Review Article

Treatment of Refractory Status Epilepticus: Literature Review and a Proposed Protocol

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Refractory status epilepticus describes continuing seizures despite adequate initial pharmacologic treatment. This situation is common in children, but few data are available to guide management. We review the literature related to the pharmacologic treatment and overall management of refractory status epilepticus, including midazolam, pentobarbital, phenobarbital, propofol, inhaled anesthetics, ketamine, valproic acid, topiramate, levetiracetam, pyridoxine, corticosteroids, the ketogenic diet, and electroconvulsive therapy. Based on the available data, we present a sample treatment algorithm that emphasizes the need for rapid therapeutic intervention, employs consecutive medications with different mechanisms of action, and attempts to minimize the risk of hypotension. The initial steps suggest using benzodiazepines and phenytoin. Second steps suggest using levetiracetam or valproic acid, which exert few hemodynamic adverse effects and have multiple mechanisms of action. Additional management strategies that could be employed in tertiary-care settings, such as coma induction guided by continuous electroencephalogram monitoring and surgical options, are also discussed. © 2008 by Elsevier Inc. All rights reserved.

Introduction

Status epilepticus is a medical emergency consisting of persistent or recurring seizures. It is not a single entity, but can be divided into subtypes and has multiple underlying etiologies. Care involves both the termination of seizures and the identification and management of any underlying conditions. The prognosis is dependent on management of the underlying condition and on treatment of seizures.

Status epilepticus was initially defined as "an enduring epileptic condition," without specifying exact durations. Since then, the definition has undergone multiple revisions to include and then modify the required duration, shortening the required seizure duration from 30 minutes to 5 minutes [1]. This shortening of time was based largely on data demonstrating that seizures that do not cease in 5-10 minutes are less likely to terminate without intervention [2]. To describe this time period better, it may be divided into the impending or early stage of status epilepticus (5-30 minutes), and the established stage of status epilepticus (30-60 minutes). Impending status epilepticus was defined as "an acute epileptic condition characterized by continuous generalized convulsive seizures for at least 5 minutes or by continuous non-convulsive seizures or focal seizures for at least 15 minutes, or by two seizures without full recovery of consciousness between them" [3]. Many of these seizures will not end independently, and there is an urgent need for treatment to prevent the development of full status epilepticus. Established status epilepticus is defined as "an acute epileptic condition characterized by continuous seizures for at least 30 minutes, or by 30 minutes of intermittent seizures without full recovery of consciousness between the seizures" [3].

In some children with status epilepticus, seizures persist despite treatment with adequate doses of an initial two or three anticonvulsant medications, and this condition constitutes refractory status epilepticus. The exact definition is still unclear, with different studies defining refractory status epilepticus with varying durations (no time criteria, 30 minutes, 1 hour, or 2 hours) and a lack of response to different numbers (two or three) and types of medications. Refractory status epilepticus occurs in 10-70% of adults [4-6] and children [7-9] with status epilepticus. Studies in

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children indicated that status epilepticus lasted >1 hour in 26-45% [10,11], >2 hours in 17-25% [11,12], and >4 hours in 10% [11]. In a recent prospective, population-based study of children with status epilepticus that led to emergency room presentation, the incidence of status epilepticus lasting >60 minutes was higher than the incidence of status epilepticus lasting <60 minutes across all ages and etiologies [13]. However, some children with nonrefractory status epilepticus may not have been transported to the emergency room. Refractory status epilepticus is associated with high morbidity and mortality [6,9,14].

In a subgroup of patients, refractory status epilepticus may last for weeks or months, despite treatment with multiple anticonvulsant and coma-inducing medications. This lengthy course was reported in 20% of adults with refractory status epilepticus [15], and was referred to as malignant, refractory status epilepticus [15]; de novo, cryptogenic, refractory, multifocal, febrile status epilepticus [16]; or new-onset, refractory status epilepticus [17]. Malignant refractory status epilepticus was associated with an encephalitic etiology, younger age, previous good health, and high morbidity and mortality [15-17]. Similar cases were described in children [18]. It remains unclear whether this condition represents a specific disease entity, or simply a particularly severe variant of refractory status epilepticus because of certain etiologies.

Most seizures terminate spontaneously within several minutes [2], possibly due to a γ-aminobutyric acid-mediated recurrent inhibition that occurs in response to seizures. However, with continuing seizures, inhibitory γ-aminobutyric acid receptors are internalized in clathrin-coated vesicles, some of which are recycled to the cellular membrane, and some of which are destroyed in lysosomes. At the same time, excitatory N-methyl-D-aspartate receptors may be mobilized to the membrane. This receptor-trafficking results in a decreased inhibitory control and increased excitation that may lead to continuing status epilepticus. Alterations in neuropeptide and other gene expressions over several hours may also contribute to sustained status epilepticus [19]. The internalization of γ-aminobutyric acid receptors may explain the clinical finding that bezodiazepines, which work via γ-aminobutyric acid mechanisms, are less effective as seizure durations increase [8], and may suggest a role for N-methyl-D-aspartate-modulating medications such as ketamine.

To date, there have been no randomized trials for refractory status epilepticus, although there is increasing published experience regarding various treatment options. Most published protocols list several options for the treatment of refractory status epilepticus, because there is no clear standard. Here, we review the treatment options for pediatric refractory status epilepticus, provide an example of a protocol based on our experience and the limited available data, and highlight key issues that future investigations must confront.

Data Search

A literature search of MEDLINE was performed using the search terms "refractory status epilepticus" and "status epilepticus," cross-referenced in series with specific medications and treatment modalities, including benzodiazepine, midazolam, diazepam, lorazepam, phenytoin, phenobarbital, pentobarbital, thiopental, propofol, isoflurane, desflurane, anesthetic, valproic acid, topiramate, levetiracetam, ketamine, pyridoxine, the ketogenic diet, surgery, resection, hemispherectomy, vagal nerve stimulator, adrenocorticotropic hormone, steroid, and plasmapheresis. The results of these searches were reviewed to identify articles pertaining to children (non-neonates). Further articles were identified in the reference lists of the literature identified by the MEDLINE search. Clinical studies, meta-analyses, case series, and case reports were included. Publications that did not include significant primary data, such as commentaries or reviews, were excluded. When multiple larger studies have been reported, the initial case reports that may have prompted further investigation are not discussed. However, when only case reports and series are available for a medication, these publications are reviewed.

To be broadly inclusive of studies addressing refractory status epilepticus, we reviewed studies in which at least two medications failed to terminate status epilepticus, and we did not require specific seizure durations. In reviewing the literature, we noted that efficacy was defined variably as seizure cessation, reduction, termination without recurrence, and termination without side effects. Termination was sometimes defined clinically, and sometimes electrographically. Moreover, the efficacy and adverse-event profiles of various medications are difficult to ascertain, because studies of refractory status epilepticus generally include patients undergoing treatment with multiple medications, and their refractory status epilepticus is often due to etiologies that may lead to similar adverse reactions as do the anticonvulsant medications employed to treat refractory status epilepticus, such as respiratory depression and cardiovascular dysfunction. We aimed to describe the definitions used for each particular study. A systematic meta-analysis was not performed because of the very limited number of trials that defined refractory status epilepticus similarly and that compared similar populations, medications, and overall treatment strategies. Only the English-language literature was reviewed.

Refractory Status Epilepticus Treatment

Midazolam

Midazolam is an injectable benzodiazepine that is fast-acting, rapidly penetrates the blood-brain barrier, and exerts a short duration of action. The mechanism of midazolam involves the positive allosteric modulation of γ-aminobutyric acid type A receptors (fast, chloride-

permeable, and ionotropic), which suppresses neuronal excitability [20]. Midazolam is hydroxylated in the liver, and the metabolite is excreted by the kidneys, so that levels are affected by other medications metabolized by this isozyme and by hepatic or renal dysfunction. With more prolonged use, midazolam may accumulate, extending the terminal half-life, and tachyphylaxis may occur [21].

Several studies reported on the use of midazolam in refractory status epilepticus, using different dosing and treatment goals [7,22-31]. A meta-analysis of 111 children indicated that midazolam was as effective as other coma-inducing medications and involved a lower mortality (zero with midazolam) [28]. A multicenter, retrospective study suggested the efficacy of both midazolam boluses and continuous infusion [31]. Another study compared midazolam and diazepam in 40 children and indicated a similar efficacy (86% and 89%, respectively), but midazolam was associated with a higher recurrence (57% versus 16%) and higher mortality (38% versus 10.5%) [26]. Other studies suggested efficacy in 71-97% of patients [7,23-25,27,29,30]. Seizure control was reported as rapid, occurring in 0.3-1.1 hours [7,23-30]. Some [23,24,30] but not all [26,31] of these studies reported a longer time to control seizures when lower dose boluses were used. Breakthrough seizures were reported in 47-57% of patients [26,29], and relapse was reported in 6-19% [26,29,30]. Some studies reported no adverse reactions [7,23,25,27,30], transient desaturation [24], or respiratory depression [31]. Whereas some studies described hypotension requiring intravenous fluid administration [29] or, rarely, vasopressor support [26], other studies described cardiovascular stability even in children receiving high doses of midazolam (24 μg/kg/min [25] or 32 μg/kg/min [29]).

