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REVIEW

Improving Quality of Care for Status Epilepticus: Putting Protocols into Practice

Susanna S. O'Kula[1] · **Chloé E. Hill**[2]

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Abstract

Purpose of Review Timely treatment of status epilepticus (SE) improves outcomes, however gaps between recommended and implemented care are common. This review analyzes obstacles and explores interventions to optimize effective, evidence-based treatment of SE.

Recent Findings Seizure action plans, rescue medications, and noninvasive wearables with seizure detection capabilities can facilitate early intervention for prolonged seizures in the home and school. In the field, standardized EMS protocols, EMS education, and screening tools can address variability in SE definitions and treatment, particularly benzodiazepine dosing. In the emergency room and hospital, provider education, SE order sets and alerts, and rapid EEG technologies, can shorten time to first-line therapy, second-line therapy, and EEG initiation.

Summary Widespread, sustained improvement in SE care remains challenging. A multipronged approach including emphasis on pre-hospital intervention, treatment protocols adapted to local contexts, and SE databases to systematically collect process and outcome metrics have the potential to transform SE treatment and outcomes.

Keywords Status epilepticus · Quality improvement · Clinical practice guidelines · Seizure rescue medication · Digital health technology

Introduction

Status epilepticus treatment is often delayed. Status is an impactful neurological entity, with an incidence of 10–41 per 100,000 population and an estimated mortality near 20%, with no clear improvement in survival over the past few decades [1, 2]. Age, seizure type, and etiology are key determinants of prognosis [3, 4]; however, there is robust evidence that timely, appropriate treatment is associated with improved prognosis [5–8].

Challenges specific to status epilepticus impair urgent treatment. Diagnosis can be difficult due to great heterogeneity of clinical presentation [9], clinically subtle presentations such as nonconvulsive status epilepticus [10], and seizures that appear to resolve but then recur [11]. Not only do logistical complications of drug obtainment and administration lead to substantial treatment delay [12], but these medications are also commonly underdosed [13]. Lastly, a patient's sojourn frequently begins at home but may continue to an ambulance, to the emergency room, and to the ICU, and there is significant variability in treatment between locations and among providers.

Guidance in the treatment of status epilepticus is critical to overcoming obstacles and to coordinating care across environments, so protocols play an essential role. Evidence-based status epilepticus treatment protocols set out therapeutic options and target treatment times, but there are substantial gaps between recommended care and implemented care [14]. This review will focus on interventions to improve rapid, accurate execution of evidence-based treatment for adult and pediatric status epilepticus patients in the United States. Critical to these interventions is a hyper-attentiveness to local context and pragmatism.

✉ Susanna S. O'Kula
susanna.okula@downstate.edu

✉ Chloé E. Hill
chloehi@med.umich.edu

[1] Department of Neurology, SUNY Downstate Health Sciences University, 445 Lenox Road, A7-387, MSC 1275, Brooklyn, NY 11203, USA

[2] Department of Neurology, University of Michigan, 1500 E. Medical Center Drive, Ann Arbor, MI 48109, USA

Pre-Hospital Care

Preventative

Initiatives to prevent status epilepticus in adults and children have taken various approaches, whether focusing on access to seizure rescue medication, increasing availability of seizure action plans, operationalizing data from wearables, or risk stratifying those most likely to progress to status epilepticus.

As some data suggest fewer than half of pediatric patients receive antiseizure medications (ASMs) in the pre-hospital setting [15], Gainza-Lein et al. conducted a cross-sectional observational study that enrolled 100 families of pediatric patients with epilepsy and administered questionnaires about seizure rescue medications. Eighty-seven percent of patients were prescribed rescue medication, but only 61% of families received training in how to deliver it. Predictors of rescue medication prescription were average seizure duration greater than 30 s ($p = 0.04$) and a history of status epilepticus ($p = 0.02$). Comparing the prescriptions to recommended dosing ranges, a low dose was prescribed in more than half (51.2%) as opposed to 40.7% in the recommended range. A seizure action plan was associated with better family awareness of medication name ($p = 0.04$) and timing ($p = 0.004$), improved educator awareness ($p < 0.001$), and improved access to the medication at the child's school ($p = 0.02$) [16]. Lessons from this pediatric focus on rescue medications and action plans could be applied as improvement initiatives in the adult outpatient clinic.

