

REVIEW ARTICLE

The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol

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Super-refractory status epilepticus is defined as status epilepticus that continues or recurs 24 h or more after the onset of anaesthetic therapy, including those cases where status epilepticus recurs on the reduction or withdrawal of anaesthesia. It is an uncommon but important clinical problem with high mortality and morbidity rates. This article reviews the treatment approaches. There are no controlled or randomized studies, and so therapy has to be based on clinical reports and opinion. The published world literature on the following treatments was critically evaluated: anaesthetic agents, anti-epileptic drugs, magnesium infusion, pyridoxine, steroids and immunotherapy, ketogenic diet, hypothermia, emergency resective neurosurgery and multiple subpial transection, transcranial magnetic stimulation, vagal nerve stimulation, deep brain stimulation, electroconvulsive therapy, drainage of the cerebrospinal fluid and other older drug therapies. The importance of treating the identifying cause is stressed. A protocol and flowchart for managing super-refractory status epilepticus is suggested. In view of the small number of published reports, there is an urgent need for the establishment of a database of outcomes of individual therapies.

Keywords: status epilepticus; treatment; refractory; super-refractory

Abbreviations: GABA = γ -aminobutyric acid; PRIS = propofol infusion syndrome

Introduction

Tonic-clonic status epilepticus is a medical emergency. Treatment is aimed at stopping seizures largely in order to avoid cerebral damage and other morbidity.

All contemporary protocols take a staged approach to treatment (Fig. 1). Typically, in Stage 1 (early status epilepticus), therapy is with benzodiazepines. If seizures continue despite this therapy, the patient is said to be in Stage 2 (established status epilepticus) and therapy is with intravenous anti-epileptic drugs such as phenytoin, phenobarbital or valproate. If seizures continue despite this

treatment for up to 2 h, the patient is said to be in Stage 3 (refractory status epilepticus) and general anaesthesia is usually recommended, at a dose that results in EEG burst suppression (a level of anaesthesia at which all seizure activity is usually controlled). It is interesting in passing to note that anaesthesia has been recommended since the mid-19th century, and John Hughlings Jackson (who is commemorated in this issue of *Brain*) for instance writes that 'chloral is the best drug; and if the fits are very frequent, etherisation will help' (Hughlings Jackson, 1888).

A protocol such as this (albeit with variations) has been recommended on numerous occasions in the past three decades

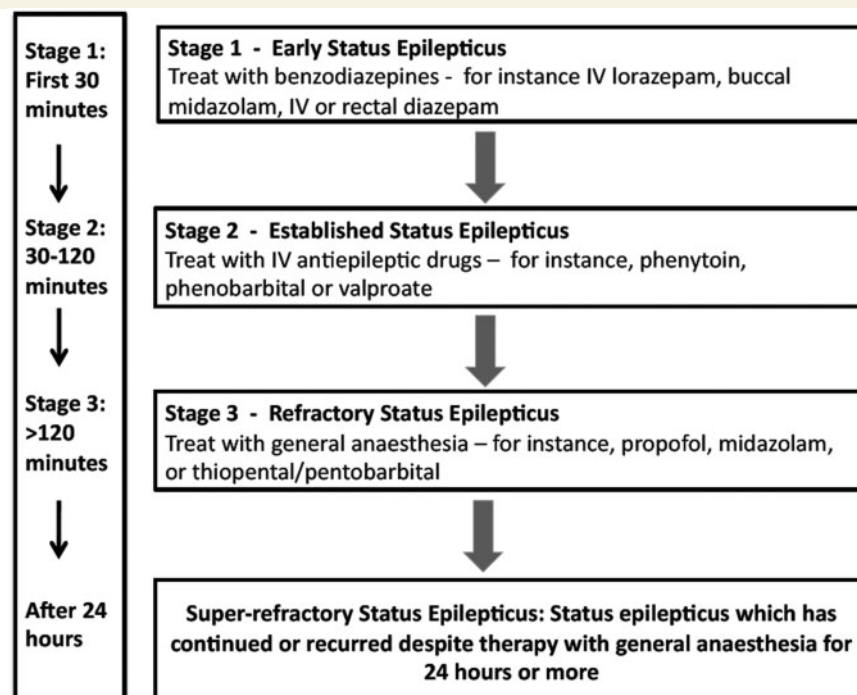


Figure 1 The stages of treatment of status epilepticus. It is universal practice to stage therapy of status epilepticus. A typical protocol is summarized above. If Stage 1 therapy is ineffective after 30 min, Stage 2 therapy is initiated, and if this is ineffective within 2 h, Stage 3 therapy with general anaesthesia is instituted. Status epilepticus that has either not responded or has recurred 24 h after the initiation of anaesthetic therapy can be considered to have reached the stage of 'super-refractory status epilepticus'. IV = intravenous.

(Delgado-Escueta *et al.*, 1984; EFA Working Group, 1993; Shorvon, 1994; Appleton *et al.*, 2000; SIGN, 2003; Meierkord *et al.*, 2006, 2010; Minicucci *et al.*, 2006; Shorvon *et al.*, 2008).

In most patients, this treatment regimen is sufficient to control the seizures. In some though seizures continue or recur. Super-refractory status epilepticus is defined as status epilepticus that continues or recurs 24 h or more after the onset of anaesthetic therapy, including those cases that recur on the reduction or withdrawal of anaesthesia. It was a term used first in the Third London-Innsbruck Colloquium on status epilepticus held in Oxford on 7–9th April 2011 (Shorvon and Trinka, 2011).

Super-refractory status epilepticus is not uncommonly encountered in neurointensive care, but its exact frequency is not known. In the only prospective study, 22% of all the cases with status epilepticus (29 of 108 cases) admitted to hospital failed to respond to first and second lines of therapy, and of these, 41% (12 cases) required coma induction (however, it should be noted that only 47 of the 108 patients had convulsive status epilepticus and presumably it is mainly in these in whom coma induction was needed). Other retrospective studies have shown that 12–43% of the cases with status epilepticus become refractory (Lowenstein and Aldredge, 1993; Mayer *et al.*, 2002; Holtkamp *et al.*, 2005; Rosetti *et al.*, 2005). In the series of 35 patients of Holtkamp *et al.* (2005), seven (20%) recurred within 5 days of tapering the anaesthetic drug and in all other studies at least 50% of those requiring anaesthesia will become super-refractory. From these published findings, it can be estimated that ~15% of all the cases with status epilepticus admitted to hospital will become super-refractory. All neurologists are likely to be involved

with the care of patients with super-refractory status epilepticus, or consulted by their intensivist colleagues about how best to proceed in this situation. The treatment of this issue is a *terra incognita* from the point of view of evidence-based medicine, yet a landscape where action is required. This review outlines available approaches for treatment and medical management of patients in what can be a dire clinical predicament.

Why does status epilepticus become super-refractory?

This question is obviously crucial to successful management. It is a common clinical experience that the more severe the precipitating insult (for instance, in status epilepticus after trauma infection or stroke), the more likely is the status epilepticus to become super-refractory. However, super-refractory status epilepticus also occurs frequently in previously healthy patients without obvious cause.

In all these cases, the processes that normally terminate seizures have proved insufficient (for review, see Lado and Moshe, 2008). At a cellular level, one of the most interesting recent discoveries has been the recognition that receptors on the surface of axons are in a highly dynamic state, moving onto (externalization), away from (internalization) and along the axonal membrane. This 'receptor trafficking' intensifies during status epilepticus, and the overall effect is a reduction in the number of functional γ -aminobutyric acid (GABA) receptors in the cells affected in the seizure discharge (Arancibia and Kittler, 2009; Smith and Kittler, 2010). As GABA is the principle inhibitory transmitter, this reduction in GABAergic activity may be an important reason for seizures to become

persistent. Furthermore, the number of glutaminergic receptors at the cell surface increases, and the reduction in the density of the GABA receptors is itself triggered it seems by activation of the glutaminergic receptor systems. Why this should happen is unknown, and from the epilepsy point of view is certainly maladaptive. This loss of GABAergic receptor density is also the likely reason for the increasing ineffectiveness of GABAergic drugs (such as benzodiazepines or barbiturates) in controlling seizures as the status epilepticus becomes prolonged (Macdonald and Kapur, 1999). It has also been repeatedly shown that the extracellular ionic environment, which can change in status epilepticus, may be an important factor in perpetuating seizures, and the normally inhibitory GABA(A)-mediated currents may become excitatory with changes in extracellular chloride concentrations (Lamsa and Taira, 2003).

