First-line medication dosing in pediatric refractory status epilepticus

Alejandra Vasquez, MD, Marina Gaínza-Lein, MD, Nicholas S. Abend, MD, MSCE, Marta Amengual-Gual, MD, Anne Anderson, MD, Ravindra Arya, MD, J. Nicholas Brenton, MD, Jessica L. Carpenter, MD, Kevin Chapman, MD, Justice Clark, MPH, Raquel Farias-Moeller, MD, William D. Gaillard, MD, Tracy Glauser, MD, Joshua L. Goldstein, MD, Howard P. Goodkin, MD, PhD, Rejean M. Guerriero, DO, Kush Kapur, PhD, Yi-Chen Lai, MD, Tiffani L. McDonough, MD, Mohamad A. Mikati, MD, Lindsey A. Morgan, MD, Edward J. Novotny, MD, Adam P. Ostendorf, MD, Eric T. Payne, MD, Katrina Peariso, MD, PhD, Juan Piantino, MD, James J. Riviello, MD, Kumar Sannagowdara, MD, Robert C. Tasker, MBBS, MD, Dmitry Tchapyjnikov, MD, Alexis Topjian, MD, MSCE, Mark S. Wainwright, MD, PhD, Angus Wilfong, MD, Korwyn Williams, MD, PhD, and Tobias Loddenkemper, MD, on behalf of the Pediatric Status Epilepticus Research Group (pSERG)

Correspondence

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

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Abstract

Objective

To identify factors associated with low benzodiazepine (BZD) dosing in patients with refractory status epilepticus (RSE) and to assess the impact of BZD treatment variability on seizure cessation.

Methods

This was a retrospective study with prospectively collected data of children with convulsive RSE admitted between June 2011 and January 2019. We analyzed the initial and total BZD dose within 10 minutes of treatment initiation. We used logistic regression modeling to evaluate predictors of low BZD dosing and multivariate Cox regression analysis to assess the impact of low BZD dosing on time to seizure cessation.

Results

We included 289 patients (55.7% male) with a median age of 4.3 (1.3–9.5) years. BZDs were the initial medication in 278 (96.2%). Of those, 161 patients (57.9%) received a low initial dose. Low initial BZD doses occurred in both out-of-hospital (57 of 106; 53.8%) and in-hospital (104 of 172; 60.5%) settings. One hundred three patients (37.1%) received low total BZD dose. Male sex (odds ratio [OR] 2, 95% confidence interval [CI] 1.18–3.49; $p = 0.012$), older age (OR 1.1, 95% CI 1.05–1.17; $p < 0.001$), no prior diagnosis of epilepsy (OR 2.1, 95% CI 1.23–3.69; $p = 0.008$), and delayed BZD treatment (OR 2.2, 95% CI 1.24–3.94; $p = 0.007$) were associated with low total BZD dose. Patients who received low total BZD dosing were less likely to achieve seizure cessation (hazard ratio 0.7, 95% CI 0.57–0.95).

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

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Coinvestigators are listed at [links.lww.com/WNL/B215](https://www.links.lww.com/WNL/B215).

Glossary

ASM = antiseizure medication; BZD = benzodiazepine; CI = confidence interval; DZP = diazepam; ESETT = Established Status Epilepticus Treatment Trial; HR = hazard ratio; ICU = intensive care unit; IM = intramuscular; LZP = lorazepam; MDZ = midazolam; OR = odds ratio; PR = per rectum; pSERG = Pediatric Status Epilepticus Research Group; p25–p75 = interquartile range; RSE = refractory SE; SE = status epilepticus.

Conclusion

BZD doses were lower than recommended in both out-of-hospital and in-hospital settings. Factors associated with low total BZD dose included male sex, older age, no prior epilepsy diagnosis, and delayed BZD treatment. Low total BZD dosing was associated with decreased likelihood of Seizure cessation.

Classification of evidence

This study provides Class III evidence that patients with RSE who present with male sex, older age, no prior diagnosis of epilepsy, and delayed BZD treatment are more likely to receive low total BZD doses. This study provides Class III evidence that in pediatric RSE low total BZD dose decreases the likelihood of seizure cessation.

Status epilepticus (SE) is a life-threatening neurologic condition. Approximately 33% of SE episodes fail to respond to appropriate doses of 2 antiseizure medications (ASMs),¹ usually a first-line benzodiazepine (BZD) and a second-line non-BZD ASM,² progressing to refractory SE (RSE).³ In this context, rapid SE control is crucial because delays in treatment lead to increased seizure duration and worse clinical outcomes.^{4–7} BZDs are considered first-line medication in SE due to their relatively safe profile and effectiveness in different seizure types.^{8–10}

Despite current guideline recommendations on BZD doses and time frames for administration,^{10,11} data indicate that guidelines are inconsistently followed.^{12–15} An observational study performed in pediatric SE before admission to the intensive care unit (ICU) showed that the primary medication was not a BZD in 11% of cases, and if given, the BZD dose was different from guideline recommendations in 22.5% of patients.¹³ Another study demonstrated that out-of-hospital administered diazepam (DZP) was underdosed in 75% of cases.¹⁶ While these studies suggest variability in the initial management of SE, there is limited knowledge regarding the factors contributing to nonadherence to BZD treatment recommendations and the overall impact on treatment efficacy. To address this gap in knowledge, we aimed to identify potential predictors of low BZD dosing in patients with RSE and to assess the impact of BZD treatment variability on seizure cessation. We hypothesized that patients who received lower-than-recommended BZD doses would be less likely to achieve seizure cessation.

Methods

Standard protocol approvals, registrations, and patient consents

The study was approved by the local Institutional Review Board at each participating institution, with written informed consent from the patients' parents or legal representatives.