Wearable digital health technology (DHT) is a promising tool, particularly as artificial intelligence models rapidly evolve and train on larger datasets to improve both seizure detection and forecasting. Current commercial devices may have some or all of the following peripheral sensors: movement, electrodermal/skin conductance, heart rate, muscle contraction, breathing/oxygen saturation, audio and EEG, which can signal possible seizures wirelessly to a paired device [17]. In an initial study by Tang et al., a machine learning model used data from non-invasive multimodal biosensor wrist or ankle wearables during 548 seizures of 94 pediatric patients, using video EEG reviewed by an epileptologist as ground truth. While the model learned on nine seizure subtypes, the model performed best and better than chance when combining all seizure types and using accelerometer and blood volume pulse data (AUC-ROC = 0.752) [18]. In a subsequent study in which the dataset was expanded to analyze 900 seizures from 166 pediatric patients for 28 seizure types, combining accelerometer and blood volume pulse data resulted in the best detection performance (83.9% sensitivity, 35% false positive rate). This model had better than chance seizure detection for 19 of the 28 seizure types (AUC-ROC > 0.8) [19]. Turning to seizure forecasting, Meisel et al. applied machine learning to data from a multimodal biosensor worn by 69 pediatric patients with focal or generalized seizures, capturing 452 seizures; again, video EEG data was used as ground truth. The model was significantly better than chance at seizure prediction in 43% of patients. For those patients, mean prediction horizon was about 32 min, suggesting this technology could ultimately provide sufficient warning for activity modification or other precautions [20].

A recent review by Donner et al. of wearable DHT for seizure detection for seizure detection summarized the presently approved indications and future applications for these devices [17]. Wearable DHT are currently of highest yield for adults and children with convulsive seizures with one meta-analysis of 23 studies reporting a 91% mean sensitivity (99% CI 85–96) for tonic–clonic seizure detection [21], but the benefit depends on having family or partners in physical proximity to respond quickly [17]. Detection of nonconvulsive seizures and interventions for those with convulsive seizures who live alone or sleep unattended remain areas for improvement [17]. The International League Against Epilepsy (ILAE) echoed these findings in their 2021 clinical practice guideline conditionally recommending wearing clinically-validated DHT in patients with generalized or focal to bilateral tonic–clonic seizures, only if intervention could occur within 5 min of an alarm [22].

In children, attempts have been made to identify factors that are protective against refractory status epilepticus. Pearisio et al. with the pediatric Status Epilepticus Research Group (pSERG) conducted an observational case–control study of 595 episodes of convulsive status epilepticus at a children's hospital, comparing clinical variables between patients whose status epilepticus responded to a first-line benzodiazepine and second-line medication and those who required more medication. While time to treatment was not associated with progression to refractory status epilepticus, both a prescription for rectal diazepam ($p < 0.0012$) and a family history of seizures ($p = 0.0022$) were protective [23], suggesting an area for intervention could include greater emphasis on rescue medication prescription and availability.

In the Field

Undertreatment of status epilepticus in the field is well-described, particularly with first-line benzodiazepine treatment [24–26]. A study by Guterman et al. of over 9000 pre-hospital encounters with a paramedic impression of status epilepticus in adult patients across the United States found that only 3.9% (95% CI, 3.5–4.3%) of patients received both the expert-recommended dose and route of initial

benzodiazepine [24]. Subsequent work by Guterman et al. has suggested route of benzodiazepine administration may also impact efficacy [26].