Other cellular events might also be important. Mitochondrial failure or insufficiency may be one reason for the failure of seizure termination and cellular damage and mitochondrial processes are involved in cell necrosis and apoptosis (Cock *et al.*, 2002). Another category of disease triggering persistent status epilepticus is inflammatory disease (Tan *et al.*, 2010), and inflammatory processes may be important in the persistence of status epilepticus. The opening of the blood–brain barrier almost certainly plays a major role in the perpetuation of seizures, due to a variety of possible mechanisms (Friedman and Dingledine, 2011), and this may be especially the case in status epilepticus due to inflammation (Marchi *et al.*, 2011). This may explain the benefits of steroids in the therapy of status epilepticus. Leakage of the blood–brain barrier will also lead to higher potassium levels and excitation (David *et al.*, 2009). No genetic mechanism has been identified to explain the failure of seizure termination although massive changes in gene expression occur within minutes of the onset of status epilepticus.

At a systems level, it has been suggested rather fascinatingly and counter intuitively that status epilepticus results from a failure to synchronize seizure activity (Schindler *et al.*, 2007a, b; Walker, 2011), and that the lack of synchrony somehow prevents seizure termination.

These mechanisms influence strategies for therapy. However, often overriding is the importance of establishing cause of the status epilepticus, for emergency therapy directed at the cause may be crucial in terminating the episode (for review of the influence of aetiology on prognosis, see Neligan and Shorvon, 2011).

Cerebral damage induced by status epilepticus

The cerebral damage of status epilepticus includes neuronal cell necrosis, gliosis and network reorganization. The classic work by Meldrum and colleagues (1973a, b) suggested that the major initiating process causing cell death was excitotoxicity (as opposed to anoxia or hypoglycaemia for instance; for review see Meldrum, 1991). The process is driven by massive glutaminergic receptor over-activity, which accompanies continuous seizures. This causes calcium influx into the cells that triggers a cascade of harmful processes resulting in necrosis or apoptosis. This cascade is

usually initiated after a few hours of continuous seizure activity, and it is because of this that the recommendation is made to initiate anaesthesia after seizures have persisted for >1–2 h. The processes induced by this cascade, however, may occur rapidly over minutes or take weeks to take full effect, and these include mitochondrial dysfunction, oxidative stress, release of neurotrophins and neurohormones, inflammatory reactions, dendritic remodelling, neuromodulation, immunosuppression and the activation of several molecular signalling pathways that mediate programmed death (Löscher and Brandt, 2010). In the longer term, structure changes and histological changes include neurogenesis and angiogenesis (Pitkanen and Lukasiuk, 2009, 2011).

To prevent excitotoxicity, all electrographic activity should be suppressed and so anaesthesia is usually recommended to be administered at a dose that achieves the level of EEG burst suppression (a depth of anaesthesia that has usually been found sufficient to stop EEG epileptic activity; Amzica, 2011). A number of neuroprotective strategies have been suggested to prevent the consequences of the excitotoxicity cascade, and some have been incorporated into therapy (for instance, hypothermia, barbiturate, steroids and ketamine), although how these influence outcome clinically is not known.

Aims of treatment in super-refractory status epilepticus

The primary aim of treatment in the earlier phases of status epilepticus is to control seizures with the objective of preventing initial excitotoxicity. In super-refractory status epilepticus, this also remains an objective but it should be recognized that, after 24 h of continuous or recurring seizures, the excitotoxic processes causing cerebral damage are very likely already to have been initiated—and to what extent further control of seizures can prevent the damage caused by the direct processes of excitotoxicity is unknown.

A second aim is neuroprotection—an attempt to block the progression over time of the secondary processes triggered by initial excitotoxicity.

A third aim, as the episode of status epilepticus becomes prolonged, is the need to avoid or treat the systemic complications of prolonged unconsciousness and of prolonged anaesthesia.

The mortality rate of status epilepticus increases the longer the episode continues (for review, see Neligan and Shorvon, 2011), with death being due to a range of complications both of the status epilepticus and also its treatment. These complications include: hypotension, cardiorespiratory collapse and failure, hepatic failure, renal failure, acute hypersensitivity and allergic reactions, disseminated intravascular coagulation and disorders of bleeding, infection, rhabdomyolysis, ileus and gastrointestinal disturbance and intensive treatment unit neuropathy.

The evidence base of treatment

Super-refractory status epilepticus is uncommon but not rare and yet is ill-studied. We carried out a literature search of all papers reporting therapy in refractory status epilepticus, and we also

searched the reference lists of relevant review articles and book chapters and identified 159 papers that form the evidence base for therapy (some papers describing several therapies). These covered all the therapeutic approaches discussed in this article, and we have critically reviewed these reports. The articles identified for each treatment are shown in the Supplementary material.

It is salutary to note that there is only one randomized or controlled study of any of these therapies (a trial comparing thiopental and midazolam). However, the trial required 150 patients for adequate power and recruited only 24 patients (Rosetti *et al.*, 2011). Apart from this, the evidence base consists entirely of single case reports or small series. None of the widely recommended drugs or treatment approaches has been subjected to any sort of systematic review (Table 1), despite their adoption worldwide. This is an unsatisfactory state of affairs.

Moreover, where outcome has been reported, it is usually of seizure control and/or mortality and few have focused on other aspects of outcome such as cognitive change or continuing epilepsy, or the prevention of complications or neuroprotection.

The dangers of the condition though are clear from one published series of outcome in patients with super-refractory status epilepticus. This series was collected retrospectively from an intensive treatment unit setting, and patients were included where status had continued for 7 days or more (Cooper *et al.*, 2009). Fourteen cases were identified, eight of whom had presented with status *de novo* without a previous history of epilepsy, and in

whom an acute structural cause was evident in seven. In one case, no cause was discovered. The patients were treated with anaesthesia (usually midazolam or barbiturate) and anti-epileptic drugs. All developed complications and six patients died in hospital. The median duration of the intensive treatment unit stay was 21 days (range 7–97 days). Among the survivors, all were in a poor functional state on discharge (and some vegetative). Follow-up data were sparse but some patients showed significant improvement over time. It is against this rather dismal background that treatment strategies should be tested.

The treatment of super-refractory status epilepticus

Establishing the cause of the status epilepticus

The greatest influence on the outcome of status epilepticus is the underlying cause (Tan *et al.*, 2010; Nelligan and Shorvon, 2011). Where possible, the cause of the status epilepticus must therefore be identified and treated appropriately. Failure to do so may result in the persistence of the status, worsening complications and a worse overall outcome.

Super-refractory status epilepticus is usually due to a severe brain insult (e.g. trauma, infection and stroke), and the cause is readily apparent from the history and neuroimaging. However, there are also a range of less common causes and a literature review of these identified 188 causes, which in the great majority of cases could be assigned to one of five categories: immunological disorders; mitochondrial disorders; uncommon infectious diseases; drugs or toxins; and uncommon genetic diseases (for lists of these causes, see Tan *et al.*, 2010; Shorvon *et al.*, 2011).

There is a further group of patients in whom no obvious cause is found, and who develop status epilepticus *de novo* and whose status epilepticus becomes super-refractory. It has been suggested that these cases constitute a 'syndrome' (and several different acronyms have been applied, such as NORSE (new-onset refractory status epilepticus) or DESC (devastating epileptic encephalopathy in school-aged children)). However, we feel that it is irrational to consider this category to be a 'syndrome' simply because the cause is unknown, and especially in this situation where causation is likely to be heterogeneous. Some of these cases have an immunological basis and as knowledge of immunology advances, cases are likely to be assigned to their aetiological categories (the discovery that many cases of what had been considered cryptogenic status epilepticus are due to *N*-methyl-D-aspartate receptor antibodies is an example). The NORSE and DESC categories also may have included some cases now referred to as FIRES (febrile infection-related epilepsy syndrome), which is a more specific childhood encephalopathy syndrome, likely to be immunologically mediated.

