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RESEARCH ARTICLE

Optimizing pediatric status epilepticus management: The role of early midazolam infusion and adherence to clinical practice guidelines

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Abstract

Objective: This study was undertaken to describe a cohort of pediatric patients with status epilepticus (SE) in Italy over the past decade, focusing on the variability of treatment protocols among centers, adherence to guidelines, and potential predictors of refractoriness.

Methods: This is a multicenter retrospective observational cohort study including patients aged 1 month to 18 years who experienced convulsive SE (CSE) between January 2010 and June 2022. Variables analyzed included age at CSE onset, etiology, and treatment.

Results: We included 1374 CSE episodes in 1071 patients (median age = 3.3 years); 46% occurred in the first 3 years of life. The prominent etiology was remote symptomatic (32%). Resolution was obtained only with benzodiazepine administration in 19.2% of SE episodes. Phenytoin, phenobarbital, and midazolam by infusion were the drugs most frequently used. Maximum therapeutic response occurred with low-dose (<.2 mg/kg/h) midazolam infusion administered at an

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early stage, following a single dose of benzodiazepine or an antiseizure medication (ASM; 59%). Midazolam effectiveness decreased to 37% when it was used after multiple ASMs, even at high doses. CSE was refractory in 39% of cases. Predictors of refractoriness included nonadherence to current guidelines, type of CSE, and etiology.

Significance: This study emphasizes that low-dose midazolam infusion, not requiring endotracheal intubation and administered at an early phase, appears to be effective in permanently stopping seizure and preventing the evolution toward a refractory CSE. Given its proven efficacy and widespread use in many hospitals, early midazolam infusion could be considered in the management of pediatric CSE. Adherence to treatment protocols, specific etiologies, and type of CSE are correlated with refractoriness; thus, when facing SE in infants, these factors should guide treatment protocol selection, including medication choice and timing.

KEYWORDS

guideline adherence, midazolam infusion, pediatric status epilepticus, refractory status epilepticus, status epilepticus etiology

1 | INTRODUCTION

Convulsive status epilepticus (CSE) is one of the most critical neurological emergencies, particularly in the pediatric population. The traditional definition of status epilepticus (SE) is a single seizure or series of seizures without intervening recovery of consciousness lasting ≥30 min. A widely accepted, operational definition of SE reduces the duration to 5 min, which recognizes the need for rapid treatment to prevent long-term neurological damage and decrease the risk of mortality.[1,2]

The challenges in managing pediatric CSE are numerous and multifaceted. In addition to the need for rapid treatment, factors such as the underlying etiology, patient age, and response to first-line and second-line treatments can significantly influence the progression and outcome of the condition.[3] SE not responding to first-line and second-line antiseizure medications (ASMs) is defined as refractory (refractory CSE [RCSE]) and requires intensive care unit treatment.[4] The transition from non-RCSE to RCSE presents additional therapeutic challenges and is associated with poorer outcomes, including increased rates of morbidity and mortality.[5,6]

There is a consensus over the first- and second-line treatments of CSE,[7–9] whereas there is currently neither evidence nor consensus to guide either the optimal choice of therapy or treatment goals for RCSE, which is generally treated with coma induction using anesthetics (third-line therapy).[10]

Despite well-established guidelines for the management of CSE, significant variation in their implementation persists across health care institutions.[11–14] This inconsistency can negatively impact patient outcomes, highlighting the need for a deeper understanding of how CSE is managed in real-world settings.[11–14]

Despite these risks, adherence to CSE treatment guidelines is not always consistent. A review of the current literature suggests that deviations from recommended protocols are common and may result in prolonged seizure duration, increased drug administration, and a greater need for more invasive interventions such as intubation.[12]

Key points

- SE is confirmed as a frequent neurological emergency in children requiring immediate and appropriate diagnosis and treatment.
- In our study, approximately 40% of pediatric SE episodes are refractory to first- and second-line treatments.
- Refractoriness correlates with the poor step-by-step application of current clinical practice guidelines during the acute phase of an SE episode.
- Refractoriness is also related to etiology and type of SE.
- Based on our descriptive data, MDZ infusion, administered at an early stage, might be effective for treatment of pediatric SE episodes.

The reasons for this nonadherence are variable, ranging from logistical challenges to differences in clinical judgment. This variability underscores the importance of examining real-world data to better understand the factors that contribute to successful or unsuccessful CSE management.[12–14]

Although randomized controlled trials (RCTs) are considered the gold standard for evaluating medical interventions, conducting such studies in the context of CSE poses significant ethical challenges.[15] The urgency of the condition makes it difficult to withhold or randomize treatment, as delayed intervention could lead to irreversible harm.[16] Consequently, the analysis of real-world data has emerged as a valuable alternative for studying CSE. By examining data from actual clinical practice, researchers can gain insights into how CSE is managed in diverse health care settings and identify the key factors that influence treatment success.[12–14]

This study focuses on the real-world application of currently available CSE treatment guidelines[7–9] across 11 Italian tertiary pediatric hospitals.

The aim is to explore the relationship between guideline adherence and the resolution of CSE, thus preventing refractoriness. By analyzing data from a large cohort of pediatric CSE patients, this study seeks to provide a comprehensive understanding of how current treatment protocols[7–9] are applied in practice and what factors contribute to successful management. In doing so, it hopes to inform future guidelines and improve the standardization of care for pediatric CSE, ultimately leading to better patient outcomes.

