EPILEPSY CURRENTS

American Epilepsy Society Guideline

Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society

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CONTEXT: The optimal pharmacologic treatment for early convulsive status epilepticus is unclear. OBJECTIVE: To analyze efficacy, tolerability and safety data for anticonvulsant treatment of children and adults with convulsive status epilepticus and use this analysis to develop an evidence-based treatment algorithm. DATA SOURCES: Structured literature review using MEDLINE, Embase, Current Contents, and Cochrane library supplemented with article reference lists. STUDY SELECTION: Randomized controlled trials of anticonvulsant treatment for seizures lasting longer than 5 minutes. DATA EXTRACTION: Individual studies were rated using predefined criteria and these results were used to form recommendations, conclusions, and an evidence-based treatment algorithm. RESULTS: A total of 38 randomized controlled trials were identified, rated and contributed to the assessment. Only four trials were considered to have class I evidence of efficacy. Two studies were rated as class II and the remaining 32 were judged to have class III evidence. In adults with convulsive status epilepticus, intramuscular midazolam, intravenous lorazepam, intravenous diazepam and intravenous phenobarbital are established as efficacious as initial therapy (Level A). Intramuscular midazolam has superior effectiveness compared to intravenous lorazepam in adults with convulsive status epilepticus without established intravenous access (Level A). In children, intravenous lorazepam and intravenous diazepam are established as efficacious at stopping seizures lasting at least 5 minutes (Level A) while rectal diazepam, intramuscular midazolam, intranasal midazolam, and buccal midazolam are probably effective (Level B). No significant difference in effectiveness has been demonstrated between intravenous lorazepam and intravenous diazepam in adults or children with convulsive status epilepticus (Level A). Respiratory and cardiac symptoms are the most commonly encountered treatment-emergent adverse events associated with intravenous anticonvulsant drug administration in adults with convulsive status epilepticus (Level A). The rate of respiratory depression in patients with convulsive status epilepticus treated with benzodiazepines is lower than in patients with convul-

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Epilepsy Foundation
Child Neurology Society
American College of Emergency Physicians
Association of Child Neurology Nurses
American Association of Neuroscience Nurses

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sive status epilepticus treated with placebo indicating that respiratory problems are an important consequence of untreated convulsive status epilepticus (Level A). When both are available, fosphenytoin is preferred over phenytoin based on tolerability but phenytoin is an acceptable alternative (Level A). In adults, compared to the first therapy, the second therapy is less effective while the third therapy is substantially less effective (Level A). In children, the second therapy appears less effective and there are no data about third therapy efficacy (Level C). The evidence was synthesized into a treatment algorithm. CONCLUSIONS: Despite the paucity of well-designed randomized controlled trials, practical conclusions and an integrated treatment algorithm for the treatment of convulsive status epilepticus across the age spectrum (infants through adults) can be constructed. Multicenter, multinational efforts are needed to design, conduct and analyze additional randomized controlled trials that can answer the many outstanding clinically relevant questions identified in this guideline.

Background

Traditionally, brief seizures are defined as lasting less than 5 minutes, while prolonged seizures last between 5 and 30 minutes; status epilepticus is defined as more than 30 minutes of either 1) continuous seizure activity or 2) two or more sequential seizures without full recovery of consciousness between seizures (1). The 30-minute definition is based on the duration of convulsive status epilepticus that may lead to permanent neuronal injury by itself (2). Since the majority of seizures are brief, and once a seizure lasts more than 5 minutes it is likely to be prolonged (3), status treatment protocols have used a 5-minute definition to minimize both the risk of seizures reaching 30 minutes and the adverse outcomes associated with needlessly intervening on brief, self-limited seizures (2, 4). This guideline follows this convention and, for purposes of treatment, uses the term status epilepticus to represent studies involving both prolonged seizures and traditionally defined status epilepticus.

Status epilepticus presents in several forms: 1) convulsive status epilepticus consisting of repeated generalized tonic–clonic (GTC) seizures with persistent postictal depression of neurologic function between seizures; 2) nonconvulsive status epilepticus where seizures produce a continuous or fluctuating "epileptic twilight" state; and 3) repeated partial seizures manifested as focal motor signs, focal sensory symptoms, or focal impairment of function (e.g., aphasia) not associated with altered awareness (epilepsia partialis continua).

Between 50,000 and 150,000 Americans each year have status epilepticus (5–7), with mortality estimated at less than 3% in children but up to 30% in adults (5, 6, 8). The goal of therapy is the rapid termination of both clinical and electrical seizure activity, since appropriate and timely therapy of status epilepticus reduces the associated mortality and morbidity (9). Ultimately, the prognosis is most strongly related to the etiology, duration of status epilepticus, and the age of the patient (10–12). Basic critical care and emergency principles of therapy such as supporting respiration, maintaining blood pressure, gaining intravenous (IV) access, and identifying and treating the underlying cause have achieved widespread acceptance and are routinely implemented by both neurologists and non-neurologists. Despite this recognition of the need to address status epilepticus as a critical care emergency, the goals of therapy and approaches to the pharmacologic treatment of status epilepticus continue to vary dramatically. Unfortunately, patients still receive inadequate treatment for a variety of reasons including, but not limited to, therapy aimed at reduction instead of termination of seizures, use of inefficient therapies such as sedatives and paralytics, and administration of insufficient anticonvulsant doses.

In 1993, the Epilepsy Foundation of America asked its professional advisory board to convene a working group of experts to develop a treatment protocol and related educational materials depicting the best current medical management of convulsive status epilepticus. The subsequent consensus guideline provided physicians with a consistent, rational approach (2). Over the past 2 decades, new medical therapies and new clinical trial data have emerged relating directly to the treatment of this most feared type of seizure activity. Coupled with the acceptance of evidence-based rather than consensus-based guidelines, the Epilepsy Foundation in 2004 and the American Epilepsy Society in 2012 began the process of reevaluating the existing medical literature and developing a new guideline. This writing team started their activity on behalf of the Epilepsy Foundation and completed their task with the support of the American Epilepsy Society.

Purpose of This Guideline and Definition of Terms

The goal of this current guideline is to provide evidence-based answers to efficacy, safety, and tolerability questions regarding the treatment of convulsive status epilepticus and to synthesize these answers into a treatment algorithm. This guideline focuses on convulsive status epilepticus because it is both the most common type of status epilepticus and is associated with substantial morbidity and mortality. Anticonvulsant "efficacy" is the ability of the drug to stop convulsive status epilepticus, "tolerability" involves the "incidence, severity and impact" of anticonvulsant related adverse effects (13, 14), "effectiveness" encompasses both anticonvulsant efficacy and tolerability, and "safety" refers to life-threatening adverse events.

The guideline's recommendations aim to help clinicians worldwide understand the relevant existing evidence for treatment of patients with status epilepticus. The guideline is intended for use by individual clinicians, hospitals, health authorities, and providers. We recognize that this guideline

will need local scrutiny and adjustment in order to make it relevant to the social and economic environments in which it will be used. This process should lead to a sense of ownership of any adjusted guideline, which will be essential for effective implementation and will lead to improvement in healthcare outcomes for people with convulsive status epilepticus.

Scope of This Guideline

This guideline will address the evidence regarding the treatment of convulsive status epilepticus. For the purposes of this guideline, only studies that enrolled subjects having a seizure duration of at least 5 minutes were considered. The guideline's analysis is presented by subject age (adult studies, pediatric studies), since studies arbitrarily focused on either adult or pediatric subjects. The guideline's treatment algorithm is not age specific since 1) the disease pathophysiology of prolonged seizures and status epilepticus and 2) anticonvulsant drug effects on neuronal receptors are the same from infants through adults, permitting a unified approach for all patients older than neonates. The following issues are not examined in this guideline: merits of various definitions of status epilepticus, treatment of refractory status epilepticus, treatment of neonatal status epilepticus, subsequent chronic anticonvulsant therapy, etiology-specific therapy (e.g., for cerebral malaria), the role of different diagnostic tests (e.g., EEG, CT, MRI) for patients with status epilepticus, the role of epilepsy surgery, neurostimulation, or the ketogenic diet in the treatment of patients with status epilepticus. There is an American Academy of Neurology practice parameter on the diagnostic evaluation of the child with status epilepticus (15).

The variability in anticonvulsant costs makes it difficult for this guideline to address or incorporate issues of cost-effectiveness and related economic analyses. However, it is recognized that cost and formulary availability are practical parameters modifying the selection of initial anticonvulsant therapy. This guideline should not be construed as rigid. Rather, therapy choice ultimately must include consideration of the individual patient's clinical data along with the local availability and cost feasibility of different treatment options.