A similar clinical mistake is to assume that such patients have a 'presumed viral encephalitis', a misattribution sometimes made on the basis of CSF pleocytosis and oligoclonal bands even though no viral cause is serologically demonstrated. It seems likely to us that

Table 1 The evidence base for treatments used in super-refractory status epilepticus

Therapy	Published cases in controlled or randomized studies (n)	Published cases in open series or as case reports (reports, n)
Pentobarbital/thiopental	9 ^a	377 (32)
Midazolam	0	661 (29)
Propofol	14 ^a	183 (34)
Ketamine	0	17 (8)
Inhalational anaesthetics	0	32 (11)
Hypothermia	0	10 ^c (5)
Magnesium	0	11 (3)
Pyridoxine	0	14 (5)
Steroids/immunotherapy	0	50 (15)
Ketogenic diet	0	20 (6)
Transcranial magnetic stimulation	0	0
Vagal nerve stimulation	0	4 (4)
Deep brain stimulation	0	1 ^b (1)
Resective neurosurgery	0	36 (15)
CSF drainage	0	1 (1)
Electroconvulsive therapy	0	8 (6)

Published reports are included where the therapy is specifically mentioned, whether or not that therapy is the main focus of a paper.

a Randomized, single blind trial. Twenty-four patients recruited of the 150 needed, nine treated with barbiturate and 14 with propofol and one recovered before treatment (Rosetti *et al.*, 2011).

b A case of focal motor status, not tonic-clonic status epilepticus.

c Includes one patient considered to be treated with hypothermia, but in whom the body temperature fell only to 36.5°C.

the status epilepticus in many such patients is in fact due to a non-viral immunologically mediated condition.

Intensive treatment unit care and monitoring

The status epilepticus is conventionally treated with the full panoply of intensive treatment unit care, including assisted ventilation and full cardiovascular monitoring. The benzodiazepine and barbiturate anaesthetic drugs invariably cause hypotension and cardiorespiratory depression, which is sometimes severe and limits treatment, and pressor agents are usually necessary. Invasive blood pressure and haemodynamic monitoring, for instance with PiCCO® or pulmonary artery catheter has been recently proposed (Schmutzhard, 2011), and invasive EEG recording (Friedman *et al.*, 2009). In some centres, such aggressive monitoring is performed routinely, but the extent to which this improves outcome has not been the subject of evaluation.

Anaesthetic drugs

There is universal agreement that general anaesthesia is required as the backbone of therapy for super-refractory status epilepticus, at least in the first weeks. However, there is no agreement about the optimal choice of anaesthetic. The conventional choice is between three anaesthetic drugs—thiopental (or pentobarbital, which is a main metabolite of thiopental), propofol and midazolam. Each has advantages and drawbacks and there are no controlled or randomized comparative data on which to base a choice.

Thiopental and pentobarbital

Barbiturate anaesthesia, using either thiopental or pentobarbital, is the traditional anaesthetic therapy for status epilepticus. The advantages are its strong anti-epileptic action, its relative safety and long experience of its use, its tendency to lower body temperature and its theoretical neuroprotective effects. The barbiturates exert their action mainly by enhancing the action of the GABA(A) receptor, but they may also have added neuroprotective effects and do lower core temperature, which may be beneficial in status epilepticus. Thiopental and pentobarbital, however, have two main disadvantages. The first relates to their pharmacokinetics. They exhibit zero order kinetics and due to rapid redistribution have a profound tendency to accumulation resulting in a long half-life in anaesthesia (Shorvon, 1994) and thus long recovery time (Lowenstein *et al.*, 1988). It is not uncommon for anaesthesia to persist for days even after an infusion of only 12 h or so. The barbiturates are metabolized in the liver, suffer from autoinduction and also have many drug–drug interactions. The second main disadvantage is the strong propensity of barbiturate anaesthesia to cause hypotension and cardiorespiratory depression, which can seriously complicate high-dose infusions and usually requires the use of additional pressor agents. Other disadvantages are the tendency for pharmacological tolerance to develop, and the risk of pancreatic and hepatic dysfunction and toxicity, especially in the elderly.

Midazolam

Midazolam is given by infusion and rapidly enters brain tissue and exerts a powerful short-duration action and as such is the only benzodiazepine that has pharmacokinetic properties suitable for prolonged infusion without accumulation. It acts largely by binding to and enhancing the action of the GABA(A) receptor. In 29 published reports, 661 patients have been identified. The main advantage of its use is its strong anti-epileptic action. Its disadvantages include a purported strong tendency for rapid and acute tolerance to develop (sometimes after only 1 day of use) and thus the risk of seizure relapse. Such breakthrough seizures occurred in 47–57% of patients in two studies (Singhi *et al.*, 2002; Morrison *et al.*, 2006). There are also risks of hepatic and renal impairment. Midazolam is a strong respiratory depressant, and has cardiodepressant effects also, but these are generally less marked than those of barbiturate anaesthesia.

Propofol

Propofol is a modern and versatile anaesthetic with remarkable properties. It too probably exerts its main action via modulation of the GABA(A) receptor (as do the barbiturates and midazolam). Its pharmacokinetic properties include very rapid onset and recovery even after prolonged infusion, and this responsiveness allows a much greater control of the level of anaesthesia than is possible with thiopental/pentobarbital or midazolam. It is safe to use in porphyria and has no serious drug–drug interactions. Its pharmacology also has been extensively studied, as it is a widely used anaesthetic drug. It can cause hypotension or cardiocirculatory depression, although at a lower frequency and severity than that with barbiturate or midazolam. Its main disadvantage in prolonged anaesthesia is the risk of the propofol infusion syndrome (PRIS), which is a rare but potentially lethal toxic effect on mitochondrial and cellular metabolic function. The clinical features of PRIS include metabolic acidosis, lactic acidosis, rhabdomyolysis, hyperkalaemia, hyperlipidaemia, bradycardia and cardiac dysfunction, and renal failure. There is a high morbidity and mortality rate. PRIS, originally reported in children, is more common in those co-medicated with corticosteroids or catecholamines, and has a higher frequency in prolonged high-dose infusions that are typically required in status epilepticus. In a study of 31 patients receiving prolonged propofol infusions for status epilepticus from the Mayo clinic [median infusion of 67 h (range 2–391 h) and median cumulative dose of 12 850 mg (range 336–57 545 mg; note that abstract cites different figures from these in the text)], there were three sudden unexplained cardiorespiratory arrests, with two deaths and 11 further patients with less severe features of PRIS (Iyer *et al.*, 2009). This led the authors to recommend removal of propofol from their treatment protocols (Cooper *et al.*, 2009). On the other hand, Power *et al.* (2011) report a much more positive experience with propofol infusions for generally shorter periods and at lower doses. There is one case report of PRIS when the ketogenic diet was initiated, and the two therapies should probably not be co-administered. Other disadvantages of propofol include pain at the injection site and the risk of misinterpreting common drug-induced involuntary movements as seizures. These involuntary movements can have a myoclonic appearance, or mimic

convulsive seizures. Differentiation from epilepsy can be difficult and is not helped by the EEG, which is often obscured by the movement artefact. It has been suggested that the propofol-induced movements are of peripheral origin or due to the lack of cortical inhibition, and a small dose of a non-depolarizing muscle relaxant such as vecuronium, may help distinguish myoclonus of peripheral and central origin. The situation is complicated by the possibility that propofol possibly induces seizures in some patients (Voss *et al.*, 2008).

