CURRENT
OPINION

Continuous infusion, general anesthesia and other intensive care treatment for uncontrolled status epilepticus

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Purpose of review

To discuss the use of continuous infusions, general anesthesia, hypothermia, and ketogenic diet as treatment for uncontrolled status epilepticus in pediatric patients.

Recent findings

Recent studies demonstrate that clinical practitioners have a hierarchy in approach in controlling refractory status epilepticus (RSE) and super-refractory status epilepticus in children. In the acute setting of RSE, midazolam achieves clinical seizure control at a mean of 41 min after starting an infusion. When midazolam has failed to control RSE, the evidence points to barbiturate anesthesia as the next frequently used option. When both midazolam and barbiturates have failed, use of isoflurane or ketamine anesthesia has been tried at a mean of 10 days after RSE onset, although the studies are largely anecdotal. Increasingly, the use of therapeutic hypothermia or ketogenic diet is described as a strategy for super-refractory status epilepticus, and better evidence for their use may become available from ongoing randomized studies.

Summary

Uncontrolled episodes of status epilepticus require intensive care treatment and the literature describes a common pathway of care used by many. However, cases of truly refractory and super-refractory status epilepticus are seen infrequently at any given institution. One strategy to improve the quality of evidence is to develop prospective, national and multinational case registries to determine the range of presentations and causes, efficacy of treatments, and clinical outcomes.

Keywords

hypothermia, ketamine, ketogenic diet, midazolam, pentobarbital, refractory status epilepticus

INTRODUCTION

The management of the critically ill child presenting in status epilepticus requires attention to three targets: seizure control [1,2], diagnosis of underlying cause [3], and life-supporting therapies [4▪▪]. The other reviews in this issue of *Current Opinion in Pediatrics* have dealt with emergency care and the use of first-line and second-line antiepileptic drugs (AEDs) [1–3]. If these therapies fail, what other treatments should we use? This review presents the evidence to help guide use of AEDs by continuous infusion, general anesthesia, and other intensive care therapies.

The definition of when a prolonged seizure becomes an episode of refractory status epilepticus (RSE) has changed over the last 20 years [2,3,4▪▪,5]. Rather than indicating a specific duration of seizure, terms such as RSE and super-refractory status

epilepticus are now frequently used to indicate when first-line and second-line AEDs have failed [4▪▪]. For example, super-refractory status epilepticus is a stage of RSE characterized by unresponsiveness to continuous infusion of AEDs and anesthetic therapy, and is defined as 'SE that continues or recurs 24 h or more after the onset of general anesthesia, including those

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KEY POINTS

- Once first-line and second-line therapies have failed to control an episode of ongoing status epilepticus, practitioners often resort to the use of antiepileptic drugs (AEDs) by continuous infusion, general anesthesia, and other pediatric intensive care unit therapies.

- Terms such as refractory and super-refractory status epilepticus are now frequently used to indicate a state when first-line, second-line, and third-line AEDs have failed to control status epilepticus.

- The hierarchy in anesthetic therapies is high-dose midazolam, then barbiturate anesthesia, and then other agents such as ketamine or inhaled isoflurane.

- There are anecdotal studies of using therapeutic hypothermia or the ketogenic diet for super-refractory status epilepticus, and more evidence may become available when ongoing randomized studies are completed.

cases in which SE recurs on the reduction or withdrawal of anesthesia' [6].

CONTINUOUS INFUSION OF HIGH-DOSE MIDAZOLAM FOR REFRACTORY STATUS EPILEPTICUS

There is no evidence that one particular AED by continuous infusion is more efficacious than any other in the treatment of RSE. We must therefore weigh the risks and benefits of each agent. The use of midazolam for RSE in children is a relatively new practice – the initial pediatric intensive care unit (PICU) experiences were reported in the 1990s [7].

Midazolam injection contains 0.5% midazolam hydrochloride in water (buffered to pH 3.3–3.5). Midazolam undergoes a facile 1,4-benzodiazepine ring-opening in an acidic aqueous solution to form a benzophenone derivative. At high infusion rates, up to $200\,\mu g/kg/min$ ($12\,mg/kg/h$), the acidic diluent can cause severe hyperchloremic, nonanion gap metabolic acidosis and resultant hemodynamic compromise [8]. The reverse cyclization reaction of the benzophenone to midazolam occurs *in vivo* at pH 7.4, which creates a highly lipophilic structure that penetrates rapidly into the brain. This imidazobenzodiazepine has a short elimination half-life (1.5–3.5 h), and little accumulation. These pharmacokinetics allow for repeat bolus dosing, aggressive titration of an infusion, and relatively fast recovery time.