Challenges arise due to nationwide variability in EMS infrastructure. Betjemann et al. examined protocols for prehospital treatment of adults with generalized convulsive status epilepticus across 33 EMS protocols in California, finding 21.7% correctly defined generalized convulsive status epilepticus according to American Epilepsy Society (AES) or ILAE guidelines and only 18.2% recommended the correct dose and route for more than one of the first-line medications (midazolam, lorazepam, diazepam). As an initial improvement, the authors suggest standardizing the definition of generalized convulsive status epilepticus and distinguishing it from a seizure in EMS protocols statewide [27]. In a cross-sectional analysis of adult and pediatric status epilepticus protocols across 33 states, Han et al. similarly found that only 48% of adult protocols specify criteria for status epilepticus. In this analysis, adult and pediatric protocols all listed midazolam, lorazepam, diazepam as first-line agents but with differing initial dose, maximum dose, and routes. Only a third of these adult protocols recommended the correct maximum midazolam dose, whereas weight-based pediatric dosing of intramuscular midazolam was aligned with expert recommendation in 64% and intranasal midazolam in 79% of state protocols. This analysis excluded states with county or geographical variance in EMS protocols. The authors also point to the absence of nationwide standardized EMS protocols for adult and pediatric status epilepticus as a starting place to improve prehospital treatment [28].

A review of pediatric status epilepticus EMS protocols by Amengal-Gual et al. used either the statewide EMS protocol or the protocol for the most populous or capital city for that state. With the exception of one state, the authors found most EMS providers could not administer second-line ASMs in the field per protocol, only benzodiazepines, even if the patient was not benzo-responsive. Some protocols suggested a consultation call with a physician, but the authors emphasize there is no national or state infrastructure to support this, in contrast to stroke telehealth [29]. Optimization strategies included changing regulations for EMS to administer prehospital status epilepticus treatment and relying on robust outpatient seizure action plans in the interim.

Techniques to improve diagnosis in the field include a clinical tool to predict status epilepticus. In a retrospective study of 292 Spanish adults (16 years and older) presenting to the ED with an epileptic seizure, Requena et al. used the clinical history of the 49 patients who proved to be in status epilepticus to identify independent variables associated with status epilepticus: abnormal speech ($p < 0.001$), ocular deviation ($p = 0.001$), oral or manual automatism ($p = 0.050$), two prehospital seizures ($p < 0.001$), and more than two prehospital seizures ($p < 0.001$). These variables were all assigned a point value of 1, except > 2 prehospital seizures, which was assigned 2 points on the ADAN scale (Abnormal speech, eye Deviation, Automatism, Number of seizures). This scale was then tested on a validation set of 197 patients, with a predictive capability of 98.7% (95% CI 97.3–100). An ADAN score of > 1 was 95.3% sensitive, 95.5% specific in predicting status epilepticus in this cohort [30]. While promising, such a tool requires prospective validation for wider uptake as well as practical implementation strategies.

Emergency Room and Inpatient Care

As pervasive delays in medication administration are well documented [14], several quality improvement interventions have been implemented to improve time to drug administration from clinical recognition of seizure. In a study by Ostendorf et al., the authors aimed to improve timely benzodiazepine treatment within 10 min of status epilepticus onset for hospitalized children in non-intensive care units from baseline of 39% to 60% (50% improvement) within 1.5 years and to maintain this improvement for six months. A bundle of interventions was implemented including encouraging use of intranasal midazolam, revising the protocol for nurse response to seizures, creating tools for documentation, relocating supplies/medicines, and education. The primary aim was achieved- 79% of patients received a benzodiazepine within 10 min (compared to 12-month baseline of 39%). A control chart demonstrated an initial shift that occurred in the planning stage prior to intervention, however reliability improved with subsequent PDSA (plan-do-study-act) cycles. Applying traditional analysis, the median time to treatment decreased from 14 to 7.5 min ($p = 0.01$) [31]. To reduce time to second-line therapy for pediatric patients with generalized convulsive status epilepticus from 30 to 15 min (50% reduction) and sustain for a year, Vidaurre et al. implemented training programs on status epilepticus (diagnosis, drugs, and timing) and ran simulations for Emergency Medicine physicians and nurses, improved documentation, distributed badge buddies with the protocol, and improved access to fosphenytoin in the Pyxis. A control chart demonstrated a centerline shift due to a combination of interventions. By traditional analysis, the delay to administering fosphenytoin after benzodiazepines decreased from an average 30 min to 11.4 min ($p = 0.043$) [32].