Methods

The methodology used to construct the evidence-based portion of this guideline was based on elements of guideline development used by the American Academy of Neurology (http://www.aan.com/Guidelines/) and the International League Against Epilepsy. The methodology was specified before the searches were conducted. A literature search was performed, including MEDLINE and Current Contents, for relevant articles published between January 1940 and September 2014 (inclusive). In addition, the Cochrane Library (Database of Systematic Reviews, Central Register of Controlled Trials, Methodology Register, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database, and NHS Economic Evaluation Database) was serially searched (last in April 2015). Studies were considered potentially relevant if they included the term "status epilepticus," examined anticonvulsant efficacy, safety, tolerability, or mode of use, and were a randomized controlled trial (RCT), cohort study, case control study, observational study, case series, meta-analysis, or systematic review. All languages were included. No sex or age limits were imposed, but searches were limited to human subjects. No studies published only as abstracts were included. Articles were excluded from further analysis if they related to nonepilepsy uses of anticonvulsants or focused on basic anticonvulsant mechanisms.

Each potentially relevant study found through this search methodology was abstracted for specific data, which were placed in evidence tables for further analysis. The review panel consisted of a group of neurologists, neurology nurses, emergency medicine physicians, clinical pharmacists, methodologists, and neurocritical care physicians with experience in status epilepticus and anticonvulsants. Potentially relevant studies were evaluated for their class of evidence using criteria detailed in Table 1. The guideline's conclusions and recommendations were based on criteria detailed in Table 2. These tables integrate the United States Agency for Health Care and Policy Research (16) and the American Academy of Neurology scoring system (17). However, two major modifications to the scoring system were made owing to the ethical and logistic difficulties in conducting convulsive status epilepticus trials:

1) A 10% noninferiority margin between test drug and comparator drug was considered to be clinically appropriate for noninferiority analyses and failed superiority studies (Table 1).

2) Fewer class I or II studies were needed to reach a Level A or B recommendation than for other neurologic conditions because of the challenges in conducting randomized, controlled, double-blind, status epilepticus studies (Table 2).

The analysis addressed five questions involving adults/children with seizures lasting more than 5 minutes:

Q1. Which anticonvulsants are efficacious as initial and subsequent therapy?

Q2. What adverse events are associated with anticonvulsant administration?

Q3. Which is the most effective benzodiazepine?

Q4. Is IV fosphenytoin more effective than IV phenytoin?

Q5. When does anticonvulsant efficacy drop significantly (i.e., after how many different anticonvulsants does status epilepticus become refractory)?

The completed evidence-based guidelines and algorithm were reviewed and approved by the American Epilepsy Society Guidelines Committee (members of which were not part of the writing group). It was also reviewed and commented on by the Council on Clinical Activities, whose comments were incorporated and subsequently approved. Following committee and council approval, it was submitted to the American Epilepsy Society Board; and after review, comments, and revisions, the guideline was approved prior to submission for publication.

TABLE 1. ***Rating of Articles***

Class I: Prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population. The following are also required:
a. No more than two primary outcomes specified
b. Concealed allocation
c. Exclusion/inclusion criteria clearly defined
d. Relevant baseline characteristics presented and substantially equivalent between treatment groups, or appropriate statistical adjustment for differences
e. Adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) with numbers sufficiently low to have minimal potential for bias
f. Demonstration of superiority in a superiority study design or demonstration of noninferiority using a 10% margin in a noninferiority design
Class II: A prospective, randomized, controlled clinical trial with masked outcome assessment that lacks one or two criteria a–e (see class I) or a prospective matched group cohort study in a representative population with masked outcome assessment that meets criteria a–e
Class III: All other controlled trials in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurements
Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion

TABLE 2. ***Translation of Article Ratings to Conclusions and Recommendations***

Translation of Evidence to Recommendation	Conclusion and Recommendation
Level A rating:	
One or more class I studies *or* two or more consistent class II studies	Conclusion, level A: Established as effective, ineffective, or harmful for the given condition in the specified population Recommendation: Should be done or should not be done
Level B rating:	
One or more class II studies *or* three or more consistent class III studies	Conclusion, level B: Probably effective, ineffective, or harmful for the given condition in the specified population Recommendation: Should be considered or should not be considered
Level C rating:	
Two or more consistent class III studies	Conclusion, level C: Possibly effective, ineffective, or harmful for the given condition in the specified population Recommendation: May be considered or may not be considered
Level U:	
Lack of studies meeting level A, B, or C designation	Conclusion, level U: Data inadequate or insufficient. Given current knowledge, treatment is unproven. Recommendation: None

Results

Article and Meta-Analysis/Systematic Review Identification

Four search strategies yielded the following results (all searches were performed for the time frame of January 1, 1940 through September 30, 2014). For Pubmed, the following terms were used:

1) Search—status epilepticus, Limits—humans (*n* = 6,953 articles);

2) Search—status epilepticus, Limits—humans, clinical trial, randomized controlled trial (*n* = 210 articles);

3) Search—status epilepticus AND ((clinical [Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]); Limits—humans (*n* = 3,101 articles);

4) Search—status epilepticus *and* systematic[sb]; Limits—humans (*n* = 159 articles).

Similar searches were performed on the other databases. These computerized searches were last performed on October 9, 2014. The resulting studies were reviewed for relevance. The reference lists of all included studies were reviewed to identify any additional relevant studies not identified by the above searches. In total, 38 relevant RCTs were identified. A search of the Cochrane Library yielded four additional completed and relevant published meta-analyses (18–21). Pharmaceutical companies provided requested additional information on three RCTs.

Q1. Which Anticonvulsants Are Efficacious as Initial and Subsequent Therapy?

Adult Studies

Nine RCTs (three class I [22–24], one class II [25], and five class III [26–30]) addressed the efficacy of initial therapy. The 1998 Veteran's Affairs status epilepticus study was a multicenter randomized comparison of four different IV treatments: lorazepam (0.1 mg/kg), diazepam (0.15 mg/kg) followed by phenytoin (18 mg/kg), phenobarbital (18 mg/kg), and phenytoin alone (18 mg/kg) in adults with either overt or subtle status epilepticus (22). Overt status epilepticus was defined as a continuous GTC seizure lasting 10 minutes or longer, or two or more GTC seizures without full recovery of consciousness. A treatment was successful if the status epilepticus stopped within 20 minutes after infusion started with no recurrence prior to 60 minutes. Overall, 570 patients were randomized to either lorazepam (*n* = 146), diazepam plus phenytoin (*n* = 146), phenobarbital (*n* = 133), or phenytoin (*n* = 145). Differential anticonvulsant efficacy was found in overt status epilepticus where the four treatment arms had an overall difference ($p = 0.02$) for the primary outcome variable. Only one head-to-head comparison met the prespecified statistical significance difference: lorazepam was superior to phenytoin ($p = 0.001$). There was no difference on the intent to treat (ITT) analysis (22).

A second class I study in adults (older than 18 years) with status epilepticus was initiated outside the hospital by paramedics (23). In this 2001 study, patients were randomized to receive 2 mg IV lorazepam or 5 mg IV diazepam or IV placebo in the ambulance. The protocol allowed a repeat dose if the seizure continued after 4 minutes (for a maximum lorazepam dose of 4 mg and diazepam dose of 10 mg). For this study, status epilepticus was defined as continuous or repeated seizure for >5 minutes without recovery of consciousness. Overall, 205 patients were randomized (lorazepam, *n* = 66; diazepam, *n* = 68; placebo, *n* = 71). The treatment was deemed successful if the status epilepticus had terminated at the time of arrival in the emergency department. Both lorazepam and diazepam were superior to placebo: lorazepam (59.1%) > placebo (21.1%) (OR, 4.8; 95% CI: 1.9–13.0) and diazepam (42.6%) > placebo (21.1%) (OR, 2.3; 95% CI: 1.0–5.9) (23).

A third class I study, the 2012 RAMPART trial, was a multicenter, double-blind randomized noninferiority comparison of intramuscular (IM) midazolam (test drug) to IV lorazepam (comparator) in adults and children with status epilepticus (24). Dosing was standardized to 10 mg (5 mg in children weighing 13–40 kg) IM midazolam or 4 mg (2 mg in children weighing 13–40 kg) IV lorazepam. Status epilepticus was defined as convulsions persisting for longer than 5 minutes that were still occurring after paramedic arrival. Treatment success was defined as absence of seizures without additional rescue therapy at time of arrival in the emergency department, with a prespecified noninferiority margin of 10%. A total of 893 subjects (*n* = 748; aged 21 years or older) were randomized to either IM midazolam (*n* = 448) or IV lorazepam (*n* = 445). The primary efficacy endpoint was achieved in 73% of subjects in the IM midazolam group compared with 63% in the IV lorazepam group, resulting in an absolute difference between groups of 10% (95% CI: 4.0–16.1), not only meeting the prespecified noninferiority requirement but also demonstrating superiority of midazolam for both the per protocol and ITT analyses in patients without established IV access (24).

