Update on the management of status epilepticus

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Purpose of review
Randomized controlled trials investigating the initial pharmacological treatment of status epilepticus have been recently published. Furthermore, status epilepticus arising in comatose survivors after cardiac arrest has received increasing attention in the last years. This review offers an updated assessment of status epilepticus treatment in these different scenarios.

Recent findings
Initial benzodiazepines underdosing is common and correlates with development of status epilepticus refractoriness. The recently published ESETT trial provides high-level evidence regarding the equivalence of fosphenytoin, valproate, and levetiracetam as a second-line option. Myoclonus or epileptiform transients on electroencephalography occur in up to 1/3 of patients surviving a cardiac arrest. Contrary to previous assumptions regarding an almost invariable association with death, at least 1/10 of them may awaken with reasonably good prognosis, if treated. Multimodal prognostication including clinical examination, EEG, somatosensory evoked potentials, biochemical markers, and neuroimaging help identifying patients with a chance to recover consciousness, in whom a trial with antimyoclonic compounds and at times general anesthetics is indicated.

Summary
There is a continuous, albeit relatively slow progress in knowledge regarding different aspect of status epilepticus; recent findings refine some treatment strategies and help improving patients' outcomes. Further high-quality studies are clearly needed to further improve the management of these patients, especially those with severe, refractory status epilepticus forms.

Keywords
outcome, postanoxic coma, prognosis, randomized controlled trial, treatment

INTRODUCTION

Status epilepticus was defined by the International League against Epilepsy in 2015 as a condition resulting from failure of the mechanisms responsible for seizure termination, or from mechanisms inducing abnormally prolonged seizures [1]. Classification includes four axes: semiology (typically subdivided into convulsive and nonconvulsive), cause (acute, remote, progressive, defined epileptic syndromes, or unknown), EEG appearance [2,3], and age. More recently, a consensus statement redefined the clinical entity of new-onset refractory status epilepticus (NORSE, proposed for the first time in 2005 [4]) in subjects without known epilepsy and lacking a clear acute or active structural, toxic, or metabolic cause. Febrile infection-related epilepsy syndrome (FIRES) represents a subcategory of NORSE, implying a febrile infection occurring between 2 weeks and 24 h prior to status epilepticus onset, regardless of age [5▪▪].

Status epilepticus is clinically highly relevant, as it represents one of the most frequent neurological emergencies and is associated with a relevant risk of morbidity and mortality [6▪]; it appears thus very important to get an optimal knowledge regarding risk factors and treatment options. Since 2016 and the last update on status epilepticus in this Journal [7], the literature has evolved, including the publication of results of randomized controlled trials. Furthermore, increasing attention has been directed toward status epilepticus-related conditions arising in survivors of hypoxic-ischemic encephalopathy following cardiac arrest, which represent a relatively common challenge in ICUs. The present review

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KEY POINTS

- Midazolam (intramuscular and intranasal) is at least as effective as intravenous lorazepam; intravenous clonazepam seems to represent a valuable alternative for early status epilepticus management.
- (Fos)phenytoin (20 mg/kg), valproate (40 mg/kg), and levetiracetam (60 mg/kg) are equivalent second-line options in adult and pediatric populations.
- Status epilepticus treatment protocols are poorly followed in real-life, and benzodiazepines are frequently underdosed. This contributes to status epilepticus refractoriness.
- Status epilepticus arises in up to 1/3 of comatose survivors after cardiac arrest, but is compatible with good clinical outcome in up to 1/10 of them. Multimodal prognostication should be applied to select patients that may improve, and thus deserve consequent antiseizure drugs treatment.

intends to offer an update on status epilepticus clinical management, offering also a view from the specific angle of cardiac arrest. Of note, the majority of the compounds described below do not have specific approval for the use in status epilepticus, and regulations differ by countries.

STEPWISE THERAPEUTIC APPROACH

As for every life-threatening condition, treatment protocols have been published to guide status epilepticus management [8], where a sequential approach is recommended.

First line

Converging studies provide strong evidence about benzodiazepines efficacy at the initial step [9]. The prehospital RAMPART study [10] showed that intramuscular midazolam (MDZ, 10 mg for adults >40 kg) is as effective as intravenous lorazepam (LZP, 4 mg for adults >40 kg). Indeed, 73% of MDZ-treated patient did not require rescue therapy, as opposed to 63.5% in the LZP group, with a similar intubation rate (14.1 vs. 14.4%, respectively); this also reflects the ease of intramuscular vs. intravenous administration.

Intranasal MDZ has been recently studied in a retrospective assessment in adults [11], showing that more than half (57%) of 42 status epilepticus episodes were controlled with a median dose of 5 mg MDZ. Not available in the USA as intravenous formulation, but widely used in several other countries, intravenous clonazepam (CLZ) has repetitively shown encouraging data. It is given at 0.015 mg/kg (1 mg for an adult of average weight), does not required cold storage (as opposed to LZP) and has a rapid brain penetration and long half-life [12]. An observational study showed that fewer episodes became refractory, and that less subsequent agents were required to control status epilepticus when CLZ was used compared with LZP [13]. A French randomized trial assessing the immediate combination of CLZ and levetiracetam (LEV) in a prehospital setting failed to demonstrate any benefit of initial bi-therapy, mainly because of the high success rate (84%) of CLZ alone [14].

Despite strong evidence on benzodiazepines as first-line therapy and several published treatment algorithms, protocols seem still poorly followed in real-life setting. In the European SENSE registry [15▪] 3/4 of patients received an underdosed benzodiazepine; this appears similar in North America [13]. Importantly, initial underdosing correlates with development of refractory status epilepticus [15▪].

Second-line treatment

In practice, intravenous antiseizure drugs (ASD) such as phenytoin (PHT) or fosphenytoin (fPHT), valproate (VPA), and LEV are often administered together with benzodiazepines. They have been used for many years. However, solid data were lacking, and guidelines were mainly based on cohort or observational studies. Recently, the ESETT trial [16▪▪] demonstrated the equivalence of fPHT 45% [95% confidence interval (CI): 36–54], LEV 47% (95% CI: 39–55) and VPA 46% (95% CI: 38–55), in terms of status epilepticus control; this applied to all age groups [17▪]. Of note, the second-line medication dosages were relatively high: 20 mg/kg for fPHT, 40 mg/kg for VPA, and even 60 mg/kg for LEV.

