RESEARCH ARTICLE

Early Clinical Variables Associated With Refractory Convulsive Status Epilepticus in Children

Katrina Peariso, MD, PhD, Ravindra Arya, MD, DM, Tracy Glauser, MD, Nicholas S. Abend, MD, MSCE, Cristina Barcia Aguilar, MD, Marta Amengual-Gual, MD, Anne Anderson, MD, Brian L. Appavu, MD, J. Nicholas Brenton, MD, Jessica Carpenter, MD, Kevin E. Chapman, MD, Justice Clark, MPH, William D. Gaillard, MD, Marina Gaínza-Lein, MD, Joshua Goldstein, MD, Howard Goodkin, MD, PhD, Zachary Grinspan, MD, Rejean M. Guerriero, DO, Paul S. Horn, PhD, Linda Huh, MD, Robert Kahoud, MD, Sarah A. Kelley, MD, Eric H. Kossoff, MD, Kush Kapur, PhD, Yi-Chen Lai, MD, B. Oyinkan Marquis, MD, Tiffani McDonough, MD, Mohamad A. Mikati, MD, Lindsey Morgan, MD, Edward Novotny, MD, Adam P. Ostendorf, MD, Eric T. Payne, MD, Juan Piantino, MD, James Riviello, MD, Tristan Sands, MD, PhD, Carl E. Stafstrom, MD, PhD, Robert C. Tasker, MD, MBBS, Dmitry Tchapyjnikov, MD, Alejandra Vasquez, MD, Mark S. Wainwright, MD, PhD, Angus Wilfong, MD, Korwyn Williams, MD, PhD, and Tobias Loddenkemper, MD, for Pediatric Status Epilepticus Research Group (pSERG)

Correspondence
Dr. Peariso
peariska@ucmail.uc.edu

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Abstract

Background and Objectives

The objective of this study was to determine patient-specific factors known proximate to the presentation to emergency care associated with the development of refractory convulsive status epilepticus (RSE) in children.

Methods

An observational case-control study was conducted comparing pediatric patients (1 month–21 years) with convulsive SE whose seizures stopped after benzodiazepine (BZD) and a single second-line antiseizure medication (ASM) (responsive established status epilepticus [rESE]) with patients requiring more than a BZD and a single second-line ASM to stop their seizures (RSE). These subpopulations were obtained from the pediatric Status Epilepticus Research Group study cohort. We explored clinical variables that could be acquired early after presentation to emergency medical services with univariate analysis of the raw data. Variables with $p < 0.1$ were retained for univariable and multivariable regression analyses. Multivariable logistic regression models were fit to age-matched and sex-matched data to obtain variables associated with RSE.

Results

We compared data from a total of 595 episodes of pediatric SE. Univariate analysis demonstrated no differences in time to the first BZD (RSE 16 minutes [IQR 5–45]; rESE 18 minutes [IQR 6–44], $p = 0.068$). Time to second-line ASM was shorter in patients with

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From the Department of Neurology and Physical Medicine and Rehabilitation (K.P.), University of Cincinnati College of Medicine, OH; Division of Pediatric Neurology (R.A., T.G., P.S.H.), Department of Pediatrics, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, OH; Division of Neurology (N.S.A.), The Children's Hospital of Philadelphia, The Perelman School of Medicine at the University of Pennsylvania; Division of Epilepsy and Clinical Neurophysiology (C.B.A., Justice Clark, M.G.-L., K.K., T.L.), Department of Neurology, Boston Children's Hospital, Harvard Medical School, MA; Department of Child Neurology (CBA), Hospital Universitario La Paz, Universidad Autonoma de Madrid, Spain; Pediatric Neurology Unit (M.A.-G.), Department of Pediatrics, Hospital Universitari Son Espases, Universitat de Les Illes Balears, Palma, Spain; Section of Neurology and Developmental Neuroscience (A.A., J.R.), Department of Pediatrics, Baylor College of Medicine, Houston, TX; Department of Pediatrics (B.L.A., K.E.C., A.W., K.W.), University of Arizona College of Medicine and Barrow's Neurological Institute at Phoenix Children's Hospital; Department of Neurology and Pediatrics (J.N.B., H.G.), University of Virginia Health System, Charlottesville; Division of Pediatric Neurology (Jessica Carpenter), University of Maryland School of Medicine, Baltimore; Center for Neuroscience (W.D.G.), Children's National Hospital, George Washington University School of Medicine and Health Sciences, DC; Instituto de Pediatría (M.G.-L.), Facultad de Medicina, Universidad Austral de Chile, Valdivia; 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.), Northwestern University Feinberg School of Medicine, Chicago, IL; Division of Pediatric Neurology and Epilepsy (Z.G., B.O.M.), Department of Pediatrics, Weill Cornell Medicine, New York; Division of Pediatric and Developmental Neurology (R.M.G.), Washington University School of Medicine, St. Louis, MO; Department of Pediatrics (L.H.), British Columbia Children's Hospital, the University of British Columbia, Canada; Division of Child and Adolescent Neurology (R.K., A.V.-A.), Department of Neurology, Mayo Clinic, Rochester, MN; Division of Pediatric Neurology (S.A.K., E.H.K., C.E.S.), Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD; Section of Pediatric Critical Care Medicine (Y.-C.L.), Department of Pediatrics, Baylor College of Medicine, Houston, TX; Department of Pediatrics (T.M.), Division of Neurology and Epilepsy, Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, IL; Division of Pediatric Neurology (M.A.M., D.T.), Duke University Medical Center, Duke University, Durham, NC; Department of Neurology (L.M., E.N., M.S.W.), Division of Child Neurology, Seattle Children's Hospital, WA; Department of Pediatrics (A.P.O.), Nationwide Children's Hospital, The Ohio State University, Columbus; Division of Neurology (E.T.P.), Department of Pediatrics, Alberta Children's Hospital, Calgary, Canada; Division of Neurology (J.P.), Doernbecher Children's Hospital, Oregon Health & Science University, Portland; Division of Child Neurology & Institute for Genomic Medicine (T.S.), Columbia University Irving Medical Center, New York Presbyterian Hospital; and Department of Anesthesiology (R.C.T.), Critical Care and Pain Medicine, Boston Children's Hospital, Harvard Medical School, MA.