2 | MATERIALS AND METHODS

2.1 | Study design

This is a multicenter retrospective observational cohort study involving epileptologists and intensivists from 11 Italian tertiary pediatric hospitals that, in June 2021, formally joined to launch a nonprofit association: the Italian Pediatric Status Epilepticus (IPSE) group. The research protocol was approved by the institutional review boards of all 11 participating institutions: Salesi Children's Hospital (Ancona), IRCCS AOU (Bologna), IRCCS Meyer Children's Hospital (Florence), IRCCS Gaslini (Genoa), Buzzi-Sacco Hospital (Milan), University Hospital (Padua), IRCCS Bambino Gesù (Rome), IRCCS Gemelli (Rome), Regina Margherita Hospital (Turin), IRCCS Burlo Garofolo (Trieste), and University Hospital (Verona). The Tuscan Pediatric Ethics Committee (Coordinating Center) approved this study on April 15, 2020 (105/2020), and it was approved by the Italian Medicine Agency on May 5, 2020. For patients from whom consent could not be obtained, due to the retrospective and anonymous nature of the data, the local ethics committee approved a waiver of consent. All personal data were handled confidentially and anonymously, in accordance with the Declaration of Helsinki and local data protection regulations.

2.2 | Specific and detailed aims of the study

Aims of the study were as follows:

1. To describe a cohort of pediatric patients with CSE sourced from main Italian tertiary children's hospitals with pediatric intensive care units over the past 11 years;
2. To describe the variability of pediatric CSE treatment protocols at each participating center and the efficacy of first-, second-, and third-line treatments;
3. To compare the subgroup of patients whose treatment adhered to currently used guidelines[7–9] with the subgroup in which treatment was not adherent to such recommendations; and
4. To explore potential predictors of CSE refractoriness.

2.3 | Patients

Patients aged from 1 month to 18 years, admitted for CSE to one of the 11 hospitals from January 1, 2010 to June 30, 2022, were identified using different search methods, including the International Classification of Diseases, 9th Revision system, local databases, discharge letters, and electroencephalographic (EEG) recording databases. Patient selection could be biased by the modifications of definition of SE over time. Only individuals in whom CSE episodes had been clinically and/or EEG documented were included in the study. Patients referred from other hospitals were included in the study only if CSE was still ongoing.

2.4 | Data collection

An electronic case report form was developed ad hoc using Research Electronic Data Capture. The variables analyzed in the present work include the following: sex, age, type of CSE,[2] etiology of CSE,[2] type of epilepsy,[17] type of syndrome,[18] administered drugs, route of administration, maximum dosage, order of administration, CSE onset setting, duration of CSE, CSE without previous epilepsy diagnosis, presence of mechanical ventilation, type of ventilation, duration of mechanical ventilation, adverse events, pediatric intensive care unit (PICU) admission, reason for PICU admission, duration of stay in PICU, total length of hospital stay, adherence to therapy, and refractoriness. Genetic etiology was considered as presumed when a genetic predisposition was supposed but could not be proved. Genetic etiologies whether known or presumed, with or without structural brain abnormalities, were considered as a remote cause of CSE.

2.5 | Definitions

We adopted the definition of SE proposed by the International League Against Epilepsy (ILAE) classification, which considers all tonic–clonic seizures lasting longer than 5 min as SE and focal motor seizures with impaired consciousness lasting longer than 10 min as focal SE.[2]

We adopted the previous ILAE classification of seizures and epilepsy by Berg et al.[18] for the definition of electroclinical syndromes, as the data were collected before the latest ILAE classification of epilepsies and epileptic syndromes.[19,20]

Refractoriness has been defined as failure to stop seizures despite the administration of appropriately dosed benzodiazepines (BDZs) and at least one second-line ASM.[4]

In cases where the order of drug administration was not as indicated by the currently available guidelines,[7–9] we defined refractory episodes of CSE as lasting longer than 60 min or requiring more than three drugs regardless of the sequence.

The term adherence was adopted to define the treatment of CSE according to currently used guidelines.[7–9]

We also considered as adherent the use of midazolam (MDZ) infusion at dosages applicable in neurological wards (≤.2 mg/kg/h). To help avoid complications of refractory SE (RSE) clinicians often use infusions of MDZ, this procedure is also commonly used in Italian hospitals and was widely represented in the reviewed medical records.

We defined early MDZ infusion at a dose lower than .2 mg/kg/h, specifically to distinguish it from high-dose MDZ at anesthetic levels.[21] This term applies also to patients who received MDZ infusion immediately after a single dose of first-line treatment (BDZs), following an initial bolus of MDZ, or in cases where MDZ was administered after the failure of a single dose of a second-line ASM. The threshold dose of .2 mg/kg/h and the timing of administration reflect a long-standing practice adopted in several of the participating centers, based on more than 20 years of clinical experience in pediatric CSE management in Italy.

Treatment was considered to be effective when leading to seizure termination; according to clinical practice, the time scale for seizure termination was considered to be approximately 5 min; the end of the CSE was clinically defined with the integration of EEG data when available.

2.6 | Statistical analysis

For the first aim, concerning the description of a cohort of pediatric patients with CSE in Italy over the past decade, continuous variables were summarized using median and interquartile range (IQR) for the continuous variables, whereas categorical variables were presented as frequency and percentage (relative frequency). Because this was a purely descriptive analysis, no inferential statistical tests were applied.