A 1983 class II study compared IV lorazepam 4 mg and IV diazepam 10 mg in adults with convulsive status epilepticus (defined as ≥3 GTC seizures in 1 hour or ≥2 in rapid succession), absence status epilepticus, or complex partial status epilepticus (25). The patients could receive a second dose of medication if the seizures continued after 10 minutes. For all patients, phenytoin was given after 30 minutes. A total of 70 patients were randomized to either lorazepam (*n* = 37) or diazepam (*n* = 33) (25). Lorazepam was successful for 78% of subjects after one dose and 89% after two doses; diazepam was successful for 58% of subjects after one dose and 76% after two doses. The study found no statistically significant difference between lorazepam and diazepam in seizure cessation after one or two medication administrations.

The five open-label class III initial therapy RCTs examined the efficacy of IV valproic acid (*n* = 2) (26, 27), IV phenytoin (*n* = 2) (26, 27), IV phenobarbital (*n* = 1) (29), IV diazepam plus phenytoin (*n* = 1) (29), IV levetiracetam (*n* = 1) (30), rectal diazepam (*n* = 1) (28), and IV lorazepam (*n* = 1) (30) in cohorts ranging from 9 to 41 patients. Valproic acid had

higher efficacy than phenytoin in one study (valproic acid, 66%, vs phenytoin, 42%; $p = 0.046$) (27) and was similar to phenytoin in the other (valproic acid, 87.8%, vs phenytoin, 88%) (26).

Two RCTs, both class III (31, 32), addressed second-therapy efficacy in adults after failure of initial benzodiazepine therapy. Intravenous valproic acid's efficacy was similar to IV phenytoin (88% vs 84%) in one study (31) and similar to continuous IV diazepam (56% vs 50%) in the second study (32).

Each arm of the Veterans Affairs status epilepticus study had a second blinded treatment if initial therapy was unsuccessful (22). Specifically, initial lorazepam therapy was followed by IV phenytoin; phenobarbital was followed by phenytoin; phenytoin was followed by lorazepam; and diazepam plus phenytoin was followed by lorazepam (22). There was no difference in efficacy between the four treatment arms when initial and second therapies together were examined (33).

The following conclusions were drawn. In adults, IM midazolam, IV lorazepam, IV diazepam (with or without phenytoin), and IV phenobarbital are established as efficacious at stopping seizures lasting at least 5 minutes (level A). Intramuscular midazolam has superior effectiveness compared with IV lorazepam in adults with convulsive status epilepticus without established IV access (level A). Intravenous lorazepam is more effective than IV phenytoin in stopping seizures lasting at least 10 minutes (level A). There is no difference in efficacy between IV lorazepam followed by IV phenytoin, IV diazepam plus phenytoin followed by IV lorazepam, and IV phenobarbital followed by IV phenytoin (level A). Intravenous valproic acid has similar efficacy to IV phenytoin or continuous IV diazepam as second therapy after failure of a benzodiazepine (level C). Insufficient data exist in adults about the efficacy of levetiracetam as either initial or second therapy (level U).

Pediatric Studies

Overall, 26 RCTs (two class I [24, 34] and 24 class III [27, 30, 35–56]) examined efficacy of initial therapy. In 25 of these RCTs, benzodiazepines were one or both of the study medications (two class I studies and 23 class III studies). In one class I trial (34), 273 children (aged 3 months to 18 years) were enrolled and randomized to either diazepam 0.2 mg/kg (maximum dose 8 mg) or lorazepam 0.1 mg/kg (maximum dose 4 mg). If seizures continued after 5 more minutes, then half of the initial study drug dose could be repeated. If seizures continued another 7 more minutes, then fosphenytoin was given. There was no difference between IV diazepam (101/140, 72.1%) and IV lorazepam (97/133, 72.9%) in the primary efficacy outcome of termination of status epilepticus by 10 minutes without reappearance within 30 minutes (absolute difference of 0.8%, 95% CI: −11.4–9.8%). The study concluded that there was no evidence to support the hypothesis that lorazepam was superior to diazepam as initial therapy for pediatric status epilepticus.

A second class I study, the RAMPART trial (24), included 120 children randomized to IM midazolam ($n = 60$) or IV lorazepam ($n = 60$). No statistical difference in efficacy was found between the IM midazolam (68.3%) and IV lorazepam (71.7%), but the relatively few children studied results in wide confidence intervals preventing any firm conclusions (57).

The class III benzodiazepine RCTs involved diazepam ($n = 20$), midazolam ($n = 16$), and lorazepam ($n = 6$). The different routes of administration included IV ($n = 13$), rectal ($n = 10$), intranasal ($n = 9$), buccal ($n = 6$), IM ($n = 3$), and sublingual ($n = 1$). The size of the studies ranged from 24 patients to 436 patients. Although all studies were prospective and randomized, they were class III because treating physicians were either not blinded to treatment allocation or lacked outcome masking (meaning the outcome assessors were not blinded to treatment allocation).

One class III study compared lorazepam (0.05–0.1 mg/kg) to diazepam (0.3–0.4 mg/kg) administered either IV or rectally for children presenting to the emergency department with ongoing convulsions. There was no difference between the treatments either in the time for the initial (presenting) seizure to stop after anticonvulsant administration or in the total number of seizures in first 24 hours of admission. However, fewer lorazepam patients required multiple doses to stop the seizures (lorazepam 8/33 vs diazepam 25/53; $p < 0.05$) or additional anticonvulsants to terminate the seizure (lorazepam 1/33 vs diazepam 17/53; $p < 0.01$) (35).

One class III study compared IV lorazepam (0.1 mg/kg) to a combination of IV diazepam (0.2 mg/kg) and IV phenytoin (18 mg/kg) in 178 children presenting with convulsive status epilepticus to an emergency department. Efficacy in stopping seizure activity within 10 minutes with no recurrence during an 18-hour period after seizure control was 100% for both groups. No significant difference was demonstrated between treatment groups either in the time to seizure cessation or the need for additional doses of study medication to terminate convulsive status epilepticus (49).

Intranasal lorazepam was examined in two studies. A study of 6- to 14-year-old children with ongoing seizures in the emergency department compared IV lorazepam with intranasal lorazepam (both 0.1 mg/kg/dose, maximum dose 4 mg) (52). No difference was detected between IV lorazepam (56/70, 80%) and intranasal lorazepam (59/71, 83.1%) based on clinical seizure remission within 10 minutes of study drug administration. The authors concluded that intranasal lorazepam was not inferior to IV lorazepam (52). Another class III study compared intranasal lorazepam (0.1 mg/kg) to IM paraldehyde (0.2 mL/kg) in 160 pediatric patients presenting to an emergency department with convulsive status epilepticus. No statistically significant difference was found between intranasal lorazepam and IM paraldehyde for the primary outcome of efficacy in stopping seizure activity 10 minutes after administration (intranasal lorazepam, 75%; IM paraldehyde, 61%; $p = 0.06$) or in time to seizure cessation or seizure recurrence within 24 hours after administration. The study did find that subjects treated with paraldehyde were more likely to require two or more additional anticonvulsant doses (intranasal lorazepam, 10%; IM paraldehyde, 26%; $p = 0.007$) (44).

Sublingual lorazepam (0.1 mg/kg) was compared with rectal diazepam (0.5 mg/kg) in children 5 months to 10 years old with convulsions lasting more than 5 minutes (54). This

class III RCT was conducted across nine hospitals in Sub-Saharan Africa and involved 436 children. The efficacy of sublingual lorazepam (131/234, 56%) was significantly lower than that for rectal diazepam (160/202, 79%; $p < 0.001$) for terminating seizures within 10 minutes of study drug administration (54).

Sixteen class III studies compared midazolam with diazepam. In five studies, buccal midazolam was compared with rectal diazepam (40–42, 47, 50). In one study, in 177 children experiencing 219 separate seizures, buccal midazolam was more effective than rectal diazepam in stopping seizures whether all seizures were considered (56% vs 27%) or just initial episodes (42). The largest study of 330 children in Uganda found a lower rate of treatment failure (seizures lasting longer than 10 minutes after medication administration or seizure recurrence within 1 hour) for buccal midazolam compared with rectal diazepam (30.3% vs 43%; $p = 0.016$). This superiority was limited to a subgroup of patients without malaria, with buccal midazolam superior to rectal diazepam with respect to treatment failure (26.2% vs 55.9%; $p = 0.002$) (47). In an RCT of 98 children (aged 3 months to 12 years), buccal midazolam was superior to rectal diazepam for control of seizures within 5 minutes of administration (49/49, 100%, vs 40/49, 82%; $p < 0.001$), treatment initiation time (median 2 vs 3 minutes; $p < 0.001$), and drug effect time (median 4 vs 5 minutes; $p < 0.001$) (50). In the two smaller studies ($n = 79$ and $n = 43$), there was no difference in efficacy between buccal midazolam and rectal diazepam (40, 41).

