Association of guideline publication and delays to treatment in pediatric status epilepticus

Iván Sánchez Fernández, MD, MPH, MBI, Nicholas S. Abend, MD, MSCE, Marta Amengual-Gual, MD,
Anne Anderson, MD, Ravindra Arya, MD, DM, Cristina Barcia Aguilar, MD, James Nicholas Brenton, MD,
Jessica L. Carpenter, MD, Kevin E. Chapman, MD, Justice Clark, MPH, Raquel Farias-Moeller, MD,
William D. Gaillard, MD, Marina Gaínza-Lein, MD, Tracy Glauser, MD, Joshua Goldstein, MD,
Howard P. Goodkin, MD, PhD, Réjean M. Guerriero, DO, Yi-Chen Lai, MD, Tiffani McDonough, MD,
Mohamad A. Mikati, MD, Lindsey A. Morgan, MD, Edward Novotny, Jr., MD, Eric Payne, MD, MPH,
Katrina Peariso, MD, PhD, Juan Piantino, MD, Adam Ostendorf, MD, Tristan T. Sands, MD, PhD,
Kumar Sannagowdara, MD, Robert C. Tasker, MBBS, MD, Dimtry Tchapyjnikov, MD,
Alexis A. Topjian, MD, MSCE, Alejandra Vasquez, MD, Mark S. Wainwright, MD, PhD, Angus Wilfong, MD,
Kowryn Williams, MD, PhD, and Tobias Loddenkemper, MD, on behalf of pSERG

Correspondence
Dr. Loddenkemper
tobias.loddenkemper@
childrens.harvard.edu

Abstract

Objective
To determine whether publication of evidence on delays in time to treatment shortens time to treatment in pediatric refractory convulsive status epilepticus (rSE), we compared time to treatment before (2011–2014) and after (2015–2019) publication of evidence of delays in treatment of rSE in the Pediatric Status Epilepticus Research Group (pSERG) as assessed by patient interviews and record review.

Methods
We performed a retrospective analysis of a prospectively collected dataset from June 2011 to September 2019 on pediatric patients (1 month–21 years of age) with rSE.

Results
We studied 328 patients (56% male) with median (25th–75th percentile [p_{25}–p_{75}]) age of 3.8 (1.3–9.4) years. There were no differences in the median (p_{25}–p_{75}) time to first benzodiazepine (BZD) (20 [5–52.5] vs 15 [5–38] minutes, $p = 0.3919$), time to first non-BZD antiseizure medication (68 [34.5–163.5] vs 65 [33–142] minutes, $p = 0.7328$), and time to first continuous infusion (186 [124.2–571] vs 160 [89.5–495] minutes, $p = 0.2236$). Among 157 patients with out-of-hospital onset whose time to hospital arrival was available, the proportion who received at least 1 BZD before hospital arrival increased after publication of evidence of delays (41 of 81 [50.6%] vs 57 of 76 [75%], $p = 0.0018$), and the odds ratio (OR) was also increased in multivariable logistic regression (OR 4.35 [95% confidence interval 1.96–10.3], $p = 0.0005$).

Conclusion
Publication of evidence on delays in time to treatment was not associated with improvements in time to treatment of rSE, although it was associated with an increase in the proportion of patients who received at least 1 BZD before hospital arrival.

From the Division of Epilepsy and Clinical Neurophysiology (I.S.F., M.A.-G., C.B.A., J.C., M.G.-L., A.V., T.L.), Department of Neurology, and Department of Neurology (R.C.T.), Department of Anesthesiology, Critical Care and Pain Medicine, Boston Children's Hospital, Harvard Medical School, MA; Department of Child Neurology (I.S.F.), Hospital Sant Joan de Déu, Universitat de Barcelona, Spain; Division of Neurology (N.S.A.), Departments of Neurology and Pediatrics, Children's Hospital of Philadelphia and University of Pennsylvania; Pediatric Neurology Unit (M.A.-G.), Department of Pediatrics, Hospital Universitari Son Espases, Universitat de les Illes Balears, Palma, Spain; Section of Pediatric Critical Care Medicine (A.A., Y.-C.L.), Department of Pediatrics, Baylor College of Medicine, Houston, TX; Division of Neurology (R.A., T.G., K.P.), Cincinnati Children's Hospital Medical Center, University of Cincinnati, OH; University of Virginia Health (J.N.B., H.P.G.), Charlottesville; Center for Neuroscience (J.L.C., W.D.G.), Children's National Medical Center, George Washington University School of Medicine and Health Sciences, Washington, DC; Departments of Pediatrics and Neurology (K.E.C.), Children's Hospital Colorado, University of Colorado School of Medicine, Aurora; Department of Pediatric Neurology (R.F.-M., K.S.), Children's Hospital of Wisconsin, Medical College of Wisconsin, Milwaukee; Instituto de Pediatría (M.G.-L.), Facultad de Medicina, Universidad Austral de Chile, Valdivia, Chile; Servicio de Neuropsiquiatría Infantil (M.G.-L.), Hospital Clínico San Borja Arriarán, Universidad de Chile, Santiago; Ruth D. & Ken M. Davee Pediatric Neurocritical Care Program (J.G., T.M.), Northwestern University Feinberg School of Medicine, Chicago, IL; Division of Pediatric and Developmental Neurology (R.M.G.), Department of Neurology, Washington University School of Medicine, St. Louis, MO; Division of Pediatric Neurology (M.A.M., D.T.), Duke University Medical Center, Duke University, Durham, NC; Department of Pediatrics and Neurology (L.A.M., E.N., M.S.W.), Seattle Children's Hospital, University of Washington; Center for Integrative Brain Research (L.A.M., E.N., M.S.W.), Seattle Children's Research Institute, WA; Department of Neurology (E.P.), Mayo Clinic, Mayo Clinic School of Medicine, Rochester, MN; Department of Neurology (J.P.), Doernbecher Children's Hospital, Oregon Health & Science University, Portland; Department of Neurology (A.O.), Nationwide Children's Hospital, Ohio State University, Columbus; Division of Child Neurology and Institute for Genomic Medicine (T.T.S.), Columbia University Irving Medical Center, New York Presbyterian Hospital, New York; Division of Critical Care Medicine (A.A.T.), The Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania; Division of Child and Adolescent Neurology (A.V.), Department of Neurology, Mayo Clinic, Rochester, MN; Barrow Neurological Institute (A.W., K.W.), Phoenix Children's Hospital; and Department of Pediatrics (A.W., K.W.), University of Arizona School of Medicine, Phoenix.

Glossary

ASM = antiseizure medication; **BZD** = benzodiazepine; **CI** = confidence interval; **HR** = hazard ratio; **ICU** = intensive care unit; **OR** = odds ratio; **p25** = 25th percentile; **p75** = 75th percentile; **pSERG** = Pediatric Status Epilepticus Research Group; **RMST** = restricted mean survival time; **rSE** = refractory convulsive SE; **SE** = status epilepticus.