For the second aim, focusing on describing the variability among protocols used at participating centers, the efficacy of first-, second-, and third-line treatments was compared using descriptive statistics. Data from all CSE events were summarized in a table presenting absolute and relative frequencies. Percentages within this table were calculated by row (within each drug), in contrast to other tables where column percentages were used. Additionally, temporal trends were plotted and evaluated using the Mann–Kendall test.

For the third aim, comparing patients based on adherence to guidelines at the first observed CSE episode, continuous variables were analyzed using the Mann–Whitney *U*-test, whereas categorical variables were compared using the chi-squared test or Fisher exact test, as appropriate.

Furthermore, Benjamini–Hochberg correction of the *p*-values (*q*-values) was performed to control the false discovery rate.[22]

For the fourth aim, univariable and multivariable logistic regression analyses were performed for the prediction of refractoriness. According to clinical judgment, the following variables were considered as predictor of refractoriness: adherence to therapy, type of CSE, CSE etiology, age, gender, and new onset CSE without preceding epilepsy. Because the few cases of epilepsia partialis continua (nine in total) were all refractory to treatment, these cases were excluded from regression analyses to avoid the quasicomplete separation issue.[23] Moreover, as multiple events were recorded for approximately 14% of the patients, special consideration was required in estimating the variance of regression coefficients. To address the issue of repeated data, Huber–White's robust sandwich variance with clusters of patients was employed to estimate covariance.[24] The results were provided as odds ratio (OR) and 95% confidence interval (CI). For all analyses, a *p*-value and a *q*-value of <.05

were significant. Statistical analyses were performed using the R System version 4.3.3 and package rms.[25]

3 | RESULTS

3.1 | Aim 1: Cohort and CSE episodes description

3.1.1 | Patients

A total of 1374 CSE episodes in 1071 patients were included, with a median age at SE occurrence of 3.3 (IQR = 1.3–7.4) years; 591 (55%) were males. A significant portion of the CSE episodes (640/1374, 46%) occurred within the first 3 years of life, with 40% (252/640) during the first year and 60% (388/640) between 1 and 3 years of age. Convulsive SE occurred more than once in 14% (151/1071) of patients, with 38% (57/151) having between two and 18 CSE episodes. Convulsive SE first occurred in children without prior epilepsy in 27% (285/1071) of cases (new onset SE without preceding epilepsy). The median age of new onset cases was 23 months (IQR = 1.4–6.3). Demographics and clinical features are summarized in Table 1.

3.1.2 | CSE etiology

Remote symptomatic etiology, the most observed in the entire cohort, was documented in 32% (341/1071) of patients, including genetic factors (148/341, 43%), sequelae of acute brain injuries (83/341, 24%), cortical malformations (81/341, 24%), metabolic disorders (8/341, 2.3%), and brain tumors (7/341, 2.1%). Etiology was acute symptomatic in 25% (267/1071) of patients, including central nervous system infections (111/267, 46%), inflammatory/autoimmune conditions (28/267, 12%), including new onset RSE (NORSE; 10 patients) and febrile infection-related epilepsy syndrome (FIRES; 12 patients), and cerebrovascular diseases (50/267, 21%), including ischemic stroke (24/50), hypoxic–ischemic encephalopathy (10/50), hemorrhagic stroke (10/50), and posterior reversible encephalopathy syndrome (6/50). In 19% (207/1071) of patients, the first CSE episode observed occurred in the context of electroclinical syndromes. Among these, 32% (66/207) of cases had a genetic origin. CSE occurred in the context of a febrile condition in 12.7% (135/1071) of patients. In 5.6% (60/1071) of patients, CSE was associated with a progressive disease, including metabolic conditions (39/60, 65%), tumor-related conditions (11/60, 18%), and progressive myoclonic epilepsy (5/60, 8.3%). Underlying CSE etiology could not be identified in 5.7% (61/1071) of patients. Between 1 and 3 years, febrile and acute causes prevailed (Figure 1).

TABLE 1 Demographic and clinical characteristics of patients and CSE episodes.

Patient characteristic	Value (N = 1071)[a]
Sex	
Male	591 (55%)
Female	480 (45%)
CSE without preceding epilepsy	
No	786 (73%)
Yes	285 (27%)
CSE etiology	
Remote	341 (32%)
Acute	267 (25%)
Electroclinical syndrome	207 (19%)
Febrile	135 (12.7%)
Progressive	60 (5.6%)
Unknown etiology	61 (5.7%)

CSE episode characteristic	Value (N = 1374)[a]
Age at CSE, years	3.3 (1.3–7.4)
CSE onset setting	
Prehospital CSE onset	799 (62%)
In-hospital CSE onset	225 (17%)
Other hospital	277 (21%)
Type of CSE	
Focal	447 (33%)
Focal onset evolving into bilateral convulsive	454 (33%)
Generalized convulsive	337 (24%)
Generalized myoclonic	85 (6.2%)
Generalized tonic	42 (3.1%)
Epilepsia partialis continua	9 (.7%)
Duration of CSE	
<30 min	274 (20%)
30–60 min	245 (18%)
1–24 h	328 (24%)
>24 h	527 (38%)
Duration of hospital stay, days	8 (4–19)
Adverse events	
Yes	63 (5%)
No	1311 (95%)
PICU admission	
Yes	694 (51%)
No	680 (49%)
Duration of PICU stay, days	3 (1–8)
Reason for PICU admission	
Seizure treatment	400 (58%)
Respiratory failure	179 (26%)
Other	115 (16%)

(Continues)

TABLE 1 (Continued)

CSE episode characteristic	Value ($N=1374$)[a]
Mechanical ventilation	
Yes	459 (66%)
No	233 (34%)
Type of ventilation	
Invasive mechanical	421 (92%)
Noninvasive	38 (8%)

Abbreviations: CSE, convulsive status epilepticus; PICU, pediatric intensive care unit.