Intranasal midazolam was compared with IV diazepam in four class III pediatric studies (38, 39, 46, 53). In one study involving children with prolonged febrile seizures, time to drug administration of intranasal midazolam was faster ($p < 0.001$) but the time period between drug administration and seizure cessation was shorter for IV diazepam ($p < 0.001$) (38). The second study found that the mean time to achieve seizure control was faster for IV diazepam compared with intranasal midazolam ($p < 0.007$) (39). A third study found intranasal midazolam was significantly faster to administer than IV diazepam, with a slower mean time to seizure cessation after medication administration for intranasal midazolam compared with IV diazepam, but a faster time to seizure cessation after hospital arrival with intranasal midazolam ($p < 0.001$ for all comparisons) (46). Lastly, an RCT of 60 children (aged 2 months to 15 years), equally divided between intranasal midazolam (0.2 mg/kg) and IV diazepam (0.3 mg/kg), found the time to control seizures was shorter using intranasal midazolam compared with IV diazepam (3.16 ± 1.24 minutes vs 6.42 ± 2.59 minutes; $p < 0.001$) when the time needed to establish IV access was included (53).

Three trials examined the efficacy of intranasal midazolam compared with rectal diazepam (37, 45, 51). Intranasal midazolam (0.2 mg/kg, maximum dose, 10 mg) was compared with rectal diazepam (0.3 to 0.5 mg/kg, maximum dose, 20 mg) for prehospital seizures lasting longer than 5 minutes. Overall, 92 children received study medication, and no difference in total seizure time after medication administration between therapies was identified (51). Another trial involving 46 children experiencing 188 seizures compared the efficacy of intranasal midazolam 0.3 mg/kg (92 episodes) to rectal diazepam 0.2 mg/kg (96 episodes) for terminating seizures within 10 minutes of drug administration. The time to seizure cessation was significantly faster for intranasal midazolam (116.7 ± 126.9 seconds vs 178.6 ± 179.5 seconds; $p = 0.005$), with a trend toward a higher success rate with intranasal midazolam (89/92, 96.7%) compared with rectal diazepam (85/96, 88.5%; $p = 0.060$) (45). A third smaller trial ($n = 45$) found intranasal midazolam was more effective than rectal diazepam (87% vs 60%; $p < 0.05$) (37).

Intramuscular midazolam was compared with IV diazepam in three class III studies (36, 43, 55). In all three studies, IM midazolam had a shorter interval to seizure cessation, but there was no significant difference in overall efficacy for termination of seizures (36, 43, 55).

One study compared buccal midazolam 0.2 mg/kg with IV diazepam 0.3 mg/kg, with no significant difference found in overall efficacy (defined as complete cessation of seizures 5 minutes after administration of study treatment) (48). Time to seizure cessation from identification of the seizure in the emergency department was significantly shorter for buccal midazolam compared with IV diazepam (2.39 minutes vs 2.98 minutes, respectively), with most of the difference driven by more rapid time to initiation of treatment (48).

Intravenous lorazepam (0.1 mg/kg over 2–4 minutes) was compared with IV levetiracetam (20 mg/kg over 15 minutes) in a class III RCT involving children with either convulsive or subtle convulsive status epilepticus (30). As first therapy, lorazepam success rate (29/38, 76.3%) was similar to that for levetiracetam (31/41, 75.6%) (30).

In one RCT, children with convulsive seizures at time of presentation received either IV valproic acid (20 mg/kg) with diazepam (0.3 mg/kg) ($n = 16$) or IV phenytoin (20 mg/kg) with diazepam (0.3 mg/kg) ($n = 17$) (56). There was no difference in efficacy outcomes between these two arms (56).

The only class III pediatric RCT not involving a benzodiazepine compared IV phenytoin ($n = 33$) and IV valproic acid ($n = 35$). Overall, valproic acid had higher efficacy than phenytoin (valproic acid, 66%, vs phenytoin, 42%; $p = 0.046$), but only 23% and 12% of the cohorts were 15 years old or younger, with no statistical adjustment for these dissimilar proportions (27).

Two RCTs (one class II [58] and one class III [31]) addressed second-therapy efficacy in children after failure of initial benzodiazepine therapy. The class II study compared IV valproic acid (20 mg/kg, $n = 30$) with IV phenobarbital (20 mg/kg, $n = 30$) in children 3 to 16 years old whose seizures did not respond to IV diazepam (0.2 mg/kg) within 5 minutes. No significant difference was noted in efficacy between valproic acid and phenobarbital (27/30, 90%, vs 23/30, 77%; $p = 0.189$) for terminating seizures within 20 minutes, but the valproic acid group experienced significantly fewer clinically significant adverse effects (24% vs 74%; $p < 0.001$) (58). The second study involved both adults and children and found that the efficacy of IV valproic acid was similar to that of IV phenytoin (88% vs 84%) in patients whose seizures did not respond to 0.2 mg/kg of IV diazepam (31).

The following conclusions were drawn. In children, IV lorazepam and IV diazepam are established as efficacious

at stopping seizures lasting at least 5 minutes (level A). Rectal diazepam, IM midazolam, intranasal midazolam, and buccal midazolam are probably effective at stopping seizures lasting at least 5 minutes (level B). Insufficient data exist in children about the efficacy of intranasal lorazepam, sublingual lorazepam, rectal lorazepam, valproic acid, levetiracetam, phenobarbital, and phenytoin as initial therapy (level U). Intravenous valproic acid has similar efficacy but better tolerability than IV phenobarbital (level B) as second therapy after failure of a benzodiazepine. Insufficient data exist in children regarding the efficacy of phenytoin or levetiracetam as second therapy after failure of a benzodiazepine (level U).

Q2. What Adverse Events Are Associated With Anticonvulsant Administration?

Adult Studies

Three class I studies (22–24) and one class II study (25) present the best evidence about treatment-emergent adverse events associated with IV lorazepam and diazepam therapy. In the 1998 class I Veterans Affairs status epilepticus study, there were no significant differences in adverse-event rates between lorazepam, diazepam, phenobarbital, and phenytoin (22). The treatment-emergent adverse events associated with lorazepam administration in 97 patients with overt status epilepticus were hypoventilation, 10.3%; hypotension, 25.8%; and cardiac rhythm disturbance, 7.2%. This is similar to the adverse events seen with IV diazepam therapy in 95 patients with overt status epilepticus: hypoventilation, 16.8%; hypotension, 31.6%; and cardiac rhythm disturbance, 2.1%. A similar spectrum of cardiorespiratory complications was seen in both the phenobarbital arm (hypoventilation, 13.2%; hypotension, 34.1%; cardiac rhythm disturbance, 3.3%) and the phenytoin arm (hypoventilation, 9.9%; hypotension, 27.0%; cardiac rhythm disturbance, 6.9%) (22).

In the 2001 prehospital status epilepticus RCT, 10.6% of patients receiving IV lorazepam experienced treatment-emergent adverse events (hypotension, cardiac dysrhythmia, respiratory intervention). Similarly, 10.3% of patients receiving IV diazepam experienced hypotension, cardiac dysrhythmia, or the need for respiratory intervention. Both of these rates were lower ($p = 0.08$) than the 22.5% treatment-emergent adverse-event rate seen in patients with status epilepticus receiving IV placebo (23).

In the 2012 class I RAMPART trial comparing IM midazolam and IV lorazepam (24), treatment-emergent adverse events were identified in 26.7% of subjects in the IM midazolam group compared with 30.6% of subjects in the IV lorazepam group. Most common treatment-emergent adverse events were decreased level of consciousness (IM midazolam, 9.5%, vs IV lorazepam, 8.8%) and respiratory depression (IM midazolam, 6.4%, vs IV lorazepam, 10%), while hypotension only occurred in 1.2% of subjects overall (24).

The 1983 class II study compared lorazepam 4 mg and diazepam 10 mg in adults with convulsive status epilepticus (defined as ≥3 GTC seizures in 1 hour or ≥2 in rapid succession), absence status epilepticus, or complex partial status epilepticus (25). Patients were permitted to receive a second dose of medication if the seizures continued after 10 minutes. For all patients, phenytoin was given after 30 minutes. A total of 70 patients were randomized to either lorazepam ($n = 37$) or diazepam ($n = 33$). In this comparative trial, 12% of lorazepam patients and 13% of diazepam patients experienced treatment-emergent adverse events including respiratory depression, respiratory arrest, hypotension, and sedation; the first three of these only occurred in people with significant medical problems (25).

The following conclusions were drawn. Respiratory and cardiac symptoms are the most common encountered treatment-emergent adverse events associated with IV anticonvulsant administration in adults with status epilepticus (level A). The rate of respiratory depression in patients with status epilepticus treated with benzodiazepines is lower than in patients with status epilepticus treated with placebo (level A), indicating that respiratory problems are an important consequence of untreated status epilepticus. No substantial difference exists between benzodiazepines and phenobarbital in the occurrence of cardiorespiratory adverse events in adults with status epilepticus (level A).