The equivalence of second-line therapy was also found in a meta-analysis of five randomized trials [18]: no difference was found regarding seizure cessation [surface under the cumulative ranking curve: PHT 55.6, VPA 59.9, LEV 53.7, lacosamide (LCM) 34.5, fPHT 46.2], whereas LCM and VPA ranked best for safety. Limited data prevented drawing strong conclusions regarding LCM. A small randomized study focusing on repetitive seizures in coma, detected on continuous EEG, showed equivalence in terms of seizures control and side effects between intravenous LCM 400 mg and fPHT 20 mg/kg [19▪]. An observational study with 40% of status epilepticus episodes responding to LCM suggested that doses more than 9 mg/kg are associated with serum levels within the recommended range, albeit without clinical correlation [20].

Table 1. Recent randomized trials for second-line treatments in status epilepticus or repetitive seizures

Study	Author	Population	Primary outcome	Drug, dose, and results regarding primary outcome		
ESETT [16▪▪]	Kapur *et al.* (2019)	384 Adults and children with SE continuing after first-line treatment	Absence of clinical seizure within 60 min after drug administration	LEV 60 mg/kg 47% (95% CI: 39–55%)	fPHT 20 mg/kg 45% (95% CI: 36–54%)	VPA 40 mg/kg 46% (95% CI: 38–55%)
TRENdS [19▪]	Husain *et al.* (2018)	74 Adult patients with repetitive seizures in coma	Absence of electrographic seizures for 24 h	LCM 400 mg 63.3%	fPHT 20 mg/kg 50%	Remark: LCM non inferior with risk ratio of 1.27 (90% CI: 0.88–1.83)
ConSEPT [21▪▪]	Dalziel *et al.* (2019)	233 Children with SE continuing after first-line treatment	Absence of clinical seizure within 5 min after drug administration	PHT 20 mg/kg 60%	LEV 40 mg/kg 50%	Remark: Risk difference: −9.2% (95% CI: −21.9–3.5%)
EcLIPSE [22▪▪]	Lyttle *et al.* (2019)	286 Children with SE continuing after first-line treatment	Time to cessation of convulsive status epilepticus	PHT 20 mg/kg 45 min in 64% of cases	LEV 40 mg/kg 35 min in 70% of cases	Remark: hazard ratio 1.20 (95% CI: 0.91–1.60)

CI, confidence interval; fPHT/PHT, fosphenytoin/phenytoin; LCM, lacosamide; LEV, levetiracetam; SE, status epilepticus; VPA, valproate.

In the pediatric population, two recent trials, – ConSEPT [21▪▪] and EcLiPSE [22▪▪] – also proved that LEV is equivalent to PHT. In the former, carried out in Australia and New Zeeland and including 233 children with ongoing convulsive generalized status epilepticus after a benzodiazepine, LEV 40 mg/kg terminated seizures activity in 50% and 20 mg/kg of PHT in 60% (NS). In EcLiPSE, performed in the United Kingdom and including 286 children with ongoing convulsive generalized status epilepticus after a benzodiazepine, 40 mg/kg LEV terminated status epilepticus in 70% with a median time of 35 min, and 20 mg/kg PHT in 64% within 45 min. In both trials there was no serious side effect. These two studies suggest that LEV can be an easy-to-use alternative to PHT as second line treatment also in this population.

Table 1 summarizes four recent randomized studies for this treatment step. These data are contributing to the marked decline in PHT prescriptions [23]: a 'slow agonizing death' has been described [24], following the evidence that better-tolerated ASD with simpler pharmacokinetics are equally effective.

Newly approved ASD might offer some interest in status epilepticus management, such as brivaracetam (BRV) and perampanel (PER). BRV is derived from LEV and available in intravenous formulation, showing some efficacy at 100 mg to 300 mg loading dose [25]. PER, in view to its specific antiseizure mechanism (2-Amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propanoic acid (AMPA) receptors blockade) also looks promising [25]. However, only an oral formulation is available so far. Further studies are needed to define to role of these new ASD in status epilepticus management protocols.

Refractory status epilepticus and super-refractory status epilepticus

The need to rapidly control status epilepticus has been based on several animal and some human data showing neuronal damage after ongoing seizure activity [26,27]; however, recent works seem to question these findings [28]. In any case, the management of refractory status epilepticus (RSE) and super-refractory status epilepticus (SRSE), occurring in about 33%, respectively 4% of status epilepticus episodes [29], still lacks high-level evidence. Routine use of therapeutic coma remains controversial [30], with some observational studies showing an independent association between therapeutic coma and mortality [31–33], or a 60% prolongation of hospital stay, without any favorable effect on mortality [34].

The optimal sedation depth is not known, either. An observational study assessed cognitive outcome after RSE according to the EEG-suppression degree [35▪], including 61 adults under propofol (PRO) and/or MDZ. While 39% were considered as deeply sedated (23 with 'burst-suppression', one with complete suppression), 60% had only a 'seizure-suppression' pattern with a continuous EEG background. There were no differences regarding demographics and status epilepticus severity or

semiology between these groups. At 1-year follow-up, half of patients with poor outcome had undergone deep sedation, vs. only 19.2% in those with good outcome. Significantly, no significant associations were observed between outcome and etiology or therapeutic coma duration. At 2 years (50 available patients), only lack of 'deep sedation' was associated with good outcome. This suggests that profound sedation may correlate with worse long-term prognosis, regardless of status epilepticus cause or complications: pending further studies, a 'seizure-suppression' pattern seems a preferable option.

Stopping therapeutic coma represents a difficult task, as seizure recurrence may occur. Predictors of a successful anesthetic weaning are scarce. Visual EEG analysis, such as length of interburst intervals, did not correlate with RSE termination in a cohort of 17 successful and 20 unsuccessful lifting attempts in 19 patients [36], but absence of 'epileptiform' characteristics of the bursts predicted successful weaning. Recently, quantitative EEG analysis – spatial correlation-based measures of functional connectivity – has been suggested in this setting [37▪]: among 47 RSE episodes undergoing anesthetic weaning (23 successes, 24 failures), higher connection density and clustered spatial functional networks seem to predict successful weaning. If confirmed in an independent, larger dataset, and providing generalizability of the methodological approach, this tool might be used to guide stopping therapeutic coma as early as possible.