[a] *n* (%) or median (interquartile range).

3.2 | Aim 2: Variability of pediatric CSE treatment protocols at each participating center and the efficacy of first-, second-, and third-line treatments

3.2.1 | CSE treatment

Treatment protocols differed among the 11 hospitals in terms of dosage, type, and order of medication administration. In Table 2 are summarized all the drugs administered to patients during the course of each CSE event that was documented during the study period. Rectal diazepam and buccal MDZ were the most administered early treatments. Phenytoin (PHT), phenobarbital, and MDZ were the most frequently used compared with levetiracetam, lacosamide, and valproic acid. Specifically, PHT was the ASM of first choice in the treatment of 137 episodes of focal SE, 117 episodes of focal to bilateral tonic–clonic SE, and 76 episodes of generalized tonic–clonic SE, being effective in 65 (47%), 58 (50%), and 37 (49%) cases, respectively. Phenobarbital was the ASM of first choice in 37 generalized myoclonic SE and 13 generalized tonic SE cases, being effective in 14 (38%) and five (38%) cases, respectively. MDZ was the drug most frequently used. Continuous intravenous infusion of MDZ ≤ .2 mg/kg/h was effective in 59% (200/339) of cases when used following the failure of a first-line therapy in 127 CSE episodes and after a single dose of ASM in 73. However, its efficacy, even at a dosage of >.2 mg/kg/h, dropped to 37% (58/158) when administered after the failure of more than one ASM or another anesthetic (Table 2). Third-line therapy was required in 370 of 1374 episodes of CSE (27%). In 51% (190/370) of CSE episodes, only one anesthetic was effective in stopping SE, whereas more than two anesthetics were needed in 13% (47/370) of cases. Among third-line therapies, propofol (PR) was the most effective anesthetic (112/198, 57%) and even the earliest administered, being the anesthetic of first choice