Pediatric Studies

The single class I purely pediatric study (34) provides the best adverse-event evidence about IV lorazepam and IV diazepam use in children with convulsive status epilepticus. There were no differences between the two arms in the rate of assisted ventilation (lorazepam, 17.6%, versus diazepam, 16.0%; absolute risk difference, 1.6%; 95% CI: −9.9–6.8%) or aspiration pneumonia (two subjects in each group). The incidence of sedation was higher in the lorazepam cohort (99/148, 66.9%) compared with the diazepam cohort (81/162, 50%; absolute risk difference, 16.9%; 95% CI: 6.1–27.7%) (34).

Class III trials identified similar rates of respiratory depression with IV benzodiazepine use (35, 49, 55). One class III trial reported 21% of patients receiving IV diazepam and 4% of patients receiving IV lorazepam were reported to have respiratory depression defined as poor respiratory effort, reduced rate of breathing, or requiring oxygen administration via face mask (35). In another class III study, respiratory depression was reported in 4.4% of children receiving IV lorazepam and 5.6% of children receiving IV diazepam and phenytoin, but no subject in either group required mechanical ventilation (49).

Respiratory depression after rectal administration of diazepam in children was reported in five class III trials, ranging from 1.2 percent to 6.4 percent (35, 41, 42, 45, 47), while two class III trials (37, 40) and two class I trials in acute repetitive seizures (59, 60) reported no incidence of respiratory depression with rectal diazepam use in children. No respiratory depression was reported in one study of six children treated with rectal lorazepam (35). As noted above, drowsiness was the most common adverse effect reported in two class I trials of rectal diazepam in a mixed adult and pediatric study (59, 60).

Two class III studies reported respiratory depression with use of buccal midazolam in children (42, 47), in contrast to two class III studies, which reported no respiratory depression associated with use of buccal midazolam in the pediatric population (40, 41). Respiratory depression, defined as having a need

for assisted ventilation because of a drop in oxygen saturation or a reduction in respiratory rate or effort, was reported in 1.2% and 4.6% of patients in these studies (42, 47). Two of the class III IM or intranasal midazolam studies reported significant respiratory depression (36–39, 43, 45, 46, 53). Single children in each study (6.25% and 2%) in the IM midazolam group experienced respiratory failure resulting in artificial ventilation (51, 55).

Two class III studies involved intranasal lorazepam. In one study of 80 children, a drop of ≥5 mm Hg in systolic and diastolic blood pressure was noted in 15 (18.8%) and 12 (15%) children, respectively, while only two (2.5%) had a fall in oxygen saturation below 92% (44). In a second study of 71 children, none developed significant hypotension and only one (1.4%) required assisted ventilation (52).

The following conclusions were drawn. Respiratory depression is the most common clinically significant treatment-emergent adverse event associated with anticonvulsant drug treatment in status epilepticus in children (level A). No substantial difference probably exists between midazolam, lorazepam, and diazepam administration by any route in children with respect to rates of respiratory depression (level B). Adverse events, including respiratory depression, with benzodiazepine administration for status epilepticus have been reported less frequently in children than in adults (level B).

Q3. Which Is the Most Effective Benzodiazepine?

Adult Studies

In a class I prehospital status epilepticus study (23), the percentage of patients' status epilepticus stopped by lorazepam was higher but not significantly different than with diazepam (odds ratio [OR], 1.9; 95% CI: 0.8–4.4). However, the study's sample size was selected to be able to detect a difference between the active drugs and placebo, not to detect a difference between the two active drugs (23). In a class II lorazepam–diazepam comparative trial (25), there was no difference between the two arms in the percentage of patients having control of seizures after either one injection (lorazepam, 78%; diazepam, 58%; not significant [NS]) or two injections (lorazepam, 89%; diazepam, 76%; NS). There was no significant difference between the two arms in the latency of action (lorazepam median, 3 minutes; diazepam median, 2 minutes; NS) (25).

The class I RAMPART trial (24) reported seizures were absent in 73% of subjects in the IM midazolam group compared with 63% in the IV lorazepam group, resulting in an absolute difference of 10% (95% CI: 4.0–16.1; $p < 0.001$) that met the prespecified noninferiority requirements plus additional superiority for both per protocol and ITT analyses. Median time from active treatment to cessation of convulsions was shorter for IV lorazepam (1.6 minutes) compared with IM midazolam (3.3 minutes), which was offset by more rapid IM midazolam administration (IV lorazepam, 4.8 minutes, vs intranasal midazolam, 1.2 minutes) (24).

There is no difference in the treatment-emergent adverse-event profiles between lorazepam and diazepam in the three adult class I and class II status epilepticus studies (22, 23, 25). No differences in treatment-emergent adverse-event profiles were found between IM midazolam and IV lorazepam (24). There is pharmacokinetic evidence to suggest a longer duration of action (but not longer half-life) for lorazepam compared with diazepam (61).

The following conclusions were drawn. In adults with status epilepticus without established IV access, IM midazolam is established as more effective compared with IV lorazepam (level A). No significant difference in effectiveness has been demonstrated between lorazepam and diazepam in adults with status epilepticus (level A).

Pediatric Studies

As described in detail in Question 1, one class I trial enrolled and randomized 273 children to either IV diazepam or IV lorazepam (34). Efficacy was similar between IV diazepam (101/140, 72.1%) and IV lorazepam (97/133, 72.9%). As described in detail in Question 2, side-effect profiles of the two treatments were similar (34).

A meta-analysis of six class III pediatric studies (36, 38–40, 42, 47) found non-IV midazolam (IM/intranasal/buccal) was more effective than diazepam (IV/rectal) at achieving seizure cessation (relative risk [RR] =1.52, 95% CI: 1.27–1.82) with similar respiratory complications (RR = 1.49; 95% CI: 0.25–8.72) (62). Time to seizure cessation was shorter for intranasal midazolam compared with IV diazepam in two studies (38, 46) and longer in one study (39). Comparing intranasal midazolam and rectal diazepam, intranasal midazolam was more effective in terminating seizures (37) and demonstrated a shorter time to seizure termination (45). Comparing IM midazolam to IV diazepam, a shorter interval to seizure cessation was found for IM midazolam in both studies (36, 43). Only one study found a significantly shorter time to seizure cessation for buccal midazolam compared with rectal diazepam (42).

One study comparing lorazepam to diazepam found no difference between the treatments in the time for the initial (presenting) seizure to stop after anticonvulsant administration but did find fewer lorazepam patients required multiple doses (lorazepam, 8/33, vs diazepam, 25/53; $p < 0.05$) or additional anticonvulsants (lorazepam, 1/33, vs diazepam, 17/53; $p < 0.01$) for seizure cessation (35).

The following conclusions were drawn. In children with status epilepticus, no significant difference in effectiveness has been established between IV lorazepam and IV diazepam (level A). In children with status epilepticus, non-IV midazolam (IM/intranasal/buccal) is probably more effective than diazepam (IV/rectal) (level B).

Q4. Is IV Fosphenytoin More Effective Than IV Phenytoin?

Three class III RCTs examined the comparative tolerability of IV fosphenytoin and IV phenytoin (63). A single-dose, randomized, double-blind, class III tolerability study in patients needing infusion of phenytoin compared fosphenytoin ($n = 39$, 12.7 mg/kg, 82 mg phenytoin equivalent [PE]/min [range, 40–103 mg PE/min]) to phenytoin ($n = 13$, 11.3 mg/kg, 42.4 mg/min). In contrast to phenytoin, there were no fosphenytoin-related significant cardiac arrhythmias, change in heart rate, respiration or blood pressure (63). A second study involved patients requiring a phenytoin loading dose and

then 3 to 14 days of maintenance therapy. This randomized, double-blind, class III tolerability study in patients needing infusion and maintenance of phenytoin compared fosphenytoin (n = 88, 15.3 mg/kg, 37 mg PE/min) to phenytoin (n = 28, 15.0 mg/kg, 33 mg/min) and found pain at the infusion site was greater for phenytoin than fosphenytoin (17% vs 2%) (63). A third study was a single-dose, randomized, double-blind, class III tolerability study of fosphenytoin at 150 mg PE/min (n = 90) vs phenytoin at 50 mg/min (n = 22) (63). The infusion was slowed or discontinued more often with IV phenytoin compared with IV fosphenytoin; 63.6% of phenytoin patients experienced pain at site of infusion; 48.6% of fosphenytoin patients encountered pruritus; and the average blood pressure decrease with fosphenytoin was 13.7 mm Hg compared with 5.9 mm Hg with phenytoin.

The following conclusions were drawn. Insufficient data exist about the comparative efficacy of phenytoin and fosphenytoin (level U). Fosphenytoin is better tolerated compared with phenytoin (level B). When both are available, fosphenytoin is preferred based on tolerability, but phenytoin is an acceptable alternative (level B).

Q5. When Does Anticonvulsant Efficacy Drop Significantly (i.e., After How Many Different Anticonvulsants Does Status Epilepticus Become Refractory)?

