Timing Is Everything: Where Status Epilepticus Treatment Fails

Chloe E. Hill, MD,[1,2] Alomi O. Parikh, BA,[1] Colin Ellis, MD,[1] Jennifer S. Myers, MD,[2,3] and Brian Litt, MD[1,4]

Status epilepticus is an emergency; however, prompt treatment of patients with status epilepticus is challenging. Clinical trials, such as the ESETT (Established Status Epilepticus Treatment Trial), compare effectiveness of antiepileptic medications, and rigorous examination of effectiveness of care delivery is similarly warranted. We reviewed the medical literature on observed deviations from guidelines, clinical significance, and initiatives to improve timely treatment. We found pervasive, substantial gaps between recommended and "real-world" practice with regard to timing, dosing, and sequence of antiepileptic therapy. Applying quality improvement methodology at the institutional level can increase adherence to guidelines and may improve patient outcomes.

ANN NEUROL 2017;82:155–165

While "time is brain" has traditionally described the pathophysiology of stroke, our present-day understanding of status epilepticus reaffirms this mantra. Status epilepticus, prolonged seizures or multiple seizures with incomplete return to baseline, is an emergency that requires prompt treatment.[1–3] On the cellular level, changes in receptor trafficking and neuropeptide expression occur within minutes to encourage a hyperexcitable state.[1,4] Clinically, seizure cessation becomes less likely as time to therapy lengthens.[5] Yet despite its importance, timely treatment is not achieved for the majority of patients presenting with status epilepticus.

Status epilepticus has an incidence of 10 to 40 per 100,000 population, and the impact is considerable.[4] Mortality is estimated at 20% to 30%,[2,4] and up to 23% of patients will deteriorate in neurological function.[6] Additionally, its estimated annual direct inpatient costs in the United Status are >$4 billion.[4] While age and etiology are critical determinants of prognosis,[7] prolonged seizure duration is associated with higher mortality and morbidity,[8,9] worse functional outcome,[10] and increased risk of subsequent epilepsy.[11] Furthermore, seizure duration is the only modifiable prognostic factor[7] and can be improved by expeditiously administering antiepileptic medication.

Expert opinion supports utilizing a protocol to facilitate urgent treatment.[12,13] The initial first-line agent should be administered within 5 to 10 minutes of seizure onset, a second-line agent within 20 to 40 minutes, and a third-line agent within 60 minutes.[14,15] Class I evidence supports using a benzodiazepine as the first-line agent, but weaker evidence guides choice of a second-line agent and beyond.[13,15,16] The 2016 Guideline Committee of the American Epilepsy Society proposed fosphenytoin, valproic acid, and levetiracetam as second-line options,[15] and the ESETT (Established Status Epilepticus Treatment Trial) is currently underway to compare effectiveness of these three second-line therapies.[17,18] Given that prompt therapy is a critical component of effective therapy, delivery of care warrants similarly rigorous examination.

We performed a review of the literature to characterize observed divergences from recommended guidelines, consider their clinical significance, and explore initiatives to improve adherence to treatment protocols. We aim to identify opportunities and approaches to

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.24986

Received Feb 27, 2017, and in revised form Jun 7, 2017. Accepted for publication Jun 25, 2017.

Address correspondence to Dr Chloe E. Hill, Department of Neurology, University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. E-mail: chloe.hill@uphs.upenn.edu

From the [1]Department of Neurology, University of Pennsylvania, Philadelphia, PA; [2]Center for Healthcare Improvement and Patient Safety, University of Pennsylvania, Philadelphia, PA; [3]Department of Medicine, University of Pennsylvania, Philadelphia, PA; and [4]Department of Bioengineering, University of Pennsylvania, Philadelphia, PA.

optimize antiepileptic drug delivery to patients presenting with status epilepticus.

Materials and Methods

Search Strategy and Selection Criteria

The electronic database PubMed was searched in June 2017 using the following criteria to identify delays and deviations from status epilepticus treatment protocols: "("status epilepticus"[Title] OR seizure*[Title]) AND (treat*[Title] OR therap*[Title] OR drug*[Title] OR medication*[Title] OR anticonvulsant*[Title] OR management[Title] OR cessation[Title] OR factor*[Title]) AND (delay*[Title/Abstract] OR "time to treatment"[Title/Abstract] OR administration[Title/Abstract] OR timeliness[Title/Abstract] OR devia*[Title/Abstract] OR protocol[TItle/Abstract] OR pathway[Title/Abstract])". This search strategy yielded 1,064 studies; publications preceding 2000 were filtered out yielding 766 studies. The abstracts of these 766 studies were screened and papers were excluded if they met any of the following criteria: (1) unrelated to prolonged seizures or status epilepticus; (2) no measure of deviation from protocol/recommendations in drug timing, dosing, and/or sequence of therapies; or (3) an interventional study. Only the initial publication was included in the case of republished data with secondary analysis. This approach yielded 17 studies. A subsequent search used the additional search terms of quality, improve*, intervention*, pathway, and protocol[19]; this strategy identified three additional studies that used interventions to expedite treatment of patients presenting with clinical status epilepticus.