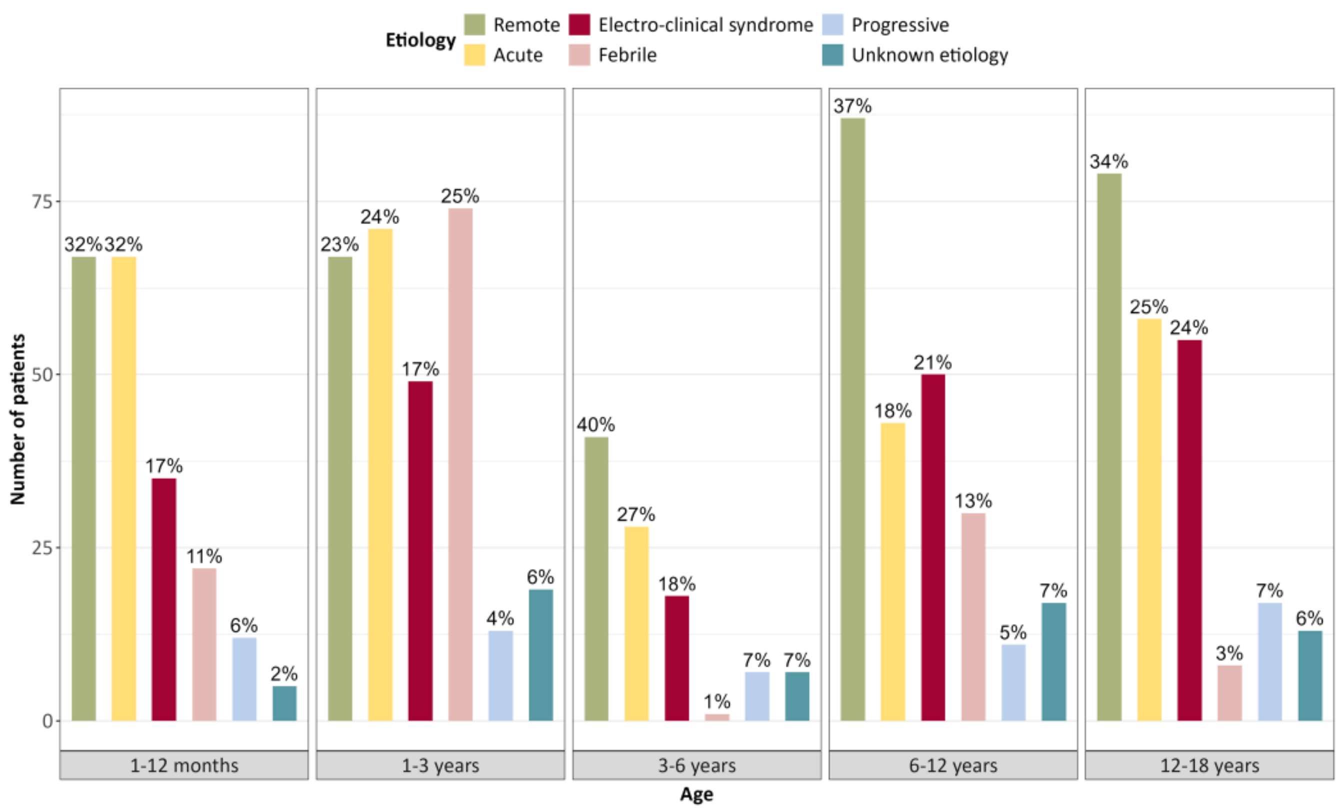

FIGURE 1 Etiology and age at first convulsive status epilepticus (CSE) episode. Distribution of patients at the first observed episode of CSE is shown by etiology and age group.

TABLE 2 Efficacy of second- and third-line therapy.

Drug	Efficacy, *n* (%)[a]	Nonefficacy, *n* (%)[a]	Total, *n* (%)[a]
Antiseizure medications			
Phenytoin	171 (46%)	199 (54%)	370 (100%)
Phenobarbital	116 (39%)	184 (61%)	300 (100%)
Levetiracetam	81 (37%)	140 (63%)	221 (100%)
Lacosamide	9 (21%)	33 (79%)	42 (100%)
Valproic acid	19 (28%)	49 (72%)	68 (100%)
Midazolam, ≤.2 mg/kg/h	200 (59%)	139 (41%)	339 (100%)
Anesthetics			
Midazolam, >.2 mg/kg/h	58 (37%)	100 (63%)	158 (100%)
Propofol	112 (56%)	88 (44%)	200 (100%)
Thiopental	50 (45%)	62 (55%)	112 (100%)
Ketamine	43 (41%)	63 (59%)	106 (100%)

[a]Percentages in this table were calculated by row (within each drug), unlike other tables where percentages are by column.

in most cases. Over the 12 years of observation, MDZ and PR were the most frequently used third-line drugs, although ketamine use increased ($p = .007$; Figure 2).

3.3 | Aim 3: Comparison of treatment guideline-adherent group versus nonadherent group

3.3.1 | Adherence to treatment guidelines

The treatment was adherent in 65% (895/1374) CSE episodes and nonadherent in the remaining 35% (479/1374). As shown in Table 3, age groups, context of onset, type, etiology, duration of CSE, length of hospital stay, admission to the PICU, reason for PICU admission, length of PICU stay, and use of mechanical ventilation were statistically significantly different between the adherent and nonadherent groups. Nonadherence to treatment guidelines was more commonly observed in patients referred from other hospitals, and it was associated with the administration of a third-line medication before ASM in 111 of 277 (40%) CSE episodes. Furthermore, nonadherence to guidelines was associated with a significant increase in the duration of CSE, length of hospital stays, admission to PICU, mechanical ventilation, and length of PICU stay (Table 3).

3.4 | Aim 4: Potential predictors of CSE refractoriness

3.4.1 | Refractoriness

CSE was not refractory in 61% (845/1374) and refractory in 39% (529/1374) of the cases. The management of 51% (694/1374) of CSE episodes required admission to the PICU; however, only 58% (400/694) of these admissions were for treatment of CSE. The remaining hospitalizations were necessary to manage complications such as respiratory failure or to improve general medical management of the patients' conditions (Table 1).

3.4.2 | Predictors of refractoriness

The results of the univariable and multivariable logistic regression analyses aiming at identifying the predictors of refractoriness are reported in Table 4. In the univariable analysis, adherence to therapy, CSE etiology, CSE semiology, age, and CSE without preceding epilepsy were significantly associated with refractoriness. The role of these factors, except for CSE without previous epilepsy and age at onset, was confirmed by the multivariable analysis (Table 4). In the multivariable analysis, a significant reduction in the risk of refractoriness of approximately 75% was observed in patients treated according to guidelines (OR = .25, 95% CI = .19–.32, $p < .001$).[7–9] Moreover, compared to CSE episodes with focal to bilateral seizures, those with generalized myoclonus and generalized tonic–clonic seizures showed a significant association with refractoriness ($p = .002$ and $p = .0036$, respectively). Specifically, an increased risk of refractoriness was observed in the former (OR = 2.37, 95% CI = 1.38–4.06), whereas a reduced risk was observed in the latter (OR = .69, 95% CI = .49–.98). Overall, in the multivariable model, the predicted effect of age on refractoriness—modeled using a restricted cubic spline to allow for nonlinearity (Figure S1)—was not statistically significant (linear term: OR = .99, 95% CI = .98–1.00, p =. 097; nonlinear term: OR = 1.01, 95% CI =