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Coinvestigators are listed at links.lww.com/WNL/C888.

Glossary

ASM = antiseizure medication; **BZD** = benzodiazepine; **ESETT** = Established SE Treatment Trial; **IQR** = interquartile range; **pSERG** = Previous work from the pediatric SE Research Group; **rESE** = responsive established SE; **RSE** = refractory SE; **SE** = status epilepticus.

RSE (RSE 65 minutes; rESE 70 minutes; $p = 0.021$). Both univariable and multivariable regression analyses revealed a family history of seizures (OR 0.37; 95% CI 0.20–0.70, $p = 0.0022$) or a prescription for rectal diazepam (OR 0.21; 95% CI 0.078–0.53, $p = 0.0012$) was associated with decreased odds of RSE.

Discussion

Time to initial BZD or second-line ASM was not associated with progression to RSE in our cohort of patients with rESE. A family history of seizures and a prescription for rectal diazepam were associated with a decreased likelihood of progression to RSE. Early attainment of these variables may help care for pediatric rESE in a more patient-tailored manner.

Classification of Evidence

This study provides Class II evidence that patient and clinical factors may predict RSE in children with convulsive seizures.

Pediatric status epilepticus (SE) is a common and life-threatening neurologic emergency, occurring in 3–42 per 100,000 children per year, with 12%–40% of all cases being refractory to treatment with 2 appropriate antiseizure medications (ASMs), for example, benzodiazepine (BZD) and a second-line ASM.[1,2] While multiple studies have shown that etiology is the most consistent factor associated with the severity of the condition and patient outcomes,[3-7] the etiology is not always apparent on presentation.[8,9] Previous work from the pediatric SE Research Group (pSERG) and others has demonstrated that, in cohorts of patients with refractory SE (RSE), prolonged time to treatment with a BZD and second-line ASM, which then increases the duration of subsequent escalation of treatment, were associated with the duration of SE.[10,11] Unfortunately, such delays in treatment are common, but most patients do not proceed to develop RSE.[1,12] Sparing these patients with responsive established SE (rESE) from unnecessary escalation of therapy is also an important goal because the treatment of RSE frequently involves prolonged administration of intravenous anesthetics, which has been suggested to be an independent contributor to poor outcomes after SE.[13,14] Recent publication of the Established SE Treatment Trial (ESETT) has demonstrated that cessation of BZD-refractory SE, and thus prevention of progression to RSE, was not influenced by the primary mechanism of the second-line ASM.[15,16] Therefore, we hypothesized that there are alternative patient-related and seizure-related variables available during the acute treatment of children presenting with SE that may identify those at greater risk of progression to RSE. This study seeks to answer whether specific patient or clinical factors that would be known early after presentation to emergency medical care were associated with an increased likelihood of developing RSE.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

Approval for conduct of this research was obtained from each institutional review board. Written informed consent was obtained from the parents or guardians of each patient in addition to written assent from the patient where applicable.

Data from June 2011 to April 2019 were extracted from the multicenter pSERG consortium, a large network of 21 pediatric hospitals in North America. Common inclusion criteria for our cohort with convulsive rESE and convulsive RSE were as follows: (1) age 1 month to 21 years; (2) convulsive seizures at onset; (3) application of 2 or more ASMs for convulsive seizures, and (4) consent obtained. We did not enroll patients with the following characteristics: (1) nonconvulsive SE detected on EEG (without convulsive seizures at onset); (2) nonconvulsive SE and infrequent myoclonic jerks; and (3) inability to obtain consent/assent. Data regarding the patient's demographic information, medical history, and the episode of SE were obtained through an interview with the parent or primary caregiver during enrollment and chart review. While each site endeavored to enroll all patients meeting the common inclusion criteria, this was not always possible secondary to study staffing constraints, particularly for the patients in the rESE group because they generally had a much shorter hospital length of stay. Data were stored in a central database at Cincinnati Children's Hospital. Data were acquired according to detailed data dictionaries with overview by site investigators and central data re-review for quality ascertainment in case of disagreement by the consortium steering committee, consortium coordinator, and consortium PI.