Definitions

For the purpose of comparing between studies, "first-line therapy" is defined as a benzodiazepine (typically lorazepam, diazepam, or intramuscular midazolam), "second-line therapy" is defined as the initial nonbenzodiazepine drug (typically phenytoin, fosphenytoin, valproic acid, levetiracetam, or phenobarbital), and "third-line therapy" is defined an anesthetic medication (typically propofol or intravenous [IV] midazolam). Status epilepticus and/or prolonged seizure are defined differently within each study, and the working definition used for inclusion in each study is reported within Tables 1 and 2.

Statistical Analysis

Study sample size and statistical analysis varied greatly across papers. For this review, we have reported median, mean, percentage, range, interquartile range (IQR), confidence interval (CI), and/or p value as provided by each study's authors. Our tables provide complete reporting of the statistics as made available in each original paper.

Results

Of the 17 studies identified, all assessed delivery of first-line therapy for patients presenting in status epilepticus, five studies assessed delivery of second-line therapy and five studies assessed delivery of third-line therapy. Seven studies included only pediatric patients and seven studies included only adult patients. Nine studies considered exclusively patients presenting with convulsive status epilepticus. All studies but four reviewed patient records retrospectively; two prospective studies gathered information at the time of the patient encounter and two studies analyzed prospectively collected data sets. Authors considered time-related aspects of care such as time from seizure onset to administration of first-line, second-line, and third-line agents (Table 1) and medication-related aspects of care such as drug sequence and dosing (Table 2). Last, authors examined adherence to the treatment protocol, either institution-specific or consensus guidelines, and analyzed the time to seizure cessation and patient outcome (Table 3).

Three quality improvement (QI) reports were identified in our review; all three studies focused on interventions for pediatric patients presenting with clinical status epilepticus. Guidelines for the reporting of QI work have been published previously,[20] and these QI reports are summarized with attention to these guidelines in Table 4.

Prehospital Care

From time of seizure onset, the median delays to paramedic arrival ranged from 12.5 (IQR, 18; range, 0–95) to 30 minutes[21,22] and to hospital presentation ranged from 30 minutes (range, 5–120) to 1 hour 45 minutes.[21–25] Before reaching the emergency department (ED), antiepileptic medication was administered to 34% (16 of 47) to 51% (56 of 109) of patients.[21–24,26,27] One study found that no patients received treatment during ambulance transfer.[24] When out-of-hospital first-line therapy was administered, the median delay was 1 hour 10 minutes.[21]

Time to Therapy

A >30-minute delay to first-line treatment was observed for 17% (26 of 157) to 64% (97 of 151) of patients,[29–32] with the median delays to first-line therapy ranging from 30 to 70 minutes[21,22,27,33,34] (see Table 1). Median delays to second-line treatment ranged from 69 minutes to 3 hours. Median delays to third-line treatment ranged from 2 hours 38 minutes to 3 hours.[27,33,34] In these studies, the ranges for delay were very wide, from minutes to several days. A study of international practice observed that 16% of patients received third-line therapy within 1 hour.[35]

Treatment of nonconvulsive status epilepticus and epilepsia partialis continua started significantly later, with 18% (17 of 92) of patients receiving initial treatment at >24 hours compared to 0% (0 of 70) of patients with

TABLE 1. Time-Related Deviations From Protocol

Citation	Patient Population	Method	Presentation of Included Patients	Delay to First-Line Therapy	Delay to Second-Line Therapy	Delay to Third-Line Therapy
Pellock et al. (2004)[29]	889 adults and children with SE at multiple hospitals in the US	Prospective database	Sz ≥30 min	>30 min for 58% (520/889) of pts; >60 min for 29% (256/889) of pts		
Eriksson et al. (2005)[31]	157 children with convulsive sz in the ED or pediatric ICU at an academic hospital in Finland	Retrospective review	Convulsive sz ≥5 min	>30 min for 17% (26/157) of pts		
Lewena et al. (2009)[23]	542 episodes in 467 children with convulsive sz in the ED of eight hospitals in Australia and New Zealand	Retrospective review	Motor sz activity >10 min		Median 24 min from hospital presentation (IQR, 15–36 min)	Median 45 min from hospital presentation (IQR, 25–68 min)
Hillman et al. (2013)[21]	109 consecutive visits in 100 adults with SE in the ED at an academic hospital in Finland	Retrospective review	Sz ≥30 min or recurring szs without return to baseline in between	Median 70 min for out-of-hospital treatment		
Kämppi et al. (2013)[33]	82 adults with SE in the ED at an academic hospital in Finland	Retrospective review	Continuous sz ≥30 min, recurrent szs without return of consciousness, or >4 szs within 60 min	Median 35 min (range 0 min–77 h 5 min)	Median 3 h (range 30 min –77 h 5 min)	Median 2 h 55 min (range 0 min –81 h 45 min)
Rantsch et al. (2013)[30]	167 episodes in 118 adults with SE seen by neurology at an academic hospital in Germany	Retrospective review	Continuous sz ≥5 min or ≥2 discrete szs with incomplete return to baseline in between	>30 min for 61% (99/162) of pts		
Rossetti et al. (2013)[36]	263 episodes in 225 adults with SE at an academic center in Switzerland	Prospective data set	Continuous sz >5 min or repeated szs without return to baseline in between	>60 min for 62% (139/225) of pts		
Seinfeld et al. (2014)[22]	179 children with febrile (convulsive) SE at five academic hospitals in the US	Prospective observation	Sz ≥30 min or a series of szs without full recovery in between lasting ≥30 min	Median 30 min (IQR, 35; range 1–175 min)		
Ferlisi et al. (2015)[35]	488 children and adults with refractory SE in an ICU, multinational	Online registry dataset	Refractory SE with initiation of anesthetic agent in the ICU	>60 min for 62% (282/453) of pts		>60 min for 84% (393/466) of pts
Kämppi et al. (2015)[34]	70 adults with generalized convulsive SE in the ED at an academic hospital in Finland	Retrospective review	≥1 convulsive sz within (a) continuous sz ≥30 min, (b) recurrent szs without return of consciousness, or (c) >4 szs within 60 min irrespective of return of consciousness	Median 30 min (range 0 min–8 h 5 min)	Median 2 h 40 min (range 30 min –61 hours 54 min)	Median 2 h 38 min (range 0 min –66 h 20 min)
Sánchez Fernández et al. (2015)[27]	81 children with refractory convulsive SE at nine tertiary pediatric hospitals in the US	Prospective observation	Focal or generalized convulsive szs at onset with (a) failure of ≥2 AEDs, or (b) initiation of continuous AED infusion	Median 30 min (IQR 6–70 min)	Median 69 min (IQR 40–120 min)	Median 180 min (IQR 120–645 min)
Cheng et al. (2016)[32]	151 adults treated for SE at an academic hospital in the US	Retrospective review	≥5 min of (a) continuous clinical and/or electrographical sz activity, or (b) recurrent szs without recovery in between	>30 min for 64% (97/151) of pts		

