Status epilepticus – time is brain and treatment considerations

Caroline Der-Nigoghossian[a], *Clio Rubinos*[b], *Ayham Alkhachroum*[b], *and Jan Claassen*[b]

Purpose of review
Status epilepticus is a neurological emergency associated with high morbidity and mortality. There is a lack of robust data to guide the management of this neurological emergency beyond the initial treatment. This review examines recent literature on treatment considerations including the choice of continuous anesthetics or adjunctive anticonvulsant, the cause of the status epilepticus, and use of nonpharmacologic therapies.

Recent findings
Status epilepticus remains undertreated and mortality persists to be unchanged over the past 30 years. New anticonvulsant choices, such as levetiracetam and lacosamide have been explored as alternative emergent therapies. Anecdotal reports on the use of other generation anticonvulsants and nonpharmacologic therapies for the treatment of refractory and super-refractory status epilepticus have been described.
Finally, recent evidence has examined etiology-guided management of status epilepticus in certain patient populations, such as immune-mediated, paraneoplastic or infectious encephalitis and anoxic brain injury.

Summary
Randomized clinical trials are needed to determine the role for newer generation anticonvulsants and nonpharmacologic modalities for the treatment of epilepticus remains and evaluate the long-term outcomes associated with continuous anesthetics.

Keywords
anticonvulsants, continuous anesthetics, continuous electroencephalography, refractory status epilepticus, status epilepticus

INTRODUCTION/EPIDEMIOLOGY

Status epilepticus is a neurological emergency associated with high mortality and morbidity [1]. It is defined as continuous clinical or electrographic seizure activity that lasts at least 5–10 min or recurrent seizure activity without recovery to baseline neurologic status between seizures [1–3]. Critically ill patients commonly have seizures that are mostly not associated with convulsions, also known as nonconvulsive seizures [4]. Nonconvulsive status epilepticus has been reported in up to 10% of medical and surgical ICU comatose patients undergoing continuous electroencephalography (EEG) monitoring and this type of status epilepticus is even more common in patients with acute brain injury [5–6]. Current evidence suggests that seizures may cause additional damage if they persist, potentially leading to neuronal death [7–8]. Furthermore, time-dependent pharmacoresistance to benzodiazepines and anticonvulsants occurs in status epilepticus [9–10].

Despite the risk of further brain injury, these seizures often are undertreated as shown by the prospective Sustained Effort Network for treatment of Status Epilepticus (SENSE) registry [11▪▪]. Up to 78% of patients with generalized and nongeneralized convulsive status epilepticus received an initial administration of benzodiazepine or other anticonvulsant that was below recommended dosage. Of concern, patients with refractory status epilepticus

[a]Department of Pharmacy, NewYork-Presbyterian Hospital and [b]Division of Neurocritical Care, Department of Neurology, Columbia University, New York, New York, USA

Correspondence to Jan Claassen, MD, Neurological Institute, Columbia University New York Presbyterian Hospital, 177 Fort Washington Avenue, MHB 8 Center, Room 300, New York, NY 10032, USA.
Tel: +1 212 305 7236; fax: +1 212 305 2792;
e-mail: jc1439@columbia.edu

Curr Opin Crit Care 2019, 25:000–000
DOI:10.1097/MCC.0000000000000661

KEY POINTS

- Timely initiation of adequate doses of benzodiazepines and anticonvulsants is crucial for the treatment of status epilepticus.
- An ongoing randomized clinical trial will determine the most effective urgent anticonvulsant after failure of benzodiazepines.
- Randomized controlled trials are needed to determine the role of new anticonvulsants and nonpharmacologic options for the treatment of refractory and super refractory status epilepticus

received significantly lower cumulative bolus doses in the initial 12 h of treatment than patients with nonrefractory disease.

Emergent control of clinical and electrographic seizures by rapid initiation of treatment, adequate dosing, and rapid escalation of therapy is required [1–2]. Here we will discuss the management of status epilepticus focusing on the critical care setting.

TIME IS BRAIN: TREATMENT ALGORITHM

Emergent control therapy

Multiple studies evaluating the initial treatment approach have established benzodiazepines as the preferred first-line therapy [12–14]. Use of benzodiazepines as the initial drug has been associated with faster cessation of status epilepticus compared with placebo [13]. In the United States, intravenous lorazepam and in Europe, intravenous clonazepam are the preferred agents whenever intravenous access is available. Intramuscular midazolam can be used as an alternative when intravenous access is not available, as it was demonstrated to be noninferior to lorazepam in the prehospital setting [14]. Finally, rectal diazepam, and nasal or buccal midazolam, are recommended when the previous options are not available [1]. Despite the potential risk of respiratory depression with benzodiazepines, there was a trend towards higher incidence of respiratory depression in patients with untreated status epilepticus compared with patients who received adequate doses of benzodiazepines [13]. Thus, adequate initial dosing is strongly recommended [1].

Urgent control therapy

In patients with status epilepticus, treatment with an additional intravenous anticonvulsant drug should always follow emergent benzodiazepine therapy. A loading dose of these agents should be administered to rapidly achieve therapeutic levels and prevent recurrent seizures. To date, the best anticonvulsant drug for these patients is unknown [15]. The preferred agents are valproic acid or phenytoin/fosphenytoin, and alternative options include levetiracetam, phenobarbital or continuous infusion midazolam [1].