Only one class I RCT (the Veterans Affairs status epilepticus trial) (22) provides clear data to address this question. Treatment success was defined as status epilepticus stopping within 20 minutes after infusion started with no recurrence prior to 60 minutes after the start of the infusion. In this four-arm double-blind RCT, in order to maintain the blinding, if the first administered anticonvulsant was not successful, then the patient was randomized to another treatment arm; if the second anticonvulsant was not successful, then the patient was randomized to another treatment arm. In adults with overt status epilepticus, the overall success rate of the first administered therapy was 55.5%. If the first study drug did not succeed, the second study drug was able to stop the status epilepticus for an additional 7.0% of the total population; the third drug helped only an additional 2.3% of patients. It took intensive "non-study" therapy to stop the status epilepticus in 23.2% of the initial patient population, and no drug was successful within 12 hours in 11.7%. In this study, if the patient did not respond to lorazepam or phenytoin, the response rate to phenobarbital was 2.1% (D. Treiman, verbal communication).

Three other RCTs (31, 32, 58), detailed earlier, reported higher rates of second-therapy efficacy in adults and children after failure of initial benzodiazepine therapy. However, in each of these studies, initial therapy was not part of an RCT nor was it blinded. For second therapy, the class II RCTs reported success ranging from 77 percent to 90 percent, while the two class III RCTs reported success ranging from 50 percent to 88 percent.

The following conclusions were drawn. In adults, the second anticonvulsant administered is less effective than the first "standard" anticonvulsant, while the third anticonvulsant administered is substantially less effective than the first "standard" anticonvulsant (level A). In children, the second anticonvulsant appears less effective, and there are no data about third anticonvulsant efficacy (level C).

Recommendations and Algorithm

Based on the evidence-based answers to the above questions, a treatment algorithm is proposed for convulsive status epilepticus (Figure 1). As stated earlier, clinical trials have arbitrarily focused on either adults or children, and only three trials (24, 27, 30) included both. The guideline's treatment algorithm is not age specific because the disease pathophysiology of prolonged seizures/status epilepticus and anticonvulsant drug effects on neuronal receptors are the same from infants through adults, permitting a unified approach for all patients older than neonates.

The algorithm starts with a stabilization phase (0–5 minutes), which includes standard initial first aid for seizures. The initial therapy phase should begin when the seizure duration reaches 5 minutes and should conclude by the 20-minute mark when response (or lack of response) to initial therapy should be apparent. A benzodiazepine (specifically IM midazolam, IV lorazepam, or IV diazepam) is recommended as the initial therapy of choice, given their demonstrated efficacy, safety, and tolerability (level A, four class I RCTs). Although IV phenobarbital is established as efficacious and well tolerated as initial therapy (level A, 1 class I RCT), its slower rate of administration, compared with the three recommended benzodiazepines above, positions it as an alternative initial therapy rather than a drug of first choice. For prehospital settings or where the three first-line benzodiazepine options are not available, rectal diazepam, intranasal midazolam, and buccal midazolam are reasonable initial therapy alternatives (level B). Initial therapy should be administered as an adequate single full dose rather than broken into multiple smaller doses. Initial therapies should not be given twice except for IV lorazepam and diazepam that can be repeated at full doses once (level A, two class I, one class II RCT). Doses listed in the initial therapy phase are those used in class I trials. Note that some consensus guidelines list slightly different dosages; for example, phenobarbital is often recommended at 20 mg/kg (2).

The second-therapy phase should begin when the seizure duration reaches 20 minutes and should conclude by the 40-minute mark when response (or lack of response) to the second therapy should be apparent. Reasonable options include fosphenytoin (level U), valproic acid (level B, one class II study) and levetiracetam (level U). There is no clear evidence that any one of these options is better than the others. The ongoing Established Status Epilepticus Treatment Trial (ESETT) should provide the answer in the next few years (64). Because of adverse events, IV phenobarbital is a reasonable second-therapy alternative (level B, one class II study) if none of the three recommended therapies are available.

The third therapy phase should begin when the seizure duration reaches 40 minutes. There is no clear evidence to guide therapy in this phase (level U). Compared with initial therapy, second therapy is often less effective (adults—level A, one class I RCT; children—level C, two class III RCTs), and the third therapy is substantially less effective (adults—level

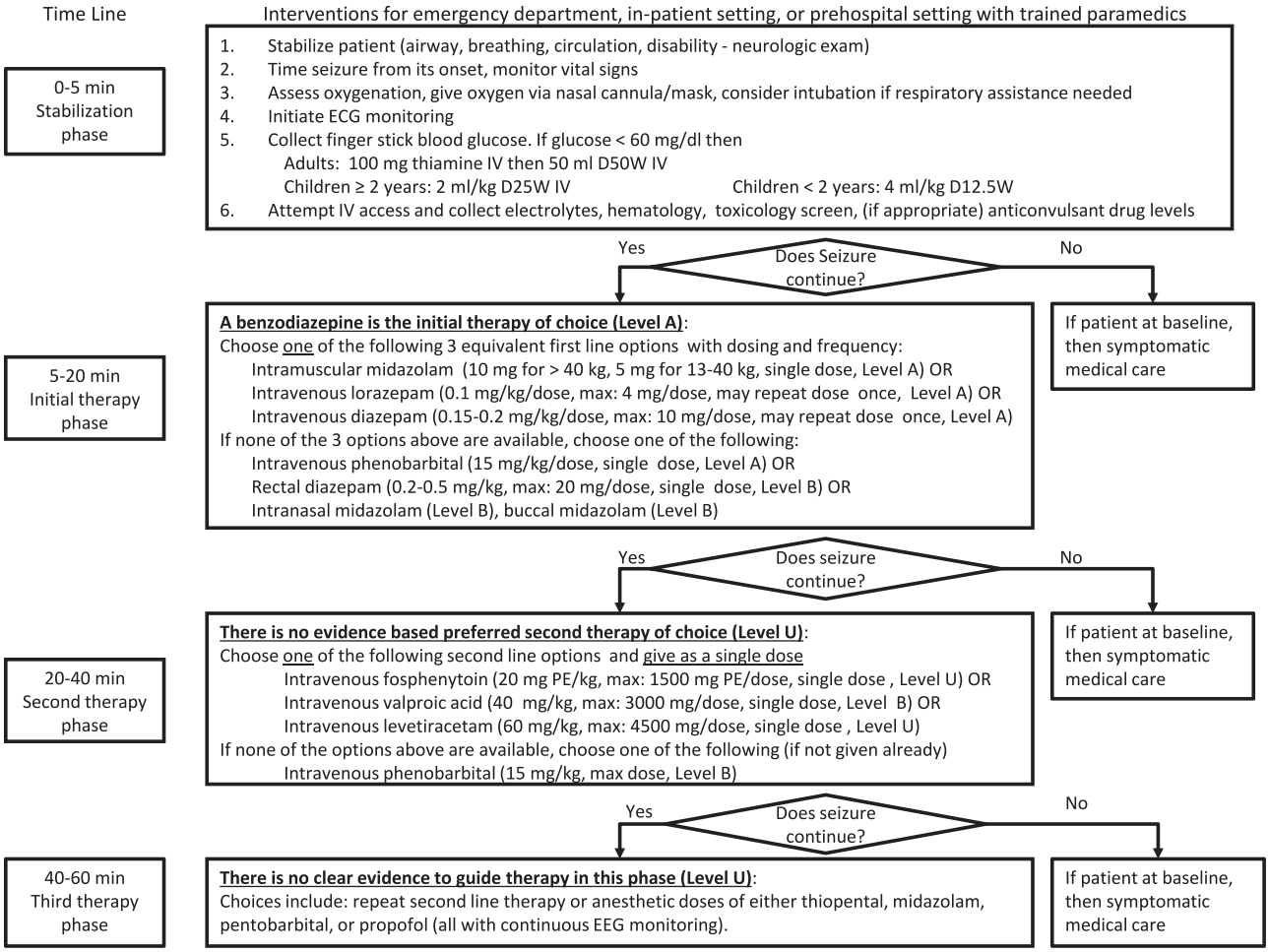

FIGURE 1. Proposed treatment algorithm for status epilepticus.

Disclaimer: This clinical algorithm/guideline is designed to assist clinicians by providing an analytical framework for evaluating and treating patients with status epilepticus. It is not intended to establish a community standard of care, replace a clinician's medical judgment, or establish a protocol for all patients. The clinical conditions contemplated by this algorithm/guideline will not fit or work with all patients. Approaches not covered in this algorithm/guideline may be appropriate.

A, one class I RCT; children—level U) than initial therapy. Thus, if second therapy fails to stop the seizures, treatment considerations should include repeating second-line therapy *or* anesthetic doses of either thiopental, midazolam, pentobarbital, or propofol (all with continuous EEG monitoring). Depending on the etiology or severity of the seizure, patients may go through the phases faster or even skip the second phase and move rapidly to the third phase, especially in sick or intensive care unit patients. The evidence-based treatment of refractory status epilepticus is beyond the scope of this guideline, though others have addressed the issue (65).