For RSE and SRSE, administration of high-dose phenobarbital (≥10 mg/kg loading dose), even in nonintubated patients, may lead to seizure control [38▪]; indeed, this may prove valuable in highly refractory cases, despite the risk of pharmacological interactions (phenobarbital being a potent enzyme inducer). Ketamine (KET) regained some interest since a retrospective study performed in 10 academic centers with 60 RSE episodes: more than half of them were eventually controlled, 12% of cases had a clear response with KET being the last administered drug [39]. Of note no episode was controlled with KET dosage less than 0.9 mg/kg/h and when started after 8 days from status epilepticus onset, suggesting that this compound should be started early – maybe after a first MDZ/PRO weaning failure – and at least at 1 mg/kg/h. Ketogenic diet might also be a valuable alternative in RSE/SRSE. A systematic review showed a high success rate (82% of status epilepticus control); the most common side effects were metabolic acidosis, hyperlipidemia, and hypoglycemia [40]. As with KET, randomized trials are urgently awaited, as publication bias may represent an important issue.

Vagus nerve stimulation (VNS) might also be an option in these very difficult to treat patients. A recent review of case reports/series [41] describes that acute implantation was associated with status epilepticus cessation in up to 74% of 38 patients in RSE and SRSE, within a median delay of 18 days (range: 3–1680 days) and 8 days (range: 3–84 days), respectively; of course a publication (and thus information) bias appears also likely.

Thoughts on febrile infection-related epilepsy syndrome/new-onset refractory status epilepticus

Sometimes RSE and SRSE might be of unknown origin, particularly in younger subjects: a series published in 2015 [42], described the characteristic of 130 NORSE patients, without obvious cause after initial assessment; an underlying auto-immune cause was frequently found. The role of immune therapy is, however, not clearly established yet, probably reflecting the complicated interplay of epileptogenesis and immunological factors. In a retrospective cohort of nearly 1000 status epilepticus adult patients, intravenous corticoids were prescribed in slightly more than 1%; in 5/12 (42%) of these episodes, status epilepticus resolved following this administration (all within 3 days). The outcome was better in this responder's group [43]. Moreover, in a small cohort of 11 NORSE cases [44] better outcomes were observed in those receiving an immune treatment (corticoids, intravenous immunoglobulins (IVIG), or plasma exchange) compared with untreated patients. Other 'less conventional' immune therapies have been studied in this setting. Anakinra (an IL-1 receptor antagonist) showed repetitive seizures control in a child with a FIRES [45]. Tocilizumab (an IL-6 receptor inhibitor) terminated status epilepticus after one or two doses in six out of seven Korean patients with NORSE refractory to conventional immunotherapy [46▪]. These data (albeit limited) reinforce the rationale to actively look for an immune cause in NORSE patients, and consider early immune treatment after excluding a brain infection.

Seizure management for status epilepticus based on the evidence level

Figure 1 summarizes our recommendations based on current evidence; we propose two different escalation protocols. The rapid one aims at a quick therapeutic coma induction – mostly for convulsive status epilepticus or nonconvulsive status epilepticus in coma – to avoid brain damages secondary to seizure activity. The slower one aims to circumvent therapeutic coma and its iatrogenic side-effects, by adding additional nonsedative ASD for less severe

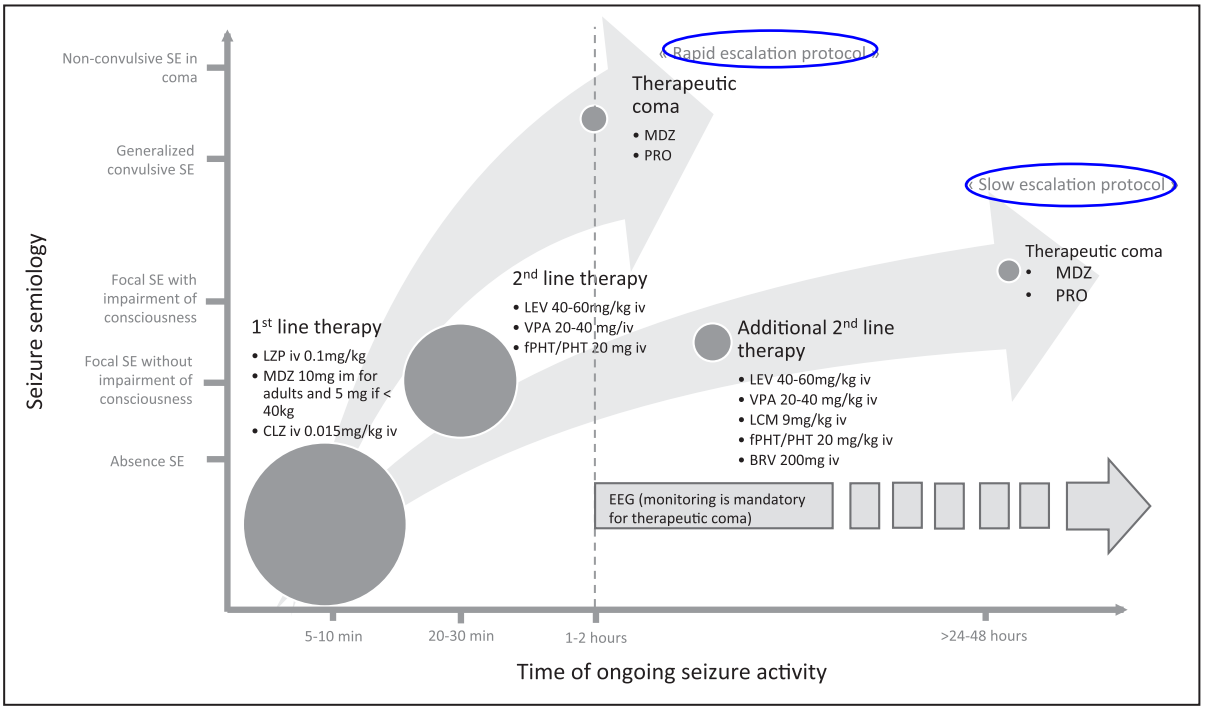

FIGURE 1. Summary of seizure management recommendations for the initial steps of status epilepticus according to current level of evidence. Circle size represents estimated level of evidence. Dash line represents timing where electroencephalography is needed in case of – or doubt of – ongoing seizure activity. Based on the current evidence with propose two different 'escalation protocols'. The rapid one aims to a rapid induction of therapeutic coma mostly for convulsive status epilepticus or nonconvulsive status epilepticus in coma. The slower one aims at avoiding therapeutic coma induction by adding additional nonsedative antiseizure drugs for less severe forms of status epilepticus. BRV, brivaracetam; CLZ, clonazepam; fPHT/PHT, fosphenytoin/phenytoin; LCM, lacosamide; LEV, levetiracetam; LZP, lorazepam; MDZ, midazolam; PRO, propofol; SE, status epilepticus; VPA, valproate.

status epilepticus forms. It is important to remind here that clear evidence only exist to guide first-line and second-line therapies, as opposed for the situation of status epilepticus and SRSE. Management of these patients should thus be based on a case-by-case evaluation, keeping in mind the balance between potential brain damage related to ongoing status epilepticus and potential side-effects of pharmacological coma induction.