Another approach to improving timely intervention focuses on treatment of seizures detected on EEG monitoring. In an initiative by Williams et al., an ICU EEG monitoring pathway was developed with a range of components including education, accessible pathway document, more efficient initiation of EEG monitoring, levetiracetam in

the ICU Pyxis, improved bedside documentation, greater involvement of EEG techs in screening/communicating, and streamlined communication. A control chart was not utilized- traditional pre-post statistical analysis was performed. Among the target population of critically ill children within electrographic-only seizures, there was a decrease in median duration from seizure to medication administration in the intervention group compared to the baseline group (64 min vs. 139 min, $p = 0.0006$) [33]. In a another study, Gupta et al. aimed to improve efficiency of treatment of nonconvulsive status epilepticus. Interventions included housestaff education (EEG review, simulations, lectures, pocket cards), addition of lacosamide and levetiracetam to Neurology and Neurological ICU Omnicells, creation of a status epilepticus order set, and nursing education. Control charts typical of quality improvement methodology were not presented; the results showed nonsignificant reductions in delay from seizure to order and order to administration for first-line and second-line therapies as assessed by pre-post comparisons of median latencies [34].

Status epilepticus order sets have great potential to improve timeliness and dosing accuracy in drug administration as well as to facilitate subsequent process review. In the Gupta et al. study, there was an ASM arm within the order set and an anesthetic arm within the order set, both with dosing based on status epilepticus guidelines. The authors explain that the order set within the electronic medical record also allowed data abstraction and visualization of deficiencies [34].

Status epilepticus alerts and codes have also been employed to improve time to second-line therapy [35]. Villamar et al. implemented a status epilepticus alert system for hospitalized or emergency room patients with convulsive or electrographic status epilepticus. This alert, modeled after a stroke protocol, texted the neurology house staff, pharmacists, the rapid response team, and the primary team. Each person alerted had prespecified responsibilities with regard to clinical evaluation, entering orders, communications, ASM order verification/mixing/delivery, airway management, IV placement, and bed assignment. Implementation of the alert system decreased mean time to administration of second-line therapy as compared to the control group (22.2 min vs. 58.3 min, $p < 0.0001$) [36]. There is additional evidence that presence of a pharmacist is beneficial to timely care. Gawedzki et al. found nonsignificant decreases in median times to first-line and second-line medication administrations with a pharmacist present for treatment of status epilepticus patients in the emergency room as compared the control group. When a pharmacist was present, however, a higher median dose of lorazepam equivalents (2.5 vs. 2 mg, $p = 0.04$) was administered to patients [37].

Delay in diagnosis of status epilepticus may lead to untimely treatment, and thus improved time to EEG is an important goal. The prospective observational trial of Rapid EEG (DECIDE trial) demonstrates that use of rapid EEG can improve median time to EEG in the ICU setting (rapid EEG 5 min vs. traditional EEG 239 min, $p < 0.01$) and may improve sensitivity, specificity, and confidence of bedside physician's diagnosis [38]. Few quality improvement reports with employment of rapid EEG have been published to date; one quality improvement initiative incorporated rapid EEG to diagnose nonconvulsive seizures in a community hospital with limited EEG resources [39].

Timely diagnosis may also be assisted by more rapid identification of status epilepticus during EEG monitoring and more efficient communication. In one study by Baldassano et al., a platform was developed to analyze multimodal data (ICU monitoring and EEG) and algorithms were applied to detect a range of events (e.g. elevated intracranial pressure or faulty electrodes). This data was then communicated to hospital staff through a secure application [40]. This approach- a monitoring platform integrated into provider workflow- could be modified in the future and applied to the diagnosis of status epilepticus.

