



Review

Towards acute pediatric status epilepticus intervention teams: Do we need “Seizure Codes”?

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ABSTRACT

Purpose: To identify areas of treatment delay and barriers to care in pediatric status epilepticus, review ongoing quality improvement initiatives, and provide suggestions for further innovations to improve and standardize these patient care processes.

Methods: Narrative review of current status epilepticus management algorithms, anti-seizure medication administration and outcomes associated with delays, and initiatives to improve time to treatment. Articles reviewing or reporting quality improvement initiatives were identified through a PubMed search with keywords “status epilepticus,” “quality improvement,” “guideline adherence,” and/or “protocol;” references of included articles were also reviewed.

Results: Rapid initiation and escalation of status epilepticus treatment has been associated with shortened seizure duration and more favorable outcomes. Current evidence-based guidelines for management of status epilepticus propose medication algorithms with suggested times for each management step. However, time to antiseizure medication administration for pediatric status epilepticus remains delayed in both the pre- and in-hospital settings. Barriers to timely treatment include suboptimal preventive care, inaccurate seizure detection, infrequent or restricted use of home rescue medications by caregivers and pre-hospital emergency personnel, delayed summoning and arrival of emergency personnel, and use of inappropriately dosed medications. Ongoing quality improvement initiatives in the pre- and in-hospital settings targeting these barriers are reviewed.

Conclusion: Improved preventive care, seizure detection, and rescue medication education may advance pre-hospital management, and we propose the use of acute status epilepticus intervention teams to initiate and incorporate in-hospital interventions as time-sensitive “Seizure Code” emergencies.

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1. Introduction

Status epilepticus (SE) is one of the most common pediatric neurologic emergencies, affecting between 17 and 23/100,000 children per year and 10–20% of pediatric epilepsy patients [1–3]. While etiology and age are the main predictors of outcome after SE, seizure duration may additionally affect outcome. Importantly, seizure duration is the only modifiable risk factor [4]. Studies have yielded mixed results regarding the impact of seizure duration and

adherence to management guidelines. Some studies have identified no impact on outcome related to adherence to treatment guidelines [5] or seizure duration [6,7]. Conversely, other studies have shown that rapid administration of antiseizure medications (ASMs) is associated with shorter seizure duration and more favorable outcomes including mortality [8,9]. The Neurocritical Care and American Epilepsy Societies have published evidence-based and consensus guidelines with SE management algorithms and suggested treatment timelines [10,11]. However, time to ASM administration is often substantially delayed in cases of both pre- and in-hospital seizure onset [8,12].

Barriers to timely management may occur at any step of the care process, from preventive care and education to acute, in-hospital management. Even prior to SE occurrence, lack of regular epilepsy clinic appointments are associated with a higher risk of emergency department (ED) visits or hospital admissions [13]. Seizure detection by patients, caregivers, and healthcare professionals may be

Abbreviations: ASM, antiseizure medication; ED, emergency department; EMS, emergency medical services; GABA, gamma-aminobutyric acid; IV, intravenous; OR, odds ratio; RR, relative risk; SE, status epilepticus.

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inaccurate or missed [14,15]. Additionally, many caregivers report that they have not been trained to administer seizure rescue medication [16] and demonstrate clinically relevant administration errors when observed [17]. Some schools may be unable to administer rescue medications due to legal restrictions [18], and school nurses may feel uncomfortable with acute seizure management [19]. Further delays exist in ambulance arrival time [20] and seizure recognition by emergency medical services (EMS) [21], with pre-hospital ASMs administered in only a minority of patients [8,20,21]. Even when ASM administration is initiated by EMS, it involves almost exclusively benzodiazepines without progression to second-line ASMs [8,21]. In-hospital management is also often delayed [8], with inaccurate weight-based benzodiazepine dosing as well as delays in subsequent treatment steps [22,23].

With the identification of these barriers to timely SE management, multiple centers have taken on initiatives to improve management and time to ASM administration [13,24–29]. The cost-effectiveness of each intervention has not yet been studied, but the cost for adult SE care in the United States [30] and Europe [31] invites means for improvement. Gaps remain and provide opportunities for ongoing innovation and improvement. This review summarizes current guidelines on pediatric SE management, outcomes associated with delayed treatment and prolonged seizures, and barriers to rapid management, highlighting approaches which might lead to optimized care.