Study design

This was a retrospective study of prospectively collected data performed at 17 pediatric referral hospitals collaborating within the Pediatric Status Epilepticus Research Group (pSERG). pSERG is a consortium of pediatric hospitals in the United States and Canada focused on RSE treatment and outcome assessment that aims to improve prognosis of children with RSE.¹⁷ This study was compliant with Strengthening the Reporting of Observational Studies in Epidemiology guidelines (appendix e-3, doi.org/10.5061/dryad.05qftf02).

Study questions

The primary study question was the following: what are the predictors of low BZD dosing in the initial treatment of RSE (Classification of Evidence III)? The secondary study question was, is there an association between low BZD dosing and seizure cessation (Classification of Evidence III)?

Study population

We included children aged 1 month to 21 years of age with convulsive RSE enrolled between June 2011 and January 2019. RSE was defined as the failure of convulsive seizure termination after an initial BZD (1 or multiple doses) followed by a non-BZD ASM or the requirement of a continuous infusion. If the patient presented with >1 SE episode, then only the first episode was included. Exclusion criteria were (1) nonconvulsive SE at onset; (2) psychogenic nonepileptic seizures; (3) no data on demographic variables; (4) no data on time of administration of the first BZD or time of administration of the first non-BZD ASM; and (5) no data on BZD dosing within 10 minutes of treatment initiation.

Outcomes and definitions

Our primary outcome was low total BZD dose within 10 minutes of treatment initiation.

We first described the initial BZD dose, which was defined as the dose administered for treatment at presentation of SE. In

our cohort, many patients received >1 type of BZD after the initial BZD dose. Therefore, for our primary outcome, we calculated the total BZD dose given within 10 minutes of treatment initiation, regardless of the BZD type. We performed this calculation as follows: for each BZD type administered, we calculated the percentage of the minimum recommended dose on the basis of route of administration and the patient's age/weight; then we added all of these BZD dose percentages given within 10 minutes to calculate the total BZD dose as a percentage of minimum dosing. We defined low total BZD dose if a patient failed to receive 100% of the minimum recommended dose within 10 minutes of treatment initiation.^{1,8,10,18–20}

The rationale behind our primary outcome definition is explained by 2 practices observed at the point of care. First, although the American Epilepsy Society recommends the administration of an adequate single full dose of BZD as initial therapy phase for SE, which may be repeated if seizures persist, health care providers tend to administer smaller, repeated doses of BZDs in this setting.⁸ Second, it is also common to use different BZDs through distinct routes of administration during this earlier stage of SE therapy. Therefore, we aimed to account for these variabilities through the calculation of total percentage of recommended BZD doses within 10 minutes of treatment initiation. Moreover, we considered a cutoff time of 10 minutes because medications given within 10 minutes can be loosely considered the same dose.

We calculated our primary outcome on the basis of the following recommended doses (data available from Dryad, table e-1, doi.org/10.5061/dryad.05qftf02): (1) lorazepam (LZP) IV, intramuscular (IM): 0.1 mg/kg, maximum of 4 mg per dose, for the patients >40 kg, 4 mg per dose; (2) diazepam (DZP) IV/intraosseous/oral: 0.15 mg/kg, maximum of 10 mg per dose; DZP per rectum (PR): 0.5 mg/kg (2–5 years), 0.3 mg/kg (6–11 years), 0.2 mg/kg (≥12 years), with a maximum of 20 mg per dose; and (3) midazolam (MDZ) IV, intranasal: 0.2 mg/kg, maximum of 10 mg per dose; buccal 0.5 mg/kg; IM MDZ: 10 mg for patients >40 kg, single dose and 5 mg for patients weighing 13–40 kg, single dose.^{1,8} There is currently no recommendation for IM MDZ in patients <13 kg.¹⁸ We used the dose indicated for seizures in the emergency department corresponding to 0.2 mg/kg with a maximum of 10 mg per dose.¹⁹ Minimum recommended doses for clonazepam include 0.01 mg/kg orally for patients <10 years old or with a weight ≤30 kg, with a maximum of 0.2 mg/kg/d. For patients ≥10 years old or weight >30 kg, the minimum recommended dose is 0.5 mg per dose, with a maximum of 20 mg/d.²⁰ Clobazam is generally used for long-term control of seizure rather than first-line SE treatment. The recommended doses of clobazam vary according to patient weight: <30 kg, 5 mg per dose orally; and ≥30 kg, 10 mg per dose orally.²¹

Our secondary outcome was seizure cessation. Seizure cessation was defined as cessation of both clinical and electrographic seizures.

Statistical analysis

We summarized demographic and clinical features with descriptive statistics. Our data did not follow a normal distribution; therefore, we reported continuous variables with median and interquartile ranges (p25–p75), and categorical values as numbers and percentages. We analyzed all patients who received BZD as initial ASM and described the initial dose and setting of administration for each BZD group. We conducted univariate analysis to compare demographics, clinical characteristics, and outcomes between patients who received low and recommended total BZD doses. For this analysis, we used the Fisher exact and χ^2 tests for categorical variables, and the Wilcoxon rank-sum test for continuous variables. A value of $p < 0.05$ was considered statistically significant for all analyses. We adjusted for multiple comparisons using Benjamini-Hochberg false discovery rate control method with a q value of 0.05.