Together, these studies suggest that an initial bolus of 0.1-0.5 mg/kg, followed by an infusion of 1-2 μg/kg/min that is increased as needed to 30 μg/kg/min, controls refractory status epilepticus in most children. Higher boluses and more rapid escalation may be associated with more prompt seizure control. Side effects are minimal, but may rarely include hypotension. Breakthrough and recurrent seizures are common.

Pentobarbital

Pentobarbital is an intravenous anesthetic barbiturate that depresses neuronal excitability by enhancing γ-aminobutyric acid-coupled responses. Pentobarbital is the first metabolite of thiopental. Compared with phenobarbital, pentobarbital has faster brain penetration (allowing faster control of seizures) and a shorter half-life (allowing faster waking from coma upon weaning), although due to lipid solubility, accumulation may occur with prolonged administration. Pentobarbital is associated with respiratory depression, myocardial depression, hypotension, and low cardiac output.

Surveys of epileptologists and critical-care physicians in the United States and Europe reported that barbiturates [32], and specifically pentobarbital, are the treatments of choice for refractory status epilepticus [33]. A meta-analysis of 28 articles that included 193 adults with refractory status epilepticus compared pentobarbital, midazolam, and propofol. Pentobarbital was associated with a significantly lower incidence of short-term treatment failure, breakthrough seizures, and the need to change to a different medication, but was also associated with a significantly higher frequency of hypotension [34]. However, patients treated with pentobarbital tended to be treated to the point of burst suppression, whereas those treated with midazolam or propofol tended to be treated to seizure suppression.

Studies of pentobarbital for refractory status epilepticus in children reported an efficacy of 74-100% [28,35,36] and a high incidence of hypotension [36]. The largest of these studies included 26 children aged 1 day to 13 years, and employed a loading dose of 5 mg/kg followed by an infusion of 1-3 mg/kg/hr, and after 48 hours of seizure freedom, a reduction to 0.5 mg/kg/hr. Efficacy was reported for 74% of patients, and there was relapse in 22% [35]. These studies suggest that pentobarbital is effective in promptly controlling seizures and producing a burst-suppression pattern. The initial bolus is generally 5 mg/kg followed by an infusion of 1 mg/kg/hr, which can increase as needed to 3 mg/kg/hr. Continuous blood-pressure monitoring is important, because hypotension may occur with dose escalation.

High-Dose Phenobarbital

Phenobarbital is a barbiturate that depresses neuronal excitability by enhancing the γ-aminobutyric acid receptor-coupled response, and that has a longer half-life than pentobarbital. Studies reported a high efficacy of phenobarbital in treating initial status epilepticus in children. A prospective study of 36 children with status epilepticus indicated that phenobarbital stopped seizures faster than did a combination of diazepam and phenytoin, and the safety profiles were similar [37]. Thus, phenobarbital is often one of the first-line medications administered for status epilepticus. In cases where the initial treatment with phenobarbital is ineffective and refractory status epilepticus ensues, several studies reported on the efficacy of high-dose phenobarbital in refractory status epilepticus. A retrospective report of 50 children with refractory status epilepticus treated with high-dose phenobarbital to achieve serum levels of up to 1481 μmol/L described that seizures were controlled in 94%. Intubations were common, but hypotension was unusual and mild [38]. A recent report described three children with presumed viral encephalitis causing refractory status epilepticus that persisted despite treatment with midazolam and thiopental infusions, who were treated with phenobarbital at doses of 70-80 mg/kg/day, resulting in serum levels of >1000 μmol/L. All three had improved seizure control, although breakthrough seizures occurred [39]. In addition, after a

coma is achieved with pentobarbital, high-dose phenobarbital (to achieve a maximum serum level 1249 μmol/L) is reported to improve seizure control during pentobarbital weaning [40].

Propofol

Propofol is an intravenous alkyl-phenol general anesthetic thought to modulate γ-aminobutyric acid receptors, and that is rapidly acting and is easily titratable. It is primarily metabolized in the liver and generally has a short half-life, allowing rapid awakening after drug cessation, although with prolonged administration, the terminal half-life may amount to several days. Propofol, especially in children, was associated with what was termed "propofol infusion syndrome," i.e., cardiac failure, rhabdomyolysis, metabolic acidosis, renal failure, and sometimes death. Reported risk factors include high doses, prolonged use, supportive treatments with catecholamines and corticosteroids, and possibly a low body mass index. Fatalities were also reported when propofol was administered in conjunction with a ketogenic diet [41]. This complication limits the use of propofol in children [42]. However, a similar syndrome was also reported with thiopental administration for status epilepticus, and components of the syndrome may be attributable to status epilepticus alone, suggesting that the syndrome may be related not only to propofol, but to some combination of more diverse sedative-anticonvulsant regimens, status epilepticus, and pharmacologic suppression of cerebral activity [43].

A retrospective study of 33 children (aged 4 months to 15 years) with refractory status epilepticus indicated that propofol was more effective than thiopental in terminating seizures (64% versus 55%). The mean treatment duration with propofol was 57 hours (range, 10-264 hours). Propofol was initiated with a bolus of 1-2 mg/kg followed by an infusion of 1-2 mg/kg/hr, which was increased as needed to a maximum of 5 mg/kg/hr. Complications, including rhabdomyolysis and hypertriglyceridemia, prompted discontinuation in 18% of patients, although these laboratory values normalized after propofol was discontinued, and no deaths were attributable to propofol [44].

Studies in adults indicated that propofol infusion terminates seizures in 67% of patients [45]. Propofol induces burst suppression within 35 minutes of initiation [46], but maintenance of burst suppression requires frequent titration [46]. Hypotension requiring vasopressor administration occurs in 50-70% of patients [45,46].

These studies suggest that propofol may be effective in terminating refractory status epilepticus quickly, but propofol was not demonstrated to be more effective than other medications, and may be associated with higher risk and higher mortality. Optimal dosing has not been established. Given the wide range of doses reported to produce burst suppression and the high incidence of hypotension, an initial low-dose bolus of 1-2 mg/kg, followed by an infusion of 2 mg/kg/hr that is titrated as needed, seems

appropriate. The maximum dose or duration of infusion that is safe and effective has not been established. Laboratory testing to monitor for side effects seems advisable.

Inhaled Anesthetics

Although the mechanism of action of inhalational anesthetics is not well-understood, the antiepileptic effects of isoflurane may be attributable to the potentiation of inhibitory postsynaptic γ-aminobutyric acid type A receptor-mediated currents on thalamocortical pathways. Both isoflurane and desflurane produce dose-dependent electroencephalogram changes, at first increasing the frequency and lowering the voltage, and then progressively decreasing the voltage and producing burst suppression [47]. Not all inhalation medications have similar properties; some inhalational medications such as sevoflurane may induce epileptiform discharges at therapeutic levels [48].

A case series reported on the use of isoflurane for 1-55 hours in 9 patients (11 episodes), including 5 children, with refractory status epilepticus. All achieved burst suppression, and all developed hypotension requiring vasopressors. Seizures recurred after isoflurane was discontinued in 73% (8 of 11). All three patients who survived had cognitive deficits. The authors concluded that isoflurane may be administered for seizures when other agents in anesthetic doses are ineffective or produce unacceptable side effects [49].

A retrospective case series of seven patients, including one 17-year-old, with refractory status epilepticus treated with inhalational anesthetic agents (isoflurane in 6, desflurane in 1) reported that seizures were consistently terminated and burst suppression was achieved within several minutes of initiation. The maximal end-tidal isoflurane concentration ranged from 1.2-5.0%, and was administered for a mean period of 11 days (maximum, 26 days). All patients had hypotension requiring vasopressor support and atelectasis, and several had infections, paralytic ileus, and deep venous thrombosis. After discontinuation, subclinical seizures occurred in one patient, and nonconvulsive status epilepticus occurred in two patients. Three patients died, but the four survivors had good or excellent outcomes [50].

These studies suggest that inhalational anesthetics (particularly isoflurane) are effective in terminating refractory status epilepticus and inducing burst suppression, but all patients will exhibit hypotension requiring vasopressors, and there is frequent seizure recurrence when the anesthetic is gradually withdrawn. Optimal protocols for initiation and titration have not been established.

Ketamine

Ketamine is a noncompetitive N-methyl-D-aspartate glutamate receptor antagonist that may be effective in later stages of refractory status epilepticus, because it acts independently of γ-aminobutyric acid-related mecha-

nisms. Animal models demonstrated a late (at 1 hour) but not early (at 15 minutes) efficacy of ketamine, implying that before receptor changes occur, it will be ineffective [51]. In addition, ketamine may be neuroprotective by reducing N-methyl-D-aspartate receptor-mediated excitotoxic injury [52]. Ketamine is metabolized by P450 liver enzymes into an active metabolite norketamine, and thus levels may be affected by other anticonvulsants.