Status epilepticus (SE) is one of the most frequent neurologic emergencies in children, with an incidence of 5 to 25 per 100,000.[1–4] Longer SE episodes require more invasive and resource-intensive medical care and are associated with higher morbidity and mortality.[5] Although long-term outcomes in SE survivors depend largely on etiology,[6,7] observational studies showed that delayed treatment is independently associated with worse outcomes[8–12] and increased mortality[12] in the short term. Therefore, shortening SE duration through timely and effective treatment[13–15] may improve short-term outcomes.

The American Epilepsy Society guideline recommends initial treatment with benzodiazepine (BZD) within 20 minutes, treatment with non-BZD antiseizure medication (non-BZD ASM) within 40 minutes, and treatment with continuous infusions within 60 minutes,[16] but a growing body of literature identifies marked delays from these benchmarks.[17] Interdisciplinary quality improvement interventions have shown that it is possible to improve time to treatment of electrographic seizures in the intensive care unit (ICU)[18] and time to treatment of SE in the hospital.[19,20] There are no data on whether publication of evidence on delayed treatment in SE has independently modified time to treatment.

We aimed to address this gap in knowledge by comparing time to treatment before (2011–2014) and after (2015–2019) publication of evidence of delays in time to treatment within the Pediatric Status Epilepticus Research Group (pSERG). Our hypothesis was that published evidence identifying a gap in clinical practice (delayed time to treatment) would lead to improved clinical practice (reduced times to treatment).

Methods

Standard protocol approvals, registrations, and patient consents

This study was approved by the Institutional Review Board at each institution. Written informed consent was obtained from parents or guardians.

Study design

This was a retrospective analysis of prospectively collected data from a multicenter observational study. pSERG is a consortium of pediatric hospitals in the United States and Canada that aims to improve the treatment and, eventually, the prognosis of children with SE.[21] pSERG, as an ongoing study, has reported the initial patients in the cohort on different outcomes: on delays in time to treatment,[22] use of continuous infusions,[23] differences in time to treatment between patients with and without a prior diagnosis of epilepsy,[24] factors associated with delays in time to treatment,[25] and the association of treatment delays with unfavorable outcomes.[12]

Patients

We studied patients with refractory convulsive SE (rSE). Inclusion criteria were (1) age from 1 month to 21 years; (2) admission to a pSERG hospital between June, 1, 2011, and September, 1, 2019; and (3) focal or generalized convulsive seizures at onset that continued after administration of at least 2 ASMs, including at least 1 non-BZD ASM or the use of a continuous infusion. Exclusion criteria were (1) nonconvulsive SE detected on EEG lacking convulsive seizures at onset; (2) nonconvulsive SE with motor manifestations limited to infrequent myoclonic jerks; (3) no information on time to administration of the first BZD; (4) no information on time to administration of the first non-BZD ASM; and (5) no information on basic demographic and clinical features such as age, sex, race, time of SE onset, hospital onset, type of SE, or duration of SE. In order not to violate the assumption of independent observations in statistical tests, we included only the first rSE episode for patients who had >1 rSE episode during the study period.

Variables

The main outcomes were time to the first BZD, time to the first non-BZD ASM, and time to the first continuous infusion among patients who received any. Secondary outcomes were the proportion of patients who received the first class of each medication (BZD, non-BZD ASM, and continuous infusion) beyond recommended timelines and beyond clinically prespecified outlier times and, among patients with rSE onset out of the hospital, the proportion of patients who received at least 1 BZD before hospital arrival. The main intervention for all analyses was publication of evidence from pSERG showing delays in time to treatment.[22] By the end of 2014, the first article with pSERG data showed that delays in time to treatment of rSE occurred at every step of the treatment pathway, and all pSERG members became aware of delays in time to treatment of rSE because they contributed to the article.[22] Therefore, we divided time into the periods June 2011 to December 2014 vs January 2015 to September 2019 as surrogates for preawareness and awareness of delays in time to treatment. As more patients were collected, new pSERG analyses in 2016 confirmed the initial results and showed that delays in time to treatment of rSE were common even in patients with a prior diagnosis of epilepsy.[24] Further, the American Epilepsy Society evidence-based guideline

published in 2016 emphasized initial treatment with BZD within 20 minutes, treatment with non-BZD ASM within 40 minutes, and treatment with continuous infusions within 60 minutes.[16] Therefore, as a sensitivity analysis, we compared times to treatment defining alternative periods: 2011 to 2016 vs 2017 to 2019. We also evaluated the robustness of our results with an additional sensitivity analysis considering only the hospitals that were part of pSERG since the initial years. We considered as potential confounders the type of SE (continuous or intermittent), hospital onset, SE onset during the day (8 AM–8 PM) or night (8 PM–8 AM), period in the academic year (July–December vs January–June), white race, etiology (structural vs other), history of epilepsy, prior episode of SE, age in years, and sex. The time to medication administration was extracted from families and emergency medical services for out-of-hospital SE onset and from provider documentation and medical records for SE treated in the hospital. Data were collected with a standardized data acquisition tool and then entered into an electronic database hosted by Cincinnati Children's Hospital Medical Center.[21]

Statistical analysis and statistical software

Demographic and clinical characteristics were summarized with descriptive statistics. Unless stated otherwise, continuous variables were summarized as median (25th [p_{25}] and 75th [p_{75}] percentile) and categorical variables were summarized as number (percentage). Categorical variables were compared with the Fisher exact test in univariate analysis and with logistic regression with multivariate analysis. We calculated the absolute risk difference and the number needed to treat. We compared time to treatment in univariate analysis with the Peto and Peto modification of the Gehan-Breslow-Wilcoxon test and in multivariate analysis with a Cox proportional hazards regression model. The Peto and Peto[26] modification of the Gehan-Breslow-Wilcoxon test is a nonparametric generalized maximum-likelihood estimate of the survival function for interval-censored data that gives more weight to early events and gives less weight to late events, likely outliers in this context. We calculated the differences in time to treatment between groups (before and after publication of evidence of delays) with the difference of the restricted mean survival time (RMST).[27,28] The difference of the RMST is an outcome measure that compares the time difference between 2 groups using the areas under the Kaplan-Meier curves up to a clinically meaningful prespecified time.[27,28] Considering a clinically meaningful prespecified time of, e.g., 60 minutes for the time to the first BZD, a difference of RMST of, e.g., −3 minutes means that, within the first 60 minutes, patients in the group after publication of evidence received the first BZD a mean of 3 minutes earlier than patients in the group before publication of evidence. For this study, we considered the following clinically meaningful prespecified times: (1) 20, 40, and 60 minutes for the first BZD, which represent the times by which the first-line therapy should be completed, and 20 and 40 minutes after that threshold[16]; (2) 40, 60, and 120 minutes for the first non-BZD ASM, which represent the times by which the second-line therapy should be completed, and 20