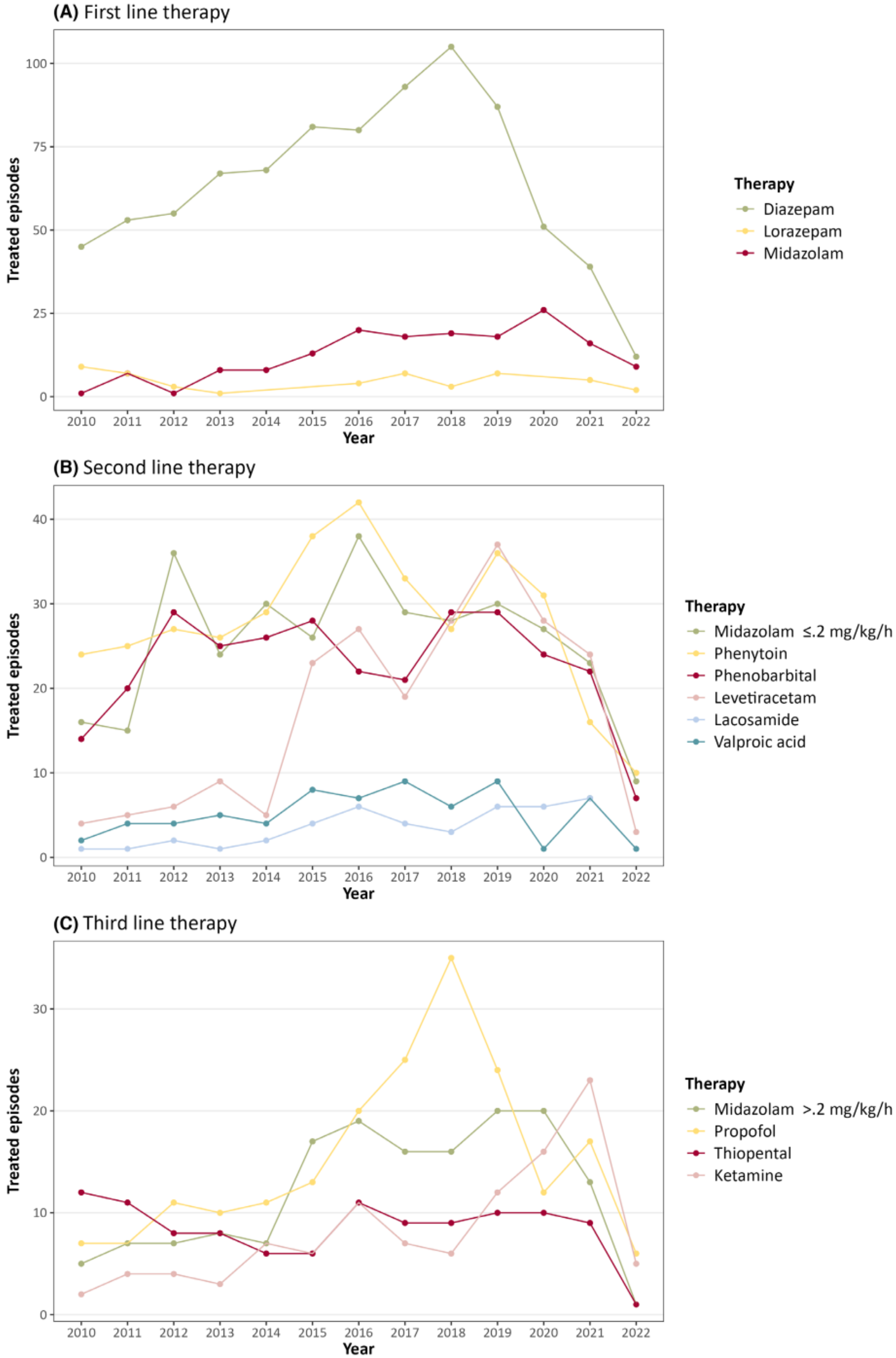

FIGURE 2 Trends in convulsive status epilepticus treatment over 12 years. (A) First line. (B) Second line. (C) Third line.

TABLE 3 Characteristics of 1071 CSE episodes according to therapy adherence.

Characteristic	Therapy adherence: No, $N=354$[a]	Yes, $N=717$[a]	q-value[b]
Sex			
Male	190 (54%)	401 (56%)	.5
Female	164 (46%)	316 (44%)	
Age at CSE, years	3.2 (1.1–7.5)	3.4 (1.3–7.3)	.2
Age groups			
1–12 months	91 (26%)	117 (16%)	**.001**
1–3 years	84 (24%)	209 (29%)	
3–6 years	40 (11%)	62 (9%)	
6–12 years	63 (18%)	175 (24%)	
12–18 years	76 (21%)	154 (21%)	
CSE onset setting			
Prehospital	189 (55%)	446 (65%)	**.009**
In-hospital	52 (15%)	94 (14%)	
Other hospital	100 (29%)	143 (21%)	
CSE without preceding epilepsy			
Yes	85 (24%)	198 (28%)	.30
No	269 (76%)	519 (72%)	
Type of CSE			
Focal	96 (27%)	224 (31%)	**.013**
Focal to bilateral	121 (34%)	243 (34%)	
Generalized convulsive	89 (25%)	193 (27%)	
Generalized tonic	12 (3.4%)	26 (3.6%)	
Generalized myoclonic	30 (8.5%)	29 (4.1%)	
Epilepsia partialis continua	6 (1.7%)	2 (.3%)	
CSE etiology			
Remote	122 (34%)	219 (31%)	**<.001**
Acute	103 (29%)	164 (23%)	
Electroclinical syndrome	47 (13%)	160 (22%)	
Progressive	33 (9.3%)	27 (3.8%)	
Febrile	33 (9.3%)	102 (14%)	
Unknown	16 (4.5%)	45 (6.3%)	
Duration of CSE, min	780 (45–6480)	45 (45–105)	**<.001**
Duration of hospital stay, days	13 (6–32)	6 (4–13)	**<.001**
PICU admission			
Yes	253 (71%)	325 (45%)	**<.001**
No	101 (29%)	392 (55%)	
Duration of PICU stay, days	4 (1–13)	2 (1–5)	**<.001**
Reasons for PICU admission			
Seizure treatment	169 (67%)	150 (46%)	**<.001**
Respiratory failure	48 (19%)	108 (33%)	
Other	36 (14%)	67 (21%)	
Mechanical ventilation			
Yes	189 (75%)	194 (60%)	**<.001**
No	63 (25%)	130 (40%)	
Type of ventilation			
Invasive mechanical	181 (95.8%)	175 (89.2%)	.051
Noninvasive	8 (4.2%)	19 (9.8%)	
Adverse events			
Yes	22 (6.2%)	32 (4.5%)	.3
No	332 (93.8%)	685 (95.5%)	

