ARTICLE

Factors associated with treatment delays in pediatric refractory convulsive status epilepticus

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Abstract

Objective

To identify factors associated with treatment delays in pediatric patients with convulsive refractory status epilepticus (rSE).

Methods

This prospective, observational study was performed from June 2011 to March 2017 on pediatric patients (1 month to 21 years of age) with rSE. We evaluated potential factors associated with increased treatment delays in a Cox proportional hazards model.

Results

We studied 219 patients (53% males) with a median (25th–75th percentiles [p_{25}–p_{75}]) age of 3.9 (1.2–9.5) years in whom rSE started out of hospital (141 [64.4%]) or in hospital (78 [35.6%]). The median (p_{25}–p_{75}) time from seizure onset to treatment was 16 (5–45) minutes to first benzodiazepine (BZD), 63 (33–146) minutes to first non-BZD antiepileptic drug (AED), and 170 (107–539) minutes to first continuous infusion. Factors associated with more delays to administration of the first BZD were intermittent rSE (hazard ratio [HR] 1.54, 95% confidence interval [CI] 1.14–2.09; $p = 0.0467$) and out-of-hospital rSE onset (HR 1.5, 95% CI 1.11–2.04; $p = 0.0467$). Factors associated with more delays to administration of the first non-BZD AED were intermittent rSE (HR 1.78, 95% CI 1.32–2.4; $p = 0.001$) and out-of-hospital rSE onset (HR 2.25, 95% CI 1.67–3.02; $p < 0.0001$). None of the studied factors were associated with a delayed administration of continuous infusion.

Conclusion

Intermittent rSE and out-of-hospital rSE onset are independently associated with longer delays to administration of the first BZD and the first non-BZD AED in pediatric rSE. These factors identify potential targets for intervention to reduce time to treatment.

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Glossary

AED = antiepileptic drug; **BZD** = benzodiazepine; **CI** = confidence interval; **EMS** = emergency medical services; **HR** = hazard ratio; p_{25}–p_{75} = 25th–75th percentiles; **pSERG** = Pediatric Status Epilepticus Research Group; **rSE** = refractory status epilepticus; **SE** = status epilepticus.

Status epilepticus (SE) is one of the most common neurologic emergencies, affecting approximately 5 to 20 children per 100,000 per year.[1–3] Mortality in pediatric SE is approximately 0% to 3% in the short term[1,4,5] and approximately 7% in the long term.[6] Sequelae, such as neurologic, cognitive, and behavioral problems, are common.[7] The main predictors of outcome are age, etiology, and duration of SE,[5,7,8] but duration of SE is often most easily modified.

To minimize seizure duration, SE guidelines suggest timely treatment with rapid escalation of antiepileptic drugs (AEDs) if needed.[9,10] Basic research and clinical studies suggest that delays in medication administration are associated with greater resistance to treatment and worse outcomes.[11–16] However, time to treatment in SE is often longer than guidelines recommend in adults[17,18] and children.[18–20] In previous studies from the Pediatric Status Epilepticus Research Group (pSERG), we showed that time to the administration of the first AEDs was slower than guideline recommendations,[21] and that treatment initiation delays were associated with worsened outcomes.[21a] However, there are limited data regarding factors associated with treatment delays. Previously, we showed that the time to AED administration was similar in patients with and without a prior diagnosis of epilepsy,[22] but it is unknown whether there are other factors associated with treatment delays that might be amenable to intervention in efforts to reduce time to treatment in SE.

We aimed to address this gap in knowledge by identifying factors independently associated with delays to administration of AEDs in pediatric patients with convulsive refractory SE (rSE). We evaluated a series of factors potentially associated with delays to administration of treatment: type of rSE (continuous vs intermittent), site of rSE onset (in hospital vs out of hospital), time of day at onset (day vs night), period in the academic year (first half vs last half), race (white vs nonwhite), and increased awareness of the existence of marked delays in rSE treatment (no vs yes).

Methods

Study design

We performed a prospective, observational study within pSERG, an ongoing multicenter consortium that aims to generate data to inform clinical decision-making and improve outcomes in pediatric rSE.[23] Detailed data on time to treatment,[21] differences between patients with and without a prior diagnosis of epilepsy,[22] and the association of treatment delays with outcomes[21a] have been previously reported.

Standard protocol approvals, registrations, and patient consents

The study was approved by the institutional review boards at each participating center.

Patients

This study involved patients with rSE. The inclusion criteria were as follows: (1) age from 1 month to 21 years; (2) admission between June 1, 2011, and March 1, 2017; and (3) focal or generalized convulsive seizures at onset that continued after administration of at least 2 AEDs, including at least one nonbenzodiazepine (non-BZD) AED or the use of a continuous infusion to treat rSE. Exclusion criteria were as follows: (1) nonconvulsive SE detected on EEG without convulsive seizures at onset, (2) nonconvulsive SE with motor manifestations limited to infrequent myoclonic jerks, and (3) insufficient basic demographic or clinical data. In summary, for the purposes of this study, rSE refers to a single convulsive seizure or a cluster of convulsive seizures without return to baseline that did not respond to administration of at least 2 AEDs, including at least one non-BZD AED or the use of a continuous infusion. If more than one rSE episode occurred during the study period, only the first episode was included in the statistical analysis.