Future Directions

Additional evidence to further define the role of other IV-administered anticonvulsants is crucial to future treatment of convulsive status epilepticus. Class III trials support efficacy and safety of valproic acid as first-line therapy (26, 27), second-line therapy (31, 32), and refractory therapy (66). Evidence for use of levetiracetam and lacosamide is limited to retrospective studies (67–72). Given the favorable pharmacokinetic characteristics and adverse-effect profiles for these medications compared with fosphenytoin and phenobarbital, comparative trials of these medications as second-line therapy will provide vital evidence to improve future treatment of convulsive status epilepticus. The current National Institute of Neurological Disorders and Stroke funded ESETT trial compares IV fosphenytoin, levetiracetam, and valproate in children and adults with status epilepticus who did not respond to initial benzodiazepine therapy. ESETT is designed to be a class I RCT that will identify the optimal second therapy for benzodiazepine-resistant status epilepticus (64).

Disclosures

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Added during proofs: While the AES guideline was developed prior to the ILAE's revised definition of status epilepticus (Trinka et al., Epilepsia 2015;56:1515–1523), the 5 minute definition used in this guideline is fully consistent with the operational 5 minute time point (t_1) for treatment initiation for convulsive status epilepticus proposed in that document.

References

1. Glauser TA. Designing practical evidence-based treatment plans for children with prolonged seizures and status epilepticus. *J Child Neurol* 2007;22(suppl 5):38S–46S.
2. Treatment of convulsive status epilepticus. Recommendations of the Epilepsy Foundation of America's Working Group on Status Epilepticus. *JAMA* 1993;270:854–859.
3. Shinnar S, Berg AT, Moshe SL, Shinnar R. How long do new-onset seizures in children last? *Ann Neurol* 2001;49:659–664.
4. Raspall-Chaure M, Chin RF, Neville BG, Bedford H, Scott RC. The epidemiology of convulsive status epilepticus in children: A critical review. *Epilepsia* 2007;48:1652–1663.
5. DeLorenzo RJ, Hauser WA, Towne AR, Boggs JG, Pellock JM, Penberthy L, Garnett L, Fortner CA, Ko D. A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. *Neurology* 1996;46:1029–1035.
6. Wu YW, Shek DW, Garcia PA, Zhao S, Johnston SC. Incidence and mortality of generalized convulsive status epilepticus in California. *Neurology* 2002;58:1070–1076.
7. Hauser WA. Status epilepticus: Epidemiologic considerations. *Neurology* 1990;40:9–13.
8. Maytal J, Shinnar S, Moshe SL, Alvarez LA. Low morbidity and mortality of status epilepticus in children. *Pediatrics* 1989;83:323–331.
9. Jagoda A, Riggio S. Refractory status epilepticus in adults. *Ann Emerg Med* 1993;22:1337–1348.
10. Logroscino G, Hesdorffer DC, Cascino GD, Annegers JF, Bagiella E, Hauser WA. Long-term mortality after a first episode of status epilepticus. *Neurology* 2002;58:537–541.
11. DeLorenzo RJ, Towne AR, Pellock JM, Ko D. Status epilepticus in children, adults, and the elderly. *Epilepsia* 1992;33(suppl 4):S15–S25.
12. Neligan A, Shorvon SD. Prognostic factors, morbidity and mortality in tonic-clonic status epilepticus: A review. *Epilepsy Res* 2011;93:1–10.
13. Considerations on designing clinical trials to evaluate the place of new antiepileptic drugs in the treatment of newly diagnosed and chronic patients with epilepsy. *Epilepsia* 1998;39:799–803.
14. Chadwick D. Monotherapy clinical trials of new antiepileptic drugs: Design, indications, and controversies. *Epilepsia* 1997;38(suppl 9):S16–S20.
15. Riviello JJ Jr, Ashwal S, Hirtz D, Glauser T, Ballaban-Gil K, Kelley K, Morton LD, Phillips S, Sloan E, Shinnar S; American Academy of Neurology Subcommittee; Practice Committee of the Child Neurology Society. Practice parameter: Diagnostic assessment of the child with status epilepticus (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 2006;67:1542–1550.
16. Agency for Healthcare Policy and Research UDoHaHS. Acute pain management: Operative or medical procedures and trauma. In: *Clinical Practice Guideline No 1*. Rockville, MD: Agency for Healthcare Policy and Research, 1993:107.
17. Edlund W, Gronseth G, So Y, Franklin G; for the Quality Standards Subcommittee (QSS) and the Therapeutics and Technology Assessment Subcommittee (TTA). *American Academy of Neurology Clinical Practice Guideline Process Manual*. St. Paul, MN: American Academy of Neurology, 2004.
18. Prasad M, Krishnan PR, Sequeira R, Al-Roomi K. Anticonvulsant therapy for status epilepticus. *Cochrane Database Syst Rev* 2014;9:CD003723. doi:10.1002/14651858.CD003723.pub3.
19. Appleton R, Macleod S, Martland T. Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. *Cochrane Database Syst Rev* 2008;3:CD001905. doi:10.1002/14651858.CD001905.pub2.
20. Prasad K, Al-Roomi K, Krishnan PR, Sequeira R. Anticonvulsant therapy for status epilepticus. *Cochrane Database Syst Rev* 2005;Oct 19;(4):CD003723 PMID:16235337.
21. Appleton R, Martland T, Phillips B. Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. *Cochrane Database Syst Rev* 2002;(4):CD001905. PMID:12519562
22. Treiman DM, Meyers PD, Walton NY, Collins JF, Colling C, Rowan AJ, Handforth A, Faught E, Calabrese VP, Uthman BM, Ramsay RE, Mamdani MB. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. *N Engl J Med* 1998;339:792–798.
23. Alldredge BK, Gelb AM, Isaacs SM, Corry MD, Allen F, Ulrich S, Gottwald MD, O'Neil N, Neuhaus JM, Segal MR, Lowenstein DH. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. *N Engl J Med* 2001;345:631–637.
24. Silbergleit R, Durkalski V, Lowenstein D, Conwit R, Pancioli A, Palesch Y, Barsan W; NETT Investigators. Intramuscular versus intravenous therapy for prehospital status epilepticus. *N Engl J Med* 2012;366:591–600.
25. Leppik IE, Derivan AT, Homan RW, Walker J, Ramsay RE, Patrick B. Double-blind study of lorazepam and diazepam in status epilepticus. *JAMA* 1983;249:1452–1454.
26. Gilad R, Izkovitz N, Dabby R, Rapoport A, Sadeh M, Weller B, Lampl Y. Treatment of status epilepticus and acute repetitive seizures with i.v. valproic acid vs phenytoin. *Acta Neurol Scand* 2008;118:296–300.
27. Misra UK, Kalita J, Patel R. Sodium valproate vs phenytoin in status epilepticus: A pilot study. *Neurology* 2006;67:340–342.