2. Evidence guiding ASM choice and administration

Prompt administration of benzodiazepines is recommended as first-line treatment. In a double-blind trial, 273 children with convulsive SE were randomized to receive either intravenous (IV) lorazepam or diazepam. Seizure cessation occurred in 72% of subjects in each group without differences in need for assisted ventilation. The authors concluded that IV lorazepam has similar safety and efficacy when compared to diazepam [32]. A meta-analysis found IV lorazepam to have fewer adverse effects than diazepam [33], though another mixed pediatric and adult meta-analysis found this trend not to be statistically significant [34]. Considering other benzodiazepine formulations when IV access is not available, a meta-analysis indicated that the most effective non-IV rescue medication for stopping seizures within 10 min of drug administration is intranasal midazolam, with rectal diazepam being less efficacious than both intranasal and buccal midazolam [35]. Additionally, in a cost-effectiveness analysis comparing non-IV first-line rescue medications, intranasal and buccal midazolam were the most cost-effective options while rectal diazepam was not cost-effective at any willingness to pay in the United States [36]. European studies also found that buccal midazolam was more cost-effective than rectal diazepam [37,38]. Given these data, evidence-based guidelines have stated that IV lorazepam and IV diazepam are effective for seizure termination [10,11], and when IV access is not available then midazolam (intranasal, buccal or intramuscular) is potentially more effective than diazepam (IV or rectal) [11].

Few studies have compared the effectiveness of second-line therapies. The ongoing Established Status Epilepticus Treatment Trial (ESETT) is evaluating levetiracetam, valproic acid, and fosphenytoin [39]. Other international pediatric trials comparing levetiracetam and phenytoin in benzodiazepine-resistant SE are additionally underway and may offer further evidence [40,41]. In surveys of neurologists [42] and pediatric emergency medicine physicians in Australia and New Zealand [43], fosphenytoin is chosen as the second-line ASM for the majority of children. A combined adult and pediatric meta-analysis comparing second-line ASM therapy reported that seizure cessation rates were 76%, 74%, 69%, and 50% with valproic acid, phenobarbital, levetiracetam,

and phenytoin, respectively. This analysis concluded that there is insufficient evidence to support phenytoin as the preferred ASM in benzodiazepine-resistant SE [44]. A recent comparison of IV levetiracetam to IV valproic acid in children found them to be equally effective, though valproic acid was associated with more adverse effects including liver dysfunction in 13% of cases [45]. Given these data, SE guidelines state that phenytoin, valproic acid, levetiracetam, and phenobarbital are appropriate second-line or urgent control therapy options, though there is currently insufficient evidence to suggest one ASM is preferred [10,11]. Continuous infusions, including midazolam, pentobarbital, propofol, and ketamine, are considered appropriate management options for refractory SE treatments [10,46,47]. However, there are even fewer data available to guide selections between these options.

3. Time to treatment recommendations & outcomes associated with delays

The recommendation for rapid administration of first-line benzodiazepines in SE stems from *in vitro* and animal models demonstrating the pathophysiology of neuronal excitation, increasing medication pharmacoresistance with longer seizures, and brain injury with prolonged seizures. In *in vitro* models, ongoing seizure activity promotes internalization of synaptic gamma-aminobutyric acid (GABA)-receptors and thus decreases neuronal inhibition [48,49], with subsequent studies showing these receptor changes were associated with increasing pharmacoresistance to benzodiazepines [50–53]. In a prospective study in children experiencing prolonged seizures, seizures lasting longer than 5–7 min were less likely to terminate spontaneously than shorter seizures [54], likely owing to the aforementioned mechanisms. Further studies revealed neuronal cell death with seizures lasting longer than 30–80 min [55–57]. Hence, while the definition of SE was initially considered to be an ongoing seizure for 30 min or longer [58], most recent management pathways suggest treatment after 5 min of seizure activity [59].

Though results are mixed and seizure duration is not a predictor of outcome in all studies [5–7], in some studies rapid SE treatment has been associated with shorter seizure duration and lower morbidity and mortality [8,9,58]. One prospective, population-based United Kingdom study demonstrated that for each minute delay from onset of SE to arrival at the ED, there was a 5% cumulative increase in the risk of the episode lasting more than 60 min [60]. In another retrospective analysis, 73% of children with aggressive ASM treatment within 60 min after initial treatment returned to neurological baseline during long-term follow-up (mean duration of 3.9 years), while all children not aggressively treated experienced new neurologic deficits and continued to deteriorate at follow-up [61]. In a study of pediatric refractory SE, patients receiving an initial benzodiazepine after 10 min had higher odds of death (adjusted odds ratio (OR) 11.0), longer seizure duration (adjusted OR 2.6), higher rates of hypotension (adjusted OR 2.3), and higher likelihood of requiring continuous infusions (adjusted OR 1.8) than patients who received timely treatment [9].

In keeping with the management goal of rapid initiation and escalation of treatment, the 2012 Neurocritical Care Society consensus guideline recommends emergent initial ASM therapy (*i.e.* first-line treatment) within 5 min of seizure onset, urgent control ASM therapy (*i.e.* second-line treatment) within 5–10 min, and refractory SE therapy (*i.e.* third and fourth-line treatment) within 20–60 min [10]. The 2016 American Epilepsy Society evidence-based guideline suggests initiation of treatment with a benzodiazepine at 5 min of ongoing seizure, second-line therapy at 20–40 min, and either repeating second-line therapy or moving directly to a continuous infusion by 40 min [11]. Fig. 1 summarizes a pediatric SE medication algorithm with a suggested timeline.

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