The SAMUKeppra trial failed to show a benefit from adding intravenous levetiracetam to intravenous clonazepam in prehospital GCSE patients [16]. The trial allowed administration of a second dose of clonazepam prior to assessment of seizure cessation, within 15 min of treatment onset. The response rate was 84% in the clonazepam group, which was higher than previous trials evaluating intravenous lorazepam (up to 65%) [12,14]. Thus, the efficacy of adding levetiracetam might have been overshadowed by the high success rate of clonazepam [17]. CONSEPT and ECLIPSE, two randomized clinical pediatric trials, compared phenytoin 20 mg/kg with levetiracetam 40 mg/kg for the treatment of convulsive status epilepticus. These studies failed to demonstrate superiority of levetiracetam over phenytoin [18,19]. However, both studies used a loading dose of levetiracetam that was lower than the dose of 60 mg/kg recommended by the American Epilepsy Society [2].

Lacosamide has gained popularity as an adjunct or second-line agent because of its availability in an intravenous formulation and low-drug interaction profile compared with older generation anticonvulsants. The Treatment of Recurrent Electrographic Nonconvulsive Seizures (TRENdS) showed that intravenous lacosamide 400 mg was noninferior to fosphenytoin 20 mg PE/kg for the treatment of nonconvulsive seizures in critically ill patients, but did not directly test it as a second-line agent for status epilepticus [20▪].

The ongoing Established Status Epilepticus Treatment Trial (ESETT) trial is designed to determine the most effective and/or the least effective urgent treatment of benzodiazepine-refractory status epilepticus in patients older than 2 years. The randomized, multicenter, double-blind, comparative efficacy study compares the following three active treatment arms: fosphenytoin 20 mg/kg, levetiracetam 60 mg/kg, and valproic acid 40 mg/kg. The primary outcome evaluated is clinical cessation of status epilepticus within 60 min of study drug administration [21]. Final results are not yet available.

Refractory and super-refractory status epilepticus

Up to 43% of patients with status epilepticus progress to refractory status epilepticus (RSE) defined as status epilepticus that cannot be controlled

with benzodiazepines and guideline-recommended urgent anticonvulsant therapies. Failure of continuous infusion of anesthetics to control seizures or seizure recurrence upon withdrawal of anesthetics are defined as super refractory status epilepticus (SRSE) [1]. Patients with RSE have a high mortality and only 29% have been found to return to their baseline functional status [22]. These outcomes are even worse in SRSE patients. Poor functional outcomes in survivors of RSE and SRSE may be because of progressive brain atrophy that occurs despite control of the seizures with anesthetic agents [23]. To date, there is absence of high- quality data to support the optimal management of RSE and SRSE. Most experts would choose intravenous anesthetics, such as propofol and midazolam over barbiturates like pentobarbital or thiopental, which are reserved for the most refractory cases. In general, studies have found that early initiation and rapid up-titration of continuous anesthetics lead to more successful status epilepticus control. A treatment protocol evaluated high-dose midazolam infusion of up to 2.9 mg/kg/hour compared with a historical cohort (the protocol in this group recommended doses up to 0.4 mg/kg/h) [24]. Despite a higher incidence of hypotension, high-dose midazolam was associated with a lower incidence of withdrawal seizures and favorable discharge mortality rates. Similarly, retrospective evaluations of ketamine found that early initiation and use of higher doses was associated with more successful resolution of status epilepticus compared with other studies [25–26]. A recent retrospective study of patients with RSE treated mainly with propofol showed that more aggressive treatment with higher anesthetics doses was associated with lower in-hospital complications, shorter duration of both mechanical ventilation, and hospital length of stay [27▪]. Concerning associations between continuous intravenous anesthetics and increased risk of infections, poor outcomes, and death have been recently raised [28–29]. These associations warrant further evaluation in a prospective setting.

Alternatively, administration of an anticonvulsant not already administered as an urgent therapy (that is, valproic acid, lacosamide, or levetiracetam) can be considered in patients who cannot be intubated and are hemodynamically stable [1].

Little data exists to support decisions regarding titration goals or duration of continuous anesthetics but these decisions should be guided by EEG endpoints (see Figs. 1 and 2). There is no evidence to support the superiority of electrographic seizure control or burst suppression over other titration goals but current guidelines recommend either one of these for 24–48 h [1]. During this time, dosing

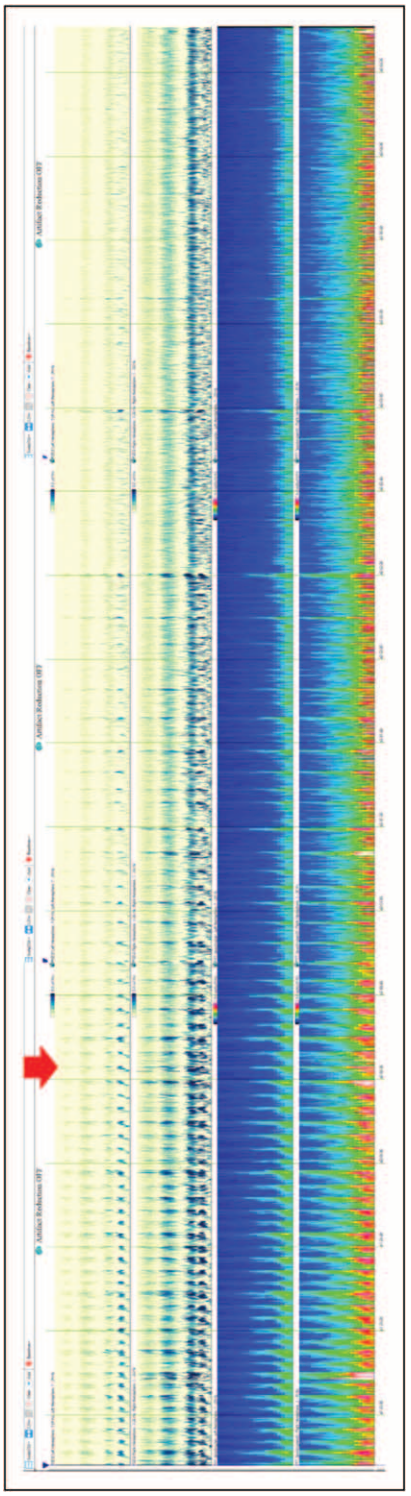

FIGURE 1. A 76-year-old man was admitted to the neurological ICU after a hemicraniectomy for the evacuation of a traumatic right subdural hematoma with 6 mm midline shift. His postsurgical neurological examination was significant for a low level of alertness. He was placed on EEG, which showed cyclic seizures originating from the right hemisphere. At that time, he was on levetiracetam 1000 mg twice daily. A dose of lacosamide 400 mg intravenously was given (arrow) and seizures subsided shortly after.