Ketamine

Ketamine is an infusional anaesthetic frequently postulated as an alternative anaesthetic for status epilepticus in super-refractory cases, although only 17 case reports of its use have in fact been published, some with few details, some duplicate the same patients and others are in abstract only without data about dosage or duration. It acts, not by binding to the GABA(A) receptor as do the other anaesthetics, but by its antagonistic action at the *N*-methyl-D-aspartate receptor. It has two major theoretical advantages over the conventional anaesthetics. First, it has no cardiac depressant properties and does not cause hypotension. In fact, it has a positive sympathomimetic action, and has the contrary risk of drug-induced hypertension although in super-refractory status epilepticus this is rarely a consideration. Secondly, it is potentially neuroprotective, because of its strong *N*-methyl-D-aspartate antagonist action, although as pointed out above, by the time it is employed, glutaminergic damage may already have been incurred. Its effectiveness experimentally was demonstrated by Borris *et al.* (2000). There are few published data on the theoretical risk of neurotoxic effects when the drug is used for prolonged periods, and its safety in prolonged use is largely untested. One case report has been published of the late development of cerebral atrophy, which was interpreted as possibly due to the excitotoxic damage caused by the drug (Ubogu *et al.*, 2003). Nevertheless, ketamine remains an important theoretical option in super-refractory status epilepticus where other anaesthetics are not suppressing seizures or are causing serious cardiac depression or circulatory compromise.

Inhalational halogenated anaesthetics

Isoflurane and desflurane are the subject of 11 reports. However, long-term use of these drugs presents serious hazards and logistical difficulties in an intensive treatment unit setting, and is associated with a high complication rate. In the largest case series, isoflurane and desflurane were used in seven patients, six of whom had not responded to previous therapy with midazolam, propofol and pentobarbital. Anaesthesia was maintained for a mean (range) of 11 (2–26) days (Mirsattari *et al.*, 2004). Four patients had good outcomes but three patients died, one of acute haemorrhagic leucoencephalitis, one of bowel infarction and one remained in a persistent vegetative state until death 5.5 months after the onset of seizures. Complications included hypotension (7/7), atelectasis (7/7), infections (5/7), paralytic ileus (3/7) and deep venous thrombosis (2/7) (Mirsattari *et al.*, 2004). The complications, risks and logistical difficulties are so great that the use of these drugs, in our opinion, should not generally be pursued.

Anti-epileptic drugs

In super-refractory status epilepticus, it is conventional practice to administer anti-epileptic drugs in tandem with the general anaesthesia. However, to what extent anti-epileptic drugs actually exert any useful anti-epileptic influence at this stage is quite unclear, and it seems likely that any such action will be insignificant compared with the suppressive effects of anaesthesia. However, anti-epileptics are important to have in place when the anaesthesia is reversed to provide adequate anti-epileptic drug cover.

There are no studies at all of the most appropriate or most effective anti-epileptic or regimen, nor of the general approach to therapy in this situation. This is in contrast to the larger number of studies of anti-epileptics in earlier phases of status epilepticus. Almost any anti-epileptic may be used, either through a nasogastric or percutaneous gastric tube or intravenously. Gastric absorption is often erratic in the setting of intensive treatment unit care or if ileus develops, and in this situation, long-term intravenous therapy has to be used but can cause problems such as phlebitis, infection or thrombosis at the injection site.

The drugs most commonly reported include carbamazepine, lacosamide, levetiracetam, phenobarbital, phenytoin, topiramate and valproate, but there is no real evidence that any one of these is reliably more or less effective than any other. The assessment of any study is complicated by the large number of co-medications used, the tendency for the status to improve spontaneously, the lack of controlled data and the fact that drug effects can be slow to become apparent. For example, in a study of topiramate used in six cases (Towne *et al.*, 2003), improvement was attributed to the drug but occurred in some patients days after therapy was initiated. In practice, patients often end up taking numerous drugs together (five anti-epileptics would not be unusual) with frequent rapid switches, both of which practices would be deprecated in conventional anti-epileptic drug therapy. Our recommendations for the use of anti-epileptic drugs in status epilepticus are outlined in the last section of this review.

Magnesium infusion

Intravenous magnesium sulphate has a unique place in the treatment of seizures. In a large well-conducted randomized controlled study, magnesium was shown to be the drug of choice in controlling seizures in eclampsia (Anon, 1995) and superior to phenytoin in this role. It is lifesaving too in the very rare congenital magnesium deficiencies, and in status due to acquired hypomagnesaemia. It was also frequently used to control status epilepticus in porphyria (especially acute intermittent porphyria). There is a body of experimental evidence demonstrating its anti-epileptic action (Nowak *et al.*, 1984), and its effect in blocking the *N*-methyl-D-aspartate receptor may be the basis of this action. However, other work has not supported an anti-epileptic effect (Link *et al.*, 1991).

The first report of its use in status epilepticus was in 1901 (Shorvon, 1994) and since then the published literature (excluding eclampsia and hypomagnesaemia) comprises few case reports. Storcheim (1933) published eight cases of status epilepticus (as it was put 'one of the gravest symptom pictures encountered by

physicians') all of whom recovered. Fisher *et al.* (1988) reported the first modern case, in which magnesium was infused to levels as high as 14.2 mEq/l in a case of severe myoclonic status epilepticus without seizure control, although the EEG patterns were changed. Recently, Visser *et al.* (2011) reported effect in *POLG1* deficiency and suggested a particular benefit in mitochondrial disease. In spite of this lack of evidence, and perhaps because of its undoubted success in eclampsia, there has been in recent times a fashion for infusing magnesium sulphate in cases of super-refractory status epilepticus. In the authors' experience, magnesium has never convincingly been shown to control adult super-refractory status epilepticus, but the infusion is safe and without significant side-effects.

Pyridoxine

Status epilepticus can be the presenting feature in patients with an inborn error of metabolism of pyridoxine (due to mutations in the *ALDH7A* gene; Mills *et al.*, 2006) and in these patients, intravenous pyridoxine therapy is curative, and lifelong supplementation is then required. However, pyridoxine-responsive super-refractory status epilepticus has also been described in 14 patients, in five reports, who needed only the immediate replacement of pyridoxine without long-term supplementation and in whom the genetic test was either negative or not done. Although this therapy will be effective in only a small number of cases, it is now commonly recommended that pyridoxine is given routinely in cases of super-refractory status epilepticus in young children, and this is reasonable as the infusion is without significant side-effects. It is not known how often this will be beneficial, or whether it is indicated, in adult patients although cases of acquired pyridoxine deficiency have been reported, for instance, in status epilepticus in pregnancy. Another resistant form of epilepsy has been described recently, which did not respond to pyridoxine treatment, but responded to pyridoxal phosphate. This has been labelled as pyridoxal phosphate-dependent neonatal epileptic encephalopathy (Bagci *et al.*, 2008).

Steroids and immunotherapy

Corticosteroids (and adrenocorticotrophic hormone) have for many years been given in super-refractory status epilepticus, although often without clear guidelines about dose or duration of therapy, and without any sort of evaluation of effectiveness. The rationale was weak, sometimes on the analogy of their use in severe childhood epilepsy (Verhelst *et al.*, 2005), sometimes on the assumption that there may be a cerebral oedema and in some cases a vasculitic cause. Intravenous immunoglobulins were also occasionally used in refractory epilepsy—the first reports were by Péchadre *et al.* (1977) and Arrizumi *et al.* (1983) and a double-blind clinical trial was carried out by van Rijkevorsel-Harmant *et al.* in 1994. The rationale for the trial was that 'immunological and immunogenetic abnormalities are found frequently in epilepsy'.

Two interesting developments in recent years have encouraged a re-awakening of interest in the potential for steroids and immunotherapy. The first has been the recognition that super-refractory status epilepticus may be due to antibodies directed

against neural elements. The first antibodies identified were against the voltage-gated potassium channels. Then antibodies against the *N*-methyl-D-aspartate receptor were discovered, which were found to be a common finding in previously cryptogenic status epilepticus. The second development has been the increasing evidence that inflammation plays an important role in epileptogenesis, and especially the activation of specific inflammatory signalling pathways such as the interleukin-1 receptor/toll-like receptor (IL-1R/TLR) pathway, both experimentally and in human tissue (Vezzani *et al.*, 2009; Maroso *et al.*, 2010; Vezzani and Ruegg, 2011; Zurolo *et al.*, 2011).