For our primary analysis, we built a multivariate logistic regression model to identify clinically relevant factors associated with low total BZD dose administration within the first 10 minutes from treatment initiation. We included in the model variables that were significant in univariate analyses (i.e., sex, age, and delayed time to first BZD) and a priori selected clinically relevant variables (i.e., history of epilepsy, intermittent SE, generalized tonic-clonic seizure at onset, and hospital SE onset). Weight and age were highly collinear in our data (correlation = 0.83); therefore, weight was excluded. Delayed time to administration of first BZD was defined as treatment administration >10 minutes from seizure onset. We considered this time frame on the basis of the American Epilepsy Society recommendations for first-line treatment administration (20 minutes from seizure onset).⁸ Therefore, we include a 10-minute delay in treatment and the 10-minute time frame considered for the BZD dosing analysis. For the secondary analysis, we assessed the association of low total BZD dose administration with seizure cessation. We used stepwise multivariate Cox regression analysis to evaluate time to seizure cessation, adjusting for age, structural etiology, febrile SE, generalized tonic-clonic seizure at onset, and delayed time to administration of first BZD. For this analysis, we excluded unclear or missing data. In addition, we calculated the absolute risk reduction and number needed to treat at various times (i.e., 2, 4, 6, 12, and 24 hours) to achieve seizure cessation.

We performed 2 sensitivity analyses to assess whether our results would remain similar considering extended times from treatment initiation for our primary and secondary outcomes, accounting for a total BDZ dose within the first 15 and 20 minutes of treatment initiation, respectively. These extended cutoffs were considered given known challenges for adherence to guideline time frames in clinical practice. We used R: A Language and Environment for Statistical Computing (R Core Team, version 3.4.1; Vienna, Austria)²² with RStudio²³ and the gmodels,²⁴ tm,²⁵ gdata,²⁶ tableone,²⁷ dplyr,²⁸ MASS,²⁹ survival,³⁰ knitr,³¹ tidyr,³² ggplot2,³³ xtable,³⁴ car,³⁵ and tidyverse³⁶ packages to analyze the data.

Table 1 Demographic characteristics of the RSE population

Characteristic	Patients with RSE		
	All (n = 289)	First-line BZD (n = 278)	First-line non-BZD ASM (n = 11)
Age, median (p25–p75), y	4.3 (1.3–9.5)	4.21 (1.3–9.6)	4.5 (2.4–8.6)
Male, n (%)	161 (55.7)	157 (56.5)	4 (36.4)
Race, n (%)			
White	183 (63.3)	176 (63.3)	7 (63.6)
Black or African American	60 (20.8)	58 (20.9)	2 (18.2)
Asian	11 (3.8)	11 (4)	—
Arabic	7 (2.4)	6 (2.2)	1 (9.1)
Native Hawaiian or Pacific Islander	1 (0.3)	1 (0.4)	—
American Indian or Alaska Native	1 (0.3)	1 (0.4)	—
Not reported	8 (2.8)	8 (2.9)	—
Unknown	18 (6.2)	17 (6.1)	1 (9.1)
Ethnicity, n (%)			
Not Hispanic or Latino	220 (76.1)	212 (76.3)	8 (72.7)
Hispanic or Latino	43 (14.9)	42 (15.1)	1 (9.1)
Not reported	16 (5.5)	15 (5.4)	1 (9.1)
Unknown	10 (3.5)	9 (3.2)	1 (9.1)
SE etiology, n (%)			
Structural	79 (27.3)	71 (25.5)	8 (72.7)
Genetic	48 (16.6)	48 (17.3)	—
Metabolic	16 (5.5)	15 (5.4)	1 (9.1)
Other	48 (16.6)	47 (16.9)	1 (9.1)
Unknown/not reported	98 (33.9)	97 (34.7)	1 (9.1)
Febrile SE, n (%)	37 (12.8)	36 (12.9)	1 (9.1)
Past medical condition, n (%) ^a			
Cerebral palsy	29 (10)	28 (10.1)	1 (9.1)
Developmental delay	150 (51.9)	144 (51.8)	6 (54.5)
Febrile seizure	32 (11.1)	31 (11.2)	1 (9.1)
Prior SE	54 (18.7)	52 (18.7)	2 (18.2)
Epilepsy	140 (48.4)	136 (48.9)	4 (36.4)
None	100 (34.6)	95 (34.2)	5 (45.5)

Table 1 Demographic characteristics of the RSE population (continued)

Characteristic	Patients with RSE		
	All (n = 289)	First-line BZD (n = 278)	First-line non-BZD ASM (n = 11)
Hospital SE onset	91 (31.5)	83 (29.9)	8 (72.2)

Abbreviations: ASM = antiseizure medication; BZD = benzodiazepine; p25–p75 = interquartile range; RSE = refractory SE; SE = status epilepticus.
^a Past medical conditions are not mutually exclusive.

Data availability

Data will be available for qualified individuals after approval of the Institutional Review Board and data use agreements between the involved institutions. Supplementary data are available from Dryad (doi.org/10.5061/dryad.05qftf02). All statistical analyses and results can be found at Dryad (appendix e-4).

Results

Demographic and clinical characteristics

Two hundred eighty-nine patients (55.7% male) were included, with a median (p25–p75) age of 4.3 (1.3–9.5) years. Among these patients, 140 (48.4%) had a diagnosis of epilepsy, and 54 (18.7%) had a prior SE event. The patients' demographic and clinical information is detailed in table 1.

Initial BZD dose and administration setting

BZDs were the initial ASM in 278 (96.2%) patients. LZP was the first choice in 156 (56.1%) patients. Of the 11 (3.8%) patients who received a non-BZD ASM as the first medication, 5 patients were treated with levetiracetam, 5 received fosphenytoin, and 1 patient received phenobarbital. Table 2 illustrates medication choices, their respective doses (initial dose), and the routes of administration. One hundred sixty-one (57.9%) patients received a low initial BZD dose: LZP 105 of 156 (67.3%), DZP 26 of 78 (33.3%), MDZ 29 of 39 (74.4%), and clonazepam 1 of 4 (25%) (figure 1).