Protocol Considerations

To achieve optimal treatment, it is critical to develop a protocol that adheres to best practice for guidelines. Best practices for clinical guidelines have been discussed in many contexts including a 1998 Institute of Medicine report that named the desirable protocol attributes to be validity, reliability and reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, scheduled review, and documentation [41]. There are several status epilepticus treatment protocols available from professional societies, including the Neurocritical Care Society (NCS) protocol [42] and the AES protocol [43]. However, treatment cannot be appropriately administered if the local environment is not considered. The "best" drug choice may not be the "best" drug within a hospital system that is experiencing a shortage of that medication or when administered by providers who lack experience or comfort with that specific medication. Local and contextual considerations are particularly important for the portions of treatment for which there is clinical equipoise; for example, second-line therapies levetiracetam, fosphenytoin, and valproic acid performed similarly in the ESETT trial [44]. When there is clinical equipoise and/or insufficient evidence base for choosing one drug over the other, then practical considerations should prevail.

Future Directions

While diagnosis and management of status epilepticus is complex, our deep dive into a range of quality improvement initiatives reveals several effective strategies that can

be applied going forward to better processes and advance outcomes (see Fig. 1).

An Ounce of Prevention is Worth a Pound of Cure Prevention has received more attention in pediatric practice and literature and could well be more universally applied to care of adults. This would include more standardized development of seizure action plans, routine prescription of seizure rescue medications, education of family/caregivers, and employment of wearables/detection devices.

Protocols are Effective When Relevant to Local Practice and Resources As highlighted in a recent review of 15 status epilepticus clinical practice guidelines by Vignatelli et al., critical elements of guideline quality such as applicability, stakeholder involvement, and rigor of development were poor [45]. Low quality clinical guidelines have real life repercussions. Unavailable drug formulations, insufficient diagnostic capabilities, and unrealistic target treatment times can render a protocol inapplicable. It is critical that protocols be *both* evidence-based *and* tailored to specific institutional constraints.

Education is Necessary but Not Sufficient Quality improvement interventions typically include some element of education. Education is critical to building teamwork and understanding but in isolation education is a fairly weak intervention. Knowing a problem exists is rarely enough to solve it, as was demonstrated in a study that showed publication of evidence of treatment delay did not improve time to treatment of status epilepticus [46].

A Key Tenet of Quality Improvement is Summarized by William Thompson's Famous Words "If You Cannot Measure It, You Cannot Improve It" [47] In 1990, the National Association of Epilepsy Centers (NAEC) created criteria for adult and pediatric specialized epilepsy centers [48], with revisions every decade [49], largely focused on guidelines for essential services, staff, and technology at presurgical and surgical epilepsy centers. Recently updated this year, the requirement for status epilepticus care consists of a written protocol, demonstration a center has emergency medications and equipment, and "qualified providers or a rapid response team" in house 24/7 [50]. While consensus-based protocol recommendations are an important first step, no system or regulatory body currently exists to validate the fidelity and efficacy of status epilepticus care nationwide. In order to improve, centers need to know the reliability and fidelity of protocol execution each time a patient presents in status epilepticus, the clinical outcomes (e.g. time to seizure termination), and how a center's performance compares to similarly-resourced peer institutions; this data is necessary to bring protocols to life.

An ideal future state for data-driven status epilepticus care could borrow from the progress made in the stroke world. In the United States, the American Heart Association (AHA) developed clinical guidelines for a variety of cardiovascular diseases and hosts standardized national Get with the Guidelines databases that track quality measures, enable streamlined certification through The Joint Commission, and offer awards and educational modules for hospitals to improve their care, reimbursements, and staff morale [51]. Each American stroke center uploads de-identified clinical

