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# *Vaikų ūminių toninių-kloninių traukulių gydymas vaistais*

# *Drug Management for Acute Tonic-Clonic Convulsions in Children*

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## 1. ABBREVIATIONS

| | |
|---|---|
| SE | Status Epilepticus |
| ILAE | International League Against Epilepsy |
| BZD | Benzodiazepines |
| ASM | Anti-Seizure Medication |
| EEG | Electroencephalogram |
| ESETT | Established Status Epilepticus Treatment Trial |
| LZP | Lorazepam |
| DZP | Diazepam |
| MDZ | Midazolam |
| RM | Rescue Medication |
| EMS | Emergency Medical Service |
| APLS | Advanced Paediatric Life Support |
| AES | American Epilepsy Society |
| CPS | Canadian Pediatric Society |
| SAM | Sveikatos Apsaugos Ministerija |
| eSE | Early Status Epilepticus |
| IQR | Interquartile Range |
| ED | Emergency Department |
| rSE | Refractory Status Epilepticus |
| ICD-10 | International Classification of Diseases |
| pSERG | Pediatric Status Epilepticus Research Group |
| ICU | Intensive Care Unit |

## 2. SUMMARY

Acute tonic-clonic convulsions in children require rapid recognition and prompt drug intervention to prevent progression to status epilepticus, a serious neurological emergency associated with significant morbidity. Despite clear guidelines by the International League Against Epilepsy emphasizing timely benzodiazepine treatment, global adherence remains suboptimal, with notable gaps in dosing accuracy and treatment timing.

Objective. This thesis aims to determine which problems exist in the treatment of pediatric status epilepticus and to characterize them. The goals are as follows: 1) Present a literature review of the treatment of children's status epilepticus and identify the global challenges in adhering to international Status epilepticus treatment guidelines and discuss the consequences. 2) Investigate, through an retrospective cross-sectional study, whether the recommendations in hospital discharge summaries align with established algorithms, identifying areas of non-adherence. 3) Propose potential solutions to overcome challenges in adhering to treatment guidelines.

Methods. PubMed, Cochrane Library, and Scopus were systematically searched (see appendices for strategy) for English or Lithuanian studies published 2017–2024 on pediatric (1 month–18 years) status epilepticus of any etiology, excluding abstract-only publications, case reports, animal studies, refractory/super-refractory seizures, and medication efficacy/safety comparisons. For this retrospective study data were collected in a single-center retrospective cross-sectional study at Vilnius University Hospital Santaros Klinikos Pediatric Center. Patients aged one month to 18 years diagnosed with epilepsy, status epilepticus, or any acute seizure (International Classification of Diseases-10 codes G40.x, G41.x, R56.x) were included if discharge summaries provided age, weight, diagnoses, treatments, and recommendations, excluding those lacking documented weight for dose/kg calculations.

Results. A review of paediatric status epilepticus management demonstrates that rapid, weight-based benzodiazepine administration followed by protocolized escalation remains the cornerstone of therapy. Global studies reveal widespread delays and underdosing in first-line treatment, delayed escalation to second-line treatment and lack of training of caregivers and medical personel. Our retrospective study of 1,540 pediatric discharges revealed that only 57.8% of patients were discharged Pediatric Center with any home rescue medication prescription. Among 890 documented prescriptions only 13.5% deviated from the guidelines. Of the patients diagnosed with status epilepticus, 21.4% were not prescribed any anti-seizure medication.

Conclusions. 1) Treatment guidelines mandate benzodiazepine treatment within five minutes of pediatric SE onset and escalation to non-benzodiazepine anti-seizure medication by twenty minutes to minimize loss of efficacy and neuronal injury, yet these timelines are frequently missed globally. Literature shows major knowledge gaps and delays among caregivers and providers, resulting in underdosing and late administration of benzodiazepines and delayed escalation to second-line therapy, prolonging seizures and raising intensive care needs. 2) A retrospective study of 1,540 pediatric discharges at Vilnius University Hospital Santaros Klinikos found that only 57.8% of children left with rescue medication. The rate of noncompliance with established treatment guidelines was calculated to be 13.5%. Of the patients diagnosed with status epilepticus, 21.4% were not prescribed any anti-seizure medication. 3) Potential solutions could be: electronic-medical-record integrated, weight-based decision support, standardized discharge aids, simulation drills, tailored action plans, instructional media, placebo practice, and peer-support networks can eliminate dosing errors and empower timely Status epilepticus recognition and treatment.