These discoveries have led to the widespread use of immunotherapy with steroids, intravenous immunoglobulins or plasma exchange in patients with super-refractory status epilepticus, even in the absence of any evident immunological cause for the status epilepticus. The rationale is that many cryptogenic cases might be due to occult immunological diseases with antibodies that have yet to be identified, or that the persistence of the status epilepticus is in part at least due to immunological processes. Steroids may have additional non-immunological effects, including the reversal of blood–brain barrier opening, which is a crucial influence on the persistence of seizure activity and which may reverse GABAergic inhibition (see above), and also effects on intracranial pressure.

Fifty cases of the use of immunotherapy in the absence of any defined immunological disease have been published in 15 separate reports (excluding duplications), which include: 38 patients given steroids, 24 cases given intravenous immunoglobulins and 7 with plasma exchange.

Ketogenic diet

The ketogenic diet was introduced in epilepsy in the 1920s, and is still used principally in the severe childhood encephalopathies. Emergency use of a ketogenic diet has also been reported in 20 cases of status epilepticus (some non-convulsive), most of whom have been children. The first series of cases published was of six children with super-refractory status epilepticus who responded to the diet (François *et al.*, 2003); Nabbout *et al.* (2010) also report the successful use of the diet in nine cases of super-refractory status epilepticus in the context of FIRES. Four adults with prolonged status epilepticus are reported (Bodenant *et al.*, 2008; Wusthof *et al.*, 2010; Cervenka *et al.*, 2011), in one of whom the diet was administered on the 101st day of hospitalization with complete seizure resolution within a day of consistent ketosis. In one case (Cervenka *et al.*, 2011), the status epilepticus, which had been refractory to intensive medical and resective surgical treatment, ceased after induction of the diet which was then switched after 29 days and continued as a modified Atkins diet. Kumada *et al.* (2010) also report one case treated successfully with the modified Atkins diet alone. It has been suggested that as well as having a well-established anti-epileptic effect, the effectiveness of the ketogenic diet in super-refractory status epilepticus may be due to a possible anti-inflammatory action, although conclusive experimental evidence of any such action is absent. The cases reported convincingly show an effect, and the diet should probably be tried in all severe cases of super-refractory status epilepticus.

Hypothermia

Hypothermia has been shown to exert anti-epileptic action and to be neuroprotective in experimental status epilepticus (Liu *et al.*, 1993; Lundgren *et al.*, 1994; Takei *et al.*, 2004; Schmitt *et al.*, 2006; Hrnčić *et al.*, 2007), and to reduce brain oedema in status epilepticus and effects of status epilepticus on learning (Wang *et al.*, 2010). In the pilocarpine model of status epilepticus in juvenile rats, mild hypothermia reduced both seizure activity and the number of apoptotic cells in the hippocampus (Yu *et al.*, 2011). In human refractory epilepsy, the first report was of 21 handicapped patients with severe epilepsy treated with extravascular hypothermia, local brain cooling at open operation and thiopental (Sourek and Trávníček, 1970). The successful use of hypothermia for status epilepticus, with thiopental anaesthesia, was first reported in three children with generalized status epilepticus (Orlowski *et al.*, 1984). In this report, moderate hypothermia (30–31°C) was induced by barbiturate anaesthesia and continued for 48–120 h resulting in the cessation of status epilepticus, although whether this was due to the barbiturate or hypothermia is not clear. Initially, this therapy seemed not to be taken up, but there has been a recent resurgence of interest in parallel with the growing experience of the use of hypothermia in other intensive treatment unit situations. In some centres, a trial of hypothermia is now routinely applied in super-refractory status epilepticus. There are theoretical reasons for recommending hypothermia. It reduces the cerebral metabolic rate, oxygen utilization, ATP consumption, glutamergic drive, mitochondrial dysfunction, calcium overload, free radical production and oxidative stress, permeability of the blood–brain barrier and pro-inflammatory reactions. Hypothermia is also now commonly used routinely in post-anoxic coma (for instance after cardiac arrest), with or without any evidence of seizures. However, in post-anoxic coma, the presence of myoclonic status epilepticus is a very poor prognostic sign with few patients surviving (Rossetti *et al.*, 2007; Fugate *et al.*, 2010) and to what extent, if any, aggressive therapy confers any benefit is not known.

The evidence base in super-refractory status epilepticus amounts to only 10 case reports. The most detailed study is by Corry *et al.* (2008) who reported four patients with refractory tonic–clonic status epilepticus in whom hypothermia to 31–35°C was achieved for 20–61 h using endovascular cooling. Even mild hypothermia is not without its risks, and these include acid–base and electrolyte disturbances, disseminated intravascular coagulation, coagulation disorders, thrombosis, infection, cardiac arrhythmia, bowel ischaemia and paralytic ileus (Corry *et al.*, 2008).

Emergency neurosurgery

In selected situations, mainly where there is a clearly definable radiological lesion and/or electrophysiological evidence of a focal onset, emergency surgical resection has been used as a 'last-resort' treatment of super-refractory status epilepticus. The published evidence base consists of 36 patients reported in 15 small series and case reports, and the operations carried out include focal cortical resection, lobar and multi-lobar resection, anatomic and functional hemispherectomy, corpus callosotomy and multiple subpial transaction (excluding patients with status gelasticus and epilepsy

partialis continua, in which general anaesthesia was not required). The most common surgical procedure was focal resection in cases of malformation of cortical development. Corpus callosotomy is usually considered 'palliative' rather than curative, but one patient is described with no residual seizures after 2 years of follow-up (Ma *et al.*, 2001). Multiple subpial transaction has been described in five patients (D'Giano *et al.*, 2001; Ng *et al.*, 2006; Schrader *et al.*, 2009) in combination with lesion resection in four. Investigations include EEG, MRI, PET and single-photon emission computed tomography, and many patients underwent intraoperative electrocorticography in order to delineate the ictal-onset zone. Surgery has been carried out as early as 8 days after the onset of status epilepticus (Ng *et al.*, 2006) but generally considered only after weeks of status epilepticus. Whether surgical therapy should be carried out earlier is unclear, but some authors have suggested that emergency surgery should be considered after a 2 week period of failed medical treatment (Lhatoo and Alexopoulos, 2007). However, in status epilepticus, there are often widespread epileptogenic areas and the outcome after emergency surgery can be poor.

Electrical and magnetic stimulation therapies

There has been a long-standing interest in cerebral stimulation as therapy. It is postulated that these can alter the synchronization of epileptic discharges, increase the refractory period of neuronal discharge or alter membrane or neurotransmitter function. Several modalities have been discussed.

Transcranial magnetic stimulation

This form of brain stimulation has generally had dismal results in epilepsy, although recent promising reports of use in epilepsy partialis continua have been published (Misawa *et al.*, 2005; Morales *et al.*, 2005; Schrader *et al.*, 2005; Rotenberg *et al.*, 2009). It has not been used in super-refractory status epilepticus, and because of the drug-induced cortical inexcitability, it is doubtful whether it could have any significant effect.

Vagal nerve stimulation

There are four published cases reporting benefit from the implantation of vagal nerve stimulation in the treatment of status epilepticus, in children (Winston *et al.*, 2001; de Herdt *et al.*, 2009 in a non-convulsive case) and in adults (Patwardhan *et al.*, 2008; O'Neil *et al.*, 2011). In all these cases, there was extensive additional therapy complicating the assessment of the effect and delayed response of the vagal nerve stimulation.

Deep brain stimulation

Deep brain stimulation in epilepsy has a history going back to at least the 1940s. There is evidence that stimulation of anterior and centromedian nuclei of the thalamus, subthalamic nucleus, striatum, globus pallidus and cerebellum can influence seizures (Chabardes *et al.*, 2002). Furthermore, there is unequivocal evidence that stimulation of the anterior thalamic nucleus can inhibit experimental status epilepticus (in the pilocarpine rat model, Hamani *et al.*, 2008). Its use is frequently postulated in super-refractory status epilepticus, but we are unable to find any

published cases describing its use in super-refractory tonic–clonic status epilepticus, although there is one report of its successful use in focal motor status epilepticus in Rasmussen encephalitis (Franzini *et al.*, 2008).