STATUS EPILEPTICUS RELATED TO HYPOXIC-ISCHEMIC ENCEPHALOPATHY

In adults, cardiac arrest represents the most frequent cause of deaths in Western countries [47]; comatose survivors show a hypoxic-ischemic encephalopathy and often undergo targeted temperature management for 24 h (TTM, at 33–36 °C), under sedation with standardized doses of PRO or MDZ, before controlled rewarming. At this step, early prognostication is performed through a multimodal battery of tests, including clinical examination, EEG, somatosensory evoked potentials, biochemical markers (particularly neuron-specific enolase, NSE), and neuroimaging [48▪].

Looking at the clinical presentation, while overt generalized tonic–clonic or focal motor seizures are exceptional in cardiac arrest survivors, myoclonus occurs in about 20%, 2/3 of them showing a concomitant epileptiform EEG [49,50]. From an EEG angle, repetitive epileptiform discharges occur in 20–30% of cardiac arrest survivors [51,52▪], and about 2/3 of them may exhibit myoclonus [53]. A lively debate exists regarding the attribution of these electro-clinical features to status epilepticus, and indeed the latest status epilepticus classification reports them as boundary entities [1]. In our opinion, repetitive, epileptiform EEG patterns occurring in such patients, which may have clinical (myoclonic) counterparts and can be amenable to treatment and subsequently consciousness recovery with ASD commonly used for status epilepticus, may fulfill its definition and classification.

How to detect it and stratify prognosis

EEG evolves over the hours and days following cardiac arrest [54▪▪], therefore continuous or repeated assessments are strongly recommended