SE = status epilepticus; US = United States; sz = seizure; min = minute(s); pts = patients; ED = emergency department; ICU = intensive care unit; IQR = interquartile range; h = hour(s); EEG = electroencephalogram; AED = antiepileptic drug.

TABLE 2. Medication-Related Deviations From Protocol

Citation	Patient Population	Method	Presentation of Included Patients	Non-BZD Initial Therapy	Suboptimal Dosing	Overall Nonadherence to Protocol
Muayqil et al. (2007)[37]	45 adults with convulsive SE in the ED at an academic hospital in Canada	Retrospective review	Sz with continuous motor activity ≥30 min or ≥2 convulsions without return to baseline consciousness	7% (3/45)	100% (27/27) of pts treated with second-line phenytoin received doses <20 mg/kg	29% (13/45) nonadherence due to incorrect drug sequence
Tobias et al. (2008)[25]	92 children with SE in a pediatric ICU at an academic hospital in the US	Review of pre-ICU care records	30 min of either (a) 1 continuous sz, or (b) ≥2 discrete szs with incomplete return to baseline in between	11% (10/92)	25% (20/80) of pts treated with lorazepam or diazepam received a suboptimal dose	
Lewena et al. (2009)[23]	542 episodes in 467 children with convulsive sz in the ED of eight hospitals in Australia and New Zealand	Retrospective review	Motor sz activity >10 min	A few		
Tirupathi et al. (2009)[24]	47 children with convulsive SE in the ward and ICU at a tertiary pediatric hospital in Ireland	Retrospective review	Generalized tonic-clonic sz or multiple szs without intervening consciousness ≥30 min	0% (0/47)	49% (23/47) of pts received >2 BZD doses	47% (22/47) nonadherence due to >2 BZD doses and/or second-line agent at >30 min
Kämppi et al. (2013)[33]	82 adults with SE in the ED at an academic hospital in Finland	Retrospective review	Continuous sz ≥30 min, recurrent szs without return of consciousness, or >4 szs within 60 min	4% (3/81)		42% (32/77) of pts treated with second-line therapy received an anesthetic agent first
Rossetti et al. (2013)[36]	263 episodes in 225 adults with SE at an academic center in Switzerland	Prospective data set	Continuous sz >5 min or repeated szs without return to baseline in between			37% (83/225) nonadherence due to improper drug dose or sequence
Langer et al. (2014)[26]	177 episodes in 170 children and adults with generalized convulsive SE at an academic hospital in the US	Retrospective review	Sz on paramedic or ED arrival or >2 szs without return to baseline with description of jerking, twitching, or similar movement	<1% (1/177)	90% (159/176) of pts received a single suboptimal BZD dose	
Seinfeld et al. (2014)[22]	179 children with febrile (convulsive) SE at five academic hospitals in the US	Prospective observation	Sz ≥30 min or a series of szs without full recovery in between lasting ≥30 min	7% (13/179)	22% (32/146) of pts received suboptimal dosing of lorazepam or diazepam; 23% (41/179) of all pts received >2 BZD doses	
Ferlisi et al. (2015)[35]	488 children and adults with refractory SE in an ICU, multinational	Online registry data set	Refractory SE with initiation of anesthetic agent in the ICU	67% (318/474)		
Sánchez Fernández et al. (2015)[27]	81 children with refractory convulsive SE at nine tertiary pediatric hospitals in the US	Prospective observation	Focal or generalized convulsive szs at onset with (a) failure of ≥2 AEDs, or (b) initiation of continuous AED infusion	4% (3/81)	40% (31/78) of pts received >2 BZD doses	
Siefkes et al. (2016)[28]	126 episodes in children with convulsive szs transported to a tertiary pediatric hospital in the US	Retrospective review	Acute convulsive sz necessitating AED administration		32% (37/117) of pts received initial suboptimal BZD dose; 37% (47/126) of all pts received >2 BZD doses	61% (77/126) nonadherence attributed to >2 BZD doses, non-BZD initial therapy, or early intubation