Variables

The primary outcome was time to administration of AEDs: first BZD, first non-BZD AED, and, for patients who received continuous infusion, time to first continuous infusion. The time to treatment was determined based on information provided by family and emergency medical services (EMS) for out-of-hospital onset and from provider information and hospital records once in the hospital. To minimize bias, we cross-referenced time information between all available sources of information. We evaluated the following dichotomous variables potentially associated with delays in treatment administration: type of rSE (continuous vs intermittent), site of rSE onset (in hospital vs out of hospital), time of day at onset (day vs night), period in the academic year (first half vs last half), race (white vs nonwhite), and increased awareness of the existence of marked delays in rSE treatment (no vs yes). Awareness of delays in treatment administration were dichotomized into the period 2011–2014 (when the existence of delays to treatment was a study question within pSERG) and the period 2015–2017 (when the existence of treatment delays was demonstrated[21]) as a rough surrogate marker of awareness. Time of day was dichotomized into day (8 AM to 8 PM) and night (8 PM to 8 AM) based on office working hours, although working schedules may vary among hospitals. The academic year was dichotomized into first half (July to December) and second half (January to June) to address the education and experience of new residents, although we

acknowledge that the degree of reliance on residents may be different among institutions and at different times of the day within institutions. Racial inequalities in health and access to health care are well documented, and race is an indirect marker of access to health care.[24,25] rSE was classified as continuous when it consisted of a single prolonged seizure and as intermittent when it consisted of repeated seizures without return to baseline, as based on all available information. We also controlled for potential confounders in the multivariable analysis: etiology (structural vs nonstructural vs unknown), prior diagnosis of epilepsy (no vs yes), prior episode of SE (no vs yes), and age (in years). Potential reasons for delay in time to treatment were considered based on prior knowledge.

Statistical analysis

Descriptive statistics summarized demographic and basic clinical features. We compared quantitative variables among 2 groups with the Wilcoxon rank sum test and among more than 2 groups with the Kruskal-Wallis test. Times to administration of AEDs were analyzed using Cox proportional hazard regression models. We evaluated the proportional hazard assumption with log-log and residuals graphs for each Cox model. There were no major departures from the proportional hazards assumptions. Because the location of rSE onset is a potential effect modifier, we supplemented our analysis of the entire population with a stratified analysis dividing patients by location of rSE onset: out of hospital vs in hospital. Within each population, a patient may have received treatment at various sites (home, by EMS, non-pSERG hospital, and pSERG hospital). Unless stated otherwise, quantitative variables are presented as median (25th–75th percentiles [p_{25}–p_{75}]) and categorical variables are presented as number and percentage. By convention, a 2-sided α level was set at 0.05 to denote statistical significance. We controlled for multiple comparisons with the Benjamini and Hochberg false discovery rate, with a threshold (q value) of 0.05.[26] False discovery rate controls for expected proportion of false discoveries relative to total discoveries, in order to control for multiple comparisons across multiple tests.[26] All analyses were performed using R: a language and environment for statistical computing (Vienna, Austria),[27] RStudio,[28] and the packages gmodels,[29] lubridate,[30] gdata,[31] car,[32] and survival.[33]

Data availability

All statistical analyses and results are available in supplemental data (links.lww.com/WNL/A432). The original data are available on request.

Results

Demographic and clinical features

We enrolled 219 patients (53% males) with a median (p_{25}–p_{75}) age of 3.9 (1.2–9.5) years (table 1; table e-1, links.lww.com/WNL/A431). rSE episodes started out of the hospital in 141 patients and in the hospital in 78 patients. The median (p_{25}–p_{75}) time to first BZD administration was 16 (5–45) minutes (figure 1A). The first BZD was administered at home in 35 (16%) patients, by the EMS in 47 (21.5%) patients, in a non-pSERG hospital in 49 (22.4%) patients, and in a pSERG hospital in 88 (40.2%) patients. The median (p_{25}–p_{75}) time to first BZD varied by site of administration: at home 5 (4–14) minutes, by EMS 20 (11–24.5) minutes, in a non-pSERG hospital 45 (15–88) minutes, and in a pSERG hospital 13.5 (5–54.3) minutes ($p < 0.0001$). The median (p_{25}–p_{75}) time to first non-BZD AED was 63 (33–146) minutes (figure 1B). The first non-BZD AED was administered by the EMS in 10 (4.6%) patients, in a non-pSERG hospital in 82 (38%) patients, and at a pSERG hospital in 124 (57.4%) patients. The median (p_{25}–p_{75}) time to first non-BZD AED did not vary by site of administration: by EMS 35.5 (19.8–128.8) minutes, in a non-pSERG hospital 60 (38.5–100) minutes, and in a pSERG hospital 66.5 (29.8–162) minutes ($p = 0.336$). Among 107 patients who received at least one continuous infusion, the median (p_{25}–p_{75}) time to first continuous infusion was 170 (107–539) minutes (figure 1C).