Of the 161 patients treated with a low initial BZD dose, 57 were treated in the out-of-hospital setting (of 106 patients, 53.8%), and 104 were cared for in the in-hospital setting (of 172 patients, 60.5%). In the LZP group, the initial dose was administered in hospital in 136 of 156 (87.2%) patients and out of hospital in 20 of 156 (12.8%) patients. Ninety-two of 136 (67.6%) patients received a low LZP dose in the in-hospital setting, while 13 of 20 (65%) received low doses before hospital arrival. DZP was more often administered in the out-of-hospital setting (53 of 78 patients, 67.9%), and 20 of 53 (37.7%) of these patients received a low dose. Of the 25 patients who received DZP at the hospital, 6 (24%) patients received low DZP doses. Similarly, MDZ administration was more common in the out-of-hospital setting (29 of 39 patients, 74.3%), with 23 of 29 (79.3%) patients receiving

Table 2 First-line medication choices for convulsive RSE

Medication	No. (%) ^a (n = 289)	Median initial dose	p25–p75	Minimum recommended dose
BZDs				
Total	278			
LZP				
Total	156			
<40 kg IV/IM	134 (85.9)	0.09 mg/kg	0.06–0.10	0.10 mg/kg
≥40 kg IV/IM	22 (14.1)	2 mg/dose	2.00–2.00	4 mg/dose
DZP				
Total	78			
<2 y PR	17 (21.8)	5 mg/dose	2.50–5.00	—
2–5 y PR	27 (34.6)	0.45 mg/kg	0.33–0.55	0.50 mg/kg
6–11 y PR	8 (10.3)	0.33 mg/kg	0.27–0.42	0.30 mg/kg
≥12 y PR	12 (15.4)	0.33 mg/kg	0.27–0.36	0.20 mg/kg
<66.6 kg IV/IO/oral	13 (16.6)	0.21 mg/kg	0.09–0.30	0.15 mg/kg
≥66.6 kg IV/IO/oral	1 (1.3)	5 mg/dose	—	10 mg/dose
MDZ				
Total	39			
<13 kg IM	4 (10.3)	0.15 mg/kg	0.09–0.20	0.20 mg/kg
13–40 kg IM	3 (7.7)	1.3 mg/dose	0.90–1.52	5 mg/dose
IV	12 (30.8)	0.09 mg/kg	0.06–0.15	0.20 mg/kg
Intranasal	20 (51.2)	0.17 mg/kg	0.10–0.20	0.20 mg/kg
Clonazepam				
Total	4			
<10 y or ≤30 kg orally	2 (50)	0.02 mg/kg	0.02–0.03	0.01 mg/kg
≥10 y or >30 kg orally	2 (50)	0.31 mg/dose	0.22–0.41	0.5 mg/dose
Clobazam				
Total	1			
<30 kg orally	1 (100)	5 mg/dose	—	5 mg/dose
Non-BZD ASM				
Total	11			
Levetiracetam IV	5 (45)	21.28 mg/kg	15.46–39.02	60 mg/kg
Fosphenytoin IV	5 (45)	19.88 mg/kg	19.86–20.20	20 mg/kg
Phenobarbital IV	1 (10)	19.39 mg/kg	—	15 mg/kg

Abbreviations: ASM = antiseizure medication; BZD = benzodiazepine; DZP = diazepam; IM = intramuscular; IO = intraosseous infusion; LZP = lorazepam; MDZ = midazolam; PR = per rectum; RSE = refractory status epilepticus.

Median of the initial dose administered for status epilepticus treatment.

^a Percentages correspond to each BZD and non-BZD ASM.

lower-than-recommended doses. The MDZ doses given in hospital were low in 6 of 10 (60%). The 4 patients who received clonazepam were treated in the out-of-hospital

setting, and 1 of 4 (25%) received a dose that was lower than recommended. Clobazam was administered in hospital in 1 patient at a recommended dose.

Figure 1 Initial BZD dose in the out-of-hospital and in-hospital settings

One hundred sixty-one patients received a low initial benzodiazepine (BZD) dose; 57 were treated in the out-of-hospital setting (of 106 patients, 53.8%), and 104 were cared for in the in-hospital setting (of 172 patients, 60.5%).

Total BZD dose

The median percentage of total BZD dose was 104.9 (79.8–187.8). One hundred three (37.1%, 69 male) patients with a median age of 7.07 (2.3–11.6) years were included in the low total BZD dose group. One hundred seventy-five (62.9%, 88 male) patients with a median age of 3.7 (1.2–8.4) years received at least the minimum recommended total BZD dose. Table 3 provides the clinical data for the 2 groups.

Factors associated with low total BZD dose

Multivariate analysis revealed that male sex (odds ratio [OR] 2, 95% confidence interval [CI] 1.18–3.49; $p = 0.012$), older age (OR 1.1, 95% CI 1.05–1.17; $p < 0.001$), no prior diagnosis of epilepsy (OR 2.1, 95% CI 1.23–3.69; $p = 0.008$), and delayed time to treatment (OR 2.2, 95% CI 1.24–3.94; $p = 0.007$) were independent risk factors for receiving a low total BZD dose (figure 2).

Low total BZD dose and seizure cessation

The median seizure duration was significantly longer in patients receiving a low total BZD dose than in those within the recommended total BZD dose group (4.1 [2–21.7] vs 2.7 [1.3–6] hours; $p = 0.023$). Multivariate Cox proportional hazards regression analysis demonstrated that there was a decreased likelihood of seizure cessation in patients receiving low total BZD dose after controlling for confounders (hazard ratio [HR] 0.7, 95% CI 0.57–0.95) (table 4). Absolute risk reduction and number needed to treat at 2, 4, 6, 12, and 24 hours are shown in table 5. A similar trend, although not significant, was seen for patients with delayed first BZD administration (HR 0.8, 95% CI 0.62–1.03). Sensitivity analyses results are available from Dryad (tables e-3–e-5, doi.org/10.5061/dryad.05qftf02).