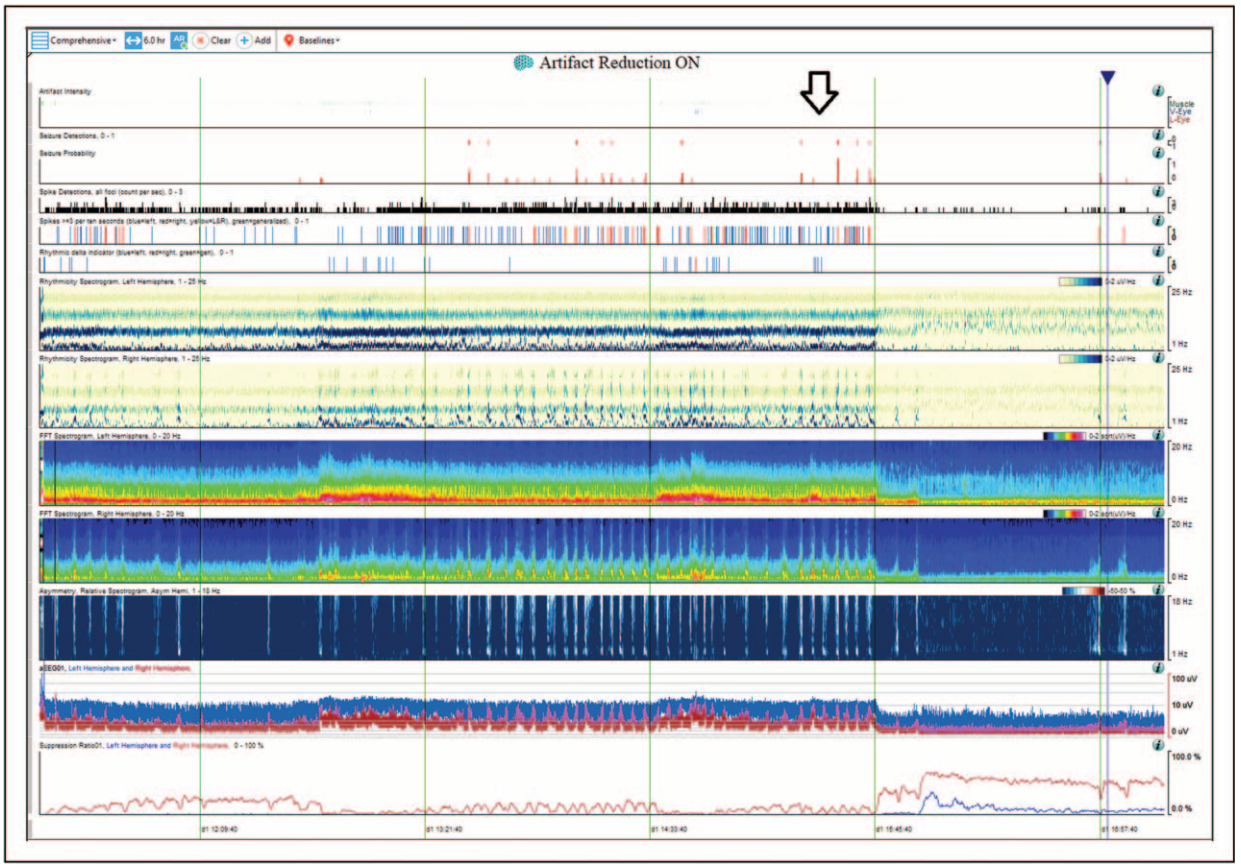

FIGURE 2. A 65-year-old woman was admitted after decompressive hemicraniectomy for a right middle cerebral artery stroke. Her neurological examination prior surgery was significant for left hemiplegia and a left facial droop but she was following commands briskly on the right. After the surgery, she was no longer following commands and her motor exam was 1/5 on right hemibody. EEG recording showed cyclic seizures origination from the right hemisphere. A load of levetiracetam 2000 mg intravenously was given without improvement. A continuous infusion of midazolam was started (arrow) and was rapidly titrated for seizure control. EEG, electroencephalography.

of anticonvulsants should be optimized and guided by drug level monitoring whenever applicable to prevent withdrawal seizures and recurrence of status epilepticus upon tapering of anesthetics (see Table 1).

TREATMENT CONSIDERATIONS

Choice of continuous anesthetic

To date, the only randomized controlled trial for the treatment of RSE compared propofol and barbiturates [30]. The trial was terminated early, because of poor recruitment, and demonstrated no difference in RSE control, mortality, or adverse events. As perhaps expected, barbiturates were associated with a longer duration of mechanical ventilation.

Midazolam is the preferred benzodiazepine used as a continuous infusion for the treatment of RSE. Contrary to lorazepam and diazepam, midazolam is not formulated in propylene glycol, rendering its administration at high doses quite safe. Tachyphylaxis can occur with its use, necessitating an increase in the dose or adding another agent to maintain the EEG response. Propofol is an alternative to midazolam; however, its prolonged use is limited by the development of hypertriglyceridemia because of its formulation in a lipid emulsion [31]. Another rare but fatal adverse event of propofol seen with high doses and prolonged use is propofol-related infusion syndrome (PRIS), which manifests as cardiac arrhythmias, rhabdomyolysis, metabolic acidosis, and shock [32].