and 80 minutes after that threshold[16]; and (3) 60, 120, and 240 minutes for the first continuous infusion, which represent the times by which the third-line therapy should be completed, and 60 and 180 minutes after that threshold.[16] We considered onset of rSE (in the hospital or out of the hospital) as an effect modifier because time to treatment is likely to be different in these 2 environments. Thus, we stratified the analyses by in-hospital or out-of-hospital rSE onset. We used a conventional 2-sided α level of 0.05 for all tests because, even if the expected effect of publication of evidence of delays is to reduce times to treatment, longer times to treatment might have happened due to a secular effect. We adjusted the main results for multiple comparisons with the Benjamini and Hochberg false discovery rate with a q value of 0.05.[29] The false discovery rate controls for the expected proportion of false discoveries in order to control for multiple comparisons across multiple tests.[29] All statistical analyses were performed with R (version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria), a language and environment for statistical computing[30] with RStudio,[31] and the packages gdata,[32] car,[33] lubridate,[34] gmodels,[35] survival,[36] and survRM2.[37]

Data availability

All statistical analyses and results are available in appendix e-1 (github.com/IvanSanchezFernandez/pSERGbeforeafter). The original data are available on request.

Results

Demographic and clinical characteristics

We evaluated 328 patients (56% male) with a median (p_{25}–p_{75}) age of 3.8 (1.3–9.4) years, 151 (46%) with an rSE episode in the period 2011 to 2014 and 177 (54%) in the period 2015 to 2019. SE started out of hospital in 222 (67.7%) patients and in hospital in 106 (32.3%) patients. The median (p_{25}–p_{75}) length of ICU stay was 4 (2–11) days, and 11 (3.4%) patients died during hospitalization (table 1).

Time to treatment

The median (p_{25}–p_{75}) time to the administration of the first BZD was 17 (5–45) minutes. There was no statistically significant difference between the periods 2011 to 2014 and 2015 to 2019 (20 [5–52.5] vs 15 [5–38] minutes, p = 0.3919) (figure 1A), and it was not significant after adjustment for potential confounders (confounders described in the Methods section) (hazard ratio [HR] 1.01 [95% confidence interval (CI) 0.81–1.27], p = 0.9130) (table e-1, available in GitHub at github.com/IvanSanchezFernandez/pSERGbeforeafter and in zenodo at zenodo.org/badge/latestdoi/230197648). The median (p_{25}–p_{75}) time to the administration of the first non-BZD ASM was 65.5 (33.8–150) minutes. There was no difference between the periods 2011 to 2014 and 2015 to 2019 (68 [34.5–163.5] vs 65 [33–142] minutes, p = 0.7328) (figure 1B), and it was not significant after adjustment for potential confounders (HR 1.01 [95% CI 0.81–1.27], p = 0.9111) (table e-2, available in GitHub and

Table 1 Demographic and clinical characteristics

	2011–2014 (n = 151)	2015–2019 (n = 177)	Total (n = 328)
Age, y	3.8 (1.2–8.9)	4.1 (1.3–9.6)	3.8 (1.3–9.4)
Sex, n (%)			
Male	80 (53)	103 (58.2)	183 (55.8)
Female	71 (47)	74 (41.8)	145 (44.2)
Race, n (%)			
White	81 (53.6)	128 (72.3)	209 (63.7)
Black	38 (25.2)	27 (15.3)	65 (19.8)
Arabic	7 (4.6)	3 (1.7)	10 (3)
Asian	6 (4)	5 (2.8)	11 (3.4)
Native American	1 (0.7)	2 (1.1)	3 (0.9)
Unknown	18 (11.9)	12 (6.8)	30 (9.2)
Ethnicity, n (%)			
Not Hispanic	111 (73.5)	136 (76.8)	247 (75.3)
Hispanic	26 (17.2)	25 (14.1)	51 (15.5)
Unknown	14 (9.3)	16 (9)	30 (9.2)
Medical history,[a] n (%)			
Developmental delay/intellectual disability	76 (50.3)	91 (51.4)	167 (50.9)
Prior epilepsy	71 (47)	90 (50.8)	161 (49.1)
History of SE	26 (17.2)	36 (20.3)	62 (18.9)
History of cerebral palsy	13 (8.6)	18 (10.2)	31 (9.5)
No prior neurologic history	56 (37.1)	54 (30.5)	110 (33.5)
Etiology, n (%)			
Unknown	47 (31.1)	65 (36.7)	112 (34.1)
Structural	44 (29.1)	39 (22)	83 (25.3)
Genetic	24 (15.9)	38 (21.5)	62 (18.9)
Metabolic	11 (7.3)	4 (2.3)	15 (4.6)
Other	25 (16.6)	31 (17.5)	56 (17.1)
SE onset, n (%)			
Out of the hospital	105 (69.5)	117 (66.1)	222 (67.7)
In the hospital	46 (30.5)	60 (33.9)	106 (32.3)
Convulsive duration (n = 328), min	135 (60–275)	120 (60–286)	124.5 (60–281.5)
Length of ICU stay (n = 311), d	4.3 (2–11.9)	4 (1.7–11)	4 (2–11)
In-hospital mortality (n = 328), n (%)	5 (3.3)	6 (3.5)	11 (3.4)

Abbreviations: ASM = antiseizure medication; BZD = benzodiazepine; SE = status epilepticus.
Continuous variables are summarized as median (25th–75th percentiles); categorical variables are summarized as number and percentage.
[a] These conditions are not mutually exclusive; therefore, the percentages can sum to >100%.

zenodo). Among the 152 patients who received at least 1 continuous infusion, the median (p_{25}–p_{75}) time to the administration of the first continuous infusion was 173.5 (113.5–543.2) minutes. There was no statistically significant difference between the periods 2011 to 2014 and 2015 to 2019 (186 [124.2–571] vs 160 [89.5–495] minutes, p =

0.2236) (figure 1C), and it was not significant after adjustment for potential confounders (HR 1.08 [95% CI 0.77–1.51], $p = 0.6428$) (table e-3, available in GitHub at and zenodo).

Treatment within clinical recommendations and outliers

Forty-three percent, 27%, and 19% of patients received their first BZD beyond 20, 40, and 60 minutes from seizure onset, respectively. Seventy percent, 54%, and 29% of patients received their first non-BZD ASM beyond 40, 60, and 120 minutes from seizure onset, respectively. Eighty-nine percent, 70%, and 39% of patients received their first continuous infusion beyond 60, 120, and 240 minutes from seizure onset, respectively. These proportions were similar between the periods 2011 to 2014 and 2015 to 2019 (table 2).