Discussion

We identified 4 key aspects of BZD administration with important clinical implications in contemporary management of pediatric RSE. First, although most patients who went on to experience RSE received a BZD as first-line ASM, the initial dose was lower than guidelines' recommendations in more than half of the children. This practice was not exclusive to out-of-hospital care but was equally evident for in-hospital practice. Second, in pediatric patients with RSE receiving >1 BZD dose within the first 10 minutes of treatment initiation, more than one-third received low total BZD dose. Third, boys, older children, and children without a prior diagnosis of epilepsy were more likely to be administered low total BZD doses. Fourth, low total BZD dose was associated with lower likelihood of seizure cessation compared to the group treated with at least the minimum recommended BZD dosing.

Most patients received BZDs as initial treatment for SE. LZP IV, DZP PR, and MDZ IM were the most common choices. In accordance with guidelines,^{1,8} BZDs remain the mainstay of initial SE treatment.¹ The administration route varies depending on the setting of SE onset and the availability of IV access. PR, IM, intranasal, or buccal BZDs are considered first if the seizure starts out of hospital without availability to IV access. Prior studies compared different BZD types in terms of efficacy and routes of administration in pediatric acute seizures or SE.^{18,37–39} A study including 81 SE episodes showed that IV LZP and DZP were equally effective in stopping generalized seizures.³⁹ Moreover, a study evaluating LZP IV and DZP IV or PR demonstrated no difference between treatments regarding seizure cessation⁴⁰; however, patients with LZP IV required fewer doses to stop seizures than patients treated with DZP. A

Table 3 Relationship between demographic and clinical features of the patients and administered BZD doses

	Low total BZD dose (n = 103)	Recommended total BZD dose (n = 175)	p Values (test)
Demographics			
Male, n (%)	69 (67)	88 (50.3)	0.042 (χ^2)
Median age, y	7.1 (2.3–11.6)	3.7 (1.2–8.4)	0.023 (Wilcoxon)
Weight, kg	22.9 (11.8–41.1)	15 (10.6–24)	0.018 (Wilcoxon)
No history of epilepsy, n (%)	63 (61.2)	79 (45.1)	0.051 (χ^2)
SE characteristics			
Etiology, n (%)			
Structural	28 (27.2)	43 (24.6)	0.822 (χ^2)
Genetic	14 (13.6)	34 (19.4)	0.431 (χ^2)
Metabolic	4 (3.9)	11 (6.3)	0.685 (Fisher)
Other	22 (21.4)	25 (14.3)	0.297 (χ^2)
Unknown	35 (34)	62 (35.4)	0.946 (χ^2)
Febrile seizure, n (%)	10 (9.7)	26 (14.9)	0.431 (χ^2)
Initial seizure type, n (%)			
Generalized tonic-clonic	53 (51.5)	82 (46.9)	0.686 (χ^2)
SE type n (%)			
Intermittent SE	71 (68.9)	116 (66.3)	0.822 (χ^2)
Hospital SE onset, n (%)	30 (29.1)	53 (30.3)	0.946 (χ^2)
Time to first BZD, min	21 (7–55)	12 (5–30)	0.023 (Wilcoxon)
Outcomes			
Continuous infusion, n (%)	57 (55.3)	74 (42.3)	0.131 (χ^2)
Convulsion duration (n = 272), min	137 (60–300)	120 (59–230)	0.485 (Wilcoxon)
Seizure duration (n = 275), h	4.1 (2–21.7)	2.7 (1.3–6)	0.023 (Wilcoxon)
Need for intubation (n = 276), n (%)			0.297 (χ^2)
Yes	75 (74.3)	125 (71.4)	
No	26 (25.7)	50 (28.6)	
Hypotension (n = 276), n (%)			0.075 (χ^2)
Yes	37 (36.6)	44 (25.1)	
No	64 (63.4)	131 (71.4)	

Table 3 Relationship between demographic and clinical features of the patients and administered BZD doses (continued)

	Low total BZD dose (n = 103)	Recommended total BZD dose (n = 175)	p Values (test)
ICU (n = 255), d	5 (2–15.5)	4 (2–10.2)	0.226 (Wilcoxon)
Return to baseline neurologic function (n = 276), n (%)			
Yes	66(65.3)	124(70.9)	0.297 (χ^2)
No	27(26.7)	35(20)	
Unclear	8 (7.9)	16(9.1)	
Mortality (n = 276), n (%)			
Yes	4(4)	3(1.7)	0.191 (Fisher)
No	97(96)	172(98.3)	

Abbreviations: BZD = benzodiazepine; GTC = generalized tonic-clonic; ICU = intensive care unit; SE = status epilepticus. Continuous variables are presented as medians (interquartile range) and categorical variables as numbers (percent).

systematic review including 1,662 seizures in 1,331 patients showed no difference between intranasal and buccal MDZ for seizure cessation.⁴¹ In terms of dosing, patients often receive different BZDs within the first 10 minutes of initiation of treatment. The doses per trial are frequently low, despite consideration of the BZD type or when given in combination with other BZDs. A small percentage of patients received clonazepam and clobazam as first-line ASM. Clonazepam has properties similar to those of LZP with the additional advantages of being heat stable and having a higher bioavailability and a longer half-life.⁴² Improved BZD dosing for the most appropriate agent and consideration of previously given BZDs doses may be areas for improvement in the future.

