

Management of refractory status epilepticus in adults: still more questions than answers

Andrea O Rossetti, Daniel H Lowenstein

Lancet Neurol 2011; 10: 922–30

Department of Clinical Neurosciences, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland (A O Rossetti MD); Université de Lausanne, Lausanne, Switzerland (A O Rossetti); and Department of Neurology, University of California San Francisco, San Francisco, CA, USA (Prof D H Lowenstein MD)

Correspondence to: Dr Andrea O Rossetti, Département des Neurosciences Cliniques, Service de Neurologie, CHUV BH-07, Lausanne CH-1011, Switzerland
andrea.rossetti@chuv.ch

Refractory status epilepticus (RSE) is defined as status epilepticus that continues despite treatment with benzodiazepines and one antiepileptic drug. RSE should be treated promptly to prevent morbidity and mortality; however, scarce evidence is available to support the choice of specific treatments. Major independent outcome predictors are age (not modifiable) and cause (which should be actively targeted). Recent recommendations for adults suggest that the aggressiveness of treatment for RSE should be tailored to the clinical situation. To minimise intensive care unit-related complications, focal RSE without impairment of consciousness might initially be approached conservatively; conversely, early induction of pharmacological coma is advisable in generalised convulsive forms of the disorder. At this stage, midazolam, propofol, or barbiturates are the most commonly used drugs. Several other treatments, such as additional anaesthetics, other antiepileptic or immunomodulatory compounds, or non-pharmacological approaches (eg, electroconvulsive treatment or hypothermia), have been used in protracted RSE. Treatment lasting weeks or months can sometimes result in a good outcome, as in selected patients after encephalitis or autoimmune disorders. Well designed prospective studies of RSE are urgently needed.

Introduction

With an annual incidence of 10–40 per 100 000 population,^{1–3} status epilepticus (SE) is the second most frequent neurological emergency (acute stroke being the first) with a risk of major morbidity or mortality.⁴ Irrespective of the timeframe, SE that persists despite adequate administration of benzodiazepines and at least one antiepileptic drug is labelled refractory SE (RSE).^{5,6} This resistance to treatment occurs in 23–43% of patients with SE; the only prospective study of RSE frequency⁶ estimates lower proportions than retrospective assessments that are based in the intensive care unit (ICU).^{7–9} RSE is mostly associated with acute, severe, and potentially fatal underlying causes, such as encephalitis, massive stroke, or rapidly progressive primary brain tumours, and is typically accompanied by severe impairment of consciousness.^{6,7,10}

Over the past few decades, important advances in the understanding of the basic mechanisms underlying SE and RSE have been achieved, mostly from seminal animal studies. However, animal data cannot be automatically translated to patients, and up to now, well designed studies of epidemiological, clinical, and therapeutic aspects remain scarce. Treatment for RSE is not evidence-based, despite the disorder being recognised as an important entity in emergency and intensive care settings.

Our principal aim in this Review is to summarise present knowledge of RSE in adults, with particular attention to the balance between risks and benefits of different treatment strategies, including rarely used options. In view of the substantial differences in pathophysiological mechanisms and treatment approaches in neonates and infants, our focus is on older children and adults. We also identify areas in need of further research, and draw attention to some practical difficulties that need to be overcome for well designed, prospective clinical studies to take place.

Mortality and morbidity

The short-term fatality rates for RSE have been estimated to be between 16% and 39%;^{6–9} mortality after RSE is about three times higher than for non-refractory SE.^{6,7} For most fatalities, death does not occur during persisting SE but after its (sometimes late) resolution, and is generally attributable to underlying clinical problems.⁶ This observation illustrates the crucial prognostic importance of SE causation: together with age, cause is consistently identified as the principal independent outcome predictor.^{6,11–14} The classic subdivision between acute symptomatic versus remote causes, with acute causes believed to be more dangerous, is only partly indicative of the prognostic power. Indeed, withdrawal from antiepileptic drugs is an acute cause that is often related to good outcome, and primary brain tumours are remote causes with poor prognosis. Another aetiological classification has been suggested, in which potentially fatal disorders (implying that these disorders can lead to death if not specifically treated, such as large ischaemic stroke or haemorrhage, CNS infection, severe systemic infection, malignant brain tumour, AIDS with CNS complications, eclampsia, intracranial tumour, and others) are significantly better predictors of outcome after SE than are acute causes under the classic subdivision.^{6,12} A long duration of untreated SE can also make control more difficult;¹³ however, this factor does not seem to be a robust predictor;¹¹ and applies mostly to generalised convulsive forms¹² during the first few hours.¹⁵

The risk of epilepsy after an incident symptomatic SE event, especially if refractory,⁷ is three times higher than after a first symptomatic seizure.¹⁶ The risk of cognitive sequelae seems to depend on the underlying cause; patients diagnosed with epilepsy, in whom SE is usually due to withdrawal from antiepileptic drugs or spontaneous fluctuations of the epileptic threshold (causes that rarely trigger RSE), do not seem to have aggravated neuropsychological performances after an episode of SE.¹⁷

Functional outcome seems to be poor after RSE,⁶ especially generalised convulsive RSE.¹⁸ The likelihood of a return to baseline clinical conditions after RSE is as low as 21%, as opposed to 63% for non-refractory SE. The need for admission to acute rehabilitation facilities for surviving patients doubles after RSE compared with non-refractory SE (82% vs 35%).⁶

Rationale for early treatment

In view of the danger of RSE and the effects of duration on outcome, broad consensus exists about the need for timely and effective pharmacological treatment.^{5,19–22} Additionally, data from the Veteran Affairs Cooperative Study²³ showed that SE treatment becomes less effective as the episode becomes more protracted; subtle SE (or non-convulsive SE with coma), a form usually indicative of a longer duration, was controlled by the first medication in 15% of patients compared with 55% in overt, convulsive SE. Furthermore, a second or third agent was effective in less than 10% of patients in either condition.²⁴

Generalised convulsive SE can cause many systemic complications, including cardiac arrhythmias, temperature disturbances, electrolyte and glucose imbalance, rhabdomyolysis, and pulmonary oedema.^{25,26} Apart from rhabdomyolysis, these consequences can also be recorded in laboratory models after inhibition of muscular convulsions.²⁷ Mechanisms related to refractoriness to treatment have been elucidated in animal models in the past few decades. Self-sustained SE in rats, induced by repetitive electrical stimulation of limbic structures, responds to benzodiazepines (GABA_A receptor agonists) or phenytoin (a sodium-channel blocker) only if they are administered early (ie, within the first few minutes). With time, SE becomes progressively resistant to these agents, whereas antagonists of NMDA receptors, which mediate glutamate excitatory inputs, become especially efficacious in the late phase.^{28,29} This switch of sensitivity to different pharmacological compounds is indicative of loss of inhibition in ongoing SE,³⁰ and in-vitro models show that GABA_A receptors are internalised into the neuronal cytoplasm.³¹ From these findings, the window for successful pharmacological intervention with antiepileptic compounds, including benzodiazepines, seems short. However, there is still no clinical evidence that refractoriness is exclusively accounted for by loss of inhibition. The various causes and biological backgrounds encountered in patients with SE are distinct from the controlled and uniform laboratory conditions for rodents, and are an important limitation to the translation of these findings to people.