Electroconvulsive therapy

This is the form of cerebral stimulation that has been most studied in status epilepticus. Electroconvulsive therapy was first used in epilepsy in the 1930s (Allen, 1938; Caplan, 1945). Its anti-epileptic effects were then well established due, it is suggested, to the increased presynaptic release of GABA and prolongation of the refractory period after a seizure (Sackheim *et al.*, 1983; Sanacora *et al.*, 2003). Case reports of its use in super-refractory status epilepticus in eight patients have been published in the past two decades. Fink *et al.* (1999) recommend that electroconvulsive therapy is given in advance of general anaesthesia, although this suggestion has not been taken up. To cause a formed convulsion, electroconvulsive therapy has to be given when the anaesthetic is reversed and the anti-convulsant drugs discontinued, as the anaesthetics and anti-epileptic drugs massively reduce cortical excitability. An illustrative case is that described by Lisanby *et al.* (2001). Prior to electroconvulsive therapy, the patient was on phenobarbital, phenytoin, vigabatrin, midazolam and nitrazepam. Flumazenil was given to reverse the benzodiazepine and electroconvulsive therapy given. No seizure was induced despite double electroconvulsive therapy at high currents on the first 2 days, then the phenobarbital and phenytoin were withdrawn and on the third session a seizure was induced and further seizures in the next two sessions, with further drug reduction. Some of the cases described were in non-convulsive status epilepticus (Griesemer *et al.*, 1997; Shin *et al.*, 2011). Furthermore, it is well known that non-convulsive status epilepticus is often spontaneously terminated by a convulsion (Shorvon and Walker, 2005). A feature of all these cases was the multiple drug therapy, the rapid weaning of some anti-epileptics and anaesthetic agents to prepare the patients for electroconvulsive therapy, the need for repeated sessions of electroconvulsive therapy and the slow recovery with a time course sometimes difficult to attribute to the electroconvulsive therapy *per se*. Furthermore, the functional outcome in the published cases has been often poor. It is recommended by several authors that electroconvulsive therapy should be given daily for a 5–8 day course. The current settings may need to be high.

Cerebrospinal fluid drainage

This therapy was first reported in the late 19th century and continued to be used at least for the first half of the 20th century. Repeated drainage was considered 'serviceable' by Kinnier Wilson in 1940, sometimes with the intrathecal instillation of bromide. A single recent case has been published of CSF–air exchange in a patient with super-refractory status epilepticus, with immediate resolution of the status epilepticus although this recurred a week later and did not respond to a second drainage (Kohrmann *et al.*, 2006). Whether this therapy should be considered today is unclear, but the response in this recent published case was impressive, and the potential for the co-administration of intrathecal anti-epileptic drugs is something worth reconsideration in our

view. It is not clear why CSF drainage has any effect on seizure activity, but this could be due to the removal of inflammatory or other noxious substances, a reflex autonomic effect or an effect on intracerebral pressure.

Other drugs used

A number of older drugs are still occasionally used in status epilepticus. In the earlier years of the century, chloral and bromide were universally recommended, and are still rarely used. Paraldehyde given by continuous intravenous infusion was described by Whitty and Taylor (1940) in 26 adults from a military hospital in World War II, and was still being used routinely in Oxford for super-refractory status epilepticus when one of the authors (S.D.S.) was training there in the 1970s, and could be highly effective (early case reports were by: Weschler, 1940; McGreal, 1958; de Elio *et al.*, 1949). In the 1980s and 1990s, there was interest in the use of etomidate as an anaesthetic in status epilepticus, with nine patients reported (Opitz *et al.*, 1983; Yeoman *et al.*, 1989; Kofke *et al.*, 1997) but this is now seldom considered. Lignocaine is mostly used in early status although occasionally also as an anaesthetic in super-refractory cases by continuous infusion. It should be noted also that phenobarbital in high dosage has also been used in the past as an anaesthetic, especially in children, but thiopental and pentobarbital have largely replaced this. A range of other barbiturate and benzodiazepines such as bromethol, hexobarbital, methohexital, butallylonal, secobarbital, amylobarbitol, diethylamine barbiturate, nitrazepam, clorazepate and clonazepam have all been used in prolonged infusion in status epilepticus (for review, see Shorvon, 1994).

Conclusion

Super-refractory status epilepticus is a serious condition. The mortality rate is substantial, reported in various series between 30 and 50%. Yet, despite the fact that it remains an important clinical problem in all neurology centres worldwide, for many therapies, and treatment approaches, there is a remarkable lack of published data concerning effectiveness, safety or outcome. Treatment protocols, therefore, are needed and in Fig. 2, a general approach to treatment is proposed, based on the clinical experience and the published literature. Doses and parameters of treatment are shown in Tables 2 and 3.

Recommended treatment protocol for super-refractory status epilepticus

In all cases of super-refractory status epilepticus

Identify and treat cause

All efforts should be made to identify the cause and to treat this where possible. Successful therapy will often terminate the status

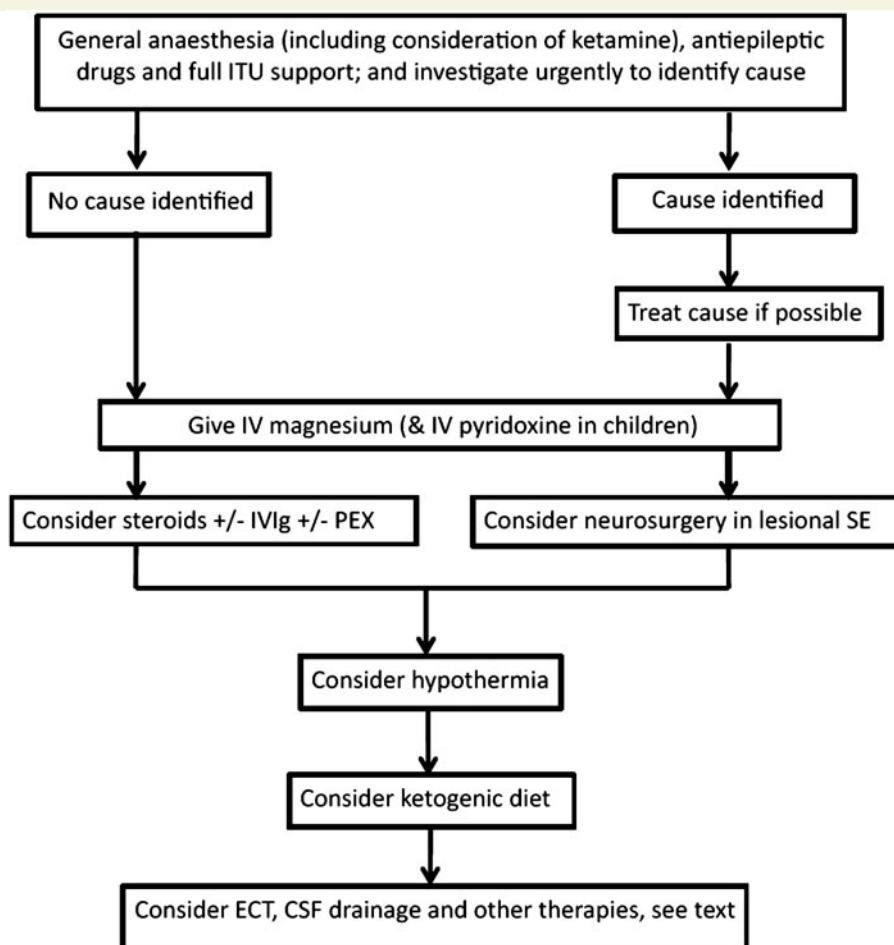


Figure 2 Flowchart for the treatment of super-refractory status epilepticus. The flowchart is proposed as the basis of a protocol for the treatment of super-refractory status epilepticus (SE). The order and choice of therapy proposed will depend on the clinical context and the local facilities. ECT = electroconvulsive therapy; ITU = intensive treatment unit; IV = intravenous; PEX = plasma exchange.

epilepticus. A detailed history should be obtained (including family history) and the investigations required depend on the context, and often will include MRI, EEG, CSF examination, metabolic and drug screen, toxicological and auto-immune screen.