Enrolled patients were divided into 2 groups: (1) cases with rESE were defined as patients whose SE was aborted with the administration of BZD and a second-line ASM and (2) cases with RSE were defined as those whose SE did not respond to a BZD and a second-line ASM and went on to require additional bolus doses of ASMs or a continuous infusion of anesthetic(s). To avoid bias, only the first presentation of SE for an individual patient during this study period was used, resulting in 595 unique patient episodes of SE included in the analysis.

We assessed the following variables: age, sex, semiology of the SE (sustained convulsive vs intermittent convulsions without return to baseline in between), medical history (epilepsy, developmental delay, and cerebral palsy), first-degree and second-degree family history of seizures (e.g., epilepsy, febrile seizures, etc.), potentially associated etiologies (structural, genetic, metabolic, and other/unknown), inpatient vs outpatient onset, time to treatment with first-line BZD, time to treatment with second-line ASM, and head CT scan results on arrival (SE onset in the case of inpatients) because these clinical and historical variables would be available to the clinician (through electronic medical record and brief caregiver interview) during the initial evaluation of the patient.

Statistical Analysis

Data were first examined for consistency using frequencies for categorical variables and kernel density plots for continuous variables. Univariate relationships between groups (RSE vs rESE) were examined with Fisher exact tests and *t* tests for independent samples for categorical and continuous variables, respectively.

Data were analyzed using a multivariable logistic regression model where refractoriness of SE (RSE vs rESE) was the response. Clinical variables from the univariable logistic regressions with $p < 0.1$ were included, along with their first-order interactions, in the multivariable model. The model was run on the full dataset with the selected variables to include as many observations as possible. We used backward elimination to provide a more parsimonious model. Variables with $p \leq 0.05$ (or interaction terms ≤ 0.05) were retained in the model. The model was rerun on the full dataset with the selected variables to include as many observations as possible. For the full model with all covariates, 156 observations were excluded because of missing values. This number was reduced to 64 observations with the selected covariates. The statistical significance of the covariates was similar for the 2 models. The latter model that omitted only 64 observations was used in this analysis.

For comparison, the age-matched and sex-matched data were also analyzed using a propensity score analysis. A propensity score based on age (during rESE/RSE) and sex was obtained with logistic regression using SE group (binary outcome RSE vs rESE) as the dependent variable.[17-19] Using the predicted probabilities from this logistic regression, a full matching was performed (default caliper 0.25), which resulted in 147 cases with rESE matched with 296 cases with RSE, with nearly 1:2 matching. See eTable 1, links.lww.com/WNL/C887 for a univariate comparison of the matched groups.

Using the matched data thus obtained, multivariable logistic regression was fit using clinical variables with $p \leq 0.1$ on univariate analysis as independent variables (Table 1), and the SE group (binary outcome RSE vs rESE) as the dependent variable, including up to second-order interaction effects among independent variables. Among independent variables, we also excluded those with high internal correlation (Spearman $\rho > 0.75$), retaining the variables with fewer missing values from the correlated variables. The model was optimized using stepwise elimination to select the most parsimonious model with minimum Akaike information criterion. ORs along with 95% CIs were obtained. In addition, OR for the interaction terms are provided showing the effects of different levels of the covariates on the response. Variables determined to be significant in both the univariate and the matched analyses were considered to have a significant association. Data analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC) and R version 3.5 (R foundation for statistical computing, Vienna, Austria), including the R "MatchIt" package.

Data Availability

Primary data were not provided in the article because of space limitations, but it may be shared (anonymized) at the request of any qualified investigator to replicate procedures and results.

Results

Using univariate analysis, we analyzed data from a cohort of 595 pediatric patients presenting with convulsive SE who did not respond to initial BZD therapy treated over an 8-year period. Table 1 provides the demographics for the RSE and rESE groups. There were no differences among factors in the patients' medical history that were associated with a risk of seizures and/or SE, including epilepsy, febrile seizures, developmental delay, and cerebral palsy. However, having a family history of seizures was less frequent in patients with RSE (21%) than those with rESE (31%) ($p = 0.013$). Having a prescription for rectal diazepam was also noted less frequently in patients with RSE (39%) than in patients with rESE (49%) ($p = 0.030$).

Analyzing factors that would be specific to the episode of SE, both groups were remarkably similar, and there were no differences between the RSE and rESE groups regarding onset location (in hospital or out of hospital), etiology that could be discerned during presentation, or observed changes in acute CT head imaging. There was a difference in the time to the second-line ASM, with the RSE group receiving it in a shorter time (65 minutes, IQR 34.5–153) from SE onset than the rESE group (70 minutes, IQR 40–103; $p = 0.021$). The univariate analysis did not show a difference in the presentation of intermittent convulsive seizures without return to baseline

Table 1 Univariate Analysis Comparing Patients With Refractory Status Epilepticus and Responsive Established Status Epilepticus[a]