Basic principles of SE treatment

The principal aims in treatment of a patient with SE are to achieve rapid control of seizures and to avoid complications. During the early stages, imitators should be ruled out, since the correct diagnosis could be impossible to make once a patient has been placed under

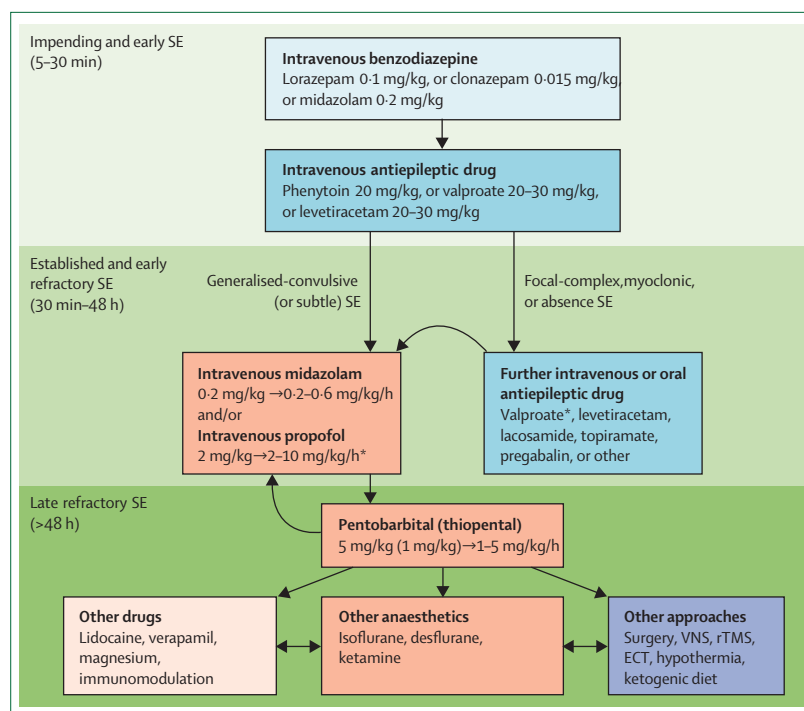


Figure: Status epilepticus treatment

Increasing refractoriness is indicated by the background green intensity. Light blue=first-line drugs. Dark blue=second-line drugs. Orange=third line drugs. *Great caution is needed for use of valproate in children younger than 2 years (because of hepatic toxicity), and propofol in young children (because of propofol infusion syndrome). In this setting, benzodiazepines, phenytoin, and barbiturates are the most widely used options. VNS=vagus nerve stimulation. rTMS=repertitive transcranial magnetic stimulation. ECT=electroconvulsive therapy. SE=status epilepticus.

pharmacological coma, potentially leading to dangerous iatrogenic complications. Acute movement disorders, such as focal or segmental dystonias, tremors, and choreatic movements,³² can sometimes present unilaterally in confused patients. At times, clonus in the context of spasticity, which is lost after a passive movement, or shivering in a sedated patient, characterised by high-frequency, rhythmic, proximally located movements, can be mistaken for SE. One especially challenging group is those with psychogenic non-epileptic seizures (PNES). By contrast with seizures, PNES episodes are suggestion-prone, generally not stereotyped, and can occur with or without subjective consciousness impairment. During the ictus, the eyes are often closed, ventilatory drive is maintained, and the episode can present as uncoordinated, discontinuous, and fluctuating in intensity.³³ Importantly, physical injuries might be recorded in patients having PNES.³⁴ A substantial proportion of patients with PNES have longstanding seizures that can be misdiagnosed as SE (accounting for up to 50% of patients treated for RSE in a retrospective study), leading to intensive care admissions with much risk of overtreatment.^{34–36} Laboratory studies can be helpful in this setting; by contrast with patients with SE, patients with PNES do not have raised serum lactate, prolactin, or creatine kinase.

	Loading dose	Maintenance dose	Comments
Midazolam	0.2 mg/kg	0.2–0.6 mg/kg per h	Increasing doses needed with time
Propofol	2 mg/kg	2–5 mg/kg per h, in some cases can be raised to 10 mg/kg per h	Attention to PRIS, especially in young children; combine with benzodiazepines
Barbiturates	Thiopental: 1–2 mg/kg Pentobarbital: 5 mg/kg	Thiopental: 1–5 mg/kg per h Pentobarbital: 1–5 mg/kg per h	Both need loading with repetitive boluses and have long wash-out times

PRIS=propofol infusion syndrome.

Table 1: Anaesthetic agents for refractory status epilepticus^{5,53,56}

The first steps of SE treatment run in parallel with diagnostic procedures. After attending to pulmonary and cardiac function, control of seizures is the top priority and generally follows the intravenous administration of a sequence of three groups of drugs^{4,37,38} (figure): benzodiazepines aimed at rapid SE control, classic antiepileptic drugs targeted at early resistant forms and longer term coverage, and general anaesthetics for RSE. Benzodiazepines are the only evidence-based treatment, as shown in three trials and a Cochrane review.^{23,39–41} However, only one trial has been done to compare them with other medications; lorazepam had statistically better results than phenytoin (but not phenobarbital or diazepam combined with phenytoin).²³ Use of an accepted and available protocol greatly facilitates a smooth interplay between different care providers (eg, paramedics, neurologists, and emergency or ICU team) and probably contributes to an improved prognosis.⁴²

The overall aggressiveness of treatment depends on the type of SE. Generalised convulsive SE should be treated aggressively in view of the danger of systemic and neurological injury with ongoing seizures.^{5,43} Conversely, non-convulsive SE without noticeable impairment of consciousness can usually be treated more conservatively, because its underlying pathophysiological mechanism is not associated with the same degree of injury as that of generalised convulsive SE. For example, in patients with idiopathic generalised epilepsy, epilepsy specialists typically treat SE episodes (absence or myoclonic SE) with benzodiazepines and valproate, and do not rely on admission to ICU.⁴⁴ The precise criteria for turning to induction of coma for the treatment of focal complex SE are debated^{45–49} because the treatment can lead to various complications, such as infections (many patients with mechanical ventilation develop pneumonia) or drug side-effects, ileus, neuropathy, myopathy, thrombosis, and embolic events, to cite only the most frequent.⁵⁰ Therefore, these risks should be balanced against the benefit of rapid seizure control. The validated clinical SE severity score (STESS) can help to orient early treatment strategy.^{51,52} With four variables (age, seizure semiology, extent of consciousness impairment, and history of previous seizures, as a surrogate for cause), the STESS is readily applicable in emergency settings, relies on

straightforward clinical criteria, and has a robust negative predictive value for mortality (ie, patients with a low score are very unlikely to have a fatal outcome). Thus, to proceed straight to third-line, coma-inducing treatment seems reasonable if the second-line treatment with intravenous antiepileptic agents (which take at least 20–30 min to be effective) has failed in patients with generalised convulsive SE (who have a high STESS).^{4,53} Conversely, at least in some patients, focal RSE without major impairment of consciousness (and therefore a low STESS) can initially be managed without anaesthetic agents for the first 24–36 h.^{5,6,22,37,38,54,55}

Choice of anaesthetic agents

When elective coma induction is warranted to control RSE, the initial drug is restricted to three groups of compounds⁵⁶ (table 1), whose shared characteristic is the modulation of GABA_A receptors, although each acts on specific sites. Midazolam is a benzodiazepine that is already being used as a first-line treatment. Its half-life, which is short after a single bolus, increases to 6–50 h after prolonged administration. However, tachyphylaxis often develops within 24–48 h,⁵⁷ so the perfusion dose needs to be constantly increased to maintain a constant pharmacological action. Midazolam is therefore mostly used initially, or in combination with propofol. No particular problems inherent to its pharmacodynamic or pharmacokinetic properties have been described, and availability of an antidote (flumazenil) is a theoretical advantage over the other two groups.

