ORIGINAL RESEARCH

Towards Successes in the Management of Nonconvulsive Status Epilepticus: Tracing the Detection-to-Needle Trajectories

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Purpose: Data on the timeliness of emergent medication delivery for nonconvulsive status epilepticus (NCSE) are currently lacking.

Methods: Retrospective chart reviews (between 2015 and 2018) and analyses of all patients with NCSE were performed at the University of Nebraska Medical Center, a level 4 epilepsy center, to determine the latencies to order and administration of the first, second, and third antiepileptic drugs (AEDs). Recurrent NCSE cases were considered independently and classified as comatose and noncomatose.

Results: There were 77 occurrences of NCSE in 53 patients. The first, second, and third AEDs were delivered with substantial delays at median times of 80 (25%–75% interquartile range, 44–166), 126 (interquartile range, 67–239), and 158 minutes (interquartile range, 89–295), respectively, from seizure detection. The median times to the order of the first and second AEDs were 33 and 134.5 minutes longer in comatose NCSE patients compared with those with noncomatose forms, respectively ($P = 0.001$ and 0.004, respectively). The median times between the AED orders and their administration in these two groups were the same ($P = 0.60$ and 0.37, respectively). With bivariate analysis, the median latencies to administration of the first, second, and third AEDs were significantly increased by 33, 109.5, and 173 minutes, respectively, in patients who died within 30 days compared with those who survived ($P = 0.047$, $P = 0.02$, $P = 0.0007$, respectively).

Conclusions: The administration of the first, second, and third AEDs for NCSE was delayed. Slow initiation of acute treatment in comatose patients was caused by delays in the placement of the medication order.

Key Words: Nonconvulsive status epilepticus, Nonconvulsive seizures, Treatment delay, Mortality.

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The duration of seizure activity is a major factor contributing to marked functional impairment and high mortality in patients hospitalized for seizures.[1] Therefore, status epilepticus (SE), defined as a convulsive seizure persisting longer than 5 minutes or a cluster of recurrent seizures without return to baseline neurologic function, is regarded as a neurologic emergency.[2] Prompt termination of SE is imperative to prevent neuronal injury,[1,3] and the standardized approach to treatment of SE has been recently formalized to complement these efforts.[3] Although the development of treatment guidelines has been largely centered around the convulsive SE, less emphasis is being placed on the standardization of management of nonconvulsive status epilepticus (NCSE).[4]

Nonconvulsive status epilepticus, which constitutes 20% to 25% of all SE occurrences,[5] is characterized by EEG ictal activity persisting longer than 30 minutes with subtle or absent clinical correlates.[6,7] As clinical and electrographic criteria for NCSE continue to evolve,[8] the data on treatment approaches and patients' outcomes in NCSE remain sparse compared with the convulsive forms.[5,9] Nearly 40% of patients with NCSE present with alteration of cognitive function rather than overt signs of seizures[5]; thus, recognition of NCSE may be delayed when it is not supported by EEG.[8] The ensuing delays in the treatment of nonconvulsive seizures could be perpetuated by deficiencies in the hospital response system[10] or insufficient awareness of the hospital staff.[11]

Previous observational studies have concluded that longer duration of NCSE and delay to seizure diagnosis in critically ill children and adults lead to deleterious health outcomes and increased mortality.[12–16] Barriers to timely treatment were previously examined for in-hospital seizure emergencies,[10,17,18] and delays in the treatment of NCSE in pediatric patients were addressed with the implementation of the standardized seizure management pathway.[17,19] However, the timeliness of treatment for adult patients with NCSE has not been previously assessed. Such information is important because it will allow further analysis and potential mitigation of the risks of prolonged nonconvulsive seizures in critically ill patients.

In the present study, we examined the efficiency of the pharmacological management of NCSE in patients without cerebral anoxia by examining the time to administration of the first, second, and third anticonvulsants and assessing the relevant patient outcomes. To our knowledge, this is the first study that systematically examined latencies to the administration of antiepileptic drugs (AEDs) for NCSE and dissected the inefficiencies inherent to both the initiation and the completion of the emergent medication orders. The overarching goal of this project

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was to establish causes of delay in the delivery of treatment for acute nonconvulsive seizures at our epilepsy center. Based on the previous reports of the higher mortality and worse neurobiological outcomes among survivals of electrographic seizures and status epilepticus,[7,12,13,15,20–22] we hypothesized that patients with shorter seizure duration have better outcomes.