The initial and total BZD doses for RSE were lower than recommended by guidelines in 57.9% and 37.1% of cases, respectively. Previous studies also report low BZD doses in the treatment of SE.^{12,16,43,44} For example, a prospective study in adult patients managed at 4 hospitals in the United States and Switzerland found that the initial loading dose of LZP as first-line treatment for SE was lower than that recommended dose by their hospital protocols in 87% (72 of 82) of patients.¹² The LZP group required more ASMs to achieve seizure control compared to either the MDZ or clonazepam group. Another study in adult patients showed that only 38% of 118 episodes of SE were treated with the recommended dose of initial treatment. Patients who received low BZD doses were more likely to require more BZDs and non-BZD ASMs.⁴⁴ Similarly, a prospective study in children with convulsive SE showed that of 141 episodes treated out of hospital with DZP PR,

Figure 2 Adjusted odds ratios and 95% confidence intervals of the association between demographic/clinical characteristics and low total BZD dose administration

Results of the multivariable logistic regression showing that patients who received low total benzodiazepine (BZD) dose within 10 minutes of treatment initiation were more often male patients, older children, patients with delayed BZD treatment, and children without a prior diagnosis of epilepsy. The corresponding *p* values for the independent variables included in the model are as follows: male *p* = 0.012; intermittent status epilepticus (SE) *p* = 0.739; hospital SE onset *p* = 0.769; generalized tonic-clonic (GTC) seizures *p* = 0.554; no prior diagnosis of epilepsy *p* = 0.008; delayed BZD treatment *p* = 0.007; and age (years) *p* < 0.001. Sensitivity analysis assuming a cutoff of 15 minutes from treatment initiation for total BZD dose yielded similar results: male *p* = 0.007; intermittent SE *p* = 0.543; hospital SE onset *p* = 0.771; GTC seizures *p* = 0.443; no prior diagnosis of epilepsy *p* = 0.028; delayed BZD treatment *p* = 0.036; and age (years) *p* < 0.001. Likewise, a second multivariable logistic regression assuming a cutoff time of 20 minutes for total BZD dose yielded similar results: male *p* = 0.028; intermittent SE *p* = 0.258; hospital SE onset *p* = 0.822; GTC seizures *p* = 0.782; no prior diagnosis of epilepsy *p* = 0.007; delayed BZD treatment *p* = 0.039; and age (years), *p* < 0.001 (data available from Dryad: table e-2 and figure e-1, doi.org/10.5061/dryad.05qfttf02).

106 (75%) were treated with doses lower than recommended. From these episodes, 83 (78.3%) continued with seizure activity at hospital arrival compared to 30 of 35 episodes that were treated with recommended dosing.¹⁶ Most recently, the Established Status Epilepticus Treatment Trial (ESETT), which involves both adult and pediatric populations, identified that patients with SE commonly receive smaller and multiple doses of BZDs, with 70% (145/207) of patients receiving a lower-than-recommended first dose of BZD. Furthermore, subsequent doses continued to be smaller, and ≈12% of the patients did not receive the minimum recommended cumulative BZD dose despite multiple small doses.⁴⁵ In our cohort, low BZD doses were common in both the out-of-hospital and in-hospital settings. In the low BZD group, 60.5% patients were treated in the in-hospital setting compared to 53.8% in the out-of-hospital setting, with a higher percentage of patients in both the LZP and MDZ groups treated with low dose compared to those in the DZP group. The route of administration of DZP (PR vs IV/intraosseous/oral) may therefore contribute to this observed difference. In our cohort, DZP was more commonly administered via PR, a route of administration that does not offer the opportunity to provide smaller administered doses unless it is initially prescribed at a lower-than-recommended dose. In addition, adequate education of families, nurses, and emergency medical services personnel, who are often the first responders to prolonged seizures, may also contribute to appropriate administration of DZP.

Similar to the ESETT trial,⁴⁵ we found a pattern of administering small and multiple doses. In practice, it is possible that physicians' concern for respiratory depression leads to the use of smaller BZD doses, followed by patients' response assessment, before providing the complete recommended dose. This position is arguable from at least 2 points of view. Administering BZDs in smaller doses than recommended is likely to increase the risk of treatment failure. Alternatively, even if total doses of BZDs do not reach the target dose within the recommended interval, this does not justify delaying the escalation to non-BZD ASMs. In the out-of-hospital setting, emergency medical services staff may follow similar practice approaches leading to lower-than-recommended doses. Thus, when patients arrive at the hospital, they may receive subsequent BZD doses later. Higher initial BZD doses may provide an opportunity for improvement in some settings.

In our study, being older and being male were independently associated with receiving a lower total BZD dose. A recent study in adults showed similar results for age, with older patients more frequently receiving low LZP doses.¹² Regarding sex, the proportion of male participants in our study was similar in both the recommended and the low total BZD groups. Thus, its clinical relevance in the administration of low BZD doses needs to be further studied. It is possible that estimated weights

Table 4 Multivariate Cox regression analysis for seizure cessation

Variable	HR (95% CI)
Low total BZD dose	0.7 (0.57–0.95)
Median age	0.9 (0.95–1.00)
Febrile seizure	1.3 (0.91–1.97)
Generalized tonic-clonic seizure	1.3 (1.05–1.72)
Delayed time to first BZD	0.8 (0.62–1.03)

Abbreviations: BZD = benzodiazepines; CI = confidence interval; HR = hazard ratio.

n = 275. Sensitivity analysis for total BZD dose administered within 15 minutes from treatment initiation yielded similar results: low total BZD dose HR 0.7 (95% CI 0.53–0.91); age HR 0.9 (95% CI 0.95–1.00); febrile seizure HR 1.4 (95% CI 0.93–1.99); generalized tonic-clonic seizures HR 1.4 (95% CI 1.06–1.74); and delayed time to first BZD HR 0.8 (95% CI 0.62–1.02). Likewise, a second multivariate Cox regression analysis considering a total BZD dose administered within 20 minutes from treatment initiation showed similar results: low total BZD dose HR 0.7 (95% CI 0.51–0.87); age HR 0.9 (95% CI 0.95–1.00); febrile seizure HR 1.4 (95% CI 0.92–1.99); generalized tonic-clonic seizures HR 1.3 (95% CI 1.06–1.73); and delayed time to first BZD HR 0.8 (95% CI 0.63–1.04) (data available from Dryad, table e-3, doi.org/10.5061/dryad.05qftf02).