BZD = benzodiazepine(s); SE = status epilepticus; ED = emergency department; min = minute(s); sz = seizure; pts = patients; ICU = intensive care unit; AED = antiepileptic drug

TABLE 3. Nonadherence and Clinical Outcome

Citation	Patient Population	Seizure Type	Measures of Nonadherence	Clinical Outcomes		Conclusions
Hillman et al. (2013) [21]	Adults	Convulsive and nonconvulsive SE >30 min	Treatment delay >1 hr	Disability (modified Rankin scale)	**Positive association**	Treatment delay did not impact disability in all pts, but pts treated in the ED at <1 hr from sz onset had better recovery than those treated at >1 hr (82% vs 46%; $p < 0.05$).
Kämppi et al. (2015) [34]	Adults	Convulsive SE >30 min	Delay to second-line therapy	Delayed return of consciousness	**Positive association**	Delay to second-line therapy correlated with delayed return of consciousness (OR, 0.295; 95% CI, 0.039–0.534; $p = 0.027$).
Siefkes et al. (2016) [28]	Children	Convulsive szs requiring treatment	>2 BZD doses Non-BZD initial therapy Early intubation (before third-line therapy)	Intubation ICU admission	**Positive association**	Nonadherence (excluding early intubation) was more likely to involve intubation (RR, 2.4; 95% CI, 1.40–4.13). Nonadherence was more likely to require ICU admission (RR, 1.64; 95% CI, 1.24–2.16).
Cheng et al. (2016) [32]	Adults	Convulsive and nonconvulsive SE >5 min	Treatment delay >30 min	Mortality in-hospital Poor functional status (modified Rankin scale)	**Positive association**	Treatment delay >30 minutes increased unadjusted in-hospital mortality (OR, 2.06; 95% CI, 1.01–4.17; $p = 0.046$) and poor functional status (OR, 2.48; CI, 1.05–5.85; $p = 0.038$). When adjusted for acute etiology, sz duration, and NCSE, treatment delay >30 minutes was not associated with mortality and poor functional status.
Muayqil et al. (2007) [37]	Adults	Convulsive SE >30 min	Improper drug sequence	Morbidity and Mortality Duration of hospitalization Intubation	**No observed association**	Outcomes were similar for those who received improper drug sequence (32/45) and those who received recommended drug sequence (13/45).
Rossetti et al. (2013) [36]	Adults	Convulsive and nonconvulsive SE >5 min	Treatment delay >1 hr Treatment nonadherence (outside ideal dose range and proper sequence)	Mortality New disability	**No observed association**	Treatment delay >1 hr was not associated with mortality (15/26 vs 11/26) or new disability (53/82 vs 29/82; $p = 0.769$). Nonadherence was not associated with mortality (13/26 vs 13/26) or new disability (33/82 vs 49/82; $p = 0.157$).
Sánchez Fernández et al. (2015) [27]	Children	Convulsive SE requiring third-line therapy	Treatment delay >median	ICU stay	**No observed association**	Length of ICU stay was not associated with delay of initial doses first-line therapy (3 vs 3 days; $p = 0.26$) or second-line therapy (2.3 vs 3.5 days; $p = 0.13$).
Ferlisi et al. (2015) [35]	Adults and children	Convulsive and nonconvulsive SE requiring third-line therapy	Delay to third-line therapy >1 day	Not recovered (death or withdrawn care)	**Negative association**	Delay to third-line therapy >1 day was associated with increased recovery compared to delay <1 day (111/137 vs 182/258; $p = 0.02$).

SE = status epilepticus; min = minutes; hr = hour; pts = patients; ED = emergency department; sz = seizure; OR = odds ratio; CI = confidence interval; ICU = intensive care unit; RR = relative risk; BZD = benzodiazepine.