Up to January 2014, there had been nine English language studies on midazolam infusion in pediatric

RSE [9▪▪]. Each study has a minimum of five patients, and the total number of cases is 521. This evidence was summarized in a recent systematic review [9▪▪]. The majority of the studies reported the time from the start of status epilepticus until cessation of clinically apparent convulsive activity (ranging 30 min to 48 h). Two studies also used continuous electroencephalography (cEEG) to monitor subclinical seizures [10,11]. Midazolam infusion achieved seizure control in 76% of all patients in the nine studies. These 396 responders were treated for an average of 41 min before seizure control. However, when cEEG monitoring was used, considerably higher doses of midazolam were used [$2.8\,\mu g/kg/min$ ($0.17\,mg/kg/h$) versus $10.7\,\mu g/kg/min$ ($0.64\,mg/kg/h$)] and time to seizure control was longer. These observations raise the concern that nonconvulsive seizures may be undertreated when cEEG monitoring is not used during therapy [12]. However, this finding could be largely historical because many PICUs now consider cEEG monitoring as standard management for RSE [13▪,14]. These data also challenge the expectation that seizure control should be achieved within 1 h, as control of seizures was obtained at ~4.5 h in the two studies using cEEG [10,11].

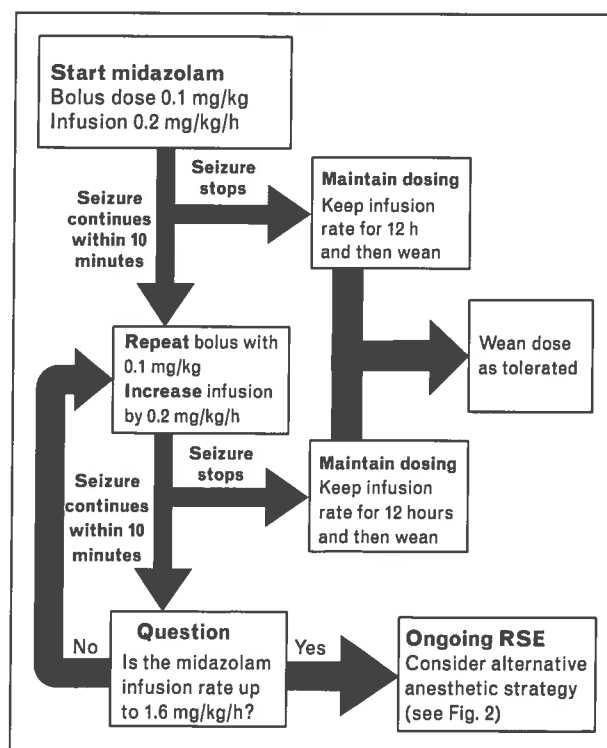Dosing of midazolam by continuous infusion is shown in Fig. 1. With regard to the upper limit, one

FIGURE 1. Midazolam infusion for refractory status epilepticus (RSE).

of the cEEG studies used the highest mean dose [14 μg/kg/min (0.84 mg/kg/h)] [10], and the other used the highest maximum dose [24 μg/kg/min (1.4 mg/kg/h)] [11]. Seven of the nine studies [9⁎⁎] also gave information about hemodynamic instability. In all, 2.3% of patients had hypotension or required inotropes.

Taken together, it is clear that midazolam by continuous infusion for RSE achieves seizure control with little need for vasoactive agents. This combination of high efficacy, ability to be rapidly titrated to seizure control and relatively benign hemodynamic profile supports its continued use as the initial agent for RSE.

GENERAL ANESTHETIC INFUSIONS FOR REFRACTORY STATUS EPILEPTICUS

If seizures persist despite continuous infusion of midazolam, then in the PICU there are intravenous anesthetics that can be used. Propofol is used in adult cases of RSE. However, the risk of propofol infusion syndrome in children is unacceptable and, therefore, continuous infusions in the PICU is not recommended in a number of countries [15].