(Continues)

Note: Bold numbers indicate $p<.05$.

Abbreviations: CSE, convulsive status epilepticus; PICU, pediatric intensive care unit.

[a]*n* (%) or median (interquartile range).

[b]Benjamini–Hochberg correction for multiple testing.

.99–1.03, $p=.138$). We also fitted a model that included the interaction between etiology and age. However, none of the interaction terms reached statistical significance (Table S1).

4 | DISCUSSION

Our large, multicenter, real-world observational study of 1374 episodes of CSE over 12 years provides some clues for important considerations on occurrence, etiology, management, and treatment of pediatric CSE.

MDZ was the most frequently administered drug, and its efficacy when used by infusion and at an early phase, following a single dose of BZD or a second-line drug, was higher than other common ASMs and similar to that reported in RCTs on second-line treatments.[26–28] Although some guidelines, in the case of failure of the first BDZ, recommend repeating a second dose or using a second-line therapy, our observation and other guidelines[29–31] suggest

TABLE 4 Regression analyses for the prediction of refractoriness.

Variable	Univariable OR (95% CI)	Univariable p[a]	Multivariable OR (95% CI)	Multivariable p[a]
Adherence				
No	1.00 (ref)		1.00 (ref)	
Yes	.22 (.17–.29)	**<.001**	.25 (.19–.33)	**<.001**
Type of CSE				
Focal to bilateral	1.00 (ref)		1.00 (ref)	
Focal	.92 (.68–1.23)	.566	.90 (.67–1.22)	.509
Generalized tonic–clonic	.62 (.45–.85)	**.003**	.70 (.49–.98)	**.041**
Generalized tonic	.93 (.48–1.80)	.825	.94 (.46–1.93)	.863
Generalized myoclonic	2.91 (1.82–4.67)	**<.001**	2.29 (1.34–3.92)	**.002**
CSE etiology				
Acute	1.00 (ref)		1.00 (ref)	
Remote	.88 (.63 1.24)	.467	.69 (.46–1.03)	.067
Febrile	.22 (.13–.36)	**<.001**	.28 (.16–.48)	**<.001**
Progressive	3.04 (1.75–5.29)	**<.001**	2.10 (1.17–3.77)	**.013**
Electroclinical syndrome	.44 (.30–.67)	**<.001**	.41 (.33–.64)	**<.001**
Unknown	.44 (.24–.79)	**.006**	.48 (.25–.94)	**.031**
Partialis continua[b]	NA	NA	NA	NA
Age, months				
Linear term	.99 (.98–.9996)	**.041**	.99 (.98–1.00)	.097
Nonlinear term	1.02 (1.001–1.03)	**.033**	1.01 (.99–1.03)	.138
Sex				
Male	1.00 (ref)		1.00 (ref)	
Female	1.22 (.92–1.62)	.178	1.16 (.86–1.58)	.317
CSE without preceding epilepsy				
No	1.00 (ref)		1.00 (ref)	
Yes	.66 (.49–.88)	**.006**	.76 (.52–1.12)	.162

Abbreviations: CI, confidence interval; CSE, convulsive status epilepticus; NA, not applicable; OR, odds ratio; ref, reference.

[a]Bold numbers indicate $p < .05$.

[b]The nine cases of epilepsy partialis continua, all refractory to treatment, were excluded from the regression analyses to avoid quasicomplete separation.

the early use of an intravenous anesthetic agent such as MDZ might be effective in stopping CSE and allowing patients to recover safely and rapidly from seizures. Early use of MDZ can be a crucial factor in case of impending SE; it might prevent its potential evolution into RSE, thus improving outcomes.