TABLE 4. Quality Improvement Reports

	Tourigny-Ruel et al. (2014)38	Xie et al. (2014)39	Harris et al. (2016)40
Problem description	Variability in treatment of impending status epilepticus in children	Prolonged time for patients to receive appropriate emergency drugs for impending status epilepticus	Variability in treatment of neonatal status epilepticus
Team	Pediatric emergency medicine division, neurology division, intensive care division	Nurses, physicians, pharmacists, administrative staff, support staff, quality control staff, family members	Neonatologists, neurologists, pharmacists
Aim	Evaluate the safety and effectiveness of a linear, single-agent protocol	Decrease time to antiepileptic treatment	Reduce treatment variation and reduce risk of treatment side effects
Intervention	Implementation of a linear, midazolam-based protocol	Employment of an automatically activated order set for all children with a diagnosis of seizure or at risk of developing seizures during hospitalization	Implementation of a standardized treatment algorithm
Results	93% (51/55) adherence to the first-line therapy (midazolam) 86% (6/7) adherence to the second-line therapy (phenytoin) 13% (6/46) of patients required intubation and 4% (2/46) required treatment for hypotension	Improved mean delay to first-line therapy (3.74 vs 7.72 minutes; $p < 0.0001$) Improved mean delay to second-line therapy (25 vs 49.5 minutes; $p < 0.0001$)	80% adherence to the protocol reached with regard to drug sequence and timing Mean maximum serum phenobarbital concentration successfully reduced (41.0 vs 56.8ug/ml) Reduction in seizures progressing to status epilepticus (13/36 vs 6/13) Reduction in mean length of stay (18.9 vs 25.7 days)
Conclusion	A linear, midazolam-based protocol is effective and safe for treating impending status epilepticus in children.	Treatment delivery can be expedited through use of an automated, standardized order set.	A standardized protocol can reduce progression to status epilepticus and can improve antiepileptic toxicity.

generalized convulsive status epilepticus ($p < 0.001$).[30] A greater proportion of patients treated within an hour had generalized convulsive seizures compared to those treated outside of 1 hour (62 of 86 vs 54 of 139; $p < 0.001$),[36] and, similarly, patients presenting with convulsive seizures were more likely to receive treatment within an hour than patients with nonconvulsive seizures (125 of 254 vs 19 of 61; $p < 0.001$).[35]

A systematic analysis of the components of delay concluded that delay to first-line drug was best explained by delay in calling paramedics and the clumsiness of administering rectal medication; delay to second-line therapy was largely because paramedics did not have the ability to administer IV fosphenytoin; and delay to third-line therapy might be attributable to diagnostic delay[33].

Choice and Dosing of Agents

While nearly all pediatric patients received a benzodiazepine as the first-line agent,[23,24,27] patients admitted to the intensive care unit (ICU) and patients treated for febrile status epilepticus had higher rates of nonbenzodiazepine initial therapy, 11% and 7% respectively[22,25] (see Table 2). Benzodiazepines were not used as the initial treatment in 7% or less of adult patient samples,[26,33,37] except for a world-wide survey of status epilepticus treatment that reported 67% of patients did not receive a benzodiazepine as a first-line therapy.[35] When benzodiazepines were administered, 22% (32 of 146) to 90% (159 of 176) of patients received suboptimal weight-based dosing.[22,25,26,28]

Because of improper drug choice, dosage, or sequence, 29% (13 of 45) to 61% (77 of 126) of patients were not treated according to protocol.[24,28,33,36,37] A common violation of the protocol was more than two administrations of benzodiazepines (rather than the recommended escalation to a second-line drug), which was observed in 23% (41 of 179) to 49% (23 of 47) of pediatric patients[22,24,27,28] and may be associated with greater risk of respiratory depression. In one study, 43% (10 of 23) of pediatric patients treated with >2 doses of benzodiazepines had respiratory compromise compared to 13% (3 of 24) patients treated with 2 or fewer doses.[24] Another study demonstrated a relative risk of intubation of 2.3 (95% CI, 1.4–3.9; $p = 0.002$) for pediatric patients treated with >2 benzodiazepine doses.[28]

Associations Between Time to Therapy and Seizure Cessation

A positive relationship between seizure duration and delayed first-line, second-line, and/or third-line therapy was demonstrated for both pediatric and adult patients presenting with convulsive status epilepticus.[22,27,31,34,37] A correlation between seizure duration and treatment delay was also noted in a cohort of adult patients not limited to convulsive seizures.[32]

Associations Between Adherence to Status Epilepticus Protocol and Clinical Outcome

Deviation from treatment recommendations during transport to the hospital for pediatric patients with convulsive status epilepticus was associated with greater risk of intubation (relative risk [RR], 2.4; 95% CI 1.4–4.13) and ICU admission (RR, 1.64; 95% CI, 1.24–2.16).[28] Delay in administering second-line therapy was correlated with delay in return of consciousness in adults with convulsive status epilepticus (odds ratio [OR], 0.295; 95% CI, 0.039–0.534; $p = 0.027$).[34] When considering functional outcome in adults presenting with status epilepticus, patients treated in the ED within 1 hour of seizure onset had better recovery than when treatment was initiated beyond 1 hour (82% vs 46%; $p < 0.05$).[21] In-hospital mortality and poor functional outcome were associated with treatment delay of >30 minutes; however, this association was weakened when adjusted for seizure etiology, seizure duration, and nonconvulsive status epilepticus[32] (see Table 3).