Factors associated with delayed treatment

Factors associated with more delays to administration of the first BZD were intermittent rSE (hazard ratio [HR] 1.54, 95% confidence interval [CI] 1.14–2.09; $p = 0.0467$) and out-of-hospital rSE onset (HR 1.5, 95% CI 1.11–2.04; $p = 0.0467$) (table 2, figure 2). Factors associated with more delays to administration of the first non-BZD AED were intermittent rSE (HR 1.78, 95% CI 1.32–2.4; $p = 0.001$) and out-of-hospital rSE onset (HR 2.25, 95% CI 1.67–3.02; $p < 0.0001$) (table 2, figure 2). None of the studied factors were associated with a delayed administration of continuous infusion.

Stratification by site of rSE onset

Out-of-hospital onset

A total of 141 patients had out-of-hospital rSE onset (tables e-2 and e-3, links.lww.com/WNL/A431). The median (p_{25}–p_{75}) time to first BZD administration was 20 (8–55) minutes (figure e-1A, links.lww.com/WNL/A430). Among 113 patients with available information on time to hospital arrival, 44 (38.9%) patients did not receive any medication before hospital arrival. The first BZD was administered at home in 34 (24.1%) patients, by the EMS in 46 (32.6%) patients, in a non-pSERG hospital in 35 (24.8%) patients, and at a pSERG hospital in 26 (18.4%) patients. The median (p_{25}–p_{75}) time to first BZD varied by site of administration: at home 5 (3.5–12.8) minutes, by EMS 18.5 (10.5–24.5) minutes, in a non-pSERG hospital 55 (30–90) minutes, and in a pSERG hospital 50 (30–181.8) minutes ($p < 0.0001$). The median (p_{25}–p_{75}) time to first non-BZD AED administration was 80 (45–165) minutes (figure e-1B). The first non-BZD AED was administered by the EMS in 9 (6.5%) patients, in a non-pSERG hospital in 67 (48.6%) patients, and at a pSERG hospital in 62 (44.9%) patients. The median (p_{25}–p_{75}) time to first non-BZD AED varied by site of administration: by EMS 35 (19–150) minutes, in a non-pSERG hospital 65 (45–118.5) minutes, and in a pSERG hospital 119.5 (63–261.8) minutes ($p = 0.0036$). Among 71 patients who received at least one continuous infusion, the median (p_{25}–p_{75}) time to first continuous infusion was 164 (97.5–641) minutes (figure e-1C). In the population with

Table 1 Demographic and clinical features in our population (n = 219)

Age, y	3.9 (1.2–9.5)
Sex	
Male	115 (52.5)
Female	104 (47.5)
Race	
White	131 (59.8)
African American	50 (22.8)
Arabic	9 (4.1)
Asian	7 (3.2)
Native Hawaiian or Pacific Islander	1 (0.5)
Unknown/not reported	21 (9.6)
Ethnicity	
Hispanic or Latino	35 (16)
Not Hispanic or Latino	163 (74.4)
Unknown/not reported	21 (9.6)
Medical history[a]	
Developmental delay/intellectual disability	108 (49.3)
Prior epilepsy	105 (47.9)
Prior status epilepticus	43 (19.6)
Cerebral palsy	22 (10)
Febrile seizures	24 (11)
No relevant neurologic history	76 (34.7)
Etiology	
Structural	60 (27.4)
Genetic	31 (14.2)
Metabolic	12 (5.5)
Other	35 (16)
Unknown	81 (37)
Convulsive duration, min	134.5 (60–270)
Time to first BZD, min	16 (5–45)
Time to first non-BZD AED, min	63 (33–146)
Time to first CI, min	170 (107–539)

Abbreviations: AED = antiepileptic drug; BZD = benzodiazepine; CI = continuous infusion.
Data are n (%) or median (25th–75th percentiles).
[a] Percentages do not add up to 100 because the categories are not mutually exclusive.

out-of-hospital rSE onset, the factor associated with more delay to the first BZD was no prior SE (HR 2.32, 95% CI 1.58–3.42; $p = 0.0053$). The factor associated with more delay to the first non-BZD AED was intermittent rSE (HR 2.33, 95% CI 1.58–3.42; $p = 0.0002$). None of the studied factors were associated with a delayed administration of continuous infusions (table e-4, figure 3).