Five children, aged 4-7 years and with known severe epilepsy with refractory nonconvulsive status epilepticus lasting 2-10 weeks (mean duration, 4.4 weeks), were treated with oral ketamine at 1.5 mg/kg/day divided twice daily, and all demonstrated a response within 48 hours, as measured by reduced seizures on electroencephalogram and improved mental status. Only one child had a recurrence of nonconvulsive status epilepticus several months later, which was again treated effectively with ketamine. No side effects were noted [53]. A previously healthy 13-year-old girl with refractory status epilepticus of unknown etiology persisting for 4 weeks received an intravenous bolus of 2 µg/kg of ketamine, and within 90 seconds, clinical and electrographic seizures terminated. She was then treated for 2 weeks with intravenous ketamine (maximum dose, 7.5 µg/kg/hr), which improved seizure control such that she had only several seizures per day [54].

It remains unclear whether ketamine can be used safely in patients with neurologic injury. There may be adverse effects such as cerebellar toxicity with prolonged ketamine administration [55]. Some studies reported increased intracranial pressure with ketamine administration for lumbar-puncture sedation [56], but a recent review of the literature did not find evidence that ketamine raised intracranial pressure. In fact, ketamine was associated with improved cerebral perfusion [57]. Ketamine may improve cerebral blood flow by increasing blood pressure because of its sympathomimetic properties, in contrast with most medications used for refractory status epilepticus, which reduce blood pressure.

Thus, ketamine may be a useful adjuvant in the treatment of refractory status epilepticus, especially in late stages when medications that rely on γ-aminobutyric acid enhancement are ineffective. However, further study is needed to determine the optimal dosing, timing of administration, and effects on intracranial pressure and cerebral blood flow.

Valproic Acid

Valproic acid is a broad-spectrum anticonvulsant thought to modulate sodium and calcium channels, as well as inhibitory γ-aminobutyric acid transmission [20]. It is available as an intravenous formulation. A study in adults with epilepsy (but not actively manifesting seizures) indicated that rapid infusion (10 mg/kg/min) was not associated with adverse effects, including local infusion-site reactions or hemodynamic effects [58]. The safety of rapid infusion in children has not been studied.

Several studies reported that valproic acid is highly effective in 78-100% of children with refractory status epilepticus, with no adverse effects [59,60]. One study of 18 children used a loading dose of 25 mg/kg, and reported 100% seizure termination within 30 minutes, with no adverse reactions [59]. A second study of 41 children loaded with 20-40 mg/kg, and then infused at 5 mg/kg/hr, reported a 78% termination of clinical and electroencephalogram signs of seizures, with 66% achieving control within 6 minutes. There were no adverse effects [60]. However, there are case reports of hypotension with valproic acid infusion for status epilepticus [61]. Valproic acid may induce encephalopathy, with or without elevated ammonia levels, and this possibility must be considered in patients with persisting encephalopathy.

These studies suggest that valproic acid exhibits high efficacy in promptly treating refractory status epilepticus, with few adverse reactions. It may be particularly useful in situations when successful intubation is unlikely, because there is a lower risk of respiratory failure than with other agents. The initial bolus may be 20-30 mg/kg. If seizures are terminated, then a continuation of periodic (twice per day) dosing may be appropriate. If seizures continue, a continuous infusion of 5 mg/kg/hr may be efficacious.

In the outpatient setting, valproic acid is estimated to cause hepatotoxicity in 1 in 500 children aged <2 years, and in children with metabolic disease, and thus must be used with caution in young children with status epilepticus of unclear etiology. According to a recent practice parameter for status epilepticus in children, the data from nine class III studies revealed that an inborn error of metabolism was diagnosed in 4.2% of children with status epilepticus [62], although this testing was generally performed on children with suspected metabolic disease; thus, the true incidence among all patients with status epilepticus is likely lower. Hepatotoxicity occurs with more prolonged outpatient use, and has not been reported with briefer intravenous use for status epilepticus.

Topiramate

Topiramate exhibits several mechanisms of action, including blockage of voltage-sensitive sodium and calcium channels, enhancement of γ-aminobutyric acid activity via modulation of the γ-aminobutyric acid type A receptor, and modulation of glutamate receptors via interaction with kainite and alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptors [20]. Because it exhibits mechanisms independent of γ-aminobutyric acid receptors, topiramate may be effective later in refractory status epilepticus, after γ-aminobutyric acid receptors have been targeted by other agents. Studies suggest that rapid titration is safe [63].

In children, topiramate was reported to be effective in controlling seizures, such that coma-inducing medications

could be weaned using various dosing regimens [64-66]. Some protocols slowly titrated the medication, resulting in control in 3-6 days [64,66], whereas others started at a higher dose and produced a response within 1 day [65], without any noted side effects. Three adult reports totaling 10 patients, including 5 without previous epilepsy, described control of refractory status epilepticus with nasogastric topiramate at doses of 300-1600 mg/day [67-69]. None of these studies reported on serum levels, and so the effect of prolonged coma on absorption could not be determined. However, pharmacokinetic studies suggest that an absence of food slightly increases the rate but not the eventual extent of absorption [70], and the reported efficacy of topiramate in refractory status epilepticus suggests at least some absorption. Whereas topiramate was not demonstrated to be useful in initial status epilepticus management, these studies suggest that it may serve as a useful add-on medication after patients have been treated with coma induction.

Levetiracetam

Levetiracetam is an anticonvulsant medication, thought to have multiple sites of action including calcium channels, glutamate receptors, and γ-aminobutyric acid modulation [20]. Recent animal studies demonstrated that treatment with levetiracetam during the maintenance phase of status epilepticus diminished or aborted seizures [71], is neuroprotective in animals experiencing status epilepticus [72], and may reduce the epileptogenic effects of status epilepticus [73]. Levetiracetam is available as oral and intravenous preparations, although the intravenous form is not approved for use in children. Refractory status epilepticus is often associated with systemic disorders, such as coagulopathy, liver failure, and hypotension, that could be complicated by traditional anticonvulsants. Intravenous levetiracetam may provide an alternative because it is not metabolized by the liver, has low protein binding, is renally excreted, and exhibits limited drug-drug interactions.

Studies in adults suggest that levetiracetam is safe in critically ill patients [74], and that it may be effective in refractory status epilepticus. In adults, intravenous infusion and oral tablets are bioequivalent [75,76], and intravenous infusion is well-tolerated [75]. A study of six patients, including an adolescent with static encephalopathy, indicated that nasogastric doses of 500-3000 mg/day controlled seizures in 12-96 hours, with no noted adverse effects [77]. In eight adults with nonconvulsive status epilepticus, a cessation of ictal electroencephalogram-activity occurred within 3 days of levetiracetam initiation, without side effects [78]. A study of 23 adults (39% with refractory status epilepticus) receiving nasogastric levetiracetam at a median dose of 2000 mg (range, 750-9000 mg) indicated that 43% responded (status epilepticus or refractory status epilepticus resolved within 72 hours of the start of, or an increase in, levetiracetam administration, without recurrence of seizures lasting >10 seconds or

more frequent than two per hour). All responders received levetiracetam within 4 days of the onset of status epilepticus, at doses of <3000 mg daily. These data suggest that levetiracetam may be efficacious when administered early, and that high doses are unlikely to provide benefits [79]. We administered intravenous levetiracetam to five children with refractory status epilepticus, achieved the expected serum levels, and noted no adverse events. A 9-year-old with refractory epilepsy developed nonconvulsive status epilepticus that resolved with a 2-week titration of levetiracetam from 10 mg/kg/day to 40 mg/kg/day [80]. However, in view of this long period of titration, the seizures may have terminated spontaneously. Further study is needed to determine the role of levetiracetam in refractory status epilepticus.

Pyridoxine

Pyridoxine-dependent seizures constitute a rare autosomal-recessive condition that generally presents in the early neonatal period. The seizures are refractory to common antiepileptic medications, but are effectively treated with pyridoxine (vitamin B6). Pyridoxine and related compounds can be converted to pyridoxal phosphate, which is an active cofactor in multiple metabolic pathways. The diagnosis of pyridoxine-related seizures is made when the administration of intravenous pyridoxine (vitamin B6, 100 mg, from 1-5 doses) terminates seizures, sometimes for several months after administration. If refractory status epilepticus terminates, it may be unclear whether this was attributable to pyridoxine, time, or other co-administered medications. After several months, other anticonvulsants and then pyridoxine must then be withdrawn. If seizures recur following pyridoxine cessation and are then controlled by a re-initiation of pyridoxine, then pyridoxine-dependent seizures are diagnosed [81]. Some children who do not respond to pyridoxine may respond to oral pyridoxal phosphate [82]. With lifelong administration, the seizures are generally well-controlled. Characteristic cerebrospinal fluid findings include elevated pipecolic acid [81].

There are reports of older infants (up to 18 months of age) with status epilepticus controlled by pyridoxine [83-85]. Patients with a neonatal onset of pyridoxine-deficient seizures may also have seizures and status epilepticus later in life when pyridoxine is discontinued accidentally [86].

These data suggest that, for patients in whom the treatable condition of pyridoxine-dependent seizures may not be recognized, all infants (at least up to 2 years of age) without a clear symptomatic etiology could benefit from a trial of intravenous pyridoxine and possibly oral pyridoxal phosphate.