Propofol has a short half-life, allowing rapid titration and withdrawal. Besides modulating GABA_A receptors, it acts on sodium and calcium channels, and possibly on NMDA receptors.⁵⁸ Because it is administered as an oil emulsion, it can induce propofol infusion syndrome, a syndrome of potentially fatal cardiocirculatory collapse with lactic acidosis, hypertriglyceridaemia, and rhabdomyolysis. Propofol infusion syndrome is due to impairment of mitochondrial activity and use of free fatty acids, with resulting mismatch between energy needs and use; catecholamines and glucocorticoids can be facilitating factors.⁵⁹ Mainly described in young children (thus suggesting a contraindication in this age group) and patients with brain trauma, propofol infusion syndrome has also been reported in patients treated for RSE.⁶⁰ A retrospective series estimated the incidence of the syndrome in RSE as 7% (fatal) and 38% (non-fatal).⁶¹ However, these proportions are in sharp contrast with results from other retrospective⁶² and prospective studies^{63,64} that report incidences of 0–7%, and might result from a selection bias. Nevertheless, protracted perfusions (for more than 48 h at doses of over 5 mg/kg per h) should be avoided, and careful monitoring of serum lactate are mandatory for early detection of this complication.⁵⁹ Concomitant benzodiazepines could lower the required propofol dose,⁶² possibly reducing the risk of propofol infusion syndrome.

The anaesthetic barbiturate thiopental, or its metabolite pentobarbital, are the oldest compounds used in this setting. In addition to GABA_A modulation, barbiturates have an NMDA-antagonist action *in vitro*, which might be of use in view of the pathophysiological mechanisms of RSE.⁶⁵ They have a long half-life (up to 36 h) after continuous administration, owing to a tendency to accumulate in adipose tissue. This accumulation can become challenging, especially in older patients with pre-existing cardiovascular problems.

A meta-analysis of the use of barbiturates, propofol, or midazolam in RSE completed a decade ago, mostly based on retrospective and heterogeneous case series, did not show any significant difference in short-term mortality, although some variations were noted in both immediate effectiveness (favouring barbiturates) and tolerability (favouring midazolam and propofol).⁶⁶ Results of another single-centre retrospective analysis failed to show any outcome difference between different anaesthetics, used alone or in combination.⁹ A multicentre randomised, unblinded trial assessing propofol and barbiturates in RSE, interrupted because of insufficient recruitment, reported that patients receiving barbiturates had a substantially increased need for mechanical ventilation, whereas long-term outcome and complications were much the same.⁶⁴ Despite the increasing elimination half-life of midazolam after protracted infusion, this compound rarely induces a complete suppression of cerebral activity for several days, whereas barbiturates do. Thus, despite absence of strong evidence (and in view of the availability of the pharmacological antidote flumazenil), midazolam seems to be the safest compound in this setting, but often needs to be combined with propofol to obtain seizure control. Propofol has the advantage of a short half-life, which allows for a rapid clinical assessment on weaning. However, the risk of propofol infusion syndrome needs very careful metabolic monitoring, and the drug should not be used in young children. Barbiturates should probably be reserved for RSE cases refractory to the other anaesthetics because of their long elimination time.

Electroencephalography targets

Electroencephalography (EEG) should be used to monitor the effects of anaesthetics in the treatment of RSE. An alternative might be the bispectral index,⁶⁷ an automated, amplitude-integrated measure of a two-channel EEG derivation (that includes a burst-suppression ratio). This index is frequently used by anaesthetists in the operation room to monitor anaesthesia depth; however, it should not routinely replace EEG with comprehensive scalp coverage if this equipment is available, because the difference between pharmacologically induced burst-suppression and seizure-suppression patterns can be difficult to assess. The optimum extent of EEG suppression—ie, seizure suppression, burst-suppression pattern, or flat recording—has not been addressed in

prospective studies, and retrospective studies do not clearly favour any of these options.^{9,68} The same uncertainty applies to the optimum length and tapering of anaesthetic treatment. In view of present knowledge, an initial course of midazolam anaesthesia targeting EEG burst-suppression patterns with an interburst interval of about 10 s for 24 h, followed by progressive tapering over 6–12 h under EEG control, seems to be a reasonable option. Propofol and, subsequently, barbiturates can be used thereafter. Because triphasic waves are often recorded during anaesthetic tapering, not every sharply contoured EEG transient should be a cause for concern, but rather the focus should be on definite seizure patterns.^{69,70}

Other pharmacological approaches

Several anecdotal case reports and small series (table 2) describe treatment options for RSE that does not respond to the first intravenous anaesthetic agents. However, because of the absence of comparative data their absolute value is difficult to assess. Other anaesthetics can be used sequentially in patients with very longlasting RSE, in alternation or combination with midazolam, propofol, or barbiturates. Inhalational anaesthetics, which act, in part, on GABA_A receptors, might be effective in aborting RSE, but the effects seem to be transient, and their administration requires the use of appropriate gas recovery systems (not typically found outside the operating theatre). Two small case series describe the use of isoflurane with an end-tidal concentration of 1.2–5% for up to 55 days. Several patients needed vasopressors, paralytic ileus occurred in some, and the high fatality rates (43–67%) were indicative of the difficult long-term control and the effect of the underlying disease.^{71,84} Furthermore, one report of isoflurane in RSE raised questions about CNS toxicity, especially in thalamic and cerebellar regions.⁸⁵ The intravenous anaesthetic agent ketamine has been tried in RSE, because of its properties as an NMDA receptor antagonist and favourable hemodynamic profiles. Only a few reports describe the use of ketamine in this setting,

	Advantages	Disadvantages/comments
Isoflurane ⁷¹	Fast acting	Possible neurotoxicity Needs closed system, ie, gas recovery
Ketamine ^{72–75}	NMDA receptor antagonist	Possible neurotoxicity; combine with benzodiazepines
Lidocaine ^{66,77}	Can rescue phenytoin-resistant refractory status epilepticus	Cardiac monitoring needed; possible seizure induction
Verapamil ^{78,79}	Safe	Does not have antiepileptic drug action; might improve availability of antiepileptic drugs in CNS
Magnesium ⁸⁰	Can enhance NMDA receptor blockade	Possible induction of neuromuscular blockade
Ketogenic diet ^{81,82}	Safe	Need skilled dietician; check for ketonuria
Immunological treatments ⁸³	Can act causally	Formal exclusion of infection needed before treatment