In-hospital onset

A total of 78 patients had in-hospital rSE onset (tables e-5 and e-6, links.lww.com/WNL/A431). The median (p_{25}–p_{75}) time to first BZD administration was 9 (5–24.8) minutes (figure e-2A, links.lww.com/WNL/A430). The first BZD was administered in a non-pSERG hospital in 14 (18.4%) patients and at a pSERG hospital in 62 (81.6%) patients. The median (p_{25}–p_{75}) time to first BZD did not vary by site of administration: in a non-pSERG hospital 8.5 (2.8–15.8) minutes and in a pSERG hospital 8.5 (5–25.8) minutes ($p = 0.4976$). The median (p_{25}–p_{75}) time to first non-BZD AED administration was 39 (21.3–73) minutes (figure e-2B). The first non-BZD AED was administered in a non-pSERG hospital in 15 (19.5%) patients and at a pSERG hospital in 62 (80.5%) patients. The median (p_{25}–p_{75}) time to first non-BZD AED did not vary by site of administration: in a non-pSERG hospital 31 (20–41.5) minutes and in a pSERG hospital 44 (21.3–91) minutes ($p = 0.1339$). Among 36 patients who received at least one continuous infusion, time to first continuous infusion was 186 (120–487.5) minutes (figure e-2C). None of the studied factors were associated with a delayed administration of the first BZD, first non-BZD AED, or first continuous infusion (tables 2 and e-7).

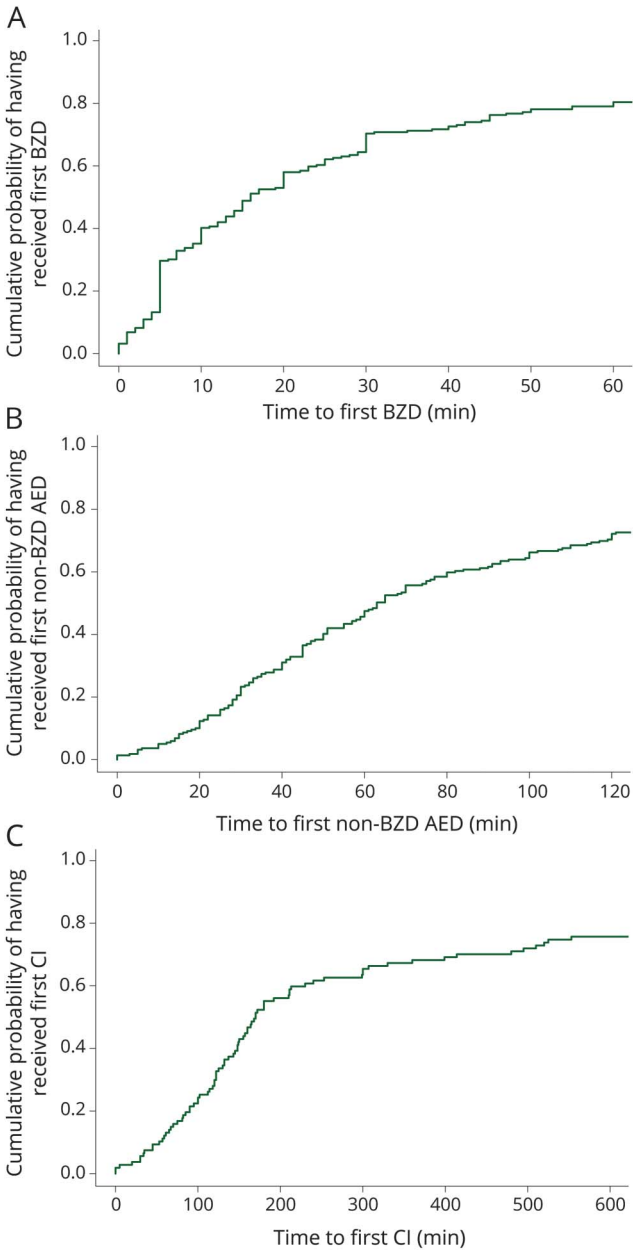
Additional information on our study population is presented in supplemental results (links.lww.com/WNL/A433).

Discussion

Intermittent rSE and out-of-hospital rSE onset are independently associated with longer delays to administration of the first BZD and the first non-BZD AED in pediatric rSE. Among patients with out-of-hospital onset, no prior SE episode was independently associated with longer delays to administration of the first BZD, and intermittent rSE was independently associated with longer delays to administration of the first non-BZD AED. These factors identify potential targets for intervention to reduce time to treatment.

We found more delays to treatment administration when rSE was intermittent. A potential explanation for treatment delay may include the perception that the episode is spontaneously resolving if clinical seizures wax and wane rather than occurring continuously. This result identifies a potential target for intervention with education on the need for emergent treatment even if seizures are not occurring continuously but intermittently. Most delays in treatment occur out of the hospital and, as in other series,[12,21] most SE and rSE episodes started out of the hospital. Hospitals currently have limited ability to start managing and treating patients with rSE continuously in the prehospital setting. Furthermore, in some states, rescue treatment via the EMS crew is restricted.