Ketogenic Diet

The ketogenic diet is high-fat and low-carbohydrate, and is useful in drug-resistant epilepsy. It requires a

precise nutrition regimen and can be administered via modified parenteral nutrition solutions. Most complications are mild and reversible, including hypoglycemia, acidosis, and hyperlipidemia, but there are rare occurrences of cardiomyopathy and pancreatitis [87]. There have been no studies of the ketogenic diet in refractory status epilepticus, although it is sometimes employed in refractory status epilepticus (personal experience at the authors' institution). The occurrence of propofol infusion syndrome with the initiation of a ketogenic diet was reported in a 10-year-old with refractory status epilepticus [41], possibly related to an impairment of fatty-acid oxidation with propofol, which suggests that the two approaches should not be used simultaneously.

Corticosteroids, Adrenocorticotropic Hormone, and Plasmapheresis

Immune-modulating therapies are sometimes employed in refractory status epilepticus treatment, including corticosteroids, adrenocorticotropic hormone, and plasmapheresis. There are a few case reports of these interventions. Some neuro-intensivists reported good outcomes with plasmapheresis [88], and there are descriptions of the efficacy of adrenocorticotropic hormone [89,90] and steroids [90] in refractory epilepsy other than infantile spasms. These therapies may be useful in the context of autoimmune etiologies for refractory status epilepticus, such as Rasmussen's encephalitis or vasculitis.

Hypothermia

Human studies demonstrated the benefit of hypothermia after cardiac arrest in adults and neonatal encephalopathy, but there are few data regarding efficacy or safety in epilepsy or status epilepticus. Animal studies demonstrated clear neuroprotective effects of moderate therapeutic hypothermia, and suggest that hypothermia has anticonvulsant properties [91], especially when administered with a benzodiazepine [92]. In one adult, before resection of a frontal tumor, a 4°C saline application for 30 seconds resulted in a transient but complete termination of interictal spikes [93]. One case series described three children with refractory status epilepticus successfully treated with hypothermia (30-31°C) along with barbiturate coma, but the effect of hypothermia could not be separated from that of medication [94]. Further data are necessary to determine whether therapeutic hypothermia is of benefit in refractory status epilepticus.

Electroconvulsive Therapy

Electroconvulsive therapy may enhance γ-aminobutyric acid transmission, and thus was proposed to be useful in the treatment of intractable epilepsy [95]. Re-

fractory epilepsy and status epilepticus are listed as indications for electroconvulsive therapy by the American Psychiatric Association Task Force [96]. Two children with intractable epilepsy demonstrated a marked decrease in seizures after electroconvulsive therapy, and in one of these children, electroconvulsive therapy effectively treated two episodes of nonconvulsive status epilepticus [97]. In one adult, six electroconvulsive therapy treatments terminated status epilepticus and allowed a gradual withdrawal from barbiturate coma; there was complete recovery in 1 month [98]. In another adult with nonconvulsive status epilepticus, electroconvulsive therapy terminated status epilepticus, allowing the patient to be weaned off coma-inducing medication, but the patient remained in a coma [99]. Electroconvulsive therapy may also induce seizures and nonconvulsive status epilepticus. Hence, continued electroencephalogram monitoring after electroconvulsive therapy is essential.

In an adult with multifocal refractory status epilepticus, stimulation of the ictal onset zones by subdural electrodes, placed as part of a surgical evaluation, temporarily terminated seizures, but did not result in a favorable outcome [100].

It remains unclear whether an earlier use of electroconvulsive therapy or subdural electrode stimulation to terminate status epilepticus might result in better outcomes.

Surgery

Epilepsy surgery is known to improve seizure control in some patients with intractable epilepsy. Several case reports and series described the efficacy of various surgical procedures in children with refractory status epilepticus. Etiologies include focal cortical dysplasias, hypothalamic hamartoma, cortical tubers, cerebral cavernous malformations, Rasmussen's encephalitis, and prenatal anterior circulation infarcts [101-103]. In one patient, a dysplastic lesion was noted on 3-T but not 1.5-T magnetic resonance imaging scans [101]. In other patients, no lesions were visible on magnetic resonance images, but resection was performed based on magnetoencephalography identified unilateral clustered interictal spike sources [103] or ictal-electroencephalogram and single-photon emission computed tomography localization [104] with successful refractory status epilepticus termination. Procedures include focal resection [101-103,105,106], lobectomy [103], multiple subpial transection [104,106], hemispherectomy [102,107], and callosal section [106,108]. One case series of 5 children indicated that 4 children exhibited a termination of seizures, and one had a reduction in seizures [101]. A second series of 10 children with preexisting epilepsy in refractory status epilepticus reported that refractory status epilepticus was terminated in all, and at follow-ups of 4 months to 6.5 years, seven patients remained seizure-free [102]. A third series of five children evaluated with magnetoencephalography in addition to standard tests reported that refractory status epilep-

ticus terminated in all. One of the patients, a 2.5-year-old with cortical dysplasia, required two operations (cortical excision followed by hemispherectomy) to terminate refractory status epilepticus. At follow-up, 2 patients were seizure-free, and 3 had episodic seizures [103].

Vagal nerve stimulators have also been used in refractory status epilepticus. A 13-year-old boy with previously diagnosed refractory epilepsy, admitted because of refractory status epilepticus, experienced complete cessation of seizures acutely with left vagal nerve stimulator placement, and demonstrated improved seizure control over the next 1.5 years compared with baseline [109].

These studies suggest that neurosurgical interventions need not be considered a last resort in children with refractory status epilepticus if a focal area of ictal onset can be identified. A rapid surgical evaluation may be indicated in children with refractory status epilepticus, and other modalities for localization, such as magnetoencephalography and single-photon emission computed tomography, may allow for successful resections, even when magnetic resonance imaging does not identify a lesion.

Other Treatment Issues: Delay in Treatment

The impact of delay in treating status epilepticus is challenging to study, because it is confounded by the etiology of the status epilepticus. However, some data are available. A recent series of 157 children, aged 1 month to 16 years, with seizures lasting >5 minutes, reported that seizures lasted 5-29 minutes in 39%, and ≥60 minutes in 61%. Treatment delays of <30 minutes did not affect response, but when the delay exceeded 30 minutes, there was an association with delay in achieving seizure control [8]. In a study of 27 children, first-line (benzodiazepine) and second-line (phenytoin or phenobarbital) medications were effective in terminating status epilepticus in 86% of patients when seizure duration was <20 minutes at presentation, and only 15% when seizure duration exceeded 30 minutes [9]. In a retrospective study of 358 children who received midazolam for status epilepticus, the effectiveness of treatment decreased as the time to treatment increased. Efficacy was significantly lower when treatment was initiated >3 hours after seizure onset, and there was a trend toward reduced efficacy even at an hour, especially when the etiology was epilepsy and not an acute symptomatic etiology [31]. Similarly, in adults with status epilepticus, response to the initial treatment occurred in 80% of patients when treatment began within 30 minutes, but in only 40% when treatment began >2 hours after the onset of status epilepticus [4].

Other Treatment Issues: Titrating Goals and Duration

When coma-inducing agents are employed, it remains unclear whether the treatment goal should be termination of seizures, burst suppression, or a complete suppression of electroencephalogram activity. Further, it remains un-

clear how long the patient should be maintained in a coma. In a survey of 63 European epileptologists and critical-care physicians that allowed for multiple responses, 34% aimed for clinical seizure termination, 63% aimed for electrophysiologic seizure termination, and 69% aimed for burst suppression [32].

Studies so far yield conflicting results, and there have been few investigations in children. Adult studies comparing the treatment goals of burst suppression versus seizure termination are inconclusive. One report indicated no difference in clinical variables and outcome [110], one report indicated that more suppression was associated with greater freedom from seizures and better survival without additional adverse reactions, including hypotension [111], and a third report indicated that burst suppression was associated with fewer breakthrough seizures but a significantly higher frequency of hypotension [34]. The largest of these studies involved a meta-analysis of 28 articles that included 193 adults with refractory status epilepticus, and indicated that titration to electroencephalogram background suppression, compared with seizure suppression, resulted in significantly fewer breakthrough seizures (4% versus 53%) but a significantly higher frequency of hypotension (29% versus 76%). There was no significant difference in short-term treatment failure, withdrawal seizures, need to change medication, or mortality [34]. Further research is needed to determine whether treatment in children should attempt to suppress all seizures or induce burst suppression with a significant reduction in seizures. If burst suppression is preferred, the optimal degree of burst suppression is also unknown.

Most protocols suggest maintaining a coma for 24-48 hours, and this was the most common duration specified in a survey of epileptologists and critical-care physicians [32], but there are few data to provide guidance in the optimal duration of a coma.

Other Treatment Issues: Weaning of Coma-Inducing Medications

There are few data regarding the optimal rate of weaning, or the amount of seizure burden or number and types of epileptiform discharges that can be tolerated. During the period of coma induction and burst suppression, there may be some uncoupling of electrographic and clinical seizures. Thus, many seizures designated as refractory status epilepticus may occur during weaning from coma-inducing medications, and may be solely electrographic. In a study of the prognoses of 22 children with refractory status epilepticus, all survivors manifested intractable epilepsy, and many children manifested persisting seizures during or shortly after weaning from antiseizure medications [112]. Further, aggressive treatment may lead to complications such as hypotension [113,114]. This finding suggests that a continuation of high-dose suppressive therapy because of some seizures during the weaning phase may not improve the likelihood of a seizure-free

outcome. Further study is needed to elucidate the optimal weaning parameters.