	RSE (n = 398)	rESE (n = 197)	*p* Value
Patient-related variables			
Age (yrs; [IQR])	4.3 (1.3–9.5)	4.6 (1.8–9.1)	0.59
Sex			
Male	225 (56%)	110 (56%)	0.93
Medical history			
Epilepsy	177/365 (48%)	95/189 (50%)	0.72
Febrile seizures	42/365 (11.5%)	18/189 (9.5%)	0.56
Developmental delay	175/365 (48%)	93/189 (49%)	0.79
Cerebral palsy	39/365 (10.7%)	26/189 (13.8%)	0.31
None	127/365 (34.8%)	57/189 (30%)	0.30
Family history[b]			
Seizures	77/359 (21%)	60/193 (31%)	**0.013**
Rectal diazepam Rx at home[b]	146/371 (39%)	90/183 (49%)	**0.030**
Status epilepticus–related variables			
Hospital onset			
Yes	105/374 (28%)	54/191 (28%)	1.0
Type status epilepticus[b]			
Intermittent	263/374 (70%)	120/191 (63%)	
Continuous	111/374 (30%)	71/191 (37%)	0.087
Etiology			
Structural	99/372 (27%)	55/192 (29%)	
Genetic	68/372 (18%)	31/192 (16%)	
Metabolic	16/372 (4%)	7/192 (4%)	
Other/unknown	189/372 (51%)	99/192 (52%)	0.48
Time to first benzodiazepine (min; [IQR])[b]	16 (5–45)	18 (6–44)	0.068
Time to second-line antiseizure medication (min; [IQR])[b]	**65 (35–153)**	**70 (40–103)**	**0.021**
CT head			
Change from baseline	42/369 (11%)	15/188 (8%)	
No change from baseline	60/369 (16%)	24/188 (13%)	
Normal	99/369 (27%)	46/188 (24%)	
Not performed	168/369 (45%)	103/188 (55%)	0.19

Abbreviations: rESE = responsive established SE; RSE = refractory SE; SE = status epilepticus.
[a] Continuous variables given as median (IQR).
[b] Variables included in the ensuing linear regression models.

relative to continuous convulsive seizures (70% of patients with RSE, 63% of patients with rESE; $p = 0.087$) and in the time to first BZD between the RSE (16 minutes) and rESE groups (18 minutes) ($p = 0.068$).

Because having a prescription for rectal diazepam was the 1 modifiable factor found to be different between the 2 groups, we performed a subgroup analysis comparing the patients with rectal diazepam prescriptions to see whether there were

Table 2 Comparison of Patients With and Without Home Diazepam Prescription

	RSE (n = 140)	rESE (n = 87)	*p* Value
Diazepam used as first benzodiazepine			
With diazepam home rx	70/140 (50%)	39/87 (45%)	
Without diazepam home rx	24/216 (11%)	7/91 (8%)	
Time to first benzodiazepine with diazepam rx (mean, min)	47 (SD 15)	59 (SD 25)	0.68
Time to first benzodiazepine without diazepam rx (mean, min)	86 (SD 21)	83 (SD 28)	0.99

Abbreviations: rESE = responsive established SE; RSE = refractory SE; SE = status epilepticus.

potential differences in the time to treatment within the group of patients who received their diazepam as the first-line ASM that may explain the effect of this medication. Only 39/87 (45%) of patients with rectal diazepam in the rESE group and 70/140 (50%) of the patients in the RSE group received their rectal diazepam as first-line ASM treatment (Table 2). While not statistically different due to the small number of patients, the magnitude of the difference in time to first BZD treatment between the patients who had a prescription for rectal diazepam compared with those who did not in both the RSE (47 minutes [SD 15] vs 86 minutes [SD 21]; $p = 0.68$) and rESE groups (59 minutes [SD 25] vs 83 minutes [SD 28]; $p = 0.53$) is notable. However, the magnitude of these differences was similar between the RSE and rESE groups. This study is not powered to assess subpopulations of patients who received rectal diazepam vs those who did not, but these data imply that the decreased odds of RSE associated with having a rectal diazepam prescription is not because of decreased time to receive a first-line BZD ASM.

Univariable and Multivariable Logistic Regression Modeling

The following variables were associated with RSE with $p < 0.1$ on univariate analysis: a family history of seizures, rectal diazepam prescription, type of SE, time to first BZD, and time to second-line ASM (Table 1). Evaluating the results and their potential first-order interactions, having a family history of seizures, or having a prescription for rectal diazepam were independently associated with not having RSE (Table 3). Time to initial BZD or first non-BZD ASM were not associated with having RSE.