METHODS

Data Selection

Retrospective chart review and analysis were conducted with the approval of the Institutional Review Board at the University of Nebraska Medical Center, a level 4 comprehensive epilepsy center. Adult patients who were hospitalized at UNMC and completed monitoring with continuous video EEG between January 1, 2015 and December 31, 2018 were identified using the EEG laboratory records; patients with NCSE were selected (Fig. 1). The patients who had convulsive seizures before NCSE were included in the analysis, but the convulsive seizures were not counted as onset of NCSE.

Definitions

Nonconvulsive status epilepticus was defined as an electrical epileptic activity that lasted longer than 30 minutes without prominent motor symptoms or a series of nonconvulsive seizures totaling 30 minutes in duration in 1 hour without complete clinical recovery between the episodes.[7] Interpretation of the EEG recordings was performed by one of six board-certified epileptologists. An additional review was performed by one of the study investigators to confirm the seizures. Based on the accompanied clinical description of the corresponding video segments and retrospective review of the neurologist notes, each NCSE occurrence was categorized as either with coma or without coma.[23–25] Standardized tests to assess background reactivity to the auditory, tactile, and noxious stimuli were performed daily. Given that the time of onset was not documented accurately for convulsive seizures, all occurrences of convulsive SE were excluded. We did not intend to differentiate between the occurrences of the new-onset NCSE and that evolving from convulsive seizures.

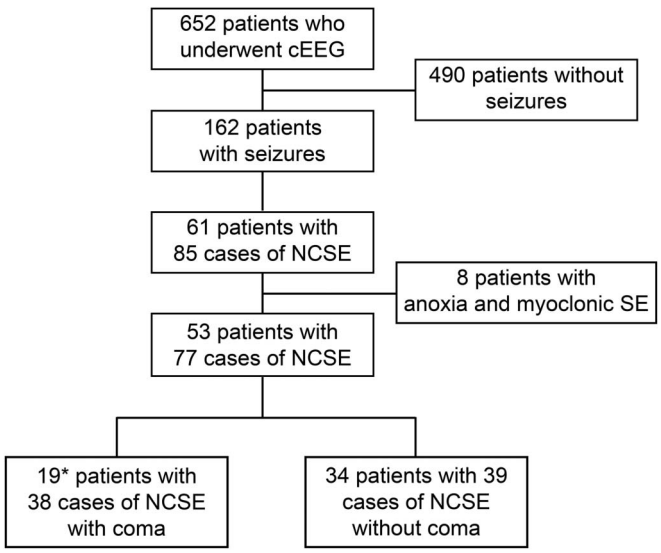

FIG. 1. Flowchart of patient selection. cEEG, continuous electroencephalography; NCSE, nonconvulsive status epilepticus; SE, status epilepticus. *Four patients developed NCSE without coma followed by NCSE with coma.

Time to Anticonvulsant Administration

The time of seizure onset was extracted from the procedure reports, whereas the times of medication orders and administration of the AEDs were obtained from clinical notes and medication administration records. In patients who had an as needed order of any benzodiazepine placed before the onset of NCSE where the same benzodiazepine was administered for the corresponding seizure episode, the time of a physician's verbal order and the time of administration of the same drug were considered to be the same. Similarly, in patients who received AEDs or an infusion of anesthetics before the onset of SE in whom the doses of these agents were increased on seizure detection, the time of the medication dose change and the time of its administration were considered to be the same.

Given that the monitoring of EEG activity was performed in real time by trained personnel and epileptologists between 7 AM and 11 PM and that all recordings were additionally assessed as needed by an epileptologist during the remaining night hours, the time of seizure onset and seizure detection were regarded as a single time point.

Statistical Analysis

The Kruskal–Wallis and Mann–Whitney tests were used to compare the median values among multiple or two groups of categorical variables, respectively, whereas Pearson χ^2 test was used to compare categorical variables. In patients with multiple SE occurrences, the latencies were considered independently for each episode of NCSE. Given the limited number of patients, all occurrences of NCSE were regarded as independent observations. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and GraphPad Prism 8.0 (GraphPad Software, Inc, San Diego, CA). The value of $P < 0.05$ denoted statistical significance.