Due to their side effect profile, barbiturates have fallen out of favor as a first line anesthetic choice and are now reserved for patients who fail midazolam and/or propofol. Historical data reported a lower rate of breakthrough and withdrawal seizures and higher rates of hypotension requiring vasopressor therapy with pentobarbital when compared with relatively low doses of midazolam or propofol [22]. Additional safety concerns with pentobarbital

Table 1. Commonly used agents for the management of status epilepticus

Drug	Loading dose	Maintenance dose	Therapeutic range	Adverse events	Considerations
Lorazepam (Ativan)	0.1 mg/kg i.v. (up to 4 mg per dose)	None	N/A	Hypotension, respiratory depression	i.v. contains propylene glycol
Diazepam (Valium)	0.15 mg/kg i.v. (up to 10 mg per dose)	None	N/A	Hypotension, respiratory depression	i.v. contains propylene glycol, can be administered rectally
Phenytoin (Dilantin)	20 mg/kg i.v.	5–7 mg/kg/day in two to three divided doses	Total: 15–25 μg/ml Free: 1.5–2.5 μg/ml	Hypotension, bradycardia, purple glove syndrome	i.v. contains propylene glycol, strong CYP inducer, tablets and suspension can adsorb to enteral feeding tubes
Fosphenytoin (Cerebryx)	20 mg PE/kg i.v.	4–6 mg/kg/day in two to three divided doses			Prodrug that converts to phenytoin in 15 min, strong CYP inducer, can be administered IM
Valproate sodium (Depacon)	20–40 mg i.v.	500–1000 mg q6–8 h	50–150 μg/ml	Hyperammonemic encephalopathy, pancreatitis, hepatotoxicity, thrombocytopenia	Carbapenems will significantly lower VPA levels and should not be used concomitantly, CYP inhibitor
Phenobarbital	20 mg/kg i.v.	1–3 mg/kg/day in two to three divided doses	15–40 μg/ml (higher levels have been reported)	Hypotension, respiratory depression	i.v. contains propylene glycol, strong CYP inducer
Lacosamide (Vimpat)	200–400 mg i.v.	200–300 mg i.v. q12 h	N/A	PR prolongation	Minimal drug-drug interactions, dose adjustment in renal impairment
Levetiracetam (Keppra)	1000–3000 mg i.v.	2,000–6000 mg/day in two to four divided doses	N/A	Psychosis	Minimal drug-drug interactions, dose adjustment in renal impairment
Topiramate (Topamax)	200–400 mg NG/PO	300–1600 mg/day NG/PO in two divided doses	N/A	Hyperchloremic metabolic acidosis	No i.v. formulation, dose adjustment in renal impairment, can potentiate hyperammonemia if administered with valproic acid
Midazolam (Versed)	0.2 mg/kg i.v.	0.05–2 mg/kg/h	Titrated to EEG	Hypotension, respiratory depression	Active metabolite renally cleared, tachyphylaxis with prolonged used
Propofol (Diprivan)	1–2 mg/kg i.v.	30–200 μg/kg/min	Titrated to EEG	Hypertriglyceridemia, propofol-related infusion syndrome (PRIS) with high doses and prolonged duration, respiratory depression	Lipid emulsion, adjust caloric intake
Pentobarbital (Nembutal)	5 mg/kg i.v.	0.5–10 mg/kg/h	10–20 μg/ml; titrated to EEG	Paralytic ileus, immunosuppression, cardiovascular depression, respiratory depression, hypokalemia	Contains propylene glycol, strong CYP inducer, may result in autoinduction
Thiopental (Pentothal)	2–7 mg/kg i.v.	0.5–5 mg/kg/h	Titrated to EEG	Paralytic ileus, immunosuppression, hypokalemia, cardiovascular depression, respiratory depression	Metabolized to pentobarbital, strong CYP inducer, may result in autoinduction
Ketamine (Ketalar)	1 mg/kg i.v.	1–10 mg/kg/h	Titrated to EEG	Hypertension, tachyarrhythmias, hypersalivation, respiratory depression	CYP2C9 substrate: phenytoin and phenobarbital will lower ketamine concentrations

Data from [1,64]. EEG, electroencephalography; i.v., intravenous.

include paralytic ileus, cardiotoxicity, hypokalemia, propylene glycol toxicity, and immune suppression. Patients may safely be weaned off pentobarbital by transitioning to phenobarbital in an attempt to reduce the rate of withdrawal seizures [33]. An advantage of ketamine compared with other anesthetics is the lack of cardiovascular depression; in fact, it can cause hypertension and tachycardia because of its sympathomimetic effects. It can also cause hyper-salivation, which should not be confounded with increased respiratory secretions. Despite theoretical dangers of increased intracranial pressure with ketamine, a systematic review has failed to confirm this concern [34]. Finally, inhaled anesthetics including isoflurane and desflurane have been shown to be effective for the treatment of RSE [35]. Long-term hippocampal atrophy may, however, be a concern [36].

Choice of adjunctive anticonvulsant

There is no evidence to support, which anticonvulsant to use as a second-line agent. A synergistic effect with specific combinations of anticonvulsants has not been demonstrated [37]; however, use of agents with different mechanisms of action may lead to complimentary effects. Newer anticonvulsants might be more favorable because of the drug–drug interaction and the side effect profiles when compared with older generation anticonvulsants [38]. Newer generation anticonvulsants include briviracetam, lacosamide, perampanel, clobazam, cannabidiol, eslicarbazepine, rufinamide, stiripentol, and zonisamide [39▪]. Most reports describe the use of these agents after failure of multiple other anticonvulsants, which may underestimate their efficacy. Of note, lacosamide and briviracetam are the only ones available in an intravenous formulation.