Figure 1 Time to treatment in the whole population



(A) Time to receive the first BZD. The x-axis is truncated at 60 minutes for clarity. (B) Time to receive the first non-BZD AED. The x-axis is truncated at 120 minutes for clarity. (C) Time to receive the first continuous infusion. The x-axis is truncated at 600 minutes for clarity. AED = antiepileptic drug; BZD = benzodiazepine; CI = continuous infusion.

Families and EMS may not be aware of the importance of a timely treatment. Therefore, delays in treatment administration may be attributable to complexities of a fragmented health care system and operational capacity (e.g., prompt availability of AEDs, pharmacy processing times) more than to physician willingness to promptly administer treatment. Among patients with out-of-hospital onset, those who received their first BZD at home or by EMS had much shorter time to first BZD than patients who received their first BZD at the hospital. Ensuring prompt initial treatment at home or by EMS might greatly reduce overall time to initial treatment. Because delays in treatment administration occur even in patients with a diagnosis of epilepsy,[22] educational programs that emphasize the need for an emergent treatment of prolonged seizures out of the hospital may greatly reduce overall time to treatment. Despite most delays occurring out of the hospital, there is also room for improvement in the time to treatment for patients with in-hospital rSE onset. An active educational and interventional campaign focusing on the risk factors for delays and establishing acute treatment pathways similar to that of stroke or myocardial infarction care may reduce time to treatment.

The longer the seizures last, the more resistant they become to the initial SE treatments. The time-dependent pharmacoresistance to BZDs has been found in animal models,[34–36] and clinical studies have shown that as seizures last longer, they often become self-sustained and progressively more resistant to treatment.[11–13] In a series of 66 patients with generalized tonic-clonic SE, one of the factors associated with death was time to treatment administration.[37] Within the pSERG series, AED administration delays are associated with higher mortality and poorer outcomes.[21a]

Despite the association of time to treatment with outcomes, delays in treatment administration still occur. In a series of 542 pediatric patients, the median time from arrival at the hospital to administration of a non-BZD AED was 24 minutes.[19] In a study of 625 adults and 264 children with SE, approximately 60% of patients received their first AED after 30 minutes and approximately 25% after 60 minutes.[18] Within the pSERG series, we previously showed that the median time to first, second, and third AED was 28 minutes, 40 minutes, and 59 minutes, respectively,[21] and treatment delays occurred even in patients already diagnosed with epilepsy.[22] The current analysis with 219 patients establishes that intermittent rSE and rSE onset out of hospital are independently associated with more delays to treatment administration.

The following factors were not independently associated with more delays in time to treatment: time of day or night, the first (2011–2014) vs the second (2015–2017) part of the cohort period, first half vs last half of the academic year, and white vs nonwhite race. Dichotomizing variables leads to some loss of information, but the number of predictors in the regression models had to be limited to prevent overfitting.

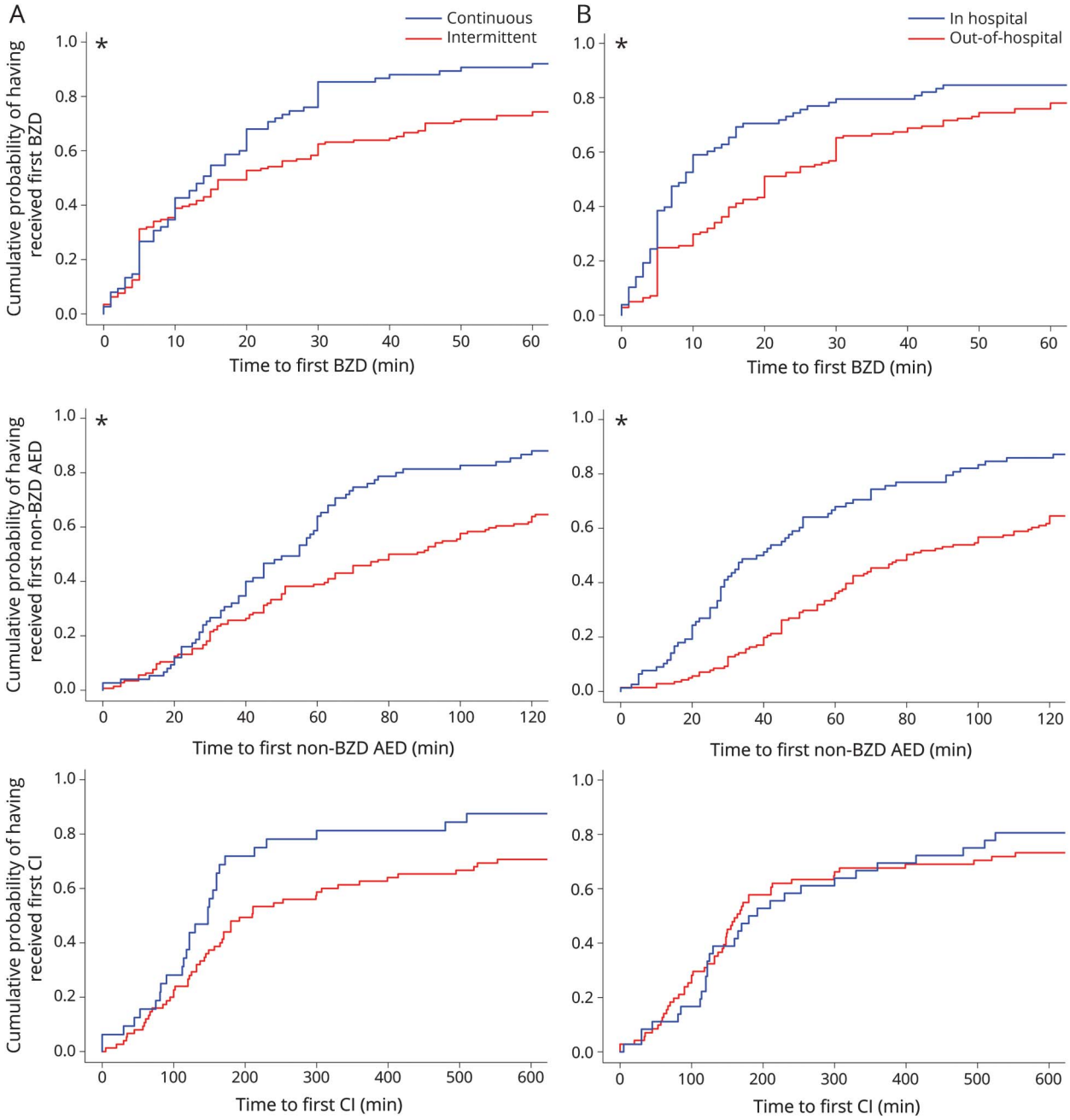
Our study population may or may not be representative of all children with SE. The pSERG consortium focuses on convulsive rSE, and our results are therefore not necessarily generalizable to patients with nonrefractory SE or with nonconvulsive SE. Times and the classification of rSE as continuous or intermittent were evaluated based on information provided by family and EMS for out-of-hospital onset and from provider information and hospital records once in the hospital. Because this method of data acquisition is subject to