RESULTS

The review of consecutive 703 continuous electroencephalography (cEEG) reports in 652 patients over the 4-year study period revealed 61 patients with 85 cases of NCSE. Eight occurrences of myoclonic NCSE in eight patients with anoxic brain injury were excluded, which yielded 77 cases of NCSE in 53 patients (Fig. 1).

Patient Characteristics

The median age of patients was 62 years (interquartile range [IQR], 43–69; Table 1). Thirty-one patients (58.5%) were female.

TABLE 1. Demographic and Clinical Characteristics of 53 Patients With NCSE

Patients' Characteristics	Total	Comatose	Noncomatose	*P*
Age, median years (IQR)	62 (43–69)	57 (30.5–63)	64.5 (44–77)	0.10
Female, *n* (%)	31 (58.5)	11 (20.8)	20 (37.7)	0.95
Admission diagnosis, *n* (%)				
Seizure	17 (32.1)	9 (17.0)	8 (15.1)	0.30
CVA/CNS hemorrhage	13 (24.5)	2 (3.8)	11 (20.8)	
Systemic infection	10 (18.9)	3 (5.7)	7 (13.2)	
Encephalitis/meningitis	7 (13.2)	3 (5.7)	4 (7.5)	
Other medical conditions	6 (11.3)	2 (3.8)	4 (7.5)	
History of seizure before admission, *n* (%)	15 (28.3)	5 (9.4)	10 (18.9)	0.81
Previous history of CNS disorders, *n* (%)				
Cerebral vascular accident	10 (18.9)	5 (9.4)	5 (9.4)	0.54
Static encephalopathy	4 (7.5)	1 (1.9)	3 (5.7)	
Malignancy	3 (5.7)	1 (1.9)	2 (3.8)	
Dementia	2 (3.8)	0 (0)	2 (3.8)	
CCI, median (IQR)	4 (2–6)	4 (2–6)	4 (2–6)	0.79
Location at the time of NCSE detection, *n* (%)				
NICU	21 (39.6)	8 (15.1)	13	0.85
MICU	8 (15.1)	2 (3.8)	6	
SICU	4 (7.5)	2 (3.8)	2	
Medical floor	20 (37.7)	7 (13.2)	13	
LOS, median days (IQR)	18 (7.5–30)	17 (15–26)	19 (6–37)	0.86
Discharge destination, *n* (%)				
Home	9 (17.0)	2 (3.8)	7 (13.2)	0.31
Inpatient rehabilitation	19 (39.6)	8 (15.1)	11 (20.8)	
30-day mortality after seizure onset, *n* (%)	22 (41.5)	9 (17.0)	13 (24.5)	0.52

CCI, Charlson Comorbidity Index; CNS, central nervous system; CVA, cerebral vascular accident; IQR, interquartile range; LOS, length of stay; MICU, medical intensive care unit; NCSE, nonconvulsive status epilepticus; NICU, neuroscience intensive care unit; SICU, surgical intensive care unit.

The admission diagnosis in 17 patients (32.1%) was seizures. Documented convulsive seizure events preceding NCSE during the same hospitalization were reported in 16 patients (30.2%; Table 1). Thirty-three patients (62.3%) were critically ill and were admitted to the neurosciences, medical, and surgical intensive care units before the development of NCSE (Table 1). Thirty-three of 53 patients (62.3%) were found to be in NCSE on the initiation of cEEG; these patients were included in the analysis.

Characterization of NCSE

Of 77 cases of NCSE in 53 patients, 38 (49.4%) and 39 (50.6%) were categorized as NCSE with and without coma, respectively. Thirteen of 53 patients (24.5%) had more than one episode of NCSE with a median latency of 7.6 hours between the episodes. The median seizure duration was 206 (IQR, 93–505) minutes in comatose NCSE and 196.5 (IQR 56.5–395) minutes in noncomatose NCSE. We did not find a difference between the groups ($P = 0.36$). Additionally, the distribution of the admission diagnosis categories and Charlson Comorbidity Index were similar in the two groups (admission diagnosis: $P = 0.35$; Charlson Comorbidity Index: $P = 0.19$).