Drug–drug interactions should be considered when choosing additional anticonvulsants. Multiple anticonvulsant drugs and anesthetics are substrates (midazolam, ketamine), inducers (phenytoin, phenobarbital, pentobarbital), or inhibitors (valproate sodium) of CYP 450 enzymes. Although CYP inhibition rapidly develops, maximum enzyme induction depends on the half-lives of the CYP enzyme and its inducer [40]. Co-administration of phenytoin and valproic acid is associated with inhibition of the metabolism of phenytoin and induction of the metabolism of valproic acid. In addition, as both are highly protein-bound, their concomitant use leads to an increase in their free levels because of displacement from plasma protein-binding site. For this reason, simultaneous use of both agents is challenging. Other important CYP interactions should also be considered (see Table 1). Close assessment of drug–drug interactions and appropriate dose adjustment are necessary.

Cause of status epilepticus

The cause of status epilepticus heavily influences patient outcomes and impacts treatment selection. Fundamentally, patients with established epilepsy (also known as chronic causes, such as remote trauma with subsequent development of epilepsy) should be distinguished from acute causes of status epilepticus (such as status epilepticus during an admission for encephalitis).

Noncompliance

The most common chronic cause of status epilepticus is noncompliance with anticonvulsant therapy or low concentration of anticonvulsant drugs. In these patients, re-initiation or titration of the patient's anticonvulsant therapy to therapeutic levels is recommended [1].

Metabolic disturbances

Critically ill patients often develop metabolic disturbances, which can lead to seizures [1]. Therefore, patients should be routinely monitored and treated for hypoglycemia, electrolyte abnormalities, liver and renal failure. In addition, commonly used antibiotics in critically ill patients, such as cefepime, have been associated with seizures and status epilepticus [41]. Adequate dose adjustment in renal and/or hepatic impairment is necessary to prevent drug accumulation and drug-induced seizures. Finally, removal of the offending agent is warranted in the setting of drug-induced seizures or status epilepticus.

Anoxic brain injury

Electrographic status epilepticus develops in up to 35% of comatose cardiac arrest survivors and is frequently associated with myoclonus [42]. It is unknown if these seizure patterns represent the extent of ischemic damage and whether aggressive management would be futile. The ongoing Treatment of Electroencephalographic Status Epilepticus After Cardiopulmonary Resuscitation (TELSTAR) study will compare the effect of aggressive medical treatment of electroencephalographic status epilepticus for 48 h to no treatment on patient outcomes [43]. Until further data provides more guidance for the management of these patients, standardized aggressive management has been recommended [44▪]. If status epilepticus is myoclonic, the use of levetiracetam, valproic acid, and/or clonazepam is

recommended whereas phenytoin and carbamazepine are contraindicated as they can worsen myoclonus [45].

New-onset refractory status epilepticus

New-onset refractory status epilepticus (NORSE) has been increasingly recognized in the literature and is defined as a clinical presentation of RSE in patients without a history of epilepsy or a structural, metabolic, or toxic cause [46]. Most common causes of NORSE include autoimmune or paraneoplastic encephalitis and infections [47]. If autoimmune encephalitis is suspected, some evidence suggests that immunotherapy with steroids, plasmapheresis, and/or intravenous immunoglobulin therapy is associated with higher incidence of favorable outcome (any outcome other than death, vegetative state, or inability to take care of oneself) [48].

Genetic predisposition

There is a rising interest in precision medicine to target specific gene mutations in the management of epilepsy. Some findings include the use of ketogenic diet for patients with SLC2A1 (GLUT1) mutations or sodium channel blockers for the management of KCNQ2, SCN2A, and SCN8A [49]. Future studies are needed to identify genetic mutations associated with status epilepticus and determine the role of precision medicine in the management of this disorder [50].

Nonpharmacologic therapies

A variety of nonpharmacologic therapies have been used in RSE and SRSE.

Hypothermia

Data from animal studies suggest anticonvulsant and neuroprotective effects of therapeutic hypothermia in status epilepticus [51]. The Hypothermia for Brain Enhancement Recovery by Neuroprotective and Anticonvulsant Action after Convulsive Status Epilepticus (HYBERNATUS) trial evaluated the benefit of therapeutic hypothermia of 32–34 °C for 24 h versus normothermia in 270 critically ill patients with convulsive status epilepticus [52]. Despite a lower rate of progression of electrographic status epilepticus, hypothermia did not improve functional outcomes at 90 days and was associated with more adverse events.

Neuromodulation techniques

A systematic review of case reports and case series evaluated the use of electroconvulsive therapy (ECT), vagal nerve stimulation (VNS), transcranial magnetic stimulation (TMS), and deep brain stimulation (DBS) for the treatment of status epilepticus [53▪]. These reports showed a high success rate (more than 80%) with all techniques in patients who were on multiple anticonvulsants and had most commonly a prolonged duration of status epilepticus. As these data are primarily isolated case reports, they should be interpreted cautiously because of the risk of publication bias. In addition, acute adverse effects should be noted, including memory impairment with ECT, asystole and bradycardia with VNS, and paresthesia and infection of the electrodes with DBS.

Surgery

Surgical resection of the epileptogenic zone is a well established therapy for some types of focal epilepsies [54]. Case reports and case series have described its use for the treatment of SRSE associated with focal seizures. In one series, surgery was performed at a median of 27 days after status epilepticus onset and lead to seizure freedom in 56% of patients [54]. Further studies are needed to get a better understanding of the place in therapy of resective surgery.