Table 2 Results of the regression model

	HR	95% CI	*p* Value (uncorrected for multiple comparisons)	*p* Value (corrected for multiple comparisons)
Time to first BZD				
Intermittent rSE	1.54	1.14–2.09	0.0055	0.0467
Out-of-hospital onset	1.5	1.11–2.04	0.0085	0.0467
Awareness	1.37	1.01–1.85	0.0466	0.1282
Day	1	0.75–1.33	0.9907	0.9907
Early academic year	1.4	1.06–1.85	0.0193	0.0708
White	0.85	0.64–1.14	0.2812	0.6185
Structural etiology	0.97	0.68–1.4	0.8859	0.9907
Nonstructural etiology	1.13	0.82–1.55	0.4548	0.7148
Prior epilepsy	0.97	0.72–1.32	0.8424	0.9907
Prior status epilepticus	1.18	0.8–1.74	0.3944	0.7148
Age (in years)	1	0.97–1.03	0.9321	0.9907
Time to first non-BZD AED				
Intermittent rSE	1.78	1.32–2.4	0.0002	0.001
Out-of-hospital onset	2.25	1.67–3.02	<0.0001	<0.0001
Awareness	1.25	0.91–1.7	0.1683	0.3408
Day	1.08	0.81–1.45	0.6056	0.6056
Early academic year	1.36	1.02–1.79	0.0334	0.0919
White	0.89	0.67–1.18	0.4211	0.5146
Structural etiology	1.1	0.78–1.56	0.592	0.6056
Nonstructural etiology	0.86	0.63–1.18	0.3568	0.4905
Prior epilepsy	0.81	0.59–1.11	0.1859	0.3408
Prior status epilepticus	1.2	0.82–1.76	0.3366	0.4905
Age (in years)	0.97	0.94–0.99	0.014	0.0513
Time to first continuous infusion				
Intermittent rSE	1.3	0.83–2.03	0.2541	0.4659
Out-of-hospital onset	1.25	0.8–1.98	0.3305	0.5194
Awareness	1.53	0.98–2.37	0.0591	0.2829
Day	1.06	0.71–1.58	0.7882	0.7882
Early academic year	1.45	0.93–2.26	0.1029	0.2829
White	0.66	0.42–1.05	0.0812	0.2829
Structural etiology	0.63	0.37–1.08	0.0922	0.2829
Nonstructural etiology	0.7	0.43–1.13	0.1403	0.3088
Prior epilepsy	1.07	0.64–1.8	0.7851	0.7882
Prior status epilepticus	0.82	0.46–1.44	0.4871	0.6697
Age (in years)	0.99	0.95–1.03	0.6214	0.7595

Abbreviations: AED = antiepileptic drug; BZD = benzodiazepine; CI = confidence interval; HR = hazard ratio; rSE = refractory status epilepticus.