Table 2: Other pharmacological and nutritional treatments for refractory status epilepticus

	Advantages	Disadvantages/comments
Resective surgery ¹⁰¹	Can act causally	Not appropriate in multifocal status epilepticus; need for skilled interdisciplinary team; surgical risks
Vagal nerve stimulation ¹⁰²	Appropriate for long-term use	Invasive procedure; cardiac arrhythmias rarely reported
Repetitive transcranial magnetic stimulation ¹⁰³	Non-invasive procedure	Possible seizure induction; need for sustained treatment
Electroconvulsive treatment ^{104,105,106}	Non-invasive procedure	Need for skilled interdisciplinary team; possible seizure induction
Mild hypothermia ¹⁰⁷	Acts on several pathophysiological mechanisms	Usually only transitory control; avoid barbiturates (ileus)
Classical music ¹⁰⁸	No known side-effects	Based on one case series

Table 3: Non-pharmacological options for refractory status epilepticus

with doses of up to 7.5 mg/kg per h for several days, and the outcomes have been mixed.^{72–75} However, ketamine is neurotoxic and this property is thought to be related to the indiscriminate blockade of both extrasynaptic and intrasynaptic NMDA receptors;⁸⁶ thus, some have suggested that ketamine should always be combined with GABAergic drugs^{87,88} because of a possible synergistic effect.⁸⁹

Several other non-sedating pharmacological approaches are available and can be administered intravenously or orally (through the nasogastric tube) as add-on compounds to optimise control of RSE. Topiramate,^{90,91} pregabalin,⁹² levetiracetam,⁹³ and lacosamide⁹⁴ (levetiracetam and lacosamide are increasingly prescribed as second-line drugs) have different and potentially synergistic pharmacodynamic actions. Lidocaine modulates sodium channels. Initial boluses of up to 5 mg/kg and perfusions of up to 6 mg/kg per h have been described,⁷⁶ but serum concentrations above 5 mg/L can induce seizures.⁷⁷ A retrospective survey of 37 children with RSE showed a response to lidocaine in 36%, and no major adverse events; mortality was not reported.⁷⁷ Verapamil might inhibit multidrug transporters that can lower availability of antiepileptic drugs in the brain.⁹⁵ Few case reports on its use in patients are available, but it seems to be safe (with cardiac monitoring) in doses of up to 360 mg per day.^{78,79} Magnesium, which under physiological conditions blocks NMDA receptors, has been mentioned anecdotally in RSE, but with unconvincing results even at serum concentrations of 14 mmol/L,^{83,96} apart from a report of two patients with mitochondrial encephalopathy.⁸⁰ Of note, high doses might induce neuromuscular blockade that could mask clinical seizures. The use of the ketogenic diet, which exerts its pharmacological action through a metabolic shift towards acidosis, in RSE is a recent and possibly promising strategy both in children and adults.^{81,82,97} The diet can be administered through a nasogastric tube and should induce ketonuria; this approach can show its effect within a few days.

Since highly refractory RSE seems to be the result of immunological processes in many instances,^{10,98–100} immunomodulatory treatment is often prescribed in this setting.^{43,83} Steroids, adrenocorticotrophic hormone, plasma exchanges, or intravenous immunoglobulins can be used alone or in sequential combination after the formal exclusion of infectious causes.

Non-pharmacological approaches

Pharmacological treatment can be supported and potentiated by non-pharmacological therapeutic strategies; however, non-pharmacological therapies are mostly last-resort approaches in cases of very refractory SE. The substantial variability in the reports in terms of clinical setting (particularly causes and concomitant therapies) greatly restricts the generalisability of these treatments (table 3).

Resective surgery can be a useful option in selected patients when a definite seizure focus generating the RSE episode can be identified in a non-eloquent brain area.¹⁰¹ Acute vagal nerve stimulation implantation has been suggested to be effective in a few patients.^{102,109,110} Although the stimulation was already initiated in the operating theatre, the intensity was progressively titrated over a few days up to 1.25 mA (with various regimens for the other stimulation indices); transitory bradycardia or asystole can arise in this setting.¹⁰² Low-frequency (0.5–1 Hz) transcranial magnetic stimulation at 90–100% of the resting motor threshold, at times applied after a short (priming) high-frequency stimulation (up to 100 Hz), has been reported to be transiently successful in patients with simple partial SE,^{103,111} although loss of effectiveness after the initial stimulations suggests the need for repetitive use. Electroconvulsive treatment has been applied in cases of highly resistant RSE. Patients were mostly exposed to 1–4 daily sessions of induced electrographic seizures over a few consecutive days, resulting in permanent RSE control in some patients.^{104–106} The antiseizure mechanism of electroconvulsive treatment is unknown.

Brain hypothermia exerts beneficial effects on several pathophysiological axes implicated in acute cerebral injuries. In animal studies of SE, hypothermia reduces seizure severity and epileptic discharges, brain oedema, and apoptosis.¹¹² However, clinical investigations in RSE are limited. Mild hypothermia (31–36°C) together with midazolam, ketamine, or thiopental for one to several days have been reported to control RSE, but seizures can recur after rewarming.^{50,107,113,114} Although side-effects (including electrolyte disturbances, coagulation dysfunction, infections, and cardiac arrhythmia) are infrequent in patients treated with hypothermia after cardiac arrest,¹¹⁵ paralytic ileus can be a challenging complication in patients with SE, especially when barbiturates are coadministered.⁵⁰

The beneficial effect of classical music has recently been reported on both electrographical and clinical parameters

in a few patients with RSE, evident within hours of exposure.¹⁰⁸ The mechanism of action is unknown.

When to stop RSE treatment

Although longlasting RSE generally heralds a poor prognosis, some exceptions exist; patients who have RSE for several days, weeks, or even months can sometimes recover with a good functional outcome.^{15,100,116–118} In some patients, most often those in whom the disorder has an infectious or autoimmune cause, the underlying disease process subsides after some time, allowing awakening of the patient without repetitive seizures. Therefore, supportive treatment, including repetitive courses of anaesthetics if needed, should not be stopped merely because of protracted treatment duration if neuroimaging is normal apart from minor signs of global atrophy¹¹⁸ and no underlying cause heralding a catastrophic prognosis is identified (eg, rapidly progressive brain tumours, paraneoplastic limbic encephalitis with disseminated primary cancer, or prion disease). This course of action applies especially to young patients, who are usually able to tolerate the cardiovascular side-effects of long-term anaesthesia.