Conversely, several authors observed no association between protocol adherence and patient outcomes. Length of ICU stay was not associated with delay to first-line or second-line therapy in children presenting with convulsive status epilepticus.[27] One study of adults presenting with convulsive status epilepticus found that while adherence to recommended treatment was associated with shorter seizure duration, the outcomes of morbidity, mortality, duration of hospital stay, and intubation were not associated with adherence to recommended drug sequence.[37] Another study reported that treatment latency did not relate to the outcomes of mortality and new disability; though there was no significant association between treatment adherence and outcome, medication sequence appeared to have a greater influence than medication dose.[36] International survey of treatment practice found paradoxically that patients who received third-line therapy later had better outcomes.[35]

Initiatives to Improve Protocol Adherence

The first phase of each QI initiative consisted of multidisciplinary engagement and careful surveillance of current practice at individual institutions. Observed causes of variation and delays included failure to correctly identify time of seizure onset, inconsistent physician orders, delayed decision making regarding when to administer drugs, lack of standing orders for medication as needed, varying experience of staff and personnel, knowledge gaps, inefficient communication, and issues with availability of antiepileptic medication.[38–40]

All three studies chose to standardize treatment by creating or modifying a treatment protocol. Following employment of a linear, single-agent protocol for pediatric patients presenting with impending status epilepticus, 93% (51 of 55) of seizures were appropriately treated with first-line midazolam and 86% (6 of 7) were

TABLE 5. Proposed Future Directions

Problem	Solutions
Minority of patients receive treatment before arrival in the hospital	Develop more effective, user-friendly methods for family and caregivers to administer rescue medication
Journey to hospital is often prolonged	Outfit paramedics with the capability to deliver second-line therapy or early polytherapy
Unreliable administration and dosage of benzodiazepines as the first-line agent	Simplify and clarify recommended first-line dosing Create an explicit single, continuous protocol bridging prehospital to in-hospital treatment
Delays in diagnosis of status epilepticus	Improve the education of emergency personnel and family members Advance technologies for EEG diagnosis in the field and/or immediately upon arrival to the ED
Unclear relationship between treatment nonadherence and patient outcome	Establish and employ standard quality indicators of treatment adherence (timing, dose, sequence) Adopt consistent clinical outcomes, covariate considerations, and definitions of status epilepticus
Difficult to retrospectively assess seizure duration and clinical decision making	Collect patient data in real-time through technology innovation
Limited and laborious data collection	Innovate data abstraction and visualization tools Encourage reporting as performance measures
Health system and institution-specific factors impact protocol adherence	Apply quality improvement methodology to explore the local context and then implement responsive, targeted countermeasures

EEG = electroencephalogram; ED = emergency department.

appropriately treated with phenytoin as second-line therapy (no comparison group available).[38] In another study that used an automatically activated electronic order set for any pediatric patient with a diagnosis of seizure, the mean time from impending status recognition to first-line therapy improved (3.74 vs 7.72 minutes; $p < 0.0001$) as did delay to second-line therapy (25 vs 49.5 minutes; $p < 0.0001$).[39] Implementing a standardized treatment protocol for neonatal status epilepticus reached 80% protocol adherence with regard to drug sequence and order. Additionally, there was a reduction in mean maximum serum phenobarbital concentration (41.0 vs 56.8ug/ml) as intended and a 10% reduction in seizures progressing to status epilepticus.[40]

Discussion

Recent major advances in our understanding of the pathophysiology of status epilepticus have not yet translated to more rapid treatment in clinical practice. The above studies demonstrate pervasive delays in treatment of status epilepticus; 17% to 64% of patients have a >30-minute delay to first-line therapy.

With only 31% to 54% of patients receiving treatment before arrival at the hospital, the prehospital period represents a substantial missed opportunity for timely intervention (Table 5). While it is difficult to decrease the time until an emergency call is made or until paramedics reach a patient, superior options for rescue medication administered by family and caregivers are certainly within reach. Furthermore, the journey to the hospital has been shown to typically be >30 minutes, and while outfitting paramedics with the capability to deliver second-line therapy or early polytherapy has not yet been shown to improve outcomes,[41] it warrants further study.[42]

Given class I evidence for use of benzodiazepines as first-line therapy, it is alarming that some studies have shown that 7% to 67% of patients are not initially receiving benzodiazepines. Furthermore, there is variability in dosing of benzodiazepines, often with patients

receiving more than 2 doses, thus delaying second-line therapy and potentially increasing risk of respiratory depression (though the relative impact of benzodiazepine vs prolonged seizure on respiratory status is unknown[43]). Simplifying and clarifying recommended first-line agent dosing would be helpful. Discontinuity and discordance between prehospital and in-hospital treatment protocols may be leading to confusion regarding choice and dosing of first-line therapy. An explicit single, continuous protocol bridging prehospital to in-hospital treatment would be advantageous.

While all patients presenting in status epilepticus can experience treatment delay, it is both intuitive and supported by substantial evidence that nonconvulsive status epilepticus is treated later than convulsive status epilepticus because of diagnostic delay. Parallel opportunities exist for educating emergency personnel and family members regarding the clinical presentation of nonconvulsive status epilepticus as well as for developing technology to advance electrographical diagnosis in the field and immediately upon arrival to the ED. Such technologies might include simplified electroencephalogram (EEG) systems deployable around the clock by non-EEG-trained staff; these systems could either accurately identify status epilepticus at the bedside or transmit data to the cloud for rapid remote interpretation by certified professionals.