for male patients result in administration of low BZD doses, particularly if the patient is seizing. In our cohort, the median weight was higher in the low total BZD group compared to the recommended total BZD dose group. Data on estimated vs real weights would be needed to confirm this hypothesis in future studies. Similarly, additional research is required to understand the association between administration of low total BZD doses and delayed BZD treatment. Children without a history of epilepsy were more likely to receive low total BZD doses. A potential explanation may be that SE management in patients with a prior diagnosis is often more aggressive due to their known condition, while in patients without an epilepsy history, SE management may be less aggressive, leading to administration of lower-than-recommended BZD doses. A study in 100 children with history of epilepsy at a single tertiary care center showed that 87% of people with epilepsy had a rescue medication prescription, facilitating rescue medication use. Families with seizure action plans were more knowledgeable about administration training and timing.⁴⁶ Therefore, efforts to improve adherence to guidelines, to standardize out-of-hospital and in-hospital treatment protocols, and to equip families and emergency providers with more detailed seizure action plans and education may help improve care integration in acute seizures and SE.

Administration of a low total BZD dose was associated with a decreased likelihood of seizure cessation over time in patients with RSE. Prior studies show that the rate of RSE in adults is different in patients receiving recommended vs lower-than-recommended BZD doses, suggesting that efficacious BZD treatment may lead to seizure cessation in a greater number of patients.^{2,15,47} Moreover, it is more likely that patients who receive low BZD doses require a higher number of ASMs to control convulsive SE.¹² Although the direct relationship between low total BZD dosing and development of RSE was not addressed in the current study due to the nature of our population, our

findings highlight the multifactorial nature of RSE development in that 62.9% of patients with RSE received at least the minimum recommended BZD dose. Nonetheless, once RSE is established, the likelihood of seizure cessation was lower in patients receiving low BZD doses. This finding is relevant given the implications of prolonged SE. Available data show that prolonged seizure duration correlates with increased medical complications, hospital length of stay, functional disability, poor neurologic outcomes, and even death.^{48–50} Therefore, investigating this study with follow-up evaluations and addressing adequate BZD administration through effective implementation of SE protocols may have an impact not only on seizure duration but potentially on long-term neurologic and functional outcomes.

Findings need to be interpreted in the setting of data acquisition. First, our findings are not generalizable to patients without RSE given that our cohort included only patients with RSE. Large prospective longitudinal studies comparing patients with RSE and without RSE are necessary to study the role of BZD dosing and other factors in the development of SE refractoriness in the pediatric population, and on the path toward these studies and important data analyses, recognition and description of the scientific gap is a crucial first step. Second, the prospectively acquired pSERG data are subject to selection and information biases. We tried to minimize these biases by offering the study to all patients at each site who met the inclusion criteria and by prospectively validating data in interviews with the patients and families. Third, considering that pSERG hospitals are tertiary epilepsy referral centers, referral bias and selection of more severe epilepsy cases may play a role. However, primary and secondary centers may struggle with similar concerns about acute seizure treatment protocol implementation and care integration given that seizure treatment is often initiated at home or by emergency medical services. Fourth, we are working with real-life data, and multiple BZDs were given to selected patients in different settings. Therefore, we created a construct to compare BZD dosing, including

Table 5 Absolute risk reduction estimations and number needed to treat to achieve seizure cessation

Time to seizure cessation, h	Low total BZD dose survival (95% CI)	Recommended total BZD dose survival (95% CI)	ARR	NNT
2	0.72 (0.64–0.82)	0.57 (0.50–0.65)	0.15	6.67
4	0.51 (0.42–0.61)	0.33 (0.27–0.41)	0.18	5.55
6	0.43 (0.34–0.53)	0.25 (0.19–0.32)	0.18	5.55
12	0.33 (0.25–0.43)	0.18 (0.13–0.25)	0.15	6.67
24	0.22 (0.15–0.32)	0.14 (0.10–0.21)	0.08	12.5

Abbreviations: ARR = absolute risk reduction; BZD = benzodiazepine; CI = confidence interval; NNT = number needed to treat. Low total BZD dose calculated within 10 minutes of treatment initiation.

fractional BZD doses, because not all patients received the same BZD serially and treating physicians may have applied a different approach to evaluating acute BZD doses. Fifth, we were not able to identify specific differences for BZD administration in select in-patient settings (i.e., emergency department, floor, ICU) due to the nature of our database. However, our findings provide insight into practices in both prehospital and in-hospital settings, and offer opportunities for improvement of SE management in these scenarios. Sixth, it is also possible that the BZD administration time frame may be longer than the proposed 10-minute cutoff in clinical practice. Therefore, in our sensitivity analyses, we considered the total BZD dose administered within 15 and 20 minutes of treatment initiation and found similar results for our primary and secondary outcomes (data available from Dryad, tables e-2–e5 and figure e-1, doi.org/10.5061/dryad.05qfttf02). Finally, power calculation (i.e., sample size) was not performed given the exploratory and preliminary nature of our data.

Most patients received BZDs as first-line ASM for RSE management. The initial and total BZD doses used in pediatric patients who went on to experience RSE were lower than the minimum recommended doses. Male patients, older children, patients with delayed BZD treatment, and children without a prior diagnosis of epilepsy were more likely to receive low total BZD doses. Moreover, patients who received low total BZD doses had a decreased likelihood of seizure cessation. Administering acute BZD doses as recommended by guidelines may provide an opportunity for care improvement.