RSE in the setting of cerebral anoxia is a controversial issue. This entity does not seem to imply an invariably poor outcome. Although studies confirm that SE occurring during therapeutic hypothermia and sedation, mostly presenting as a seizure-suppression EEG pattern, is a situation in which there is severe brain damage and very poor outcome,^{119,120} SE arising after rewarming can be treated with antiepileptic drugs if the EEG background is reactive and somatosensory evoked potentials and brainstem reflexes are preserved.¹²¹ In these rare cases, survival with reasonable functional outcome has been reported after administration of antiepileptic drugs and at times one course of anaesthetics.¹²¹ Conversely, the outcome remains dismal despite every therapeutic attempt in patients showing severe loss of CNS function and EEG non-reactivity.¹²²

Conclusions and future directions

Refractory SE represents a heterogeneous entity that arises frequently in every hospital setting. There is a strong consensus about the need for an early, effective treatment to prevent morbidity and mortality. In the first hours, it seems reasonable to tune treatment aggressiveness (pharmacological coma induction) according to the clinical subtypes; whereas generalised convulsive SE must be approached aggressively, focal SE and SE related to idiopathic generalised epilepsy (absence and myoclonic forms) can be treated initially with non-sedating agents. In the face of longlasting RSE, which is usually related to particular causes, continuation of supportive treatment is mandatory unless irreversible brain damage is found. Furthermore, cause of SE is a potentially modifiable outcome predictor that should always be specifically addressed.

By contrast with the steadily growing basic science work on SE that continues to provide important insights into underlying mechanisms, disappointingly little evidence exists for current approaches to SE treatment, apart from the first-line option of benzodiazepines.⁴³ This lack of evidence is due to the difficulty and expense of undertaking clinical studies of SE.

Translational strategies bridging animal to human studies, aimed at identification of potential molecular targets for novel treatments, need to be developed, with subsequent proof-of-concept clinical trials to assess the clinical effectiveness of candidate targets. Because SE is a highly heterogeneous entity, a single approach identified from animal models is unlikely to prove decisive. For example, ketamine does not seem to give reliably good results in human beings, as opposed to those in animal models. More than one animal model should be developed to address the multitude of causes associated with SE.

With respect to the general approach to treatment of RSE, whether other factors besides age and cause are independent outcome predictors is unclear. For example, pre-existing comorbidities (modifiable),¹²³ race (not modifiable),² and hospital settings (modifiable)^{124,125} have received scarce attention up to now. Duration of SE has been suggested as a modifiable risk factor, with long duration emphasised as predictive of poor outcome in some studies,^{13,18} but this might instead be indicative of early selection of SE forms that are intrinsically difficult to treat. The extent to which the use of a particular SE treatment protocol allows a better prognosis has only been addressed in one study.⁴² Also, the optimum sequence and timing of initial SE treatment is essentially unexplored.

Apart from these issues, in view of potentially relevant differences in both efficacy¹²⁶ and tolerability,⁶⁴ well designed, multicentre trials assessing medications as second-line and third-line treatments are needed, as are controlled assessments on depth and duration of EEG suppression. As described in the report of an aborted trial investigating third-line treatment,⁶⁴ these studies have failed up to now mainly because of difficulties in obtaining sufficient funding and the need for very many clinical sites for enrolment; for example, a three-armed trial investigating a second-line antiepileptic drug would need about 1000–1500 enrolled patients to detect differences that are potentially clinically relevant. Because a high-volume tertiary centre treats an average of 50–70 adults for SE yearly, and at best a quarter of the

Search strategy and selection criteria

Papers in English, French, and German published between 1966 and May 31, 2011 were searched through PubMed and via cross referencing, with the terms “status epilepticus”, “treatment”, “refractory”, and “therapy”. The final set of papers was selected on the basis of the quality of each publication and the pertinence to this Review.

patients will prove eligible for the study, 50 centres would need to recruit for a minimum of 2 years to complete the trial. Because more questions than answers exist in this discipline, well designed, prospective studies are urgently needed.

Contributors

AOR did the literature search. AOR and DHL interpreted the published works, drafted the Review, and produced the figure.

Conflicts of interest

AOR received research support from Pfizer, UCB, Eisai, and GlaxoSmithKline. DHL serves on the scientific advisory boards of Neurologix and NeuroVista Corporation.

Acknowledgments

We thank Shlomo Shinnar and S Andrew Josephson for valuable advice on various aspects of this paper. This work was supported partly by grant NS056975 from the National Institute of Neurological Disorders and Stroke.