Latencies to Pharmacological Treatment

The median times from seizure detection to the order of the first, second, and third AEDs for all cases of NCSE were 47 (IQR, 18–126), 68 (IQR, 39–195), and 89 (IQR, 42–251) minutes, respectively. The median times from seizure detection to the orders of the first and second AEDs were 69 (IQR, 35–215) and 183 (IQR, 61–260) minutes in the comatose group, respectively. However, the corresponding latencies were 36 (IQR, 12–63) and 48.5 (IQR, 29–137) minutes in the noncomatose group, respectively. Thus, the median latencies to order of the first and second AEDs were 33 and 134.5 minutes longer, respectively, in patients with comatose NCSE compared with those with noncomatose NCSE ($P = 0.001$, $P = 0.004$; Figs. 2A and 2B). The median times from seizure detection to the order of the third AED were 117 (IQR, 45–324.5) minutes for comatose patients and 71 (IQR, 34–331) minutes for noncomatose patients ($P = 0.19$).

The median times from the order of the first, second, and third AEDs to their administration for all NCSE occurrences were 23 (IQR, 6–50), 26 (IQR, 12–52), and 41 (IQR, 16–101) minutes, respectively. All three medications were administered with the same latencies in the groups with comatose and noncomatose forms of NCSE ($P = 0.60$, $p = 0.37$, $p = 0.37$; Figs. 2A and 2C). Interestingly, when the occurrence of SE treated with lorazepam injection or anesthetics administered via intravenous infusion were excluded from the analysis, the latency from the order to the administration of the first anticonvulsant has lengthened more than 2-fold to 45 (IQR, 27–86) minutes. The median time of the administration of benzodiazepines alone as the first AED was 9 (IQR, 6–16) minutes.

The median times from seizure detection to the administration of the first, second, and third AEDs including the scheduled

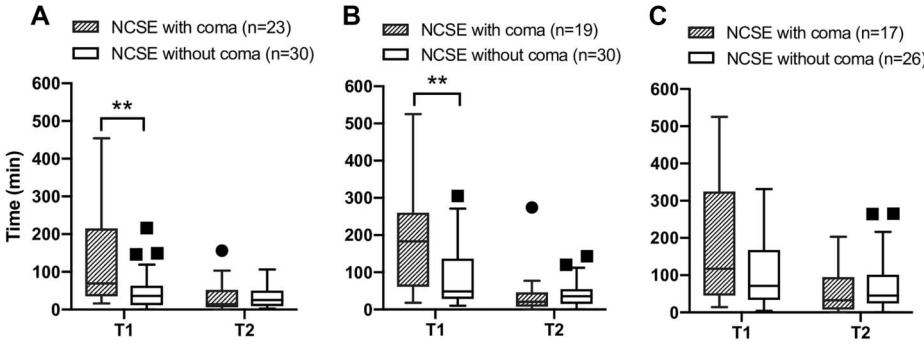

FIG. 2. Latencies to the administration of the first (**A**), second (**B**), and third (**C**) AEDs. AEDs, antiepileptic drugs; IQR, interquartile range; n, number of SE occurrences; NCSE, nonconvulsive status epilepticus; SE, status epilepticus; T1, time from seizure detection to the order of AED; T2, time from the order to the administration of AED. The horizontal bar and box represent median and IQR, respectively. The whisker shows the measures of Tukey boxplot. $^{**}P < 0.01$, Mann–Whitney tests.

anticonvulsants were 80 (IQR 44–166), 126 (IQR 67–239), and 158 (IQR 89–295) minutes, respectively. We found no difference in the corresponding times between the groups with two types of NCSE (Table 2). The analysis of the anticonvulsant selection administered for the treatment for NCSE is available in Supplemental Digital Content 1 (see Supplemental Results and Supplemental Fig. 1, http://links.lww.com/JCNP/A62).

Patient Outcomes

The median length of hospital stays in 30 patients with NCSE who survived to discharge was 18 days (IQR, 6–34). Among 30 patients who were discharged from the hospital, 10 patients (33.3%) had been treated for comatose NCSE and 20 patients (66.7%) for noncomatose NCSE. Eight patients with comatose NCSE were placed in the acute rehabilitation facility and only two patients were discharged home. However, in the group of patients with noncomatose NCSE, 11 and 7 patients had the same discharge destinations, respectively. The proportions of patients with these discharge destinations were distributed similarly in the groups with two types of NCSE ($P = 0.31$).