Importance of Seizures on Outcome

Although studies in children revealed high morbidity and mortality associated with refractory status epilepticus, it remains unclear whether this finding reflects an underlying brain injury that is causing the seizures, or a seizure-induced injury, or a combination. A study in children demonstrated that levels of serum neuron-specific enolase, a marker of neuronal injury, were elevated in children with continuous electrographic discharges, even without clinical seizures [115].

Studies in adults indicate that the prognosis is worse with seizures and especially status epilepticus, raising the possibility that the effective treatment of seizures, so that status epilepticus does not occur, may affect outcomes. A study in adults indicated that duration and time to detection predicted the outcomes in patients with nonconvulsive status epilepticus. Mortality amounted to 36% when nonconvulsive status epilepticus was diagnosed within 30 minutes of onset, and 75% when diagnosis was delayed for >24 hours. When nonconvulsive status epilepticus lasted <10 hours, 60% of patients returned home. In contrast, when nonconvulsive status epilepticus lasted >20 hours, none returned home, and 85% of the patients died [116].

Thus, in adults, persistent seizures are likely to result in poorer outcomes, as opposed to simply reflecting an underlying brain injury. However, treating or preventing seizures was not found to improve outcomes, and because some treatments may result in hypotension that can cause secondary brain injury, overly aggressive treatments may be detrimental. Thus, the optimal goals for treatment remain unclear.

Issues for Further Study

Many factors related to refractory status epilepticus have not been clearly defined, and outcome measures have not been agreed upon. Definitions of refractory status epilepticus vary in terms of both required duration and number of failed medications. Status epilepticus is a heterogeneous term comprising a variety of seizure types, including convulsive, nonconvulsive, and subclinical, and including both prolonged seizures and briefer recurrent seizures. Efficacy is defined variably as seizure cessation, seizure reduction, seizure termination without recurrence, and seizure termination without significant adverse effects. The ideal medication would offer not only high efficacy (terminating seizures without recurrence), but high effectiveness (high efficacy with acceptable side effects). Some studies define this endpoint as based on clinical seizures, whereas others rely on electroencephalogram criteria. Some define efficacy as the achievement of burst suppression, and others as the achievement of seizure termination. All of these endpoints are judged at various lengths of time, ranging from minutes to days. Defining and standardizing these terms and aims will be important, both in promoting comparisons and meta-analyses of case series, and in designing controlled studies.

We suggest the following definitions. Refractory status epilepticus involves a seizure of any type (convulsive, subtle, or solely electrographic) that continues despite treatment with adequate doses of a benzodiazepine and fosphenytoin. Refractory status epilepticus may be attributable to many etiologies, and must be divided at least into refractory status epilepticus attributable to underlying epilepsy, and refractory status epilepticus attributable to an acute symptomatic etiology, because these conditions may require different management approaches, and have different outcomes. We define treatment efficacy as the termination of all seizures (convulsive and electrographic) within 30 minutes, without seizure recurrence for 24 hours. We define effectiveness (which includes efficacy and consideration of side effects) as efficacy without hypotension requiring vasopressors, or other serious systemic effects.

Protocols for clinical use must be developed that are modular in nature, so that individual parts can be manipulated in randomized, clinical studies within the context of a generally uniform management approach. Observational studies, which make up much of the literature to date, may contain major biases and confounders, making it difficult to determine whether the efficacy in reported patients is attributable to the specific medication, the dosage, or some more complicated sequence or overall management differences. Randomized, controlled studies are needed. Standardized treatment algorithms must be agreed upon and implemented at multiple centers to allow for multisite studies, because even a simple study comparing two alternatives at a given step, aiming to detect a 15% difference (where $\alpha = 0.05$ and $\beta = 0.8$), would require about 250 children. Given the occurrence of refractory status epilepticus at our own tertiary-care institution, about 10 patients might be enrolled per year, suggesting that completion of the study in 3 years would require the involvement of about 10 centers. Separating patients based on age and the etiology of refractory status epilepticus would require an even larger sample. Investigations of the optimal management of refractory status epilepticus will require a research network.

Protocol Suggestions

Regardless of the many uncertainties surrounding refractory status epilepticus, children with refractory status epilepticus still need treatment. Treatment delay is associated with reduced response to medications. Inadequate doses of medication are common [117,118], and are predictive of treatment response [118]. The use of protocols, even if based on limited data, may improve the quality and efficiency of care.

Several principles have guided the choice of medications in our protocol. First, we aimed to employ medications that can be administered rapidly and penetrate the brain quickly, but will not cause prolonged systemic side effects. Second, assuming that intubation and skilled ventilator management are available, respiratory depression may need to be tolerated, but hypotension should be avoided, because the autoregulation of cerebral blood flow may be abnormal despite the maintenance of systemic blood pressure with vasopressors. Third, employing medications with different mechanisms of action at successive steps may be useful, although this type of rational polytherapy has not been demonstrated to be more effective.

Based on our search of the literature, we developed a protocol for refractory status epilepticus for non-neonates (Table 1). There is clear evidence that earlier treatment is beneficial, and that out-of-hospital treatment is safe and effective. Treatment may begin with buccal midazolam [119-121] or rectal diazepam [122] before arrival at the hospital. During the impending and established status epilepticus phases, initial medications should be given rapidly and in close succession, allowing 5 minutes between benzodiazepine doses and 10 minutes after fosphenytoin administration is completed to judge response. We recommend a single, large dose of fosphenytoin rather than repeated smaller doses. Fosphenytoin was chosen as the second antiseizure medication, because phenobarbital's main mechanism of action, γ-aminobutyric acid enhancement, is similar to the mechanism of action of benzodiazepines, whereas fosphenytoin acts on voltage-gated sodium channels. In addition, phenobarbital is more likely to lead to respiratory and cardiovascular compromise.

If seizures persist after adequate doses of a benzodiazepine and fosphenytoin, then refractory status epilepticus is diagnosed. Patients who are diagnosed with refractory status epilepticus need rapid treatment, but the initiation of coma-inducing medications is associated with a high incidence of side effects and the need for intensive care admission. In the initial refractory status epilepticus stage, we recommend a trial of a third anticonvulsant before the initiation of coma-inducing medications. We have employed intravenous levetiracetam in several patients with refractory status epilepticus, and produced at least a temporary termination of seizures without adverse effects. Alternatively, in patients without known risk factors for hepatotoxicity such as known liver disease or metabolic disease, data suggest that valproic acid may be a useful third-line medication. We elect to use these medications prior to phenobarbital, because recent data suggest that they may be as efficacious. Theoretically, they may be more effective than phenobarbital, given the different mechanisms of action, and they are unlikely to produce respiratory or cardiovascular compromise.

If seizures persist, then in the later phase of refractory status epilepticus, we proceed to a trial of phenobarbital (generally while plans are being made to induce coma with midazolam if phenobarbital does not terminate the seizures), or directly to coma induction. We use midazolam because more published data are available for midazolam in children, and our experience suggests that it is less associated with hypotension than is pentobarbital. After an initial bolus, the infusion is increased every 5-10 minutes, with the goal of burst suppression (approximately 50% burst, 50% suppression) on electroencephalogram. We maintain burst suppression for 24 hours, with electroencephalogram reviews and adjustment of medication as needed several times per day. Coma is then weaned over about 24 hours. If there is recurrence, then the midazolam is reinitiated, and high-dose topiramate is added. Epilepsy surgery is considered if a focal area of ictal onset is clear. Weaning is again attempted after 24 hours of burst suppression.

In September 2007, our protocol was adopted by the neurology, emergency medicine, and pediatric intensive care services at our institution to guide the treatment of status and refractory status epilepticus. The protocol was initially designed by the neurology service, but all related services were involved in refining it, which led to great improvements, both conceptually and in implementation. In our experience, issues related to implementation were often harder to solve than protocol design. Issues included how to provide easy physician access to the protocol, how to ensure that needed medications were readily available in units and did not need to be provided by the main pharmacy, and how to coordinate care and avoid delays in the often-needed transfer from emergency department to intensive care unit. A database is being established to evaluate the effectiveness of the protocol. The protocol was designed in time-locked modules such that various steps can be adjusted and studied with most of the protocol remaining constant. We expect that this approach will allow us to continue to refine medication choices and treatment goals with further experience. After it is implemented consistently, we are hopeful that the module design will allow us to use the protocol as a framework for randomized studies comparing alternative treatments within a given step.

Conclusions

Status epilepticus is associated with the progressive, time-dependent development of pharmaco-resistance. Prompt and aggressive treatment of status epilepticus may reduce the chance of persistence and the development of refractory status epilepticus. Refractory status epilepticus is associated with high mortality and morbidity, as related to both the underlying etiology and seizure control. To date, no randomized, controlled trials address refractory status epilepticus, but there is increasing published experience with multiple medications and treatment strategies for refractory status epilepticus. Treatment strategies must employ prompt treatment, the initiation of coma-inducing medications if seizures are not terminated by initial or secondary medications, and the administration of addi-

Table 1. Convulsive status epilepticus algorithm

Stage	Management

Impending SE, <5 min	Out-of-hospital
	    Consider buccal midazolam or rectal diazepam.
	Benzodiazepines
	    Lorazepam, 0.1 mg/kg IV (maximum, 5 mg) over 1 min,
	    Diazepam, 0.2 mg/kg IV (maximum, 10 mg) over 1 min,
	Allow 5 minutes to determine whether seizure terminates.
	Give oxygen. Stabilize airway, respiration, and hemodynamics as needed. Obtain IV access. Check bedside glucose.
	    Begin EKG monitoring.