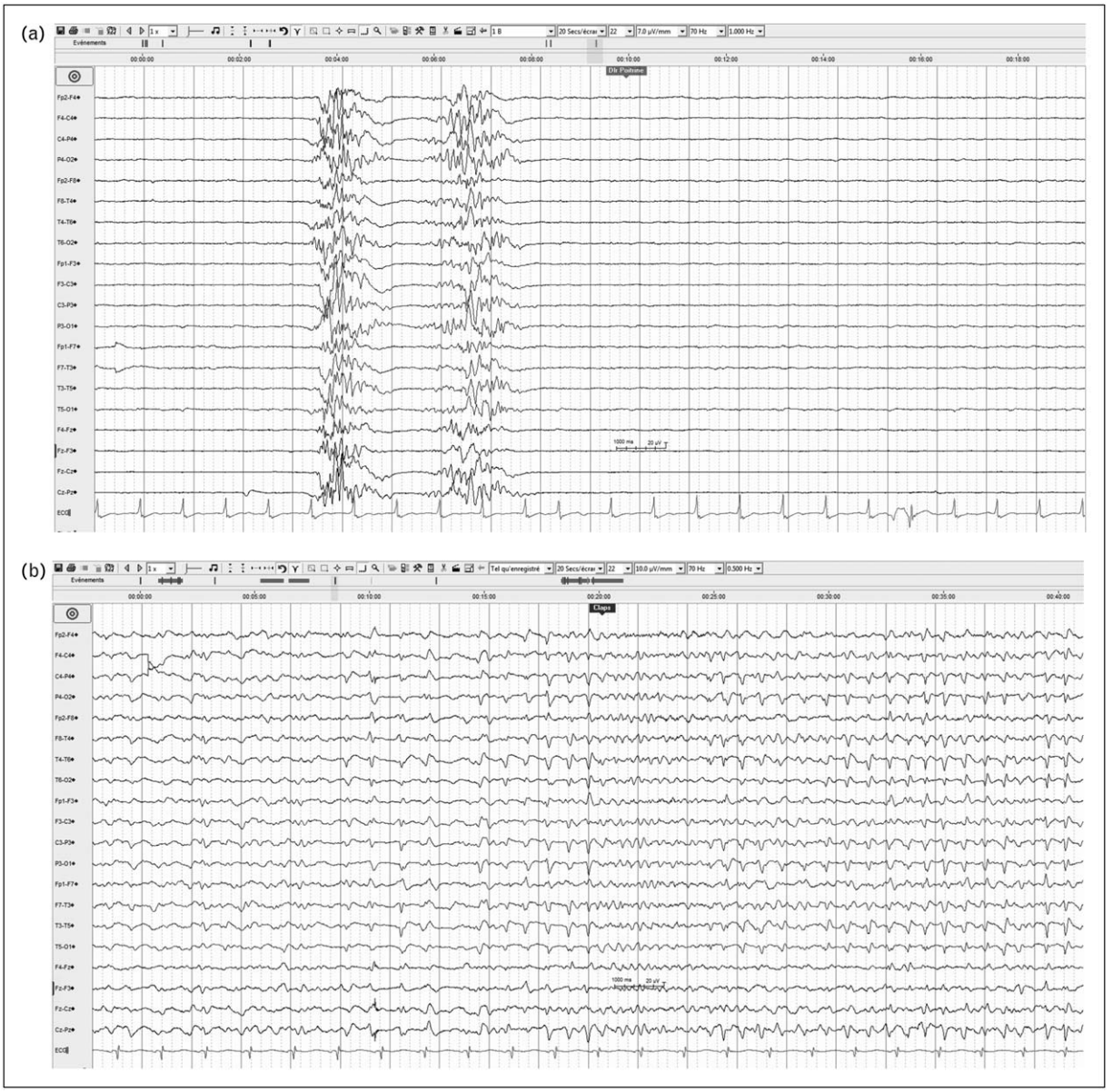

FIGURE 2. Examples of epileptiform EEGs in survivors after cardiac arrest (bipolar longitudinal montage, 15 mm/s, 10 μV/mm). (a) A 69-year-old man recorded 16 h after cardiac arrest (cardiac cause, ventricular fibrillation, return of spontaneous circulation after 25 min), showing burst-suppression with diffuse epileptiform bursts, no background activity, nor reactivity to pain (mark in the middle, top). This corresponds to a 'highly malignant' pattern. Multimodal assessment concluded to poor prognosis, the patients died 48 h later following withdrawal of life supporting treatment. (b) A 77-year-old man recorded 48 h after cardiac arrest (cardiac cause, ventricular fibrillation, return of spontaneous circulation after 17 min), showing an irregular theta background reactive to clapping hands (mark in the middle, top), with superimposed generalized periodic discharges. His EEG 24 h earlier, under sedation with propofol, was discontinuous, reactive, and lacked epileptiform transients. He received clonazepam, levetiracetam, and valproate, awoke 1 week after, reaching a cerebral performance category 2 (moderate impairment) at 3 months. Early epileptiform activity without return of an underlying background (a) highlights features related to poor outcome, as opposed to late-appearing epileptiform transients on a reactive, continuous background that are compatible with a good prognosis.

within the first 48–72 h [48▪]. In several hospitals, it is common practice to perform continuous EEG until rewarming, while repeated standard (20 min) EEG may represent a valid alternative for settings with limited resources; these two strategies are comparable in terms of outcome in retrospective studies [55,56], and in a recent trial [57]. Reduced electrode montages seem suited especially for background

assessment [51,58], and probably epileptiform patterns detection [59], but could be less sensitive for reactivity evaluation. We strongly recommend performing standardized EEG assessments following the validated American Clinical Neurophysiology Society terminology [60]. This scoring correlates robustly with other prognostic variables, highlighting the central role of EEG in multimodal prognostication [61▪,62], and identifies 'highly malignant' patterns (suppressed or burst-suppressed EEG, with or without superimposed epileptiform discharges), having 100% specificity after TTM (but sensitivity as low as 5–50%) for poor outcome [63]. Of note, the EEG predictive performance seems more accurate early, at 12–24 h after cardiac arrest [53,54▪▪], while TTM and sedation do not significantly alter EEG prognostication performance [64].

While myoclonus and/or an epileptiform EEG have been classically considered strong indicators of poor prognosis, at least 1/10 of patients may reach a good outcome [52▪,65,66]. It has been recently shown that clinical–electrophysiological correlation of myoclonus is challenging [67], and interrater variability is relatively high [68]; therefore, patients with potentially favorable prognosis should be identified using multimodal prognostication. Return of brainstem reflexes at 72 h and preserved cortical somatosensory evoked potentials seem necessary to allow clinical recovery [66], and absence of diffusion-weighted MRI alterations along with a continuous EEG portend high chances of good prognosis [69].

EEG represents indeed a key element in this context, as illustrated in Fig. 2. An underlying continuous, reactive background is associated with treatable forms, probably representing early Lance–Adams syndrome [50,70,71]. Background reactivity to stimulation may also forecast good outcome [66,72]; it is, however prone to subjectivity and variable inter-rater agreements [73,74]: video-EEG correlation and standardized stimulations [75,76] are strongly encouraged to optimize accuracy. Epileptiform activity, especially if correlating with myoclonus, is often distributed around the midline on a continuous background in patients with potentially good outcome, as opposed to those with poor prognosis, showing high-voltage bursts on a suppressed background [70]. Identical bursts seem also very specific for poor outcome [77,78]. The temporal interplay between recovery of a continuous background (the earlier, the better [54▪▪,79▪]) and the appearance of epileptiform features (the earlier, the worse [79▪]) have to be taken into account when evaluating such patients. In fact, status epilepticus appearing during TTM under concomitant sedation with antiepileptic, γ-aminobutyric acid (GABA)-ergic properties probably reflects an extremely aggressive brain injury. Developing on this, a simple score has been recently proposed and validated to identify patients with a chance to recover consciousness despite epileptiform EEG activity within the first few days [80▪▪].

How to treat it

There is still no high-level evidence supporting pharmacological treatment in patients with myoclonus and/or epileptiform EEG, beyond reduction of epileptiform activity [81]; a randomized trial is currently ongoing (TELSTAR) [82]. As outlined above, patients with potentially favorable prognosis can be identified in a multimodal approach including clinical examination, EEG, and somatosensory evoked potentials; NSE and neuroimaging may be of additional help. Cohort studies from different environments give a convergent message to attempt treating such patients with combinations of ASD and, at times, general anesthetics [52▪,70,80▪▪].

In our opinion, it is not reasonable to treat aggressively patients with a prognostic profile strongly suggestive of poor outcome, such as those without return of the principal brainstem reflexes (particularly, pupillary, and corneal at 48–72 hours), showing widespread anoxic–ischemic alterations on brain MRI, lacking concomitant EEG background activity and reactivity, or cortical responses to somatosensory evoked potentials. In subjects with potentially favorable prognosis, conversely, we recommend to consider as first line antimyoclonic ASD, such as benzodiazepines, VPA and LEV [71,81]. For instance, we routinely start with an intravenous combination of the latter two combined with low doses of CLZ (i.e., up to 2 mg/24 h). Pharmacological coma with MDZ and/or PRO under continuous EEG surveillance, in analogy with refractory status epilepticus, may be indicated in treatment-resistant cases [52▪]; we prefer using PRO, given its shorter weaning time easing clinical and EEG assessments. Additional options might include PER, zonisamide, or topiramate through the nasogastric tube [70,71,83]. There are no high-evidence data also regarding the optimal treatment duration; we recommend that a reasonable trial should last for some days, up to 2(–3) weeks, but not longer.

CONCLUSION

In patients with status epilepticus, intranasal and intramuscular MDZ is highly effective, and intravenous CLZ represents an interesting alternative for initial treatment. Recent high-level evidence shows equivalent efficacy of intravenous fPHT/PHT

(20 mg/kg), VPA (40 mg/kg), and LEV (60 mg/kg) as second-line ASD. There is still an urgent need of high-quality studies focusing on RSE and SRSE and on immunological aspects; for the time being, besides considering ketogenic diet or KET, looking for autoimmune causes and considering immunosuppressive treatment should be considered in refractory cases, especially if new-onset. Since in practice ASD including benzodiazepines are frequently underdosed, portending higher risks of RSE development, it appears straightforward to enhance treatment guidelines awareness.