The overall mortality within 30 days of seizure detection in all patients with NCSE was 41.5%; the rates were comparable in NCSE with and without coma (47.4% and 38.2%; $P = 0.52$). The median survival time after seizure detection was 6 days (IQR, 4–15). The demographic and clinical characteristics were comparable between the patient groups who died or survived 30 days after seizure detection except for the Charlson Comorbidity Index,[26] which was higher in the deceased group at 6 (IQR, 4–7) compared with the survived group at 3 (IQR, 1–5) ($P = 0.03$). With bivariate analysis, the median latencies to the administration of the first, second, and third AEDs after seizure detection were 33, 109.5, and 173 minutes longer in patients who died within 30 days of seizure detection compared with those who survived ($P = 0.047$, $P = 0.02$, and $P = 0.0007$, respectively; Fig. 3).

DISCUSSION

In the present study, we assessed the patterns of medication administration for NCSE and examined the association of patient outcomes with the delay in treatment of seizures. Even though there are no specific treatment timeline guidelines for NCSE, the time to treatment of NCSE in our study was found to be longer than expected.

We determined that the time to the emergent AED order (47 minutes) was nearly as long as the duration of the AED order processing by the inpatient pharmacy (45 minutes). These findings suggest that delays in the treatment of NCSE at our center stem from both faulty execution of the seizure response protocol and inefficiency of the inpatient pharmacy. Similar patterns of inefficient response to SE were previously reported by other authors[9,18]; however, the specific components of the delay were not examined for NCSE. The multistep communication process adopted by our hospital, which includes notification of the neurology resident as an intermediary between the epilepsy and intensive care unit teams, contributes to delays in placing of orders for AEDs.

The delayed first-dose availability after the placement of the emergent AED order may arise from lack of the electronic order alerts, tardive order verification, and drug preparation as well as an outdated system for the medication delivery to the bedside. Nationwide, an adoption of the electronic order tracking has not always been supported by the effective interface of the centralized pharmacy and its unit branches.[27] This has been of particular

TABLE 2. The Latencies From Seizure Detection to the Administration of AEDs in Patients With NCSE

Latency	NCSE With Coma, Minutes (Median, IQR)	NCSE Without Coma, Minutes (Median, IQR)	*P*
T_{AED1} ($n = 77$)	113 (54–224)	68 (39–131)	0.07
T_{AED2} ($n = 60$)	159 (67–265)	124 (67–209)	0.57
T_{AED3} ($n = 48$)	197 (83–312)	154 (94–287)	0.64

AED, antiepileptic drug; IQR, interquartile range; n, number of SE occurrences; NCSE, nonconvulsive status epilepticus; SE, status epilepticus; $T_{AED1–3}$, latency from seizure detection to the administration of the first, second, and third anticonvulsants.

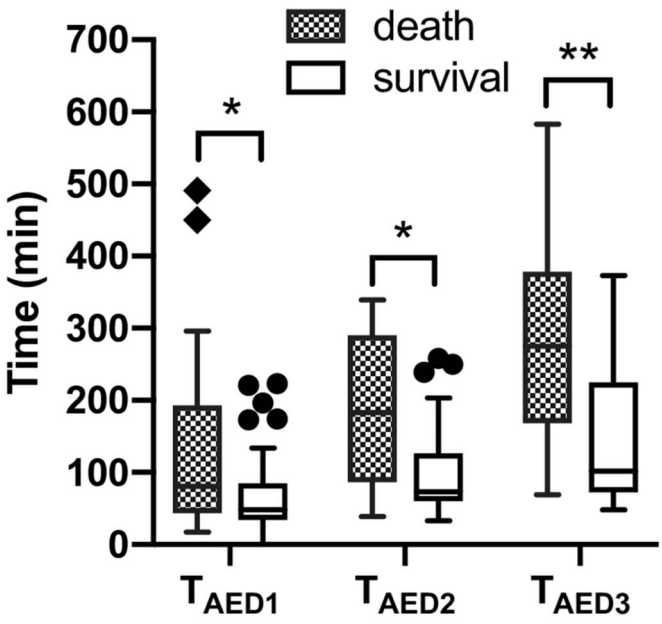

FIG. 3. The latencies from seizure detection to the administration of the first, second, and third AEDs[28] in patients with nonconvulsive status epilepticus according to the mortality. The horizontal bar and box represent median and IQR, respectively. The whisker shows the measure of Tukey boxplot. $*P < 0.05$, $**P < 0.01$; Mann–Whitney tests. AEDs, antiepileptic drugs; IQR, interquartile range.