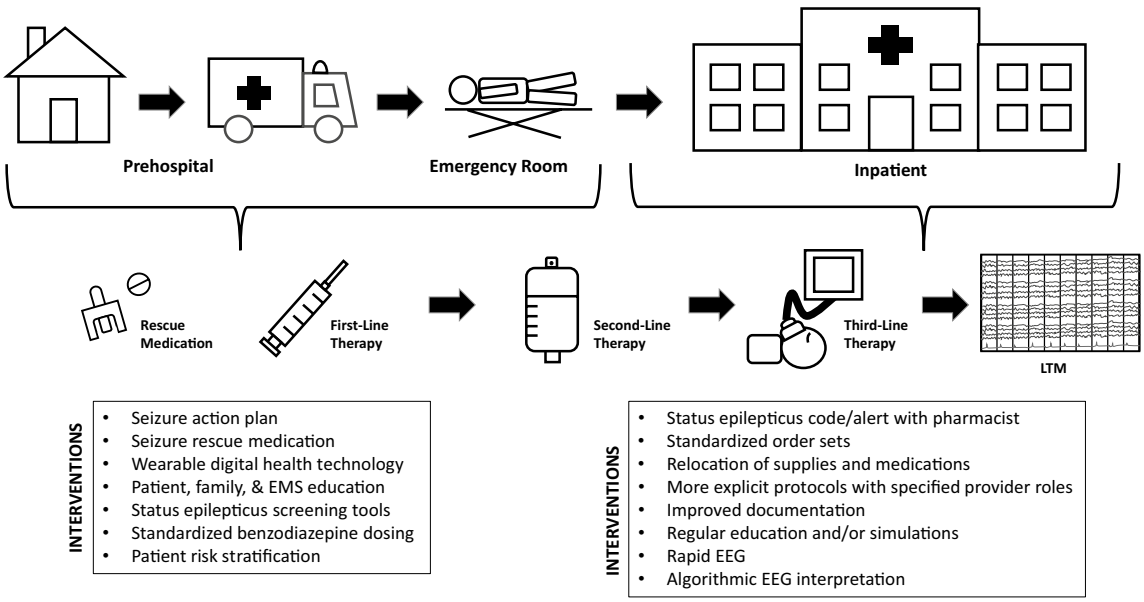

Fig. 1 Status epilepticus pathway – actionable items

data about patients admitted with acute stroke-related diagnoses as well as process measures and thrombolytic therapy outcomes [52]. This database not only facilitates accreditation and recertification of centers offering varying levels of stroke care but also serves as a hub for clinical research within and across sites [53]. Though labor intensive, a similar model might ultimately be achieved if epilepsy centers submitted data on annual admissions for status epilepticus, ASM choices, "door-to-needle" times, and clinical outcomes. The Epilepsy Learning Healthcare System offers both a model and possibly an infrastructure for national data collection, discussion between centers, and rapid dissemination of best practices for status epilepticus treatment in the near future [54].

Conclusions

While the challenges of improving treatment for status epilepticus are myriad, there are practical and promising interventions. Increased prescription of rescue medications, seizure action plan development, noninvasive wearable use, patient risk stratification, standardized drug dosing, and implementation of screening tools in the field can improve pre-hospital care. In the emergency room or hospital setting, provider education/simulations, thoughtful supply relocation, improved documentation, clearer protocols with specified provider roles, status epilepticus order sets, overhead alerts/codes, rapid EEG, and algorithmic EEG interpretation all encourage better real-time performance. Protocols that consider local practice and institutional resources are critical for operationalizing interventions and achieving sustained improvement. As has been observed for stroke-related emergencies, status epilepticus care could benefit from systematic recording and reporting of process and outcome metrics as well as from standardized national data repositories, analysis tools, and shared learning models.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Conflict of Interest C.E. Hill is supported by 1K23NS126495.

Human and Animal Rights and Informed Consent Data collection was carried out with approval by the institutional review board of the University of Pennsylvania ("An Automated Platform for ICU EEG Monitoring and Visualizing Results"). A waiver of informed consent was obtained as these data were already collected as part of standard care with minimal patient risk, rigorous data security protocols, and minimum necessary extraction of patient health information.

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