28. Remy C, Jourdil N, Villemain D, Favel P, Genton P. Intrarectal diazepam in epileptic adults. *Epilepsia* 1992;33:353–358.
29. Shaner DM, McCurdy SA, Herring MO, Gabor AJ. Treatment of status epilepticus: A prospective comparison of diazepam and phenytoin versus phenobarbital and optional phenytoin. *Neurology* 1988;38:202–207.
30. Misra UK, Kalita J, Maurya PK. Levetiracetam versus lorazepam in status epilepticus: A randomized, open labeled pilot study. *J Neurol* 2012;259:645–648.
31. Agarwal P, Kumar N, Chandra R, Gupta G, Antony AR, Garg N. Randomized study of intravenous valproate and phenytoin in status epilepticus. *Seizure* 2007;16:527–532.
32. Chen WB, Gao R, Su YY, Zhao JW, Zhang YZ, Wang L, Ren Y, Fan CQ. Valproate versus diazepam for generalized convulsive status epilepticus: A pilot study. *Eur J Neurol* 2011;18:1391–1396.
33. Treiman DM, Walton N, Collins JF, Point P. Treatment of status epilepticus if first drug fails. *Epilepsia* 1999;40:153–156.
34. Chamberlain JM, Okada P, Holsti M, Mahajan P, Brown KM, Vance C, Gonzalez V, Lichenstein R, Stanley R, Brousseau DC, Grubenhoff J, Zemek R, Johnson DW, Clemons TE, Baren J; Pediatric Emergency Care Applied Research Network (PECARN). Lorazepam vs diazepam for pediatric status epilepticus: A randomized clinical trial. *JAMA* 2014;311:1652–1660.
35. Appleton R, Sweeney A, Choonara I, Robson J, Molyneux E. Lorazepam versus diazepam in the acute treatment of epileptic seizures and status epilepticus. *Dev Med Child Neurol* 1995;37:682–688.
36. Chamberlain JM, Altieri MA, Futterman C, Young GM, Ochsenschlager DW, Waisman Y. A prospective, randomized study comparing intramuscular midazolam with intravenous diazepam for the treatment of seizures in children. *Pediatr Emerg Care* 1997;13:92–94.
37. Fisgin T, Gurer Y, Tezic T, Senbil N, Zorlu P, Okuyaz C, Akgün D. Effects of intranasal midazolam and rectal diazepam on acute convulsions in children: Prospective randomized study. *J Child Neurol* 2002;17:123–126.
38. Lahat E, Goldman M, Barr J, Bistritzer T, Berkovitch M. Comparison of intranasal midazolam with intravenous diazepam for treating febrile seizures in children: Prospective randomised study. *BMJ* 2000;321:83–86.
39. Mahmoudian T, Zadeh MM. Comparison of intranasal midazolam with intravenous diazepam for treating acute seizures in children. *Epilepsy Behav* 2004;5:253–255.
40. 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;353:623–626.
41. 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;44:771–776.
42. McIntyre J, Robertson S, Norris E, Appleton R, Whitehouse WP, Phillips B, Martland T, Berry K, Collier J, Smith S, Choonara I. Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: A randomised controlled trial. *Lancet* 2005;366:205–210.
43. Shah I, Deshmukh CT. Intramuscular midazolam vs intravenous diazepam for acute seizures. *Indian J Pediatr* 2005;72:667–670.
44. Ahmad S, Ellis JC, Kamwendo H, Molyneux E. Efficacy and safety of intranasal lorazepam versus intramuscular paraldehyde for protracted convulsions in children: An open randomised trial. *Lancet* 2006;367:1591–1597.
45. Bhattacharyya M, Kalra V, Gulati S. Intranasal midazolam vs rectal diazepam in acute childhood seizures. *Pediatr Neurol* 2006;34:355–359.
46. Mittal P, Manohar R, Rawat AK. Comparative study of intranasal midazolam and intravenous diazepam sedation for procedures and seizures. *Indian J Pediatr* 2006;73:975–978.
47. Mpimbaza A, Ndeezi G, Staedke S, Rosenthal PJ, Byarugaba J. Comparison of buccal midazolam with rectal diazepam in the treatment of prolonged seizures in Ugandan children: A randomized clinical trial. *Pediatrics* 2008;121:e58–64. doi:10.1542/peds.2007-0930.
48. Talukdar B, Chakrabarty B. Efficacy of buccal midazolam compared to intravenous diazepam in controlling convulsions in children: A randomized controlled trial. *Brain Dev* 2009;31:744–749.
49. Sreenath TG, Gupta P, Sharma KK, Krishnamurthy S. Lorazepam versus diazepam-phenytoin combination in the treatment of convulsive status epilepticus in children: A randomized controlled trial. *Eur J Paediatr Neurol* 2010;14:162–168.
50. Ashrafi MR, Khosroshahi N, Karimi P, Malamiri RA, Bavarian B, Zarch AV, Mirzaei M, Kompani F. Efficacy and usability of buccal midazolam in controlling acute prolonged convulsive seizures in children. *Eur J Paediatr Neurol* 2010;14:434–438.
51. Holsti M, Dudley N, Schunk J, Adelgais K, Greenberg R, Olsen C, Healy A, Firth S, Filloux F. Intranasal midazolam vs rectal diazepam for the home treatment of acute seizures in pediatric patients with epilepsy. *Arch Pediatr Adolesc Med* 2010;164:747–753.
52. Arya R, Gulati S, Kabra M, Sahu JK, Kalra V. Intranasal versus intravenous lorazepam for control of acute seizures in children: A randomized open-label study. *Epilepsia* 2011;52:788–793.
53. Javadzadeh M, Sheibani K, Hashemieh M, Saneifard H. Intranasal midazolam compared with intravenous diazepam in patients suffering from acute seizure: A randomized clinical trial. *Iranian J Pediatr* 2012;22:1–8.
54. Malu CK, Kahamba DM, Walker TD, Mukampunga C, Musalu EM, Kokolomani J, Mayamba RM, Wilmshurst JM, Dubru JM, Misson JP. Efficacy of sublingual lorazepam versus intrarectal diazepam for prolonged convulsions in Sub-Saharan Africa. *J Child Neurol* 2013;29:895–902.
55. Portela JL, Garcia PC, Piva JP, Barcelos A, Bruno F, Branco R, Tasker RC. Intramuscular midazolam versus intravenous diazepam for treatment of seizures in the pediatric emergency department: A randomized clinical trial. *Med Intensiva* 2014;39:160–166.
56. Rai A, Aggarwal A, Mittal H, Sharma S. Comparative efficacy and safety of intravenous valproate and phenytoin in children. *Pediatr Neurol* 2011;45:300–304.
57. Welch RD, Nicholas K, Durkalski-Mauldin VL, Lowenstein DH, Conwit R, Mahajan PV, Lewandowski C, Silbergleit R; Neurological Emergencies Treatment Trials (NETT) Network Investigators. Intramuscular midazolam versus intravenous lorazepam for the prehospital treatment of status epilepticus in the pediatric population. *Epilepsia* 2015;56:254–262.
58. Malamiri RA, Ghaempanah M, Khosroshahi N, Nikkhah A, Bavarian B, Ashrafi MR. Efficacy and safety of intravenous sodium valproate versus phenobarbital in controlling convulsive status epilepticus and acute prolonged convulsive seizures in children: A randomised trial. *Eur J Paediatr Neurol* 2012;16:536–541.
59. Cereghino JJ, Mitchell WG, Murphy J, Kriel RL, Rosenfeld WE, Trevathan E. Treating repetitive seizures with a rectal diazepam formulation: A randomized study. The North American Diastat Study Group. *Neurology* 1998;51:1274–1282.
60. Dreifuss FE, Rosman NP, Cloyd JC, Pellock JM, Kuzniecky RI, Lo WD, Matsuo F, Sharp GB, Conry JA, Bergen DC, Bell WE. A comparison of rectal diazepam gel and placebo for acute repetitive seizures. *N Engl J Med* 1998;338:1869–1875.

61. Cloyd J. Pharmacologic considerations in the treatment of repetitive or prolonged seizures. *J Child Neurol* 2007;22(suppl 5):47S–52S.
62. McMullan J, Sasson C, Pancioli A, Silbergleit R. Midazolam versus diazepam for the treatment of status epilepticus in children and young adults: A meta-analysis. *Acad Emerg Med* 2010;17:575–582.
63. DeToledo JC, Ramsay RE. Fosphenytoin and phenytoin in patients with status epilepticus: Improved tolerability versus increased costs. *Drug Saf* 2000;22:459–466.
64. Bleck T, Cock H, Chamberlain J, Cloyd J, Connor J, Elm J, Fountain N, Jones E, Lowenstein D, Shinnar S, Silbergleit R, Treiman D, Trinka E, Kapur J. The established status epilepticus trial 2013. *Epilepsia* 2013;54(suppl 6):89–92.
65. Brophy GM, Bell R, Claassen J, Alldredge B, Bleck TP, Glauser T, Laroche SM, Riviello JJ Jr, Shutter L, Sperling MR, Treiman DM, Vespa PM; Neurocritical Care Society Status Epilepticus Guideline Writing Committee. Guidelines for the evaluation and management of status epilepticus. *Neurocrit Care* 2012;17:3–23.
66. Mehta V, Singhi P, Singhi S. Intravenous sodium valproate versus diazepam infusion for the control of refractory status epilepticus in children: A randomized controlled trial. *J Child Neurol* 2007;22:1191–1197.
67. Abend NS, Monk HM, Licht DJ, Dlugos DJ. Intravenous levetiracetam in critically ill children with status epilepticus or acute repetitive seizures. *Pediatr Crit Care Med* 2009;10:505–510.
68. Aiguabella M, Falip M, Villanueva V, de la Peña P, Molins A, Garcia-Morales I, Saiz RA, Pardo J, Tortosa D, Sansa G, Miró J. Efficacy of intravenous levetiracetam as an add-on treatment in status epilepticus: A multicentric observational study. *Seizure* 2011;20:60–64.
69. Alvarez V, Januel JM, Burnand B, Rossetti AO. Second-line status epilepticus treatment: Comparison of phenytoin, valproate, and levetiracetam. *Epilepsia* 2011;52:1292–1296.
70. Goraya JS, Khurana DS, Valencia I, Melvin JJ, Cruz M, Legido A, Kothare SV. Intravenous levetiracetam in children with epilepsy. *Pediatr Neurol* 2008;38:177–180.
71. Ruegg S, Hunziker P, Marsch S, Schindler C. Association of environmental factors with the onset of status epilepticus. *Epilepsy Behav* 2008;12:66–73.
72. Santamarina E, Toledo M, Sueiras M, Raspall M, Ailouti N, Lainez E, Porta I, De Gracia R, Quintana M, Alvarez-Sabín J, Salas-Puig J. Usefulness of intravenous lacosamide in status epilepticus. *J Neurol* 2013;260:3122–3128.