The early use of low-dose MDZ infusion (<.2 mg/kg/h) observed at several participating centers is the result of a long-standing real-world practice in Italy, established over the past 2 decades. This approach was developed to achieve rapid seizure control, reducing the likelihood of progression to RCSE or superrefractory CSE. This low-dose strategy was intentionally designed to minimize the risk of respiratory depression, thus avoiding, in many cases, the need for intensive care unit admission. This pragmatic approach, which differs from some international guidelines recommending escalation to high-dose anesthetics requiring mechanical ventilation, represents a national practice model worthy of further prospective evaluation in larger, multicenter studies. The frequent use of MDZ observed in our cohort might also be partly related to the KETASER01 protocol that included 10 of the 11 hospitals participating in this study and that involved the early use of MDZ up to .36 mg/kg/h before considering other anesthetics.[32,33]

Given that 46% of CSE episodes in our cohort occurred within the first 3 years of life, with 40% occurring during the first year, early intervention with MDZ may be especially beneficial in this age group. The efficacy of early MDZ infusion has been reported in some pediatric population studies, and its use should be considered in further trials.[29–31] It is important to note that in our study the efficacy of MDZ even at dosage > .2 mg/kg/h dropped from 59% to 37% when administered after failure of several ASMs. Moreover, its efficacy as a third-line therapy was lower than that of other anesthetics. This finding reinforces the importance of early use of MDZ infusion to maximize its potential benefits, including the crucial advantage of preventing endotracheal intubation, subsequent intensive care unit admission, and their respective risks. It was recently reported that MDZ prevents neonatal seizures when injected after birth asphyxia in animal models.[34] MDZ acts on γ-aminobutyric acid type A ($GABA_A$) receptors to increase the inhibitory effect of GABA and on the mitochondrial translocator protein through which it enhances the synthesis of neurosteroids and reduces neuroinflammation, which is highly relevant for the consequences of brain damage related to asphyxia and potentially of CSE.[34]

After multivariate analysis, we found that adherence to current guidelines reduced the risk of refractoriness by almost 75%. In addition, patients who received nonadherent treatment experienced longer CSE duration, extended hospital stays, increased admission to the PICU, and a greater need for mechanical ventilation. Thus, our study underscores the need for health care professionals to adhere strictly to these guidelines and include early MDZ infusion, to prevent or improve long-term consequences of pediatric CSE.

In 35% of CSE episodes, the sequence of treatments followed in current guidelines was not respected, and refractoriness was higher in these cases. Literature from real-world evidence indicates that clinical practice in the treatment of CSE is quite different from the guidelines, depending on the context in which seizures begin, the history of previous CSE episodes, local emergency care services, distance from specialist centers, and the individual specialist's degree of confidence with medication.[14,35,36] The 11 centers involved in the present study are all tertiary pediatric hospitals to which other hospitals refer patients for treatment of prolonged epileptic seizures and of CSE. In this context, it is practically impossible to avoid administering more than the two recommended BDZ doses or an anesthetic bolus, not only to stop seizures but also during the transfer of a patient. The etiology or severity of the seizure may often justify skipping second-line treatment to rapidly move to third-line treatment, especially when intensivists are involved at an early stage.[13]

Our study also highlights the significant correlation between refractoriness and the underlying etiology, which in turn is correlated with age at CSE episode.[37] In our cohort, a significant portion of CSE episodes occurred between the ages of 1 and 3 years, confirming that CSE particularly affects infants, who in turn often have well-defined epilepsy syndromes with a specific etiology, often genetic. In addition to pharmacological management, understanding the etiology of CSE is essential for tailoring treatments. The high incidence of remote etiology, which includes genetic or presumed genetic causes, especially in younger children, makes detection of a genetic disorder essential, considering the important therapeutic implications.[38–42]

The age at onset of CSE and the development of refractoriness can help to identify underlying causes, which require timely and appropriate treatment, as in the case of NORSE/FIRES.[4,43,44]

Furthermore, in our cohort, progressive etiology and myoclonic SE were significantly associated with the highest risk of refractoriness, leading us to the consideration that in these cases a customized metabolic treatment, as in mitochondrial diseases, or a more timely use of a third-line treatment should be considered before, with, or instead of AMS.[45–49] These findings indicate the critical role of early intervention and the potential benefits of an aggressive treatment approach in patients presenting with high-risk features.

Finally, although more than 50% of CSE episodes required admission to PICUs, this was not only related to the administration of high doses of BDZ or the treatment of seizures. The intubation of patients in a critical condition is often necessary, and it is certainly easier to make this decision when extubation is safe.[50]

The study's retrospective design made us reliant on the thoroughness and accuracy of medical records from different departments and hospitals. Therefore, we are aware that documentation errors are possible, and underascertainment of cases cannot be ruled out.

A potential limitation of this study is also the lack of precise data on the time of BDZ administration from seizure onset. As the efficacy of BDZ can be time-dependent, this lack of granularity may affect the interpretation of our findings regarding treatment response. This study represents the *primum movens* for the foundation of the Italian Pediatric Status Epilepticus Group, a nationwide nonprofit organization encompassing emergency pre- and in-hospital doctors, epileptologists, child neurologists, pediatricians, and intensivists. These findings support a proactive approach using MDZ and adherence to treatment protocols as vital steps in managing pediatric CSE. In conclusion, this study provides an overview of pediatric CSE management and can guide future protocols and research to improve treatment, patient care, and outcomes.

AUTHOR CONTRIBUTIONS

Anna Rosati, Patrizia Bartolotta, Carla Marini, and Lucia Fusco contributed to the conception and design of the study; acquisition and analysis of the data; and drafting a significant proportion of the manuscript. Maria Cristina Mondardini, Duccio Maria Cordelli, Manuela L'Erario, Stefano Sartori, Fabrizio Chiusolo, Federico

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

A.R., P.Ba., C.M., and L.F. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Anonymized participant data are available upon reasonable request; the corresponding authors (C.M. and P.Ba.) will release data once the scientific board of the Italian Pediatric Status Epilepticus Group has approved the request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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