The multivariable model on propensity score–matched data provided a good fit to the data (AUC 0.74).[20] In this model,

Table 3 Univariable Logistic Regression Analyses Evaluating the Association With Risk of RSE

Effect	OR	95% CI	*p* Value
Sex (female vs male)	1.03	0.73–1.45	0.872
Rectal diazepam Rx (yes vs no)	0.67	0.47–0.96	0.028[a]
Family history of seizures (yes vs no)	0.61	0.41–0.90	0.013[a]
Type of SE (continuous vs intermittent)	1.40	0.97–2.03	0.072[a]
Age during SE (y)	1.01	0.98–1.04	0.583
Time to first nonbenzodiazepine ASM	1.00	0.99–1.00	0.066[a]
Time to first benzodiazepine	1.00	0.99–1.00	0.841

Backward elimination with first-order interactions
AUC = 0.60, 95% CI 0.55–0.64, Hosmer-Lemeshow *p* = 0.99

Rectal diazepam Rx	Family history of seizures	OR	95% CI	*p* Value
No	**Yes vs no**	**0.42**	**0.24–0.72**	**0.002**
Yes	Yes vs no	0.81	0.45–1.46	0.482
Yes vs no	**No**	**0.55**	**0.36–0.84**	**0.006**
Yes vs no	Yes	1.06	0.54–2.11	0.860

Abbreviations: ASM = antiseizure medication; AUC = Area under the receiver operating curve; RSE = refractory SE; SE = status epilepticus.
[a] $p < 0.1$.

Table 4 Best Multivariable Logistic Regression to Determine the Occurrence of RSE

	Variable	OR (95% CI)	*p* Value
Main effects	Time to second-line ASM	1.0 (0.99–1.0)	0.56
	Type of SE–intermittent	**3.2 (1.2–8.5)**	**0.022**
	Family history of seizures	**0.37 (0.20–0.70)**	**0.0020**
	Rectal diazepam Rx at home	**0.21 (0.078–0.53)**	**0.0012**
First-order interactions	**Time to second–line ASM: rectal diazepam rx**	**1.0 (1.0–1.0)**	**0.024**
	Time to second-line ASM: type of SE–intermittent	0.99 (0.99–1.0)	0.052
	Rectal diazepam rx: family history of seizures	2.2 (0.90–5.5)	0.085

Overall model fit characteristics: AIC 555.06, no. of Fisher scoring iterations 4 Model validity: AUC 0.74
Abbreviations: ASM = antiseizure medication; AIC = Akaike information criterion; AUC = Area under the receiver operating curve; RSE = refractory SE; SE = status epilepticus.

intermittent SE (OR 3.16, 95% CI 1.18–8.54, $p = 0.022$) increased the odds of SE progressing to RSE, while a family history of seizures (OR 0.37, 95% CI 0.20–0.70, $p = 0.0022$) and having a prescription for rectal diazepam (OR 0.21, 95% CI 0.08–0.53, $p = 0.0012$) decreased the odds of having RSE (Table 4). A logistic regression model was also fit with the SE group as the dependent variable, variables with $p \leq 0.1$ on univariate analyses as fixed effects, and study site as the random effect, but this was not superior to the abovementioned model on analysis of variance. This study provides Class II evidence that patient and clinical factors may predict RSE in children with convulsive seizures.

Discussion

We analyzed the pSERG data as an observational case-control study of pediatric patients with ESE. These data show that having a family history of seizures and having been prescribed rectal diazepam for home use are associated with a lower odds of having RSE. Our results suggest that these variables are good discriminators of pediatric patients more likely to develop RSE and may offer opportunities for earlier escalation of intervention. In our cohort of patients, there was no apparent association of RSE with age, sex, or latency to first-line BZD treatment.

Because the rESE group in this study consists of patients whose seizures aborted with a BZD plus a second-line ASM, the patients within both groups of this study were clinically refractory to BZD. However, with the absence of a difference in the response between the second-line seizure medications used in ESETT,[15,16] these data combined would suggest that neither the time nor specific second-line seizure medication influences whether ESE is controlled with a second-line medication or progresses to RSE in the pediatric population. Because the second-line medications used in both these studies are not necessarily directed at similar mechanisms of aborting seizure activity, these results considered together suggest there may be additional time-dependent complexity in the physiology of BZD and second-line medication responsiveness of certain SE etiologies that will require additional biomarkers to distinguish which patients will be refractory to treatment.

While the variables that differentiate RSE and rESE groups are novel in that they did not enter into prior prognostic models, in comparing age-matched and sex-matched patients with RSE and rESE, the time to first BZD and second-line ASM were not different in the multivariable models. In prior analyses of only patients with RSE from the pSERG database, the time to the initial BZD was associated with a higher OR of receiving a continuous infusion in addition to the overall duration of SE.[11,21] However, in both univariable and multivariable modeling, comparing these highly similar cohorts of RSE (patients requiring BZD + second-line ASM +third line ASM and/or continuous infusion) and rESE (patients requiring BZD + second-line ASM only) patients cared for at the same tertiary care centers, the time to initial BZD and even the time to second-line ASM were not associated with the development of RSE. In the setting of an appropriate control group, the hypothesis of time to first-line or second-line treatment having a primary influence on the progression to RSE in pediatric patients presenting with SE is not correct.

Recent investigations in rodent models of SE have demonstrated that in models of kainic acid–induced SE, the rodents never became BZD refractory, regardless of time to treatment, in contrast to what had been previously shown in lithium pilocarpine–induced SE.[22,23] These animal model data are consistent with a retrospective study of pediatric patients presenting to an emergency department demonstrating that, while delay in the first BZD treatment is associated with prolonged seizures and even prolonged SE in some patients, not all prolonged seizures become refractory to BZD.[12] Our study does not address BZD responsiveness/refractoriness. It

does, however, show that in patients resistant to BZD, the time to second-line medication also does not influence the progression to RSE. Therefore, underlying etiology may have a more profound influence than time to treatment on the responsiveness of SE to currently recommended therapies.