Pentobarbital

Pentobarbital penetrates the central nervous system quickly, allowing for rapid titration to EEG burst suppression. It has multiple actions: activation of the γ-aminobutyric acid (GABA) receptor in a way that is different to the benzodiazepines; inhibition of N-methyl-D-aspartate (NMDA) receptors; and alteration in the conductance of chloride, potassium, and calcium ion channels. These multiple mechanisms of action explain the drug's potential effectiveness in RSE that is resistant to benzodiazepine therapy [16]. Prolonged infusion of pentobarbital makes for unpredictable pharmacokinetics and very prolonged recovery with a drug effect lasting days [16].

Pentobarbital causes a reduction in cerebral metabolic rate for oxygen ($CMRO_2$) and, to a lesser degree, a matched fall in cerebral blood flow (CBF). A consequence of the fall in CBF is reduced intracranial pressure (ICP), which may be advantageous in patients with cerebral swelling [17]. Theoretically, pentobarbital may also be neuroprotective because of its inhibition of NMDA receptors, and reduction in $CMRO_2$. Anesthesia is induced by a bolus dose (range 5–15 mg/kg), usually over 30 min. Onset of action is within minutes and the peak effect is seen within 15 min. In order to achieve burst suppression in a timely manner, it is best to repeat small (1–5 mg/kg) boluses while monitoring the cEEG and hemodynamic state [18–20]. During up-titration

of pentobarbital, simply adjusting the infusion rate without providing additional boluses typically causes an unnecessary delay. The infusion rate that many use is 1–5 mg/kg/h. When patients receive prolonged treatment with pentobarbital, they develop tolerance to the sedative effect, but not to the anticonvulsant effect, which explains why tachyphylaxis is less common with pentobarbital that with midazolam infusions [21].

As of January 2014, four retrospective studies using barbiturate coma for RSE in pediatric patients had been reported in the English language literature, for a combined total of 95 patients [9⁎⁎]. The majority of patients had failed to respond to midazolam (75%), and barbiturate infusion achieved burst suppression and seizure control in 65% of these midazolam nonresponders. Two studies provided information on the infusion rate needed to obtain seizure control or burst suppression. The mean maximum dose was similar in the studies reported by Sakuma et al. [22] and Barberio et al. [18], 4.98 and 4.8 mg/kg/h of pentobarbital, respectively. A maximum hourly infusion rate of pentobarbital was reported in one study and was 10 mg/kg/h [18]. Barberio et al. [18] also reported the occurrence of breakthrough seizures in 67% of patients, even after achieving burst suppression. Kim et al. [23] found that seizures recurred in 22% of patients after stopping pentobarbital. Last, almost all patients in the literature review (96%) had hemodynamic instability requiring at least one vasoactive agent [9⁎⁎].

Overall, in spite of undesirable pharmacokinetics and side effects, pentobarbital remains a reliable drug for stopping RSE in adult [24,25⁎⁎–27⁎⁎] and pediatric practice [9⁎⁎]. Burst suppression is usually maintained for 24–48h (Fig. 2) [19–21]. Despite its tissue accumulation and long elimination half-life, breakthrough seizures can occur from abrupt discontinuation of the infusion, and so tapering the dose during weaning is recommended [23]. Hypotension should be anticipated in all patients; the drug dilates venous capacitance vessels resulting in reduced cardiac preload and output. The total systemic vascular resistance changes little, and there should not be any myocardial depression. One use of cEEG monitoring is to ensure that only the minimum infusion rate of pentobarbital to induce burst suppression is given, thereby avoiding overtreatment and hemodynamic consequences. It is also advisable to make sure that the patient has adequate preload, and that vasopressors are readily available [28]. Last, it is worth noting that pentobarbital causes white blood cell dysfunction and is associated with nosocomial infection, especially pneumonia. Patients may also be at risk of abdominal complications and ileus [29].
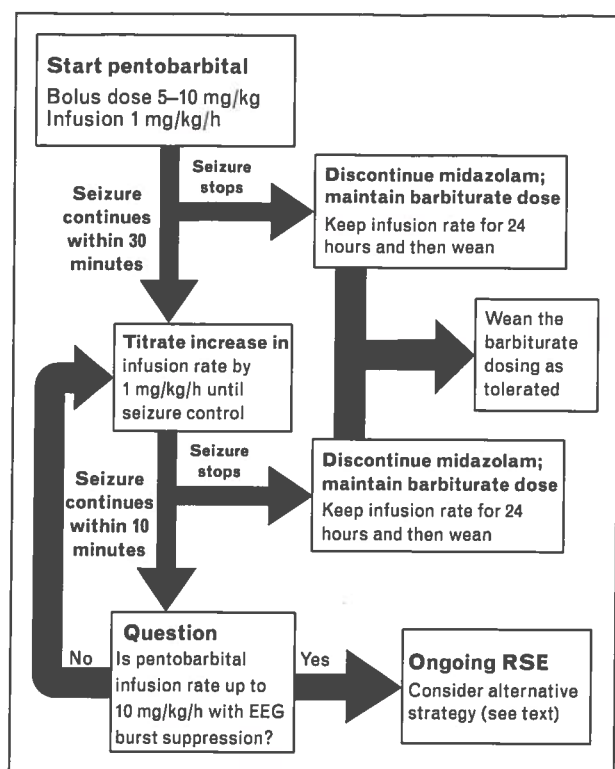
FIGURE 2. Pentobarbital infusion for refractory status epilepticus (RSE).