concern for the intensive care unit settings where the medication doses are frequently changed and where the drugs need to be dispensed emergently.[28]

In this study, the delay in initiating the order for the first AED after seizure detection on EEG was significantly longer in patients with coma compared with those without coma. These findings suggest that a less aggressive approach was applied in controlling seizures in patients with coma compared with those without coma. Nonconvulsive status epilepticus in coma frequently occurs in the settings of other medical comorbidities independently leading to deterioration of the mental status.[29] In these patients, the concern for potential further deterioration of encephalopathy caused by the AEDs could have overweighed the benefits of prompt termination of nonconvulsive seizures. Furthermore, the delay in treatment of comatose NCSE could be caused by underutilization of cEEG monitoring in this patient's population and potential nocturnal interruptions in prompt interpretation of findings concerning for NCSE. Interestingly, although the times from the seizure detection to the order of the first and second AEDs were different between the groups of patients with comatose and noncomatose NCSE, the times from the order to administration (T2) and the overall latencies from the seizure detection to initiation of these treatments were similar in these two groups. This could be because of the greater variability in the latencies for the overall time compared with the times to order of the first and second AEDs.

This study demonstrated that patients who were deceased at 30 days from onset of NCSE had longer times from the seizure detection to administration of all AEDs compared with those who have survived. Since the former group also had a higher Charlson Comorbidity Index and the small sample size precluded the multivariate logistic regression analysis, it remains unclear whether the delay in treatment of NCSE had directly contributed to the increased mortality.

Our study has several limitations. Given that 63% of patients in our cohort had the ongoing NCSE at the start of cEEG, the duration of SE and the magnitude of treatment delay may have been underestimated. Considered that the data were analyzed retrospectively, the timing of the development of encephalopathy in patients with NCSE could not be ascertained. Therefore, it was not clear whether the comatose state in some patients with SE was because of the NCSE or whether it was induced by other clinical factors. The selective inclusion of nonconvulsive forms of SE could further limit the spectra of patient comorbidities to those inherent to NCSE. Finally, the population of patients who were assessed in this study likely suffered from the utmost severe seizures that were uncontrolled and necessitated referral to our epilepsy center; thus, generalization of these findings is limited. Given the small size of the dataset, we used recurrent SE occurrences from nonunique patients, and statistical tools could not be applied to adjust for potentially correlated observations. Such approach may have resulted in higher probability of type I error and an overestimation bias leading to the higher magnitude of the effects between the groups with coma and noncoma. Similar approach to the data analysis from patients with recurrent NCSE was previously used in another study from a single center.[13]

Given the retrospective design of the study and limited details of the medication administration, we assumed that as needed doses of benzodiazepines ordered for the treatment of NCSE were administered when the order was given; however, these medications could have been injected either before or after the documentation by a nurse. Similarly, because the orders for the adjustment of the anesthetic dose and the actual time when the infusion rate was done in patients who were already sedated occurred at the same time, however, it may not be the case. More accurate documentation of the medication orders and their time of administration could be achieved in the prospective study, but it may still be imperfect in the settings of emergencies unless the rapid response team is dispatched to execute the code.

Our study was conducted in a setting where there is a gap in review of cEEG at night. There were 10 occurrences of NCSE in this time window; thus, it is possible that the lack of the real-time EEG review has affected the timeliness of treatment of NCSE. Notably, the NCSE becomes more difficult to control the longer it remains untreated; further escalation of care needed to control refractory seizures might affect overall morbidity and mortality of NCSE.[30] Thus, the lack of the real-time EEG review limits the generalizability of the findings to the centers with capabilities for uninterrupted EEG review as well as those without any on-site EEG monitoring capacity.

In summary, we found that significant delays in the delivery of pharmacological treatments for NCSE were compounded by both inefficient initiation and tardive execution of the order for emergent AEDs. The execution of SE protocol was particularly long in patients with comatose NCSE. Although the generalization of these findings is limited, a similar approach in dissecting

failures of the hospital response system to SE can be successfully applied at other epilepsy centers.

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