Established SE, 5-10 min	Repeat benzodiazepine administration.
	Administer fosphenytoin 30 mg/kg IV at 2-3 mg/kg/min (maximum, 150 mg/min), or phenytoin 30 mg/kg IV at 1
	    mg/kg/min (maximum, 50 mg/min).
	If patient's age is <2 years, consider pyridoxine 100-mg IV push.
	Testing:
	    Bedside glucose CBC Cultures
	    BMP, Mg, Phos LFT Toxicology (serum, urine)
	    AED levels PT, PTT Head CT
	Draw phenytoin level (10 min after infusion).
	Support airway, respiration, hemodynamics as needed. Continuous vital sign and EKG monitoring.
	Consult neurology service.

Initial refractory SE	If seizure continues 10 min after fosphenytoin infusion, then patient has refractory SE, regardless of time elapsed. Administer levetiracetam 20-30 mg/kg IV at 5 mg/kg/min (maximum, 3 g). If contraindication to levetiracetam and no specific concern regarding liver/metabolic disease, then administer valproate 20 mg/kg at 5 mg/kg/min.

Later refractory SE	If seizure continues 5 min after levetiracetam or valproate, administer phenobarbital 30 mg/kg IV at 2 mg/kg/min
	    (maximum rate, 60 mg/min).
	Admit to pediatric intensive care unit. Prepare to secure airway, mechanically ventilate, and obtain central venous
	    access and continuous hemodynamic monitoring through arterial line.
	After clinical seizure terminates, will likely need EEG monitoring to assess for subclinical seizures.

Coma induction	If seizure continues 10 min after completion of phenobarbital infusion, then initiate coma with midazolam 0.2 mg/
	    kg bolus (maximum, 10 mg) over 2 min, and then initiate infusion at 0.1 mg/kg/hr.
	If clinical seizures persist 5 min after initial midazolam bolus, then administer additional midazolam bolus of 0.2
	    mg/kg bolus. Continue infusion.
	If clinical seizures persist after another 5 min, then administer another midazolam bolus of 0.2 mg/kg, and increase
	    infusion to 0.2 mg/kg/hr.
	Repeat as needed. If seizures persist at maximum midazolam (generally, 2 mg/kg/hr) or midazolam infusion is not
	    tolerated, consider transition to isoflurane. Also consider pentobarbital, topiramate, ketamine, valproic acid (if not
	    already used), or levetiracetam (if not already used).

Coma phase	Continue pharmacologic coma for 24 hr after last seizure, with EEG goal of burst suppression. Continue EEG monitoring with at least t.i.d. reviews. Continue initial medications (phenytoin goal level, 20-30 μg/mL; phenobarbital goal level, 40-50 μg/mL). Daily phenobarbital and free phenytoin levels. Continue levetiracetam at 40-80 mg/kg IV, divided every 6 hours (maximum, 3 g).
Weaning phase	Reduce midazolam by 0.05 mg/kg/hr every 3 hr, with frequent EEG review. If no clinical or electrographic seizures, then wean until off. Continue EEG for at least 24 hr after end of infusion, to evaluate for recurrent electrographic seizures.

Repeat coma phase	If clinical or subclinical seizures occur, reinstitute coma with midazolam for 24 hr. Start midazolam at infusion rate
	    that achieved burst suppression (approximately 50/50), and increase according to suggested midazolam titration
	    algorithm.
	Initiate topiramate 10 mg/kg NG loading dose followed by 5 mg/kg NG divided b.i.d.
	Additional imaging (3-T magnetic resonance image, consider MEG) and surgical evaluation, as guided by
	    neurology consultation.

Repeat weaning phase	Reduce midazolam by 0.06 mg/kg/hr every 3 hr. If seizure persists, then manage as guided by neurology consultation.
Malignant refractory SE	Consider coma-inducing medications including pentobarbital, short-term propofol, or inhaled anesthetics. Consider add-on medications including levetiracetam, topiramate, ketamine, valproic acid, and ACTH. Reconsider surgical options.

Abbreviations:

ACTH	= Adrenocorticotropic hormone		LFT	= Liver function tests
AED	= Anticonvulsant levels		MEG	= Magnetoencephalography
b.i.d.	= Twice daily		Mg	= Magnesium
BMP	= Basic metabolic panel		NG	= Nasogastric
CBC	= Complete blood count		Ph	= Phosphorus
CT	= Computerized tomography		PT	= Prothrombin time
EEG	= Electroencephalogram		PTT	= Partial thromboplastin time
EKG	= Electrocardiogram		SE	= Status epilepticus
IV	= Intravenous		t.i.d.	= Three times daily

tional medications to reduce the chance of seizure recurrence during weaning. Animal models suggest that some of these additional medications may also be neuroprotective and reduce epileptogenesis, but this requires further study in humans. Further study is also needed to determine the optimal roles of neurosurgical procedures and hypothermia. There is some evidence that coma-inducing medications should be titrated to burst suppression rather than seizure suppression, but the optimal duration of suppression and degree of suppression remain unknown. Further study is needed, and given the infrequency of refractory status epilepticus at any single institution, especially after it is divided according to age and etiology, multicenter studies and reporting will be required.

References

[1] **Lowenstein** DH, Bleck T, Macdonald RL. It's time to revise the definition of status epilepticus. Epilepsia 1999;40:120-2.

[2] **Shinnar** S, Berg AT, Moshe SL, Shinnar R. How long do new-onset seizures in children last? Ann Neurol 2001;49:659-64.

[3] **Wasterlain** CG, Chen JW. Definition and classification of status epilepticus. In: Wasterlain CG, Treiman DM, eds. Status epilepticus. Cambridge, MA: MIT Press, 2006:11-6.

[4] **Lowenstein** DH, Alldredge BK. Status epilepticus at an urban public hospital in the 1980s. Neurology 1993;43:483-8.

[5] **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;339:792-8.

[6] **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.

[7] **Brevoord** JC, Joosten KF, Arts WF, van Rooij RW, de Hoog M. Status epilepticus: Clinical analysis of a treatment protocol based on midazolam and phenytoin. J Child Neurol 2005;20:476-81.

[8] **Eriksson** K, Metsaranta P, Huhtala H, Auvinen A, Kuusela AL, Koivikko M. Treatment delay and the risk of prolonged status epilepticus. Neurology 2005;65:1316-8.

[9] **Lewena** S, Young S. When benzodiazepines fail: How effective is second line therapy for status epilepticus in children? Emerg Med Australas 2006;18:45-50.

[10] **Maytal** J, Shinnar S, Moshe SL, Alvarez LA. Low morbidity and mortality of status epilepticus in children. Pediatrics 1989;83:323-31.

[11] **Dunn** DW. Status epilepticus in children: Etiology, clinical features, and outcome. J Child Neurol 1988;3:167-73.

[12] **Eriksson** KJ, Koivikko MJ. Status epilepticus in children: Aetiology, treatment, and outcome. Dev Med Child Neurol 1997;39: 652-8.

[13] **Chin** RF, Neville BG, Peckham C, Bedford H, Wade A, Scott RC. Incidence, cause, and short-term outcome of convulsive status epilepticus in childhood: Prospective population-based study. Lancet 2006;368:222-9.

[14] **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.

[15] **Holtkamp** M, Othman J, Buchheim K, Masuhr F, Schielke E, Meierkord H. A "malignant" variant of status epilepticus. Arch Neurol 2005;62:1428-31.

[16] **Van Lierde** I, Van Paesschen W, Dupont P, Maes A, Sciot R. De novo cryptogenic refractory multifocal febrile status epilepticus in the young adult: A review of six cases. Acta Neurol Belg 2003;103: 88-94.

[17] **Wilder-Smith** EP, Lim EC, Teoh HL, et al. The NORSE (new-onset refractory status epilepticus) syndrome: Defining a disease entity. Ann Acad Med Singapore 2005;34:417-20.

[18] **Kramer** U, Shorer Z, Ben-Zeev B, Lerman-Sagie T, Goldberg-Stern H, Lahat E. Severe refractory status epilepticus owing to presumed encephalitis. J Child Neurol 2005;20:184-7.

[19] **Chen** JW, Wasterlain CG. Status epilepticus: Pathophysiology and management in adults. Lancet Neurol 2006;5:246-56.

[20] **Rogawski** MA, Loscher W. The neurobiology of antiepileptic drugs. Nat Rev Neurosci 2004;5:553-64.

[21] **Naritoku** DK, Sinha S. Prolongation of midazolam half-life after sustained infusion for status epilepticus. Neurology 2000;54: 1366-8.

[22] **Kumar** A, Bleck TP. Intravenous midazolam for the treatment of refractory status epilepticus. Crit Care Med 1992;20:483-8.

[23] **Rivera** R, Segnini M, Baltodano A, Perez V. Midazolam in the treatment of status epilepticus in children. Crit Care Med 1993;21:991-4.

[24] **Koul** RL, Raj Aithala G, Chacko A, Joshi R, Seif Elbualy M. Continuous midazolam infusion as treatment of status epilepticus. Arch Dis Child 1997;76:445-8.