In total, these data demonstrate that, while time to treatment with a first-line and second-line ASM is not associated with the development of treatment-resistant RSE, the data do not refute work showing that delays in treatment may increase the duration of SE in some patients who go onto develop RSE. Therefore, early treatment is likely critical for a subset of patients that, currently, we do not have the clinical tools to identify on presentation. Identification of patient-related variables and new technologies to obtain acute electrophysiologic data may lead to an accurate method for determining which patient's SE will be refractory to early ASM treatment.

The strong association of intermittent convulsive SE (showing a 3-fold increased odds of developing RSE) when compared with continuous convulsive SE in the matched multivariable regression modeling did not have a clear association in the univariate regression modeling. This may be due to biases in the use of the propensity-matched data, which excluded approximately 25% of the original cohort from the analysis, or a lack of sensitivity in the univariate modeling. It can often be confusing as to whether seizures have stopped or are continuing, and this could lead to a delay in time to initial BZD treatment or escalation of therapy. However, the univariate data from the cohort demonstrate that there were more patients with intermittent clinical manifestations of their SE in both groups with no difference between groups in the univariate regression analysis. Ultimately, there was no difference in the time to the first BZD treatment between groups (Table 1; eFigure 1, links.lww.com/WNL/C887), which was delayed for both based on guidelines for the treatment of SE.[24-27] In addition, the RSE group received their second-line ASM faster than the rESE group (Table 1; eFigure 2), although the median times still lag behind those recommended in the 2016 American Epilepsy Society Guidelines.[26]

While intermittent SE ultimately did not demonstrate an association with RSE in both logistic regression modeling methods, an association between intermittent SE and ictal duration was present in a prior study.[2] Previous studies have investigated both the ictal duration and total duration of SE in adult (16 years and older) and pediatric (1 month–15 years) patients, comparing continuous and intermittent SE.[2] Both adult and pediatric patients with intermittent SE had a shorter duration of ictal time on EEG. However, the pediatric population had a longer total duration of SE.[2] Despite no change in the duration of SE in the adult cohort and the increased duration of SE in the pediatric cohort, mortality was lower for intermittent SE in both populations. Earlier analyses of the pSERG RSE-only cohort did not show a difference between intermittent and continuous seizure phenotypes in patients with no history of epilepsy or SE compared with those who had a history of SE or epilepsy.[21] However, a comparison of an rESE cohort with a larger RSE group using multivariable analysis of propensity score–matched groups suggests that this variable may be associated with an increased odds of developing RSE. The association of intermittent SE with decreased mortality and increased overall duration of SE[2] together with our data raises the question of an association with RSE in pediatric patients and suggests that this variable warrants further prospective study as a potential clinical marker associated with a risk of RSE.

The purpose of a home prescription for rectal diazepam is to reduce the time a patient with a tendency to prolonged or repeated seizures spends seizing by having a BZD that can be given early after seizure onset. Overall, having a prescription for rectal diazepam at home did reduce the time to initial BZD over the entire cohort; however, it did not influence the time to treatment nor the use of rectal diazepam as a first-line medication between the RSE and rESE groups (Table 2). Therefore, time to treatment does not explain the association of having a prescription for rectal diazepam with the rESE group. We hypothesize that the reduced odds of developing RSE in patients having been prescribed rectal diazepam or patients with a family history of seizures may be that these variables are effective at sorting out underlying causes of SE that tend to more easily respond to current recommended interventions for SE. These may include such underlying causes as new-onset familial epilepsies, febrile seizures, and patients with epilepsy who may have missed a dose of ASM despite the cause not being readily apparent on presentation to the emergency department. By contrast, patients with acute symptomatic etiologies, such as infectious or autoimmune encephalitis, would be unlikely to have either a family history of seizures or a prescription for rectal diazepam. In addition, patients with a family history of seizures and training in the use of rescue interventions may take additional measures that were not tracked in our analysis. This study is somewhat limited in estimating the protective effect size of having a rescue medication because only the data concerning rectal diazepam prescriptions were collected. With more studies supporting the use of intramuscular or intranasal midazolam as rescue medications, capturing data for the prescription of any rescue medication may help to improve the sensitivity of this variable.

While the study was not specifically designed to assess the utility of having a prescription for rectal diazepam in reducing time to treatment and prevention of RSE, taking a closer look at this population demonstrates an area for modifiable improvement, namely increased use of this seizure rescue medication among those with a prescription. Home rescue rectal diazepam as the first-line rescue medication was used in less than half of the patients who had a prescription. While our data do not show that time to treatment is associated with RSE, data from multiple studies support that time to rescue medication administration is directly associated with time spent seizing in patients with SE.[10,12,21] Future work directed at potential interventions to improve the use of seizure rescue

medication may have an impact on resource utilization in the treatment of SE.