Ketogenic diet

Ketogenic diet consists of a high-fat, low-carbohydrate diet that stimulates the metabolic effects of starvation and induces fatty acids oxidation to ketone bodies [55]. Proposed mechanisms of ketogenic diet include change in adenosine triphosphate production, rendering neurons more resilient during seizures, alteration of brain pH decreasing neuronal excitability, inhibition of ion channels, and increased GABA synthesis. Implementation of a ketogenic diet algorithm was evaluated in a phase I/II multicenter study of 15 adults with SRSE [56]. Patients were on a median of eight anticonvulsants and in SRSE for 10 days prior to ketogenic diet initiation. Median time to ketosis was 2 days and ketogenic diet lead to SRSE resolution in 79% of patients. Side effects reported include metabolic acidosis, hyperlipidemia, constipation, hypoglycemia, hyponatremia, and weight loss.

Outcome predictors

Mortality associated with status epilepticus ranges between 16 and 32% in adults and has not decreased over the last 30 years [57▪,58]. Multiple factors have been reported as important determinants of poor outcome and mortality including older age, fatal cause, and seizure burden [59▪▪]. The status epilepticus severity score (STESS) was developed in an effort to predict short-term mortality from status epilepticus [60]. The score ranges from 0 to 6, and factors in the following variables before initiation of therapy: extent of consciousness impairment, worst

seizure type, age, and history of previous seizures. A favorable STESS (score of 0–2) has been associated with shorter time to status epilepticus cessation, survival, and return to baseline [11▪▪,60]. Despite an excellent negative predictive value, the score has a poor positive predictive value for death and cannot be used to guide decision of withdrawing life-sustaining treatment [61▪]. Newer scores have been developed since to predict outcomes including the modified STESS, encephalitis-NCSE-Diazepam resistance-Image abnormalities-Tracheal intubation (END-IT) and the epidemiology-based mortality (EMSE) score [62▪,63] .

CONCLUSION

Prompt identification and treatment with adequate doses of benzodiazepines and anticonvulsants is essential in the management of status epilepticus. Continuous EEG monitoring should be used to titrate therapy. Prospective trials are needed to evaluate the role of newer anticonvulsants and non-pharmacologic therapies for the management of status epilepticus.

Acknowledgements

None.

Financial support and sponsorship

J.C. is supported with grant funding from the NIH R01 NS106014 and R03 NS112760, and the DANA Foundation.

