, peripheral, and autonomic systems [161]. LGI1 and Caspr2 are two antigenic targets in the potassium channel complex. LGI1 antibodies are frequently associated with limbic encephalitis and Caspr2 antibodies with peripheral nervous system manifestations, but both can affect all levels of the nervous system [162]. Up to 50% of patients with VGKC-associated encephalitis have MRI evidence of inflammation and cell loss, with enlargement, T2 hyperintensities, enhancement, and restricted diffusion in mesial temporal structures [163]. Seizures often have a focal (mesial temporal or hippocampal) onset [156, 164].

There are many other AI syndromes with different antigen associations, including anti-GAD, anti-Hu (ANNA), etc. Treatment of NMDA, VGKC, and other AI encephalidities causing RSE includes immunotherapy with high-dose IV steroids, alone or with IV immunoglobulin or plasma exchange [164]. If first-line therapy fails or is insufficient in an antibody-mediated proven or suspected case of AI-based RSE, rituximab or cyclophosphamide can be considered and are often effective [165]. These treatments are mandatory for clearly diagnosed cases of AI-caused RSE, but with less certain diagnoses the possible benefit must be weighed against the serious risk of infection in long-term ICU patients.

Ketamine As seizures progress, both in experimental animals and in human studies, they appear to become resistant to many ASDs, especially those acting through the GABA system, such as benzodiazepines (BZDs) and barbiturates [29]. NMDAR

antagonists are of limited value in blocking the initiation of SE [166], but as seizures continue they appear to become more effective and glutamate antagonists (such as ketamine) may become helpful [167, 168].

Ketamine is an anesthetic drug with action as an NMDA receptor antagonist—used increasingly for SE refractory to drugs-acting at the GABA-A receptor. It has a rapid onset of action (within seconds) and is relatively short acting, with an elimination half-life of 2–3 h. An attractive feature is the rarity of associated respiratory and cardiac depression. A multicenter retrospective review evaluated 60 episodes of RSE treated with ketamine [168]. Permanent control of SE was likely or possibly attributed to ketamine in 19 of 60 episodes, with the response best when it was administered early. Limitations of the study included an inability to control for the effects of other ASDs or etiologies of the RSE (probably the most important prognostic factor). Infusions of up to 10 mg/kg/h for up to 27 days were tolerated well, without increased complications or mortality compared to those for patients receiving lower doses, shorter courses or both. Supraventricular tachycardia occurred in 2 patients, resolving with discontinuation of ketamine. Possible long-term adverse effects of ketamine are not understood well yet. Unfortunately, under 10% of patients had good outcomes, but ketamine was probably the final of many treatments for prolonged, RSE and thus less likely to rescue the patient [46, 168]. This report discusses the possible "early use" of ketamine, which is certainly plausible for earlier stages of RSE, but its long-term effects are less well understood, and it is less familiar to most neurologists. Some guidelines recommend ketamine infusion for the most refractory cases only after at least one other highly-sedating drug has failed [4].

Barbiturate and BDZ Taper High doses of barbiturates control almost any SE, but with significant and long-lasting sedation. Nevertheless, PB's long half-life may help with a safer (relapse-avoiding) taper of highly sedating medications. Several groups have found adjustment of phenobarbital doses (gradually, but not always monotonically, lower), effective in removing highly sedating medications, particularly pentobarbital—although the ICU course may still be prolonged [51, 60, 169]. During phenobarbital lowering, patients may habituate to its sedating effects and begin spontaneous respiration and some meaningful responsiveness at surprisingly high drug levels [61]. Maintenance doses of lorazepam (e.g., a few milligrams every 6 h) may help in the same process.

Ketogenic Diet The ketogenic diet (KD) is a high fat, low carbohydrate, adequate protein diet devised to mimic a fasting state and produce ketosis. It can be effective for patients with drug-resistant epilepsy [170]. In one retrospective review of 10 adults in ICUs treated with KD for SRSE, ketosis was achieved in 9 patients after a median of 3 days [171]—but after 2 days in a prospective study [172]. Adverse reactions included included hypertriglyceridemia and transient acidosis in both studies, resolving with cessation of the KD. About 2/3 of patients had resolution of SRSE in 3–5 days after KD initiation, with subsequent withdrawal of the highly sedating medications. In both studies, many earlier medications had been administered. KD appeared to be a safe and reasonable treatment for adults with RSE and SRSE. Problems include that it can be difficult to use, requiring professional dietician help, and avoidance of many infusions that include carbohydrates (including propylene glycol, used as a carrier in many IV ASD preparations), especially in an ICU; and the 2–3 or more days required to reach ketosis.

Neurosteroids Allopregnanolone, an endogenous metabolite of progesterone, is an allosteric modulator of synaptic and extra-synaptic GABA-A receptors making it a plausible treatment for RSE and SRSE [173], even when the cause is not necessarily inflammatory or immune-based. In a clinical trial, allopregnanolone was safe and tolerated well by patients with very refractory SE and appeared to help wean the "therapeutic coma" induced by heavily sedating medications, without SE recurrence [174]. A phase 3 randomized, double-blind placebo-controlled trial, however, failed to show that it was better than placebo plus standard treatment for such weaning [175]. Other doses or protocols may be tried.

Stimulation Repetitive transcranial magnetic stimulation (rTMS) is a relatively new non-invasive technique for treatment of seizures and SE. At lower frequencies, rTMS can suppress cortical activity, but at higher frequencies (> 5 Hz) it can cause cortical excitation [176]. There are a few case reports of its use in RSE. In one, two ICU patients with refractory focal SE had at least a 50% reduction in seizure frequency after rTMS application [177]. To date, cases are too few to provide evidence of efficacy, but rTMS appears to be very safe, does not require surgery or device implantation, and does not require the cessation of earlier ASDs. Adverse effects include inducing seizures (very rarely) or headache and dizziness [178]. Its use may be restricted to epileptogenic foci close to the cortical surface because the magnetic stimulation effect falls off rapidly with distance [179].

Surgery Surgical intervention can help for patients with particularly refractory focal SE [180]. In one series of 10 children with focal SE refractory to at least 2 weeks of high dose suppressive therapy (all with focal imaging abnormalities), SE was terminated by resection of the epileptogenic zone in all, and 7 of 10 became seizure-free [110]. Other helpful procedures have included wider, lobar or even multilobar resections, even to the point of functional or anatomic hemispherectomy (usually in cases of devastating epilepsies of childhood, including Rasmussen's encephalitis); disconnection procedures such as corpus callosotomy [181]; and multiple subpial transections [109], with or without focal resections [182].

Conclusions

The risk of death, neuronal damage, or serious long-term disability with RSE and SRSE is substantial, justifying the use of aggressive treatment, which usually means continuous infusions of midazolam, pentobarbital or propofol (though not the latter for too long)—in cases of GCSE and the "subtle SE" and other NCSE that often follow GCSE. This should not, however, be the treatment for absence SE, most cases of CPSE, EPC with preserved consciousness, or myoclonic SE in the setting of primary generalized myoclonic epilepsies. It may be appropriate in some cases of "non-classical" NCSE when the clinician considers the course of the SE episode, overall condition and medical co-morbidities of the patient, and likely complications. The use of aggressive treatment is complicated, and many patients do not do well—most likely due to the underlying illnesses causing RSE and the prolonged ICU stays, during which patients encounter new and sometimes life-threatening medical illnesses. Aggressive treatment must be monitored clinically and by C-EEG, and clinicians should be willing to change course after a few days in order to get the patient out of SE and out of the ICU.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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