[25] **Igartua** J, Silver P, Maytal J, Sagy M. Midazolam coma for refractory status epilepticus in children. Crit Care Med 1999;27:1982-5.

[26] **Singhi** S, Murthy A, Singhi P, Jayashree M. Continuous midazolam versus diazepam infusion for refractory convulsive status epilepticus. J Child Neurol 2002;17:106-10.

[27] **Ozdemir** D, Gulez P, Uran N, Yendur G, Kavakli T, Aydin A. Efficacy of continuous midazolam infusion and mortality in childhood refractory generalized convulsive status epilepticus. Seizure 2005;14: 129-32.

[28] **Gilbert** DL, Gartside PS, Glauser TA. Efficacy and mortality in treatment of refractory generalized convulsive status epilepticus in children: A meta-analysis. J Child Neurol 1999;14:602-9.

[29] **Morrison** G, Gibbons E, Whitehouse WP. High-dose midazolam therapy for refractory status epilepticus in children. Intensive Care Med 2006;32:2070-6.

[30] **Koul** R, Chacko A, Javed H, Al Riyami K. Eight-year study of childhood status epilepticus: Midazolam infusion in management and outcome. J Child Neurol 2002;17:908-10.

[31] **Hayashi** K, Osawa M, Aihara M, et al. Efficacy of intravenous midazolam for status epilepticus in childhood. Pediatr Neurol 2007;36: 366-72.

[32] **Holtkamp** M, Masuhr F, Harms L, Einhaupl KM, Meierkord H, Buchheim K. The management of refractory generalised convulsive and complex partial status epilepticus in three European countries: A survey among epileptologists and critical care neurologists. J Neurol Neurosurg Psychiatry 2003;74:1095-9.

[33] **Claassen** J, Hirsch LJ, Mayer SA. Treatment of status epilepticus: A survey of neurologists. J Neurol Sci 2003;211:37-41.

[34] **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.

[35] **Kim** SJ, Lee DY, Kim JS. Neurologic outcomes of pediatric epileptic patients with pentobarbital coma. Pediatr Neurol 2001;25: 217-20.

[36] **Holmes** GL, Riviello JJ Jr. Midazolam and pentobarbital for refractory status epilepticus. Pediatr Neurol 1999;20:259-64.

[37] **Shaner** DM, McCurdy SA, Herring MO, Gabor AJ. Treatment of status epileticus: A prospective comparison of diazepam and phenytoin versus phenobarbital and optional phenytoin. Neurology 1988;38:202-7.

[38] **Crawford** TO, Mitchell WG, Fishman LS, Snodgrass SR. Very-high-dose phenobarbital for refractory status epilepticus in children. Neurology 1988;38:1035-40.

[39] **Lee** WK, Liu KT, Young BW. Very-high-dose phenobarbital for childhood refractory status epilepticus. Pediatr Neurol 2006;34:63-5.

[40] **Mirski** MA, Williams MA, Hanley DF. Prolonged pentobarbital and phenobarbital coma for refractory generalized status epilepticus. Crit Care Med 1995;23:400-4.

[41] **Baumeister** FA, Oberhoffer R, Liebhaber GM, et al. Fatal propofol infusion syndrome in association with ketogenic diet. Neuropediatrics 2004;35:250-2.

[42] **Niermeijer** JM, Uiterwaal CS, Van Donselaar CA. Propofol in status epilepticus: Little evidence, many dangers? J Neurol 2003;250:1237-40.

[43] **Enting** D, Ligtenberg JJ, Aarts LP, Zijlstra JG. Total suppression of cerebral activity by thiopental mimicking propofol infusion syndrome: A fatal common pathway? Anesth Analg 2005;100:1864-5.

[44] **van Gestel** JP, Blusse van Oud-Alblas HJ, Malingre M, Ververs FF, Braun KP, van Nieuwenhuizen O. Propofol and thiopental for refractory status epilepticus in children. Neurology 2005;65:591-2.

[45] **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.

[46] **Parviainen** I, Uusaro A, Kalviainen R, Mervaala E, Ruokonen E. Propofol in the treatment of refractory status epilepticus. Intensive Care Med 2006;32:1075-9.

[47] **Eger** EI Jr. New inhalational agents—Desflurane and sevoflurane. Can J Anaesth 1993;40:R3-8.

[48] **Jaaskelainen** SK, Kaisti K, Suni L, Hinkka S, Scheinin H. Sevoflurane is epileptogenic in healthy subjects at surgical levels of anesthesia. Neurology 2003;61:1073-8.

[49] **Kofke** WA, Young RS, Davis P, et al. Isoflurane for refractory status epilepticus: A clinical series. Anesthesiology 1989;71:653-9.

[50] **Mirsattari** SM, Sharpe MD, Young GB. Treatment of refractory status epilepticus with inhalational anesthetic agents isoflurane and desflurane. Arch Neurol 2004;61:1254-9.

[51] **Borris** DJ, Bertram EH, Kapur J. Ketamine controls prolonged status epilepticus. Epilepsy Res 2000;42:117-22.

[52] **Shibuta** S, Varathan S, Mashimo T. Ketamine and thiopental sodium: Individual and combined neuroprotective effects on cortical cultures exposed to NMDA or nitric oxide. Br J Anaesth 2006;97:517-24.

[53] **Mewasingh** LD, Sekhara T, Aeby A, Christiaens FJ, Dan B. Oral ketamine in paediatric non-convulsive status epilepticus. Seizure 2003;12:483-9.

[54] **Sheth** RD, Gidal BE. Refractory status epilepticus: Response to ketamine. Neurology 1998;51:1765-6.

[55] **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;4:70-5.

[56] **Ben Yehuda** Y, Watemberg N. Ketamine increases opening cerebrospinal pressure in children undergoing lumbar puncture. J Child Neurol 2006;21:441-3.

[57] **Himmelseher** S, Durieux ME. Revising a dogma: Ketamine for patients with neurological injury? Anesth Analg 2005;101:524-34.

[58] **Limdi** NA, Knowlton RK, Cofield SS, et al. Safety of rapid intravenous loading of valproate. Epilepsia 2007;48:478-83.

[59] **Yu** KT, Mills S, Thompson N, Cunanan C. Safety and efficacy of intravenous valproate in pediatric status epilepticus and acute repetitive seizures. Epilepsia 2003;44:724-6.

[60] **Uberall** MA, Trollmann R, Wunsiedler U, Wenzel D. Intravenous valproate in pediatric epilepsy patients with refractory status epilepticus. Neurology 2000;54:2188-9.

[61] **White** JR, Santos CS. Intravenous valproate associated with significant hypotension in the treatment of status epilepticus. J Child Neurol 1999;14:822-3.

[62] **Riviello** JJ, Ashwal S, Hirtz D, et al. Practice parameter: Diagnostic assessment of the child with status epilepticus (an evidence-based review). Neurology 2006;67:1542-50.

[63] **Glauser** TA, Clark PO, Strawsburg R. A pilot study of topiramate in the treatment of infantile spasms. Epilepsia 1998;39:1324-8.

[64] **Kahriman** M, Minecan D, Kutluay E, Selwa L, Beydoun A. Efficacy of topiramate in children with refractory status epilepticus. Epilepsia 2003;44:1353-6.

[65] **Perry** MS, Holt PJ, Sladky JRT. Topiramate loading for refractory status epilepticus in children. Epilepsia 2006;47:1070-1.

[66] **Blumkin** L, Lerman-Sagie T, Houri T, et al. Pediatric refractory partial status epilepticus responsive to topiramate. J Child Neurol 2005;20:239-41.

[67] **Towne** AR, Garnett LK, Waterhouse EJ, Morton LD, DeLorenzo RJ. The use of topiramate in refractory status epilepticus. Neurology 2003;60:332-4.

[68] **Bensalem** MK, Fakhoury TA. Topiramate and status epilepticus: Report of three cases. Epilepsy Behav 2003;4:757-60.

[69] **Reuber** M, Evans J, Bamford JM. Topiramate in drug-resistant complex partial status epilepticus. Eur J Neurol 2002;9:111-2.

[70] **Doose** DR, Walker SA, Gisclon LG, Nayak RK. Single-dose pharmacokinetics and effect of food on the bioavailability of topiramate, a novel antiepileptic drug. J Clin Pharmacol 1996;36:884-91.

[71] **Mazarati** AM, Baldwin R, Klitgaard H, Matagne A, Wasterlain CG. Anticonvulsant effects of levetiracetam and levetiracetam-diazepam combinations in experimental status epilepticus. Epilepsy Res 2004;58:167-74.

[72] **Gibbs** JE, Walker MG, Cock HR. Levetiracetam: Antiepileptic properties and protective effects on mitochondrial dysfunction in experimental status epilepticus. Epilepsia 2006;47:469-78.

[73] **Glien** M, Brandt C, Potschka H, Loscher W. Effects of the novel antiepileptic drug levetiracetam on spontaneous recurrent seizures in the rat pilocarpine model of temporal lobe epilepsy. Epilepsia 2002;43:350-7.

[74] **Szaflarski** JP, Meckler JM, Szaflarski M, Shutter LA, Privitera MD, Yates SL. Levetiracetam use in critically ill patients. Neurocrit Care 2007;7:140-7.