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Appendix 1 Authors

Author	Location	Contribution
Alejandra Vasquez, MD	Boston Children's Hospital, Harvard Medical School, MA; Mayo Clinic, Rochester, MN	Participated in drafting and revising the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data, statistical analysis, and study supervision or coordination
Marina Gaínza-Lein, MD	Boston Children's Hospital, Harvard Medical School, MA; Universidad Austral de Chile, Valdivia; Hospital Clínico San Borja Arriarán, Universidad de Chile, Santiago	Participated in drafting and revising the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data, and study supervision or coordination
Nicholas S. Abend, MD MSCE	The Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania	Participated in drafting and revising the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data, and study supervision or coordination
Marta Amengual-Gual, MD	Boston Children's Hospital, Harvard Medical School, MA; Hospital Universitari Son Espases, Universitat de les Illes Balears, Palma, Spain	Participated in drafting and revising the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data, and study supervision or coordination
Anne Anderson, MD	Baylor College of Medicine, Houston, TX	Participated in drafting and revising the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data, and study supervision or coordination
Ravindra Arya, MD, DM	Cincinnati Children's Hospital Medical Center, University of Cincinnati, OH	Participated in drafting and revising the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data, and study supervision or coordination
J. Nicholas Brenton, MD	University of Virginia Health System, Charlottesville	Participated in drafting and revising the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data, and study supervision or coordination

Appendix 1 (continued)

Jessica L. Carpenter, MD	Children's National Medical Center, George Washington University School of Medicine and Health Sciences, Washington, DC	Participated in drafting and revising the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data, and study supervision or coordination
Kevin Chapman, MD	Children's Hospital Colorado, University of Colorado School of Medicine, Aurora	Participated in drafting and revising the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data, and study supervision or coordination
Justice Clark, MPH	Boston Children's Hospital, Harvard Medical School, MA	Participated in drafting and revising the manuscript for content, including study concept and design, analysis and interpretation of data, acquisition of data, and study supervision or coordination
Raquel Farias-Moeller, MD	Children's Hospital of Wisconsin, Medical College of Wisconsin, Milwaukee	Participated in drafting and revising the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data, and study supervision or coordination
William D. Gaillard, MD	Children's National Medical Center, George Washington University School of Medicine and Health Sciences, Washington, DC	Participated in drafting and revising the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data, and study supervision or coordination
Tracy Glauser, MD	Cincinnati Children's Hospital Medical Center, University of Cincinnati, OH	Participated in drafting and revising the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data, and study supervision or coordination
Joshua L. Goldstein, MD	Northwestern University Feinberg School of Medicine, Chicago, IL	Participated in drafting and revising the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data, and study supervision or coordination

Continued

Appendix 1 (continued)

Howard P. Goodkin, MD, PhD	University of Virginia Health System, Charlottesville	Participated in drafting and revising the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data, and study supervision or coordination
Rejean M. Guerriero, DO	Washington University Medical Center, Washington University School of Medicine, St. Louis, MO	Participated in drafting and revising the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data, and study supervision or coordination
Kush Kapur, PhD	Boston Children's Hospital, Harvard Medical School, MA	Participated in drafting and revising the manuscript for content, including study concept and design, analysis and interpretation of data, acquisition of data, and study supervision or coordination
Yi-Chen Lai, MD	Baylor College of Medicine, Houston, TX	Participated in drafting and revising the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data, and study supervision or coordination
Tiffani L. McDonough, MD	Columbia University Medical Center, Columbia University, New York, NY	Participated in drafting and revising the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data, and study supervision or coordination
Mohamad A. Mikati, MD	Duke University Medical Center, Duke University, Durham, NC	Participated in drafting and revising the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data, and study supervision or coordination
Lindsey A. Morgan, MD	Seattle Children's Hospital, WA	Participated in drafting and revising the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data, and study supervision or coordination

Appendix 1 (continued)

Edward J. Novotny, MD	Seattle Children's Hospital, WA	Participated in drafting and revising the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data, and study supervision or coordination
Adam P. Ostendorf, MD	Nationwide Children's Hospital, The Ohio State University, Columbus	Participated in drafting and revising the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data, and study supervision or coordination
Eric T. Payne, MD	Mayo Clinic, Rochester, MN	Participated in drafting and revising the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data, and study supervision or coordination
Katrina Peariso, MD, PhD	Cincinnati Children's Hospital Medical Center, University of Cincinnati, OH	Participated in drafting and revising the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data, and study supervision or coordination
Juan Piantino, MD	Oregon Health and Science University, Portland	Participated in drafting and revising the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data, and study supervision or coordination
James J. Riviello, MD	Baylor College of Medicine, Houston, TX	Participated in drafting and revising the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data, and study supervision or coordination
Kumar Sannagowdara, MD	Children's Hospital of Wisconsin, Medical College of Wisconsin, Milwaukee	Participated in drafting and revising the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data, and study supervision or coordination

Appendix 1 (continued)

Robert C. Tasker, MBBS, MD	Boston Children's Hospital, Harvard Medical School, MA	Participated in drafting and revising the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data, and study supervision or coordination
Dmitry Tchapyjnikov, MD	Duke University Medical Center, Duke University, Durham, NC	Participated in drafting and revising the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data, and study supervision or coordination
Alexis Topjian, MD, MSCE	The Children's Hospital of Philadelphia, The Perelman School of Medicine at the University of Pennsylvania	Participated in drafting and revising the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data, and study supervision or coordination
Mark S. Wainwright, MD, PhD	Seattle Children's Hospital, WA	Participated in drafting and revising the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data, and study supervision or coordination
Angus Wilfong, MD	University of Arizona College of Medicine and Barrow's Neurologic Institute at Phoenix Children's Hospital	Participated in drafting and revising the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data, and study supervision or coordination
Korwyn Williams, MD, PhD	University of Arizona College of Medicine and Barrow's Neurologic Institute at Phoenix Children's Hospital	Participated in drafting and revising the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data, and study supervision or coordination
Tobias Loddenkemper, MD	Boston Children's Hospital, Harvard Medical School, MA	Participated in drafting and revising the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data, statistical analysis, and study supervision or coordination

Appendix 2 Coinvestigators

Coinvestigators are listed at links.lww.com/WNL/B215

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