General anaesthesia

Choice of anaesthetic

One of the three conventional anaesthetic agents should be given initially with choice depending on individual circumstance and preference. However, propofol infusions should only be continued for >48 h where the benefits exceed the risks of PRIS and where careful monitoring to avoid this is in place. Ketamine should be considered where other anaesthetics are failing or where drug-induced hypotension becomes a crucial problem.

Level of anaesthesia

It is usual to continue anaesthesia to a level of burst suppression. At this level, all electrographic seizure activity is usually terminated. Lighter anaesthesia may sometimes also suppress activity, and whether burst suppression is needed in all cases is not clear, and what little evidence there is, is conflicting (Krishnamoorthy *et al.*, 1999; Rossetti *et al.*, 2005; Amzica, 2011). While burst

suppression levels of anaesthesia will control seizures effectively, there is a significant risk of hypotension and other complications. As a compromise, it is now common practice to aim for burst suppression initially and then in prolonged episodes to lighter the level of anaesthesia. Recommended doses are given in Table 3.

Cycling and duration of anaesthetic cycles

It is usual practice to reverse anaesthesia initially every 24–48 h, and if seizures recur, then to re-establish it. Over time, the duration of individual cycles is increased, and after a few weeks, anaesthesia is often continued for 5 days before attempts to reverse it are made.

Speed of weaning of anaesthetics

The speed at which anaesthetic weaning should be done is also not clear, but studies in which rapid weaning occurs show high rates of recurrence and the possibility of rebound seizures. For this reason, it seems reasonable to wean slowly over days (see Table 3 for rates).

Duration of anaesthesia

How long anaesthesia should be continued has not been the subject of study. It remains possible that in very prolonged status epilepticus, the risks of anaesthesia exceed those of the status

Table 2 Anaesthetic therapies

Treatment	Dose recommended		Range of doses used (from the literature review)		Main advantages	Main disadvantages
	Children	Adult	Children	Adult		
Thiopental/ pentobarbital	Bolus: 5 mg/kg Infusion: 5 mg/kg/h	Bolus: 2–3 mg/kg Infusion: 3–5 mg/kg/h	Bolus: 4–5 mg/kg Infusion: 0.5–12 mg/kg/h	Bolus: 1–19 mg/kg Infusion: 0.5–20 mg/kg/h	Strong anti-epileptic action, potential neuroprotective action, reduces intracranial pressure, long experience of its use	Zero order pharmacokinetics, strong tendency to accumulate and thus prolonged recovery phase, acute tolerance, cardiorespiratory depression, hypotension, drug interactions, toxicity
Midazolam	Bolus: 0.1–0.2 mg/kg Infusion: 0.05–0.23 mg/kg/h ^a	Bolus: 0.2 mg/kg Infusion: 0.1–0.4 mg/kg/h	Bolus: 0.06–0.6 mg/kg Infusion: 0.036–1.2 mg/kg/h	Bolus: 0.03–0.5 mg/kg Infusion: 0.02–1.2 mg/kg/h	Strong anti-epileptic action, less tendency to accumulate than barbiturate or other benzodiazepines	Tendency for acute tolerance to develop resulting in breakthrough seizures, hypotension and cardiorespiratory depression, hepatic metabolism
Propofol	Bolus: 1–2 mg/kg Infusion: 1–7 mg/kg/h	Bolus: 3–5 mg/kg Infusion: 5–10 mg/kg/h	Bolus: 1–3 mg/kg Infusion: 0.6–26.94 mg/kg/h	Bolus: 1–3 mg/kg Infusion: 0.1–24 mg/kg/h	Excellent pharmacokinetics, ease of use, responsive anaesthetic agent, pharmacology extensively studied	PRIS, pain at the injection site, involuntary movements, no intrinsic anti-epileptic action
Ketamine	NK	Bolus: 0.5–4.5 mg/kg Infusion: up to 5 mg/kg/h	NK	Bolus: 0.5–3 mg/kg Infusion: 0.3–7.5 mg/kg/h	Lack of cardiorespiratory depression and drug-induced hypotension. <i>N</i> -methyl-D-aspartate blockade and therefore potential neuroprotective action	Potential for neurotoxicity, hypertension

^a = the rate of 2 mg/kg/h (children) is recommended by Abend & Dlugos 2008.
NK = not known.

Table 3 Non-anaesthetic therapies

Treatment	Dose recommended ^a / physical parameter	Range of doses used (from the literature review)	Major adverse effects	Contraindications
Magnesium	Infusion to increase serum level to 3.5 mmol/l ^b	Bolus: 4 g Infusion: 2–6 g/h	High dose: hypotension, arrhythmia, neuromuscular block	Kidney failure
Pyridoxine	30 mg/kg (children) 100–200 mg/day (adults)	2–300 mg/day	Bradycardia, hypothermia, apnoea, sensory neuropathy	Hypersensitivity
Hypothermia	32–35°C (for <48 h) by endovascular cooling	30–36°C	Coagulation disorders, venous thrombosis, hypotension, shivering, acid-base and electrolyte disturbances, infections, cardiac arrhythmia, ileus, bowel ischaemia	Coagulopathy. Caution in immunodepression.
VNS	Up to 1.25 mA	0.25–1.75 mA	Bradycardia, asystole, coughing, hoarseness, Horner's syndrome	History of previous neck surgery or prior cervical vagotomy
Ketogenic diet	4:1 ketogenic ratio (see text)	1:1 to 4:1 ketogenic ratio	Constipation, acidosis, hypoglycaemia, hypercholesterolaemia.	Pyruvate carboxylase and β-oxidation deficiencies, propofol anaesthesia, porphyria.
Electroconvulsive therapy	Daily sessions for 3–8 days	3 daily sessions—6 sessions over 2 weeks	Intracranial pressure increases, cardiac arrhythmias, hypo/ hypertension	Brain space-occupying lesions, recent history of myocardial infarction, cerebral vascular disease.
Steroids	Prednisolone 1 g/day intravenous for 3 days followed by 1 mg/kg/day (see text)	Various	Gastrointestinal ulceration, Cushingoid syndrome, fluid and sodium retention, psychiatric disturbance	Infection, severe hyperten- sion or diabetes mellitus
Immunoglobulins	Intravenous immunoglobulins 0.4 g/kg/day for 5 days (see text)	Various	Coagulation disorders, hypertension	Coagulopathy, selective deficiency of IgA

a Recommended on the basis of experience and/or the literature review.

b The regimen recommended by Visser *et al.*, 2011.

VNS = vagal nerve stimulation; IgA = immunoglobulin A.

epilepticus and withdrawal of anaesthesia for longer periods may be beneficial. Certainly, occasionally seizures that are reactivated on anaesthetic withdrawal then subside spontaneously. Nevertheless, it is conventional practice currently to continue anaesthesia (with withdrawal and restitution cycles as above).

Intensive treatment unit monitoring

Conventional intensive treatment unit care and careful monitoring should be employed in all patients. Meticulous attention must be paid to haemodynamic parameters, fluid balance, anti-thrombotic therapy and skin care. Also, particularly as the anaesthetics can be immunosuppressive, monitoring for and therapy of nosocomial infection becomes increasingly important as the status epilepticus becomes more prolonged. The other complications of prolonged anaesthesia (listed above) need to be identified and treated (Schmutzhard, 2011). EEG should be carried out at least once a day. In very prolonged status epilepticus, intensive and sometimes invasive intensive treatment unit and EEG monitoring should be considered (Friedman *et al.*, 2009; Schmutzhard, 2011), but this will depend on the clinical context and the facilities available. If

prolonged propofol infusions are undertaken, very careful monitoring for the signs of PRIS is required.