Stratification by hospital onset

The proportion of patients receiving their first BZD, first non-BZD ASM, and first continuous infusion beyond recommended time lines and beyond outliers was high in both out-of-hospital onset and in-hospital onset SE and did not change in the period 2015 to 2019 compared with the period 2011 to 2014 (table 2). Among the 157 patients with out-of-hospital onset whose time to hospital arrival was available, 98 (62.4%) received at least 1 BZD before hospital arrival. This proportion increased after publication of evidence of delays (41 of 81 [50.6%] vs 57 of 76 [75%], absolute risk reduction 0.24, number needed to treat 4.1, $p = 0.0018$ [adjusted $p = 0.0036$]), and the odds ratio (OR) remained significant in multivariable logistic regression adjusting for potential confounders (confounders described in the Methods section) (OR 4.35 [95% CI 1.96–10.3], $p = 0.0005$ [adjusted $p = 0.0019$]). Among the 85 patients with a history of epilepsy whose rSE began out of hospital and whose information on time to hospital arrival was available, 56 (65.9%) received at least 1 BZD before hospital arrival. This proportion increased after publication of evidence of delays (23 of 43 [53.5%] vs 33 of 42 [78.6%], absolute risk reduction 0.25, number needed to treat 4.0, $p = 0.0217$ [adjusted $p = 0.0220$]), and the OR remained significant in multivariable logistic regression with adjustment for potential confounders (OR 3.97 [95% CI 1.28–13.99], $p = 0.0220$ [adjusted $p = 0.0220$]). There were no differences between the periods 2011 to 2014 and 2015 to 2019 in time to the first BZD, time to the first non-BZD ASM, and time to the first continuous infusion for out-of-hospital or in-hospital onset (table 3, figure 2, and appendix e-1, github.com/IvanSanchezFernandez/pSERGbeforeafter).

Sensitivity analyses

There was no difference in time to treatment between the periods (1) when considering the alternative periods 2011 to 2016 vs 2017 to 2019 rather than 2011 to 2014 vs 2015 to 2019; (2) when considering only hospitals that had patients enrolled since the initial years of pSERG, using the original periods 2011 to 2014 vs 2015 to 2019; and (3) when considering only hospitals that had patients enrolled since the

Figure 1 Kaplan-Meier curves comparing the periods 2011 to 2014 and 2015 to 2019 on time to the administration of the first class of each medication (BZD, non-BZD ASM, and CI)
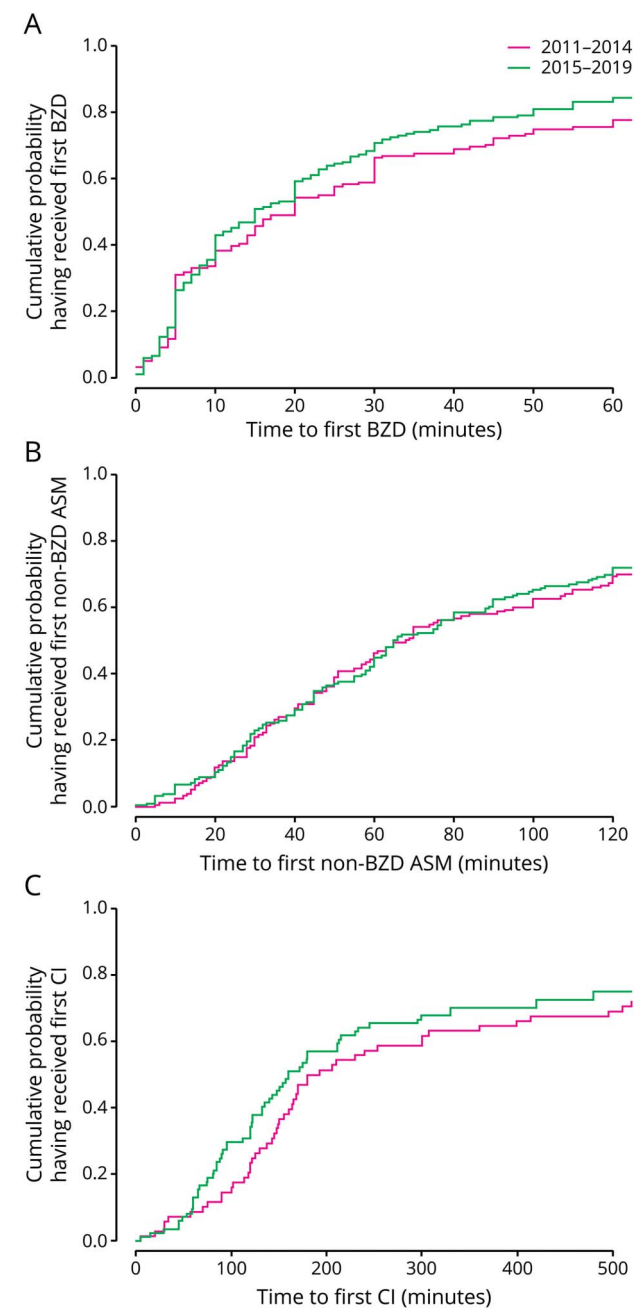
Time scales are truncated for different medications (time to first benzodiazepine [BZD] truncated at 60 minutes, time to first non-BZD antiseizure medication [ASM] truncated at 120 minutes, and time to first continuous infusion [CI] truncated at 500 minutes). (A) Cumulative probability of having received the first BZD. Time axis is truncated at 60 minutes. (B) Cumulative probability of having received the first non-BZD ASM. Time axis is truncated at 120 minutes. (C) Cumulative probability of having received the first CI (among those patients who received a CI). Time axis is truncated at 500 minutes.

initial years of pSERG, using the alternative periods 2011 to 2016 vs 2017 to 2019. These sensitivity analyses also confirmed that, among patients with out-of-hospital onset rSE,

Table 2 Proportion of patients receiving each class of medication beyond clinically relevant times