Conflicts of interest

J.C. is a minority shareholder at iCE Neurosystems. None of the other authors have significant conflicts of interest to report.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. Brophy GM, Bell R, Claassen J, *et al.,* Neurocritical Care Society Status Epilepticus Guideline Writing Committee. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care 2012; 17:3–23.
2. Glauser T, Shinnar S, Gloss D, *et al.* Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the Guideline Committee of the American Epilepsy Society. Epilepsy Curr 2016; 16:48–61.
3. Trinka E, Cock H, Hesdorffer D, *et al.* A definition and classification of status epilepticus– report of the ILAE task force on classification of status epilepticus. Epilepsia 2015; 56:1515–1523.
4. Claassen J, Mayer SA, Kowalski RG, *et al.* Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. Neurology 2004; 62:1743–1748.
5. Gilmore EJ, Gaspard N, Choi HA, *et al.* Acute brain failure in severe sepsis: a prospective study in the medical intensive care unit utilizing continuous EEG monitoring. Intensive Care Med 2015; 41:686–694.
6. Kurtz P, Gaspard N, Wahl AS, *et al.* Continuous electroencephalography in a surgical intensive care unit. Intensive Care Med 2014; 40:228–234.
7. Wasterlain CG, Fujikawa DG, Penix L, *et al.* Pathophysiological mechanisms of brain damage from status epilepticus. Epilepsia 1993; 34:S37–S53.
8. Chen JW, Waterlain CG. Status epilepticus: pathophysiology and management in adults. Lancet Neurol 2006; 5:246–256.
9. Lowenstein DH, Alldredge BK. Status epilepticus at an urban public hospital in the 1980 s. Neurology 1993; 43:483–488.
10. Naylor DE, Liu H, Wasterlain CG. Trafficking of GABAA receptors, loss of inhibition, and a mechanism of pharmacoresistance in status epilepticus. J Neurosci 2005; 25:7724–7733.
11. ▪▪ Kellinghaus C, Rossetti AO, Trinka E, *et al.* Factors predicting cessation of status epilepticus in clinical practice: Data from a prospective observational registry (SENSE). Ann Neurol 2019; 85:421–432.
Status epilepticus remains undertreated as shown in a registry of European centers. Use of benzodiazepine as a first-line therapy and higher cumulative dose of anticonvulsants are associated with shorter time to cessation of status epilepticus.
12. Treiman DM, Meyers PD, Walton NY, *et al.* A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. N Engl J Med 1998; 339:792–798.
13. Alldredge BK, Gelb AM, Isaacs SM, *et al.* A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. N Engl J Med 2001; 345:631–637.
14. Silbergleit R, Durkalski V, Lowenstein D, *et al.,* Neurological Emergency Treatment Trials (NETT) Investigators. Intramuscular versus IV therapy for prehospital status epilepticus. N Engl J Med 2012; 366:591–600.
15. Mundlamuri RC, Sinha S, Subbakrishna DK, *et al.* Management of generalised convulsive status epilepticus (SE): a prospective randomised controlled study of combined treatment with IV lorazepam with either phenytoin, sodium valproate or levetiracetam – Pilot study. Epilepsy Res 2015; 114:52–58.
16. Navarro V, Dagron C, Elie C, *et al.,* SAMUKeppra investigators. Prehospital treatment with levetiracetam plus clonazepam or placebo plus clonazepam in status epilepticus (SAMUKeppra): a randomised, double-blind, phase 3 trial. Lancet Neurol 2016; 15:47–55.
17. Claassen J Dr. No: double drug fails to eliminate status epilepticus. Lancet Neurol 2016; 15:23–24.
18. Dalziel SR, Borland ML, Furyk J, *et al.,* PREDICT research network. Levetiracetam versus phenytoin for second- line treatment of convulsive status epilepticus in children (ConSEPT): an open- label, multicentre, randomised controlled trial. Lancet 2019; 393:2135–2145.
19. Lyttle MD, Rainford NE, Gamble C, *et al.,* Paediatric Emergency Research in the United Kingdom & Ireland (PERUKI) collaborative. Levetiracetam versus phenytoin for second-line treatment of paediatric convulsive status epilepticus (EcLiPSE): a multicentre, open-label, randomised trial. Lancet 2019; 393:2125–2134.
20. ▪ Husain AM, Lee JW, Kolls BJ, *et al.* Randomized trial of lacosamide vs fosphenytoin for nonconvulsive seizures. Ann Neurol 2018; 83: 1174–1185.
Lacosamide 400 mg intravenously was noninferior to fosphenytoin 20 mg PE/kg for the treatment of nonconvulsive seizures. Treatment-related side effects were similar between both groups.
21. Cock HR; ESETT Group. Established status epilepticus treatment trial (ESETT). Epilepsia 2011; 52(Suppl 8):50–52.
22. Claassen J, Hirsch LJ, Emerson RG, *et al.* Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: A systematic review. Epilepsia 2002; 43:146–153.
23. Hocker S, Nagarajan E, Rabinstein AA, *et al.* Progressive brain atrophy in super- refractory status epilepticus. JAMA Neurol 2016; 73:1201–1207.
24. Fernandez A, Lantigua H, Lesch C, *et al.* High-dose midazolam infusion for refractory status epilepticus. Neurology 2014; 82:359–365.
25. Sabharwal V, Ramsay E, Martinez R, *et al.* Propofol–ketamine combination therapy for effective control of super-refractory status epilepticus. Epilepsy Behav 2015; 52(Pt A):264–266.
26. Gaspard N, Foreman B, Judd LM, *et al.* IV ketamine for the treatment of refractory status epilepticus: a retrospective multicenter study. Epilepsia 2013; 54:1498–1503.
27. ▪ Muhlhofer W, Layfield S, Lowenstein D, *et al.* Duration of therapeutic coma and outcome of refractory status epilepticus. Epilepsia 2019; 60:921–934.
Longer duration of therapeutic coma was associated with higher incidence of seizure recurrence. An optimal cutoff of 35 h was identified for the duration of therapeutic coma. Higher doses of anesthetics were associated with a shorter length of stay and duration of mechanical ventilation.
28. Sutter R, Kaplan PW. Can anesthetic treatment worsen outcome in status epilepticus? Epilepsy Behav 2015; 49:294–297.
29. Sutter R, De Marchis GM, Semmlack S, *et al.* Anesthetics and outcome in status epilepticus: a matched two-center cohort study. CNS Drugs 2017; 31:65–74.
30. Rossetti AO, Milligan TA, Vulliemoz S, *et al.* A randomized trial for the treatment of refractory status epilepticus. Neurocrit Care 2011; 14:4–10.
31. Devlin JW, Lau AK, Tanios MA. Propofol-associated hypertriglyceridemia and pancreatitis in the intensive care unit: an analysis of frequency and risk factors. Pharmacotherapy 2005; 25:1348–1352.

32. Krajcova A, Waldauf P, Andel M, *et al.* Propofol infusion syndrome: a structured review of experimental studies and 153 published case reports. Crit Care 2015; 19:398.

33. Pugin D, Foreman B, De Marchis GM, *et al.* Is pentobarbital safe and efficacious in the treatment of super-refractory status epilepticus: a cohort study. Crit Care 2014; 18:R103.

34. Zeiler FA, Teitelbaum J, West M, *et al.* The ketamine effect on intracranial pressure in nontraumatic neurological illness. J Crit Care 2014; 29:1096–1106.

35. Mirsattari SM, Sharpe MD, Young GB. Treatment of refractory status epilepticus with inhalational anesthetic agents isoflurane and desflurane. Arch Neurol 2004; 61:1254–1259.

36. Ikeda KM, Connors R, Lee DH, *et al.* Isoflurane use in the treatment of super-refractory status epilepticus is associated with hippocampal changes on MRI. Neurocrit Care 2017; 2:420–427.

37. Jonker DM, Voskuyl RA, Danhof M. Synergistic combinations of anticonvulsant agents: what is the evidence from animal experiments? Epilepsia 2007; 48:412–434.

38. Beuchat I, Novy J, Rossetti AO. Newer antiepileptic drugs for status epilepticus in adults: what's the evidence. CNS Drugs 2018; 32:259–267.

39. ■ Farrokh S, Bon J, Erdman M, Tesoro E. Use of newer anticonvulsants for the treatment of status epilepticus. Pharmacotherapy 2019; 39:297–316.

A systematic review of the literature supporting the use of new anticonvulsants for the treatment of status epilepticus.

40. Brodie MJ, Mintzer S, Pack AM, *et al.* Enzyme induction with anticonvulsant drugs: cause for concern? Epilepsia 2013; 54:11–27.

41. Payne LE, Gagnon DJ, Riker RR, *et al.* Cefepime-induced neurotoxicity: a systematic review. Crit Care 2017; 21:276.

42. Legriel S, Bruneel F, Sediri H, *et al.* Early EEG monitoring for detecting postanoxic status epilepticus during therapeutic hypothermia: a pilot study. Neurocrit Care 2009; 11:338–344.