References

- Coeytaux A, Jallon P, Galobardes B, Morabia A. Incidence of status epilepticus in French-speaking Switzerland: (EPISTAR). *Neurology* 2000; **55**: 693–97.
- DeLorenzo RJ, Hauser WA, Towne AR, et al. A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. *Neurology* 1996; **46**: 1029–35.
- Knake S, Rosenow F, Vescevi M, et al, for the Status Epilepticus Study Group Hessen. Incidence of status epilepticus in adults in Germany: a prospective, population-based study. *Epilepsia* 2001; **42**: 714–18.
- Lowenstein DH, Alldredge BK. Status epilepticus. *N Engl J Med* 1998; **338**: 970–76.
- Holtkamp M. Treatment strategies for refractory status epilepticus. *Curr Opin Crit Care* 2011; **17**: 94–100.
- Novy J, Logroscino G, Rossetti AO. Refractory status epilepticus: a prospective observational study. *Epilepsia* 2010; **51**: 251–56.
- Holtkamp M, Othman J, Buchheim K, Meierkord H. Predictors and prognosis of refractory status epilepticus treated in a neurological intensive care unit. *J Neurol Neurosurg Psychiatry* 2005; **76**: 534–9.
- Mayer SA, Claassen J, Lokin J, Mendelsohn F, Dennis LJ, Fitzsimmons BF. Refractory status epilepticus: frequency, risk factors, and impact on outcome. *Arch Neurol* 2002; **59**: 205–10.
- Rossetti AO, Logroscino G, Bromfield EB. Refractory status epilepticus: effect of treatment aggressiveness on prognosis. *Arch Neurol* 2005; **62**: 1698–702.
- Holtkamp M, Othman J, Buchheim K, Masuhr F, Schielke E, Meierkord H. A malignant variant of status epilepticus. *Arch Neurol* 2005; **62**: 1428–31.
- Logroscino G, Hesdorffer DC, Cascino G, Annegers JF, Hauser WA. Short-term mortality after a first episode of status epilepticus. *Epilepsia* 1997; **38**: 1344–49.
- Rossetti AO, Hurwitz S, Logroscino G, Bromfield EB. Prognosis of status epilepticus: role of aetiology, age, and consciousness impairment at presentation. *J Neurol Neurosurg Psychiatry* 2006; **77**: 611–15.
- Towne AR, Pellock JM, Ko D, DeLorenzo RJ. Determinants of mortality in status epilepticus. *Epilepsia* 1994; **35**: 27–34.
- Neligan A, Shorvon SD. Prognostic factors, morbidity and mortality in tonic-clonic status epilepticus: a review. *Epilepsy Res* 2011; **93**: 1–10.
- Drislane FW, Blum AS, Lopez MR, Gautam S, Schomer DL. Duration of refractory status epilepticus and outcome: loss of prognostic utility after several hours. *Epilepsia* 2009; **50**: 1566–71.
- Hesdorffer DC, Logroscino G, Cascino G, Annegers JF, Hauser WA. Risk of unprovoked seizure after acute symptomatic seizure: effect of status epilepticus. *Ann Neurol* 1998; **44**: 908–12.
- Adachi N, Kanemoto K, Muramatsu R, et al. Intellectual prognosis of status epilepticus in adult epilepsy patients: analysis with Wechsler Adult Intelligence Scale-revised. *Epilepsia* 2005; **46**: 1502–09.
- Legriel S, Azoulay E, Resche-Rigon M, et al. Functional outcome after convulsive status epilepticus. *Crit Care Med* 2010; **38**: 2295–303.
- Chen JW, Wasterlain CG. Status epilepticus: pathophysiology and management in adults. *Lancet Neurol* 2006; **5**: 246–56.
- Bleck TP. Refractory status epilepticus. *Curr Opin Crit Care* 2005; **11**: 117–20.
- Lowenstein DH. The management of refractory status epilepticus: an update. *Epilepsia* 2006; **47** (suppl 1): 35–40.
- Meierkord H, Holtkamp M. Non-convulsive status epilepticus in adults: clinical forms and treatment. *Lancet Neurol* 2007; **6**: 329–39.
- 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**: 792–98.
- Treiman DM, Walton NY, Collins JF, Point P. Treatment of status epilepticus if first drug fails. *Epilepsia* 1999; **40** (suppl 7): 243.
- Walton NY. Systemic effects of generalized convulsive status epilepticus. *Epilepsia* 1993; **34** (suppl 1): S54–58.
- Lothman E. The biochemical basis and pathophysiology of status epilepticus. *Neurology* 1990; **40** (suppl 2): 13–23.
- Meldrum BS, Horton RW. Physiology of status epilepticus in primates. *Arch Neurol* 1973; **28**: 1–9.
- Mazarati AM, Baldwin RA, Sankar R, Wasterlain CG. Time-dependent decrease in the effectiveness of antiepileptic drugs during the course of self-sustaining status epilepticus. *Brain Res* 1998; **814**: 179–85.
- Mazarati AM, Wasterlain CG. N-methyl-D-aspartate receptor antagonists abolish the maintenance phase of self-sustaining status epilepticus in rat. *Neurosci Lett* 1999; **265**: 187–90.
- Kapur J, Lothman EW. NMDA receptor activation mediates the loss of GABAergic inhibition induced by recurrent seizures. *Epilepsy Res* 1990; **5**: 103–11.
- Goodkin HP, Yeh JL, Kapur J. Status epilepticus increases the intracellular accumulation of GABA_A receptors. *J Neurosci* 2005; **25**: 5511–20.
- Poston KL, Frucht SJ. Movement disorder emergencies. *J Neurol* 2008; **255** (suppl 4): 2–13.
- LaFrance WC Jr. Psychogenic nonepileptic seizures. *Curr Opin Neurol* 2008; **21**: 195–201.
- Reuber M, Baker GA, Gill R, Smith DF, Chadwick DW. Failure to recognize psychogenic nonepileptic seizures may cause death. *Neurology* 2004; **62**: 834–35.
- Holtkamp M, Othman J, Buchheim K, Meierkord H. Diagnosis of psychogenic nonepileptic status epilepticus in the emergency setting. *Neurology* 2006; **66**: 1727–29.
- Dworetzky BA, Mortati KA, Rossetti AO, Vaccaro B, Nelson A, Bromfield EB. Clinical characteristics of psychogenic nonepileptic seizure status in the long-term monitoring unit. *Epilepsy Behav* 2006; **9**: 335–38.
- Outin H, Blanc T, Vinatier I. Emergency and intensive care unit management of status epilepticus in adult patients and children (new-born excluded). Société de réanimation de langue française experts recommendations. *Rev Neurol (Paris)* 2009; **165**: 297–305 (in French).
- Meierkord H, Boon P, Engelsens B, et al, for the European Federation of Neurological Societies. EFNS guideline on the management of status epilepticus in adults. *Eur J Neurol* 2010; **17**: 348–55.
- 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**: 631–37.
- Leppik IE, Derivan AT, Homan RW, Walker J, Ramsay RE, Patrick B. Double-blind study of lorazepam and diazepam in status epilepticus. *JAMA* 1983; **249**: 1452–54.
- Prasad K, Al-Roomi K, Krishnan PR, Sequeira R. Anticonvulsant therapy for status epilepticus. *Cochrane Database Syst Rev* 2005; **4**: CD003723.
- Aranda A, Foucart G, Ducassé JL, Grolleau S, McGonigal A, Valton L. Generalized convulsive status epilepticus management in adults: a cohort study with evaluation of professional practice. *Epilepsia* 2010; **51**: 2159–67.
- Shorvon S. The treatment of status epilepticus. *Curr Opin Neurol* 2011; **24**: 165–70.
- Genton P, Ferlazzo E, Thomas P. Absence status epilepsy: delineation of a distinct idiopathic generalized epilepsy syndrome. *Epilepsia* 2008; **49**: 642–49.