	Global proportion, n/N (%)	2011–2014, n/N (%)	2015–2019, n/N (%)	p Value (Fisher exact test)	RMST difference (95% confidence interval), min	p Value (RMST difference)
Total population						
First BZD >20 min	141/328 (43)	69/151 (45.7)	72/177 (40.7)	0.3728	−0.3 (−1.9 to 1.2)	0.665
First BZD >40 min	90/328 (27.4)	47/151 (31.1)	43/177 (24.3)	0.1743	−1.7 (−4.9 to 1.5)	0.286
First BZD >60 min	62/328 (18.9)	34/151 (22.5)	28/177 (15.8)	0.1568	−2.9 (−7.5 to 1.7)	0.214
First non-BZD ASM >40 min	231/328 (70.4)	106/151 (70.2)	125/177 (70.6)	1	−0.8 (−2.6 to 1.1)	0.421
First non-BZD ASM >60 min	178/328 (54.3)	81/151 (53.6)	97/177 (54.8)	0.9115	−0.6 (−4 to 2.8)	0.722
First non-BZD ASM >120 min	95/328 (29)	46/151 (30.5)	49/177 (27.7)	0.6258	−2.1 (−10.1 to 5.9)	0.607
First CI >60 min	135/152 (88.8)	62/68 (91.2)	73/84 (86.9)	0.4493	0.6 (−2.4 to 3.6)	0.698
First CI >120 min	107/152 (70.4)	52/68 (76.5)	55/84 (65.5)	0.1562	−5.4 (−14.2 to 3.3)	0.222
First CI >240 min	59/152 (38.8)	29/68 (42.6)	30/84 (35.7)	0.4067	−12.7 (−35.8 to 10.4)	0.282
Out of hospital onset						
First BZD >20 min	107/222 (48.2)	55/105 (52.4)	52/117 (44.4)	0.2821	−0.6 (−2.3 to 1.2)	0.537
First BZD >40 min	71/222 (32)	37/105 (35.2)	34/117 (29.1)	0.3874	−1.9 (−5.8 to 2)	0.332
First BZD >60 min	47/222 (21.2)	26/105 (24.8)	21/117 (17.9)	0.2505	−2.8 (−8.6 to 3)	0.338
First non-BZD ASM >40 min	178/222 (80.2)	82/105 (78.1)	96/117 (82.1)	0.5025	−0.3 (−2.1 to 1.6)	0.797
First non-BZD ASM >60 min	142/222 (64)	65/105 (61.9)	77/117 (65.8)	0.5773	0.9 (−2.7 to 4.5)	0.623
First non-BZD ASM >120 min	78/222 (35.1)	39/105 (37.1)	39/117 (33.3)	0.5757	0.3 (−9.3 to 9.8)	0.956
First CI >60 min	90/101 (89.1)	42/45 (93.3)	48/56 (85.7)	0.3373	−0.4 (−2.7 to 1.9)	0.733
First CI >120 min	73/101 (72.3)	35/45 (77.8)	38/56 (67.9)	0.3714	−5.4 (−14.8 to 4.1)	0.263
First CI >240 min	41/101 (40.6)	19/45 (42.2)	22/56 (39.3	0.8395	−6 (−32.8 to 20.8)	0.659
In hospital onset						
First BZD >20 min	34/106 (32.1)	14/46 (30.4)	20/60 (33.3)	0.835	−0.1 (−2.9 to 2.7)	0.953
First BZD >40 min	19/106 (17.9)	10/46 (21.7)	9/60 (15)	0.4467	−1.5 (−6.8 to 3.8)	0.574
First BZD >60 min	15/106 (14.2)	8/46 (17.4)	7/60 (11.7)	0.4158	−3.2 (−10.6 to 4.2)	0.400
First non-BZD ASM >40 min	53/106 (50)	24/46 (52.2)	29/60 (48.3)	0.8448	−1.6 (−5.5 to 2.2)	0.410
First non-BZD ASM >60 min	36/106 (34)	16/46 (34.8)	20/60 (33.3)	1	−3.6 (−10.3 to 3.1)	0.292
First non-BZD ASM >120 min	17/106 (16)	7/46 (15.2)	10/60 (16.7)	1	−6.3 (−20.1 to 7.4)	0.365
First CI >60 min	45/51 (88.2)	20/23 (87)	25/28 (89.3)	1	2.9 (−3.9 to 9.7)	0.410
First CI >120 min	34/51 (66.7)	17/23 (73.9)	17/28 (60.7)	0.381	−2.8 (−19.3 to 13.7)	0.739
First CI >240 min	18/51 (35.3)	10/23 (43.5)	8/28 (28.6)	0.3784	−23.4 (−64.1 to 17.4)	0.260

Abbreviations: ASM = antiseizure medication; BZD = benzodiazepine; CI = continuous infusion; RMST = restricted mean survival time.

the proportion of patients who received at least 1 BZD before hospital arrival increased after publication of evidence on delays (table e-4 and appendix e-1, available in GitHub at github.com/IvanSanchezFernandez/pSERGbeforeafter and in zenodo at zenodo.org/badge/latestdoi/230197648 and ivansanchezfernandez.github.io/pSERGbeforeafter_Filee1/).

Discussion

This study demonstrates that, in major pediatric hospitals, publication of evidence showing a gap in clinical practice (delayed treatment in rSE) was not associated with an improvement in clinical practice (sustained reduction in time to treatment for any of the management steps). It was associated, however, with a clinically meaningful improvement: the increase in the proportion of patients with out-of-hospital rSE onset who received at least 1 BZD before hospital arrival. This improvement is probably related to better education of caregivers about seizure action plans, a step that is largely dependent on epileptologists and pediatric neurologists. In turn, the failure of improving time to treatment probably reflects the lack of an implementation policy that includes dissemination of evidence among all stakeholders, modification of standardized treatment plans to emphasize time to treatment, and implementation by multidisciplinary teams.

pSERG is a large multicenter study that includes major pediatric hospitals in the United States and Canada. Evaluation of time to treatment was an open research question within pSERG in the years 2011 to 2014. Existing literature at the time suggested that treatment delay was common in both children and adults with SE, but evidence was sparse and limited to the first treatment steps.[38] A retrospective study in 625 adults and 264 children with SE in the 1989 to 1994 period in Virginia showed that the first ASM (BZD or non-BZD ASM) was given within 30 minutes of seizure onset in only 42% of cases.[39] Similarly, a study of 542 episodes of pediatric SE in the period 2000 to 2004 in Australia and New Zealand showed that the median ($p_{25}–p_{75}$) time from hospital arrival to administration of a non-BZD ASM was 24 (15–36) minutes.[40] In a study of 263 clinical SE episodes in 225 adult patients in the 2008 to 2011 period in Switzerland showed that initial treatment was delayed for >1 hour in 139 (62%) of patients, including 54 patients with generalized convulsive SE.[41] By the end of 2014, pSERG had collected data that demonstrated delays at every treatment step, and all pSERG members were aware of these delays.[22] Therefore, we compared the periods 2011 to 2014 and 2015 to 2019. Our results remained robust to the alternative comparison of periods 2011 to 2016 and 2017 to 2019 when the evidence for delays was even stronger.[24] Our results were also robust when considering only the hospitals that formed pSERG initially. Our main results remained robust to these sensitivity analyses and together show no major improvements in time to treatment within pSERG after publication of evidence of delays in time to treatment.