Figure 2 Comparison of the time to treatment between subgroups among the full cohort. Only the factors that were different are displayed in the figure

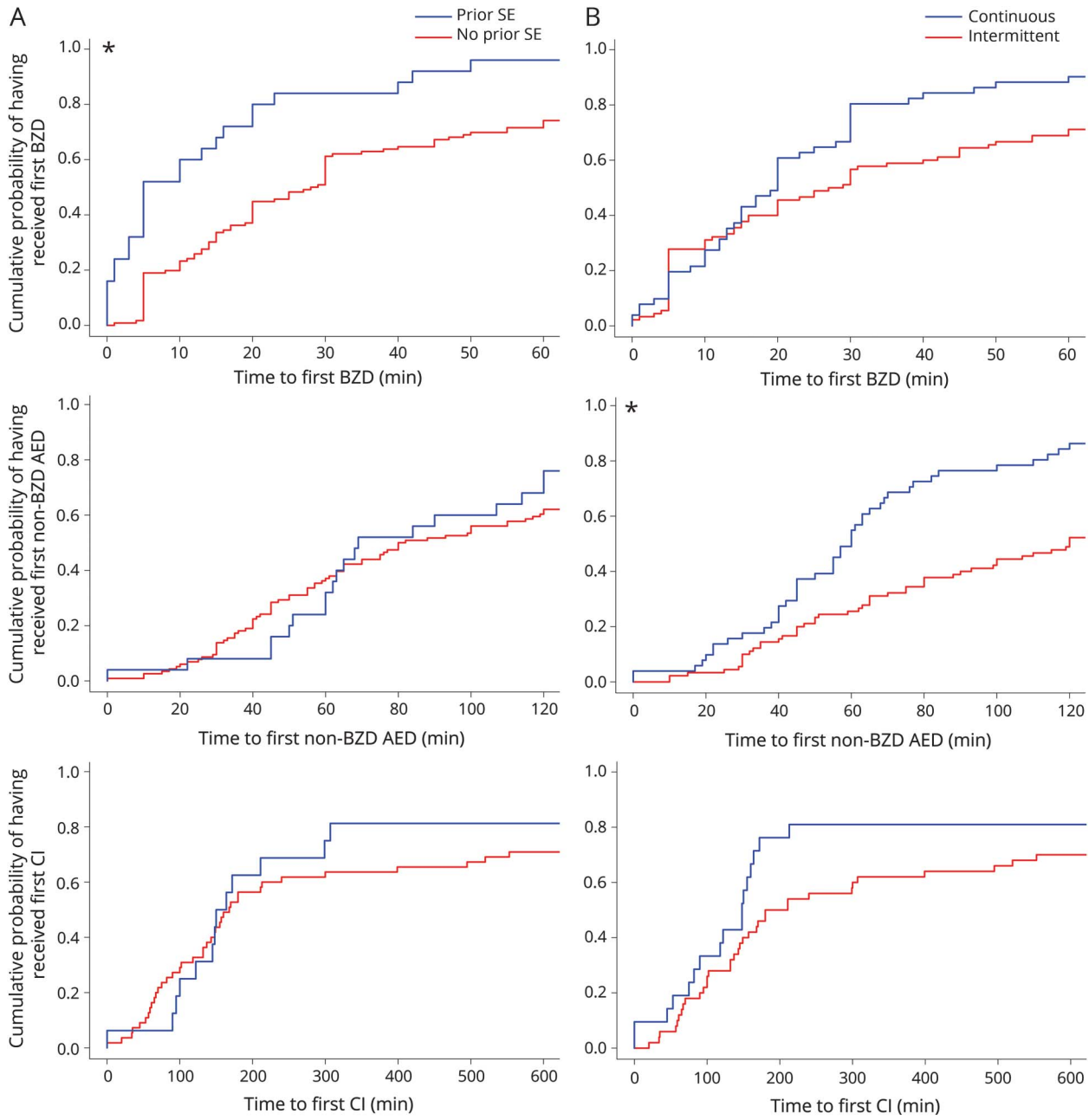


(A) Comparison between continuous (blue) and intermittent (red) rSE. (B) Comparison between patients with onset of rSE in hospital (blue) and out of hospital (red). The first row contains time to first BZD (x-axis truncated at 60 minutes for clarity), the second row time to first non-BZD AED (x-axis truncated at 120 minutes for clarity), and the third row time to first CIs (x-axis truncated at 600 minutes for clarity). *Statistically significantly different. AED = antiepileptic drug; BZD = benzodiazepine; CI = continuous infusion; rSE = refractory status epilepticus.

information and recall bias, we cross-referenced information with families, EMS records, nurses, and medication administration records when available to reduce bias. There are limitless potential factors accounting for time to treatment administration. We selected the most relevant potential predictors and potential confounders based on prior knowledge. Including more variables in the model might have resulted in overfitting and unstable results. In contrast, our results were stable in the whole population, the in-hospital and out-of-hospital subgroups, and robust to sensitivity analyses. Our results were also robust to correction for multiple testing.