- 45 Aminoff MJ. Do nonconvulsive seizures damage the brain?—No. *Arch Neurol* 1998; **55**: 119–20.
- 46 Drislane FW. Evidence against permanent neurologic damage from nonconvulsive status epilepticus. *J Clin Neurophysiol* 1999; **16**: 323–31.
- 47 Jordan KG, Hirsch LJ. In nonconvulsive status epilepticus (NCSE), treat to burst-suppression: pro and con. *Epilepsia* 2006; **47** (suppl 1): 41–45.
- 48 Kaplan PW. No, some types of nonconvulsive status epilepticus cause little permanent neurologic sequelae (or: the cure may be worse than the disease). *Neurophysiol Clin* 2000; **30**: 377–82.
- 49 Young GB, Jordan KG. Do nonconvulsive seizures damage the brain?—Yes. *Arch Neurol* 1998; **55**: 117–19.
- 50 Cereda C, Berger MM, Rossetti AO. Bowel ischemia: a rare complication of thiopental treatment for status epilepticus. *Neurocrit Care* 2009; **10**: 355–58.
- 51 Rossetti AO, Logroscino G, Bromfield EB. A clinical score for prognosis of status epilepticus in adults. *Neurology* 2006; **66**: 1736–38.
- 52 Rossetti AO, Logroscino G, Milligan TA, Michaelides C, Ruffieux C, Bromfield EB. Status Epilepticus Severity Score (STESS): a tool to orient early treatment strategy. *J Neurol* 2008; **255**: 1561–66.
- 53 Holtkamp M. The anaesthetic and intensive care of status epilepticus. *Curr Opin Neurol* 2007; **20**: 188–93.
- 54 Rossetti AO. Treatment options in the management of status epilepticus. *Curr Treat Options Neurol* 2010; **12**: 100–12.
- 55 Miller LC, Drislane FW. Treatment of status epilepticus. *Expert Rev Neurother* 2008; **8**: 1817–27.
- 56 Rossetti AO. Which anesthetic should be used in the treatment of refractory status epilepticus? *Epilepsia* 2007; **48** (suppl 8): 52–55.
- 57 Claassen J, Hirsch LJ, Emerson RG, Bates JE, Thompson TB, Mayer SA. Continuous EEG monitoring and midazolam infusion for refractory nonconvulsive status epilepticus. *Neurology* 2001; **57**: 1036–42.
- 58 Marik PE. Propofol: therapeutic indications and side-effects. *Curr Pharm Des* 2004; **10**: 3639–49.
- 59 Vasile B, Rasulo F, Candiani A, Latronico N. The pathophysiology of propofol infusion syndrome: a simple name for a complex syndrome. *Intensive Care Med* 2003; **29**: 1417–25.
- 60 Zarovnya EL, Jobst BC, Harris BT. Propofol-associated fatal myocardial failure and rhabdomyolysis in an adult with status epilepticus. *Epilepsia* 2007; **48**: 1002–06.
- 61 Iyer VN, Hoel R, Rabinstein AA. Propofol infusion syndrome in patients with refractory status epilepticus: an 11-year clinical experience. *Crit Care Med* 2009; **37**: 3024–30.
- 62 Rossetti AO, Reichhart MD, Schaller MD, Despland PA, Bogousslavsky J. Propofol treatment of refractory status epilepticus: a study of 31 episodes. *Epilepsia* 2004; **45**: 757–63.
- 63 Parviainen I, Uusaro A, Kalviainen R, Mervaala E, Ruokonen E. Propofol in the treatment of refractory status epilepticus. *Intensive Care Med* 2006; **32**: 1075–79.
- 64 Rossetti AO, Milligan TA, Vuilleumoz S, Michaelides C, Bertschi M, Lee JW. A randomized trial for the treatment of refractory status epilepticus. *Neurocrit Care* 2011; **14**: 4–10.
- 65 Zhan RZ, Qi S, Wu C, Fujihara H, Taga K, Shimoji K. Intravenous anesthetics differentially reduce neurotransmission damage caused by oxygen-glucose deprivation in rat hippocampal slices in correlation with N-methyl-D-aspartate receptor inhibition. *Crit Care Med* 2001; **29**: 808–13.
- 66 Claassen J, Hirsch LJ, Emerson RG, Mayer SA. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. *Epilepsia* 2002; **43**: 146–53.
- 67 Musialowicz T, Mervaala E, Kalviainen R, Uusaro A, Ruokonen E, Parviainen I. Can BIS monitoring be used to assess the depth of propofol anesthesia in the treatment of refractory status epilepticus? *Epilepsia* 2010; **51**: 1580–86.
- 68 Krishnamurthy KB, Drislane FW. Depth of EEG suppression and outcome in barbiturate anesthetic treatment for refractory status epilepticus. *Epilepsia* 1999; **40**: 759–62.
- 69 Rossetti AO, Oddo M. The neuro-ICU patient and electroencephalography paroxysms: if and when to treat. *Curr Opin Crit Care* 2010; **16**: 105–09.
- 70 Bauer G, Trinka E. Nonconvulsive status epilepticus and coma. *Epilepsia* 2010; **51**: 177–90.
- 71 Mirsattari SM, Sharpe MD, Young GB. Treatment of refractory status epilepticus with inhalational anesthetic agents isoflurane and desflurane. *Arch Neurol* 2004; **61**: 1254–59.
- 72 Sheth RD, Gidal BE. Refractory status epilepticus: response to ketamine. *Neurology* 1998; **51**: 1765–66.
- 73 Quigg M, Nathan B, Smith T, Kapur J. Effects of ketamine treatment for refractory status epilepticus. *Epilepsia* 2002; **43** (suppl 1): 282.
- 74 Prüss H, Holtkamp M. Ketamine successfully terminates malignant status epilepticus. *Epilepsy Res* 2008; **82**: 219–22.
- 75 Hsieh CY, Sung PS, Tsai JJ, Huang CW. Terminating prolonged refractory status epilepticus using ketamine. *Clin Neuropharmacol* 2010; **33**: 165–67.
- 76 Walker IA, Slovis CM. Lidocaine in the treatment of status epilepticus. *Acad Emerg Med* 1997; **4**: 918–22.
- 77 Hamano S, Sugiyama N, Yamashita S, et al. Intravenous lidocaine for status epilepticus during childhood. *Dev Med Child Neurol* 2006; **48**: 220–22.
- 78 Iannetti P, Spalice A, Parisi P. Calcium-channel blocker verapamil administration in prolonged and refractory status epilepticus. *Epilepsia* 2005; **46**: 967–69.
- 79 Schmitt FC, Dehnicke C, Merschhemke M, Meencke HJ. Verapamil attenuates the malignant treatment course in recurrent status epilepticus. *Epilepsy Behav* 2010; **17**: 565–88.
- 80 Visser NA, Braun KP, Leijten FS, van Nieuwenhuizen O, Wokke JH, van den Bergh WM. Magnesium treatment for patients with refractory status epilepticus due to POLG1-mutations. *J Neurol* 2011; **258**: 218–22.
- 81 Nababout R, Mazzuca M, Hubert P, et al. Efficacy of ketogenic diet in severe refractory status epilepticus initiating fever induced refractory epileptic encephalopathy in school age children (FIRES). *Epilepsia* 2010; **51**: 2033–37.
- 82 Wusthoff CJ, Kranick SM, Morley JF, Christina Bergqvist AG. The ketogenic diet in treatment of two adults with prolonged nonconvulsive status epilepticus. *Epilepsia* 2010; **51**: 1083–85.
- 83 Robakis TK, Hirsch LJ. Literature review, case report, and expert discussion of prolonged refractory status epilepticus. *Neurocrit Care* 2006; **4**: 35–46.
- 84 Kofke WA, Young RS, Davis P, et al. Isoflurane for refractory status epilepticus: a clinical series. *Anesthesiology* 1989; **71**: 653–59.
- 85 Fugate JE, Burns JD, Wijdicks EF, Warner DO, Jankowski CJ, Rabinstein AA. Prolonged high-dose isoflurane for refractory status epilepticus: is it safe? *Anesth Analg* 2010; **111**: 1520–24.
- 86 Benarroch EE. NMDA receptors: recent insights and clinical correlations. *Neurology* 2011; **76**: 1750–57.
- 87 Ubogu EE, Sagar SM, Lerner AJ, Maddux BN, Suarez JI, Werz MA. Ketamine for refractory status epilepticus: a case of possible ketamine-induced neurotoxicity. *Epilepsy Behav* 2003; **4**: 70–75.
- 88 Jevtovic-Todorovic V, Wozniak DF, Powell S, Olney JW. Propofol and sodium thiopental protect against MK-801-induced neuronal necrosis in the posterior cingulate/retrosplenial cortex. *Brain Res* 2001; **913**: 185–89.
- 89 Martin BS, Kapur J. A combination of ketamine and diazepam synergistically controls refractory status epilepticus induced by cholinergic stimulation. *Epilepsia* 2008; **49**: 248–55.
- 90 Towne AR, Garnett LK, Waterhouse EJ, Morton LD, DeLorenzo RJ. The use of topiramate in refractory status epilepticus. *Neurology* 2003; **60**: 332–34.
- 91 Stojanova V, Rossetti AO. Oral topiramate as an add-on treatment for refractory status epilepticus. *Acta Neurol Scand* 2011; published online June 29. DOI:10.1111/j.1600-0404.2011.01562.x.
- 92 Novy J, Rossetti AO. Oral pregabalin as an add-on treatment for status epilepticus. *Epilepsia* 2010; **51**: 2207–10.
- 93 Knake S, Gruener J, Hattemer K, et al. Intravenous levetiracetam in the treatment of benzodiazepine refractory status epilepticus. *J Neurol Neurosurg Psychiatry* 2008; **79**: 588–89.
- 94 Kellinghaus C, Berning S, Immisch I, et al. Intravenous lacosamide for treatment of status epilepticus. *Acta Neurol Scand* 2011; **123**: 137–41.
- 95 Potschka H, Fedorowicz M, Loscher W. P-Glycoprotein-mediated efflux of phenobarbital, lamotrigine, and felbamate at the blood-brain barrier: evidence from microdialysis experiments in rats. *Neurosci Lett* 2002; **327**: 173–76.