Unfortunately, the publication of evidence, even in major scientific journals, is not necessarily sufficient to modify clinical practice.[42,43] The major stakeholders to reduce time to treatment in SE are the primary caregivers, emergency medical services, emergency department clinicians, general pediatrics and internal medicine clinicians, and adult and child neurologists and epileptologists. Most epileptologists and adult and child neurologists are aware of the importance of early treatment but typically are not the initial responders to prolonged seizures. SE treatment is often initiated by primary caregivers, emergency medical services personnel, and

Table 3 Comparison of time to treatment before and after awareness of marked delays in treatment administration for SE

	2011–2014	2015–2019	Univariate analysis	Multivariate analysis, HR (95% confidence interval)
SE onset out of the hospital (n = 222), n	105	117		
Time to the first BZD (n = 222), min	25 (7–60)	20 (7–50)	0.2606	1.06 (0.81–1.39), p = 0.6829
Time to the first non-BZD ASM (n = 222), min	82 (45–190)	80 (55–153)	0.9441	1.02 (0.78–1.35), p = 0.877
Time to the first continuous infusion (n = 101), min	180 (137–660)	166 (86.5–586.5)	0.3165	1.27 (0.82–1.97), p = 0.279
SE onset in the hospital (n = 106), n	46	60		
Time to the first BZD (n = 106), min	8 (4.3–25.8)	9.5 (5–24)	0.6778	1 (0.67–1.52), p = 0.974
Time to the first non-BZD ASM (n = 106), min	44.5 (20.3–86.8)	36 (23–79.8)	0.8215	1.12 (0.74–1.7), p = 0.5938
Time to the first continuous infusion (n = 51), min	210 (121–462)	147.5 (90.8–420)	0.4022	1.14 (0.6–2.16), p = 0.684

Abbreviations: ASM = antiseizure medication; BZD = benzodiazepine; HR = hazard ratio; SE = status epilepticus.

Figure 2 Kaplan-Meier curves comparing the periods 2011 to 2014 and 2015 to 2019 on time to the administration of the first class of each medication (BZD, non-BZD ASM, and CI) stratified by onset out of the hospital (left) or in the hospital (right)
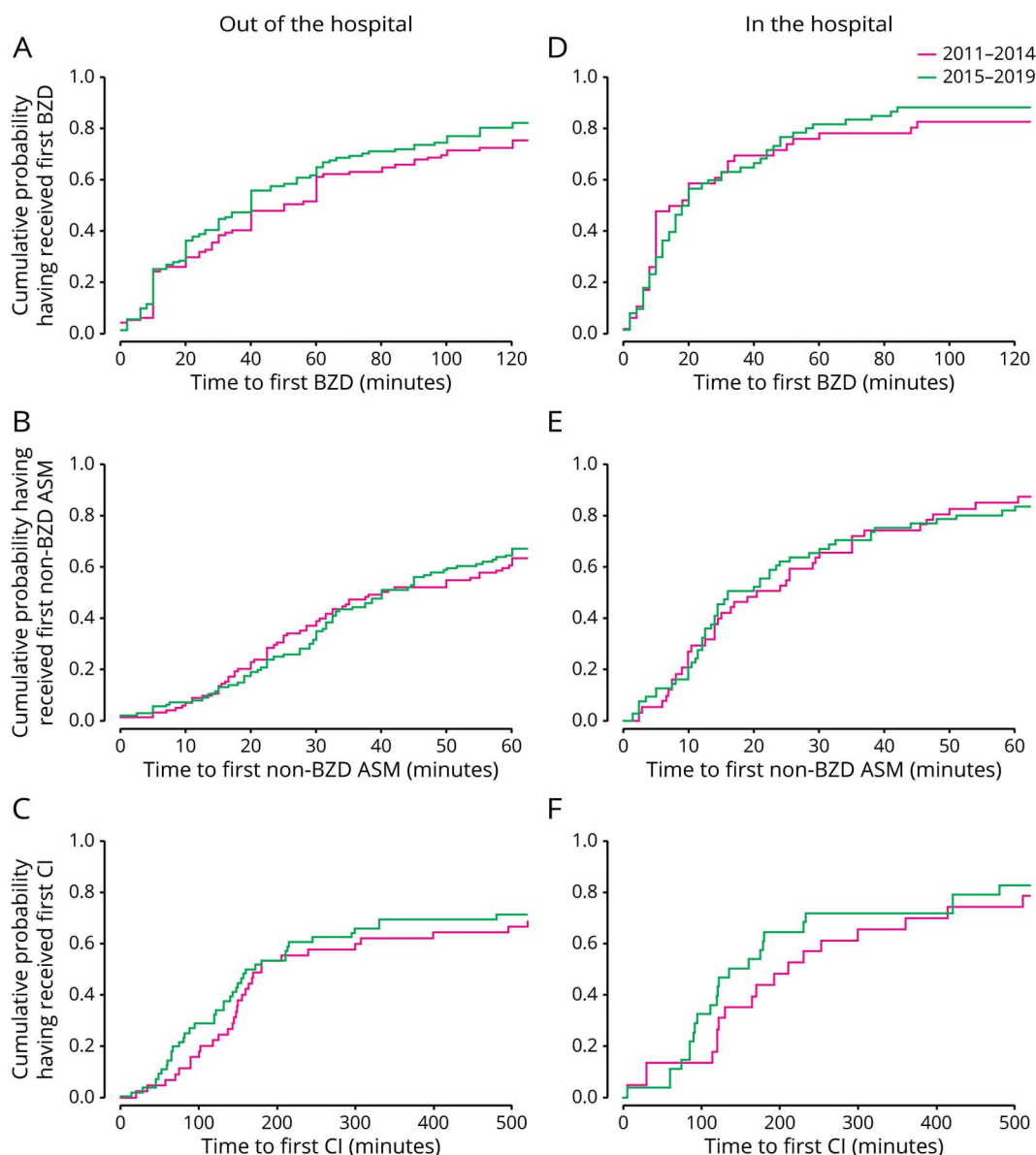
Time scales are truncated for different medications (time to first benzodiazepine [BZD] truncated at 60 minutes, time to first non-BZD antiseizure medication [ASM] truncated at 120 minutes, and time to first continuous infusion [CI] truncated at 500 minutes). (A) Cumulative probability of having received the first BZD in patients with refractory convulsive status epilepticus (rSE) onset out of the hospital. Time axis is truncated at 60 minutes. (B) Cumulative probability of having received the first non-BZD ASM in patients with rSE onset out of the hospital. Time axis is truncated at 120 minutes. (C) Cumulative probability of having received the first CI (among those patients who received a CI) in patients with rSE onset out of the hospital. Time axis is truncated at 500 minutes. (D) Cumulative probability of having received the first BZD in patients with rSE onset in the hospital. Time axis is truncated at 60 minutes. (E) Cumulative probability of having received the first non-BZD ASM in patients with rSE onset in the hospital. Time axis is truncated at 120 minutes. (F) Cumulative probability of having received the first CI (among those patients who received a CI) in patients with rSE onset in the hospital. Time axis is truncated at 500 minutes.

emergency department physicians, typically in community hospitals, who may not receive as much training in the importance of time to treatment of SE as in large academic centers. Neurologists and epileptologists need to continue to ensure a timely treatment when directly caring for a patient with active SE, but they may also improve time to treatment by acting as knowledge brokers who transfer the importance of a timely treatment to all initial responders. Educating primary caregivers about individualized seizure action plans and simulating likely SE treatment scenarios to make primary caregivers comfortable administering rescue medications may improve the timeliness and efficacy of the treatment of SE. This transfer of knowledge can occur during routine epilepsy clinic visits; local, regional, and national education; and meetings, directly or through dedicated nursing teams. Support of these education efforts by hospital administrators and

leadership and recognition by payers are crucial, as are education of and acceptance by patients and caregivers, because implementation ultimately remains a shared responsibility.