A considerable proportion of survivors after cardiac arrest may present myoclonus and/or electrographic status epilepticus. While until a few years ago this constellation was supposed to invariably herald poor prognosis, taking into account the timing of their onset, together with the clinical findings integrating neurological exam, EEG background and reactivity, evoked potentials, biochemistry, and neuroradiological results, helps identifying the subgroup of patients deserving aggressive treatment with ASD, as these may ultimately awaken. Future studies should address the optimal treatment duration and the best ASD options in these cases.

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Conflicts of interest

A.O.R. serves as consultant for Marinus Pharmaceuticals. V.A. has nothing to declare.

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. 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.
2. Leitinger M, Trinka E, Gardella E, *et al.* Diagnostic accuracy of the Salzburg EEG criteria for nonconvulsive status epilepticus: a retrospective study. Lancet Neurol 2016; 15:1054–1062.
3. Sutter R, Kaplan PW. The neurophysiologic types of nonconvulsive status epilepticus: EEG patterns of different phenotypes. Epilepsia 2013; 54:23–27.
4. Wilder-Smith EPV, Lim ECH, Teoh HL, *et al.* The NORSE (new-onset refractory status epilepticus) syndrome: defining a disease entity. Ann Acad Med Singapore 2005; 34:417–420.
5. ■■ 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.

Consensus definition of new-onset refractory status epilepticus and febrile infection-related epilepsy syndrome.

6. ■ 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; 76:897–905.

Careful, updated analysis of temporal evolution of status epilepticus-related mortality.

7. Trinka E, Brigo F, Shorvon S. Recent advances in status epilepticus. Curr Opin Neurol 2016; 29:189–198.
8. Brophy GM, Bell R, Claassen J, *et al.* Guidelines for the evaluation and management of status epilepticus. Neurocrit Care 2012; 17:3–23.
9. 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.
10. Silbergleit R, Durkalski V, Lowenstein D, *et al.* Intramuscular versus intravenous therapy for prehospital status epilepticus. N Engl J Med 2012; 366:591–600.
11. Kay L, Merkel N, von Blomberg A, *et al.* Intranasal midazolam as first-line inhospital treatment for status epilepticus: a pharmaco-EEG Cohort study. Ann Clin Transl Neurol 2019; 6:2413–2425.
12. Treiman DM. Pharmacokinetics and clinical use of benzodiazepines in the management of status epilepticus. Epilepsia 1989; 30(Suppl 2):S4–S10.
13. Alvarez V, Lee JW, Drislane FW, *et al.* Practice variability and efficacy of clonazepam, lorazepam, and midazolam in status epilepticus: a multicenter comparison. Epilepsia 2015; 56:1275–1285.
14. Navarro V, Dagron C, Elie C, *et al.* Prehospital treatment with levetiracetam plus clonazepam or placebo plus clonazepam in status epilepticus (SAMU-Keppra): a randomised, double-blind, phase 3 trial. Lancet Neurol 2015; 15:47–55.
15. ■ 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.

Large European status epilepticus cohort showing the frequent underdosage of first-line therapy linked with refractoriness.

16. ■■ Kapur J, Elm J, Chamberlain JM, *et al.* Randomized trial of three anticonvulsant medications for status epilepticus. N Engl J Med 2019; 381:2103–2113.

ESETT randomized trial, providing high-level evidence for second-line status epilepticus treatment and showing equivalence of fosphenytoin (fPHT)/levetiracetam (LEV)/valproate.

17. ■ Chamberlain JM, Kapur J, Shinnar S, *et al.* Efficacy of levetiracetam, fosphenytoin, and valproate for established status epilepticus by age group (ESETT): a double-blind, responsive-adaptive, randomised controlled trial. Lancet 2020; 395:1217–1224.

Subgroup analysis of ESETT according to age groups, confirming equivalent effects.

18. Brigo F, Del Giovane C, Nardone R, *et al.* Second-line treatments in benzodiazepine-resistant convulsive status epilepticus: an updated network meta-analysis including the ESET Trial – what did change? Epilepsy Behav 2020; 106:107035.
19. ■ Husain AM, Lee JW, Kolls BJ, *et al.* Randomized trial of lacosamide versus fosphenytoin for nonconvulsive seizures. Ann Neurol 2018; 83:1174–1185.

Randomized trial showing equivalence of lacosamide and fPHT for repetitive seizures.

20. Perrenoud M, André P, Alvarez V, *et al.* Intravenous lacosamide in status epilepticus: correlation between loading dose, serum levels, and clinical response. Epilepsy Res 2017; 135:38–42.
21. ■■ Dalziel SR, Borland ML, Furyk J, *et al.* 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.

Randomized trial providing evidence upon equivalence of LEV and phenytoin (PHT) for children.

22. ■■ Lyttle MD, Rainford NEA, Gamble C, *et al.* Levetiracetam versus phenytoin for second-line treatment of paediatric convulsive status epilepticus (EcLiPSE): a multicentre, open-label, randomised trial. Lancet 2019; 393:2125–2134.

Randomized trial providing evidence upon equivalence of LEV and PHT for children.

23. Beuchat I, Novy J, Rossetti AO. Newer antiepileptic drugs for status epilepticus in adults: what's the evidence? CNS Drugs 2018; 32:259–267.
24. Trinka E, Wheless J, Bertram EH. Second-line therapy for status epilepticus: what ' s the latest? Trial results: clinical equivalence. Epigraph 2020; 22:1–6.
25. Willems LM, Bauer S, Rosenow F, Strzelczyk A. Recent advances in the pharmacotherapy of epilepsy: brivaracetam and perampanel as broad-spectrum antiseizure drugs for the treatment of epilepsies and status epilepticus. Expert Opin Pharmacother 2019; 20:1755–1765.
26. Meldrum BS, Brierley JB. Prolonged epileptic seizures in primates. Arch Neurol 1973; 28:10–17.
27. Rabinowicz a L, Correale JD, Bracht K a, *et al.* Neuron-specific enolase is increased after nonconvulsive status epilepticus. Epilepsia 1995; 36:475–479.
28. Noè F, Cattalini A, Vila Verde D, *et al.* Epileptiform activity contralateral to unilateral hippocampal sclerosis does not cause the expression of brain damage markers. Epilepsia 2019; 60:1184–1199.
29. Delaj L, Novy J, Ryvlin P, *et al.* Refractory and super-refractory status epilepticus in adults: a 9-year cohort study. Acta Neurol Scand 2016; 10:1–8.