Intermittent rSE and out-of-hospital rSE onset are independently associated with longer delays to administration of the first BZD and the first non-BZD AED in pediatric rSE.

Figure 3 Comparison of the time to treatment between subgroups for the out-of-hospital–onset subgroup



(A) Comparison between history of SE (blue) and no history of SE (red). (B) Comparison between continuous (blue) and intermittent (red) refractory SE. The first row contains time to first BZD (x-axis truncated at 60 minutes for clarity), the second row time to first non-BZD AED (x-axis truncated at 120 minutes for clarity), and the third row time to first CIs (x-axis truncated at 600 minutes for clarity). *Statistically significantly different. AED = antiepileptic drug; BZD = benzodiazepine; CI = continuous infusion; SE = status epilepticus.

Author contributions

I.S.F. participated in drafting and revising the manuscript for content, including medical writing, in study concept and design, data acquisition, analysis and interpretation of data, statistical analysis, and study supervision or coordination. M.G.-L. participated in drafting and revising the manuscript for content, including medical writing, in study concept and design, data acquisition, analysis and interpretation of data, and study supervision or coordination. N.S.A. participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination. A.E.A. participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination. R. A. participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination. J.N.B. participated in revising the manuscript for content, including medical writing,

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He serves as a consultant for Zogenix, Upsher-Smith, Eisai, Engage, Sunovion, and Lundbeck. He performs video-EEG long-term and ICU monitoring, EEGs, and other electrophysiologic studies at Boston Children's Hospital and affiliated hospitals and bills for these procedures, and he evaluates pediatric neurology patients and bills for clinical care. He has received speaker honorariums from national societies, including the AAN, AES, and ACNS, and for grand rounds at various academic centers. His wife, Dr. Karen Stannard, is a pediatric neurologist and she performs video-EEG long-term and ICU monitoring, EEGs, and other electrophysiologic studies and bills for these procedures, and she evaluates pediatric neurology patients and bills for clinical care. Go to Neurology.org/N for full disclosures.

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FULL-LENGTH ARTICLE NPub.org/sovggt

Factors associated with treatment delays in pediatric refractory convulsive status epilepticus

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Study question

What factors are independently associated with treatment delays in pediatric refractory convulsive status epilepticus (rSE)?

Summary answer

Intermittent rSE and out-of-hospital rSE onset are independently associated with treatment delays.

What is known and what this paper adds

The duration of status epilepticus (SE) episodes is the most modifiable of the major predictors of outcomes, thus clinical guidelines recommend rapid initiation of antiepileptic drug (AED) therapy. This study identifies the key factors associated with delays in initiating rSE treatment.

Participants and setting

This multicenter study examined 219 pediatric patients (53% male; median age, 3.9 years; interquartile age range, 1.2–9.5 years) who were admitted to hospitals between June 1, 2011, and March 1, 2017. The patients experienced focal or generalized convulsive seizures that continued after the administration of ≥2 AEDs, including ≥1 nonbenzodiazepine (non-BZD) drug or the use of a continuous infusion.

Design, size, and duration

For each patient, this prospective study determined the time between seizure onset and initiation of the first BZD AED, initiation of the first non-BZD AED, and initiation of continuous AED infusion. This study also collected information on variables including the type of rSE and whether rSE onset occurred out-of-hospital.

Main results and the role of chance

Intermittent rSE and out-of-hospital rSE onset were both independently associated with greater delays in the initiation of the first BZD and initiation of the first non-BZD AED. No examined factor was associated with delays in the initiation of continuous AED infusion.

Table Variables associated with treatment delays in a regression model

Variable	HR (95% CI) for delayed initiation of first BZD	HR (95% CI) for delayed initiation of first non-BZD AED
Intermittent rSE	1.54 (1.14–2.09)	1.78 (1.32–2.4)
Out-of-hospital rSE onset	1.5 (1.11–2.04)	2.25 (1.67–3.02)

Abbreviations: AED = antiepileptic drug; BZD = benzodiazepine; CI = confidence interval; HR = hazard ratio; rSE = refractory convulsive status epilepticus.

Bias, confounding, and other reasons for caution

For cases with out-of-hospital onset, information prior to hospital admission was collected from family and emergency medical services and might have been subject to recall bias. Many factors that may influence treatment delays were not available.

Generalizability to other populations

This study's results may not be generalizable to children with non-refractory or non-convulsive SE.

Study funding/potential competing interests

This study was funded by the Epilepsy Foundation of America, the American Epilepsy Society, and the Pediatric Epilepsy Research Foundation. Some authors report serving on journal editorial boards, advisory boards for pharmaceutical companies, and various professional society committees; receiving funding from foundations, pharmaceutical companies, and government agencies; receiving patent royalties, publication royalties, and speaker's honoraria; being party to pending patents; providing expert testimony, medical services, and consulting; and having spouses who provide medical and editorial services. Go to Neurology.org/N for full disclosures.

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