We observed a clinical relevant improvement in the proportion of patients who received at least 1 BZD before hospital arrival, although this may reflect the growing body of literature suggesting room for improvement in the proportion of caregivers trained in administration of rescue medications for prolonged seizures[44] and in the proportion of patients not treated before hospital arrival.[22] In either case, if the observed improvement is the result of epileptologists and pediatric neurologists better educating families on seizure action plans, it provides a model to educate all the caregivers in the SE treatment chain. Another potential source of delays is that some systemic factors are beyond the control of clinicians. For example, emergency medical services may not be allowed to administer BZD and non-BZD ASM in the out-of-hospital setting, and once in the hospital, the period from ASM order to ASM arrival to the bedside may be long and beyond clinicians' control, likely requiring further education and dissemination efforts, as well as systematic improvements and policy changes. Despite isolated quality improvement projects, there have not been general policies within pSERG hospitals to formally disseminate information on delays in time to treatment of SE to personnel working in emergency medical services, emergency departments, general pediatrics, pharmacy, nursing, or the ICU. If knowledge is not widely disseminated, improvement based on that knowledge is unlikely to be as large as it could be. Although numbers are not large enough to study each center individually, we did not find any center with improved times after publication of evidence. The time lag from the discovery of a new research finding to its implementation into medical practice varies widely, depending on the research finding, but typically takes several years.[43] Slow tendencies toward improvement may not have been captured in this study, which spans less than a decade. In addition, a tendency for improvement may have been compensated by patients with better treatments not progressing into rSE and therefore not meeting our inclusion and exclusion criteria. Although possible, this is unlikely because we have not seen improvement even in the time to the first BZD. There have been no national or consortium-related formal mechanisms to translate research knowledge into policy changes, and work is in progress to secure funding for further implementation efforts and to amend this crucial aspect. Therefore, the transfer of knowledge between pSERG child neurologists and other stakeholders in hospitals, referring emergency department networks, and the policy changes implemented in the pSERG hospitals have been variable, in part also due to lack of overarching guideline and government input, delay of implementation of clinical findings into health care policies on a regional and national level, and further delays in implementation and monitoring of updated policies. Formal quality improvement projects can improve the efficiency and timeliness of treatment administration. A quality improvement study on the timely detection and treatment of electrographic seizures in the ICU reduced the time from seizure onset to medication administration by half and improved the percentage of seizure termination after the first ASM from 67% to 27%.[18] Its multidisciplinary approach involving all stakeholders and streamlining protocols may be a model to follow in convulsive SE.[18] A quality improvement project on the treatment of convulsive SE reduced the median time to the second-line ASM by half.[19] In a pSERG tertiary care pediatric hospital, implementation of process improvements developed through quality improvement and statistical process control methodology doubled the proportion of patients receiving a first BZD within 10 minutes, thereby resulting in decreases in morbidity, transfer to the ICU, and costs.[20] This study did not only show that multidisciplinary quality improvement projects may reduce time to treatment, but it also showed the magnitude of the downstream consequences: need for ICU transfer was reduced from 39% to 9% of SE cases, reducing hospital charges by $2.1 million in a single hospital. These data highlight the need for pSERG-wide multidisciplinary, systems-focused approaches that include streamlining of communication; formal dissemination of the research findings on the importance of a timely treatment to all stakeholders; policy changes to streamline drug delivery; a standardized education of caregivers, emergency medical services, and emergency room personnel about specific steps to treat SE in a timely manner to avoid unnecessary delays and redundant interventions (table 4); and ultimately financial motivation for payers and health care systems to implement care improvements. Publication of evidence is a first step that may or may not improve practice.[42] Lack of improvement in clinical practice after publication of evidence on a gap in practice may reflect the lack of policy changes to implement this knowledge. Epileptologists and pediatric neurologists who participated in the pSERG research studies became aware of the results. This may have contributed to the improvement in seizure action plans. Yet, there have been no pSERG-wide, regional, or national policy changes to formally disseminate knowledge on delays in time to treatment of SE to all stakeholders, work to emphasize timeliness in treatment protocols, and audit change. Quality improvement methodology does not merely rely on passive diffusion of evidence but adopts the scientific method to, through multiple cycles, identify and implement the strategies that lead to the desired goal of improved practice.[45,46]

Comparing times to treatment between periods within individual centers was not feasible with the current numbers, although descriptive data showed no improvement in any center. Our sample included patients with rSE and is not necessarily representative of all children with SE. Although pSERG collects cases with nonrefractory SE, this collection began on October 2014 and, therefore, we cannot compare time to treatment before and after publication of evidence of delays in this population. Selection bias resulting from having studied only rSE may limit the generalizability of results, but it would not be expected that time to treatment would have improved only in nonrefractory SE. Members of pSERG are

Table 4 Steps to improve time to treatment

Potential barriers to timely treatment	Proposed actions
Limited awareness of the importance of a timely and well-dosed treatment of SE to improve short-term outcomes	Neurologists and epileptologists act as knowledge brokers disseminating research findings to all involved stakeholders.
Delayed recognition of seizure by caregivers and teachers Delayed recognition of seizures during sleep	Increase general awareness through education of general public and targeted groups (e.g., teachers, day care providers, etc). Provide monitoring devices.
Limited access to rescue medications and proper seizure action plans for patients with epilepsy	Improve seizure action plan education. Develop dedicated nursing teams that simulate likely seizure action plan scenarios for each family in each epilepsy clinic visit.
Low proportion of patients with SE treatment by EMS	Modify regulations to allow EMS to administer appropriate medications in the appropriate circumstances. Educate policy makers and EMS about the importance of a timely treatment.
Delayed, reduced, or redundant ASM treatment in community emergency departments related to low volume of pediatric patients	Increase collaborations with academic children's hospitals and community hospitals referring patients. Provide training modules with emergency department professionals. Educate primary caregivers, EMS, and emergency department personnel about the importance of an appropriate dosage of rescue medications.
Delayed, reduced, or redundant ASM treatment in academic center emergency departments related to provider experience or logistical barriers	Create pathways standardizing care for SE. Train and retrain staff on current recommendations. Provide training modules with emergency department professionals. Develop multidisciplinary teams with the goal of identifying and modifying barriers to ASM ordering, acquisition, and administration. Re-engineer systems to streamline access to rescue medication in the acute treatment of SE.
Delayed or reduced ASM treatment in the ICU	Create pathways standardizing care for SE. Provide training modules with ICU professionals. Establish EEG monitoring expectations. Establish communication flow from initial point of epileptologist to endpoint of bedside caregivers.