30. Hirsch LJ. Finding the lesser of two evils: treating refractory status epilepticus. Epilepsy Curr 2015; 15:313–316.
31. Kowalski RG, Ziai WC, Rees RN, *et al.* Third-line antiepileptic therapy and outcome in status epilepticus: the impact of vasopressor use and prolonged mechanical ventilation. Crit Care Med 2012; 40:2677–2684.
32. Sutter R, Marsch S, Fuhr P, *et al.* Anesthetic drugs in status epilepticus: risk or rescue? A 6-year cohort study. Neurology 2014; 82:656–664.
33. Marchi NA, Novy J, Faouzi M, *et al.* Status epilepticus: impact of therapeutic coma on outcome nicola. Crit Care Med 2015; 43:1003–1009.
34. Alvarez V, Lee J, Westover M, *et al.* Therapeutic coma for status epilepticus: differing practices in a prospective multicenter study. Neurology 2016; 87:1650–1659.
35. ■ Caronna E, Vilaseca A, Gràcia Gozalo RM, *et al.* Long-term prognosis related to deep sedation in refractory status epilepticus. Acta Neurol Scand 2020; 142:555–562.
Careful observational study linking the depth of sedation in refractory status epilepticus (RSE) patients with unfavorable outcome.
36. Johnson EL, Martinez NC, Ritzl EK. EEG characteristics of successful burst suppression for refractory status epilepticus. Neurocrit Care 2016; 25:407–414.
37. ■ Rubin DB, Angelini B, Shoukat M, *et al.* Electrographic predictors of successful weaning from anaesthetics in refractory status epilepticus. Brain 2020; 143:1143–1157.
Sophisticated quantitative EEG approach proposed to guide anesthetic weaning in RSE patients.
38. ■ Hocker S, Clark S, Britton J. Parenteral phenobarbital in status epilepticus revisited: Mayo Clinic experience. Epilepsia 2018; 59:193–197.
Case series illustrating the value of high-dose phenobarbital in highly refractory status epilepticus.
39. Gaspard N, Foreman B, Judd LM, *et al.* Intravenous ketamine for the treatment of refractory status epilepticus: a retrospective multicenter study. Epilepsia 2013; 54:1498–1503.
40. Mahmoud SH, Ho-Huang E, Buhler J. Systematic review of ketogenic diet use in adult patients with status epilepticus. Epilepsia Open 2020; 5:10–21.
41. Dibué-Adjei M, Brigo F, Yamamoto T, *et al.* Vagus nerve stimulation in refractory and super-refractory status epilepticus – a systematic review. Brain Stimul 2019; 12:1101–1110.
42. Gaspard N, Foreman BP, Alvarez V, *et al.* New-onset refractory status epilepticus etiology, clinical features, and outcome. Neurology 2015; 85:1–10.
43. Pantazou V, Novy J, Rossetti AO. Intravenous corticosteroids as an adjunctive treatment for refractory and super-refractory status epilepticus: an observational cohort study. CNS Drugs 2019; 33:187–192.
44. Khawaja AM, DeWolfe JL, Miller DW, Szaflarski JP. New-onset refractory status epilepticus (NORSE) – the potential role for immunotherapy. Epilepsy Behav 2015; 47:17–23.
45. Kenney-Jung DL, Vezzani A, Kahoud RJ, *et al.* Febrile infection-related epilepsy syndrome treated with anakinra. Ann Neurol 2016; 80:939–945.
46. ■ Jun JS, Lee ST, Kim R, *et al.* Tocilizumab treatment for new onset refractory status epilepticus. Ann Neurol 2018; 84:940–945.
Interesting, albeit small observational study suggesting that tocilizumab (anti IL-6) may be of value in RSE patients.
47. Gräsner JT, Lefering R, Koster RW, *et al.* EuReCa ONE – 27 Nations, ONE Europe, ONE Registry: a prospective one month analysis of out-of-hospital cardiac arrest outcomes in 27 countries in Europe. Resuscitation 2016; 105:188–195.
48. ■ Cronberg T, Greer DM, Lilja G, *et al.* Brain injury after cardiac arrest: from prognostication of comatose patients to rehabilitation. Lancet Neurol 2020; 19:611–622.
Updated overview on prognostication of comatose patients after cardiac arrest, including an outlook into rehabilitation.
49. Seder DB, Sunde K, Rubertsson S, *et al.* Neurologic outcomes and post-resuscitation care of patients with myoclonus following cardiac arrest. Crit Care Med 2015; 43:965–972.
50. Dhakar MB, Sivaraju A, Maciel CB, *et al.* Electro-clinical characteristics and prognostic significance of post anoxic myoclonus. Resuscitation 2018; 131:114–120.
51. Backman S, Westhall E, Dragancea I, *et al.* Electroencephalographic characteristics of status epilepticus after cardiac arrest. Clin Neurophysiol 2017; 128:681–688.
52. ■ Beretta S, Coppo A, Bianchi E, *et al.* Neurologic outcome of postanoxic refractory status epilepticus after aggressive treatment. Neurology 2018; 91:e2153–e2162.
Single-center study describing RSE patients after cardiac arrest receiving aggressive antiseizure drugs treatment and reaching favorable prognosis.
53. Rossetti AO, Tovar Quiroga DF, Juan E, *et al.* Electroencephalography predicts poor and good outcomes after cardiac arrest: a two-center study. Crit Care Med 2017; 45:e674–e682.
54. ■■ Ruijter BJ, Tjepkema-Cloostermans MC, Tromp SC, *et al.* Early electroencephalography for outcome prediction of postanoxic coma: a prospective cohort study. Ann Neurol 2019; 86:203–214.
Careful multicenter study describing EEG evolution over time in patients after cardiac arrest, and prognostic implications.
55. Elmer J, Coppler PJ, Solanki P, *et al.* Sensitivity of continuous electroencephalography to detect ictal activity after cardiac arrest. JAMA Netw Open 2020; 3:e203751.
56. Fatuzzo D, Beuchat I, Alvarez V, *et al.* Does continuous EEG influence prognosis in patients after cardiac arrest? Does continuous EEG influence prognosis in patients after cardiac arrest? Resuscitation 2018; 132:29–32.