Our findings need to be interpreted in the setting of the data acquisition. This is an observational study that uses univariable regression of unmatched data in addition to propensity scores to match groups of patients with RSE and rESE in a case-controlled manner as opposed to prospectively recruited 1:1 case and control cohorts to determine patient and clinical variables that may help predict which patients with BZD-refractory SE will progress to RSE. There is not a single defined statistical mechanism for accurately approximating a case-control study with observational data; therefore, we have opted to find associations only among variables demonstrating significance in more than 1 model. Matching for estimated propensity scores tends to attenuate both measured and random imbalances in the data, is superior to matching based on covariate categories, and facilitates analysis of observational data as if obtained from a conventional case-control study.[28] Specifically, the propensity score matching implemented in this study reduces the dependence of causal inferences on statistical modeling assumptions, which may not always be justified in an observational study.[29] However, propensity scores are sensitive to the choice of observed covariates and modeling techniques, both of which are arbitrary.[30] In addition, the use of matching has reduced the number of patients by approximately 25% in both categories, which may lead to bias. eTable 2, links.lww.com/WNL/C887 summarizes a comparison between the patients who were matched and those who were not. These data show that the groups are well balanced except for a larger number of in-hospital onset of SE in the matched group, which may introduce bias into the matched dataset.

We have not included an additional control arm of BZD-responsive patients to address variables that associate with BZD-refractory SE. We have also not analyzed whether the dose of BZD was associated with patients developing RSE. While the rESE group was selected to be those patients whose seizures terminated after BZD and a single ASM, the determination of seizure cessation may not have been uniform (e.g., clinical vs EEG), and the decision to give a third-line ASM was dependent on the assessment of the treating physician. This may lead to some patients being considered cases with RSE or rESE when, in fact, their seizures had terminated, and they would otherwise be in the rESE group or were BZD responsive. This type of multicenter observational study is also limited by recall bias and completeness of the data entry for each patient enrolled. It is not possible for every institution to include all patients eligible for the study, given enrollment coverage constraints; thus, the patients who were more ill or had longer lengths of stay may potentially be more heavily weighted in this sample. In addition, inclusion of patients at pSERG participating institutions entails an inherent selection bias, such that a subset of patients with RSE/SRSE presenting to tertiary care pediatric hospitals may be those who are more difficult to treat. The rESE group may be biased in that those who recover well may be discharged home and not enrolled. There are also additional variables that may be available shortly on arrival to an emergency department, which were not obtained as part of our data collection. Therefore, there may be additional markers that were not considered in the analysis with the potential to aid in distinguishing the RSE from the rESE cohort during the emergency department presentation. Further studies are also planned to investigate physician decision-making regarding the prescription of rescue medications, which may inform why it seems to be a good surrogate marker for causes of SE that better respond to second-line ASM.

Using a large multicenter pediatric cohort of patients with ESE, we found that patient-related variables, specifically a family history of seizures and having a prescription for rectal diazepam, were more strongly associated with the rESE group. In these matched cohorts of patients with BZD-refractory SE, times to first-line or second-line ASM were not associated with the development of RSE. While these data do not show that delays in treatment are independently associated with the development of RSE, previous studies have shown that among cohorts of patients with RSE, delays to treatment do associate with an increased duration of SE.[11] Perhaps these patient-related variables used with acute electrophysiologic data, and potentially in combination with recently described scores (i.e., STESS and STEPSS),[31-34] will provide for an even more accurate method for predicting when SE will be refractory to early ASM treatment, allowing for a patient-tailored approach to treatment.

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Appendix 1 Authors

Name	Location	Contribution
Katrina Peariso, MD, PhD	Department of Neurology and Physical Medicine and Rehabilitation, University of Cincinnati College of Medicine, Cincinnati, OH	Drafting/revision of the article for content; major role in acquisition of study data; study concept or design; analysis or interpretation of the data; and additional contributions: study supervision or coordination
Ravindra Arya, MD, DM	Division of Pediatric Neurology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH	Drafting/revision of the article for content; major role in acquisition of study data; study concept or design, analysis or interpretation of the data; and additional contributions: statistical analysis
Tracy A. Glauser, MD	Division of Pediatric Neurology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination
Nicholas S. Abend, MD	Division of Neurology, The Children's Hospital of Philadelphia, The Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination
Christina Barcia Aguilar, MD	Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA; Department of Child Neurology, Hospital Universitario La Paz, Universidad Autonoma de Madrid, Madrid, Spain	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination
Marta Amengual-Gual, MD	Pediatric Neurology Unit, Department of Pediatrics, Hospital Universitari Son Espases, Universitat de les Illes Balears, Palma, Spain	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination
Anne Anderson, MD	Section of Neurology and Developmental Neuroscience, Department of Pediatrics, Baylor College of Medicine, Houston, TX	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination

Appendix 1 *(continued)*

Name	Location	Contribution
Brian Appavu, MD	Department of Pediatrics, University of Arizona College of Medicine and Barrow's Neurologic Institute at Phoenix Children's Hospital, Phoenix, AZ	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination
J. Nicholas Brenton, MD, PhD	Department of Neurology and Pediatrics, University of Virginia Health System, Charlottesville, VA	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination
Jessica Carpenter, MD	Division of Pediatric Neurology, University of Maryland School of Medicine, Baltimore, MD	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination
Kevin E. Chapman, MD	Department of Pediatrics, University of Arizona College of Medicine and Barrow's Neurologic Institute at Phoenix Children's Hospital, Phoenix, AZ	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: 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	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination
William D. Gaillard, MD	Center for Neuroscience, Children's National Hospital, George Washington University School of Medicine and Health Sciences, Washington, DC	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination
Marina Gaínza-Lien, MD	Instituto de Pediatría, Facultad de Medicina, Universidad Austral de Chile, Valdivia, Chile; Servicio de Neuropsiquiatría Infantil, Hospital Clínico San Borja Arriarán, Universidad de Chile, Santiago, Chile	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination
Joshua Goldstein, MD	Ruth D. & Ken M. Davee Pediatric Neurocritical Care Program, Northwestern University Feinberg School of Medicine, Chicago, IL	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination
Howard Goodkin, MD, PhD	Department of Neurology and Pediatrics, University of Virginia Health System, Charlottesville, VA	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination
Zachary Grinspan, MD	Division of Pediatric Neurology and Epilepsy, Department of Pediatrics, Weill Cornell Medicine, New York, NY	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination
Réjean M. Guerriero, MD	Neurology Clinical Services and Critical Care EEG Program, St. Louis Children's Hospital, Division of Pediatric and Developmental Neurology, Washington University School of Medicine, St. Louis, MO	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination
Paul S. Horn, PhD	Division of Pediatric Neurology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH	Performing portions of the statistical analysis. Drafting/revision of the article, specifically for the statistical methods.
Linda Huh, MD	Department of Pediatrics, British Columbia Children's Hospital, the University of British Columbia, BC Canada	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination
Robert Kahoud, MD	Division of Pediatric Critical Care Medicine, Department of Child and Adolescent Medicine, Mayo Clinic School of Medicine, Rochester, MN	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination
Sarah A. Kelley, MD	Division of Pediatric Neurology, Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination
Eric H Kossoff, MD	Division of Pediatric Neurology, Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination

Continued

Appendix 1 *(continued)*

Name	Location	Contribution
Kush Kapur, PhD	Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination
Yi-Chen Lai, MD	Section of Pediatric Critical Care Medicine, Department of Pediatrics, Baylor College of Medicine, Houston, TX	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination
B. Oyinkan Marquis, MD	Division of Pediatric Neurology and Epilepsy, Department of Pediatrics, Weill Cornell Medicine, New York, NY	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination
Tiffani McDonough, MD	Department of Neurology, Barbara Bush Childrens Hospital at Maine Medical Center, Maine Medical Partners, Scarborough, ME	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination
Mohammad Mikati, MD	Division of Pediatric Neurology, Duke University Medical Center, Duke University, Durham, NC	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination
Lindsey Morgan, MD	Department of Neurology, Division of Child Neurology, Seattle Children's Hospital, Seattle, WA	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination
Edward Novotny, MD	Department of Neurology, Division of Child Neurology, Seattle Children's Hospital, Seattle, WA	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination
Adam P. Ostendorf, MD	Department of Pediatrics, Nationwide Children's Hospital, The Ohio State University, Columbus, OH	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination

Appendix 1 *(continued)*

Name	Location	Contribution
Eric T. Payne, MD	Division of Neurology, Department of Pediatrics, Alberta Children's Hospital, Calgary, AB, Canada	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination
Juan Piantino, MD	Division of Neurology, Doernbecher Children's Hospital, Oregon Health & Science University, Portland, OR	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination
James Riviello, MD	Section of Neurology and Developmental Neuroscience, Department of Pediatrics, Baylor College of Medicine, Houston, TX	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: 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	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination
Carl E. Stafstrom, MD, PhD	Division of Pediatric Neurology, Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination
Robert C. Tasker, MD, MBBS	Department of Anesthesiology, Critical Care and Pain Medicine, Boston Children's Hospital, Harvard Medical School, Boston, MA	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination
Dmitry Tchapyjnikov, MD	Division of Pediatric Neurology, Duke University Medical Center, Duke University, Durham, NC; Current Address: Montana Children's Specialists, Kalispell, MT USA	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination
Alejandra Vasquez, MD	Division of Child and Adolescent Neurology, Department of Neurology, Mayo Clinic, Rochester, MN	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination

Appendix 1 *(continued)*

Name	Location	Contribution
Mark S. Wainwright, MD, PhD	Department of Neurology, Division of Child Neurology, Seattle Children's Hospital, Seattle, WA	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination
Angus Wilfong, MD	Department of Pediatrics, University of Arizona College of Medicine and Barrow's Neurologic Institute at Phoenix Children's Hospital, Phoenix, AZ	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination
Korwyn Williams, MD, PhD	Department of Pediatrics, University of Arizona College of Medicine and Barrow's Neurologic Institute at Phoenix Children's Hospital, Phoenix, AZ	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: 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	Drafting/revision of the article, including medical writing for content; major role in acquisition of the data; study concept or design; and additional contributions: study supervision or coordination

Appendix 2 Coinvestigators

Coinvestigators are listed at links.lww.com/WNL/C888.

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