Abbreviations: ASM = antiseizure medication; EMS = emergency medical services; ICU = intensive care unit; SE = status epilepticus.

fully aware of marked delays in time to treatment of SE because they all participated in prior pSERG studies and literature review; however, the degree to which physicians in other specialties (e.g., emergency medicine, general pediatrics, critical care medicine) are aware of the delayed time to SE treatment and the association between treatment times and outcomes is unknown.[8–12] We also are not sure to what extent delayed treatment depends on clinicians prescribing it late vs clinicians prescribing it soon but medication administration being delayed by systemic factors beyond clinician control that hinder expeditious administration of medication. Times were assessed based on caregiver and emergency medical services information for out-of-hospital onset and from health care personnel information and hospital records once in the hospital. Information was cross-referenced with caregivers, emergency medical services, nurses, and medication administration records when available to minimize potential information and recall bias. Other studies on the treatment of SE active during this period, such as the SAGE 547 trial for super-refractory SE[47] and the established SE treatment trial,[48] did not focus on time to treatment and are unlikely to have confounded the perception of treatment delays.

In a large multicenter consortium of leading pediatric hospitals, publication of evidence on delays in treatment of rSE among epileptologists and child neurologists did not translate into improvements in time to treatment, although it was associated with an increase in the proportion of patients who received at least 1 BZD before hospital arrival. Because little change has occurred, pSERG will implement interventions to increase public awareness and multidisciplinary care plans to improve time to treatment.

Study funding

Disclosure

Publication history

Appendix 1 Authors

Name	Location	Contribution
Iván Sánchez Fernández, MD, MPH, MBI	Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA	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
Nicholas S. Abend, MD, MSCE	Division of Neurology, Departments of Neurology and Pediatrics, Children's Hospital of Philadelphia and University of Pennsylvania, Philadelphia, PA	Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination
Marta Amengual-Gual, MD	Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA	Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination
Anne Anderson, MD	Section of Pediatric Critical Care Medicine, Department of Pediatrics, Baylor College of Medicine, Houston, TX	Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination
Ravindra Arya, MD, DM	Division of Neurology, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, OH	Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination
Cristina Barcia Aguilar, MD	Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA	Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination
James Nicholas Brenton, MD	University of Virginia Health, Charlottesville, VA	Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination

Name	Location	Contribution
Jessica L. Carpenter, MD	Center for Neuroscience, Children's National Medical Center, George Washington University School of Medicine and Health Sciences, Washington, DC	Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination
Kevin E. Chapman, MD	Departments of Pediatrics and Neurology, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, CO	Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination
Justice Clark, MPH	Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA	Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination
Raquel Farias-Moeller, MD	Department of Pediatric Neurology, Children's Hospital of Wisconsin, Medical College of Wisconsin, Milwaukee, WI	Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination
William D. Gaillard, MD	Center for Neuroscience, Children's National Medical Center, George Washington University School of Medicine and Health Sciences, Washington, DC	Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination
Marina Gaínza-Lein, MD	Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA	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
Tracy Glauser, MD	Division of Neurology, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, OH	Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination
Joshua Goldstein, MD	Ruth D. & Ken M. Davee Pediatric Neurocritical Care Program, Northwestern University Feinberg School of Medicine, Chicago, IL	Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination

Name	Location	Contribution
Howard P. Goodkin, MD, PhD	University of Virginia Health, Charlottesville, VA	Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination
Réjean M. Guerriero, DO	Division of Pediatric and Developmental Neurology, Departments of Neurology, Washington University School of Medicine, St. Louis, MO	Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination
Yi-Chen Lai, MD	Section of Pediatric Critical Care Medicine, Department of Pediatrics, Baylor College of Medicine, Houston, TX	Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination
Tiffani McDonough, MD	Ruth D. & Ken M. Davee Pediatric Neurocritical Care Program, Northwestern University Feinberg School of Medicine, Chicago, IL	Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination
Mohamad A. Mikati, MD	Division of Pediatric Neurology, Duke University Medical Center, Duke University, Durham, NC	Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination
Lindsey A. Morgan, MD	Department of Pediatrics and Neurology, Seattle Children's Hospital, University of Washington and Center for Integrative Brain Research, Seattle Children's Research Institute, Seattle, WA	Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination
Edward Novotny, Jr., MD	Department of Pediatrics and Neurology, Seattle Children's Hospital, University of Washington and Center for Integrative Brain Research, Seattle Children's Research Institute, Seattle, WA	Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination
Eric Payne, MD, MPH	Department of Neurology, Mayo Clinic, Mayo Clinic School of Medicine, Rochester, MN	Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination

Continued

Appendix 1 *(continued)*

Name	Location	Contribution
Katrina Peariso, MD, PhD	Division of Neurology, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, OH	Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination
Juan Piantino, MD	Department of Neurology, Doernbercher Children's Hospital, Oregon Health & Science University, Portland, OR	Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination
Adam Ostendorf, MD	Department of Neurology, Nationwide Children's Hospital, Ohio State University, Columbus, OH	Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination
Tristan T. Sands, MD, PhD	Division of Child Neurology & Institute for Genomic Medicine, Columbia University Irving Medical Center, New York Presbyterian Hospital, New York, NY	Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination
Kumar Sannagowdara, MD	Department of Pediatric Neurology, Children's Hospital of Wisconsin, Medical College of Wisconsin, Milwaukee, WI	Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination
Robert C. Tasker, MBBS, MD	Department of Neurology, Department of Anesthesiology, Critical Care and Pain Medicine, Boston Children's Hospital, Harvard Medical School, Boston, MA	Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination
Dimtry Tchapyjnikov, MD	Division of Pediatric Neurology, Duke University Medical Center, Duke University, Durham, NC	Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination
Alexis A. Topjian, MD, MSCE	Division of Critical Care Medicine, The Children's Hospital of Philadelphia, The Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA	Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination
Alejandra Vasquez, MD	Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA	Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination

Appendix 1 *(continued)*

Name	Location	Contribution
Mark S. Wainwright, MD, PhD	Departments of Pediatrics and Neurology, Seattle Children's Hospital, University of Washington, and Center for Integrative Brain Research, Seattle Children's Research Institute, Seattle, WA	Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination
Angus Wilfong, MD	Barrow Neurologic Institute, Phoenix Children's Hospital, and Department of Pediatrics, University of Arizona School of Medicine, Phoenix, AZ	Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination
Kowryn Williams, MD, PhD	Barrow Neurologic Institute, Phoenix Children's Hospital, and Department of Pediatrics, University of Arizona School of Medicine, Phoenix, AZ	Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination
Tobias Loddenkemper, MD	Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA	Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination

Appendix 2 Coinvestigators

Coinvestigators are listed at lww.com/WNL/B156

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