There is strong evidence of a positive relationship between treatment delay and seizure duration; however, whether or not adherent treatment improves morbidity and mortality is thus far equivocal. This uncertainty is likely attributed to confounding factors; for example, the paradoxical finding that patients who received late third-line therapy had better clinical outcomes[35] may be explained by slower escalation of therapy for less-severe clinical presentations.[35,36] Variable patient presentations, methods, and measurements across studies lead to divergent conclusions in the existing literature. In particular, some studies do not consider seizure type (convulsive vs nonconvulsive), which is likely to confound associations between treatment and outcome. Other studies adjust outcomes for the duration of status epilepticus, which may obscure the full impact of initiating treatment early. The threshold for dichotomizing timely versus delayed treatment (>30 vs >60 minutes) is potentially impactful because of evolving changes in neurotransmission. Furthermore, it may be that one element of adherence (drug sequence) is more important than another (drug dose). For future studies, it would be hugely beneficial to develop standardized quality indicators of treatment adherence and to use consistent clinical outcomes, covariate considerations, and definitions of status epilepticus.

Nearly all of these observational studies (15 of 17) were performed retrospectively or by review of previously collected data. As such, seizure onset and cessation times become difficult to accurately extract and clinical decision making is nearly impossible to evaluate. Potential causes of treatment delay may be conjectured, but the subtleties and details of individual patient presentations are lost when data are reviewed retrospectively. Collecting high-quality data in real time would elucidate causes of treatment delays; however, prospective data abstraction is extremely laborious. Hopefully, methods of seamless, real-time data collection will advance as public reporting of performance grows. Innovation, such as the automated extraction of clinical information with innovative technologies to create a visualization of treatment,[44] more nimble tracking, and more robust data infrastructure, would be invaluable to the field.

While the paucity of data regarding cause of delays in status epilepticus treatment is frustrating, the discipline of QI is particularly well suited to this inquiry. QI differs from traditional research in that the primary focus is understanding and improving a local process. As such, the initial phase consists of a deep dive into the "why" of a problem by examining the local environment, observing the current practice, and performing root cause analysis. Variation in choice and timing of drug therapy in status epilepticus appears to be a problem across institutions; a powerful response would be the development of common protocols that could be disseminated nationally and then tailored to local needs.

Conclusion

There is a significant gap between the recommended treatment of status epilepticus and current practice. Neurologists have long been invested in the study of antiepileptic drug effectiveness; however, attention must also be paid to successful delivery of care. More effective treatment of patients with status epilepticus may be achieved when care delivery is optimized through rigorously examining current practice, collaborating across disciplines, and creating pragmatic treatment protocols. Coupling established QI methods to technological innovation in data collection promises to make this approach even more powerful. These methods should be utilized by neurologists and other health care professionals who treat status epilepticus.

Acknowledgment

The first author was supported by the National Institute of Neurological Disorders and Stroke (NINDS) T32 Award in Neurologic Clinical Epidemiology (T32-NS-

061779, 2016). Additional support for this work was provided by the Mirowski Family Fund and the Family of Jonathan Rothberg.

Author Contributions

C.H., A.P., C.E., J.M., and B.L. contributed to study concept and design. C.H. and A.P. contributed to data acquisition and analysis. C.H., A.P., C.E., J.M., and B.L. contributed to drafting the manuscript and/or tables.

Potential Conflicts of Interest

Nothing to report.