43. Ruijter BJ, van Putten M, Horn J, *et al.,* TELSTAR study group. Treatment of electroencephalographic status epilepticus after cardiopulmonary resuscitation (TELSTAR): a study protocol for a randomized controlled trial. Trials 2014; 15:433.

44. ■ Beretta S, Coppo A, Bianchi E, *et al.* Neurologic outcome of postanoxic refractory status epilepticus after aggressive treatment. Neurology 2018; 91:e2153–e2162.

A prospective cohort study of comatose cardiac arrest survivors showed that RSE occurred in 21.7% of the patients. Survival and good neurologic outcome (CPC one or 2) at 6 months were 54.3 and 44.4% in these patients. Therefore, the authors suggest aggressive treatment of RSE if multimodal prognostic indicators were not unfavorable.

45. Levy A, Chen R. Myoclonus: pathophysiology and treatment options. Curr Treat Options Neurol 2016; 18:21.

46. Hirsch LJ, Gaspard N, van Baalen A, *et al.* Proposed consensus definitions for new - onset refractory status epilepticus (NORSE), febrile infection-related epilepsy syndrome (FIRES), and related conditions. Epilepsia 2018; 59:739–744.

47. Gofton TE, Gaspard N, Hocker SE, *et al.* New onset refractory status epilepticus research: what is on the horizon? Neurology 2019; 92:802–810.

48. Khawaja AM, DeWolfe JL, Miller DW, *et al.* New-onset refractory status epilepticus (NORSE) - the potential role for immunotherapy. Epilepsy Behav 2015; 47:17–23.

49. Reif PS, Tsai MH, Helbig I, *et al.* Precision medicine in genetic epilepsies: break of dawn? Expert Rev Neurother 2017; 17:381–392.

50. Bhatnagar M, Shorvn S. Genetic mutations associated with status epilepticus. Epilepsy Behav 2015; 49:104–110.

51. Legriel S. Hypothermia as a treatment in status epilepticus: a narrative review. Epilepsy Behav 2019. [Epub ahead of print]

52. Legriel S, Lemiale V, Schenck M, *et al.,* HYBERNATUS Study Group. Hypothermia for neuroprotection in convulsive status epilepticus. N Eng J Med 2016; 375:2457–2467.

53. ■ San-Juan D, Dávila-Rodríguez DO, Jiménez CR, *et al.* Neuromodulation techniques for status epilepticus: a review. Brain Stimul 2019; 12:835–844.

A systematic review of studies evaluating the use of different neuromodulation techniques for the treatment of status epilepticus: electroconvulsive therapy, implanted direct vagal nerve stimulation, transcranial magnetic stimulation, and deep brain stimulation.

54. Basha MM, Suchdev K, Dhakar M, *et al.* Acute resective surgery for the treatment of refractory status epilepticus. Neurocrit Care 2017; 27:370–380.

55. Baranano KW, Hartman AL. The ketogenic diet: uses in epilepsy and other neurologic illnesses. Curr Treat Options Neurol 2008; 10:410–419.

56. Cervenka MC, Hocker S, Koenig M, *et al.* Phase I/II multicenter ketogenic diet study for adult superrefractory status epilepticus. Neurology 2017; 88:938–943.

57. ■ Neligan A, Noyce AJ, Gosavi TD, *et al.* Change in mortality of generalized convulsive status epilepticus in high-income countries over time: a systematic review and meta-analysis. JAMA Neurol 2019. [Epub ahead of print]

Systematic review and meta-analysis of studies to evaluate if mortality of convulsive status epilepticus has changed over the last 30 years with more aggressive treatment recommendations. The authors found that mortality of convulsive status epilepticus was 15.9% in adults and prognosis did not change over time.

58. Hocker status epilepticus, Britton JW, Mandrekar JN, *et al.* Predictors of outcome in refractory status epilepticus. JAMA Neurol 2013; 70:72–77.

59. ■■ Kirac-Baysal L, Feddersen B, Einhellig M, *et al.* Does semiology of status epilepticus have an impact on treatment response and outcome? Epilepsy Behav 2018; 83:81–86.

Seminology of status epilepticus was not independently associated with poor outcome and death. However, fatal cause and low GCS were strong predictors of poor outcome.

60. Rossetti AO, Logroscino G, Milligan TA, *et al.* Status Epilepticus Severity Score (STESS): a tool to orient early treatment strategy. J Neurol 2008; 255:1561–1566.

61. ■ Sutter R, Semmlack S, Opić P, *et al.* Untangling operational failures of the status epilepticus severity score (STESS). Neurology 2019; 92: e1948–e1956.

Prediction of death by a STESS at least three had a false-positive rate of 51% and false-negative of 1%. The STESS inadequately predicted death particularly in patients with status epilepticus types other than nonconvulsive status epilepticus with coma and in patients with few comorbidities.

62. ■ Reindl C, Knappe RU, Sprügel MI, *et al.* Comparison of scoring tools for the prediction of in-hospital mortality in status epilepticus. Seizure 2018; 56:92–97.

A retrospective study comparing the STESS, mSTESS, EMSE-EAL, and END-IT scores in predicting in-hospital mortality after status epilepticus. STESS with a cutoff of three showed the lowest specificity whereas EMSE-EAL with a cutoff of 40 had the highest specificity.

63. Zhang Y, Chen D, Xu D, *et al.* Clinical utility of EMSE and STESS in predicting hospital mortality for status epilepticus. Seizure 2018; 60:23–28.

64. Lexi-Com IL-D. Lexi-Comp Inc. 2015