57. Rossetti AO, Schindler K, Sutter R, *et al.* Continuous vs routine electroencephalogram in critically ill adults with altered consciousness and no recent seizure: a multicenter randomized clinical trial. JAMA Neurol 2020; 77:1225–1232.
58. Tjepkema-Cloostermans MC, Hofmeijer J, Hom HW, *et al.* Predicting outcome in postanoxic coma: are ten EEG electrodes enough? J Clin Neurophysiol 2017; 34:207–212.
59. Westover MB, Gururangan K, Markert MS, *et al.* Diagnostic value of electroencephalography with ten electrodes in critically ill patients. Neurocrit Care 2020; 33:479–490.
60. Hirsch LJ, LaRoche SM, Gaspard N, *et al.* American Clinical Neurophysiology Society's standardized critical care EEG terminology: 2012 version. J Clin Neurophysiol 2013; 30:1–27.
61. ■ Beuchat I, Solari D, Novy J, *et al.* Standardized EEG interpretation in patients after cardiac arrest: correlation with other prognostic predictors. Resuscitation 2018; 126:143–146.
Single-center study describing the correlation between standardized EEG interpretation and other prognostic predictors in patients after cardiac arrest.
62. Bongiovanni F, Romagnosi F, Barbella G, *et al.* Standardized EEG analysis to reduce the uncertainty of outcome prognostication after cardiac arrest. Intensive Care Med 2020; 46:963–972.
63. Westhall E, Rossetti AO, van Rootselaar AF, *et al.* Standardized EEG interpretation accurately predicts prognosis after cardiac arrest. Neurology 2016; 87:1631.
64. Ruijter BJ, van Putten MJAM, van den Bergh WM, *et al.* Propofol does not affect the reliability of early EEG for outcome prediction of comatose patients after cardiac arrest. Clin Neurophysiol 2019; 130:1263–1270.
65. Lybeck A, Friberg H, Aneman A, *et al.* Prognostic significance of clinical seizures after cardiac arrest and target temperature management. Resuscitation 2017; 114:146–151.
66. Rossetti AO, Oddo M, Liaudet L, Kaplan PW. Predictors of awakening from postanoxic status epilepticus after therapeutic hypothermia. Neurology 2009; 72:744–749.
67. van Zijl JC, Beudel M, de Jong BM, *et al.* The interrelation between clinical presentation and neurophysiology of posthypoxic myoclonus. Ann Clin Transl Neurol 2018; 5:386–396.
68. van Zijl JC, Beudel M, Elting JWJ, *et al.* The inter-rater variability of clinical assessment in postanoxic myoclonus. Tremor Other Hyperkinet Mov 2017; 7:4–6.
69. Beuchat I, Sivaraju A, Amorim E, *et al.* MRI-EEG correlation for outcome prediction in postanoxic myoclonus: a multicenter study. Neurology 2020; 95:e335–e341.
70. Elmer J, Rittenberger JC, Faro J, *et al.* Clinically distinct electroencephalographic phenotypes of early myoclonus after cardiac arrest. Ann Neurol 2016; 80:175–184.
71. Aicua Rapun I, Novy J, Solari D, *et al.* Early Lance–Adams syndrome after cardiac arrest: prevalence, time to return to awareness, and outcome in a large cohort. Resuscitation 2017; 115:169–172.
72. Admiraal M, Horn J, Hofmeijer J, *et al.* EEG reactivity testing for prediction of good outcome in patients after cardiac arrest. Neurology 2020; 95:e653–e661.
73. Admiraal MM, van Rootselaar AF, Hofmeijer J, *et al.* Electroencephalographic reactivity as predictor of neurological outcome in postanoxic coma: a multicenter prospective cohort study. Ann Neurol 2019; 86:17–27.
74. Duez CHV, Ebbesen MQ, Benedek K, *et al.* Large inter-rater variability on EEG-reactivity is improved by a novel quantitative method. Clin Neurophysiol 2018; 129:724–730.
75. Tsetsou S, Novy J, Oddo M, Rossetti AO. EEG reactivity to pain in comatose patients: importance of the stimulus type. Resuscitation 2015; 97:34–37.
76. Fantaneanu TA, Tolchin B, Alvarez V, *et al.* Effect of stimulus type and temperature on EEG reactivity in cardiac arrest. Clin Neurophysiol 2016; 127:3412–3417.
77. Barbella G, Novy J, Marques-Vidal P, *et al.* Prognostic role of EEG identical bursts in patients after cardiac arrest: multimodal correlation. Resuscitation 2020; 148:140–144.
78. Hofmeijer J, Tjepkema-Cloostermans MC, van Putten MJAM. Burst-suppression with identical bursts: a distinct EEG pattern with poor outcome in postanoxic coma. Clin Neurophysiol 2014; 125:947–954.
79. ■ Westhall E, Rosén I, Rundgren M, *et al.* Time to epileptiform activity and EEG background recovery are independent predictors after cardiac arrest. Clin Neurophysiol 2018; 129:1660–1668.
Observational study highlighting the prognostic importance of time of the appearance of continuous background and epileptiform features in subjects with status epilepticus after cardiac arrest.

80. Barbella G, Lee JW, Alvarez V, *et al.* Prediction of regaining consciousness despite ■■ an early epileptiform EEG after cardiac arrest. Neurology 2020; 94:e1675–1683. Description and validation of a scale allowing identification of patients with potentially favorable prognosis despite postcardiac arrest status epilepticus.
81. Solanki P, Coppler PJ, Kvaløy JT, *et al.* Association of antiepileptic drugs with resolution of epileptiform activity after cardiac arrest. Resuscitation 2019; 142:82–90.
82. Ruijter BJ, van Putten MJAM, Horn J, *et al.* Treatment of electroencephalographic status epilepticus after cardiopulmonary resuscitation (TELSTAR): study protocol for a randomized controlled trial. Trials 2014; 15:1–8.
83. Beretta S, Padovano G, Stabile A, *et al.* Efficacy and safety of perampanel oral loading in postanoxic super-refractory status epilepticus: a pilot study. Epilepsia 2018; 59:243–248.