References

1. Foreman B, Hirsch LJ. Epilepsy emergencies: diagnosis and management. Neurol Clin 2012;30:11–41, vii.
2. Prasad K, Al-Roomi K, Krishnan PR, Sequeira R. Anticonvulsant therapy for status epilepticus. Cochrane Database Syst Rev 2014;(4):CD003723.
3. Trinka E, Cock H, Hesdorffer D, et al. A definition and classification of status epilepticus—report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia 2015;56:1515–1523.
4. Betjemann JP, Lowenstein DH. Status epilepticus in adults. Lancet Neurol 2015;14:615–624.
5. Lowenstein DH, Alldredge BK. Status epilepticus at an urban public hospital in the 1980s. Neurology 1993;43(3 pt 1):483–488.
6. Claassen J, Lokin JK, Fitzsimmons BF, et al. Predictors of functional disability and mortality after status epilepticus. Neurology 2002;58:139–142.
7. Sutter R, Kaplan PW, Rüegg S. Outcome predictors for status epilepticus—what really counts. Nat Rev Neurol 2013;9:525–534.
8. Towne AR, Pellock JM, Ko D, DeLorenzo RJ. Determinants of mortality in status epilepticus. Epilepsia 1994;35:27–34.
9. Lowenstein DH, Bleck T, Macdonald RL. It's time to revise the definition of status epilepticus. Epilepsia 1999;40:120–122.
10. Madžar D, Geyer A, Knappe RU, et al. Association of seizure duration and outcome in refractory status epilepticus. J Neurol 2016;263:485–491.
11. Santamarina E, Gonzalez M, Toledo M, et al. Prognosis of status epilepticus (SE): Relationship between SE duration and subsequent development of epilepsy. Epilepsy Behav 2015;49:138–140.
12. Shorvon S, Baulac M, Cross H, et al. The drug treatment of status epilepticus in Europe: consensus document from a workshop at the first London Colloquium on Status Epilepticus. Epilepsia 2008;49:1277–1285.
13. Unterberger I. Status epilepticus: do treatment guidelines make sense? J Clin Neurophysiol 2016;33:10–13.
14. Betjemann JP, Josephson SA, Lowenstein DH, Burke JF. Trends in status epilepticus-related hospitalizations and mortality: redefined in US practice over time. JAMA Neurol 2015;72:650–655.
15. Glauser T, Shinnar S, Gloss D, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the Guideline Committee of the American Epilepsy Society. Epilepsy Curr 2016;16:48–61.
16. Shorvon S. Guidelines for status epilepticus: are we there yet? Neurocrit Care 2012;17:1–2.
17. Falco-Walter JJ, Bleck T. Treatment of established status epilepticus. J Clin Med 2016;5:49.
18. Bleck T, Cock H, Chamberlain J, et al. The established status epilepticus trial 2013. Epilepsia 2013;54(suppl 6):89–92.
19. Hempel S, Rubenstein L V, Shanman RM, et al. Identifying quality improvement intervention publications—a comparison of electronic search strategies. Implement Sci 2011;6:85.
20. Ogrinc G, Davies L, Goodman D, et al. SQUIRE 2.0 (Standards for QUality Improvement Reporting Excellence): revised publication guidelines from a detailed consensus process. BMJ Qual Saf 2016;25:986–992.
21. Hillman J, Lehtimäki K, Peltola J, Liimatainen S. Clinical significance of treatment delay in status epilepticus. Int J Emerg Med 2013;6:6.
22. Seinfeld S, Shinnar S, Sun S, et al. Emergency management of febrile status epilepticus: results of the FEBSTAT study. Epilepsia 2014;55:388–395.
23. Lewena S, Pennington V, Acworth J, et al. Emergency management of pediatric convulsive status epilepticus: a multicenter study of 542 patients. Pediatr Emerg Care 2009;25:83–87.
24. Tirupathi S, McMenamin JB, Webb DW. Analysis of factors influencing admission to intensive care following convulsive status epilepticus in children. Seizure 2009;18:630–633.
25. Tobias JD, Berkenbosch JW. Management of status epilepticus in infants and children prior to pediatric ICU admission: deviations from the current guidelines. South Med J 2008;101:268–272.
26. Langer JE, Fountain NB, DeLorenzo RJ, et al. A retrospective observational study of current treatment for generalized convulsive status epilepticus. Epilepsy Behav 2014;37:95–99.
27. Sánchez Fernández I, Abend NS, Agadi S, et al. Time from convulsive status epilepticus onset to anticonvulsant administration in children. Neurology 2015;84:2304–2311.
28. Siefkes HM, Holsti M, Morita D, et al. Seizure treatment in children transported to tertiary care: recommendation adherence and outcomes. Pediatrics 2016;138:e20161527–e20161527.
29. Pellock JM, Marmarou A, DeLorenzo R. Time to treatment in prolonged seizure episodes. Epilepsy Behav 2004;5:192–196.
30. Rantsch K, Walter U, Wittstock M, et al. Treatment and course of different subtypes of status epilepticus. Epilepsy Res 2013;107:156–162.
31. Eriksson K, Metsäranta P, Huhtala H, et al. Treatment delay and the risk of prolonged status epilepticus. Neurology 2005;65:1316–1318.
32. Cheng JY. Latency to treatment of status epilepticus is associated with mortality and functional status. J Neurol Sci 2016;370:290–295.
33. Kämppi L, Mustonen H, Soinila S. Analysis of the delay components in the treatment of status epilepticus. Neurocrit Care 2013;19:10–18.
34. Kämppi L, Ritvanen J, Mustonen H, Soinila S. Delays and factors related to cessation of generalized convulsive status epilepticus. Epilepsy Res Treat 2015;2015:1–10.
35. Ferlisi M, Hocker S, Grade M, et al. Preliminary results of the global audit of treatment of refractory status epilepticus. Epilepsy Behav 2015;49:318–324.
36. Rossetti AO, Alvarez V, Januel JM, Burnand B. Treatment deviating from guidelines does not influence status epilepticus prognosis. J Neurol 2013;260:421–428.
37. 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.
38. Tourigny-Ruel G, Diksic D, Mok E, McGillivray D. Quality assurance evaluation of a simple linear protocol for the treatment of impending status epilepticus in a pediatric emergency department 2 years postimplementation. CJEM 2014;16:304–313.

39. Xie Y, Morgan R, Schiff L, et al. A computerized standard protocol order entry for pediatric inpatient acute seizure emergencies reduces time to treatment. J Child Neurol 2014;29:162–166.

40. Harris ML, Malloy KM, Lawson SN, et al. Standardized treatment of neonatal status epilepticus improves outcome. J Child Neurol 2016;31:1546–1554.

41. Navarro V, Dagron C, Elie C, et al. Prehospital treatment with levetiracetam plus clonazepam or placebo plus clonazepam in status epilepticus (SAMUKeppra): a randomised, double-blind, phase 3 trial. Lancet Neurol. 2016;15:47–55.

42. Schomer AC, Kapur J. The SAMUKeppra study in prehospital status epilepticus: lessons for future study. Ann Transl Med 2016;4: 468–468.

43. Alldredge BK, Gelb AM, Isaacs SM, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. N Engl J Med 2001;345:631–637.

44. Hafeez B, Paolicchi J, Pon S, et al. Feasibility of automatic extraction of electronic health data to evaluate a status epilepticus clinical protocol. J Child Neurol 2016;31:709—716.