Anti-epileptic drug therapy

High doses of two or three anti-epileptic drugs should be initiated via a nasogastric or other feeding tube, and these should be continued throughout the course of the status epilepticus. In the complete absence of any comparative study, advice about an appropriate treatment strategy must be arbitrary and subjective. However, a few general points seem appropriate to suggest:

Drug regimes

Polytherapy with no more than two anti-epileptics in high doses seems on general principles to be most appropriate. There is no evidence of overall benefit from more complex combinations, and morbidity will rise with more extensive drug regimens.

Changing drug regimens

Frequent changes in the anti-epileptic drug regimen should be avoided, as rapid withdrawal of anti-epileptics can lead to rebound seizures, exacerbate side-effects, risk allergic reactions and also cause pharmacokinetic changes. In very prolonged status

epilepticus, changing anti-epileptics may be tried, but the withdrawal process should be slow, carried out over weeks.

Choice of drug

This will depend on the clinical context. In general, the most powerful and effective drugs should be chosen but avoiding drugs with a primarily GABAergic mechanism of action, not least because there is evidence of loss of efficacy as status epilepticus becomes more prolonged and because the anaesthetic drugs themselves have much more powerful GABAergic effects. It would seem also sensible to use drugs that have low interaction potential and predictable kinetics, and to avoid drugs with strong allergenic potential and potential renal or hepatic toxicity.

Magnesium sulphate infusion

Although little evidence of benefit is available, intravenous magnesium has no significant toxicity or drawbacks and there is some evidence of experimental benefit. Therefore, it seems reasonable to recommend its use in all cases of super-refractory status epilepticus. The regime suggested by Visser *et al.* (2011) is with an initial intravenous bolus and then infusion at a dose that increases the serum level to ~3.5 mmol/l.

Pyridoxine infusion

In rare cases of status epilepticus in young children, pyridoxine deficiency will be present and a pyridoxine infusion will be curative. It remains unclear whether pyridoxine is useful in cases where there is no genetic (or acquired) deficiency, but the practice has grown up of giving pyridoxine in all cases of severe cryptogenic status epilepticus in young children. Pyridoxine has no toxicity or drawbacks, and this therefore seems a reasonable practice. There are reported a few cases of successful treatment of status epilepticus in adults also, but how useful routine administration of pyridoxine would be is unclear. The doses recommended in the literature have varied between 2 and 300 mg/day (Haenggeli *et al.*, 1991).

In cases where a lesional cause of the status epilepticus is identified

Resective neurosurgery and/or multiple subpial transection

Resective neurosurgery (or multiple subpial transection, with or without resection) can be considered early where lesions are found that are causing the status epilepticus. The outcome after surgery in some cases is poor, even where intensive investigation has shown a focal onset to the seizures and where that focus has been resected, but good outcome has been reported sufficiently often to consider this a treatment option.

In cases where the cause is not identified

Steroids and immunotherapy

If no underlying cause for the status epilepticus can be identified, a trial of high-dose steroids can be given, and then if there is no

resolution within 2 days, either intravenous immunoglobulins or (less commonly) plasma exchange can be added. There are no data on optimal therapy, but it is important to have a protocol. In the author's practice, this is usually initiated with high-dose prednisolone at a dose of 1 g of intravenous prednisolone per day for 3 days followed by 1 mg/kg/day in four divided doses. This is followed by one or two courses of intravenous immunoglobulins at a dose of 0.4 g/kg over 5 days, or plasma exchange. If there is a response, treatment is continued with long-term steroids, intravenous immunoglobulins and later, other immunomodulatory agents such as cyclophosphamide or rituximab. It seems reasonable to give such a regime to all patients in whom there is no cause identified for the super-refractory status epilepticus, unless there are specific contraindications (diabetes for instance). There is experimental evidence to suggest that steroids should be given early, practically speaking within the first week of super-refractory status epilepticus.

In cases where the status epilepticus continues despite the above measures

If the status epilepticus continues despite the above measures, there are a number of other approaches. First, consideration can be given to a trial of the ketogenic diet and/or of mild hypothermia. Which measure should be tried first depends on the clinical context and facilities available. Whether either therapy has specific indications is not clear. The ketogenic diet has been most investigated in the severe encephalopathies of childhood, but adults responding to the diet have been reported. Similarly, hypothermia has been studied most in the ischaemic-anoxic encephalopathies and in lesional epilepsy, and how effective it is, more generally, is again, not known.

Ketogenic diet

The ketogenic diet is easy to administer through a gastrostomy tube or via parenteral feeding, because soluble preparations are available (Ketocal). A 4:1 ketogenic diet is recommended, with the total avoidance of glucose initially. After 24 h fasting, the diet is initiated, blood sugar should be measured every 3 h for the first 3 days and then every 6 h, and glucose given if blood sugar falls below <2.5 mmol/l. Once ketosis is obtained, urinary ketosis should be measured daily and serum β -hydroxybutyrate weekly. Care is required on a number of fronts. The use of the diet is absolutely contraindicated in those rare cases in which pyruvate carboxylase and β -oxidation deficiencies are the cause of the status epilepticus. The administration of glucose needs to be severely restricted (for instance in intravenous fluids). Total fluid intake should be closely monitored. It has been suggested that if a metabolic acidosis develops, treatment should be given to maintain serum bicarbonate levels >18–20 mEq/l (Wheless, 2010). It is possible that concomitant steroid administration inhibits ketosis (Nabbout *et al.*, 2010), and a case has been reported of fatal PRIS associated with the initiation of a ketogenic diet in a 10-year old with refractory status epilepticus (Baumeister *et al.*, 2004). As propofol can impair fatty acid oxidation, the ketogenic diet should probably not be used concomitantly with propofol anaesthesia.

Hypothermia

Hypothermia is usually induced by endovascular cooling. Rossetti (2010) has recommended that only mild hypothermia (32–35°C) is given, that barbiturate anaesthetics should be avoided and that the hypothermia is carried on for 24–48 h only as a trial of therapy. If there is a response, the hypothermia can be continued. Cardiovascular and coagulation parameters, biochemistry and acid–base balance, serum lactate and physical examination (to avoid venous thrombosis) must be monitored carefully. It is important to note too that the clearance of anaesthetics and anti-epileptics used in co-medication may be significantly reduced by hypothermia (Tortorici *et al.*, 2007; Hostler *et al.*, 2010).

Other measures

If the above measures fail in prolonged status epilepticus, it may be worth attempting electroconvulsive therapy, other forms of stimulation or CSF drainage. These, however, should be considered therapies of last resort. There are no particular underlying causes that are known to influence the choice of therapy.

How long should therapy be continued?

The longer the status epilepticus continues, the worse the outcome (Neligan and Shorvon, 2010) and in very prolonged status epilepticus, the morbidity is very high. Persisting vegetative state is not uncommon in survivors after prolonged status epilepticus. Nevertheless, it is common clinical experience that good recovery can occur even after weeks or months of status epilepticus, especially in status epilepticus where no cause was found, and in this situation, the neurologist has a role in the intensive care situation in insisting that therapy is continued to ensure that premature withdrawal of care is not contemplated.

Assessing outcome and the need for a multi-centre database of therapy

Assessing outcome of individual therapies is difficult due to the complete lack of controlled data, the fact that all super-refractory patients are on multiple therapies, the tendency for authors to report effects days after the therapy is started and which can therefore be difficult to securely attribute to the therapy, and the fact that outcome fundamentally depends on the underlying aetiology, which differs in different studies (Neligan and Shorvon, 2010).

The lack of evidence and the lack of outcome data in this situation require urgent remediation. Randomized or controlled studies that are sufficiently powered are not feasible in relation to the many therapies and treatment approaches discussed above. For this reason, proposals have been made for a multinational database of therapies used in super-refractory cases and their outcome. Only with such a database can evidence of effectiveness be gathered and progress made in this uncommon but difficult clinical situation.

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Supplementary material

Supplementary material is available at *Brain* online.

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