Ketamine

Prolonged seizures are accompanied by a decline in sensitivity to GABA agonists, but not to NMDA-receptor antagonism. Ketamine is an NMDA-receptor antagonist that is associated with dissociative anesthesia and no cardiorespiratory depression.

Up to January 2014, only two pediatric case series of intravenous ketamine for RSE had been reported in the literature [9"]. One single-center study reported its use in nine children with RSE who had all failed to respond to midazolam infusion, and half had also failed to respond to barbiturate anesthesia. Rosati et al. [30] used a ketamine infusion of 36.5 (range 10–60) μg/kg/min after a median of 6 (range 2–26) days of RSE along with midazolam (to prevent emergence reactions) and found that six of nine patients had their seizures controlled. Another study of 58 cases used ketamine in 12 children after a median of 9 days of RSE (range 0–122 days), although the analysis of the pediatric data was not separated from the adult data [31"]. Ketamine was not universally effective in controlling RSE (at best 57% in the whole population with a mortality of 45%) – the authors commented 'likely response was not observed when infusion rates were lower than 15 mcg/kg/min; ketamine was introduced at least 8 days after SE onset; or after failure

of seven or more drugs'. One-third of the whole series developed complications, most commonly sepsis, shock, organ failure, and pneumonia.

Taken together, the collective experience of ketamine in North America and Europe is still small and its role in RSE requires further investigation.

INHALED ANESTHETIC FOR REFRACTORY STATUS EPILEPTICUS

The inhaled anesthetic isoflurane has been used for the treatment of RSE for over 20 years. More recently, desflurane has also been used. Unlike other anesthetics for RSE, inhaled anesthetics provide immediate control of seizure activity regardless of seizure duration or type. The mechanism by which inhaled anesthetics control seizure activity likely involves multiple receptors including GABA, nicotinic and glycine receptors, and potassium-gated ion channels. It is difficult to determine what role the volatile anesthetics should have in the treatment of RSE and super-refractory status epilepticus. Many protocols mention the use of these agents as a last resort, at a time when permanent neurological damage is likely to have already occurred, and advocates argue that initiation sooner would yield better outcomes. Overall, the inhalational anesthetics are a reliable method for controlling seizures and inducing burst suppression. These goals are achieved within minutes, and hypotension is not dose-limiting. The inhalational anesthetics are therefore easier to titrate than pentobarbital and the pattern of emergence from anesthesia is more predictable. In PICU practice this means that long-term AEDs can be started and blood levels optimized while the patient is in burst suppression. However, each PICU should decide whether they have appropriate personnel and equipment to safely initiate, supervise, and monitor inhalational anesthetic therapy [4"",9""].

Isoflurane is given via an anesthetic machine with end-tidal monitoring of isoflurane concentration. Initially, the concentration of the anesthetic is gradually increased until adequate suppression of the seizure and background EEG activity has occurred, and this dose is maintained. Then, at regular intervals, the minimum dose of anesthetic needed to achieve burst suppression should be determined. The total anesthetic exposure is calculated using the minimum alveolar concentration (MAC) units per hour of treatment, that is, the hourly end-tidal percentage concentration of isoflurane divided by 1.15 is summed for each hour of treatment. (The MAC is defined as the concentration of vapor in the lungs at one atmosphere that prevent the reaction to a standard surgical stimulus