- 96 Fisher RS, Kaplan PW, Krumholz A, Lesser RP, Rosen SA, Wolff MR. Failure of high-dose intravenous magnesium sulfate to control myoclonic status epilepticus. *Clin Neuropharmacol* 1988; **11**: 537–44.
- 97 Bodenant M, Moreau C, Sejourne C, et al. Interest of the ketogenic diet in a refractory status epilepticus in adults. *Rev Neurol (Paris)* 2008; **164**: 194–99 (in French).
- 98 Glaser CA, Gilliam S, Honarmand S, Tureen JH, Lowenstein DH, Anderson LJ, et al. Refractory status epilepticus in suspect encephalitis. *Neurocrit Care* 2008; **9**: 74–82.
- 99 Johnson N, Henry C, Fessler AJ, Dalmau J. Anti-NMDA receptor encephalitis causing prolonged nonconvulsive status epilepticus. *Neurology* 2010; **75**: 1480–82.
- 100 Maeder-Ingvær M, Prior JO, Irani SR, Rey V, Vincent A, Rossetti AO. FDG-PET hyperactivity in basal ganglia correlating with clinical course in anti-NMDA-R antibodies encephalitis. *J Neurol Neurosurg Psychiatry* 2010; **82**: 235–36.
- 101 Lhatoo SD, Alexopoulos AV. The surgical treatment of status epilepticus. *Epilepsia* 2007; **48** (suppl 8): 61–65.
- 102 De Herdt V, Waterschoot L, Vonck K, et al. Vagus nerve stimulation for refractory status epilepticus. *Eur J Paediatr Neurol* 2009; **13**: 286–89.
- 103 Rotenberg A, Bae EH, Takeoka M, Tormos JM, Schachter SC, Pascual-Leone A. Repetitive transcranial magnetic stimulation in the treatment of epilepsy partialis continua. *Epilepsy Behav* 2009; **14**: 253–57.
- 104 Kamel H, Cornes SB, Hegde M, Hall SE, Josephson SA. Electroconvulsive therapy for refractory status epilepticus: a case series. *Neurocrit Care* 2010; **12**: 204–10.
- 105 Shin HW, O'Donovan CA, Boggs JG, et al. Successful ECT treatment for medically refractory nonconvulsive status epilepticus in pediatric patient. *Seizure* 2011; **20**: 433–36.
- 106 Cline JS, Roos K. Treatment of status epilepticus with electroconvulsive therapy. *J ECT* 2007; **23**: 30–32.
- 107 Corry JJ, Dhar R, Murphy T, Diringer MN. Hypothermia for refractory status epilepticus. *Neurocrit Care* 2008; **9**: 189–97.
- 108 Miranda M, Kuester G, Ríos L, Basaez E, Hazard S. Refractory nonconvulsive status epilepticus responsive to music as an add-on therapy: a second case. *Epilepsy Behav* 2010; **19**: 539–40.
- 109 Patwardhan RV, Dellabadia J Jr, Rashidi M, Grier L, Nanda A. Control of refractory status epilepticus precipitated by anticonvulsant withdrawal using left vagal nerve stimulation: a case report. *Surg Neurol* 2005; **64**: 170–73.
- 110 Winston KR, Levisohn P, Miller BR, Freeman J. Vagal nerve stimulation for status epilepticus. *Pediatr Neurosurg* 2001; **34**: 190–92.
- 111 Misawa S, Kuwabara S, Shibuya K, Mamada K, Hattori T. Low-frequency transcranial magnetic stimulation for epilepsy partialis continua due to cortical dysplasia. *J Neurol Sci* 2005; **234**: 37–39.
- 112 Schmitt FC, Buchheim K, Meierkord H, Holtkamp M. Anticonvulsant properties of hypothermia in experimental status epilepticus. *Neurobiol Dis* 2006; **23**: 689–96.
- 113 Orlowski JP, Erenberg G, Lueders H, Cruse RP. Hypothermia and barbiturate coma for refractory status epilepticus. *Crit Care Med* 1984; **12**: 367–72.
- 114 Elting JW, Naalt J, Fock JM. Mild hypothermia for refractory focal status epilepticus in an infant with hemimegalencephaly. *Eur J Paediatr Neurol* 2010; **14**: 452–55.
- 115 Holzer M. Targeted temperature management for comatose survivors of cardiac arrest. *N Engl J Med* 2010; **363**: 1256–64.
- 116 Cooper AD, Britton JW, Rabinstein AA. Functional and cognitive outcome in prolonged refractory status epilepticus. *Arch Neurol* 2009; **66**: 1505–09.
- 117 Costello DJ, Kilbride RD, Cole AJ. Cryptogenic New Onset Refractory Status Epilepticus (NORSE) in adults—infectious or not? *J Neurol Sci* 2009; **277**: 26–31.
- 118 Dara SI, Tungpalan LA, Manno EM, et al. Prolonged coma from refractory status epilepticus. *Neurocrit Care* 2006; **4**: 140–42.
- 119 Rossetti AO, Urbano LA, Delodder F, Kaplan PW, Oddo M. Prognostic value of continuous EEG monitoring during therapeutic hypothermia after cardiac arrest. *Crit Care* 2010; **14**: R173.
- 120 Thenayan EA, Savard M, Sharpe MD, Norton L, Young B. Electroencephalogram for prognosis after cardiac arrest. *J Crit Care* 2010; **25**: 300–04.
- 121 Rossetti AO, Oddo M, Liaudet L, Kaplan PW. Predictors of awakening from postanoxic status epilepticus after therapeutic hypothermia. *Neurology* 2009; **72**: 744–49.
- 122 Thömke F, Weilemann SL. Poor prognosis despite successful treatment of postanoxic generalized myoclonus. *Neurology* 2010; **74**: 1392–94.
- 123 Koubeissi M, Alshekhlee A. In-hospital mortality of generalized convulsive status epilepticus: a large US sample. *Neurology* 2007; **69**: 886–93.
- 124 Rossetti AO, Novy J, Ruffieux C, Olivier P, Foletti GB, Hayoz D, et al. Management and prognosis of status epilepticus according to hospital setting: a prospective study. *Swiss Med Wkly* 2009; **139**: 719–23.
- 125 Vignatelli L, Rinaldi R, Baldin E, Tinuper P, Michelucci R, Galeotti M, et al. Impact of treatment on the short-term prognosis of status epilepticus in two population-based cohorts. *J Neurol* 2008; **255**: 197–204.
- 126 Alvarez V, Januel JM, Burnand B, Rossetti AO. Second-line status epilepticus treatment: comparison of phenytoin, valproate, and levetiracetam. *Epilepsia* 2011; **52**: 1292–96.