[75] **Ramael** S, Daoust A, Otou C, et al. Levetiracetam intravenous infusion: A randomized, placebo-controlled safety and pharmacokinetic study. Epilepsia 2006;47:1128-35.

[76] **Ramael** S, De Smedt F, Toublanc N, et al. Single-dose bioavailability of levetiracetam intravenous infusion relative to oral tablets and multiple-dose pharmacokinetics and tolerability of levetiracetam intravenous infusion compared with placebo in healthy subjects. Clin Ther 2006;28:734-44.

[77] **Patel** NC, Landan IR, Levin J, Szaflarski J, Wilner AN. The use of levetiracetam in refractory status epilepticus. Seizure 2006;15:137-41.

[78] **Rupprecht** S, Franke K, Fitzek S, Witte OW, Hagemann G. Levetiracetam as a treatment option in non-convulsive status epilepticus. Epilepsy Res 2007;73:238-44.

[79] **Rossetti** AO, Bromfield EB. Determinants of success in the use of oral levetiracetam in status epilepticus. Epilepsy Behav 2006;8:651-4.

[80] **Trabacca** A, Profice P, Costanza MC, Gesualdi M, De Rinaldis M. Levetiracetam in nonconvulsive status epilepticus in childhood: A case report. J Child Neurol 2007;22:639-41.

[81] **Gospe** SM Jr. Pyridoxine-dependent seizures: New genetic and biochemical clues to help with diagnosis and treatment. Curr Opin Neurol 2006;19:148-53.

[82] **Wang** HS, Kuo MF, Chou ML, et al. Pyridoxal phosphate is better than pyridoxine for controlling idiopathic intractable epilepsy. Arch Dis Child 2005;90:512-5.

[83] **Yoshii** A, Takeoka M, Kelly PJ, Krishnamoorthy KS. Focal status epilepticus as atypical presentation of pyridoxine-dependent epilepsy. J Child Neurol 2005;20:696-8.

[84] **Goutieres** F, Aicardi J. Atypical presentations of pyridoxine-dependent seizures: A treatable cause of intractable epilepsy in infants. Ann Neurol 1985;17:117-20.

[85] **Chou** ML, Wang HS, Hung PC, Sun PC, Huang SC. Late-onset pyridoxine-dependent seizures: Report of two cases. Zh Min Guo Xiao Er Ke Yi Xue Hui Za Zhi 1995;36:434-7.

[86] **Yoshikawa** H, Abe T, Oda Y. Pyridoxine-dependent seizures in an older child. J Child Neurol 1999;14:687-90.

[87] **Freeman** JM, Kossoff EH, Hartman AL. The ketogenic diet: One decade later. Pediatrics 2007;119:535-43.

[88] **Robakis** TK, Hirsch LJ. Literature review, case report, and expert discussion of prolonged refractory status epilepticus. Neurocrit Care 2006;4:35-46.

[89] **Okumura** A, Tsuji T, Kato T, Natsume J, Negoro T, Watanabe K. ACTH therapy for generalized seizures other than spasms. Seizure 2006;15:469-75.

[90] **Verhelst** H, Boon P, Buyse G, et al. Steroids in intractable childhood epilepsy: Clinical experience and review of the literature. Seizure 2005;14:412-21.

[91] **Yang** XF, DDuffy DW, Morley RE, Rothman SM. Neocortical seizure termination by focal cooling: Temperature dependence and automated seizure detection. Epilepsia 2002;43:240-5.

[92] **Schmitt** FC, Buchheim K, Meierkord H, Holtkamp M. Anticonvulsant properties of hypothermia in experimental status epilepticus. Neurobiol Dis 2006;23:689-96.

[93] **Karkar** KM, Garcia PA, Bateman LM, Smyth MD, Barbaro NM, Berger M. Focal cooling suppresses spontaneous epileptiform activity without changing the cortical motor threshold. Epilepsia 2002;43:932-5.

[94] **Orlowski** JP, Erenberg G, Lueders J, Cruse RP. Hypothermia and barbiturate coma for refractory status epilepticus. Crit Care Med 1984;12:367-72.

[95] **Sackeim** HA. The anticonvulsant hypothesis of the mechanisms of action of ECT: Current status. J Ect 1999;15:5-26.

[96] **Weiner** RD, Coffet CE, Fochtmann L. The practice of ECT: Recommendations for treatment, training and privileging, 2nd ed. Washington, DC: American Psychiatric Press, 2001.

[97] **Griesemer** DA, Kellner CH, Beale MD, Smith GM. Electroconvulsive therapy for treatment of intractable seizures. Initial findings in two children. Neurology 1997;49:1389-92.

[98] **Carrasco Gonzalez** MD, Palomar M, Rovira R. Electroconvulsive therapy for status epilepticus. Ann Intern Med 1997;127:247-8.

[99] **Lisanby** SH, Bazil CW, Resor SR, Nobler MS, Finck DA, Sackeim HA. ECT in the treatment of status epilepticus. J Ect 2001;17:210-5.

[100] **Schrader** LM, Stern JM, Wilson CL, et al. Low frequency electrical stimulation through subdural electrodes in a case of refractory status epilepticus. Clin Neurophysiol 2006;117:781-8.

[101] **Ng** YT, Kerrigan JF, Rekate HL. Neurosurgical treatment of status epilepticus. J Neurosurg 2006;105:378-81.

[102] **Alexopoulos** A, Lachhwani DK, Gupta A, et al. Resective surgery to treat refractory status epilepticus in children with focal epileptogenesis. Neurology 2005;64:567-70.

[103] **Mohamed** IS, Otsubo H, Donner E, et al. Magnetoencephalography for surgical treatment of refractory status epilepticus. Acta Neurol Scand 2007;115:29-36.

[104] **D'Giano** CH, Del CGM, Pomata H, Rabinowicz AL. Treatment of refractory partial status epilepticus with multiple subpial transection: Case report. Seizure 2001;10:382-5.

[105] **Ng** YT, Kim HL, Wheless JW. Successful neurosurgical treatment of childhood complex partial status epilepticus with focal resection. Epilepsia 2003;44:468-71.

[106] **Ma** X, Liporace J, O'Connor MJ, Sperling MR. Neurosurgical treatment of medically intractable status epilepticus. Epilepsy Res 2001;46:33-8.

[107] **Duane** DC, Ng YT, Rekate HL, Chung S, Bodensteiner JB, Kerrigan JF. Treatment of refractory status epilepticus with hemispherectomy. Epilepsia 2004;45:1001-4.

[108] **Vossler** DG, Lee JK, Ko TS. Treatment of seizures in subcortical laminar heterotopia with corpus callosotomy and lamotrigine. J Child Neurol 1999;14:282-8.

[109] **Winston** KR, Levisohn P, Miller BR, Freeman J. Vagal nerve stimulation for status epilepticus. Pediatr Neurosurg 2001;34:190-2.

[110] **Rossetti** AO, Logroscino G, Bromfield EB. Refractory status epilepticus: Effect of treatment aggressiveness on prognosis. Arch Neurol 2005;62:1698-702.

[111] **Krishnamurthy** KB, Drislane FW. Depth of EEG suppression and outcome in barbiturate anesthetic treatment for refractory status epilepticus. Epilepsia 1999;40:759-62.

[112] **Sahin** M, Menache CC, Holmes GL, Riviello JJ. Outcome of severe refractory status epilepticus in children. Epilepsia 2001;42:1461-7.

[113] **Kaplan** PW. Assessing the outcomes in patients with nonconvulsive status epilepticus: Nonconvulsive status epilepticus is underdiagnosed, potentially overtreated, and confounded by comorbidity. J Clin Neurophysiol 1999;16:341-53.

[114] **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.

[115] **O'Regan** ME, Brown JK. Serum neuron specific enolase: A marker for neuronal dysfunction in children with continuous EEG epileptiform activity. Eur J Paediatr Neurol 1998;2:193-7.

[116] **Young** GB, Jordan KG, Doig DS. An assessment of nonconvulsive seizures in the intensive care unit using continuous EEG monitoring: An investigation of variables associated with mortality. Neurology 1996;47:83-9.

[117] **Muayqil** T, Rowe BH, Ahmed SN. Treatment adherence and outcomes in the management of convulsive status epilepticus in the emergency room. Epileptic Disord 2007;9:43-50.

[118] **Cascino** GD, Hesdorffer D, Logroscino G, Hauser WA. Treatment of nonfebrile status epilepticus in Rochester, Minn, from 1965 through 1984. Mayo Clin Proc 2001;76:39-41.

[119] **Baysun** S, Aydin OF, Atmaca E, Gurer YK. A comparison of buccal midazolam and rectal diazepam for the acute treatment of seizures. Clin Pediatr (Phila) 2005;44:771-6.

[120] **McIntyre** J, Robertson S, Norris E, et al. Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: A randomised controlled trial. Lancet 2005;366:205-10.

[121] **Scott** RC, Besag FM, Neville BG. Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: A randomised trial. Lancet 1999;353:623-6.

[122] **O'Dell** C, Shinnar S, Ballaban-Gil KR, et al. Rectal diazepam gel in the home management of seizures in children. Pediatr Neurol 2005;33:166-72.