in 50% of individuals.) The anesthetic agents cause nonlinear decrease in $CMRO_2$, and once burst suppression occurs there is no further decrease in cerebral metabolism. Hence, there is little value in going beyond burst suppression and inducing electrocerebral silence. EEG monitoring is required to determine that minimum dosing is used. The anesthetic agents also decrease cerebrovascular resistance, thereby causing an increase in CBF and, potentially, ICP – this complication is seen with isoflurane, and to a lesser degree with desflurane. Increased ICP is typically mild, transient, and only of major significance in patients with evidence of preexisting intracranial hypertension [17,32]. Both isoflurane and desflurane produce a dose-dependent fall in arterial blood pressure via lowering of systemic vascular resistance and, to a much lesser degree, negative inotropy. As a consequence, a compensatory increase in heart rate is frequently seen when starting these agents. Last, there are some concerns that the volatile anesthetics may be neurotoxic when used for prolonged periods in RSE [33]. The first PICU case series of adverse neurology associated with prolonged isoflurane were reported in children treated for severe bronchospasm [34]; five of 10 patients developed extreme agitation and nonpurposeful movements after stopping isoflurane. All five patients were less than 5 years old and received at least 70 MAC hours of volatile anesthetic. Other studies reflect a similar experience of psychomotor disturbances after stopping the anesthetic abruptly [35–38]. It is unclear whether these symptoms are the result of withdrawal, or a direct neurological insult, but typically symptoms self-resolve.

As of January 2014, studies on the use of volatile anesthetics for RSE were limited to small case series, predominantly in adults [9■■]. However, one study did include five pediatric patients with RSE, and in all five patients seizure control or burst suppression was achieved [32]. Four of the patients had failed treatment with pentobarbital. Isoflurane administration ranged from end-tidal concentrations of 0.5 to 2.25% and the median duration of RSE before treatment was 7 days.

OVERVIEW ON THE USE OF ANESTHESIA AS AN OPTION FOR TREATING REFRACTORY STATUS EPILEPTICUS

The overall strategy when using general anesthesia is to achieve steady state burst suppression (3–5 s interburst interval) with the minimum dose necessary, so as to avoid hemodynamic instability. However, there are two key questions with this herapy.

First, 'how long should the patient remain in this state?' If one believes that making the diagnosis of super-refractory status epilepticus is important, then 24 h after starting anesthesia, it should be lightened so as to ascertain whether breakthrough seizures occur. Abrupt weaning may lead to breakthrough seizures and so weaning should occur slowly. The wean will be longer with intravenous anesthesia than volatile anesthetics, and it is reasonable to wean over 24 h. We maintain patients in burst suppression for 48 h and then lighten the depth of anesthesia over 24 h. This 3-day interval allows time to make choices about AEDs and optimize drug levels. If seizures recur, then anesthesia is re-established and the duration of repeat cycles of anesthesia is increased, often for 3–5 days. There is no limit to the number or duration of anesthesia cycles. Rather, as the number and length of cycles increases, the critical care and neurology teams must decide at what point the therapeutic target should change from total seizure control to accepting a particular seizure frequency. For example, there is a report of an 18-year-old with a flu-like prodrome and super-refractory status epilepticus who had pentobarbital-induced burst suppression for over 7 weeks while other AEDs were tried [39]. In our practice, making decisions about AEDs, duration of coma and setting of therapeutic targets is an ongoing multidisciplinary process between the PICU, anesthesiology, and epileptology/neurology teams.

The second key question about anesthesia for RSE is whether this therapy is more toxic than the condition for which it is being prescribed. Recent literature in adults with RSE questions whether intravenous anesthesia is doing more harm than good [26■■,27■■,40,41■■]. For example, there is class III evidence from 171 adults with RSE of a 2.9-fold relative risk for death (95% confidence interval 1.5–5.7) when comparing cases receiving anesthetic therapies with those not [26■■]. This experience is similar to two other cohort studies of anesthesia for super-refractory status epilepticus in adults [27■■,40], and concerned editorials have debated whether such therapy should be reevaluated [41■■,42■].

Taken together, the recent literature challenges the overall strategy of using anesthetic agents early in the course of treatment [25■■–27■■,40,41■■,42■]. This argument should also apply to pediatrics because the literature about these agents in children is limited (i.e., pentobarbital less than 100 cases; ketamine less than 20 cases; inhaled anesthetics less than 10 cases). Therefore, in our view, the decision about who requires anesthesia for RSE, what agent should be used, and the timing of the intervention

should be based on the combined judgment and experience of critical care and neurology attendants [9**].

OTHER INTENSIVE CARE TREATMENTS FOR REFRACTORY STATUS EPILEPTICUS

Two other treatments have reemerged as strategies for controlling seizures in children with super-refractory status epilepticus.

Hypothermia

Therapeutic hypothermia has been used to treat RSE and super-refractory status epilepticus for many years. In 1984, Orlowski et al. [43] reported three children with status epilepticus successfully treated with a combination of therapeutic hypothermia (30–31°C) and thiopental. Since then, in the English language literature, there have been other pediatric cases reported in which therapeutic hypothermia has been combined with other anesthetic agents, or bumetanide [9**]. (In the Japanese literature, there is more extensive reporting of hypothermia for RSE [44]. Imataka et al. [45*] also reported a detailed protocol). Recently, Guilliams et al. [46**] described using therapeutic hypothermia in five children with RSE; the authors also reviewed seven other children reported in the literature. Nine of these 12 children had failed to respond to midazolam, four had also failed to respond to pentobarbital and one had not responded to ketamine. In all cases, body cooling 30–35.3°C achieved acute seizure control.

Taking these studies together, therapeutic hypothermia may help control RSE, but its efficacy is transient and, like anesthetics, it should be considered a temporizing measure while other AEDs are considered. At the time of writing this review, there is a prospective randomized study [Therapeutic Hypothermia in Convulsive Status Epilepticus in Adults (HYBERNATUS)] registered with ClinicalTrials.gov, study NCT01359332 (estimated completion date April 2015).

Ketogenic diet

The ketogenic diet is a high-fat, low carbohydrate, and adequate protein diet used widely to treat refractory epilepsies in children. It has also been used in RSE and super-refractory status epilepticus in children [47–54,55*,56**] and adults [57*]. The ketogenic diet is given through a gastric tube and most studies use a 4 : 1 or 3 : 1 ketogenic ratio (grams of fat to protein and carbohydrate combined) with total avoidance of glucose initially. The ketogenic diet is started after screening to exclude underlying biochemical, metabolic, or mitochondrial disease, including β-oxidation deficiencies, and 24 h of fasting. The short-term side effects include acidosis, hypoglycemia, weight loss, and gastroesophageal reflux, which can obviously complicate the care of a critically ill patient. In the initiation phase, blood glucose should be measured at least every 3 h for the first 3 days and then, if appropriate, every 6 h thereafter. Glucose is given if blood sugar falls below 45 mg/dl. Once ketosis is achieved, urinary ketones and serum β-hydroxybutyrate should be measured daily. Later on, the frequency of the serum testing can be changed to weekly. During the ketogenic diet, glucose needs to be severely restricted and total fluid intake should be monitored closely. As steroids may inhibit the development of ketosis, its use should be avoided [49]. In rare instances, ketogenic parental nutrition has been used successfully in children with epilepsy [58], and there is now a recent proof-of-concept case study of this approach in an adult with super-refractory status epilepticus [59].

To date, in the pediatric case series that have examined the ketogenic diet in RSE and super-refractory status epilepticus [47–54,55*,56**], 33 of 43 children (proportion 77%, 95% confidence interval 61–88) have responded within 19 days. At the time of writing this review, there is a prospective randomized study of ketogenic diet for RSE in adults in a neurointensive care unit registered with ClinicalTrials.gov (NCT01796574, estimated completion date November 2014).

CONCLUSION

When a child with RSE is admitted to the PICU, there is an inadequate evidence-base for what AED strategy should be used [60**]. To date, treatments have been based on case series of last-resort therapies, with a dearth of prospectively controlled data, and this lack of objective information compromises optimal therapy. More case studies do not indicate more efficacy and new interest by the *Journals* does not equate with recommendations. This review outlines a hierarchy in approach that most authors take in controlling RSE and super-refractory status epilepticus. In the acute setting of RSE, midazolam infusion achieves clinical seizure control at a mean of 41 min. If midazolam fails to control the episode, the evidence points to barbiturate anesthesia as the next frequently used option. If both midazolam and barbiturates have failed, there are anecdotal studies on the successful use of isoflurane or ketamine anesthesia. Alternatively, others have described using either therapeutic hypothermia or ketogenic diet, with some success, and more evidence may

become available when ongoing randomized studies are completed.

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None.

Conflicts of interest

R.C.T. receives support from the NIH and he is one of the investigators in the 'Pediatric Status Epilepticus Research Group'.
There are no conflicts of interest.

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and by the American Epilepsy Society) represents a form of registry or comparative-
effectiveness-research and in a rare condition such as super-refractory status
epilepticus likely represents the most efficient way to identify what works.