SANTRAUKA

Ūminems toniniams-kloniniams vaikų traukuliams reikalingas greitas atpažinimas ir neatidėliotinas gydymas vaistais, siekiant išvengti epilepsinės būklės – sunkios neurologinės krizės, susijusios su ilgalaikiais sveikatos sutrikimais. Nepaisant aiškių Tarptautinės epilepsijos lygos rekomendacijų, kuriose akcentuojama laiku skirti benzodiazepinus, šių rekomendacijų laikymasis yra nepakankamas.

Tikslas. Šio darbo tikslas – išsiaiškinti, kokios problemos egzistuoja gydant vaikų epilepsinę būklę ir jas apibūdinti. Darbo uždaviniai: 1) Pateikti vaikų epilepsinės būklės gydymo literatūros apžvalgą, nustatyti pasaulinius iššūkius laikantis tarptautinių gydymo rekomendacijų ir aptarti jų padarinius. 2) Retrospektyviniu skerspjūvio tyrimu ištirti, ar ligoninės išrašų rekomendacijos atitinka nustatytus gydymo algoritmus, identifikuojant neatitikimo sritis. 3) Pasiūlyti galimus sprendimus rekomendacijų laikymosi gerinimui.

Metodai. Atlikta sisteminė PubMed, Cochrane Library ir Scopus duomenų bazių apžvalga (paieškos strategija pateikiama prieduose), ieškant 2017–2024 metais publikuotų anglų ir lietuvių kalbomis tyrimų apie vaikų (nuo 1 mėn. iki 18 metų) epilepsinę būklę bet kokios kilmės, išskyrus santraukų publikacijas, pavienius atvejus, tyrimus su gyvūnais, atsparius ar ypač atsparius priepuolius ir vaistų veiksmingumo ar saugumo palyginimus. Retrospektyvinio tyrimo duomenys surinkti Vilniaus universiteto ligoninės Santaros klinikų Vaikų ligoninėje. Į tyrimą įtraukti pacientai nuo 1 mėn. iki 18 metų, kuriems diagnozuota epilepsija, epilepsinė būklė ar ūmus priepuolis (Tarptautinės Ligų

Klasifikacijos-10 kodai G40.x, G41.x, R56.x), jei išrašuose buvo nurodytas amžius, svoris, diagnozės, gydymas ir rekomendacijos, išskyrus tuos, kuriems nebuvo nurodyto svorio dozės kilogramui apskaičiuoti.

Rezultatai. Literatūros apžvalga patvirtina, kad greitas, pagal svorį apskaičiuotų benzodiazepinų skyrimas yra kertinis gydymo principas. Tarptautiniai tyrimai rodo plačiai paplitusį pirmojo gydymo etapo vėlavimą ir nepakankamą dozę, pavėluotą antrinį gydymą ir nepakankamą tėvų bei medicinos personalo mokymą. Mūsų retrospektyvinis 1540 vaikų išrašų tyrimas atskleidė, kad tik 57,8 proc. pacientų buvo išrašyti iš Vaikų ligoninės su receptais namų naudojimui priepuolio atveju. Iš 890 dokumentuotų receptų tik 13,5 proc. neatitiko gydymo rekomendacijų. Iš diagnozuotų epilepsinės būklės pacientų 21,4 proc. išvis nebuvo paskirti jokie vaistai nuo traukulių.

Išvados. 1) Gydymo gairės reikalauja, kad benzodiazepinai būtų skiriami per pirmąsias 5 minutes nuo epilepsinės būklės pradžios, o antrinis gydymas – ne vėliau nei per 20 minučių, siekiant išvengti gydymo efektyvumo mažėjimo ir neuronų pažeidimų. Vis dėlto šių terminų dažnai nepaisoma visame pasaulyje. Literatūra atskleidžia didelius žinių trūkumus ir vėlavimus tarp tėvų bei medicinos darbuotojų, dėl ko benzodiazepinai skiriami nepakankamai ir pavėluotai, uždelstas ir antrinis gydymas, ilgėja priepuoliai ir išauga intensyvios terapijos poreikis. 2) Retrospektyvinis 1540 vaikų išrašų tyrimas Vilniaus universiteto ligoninės Santaros klinikose parodė, kad tik 57,8 proc. vaikų buvo išrašyti su vaistais priepuolių stabdymui namuose, o 13,5 proc. receptų neatitiko dozavimo rekomendacijų. Iš diagnozuotų epilepsinės būklės pacientų 21,4 proc. išvis nebuvo paskirti jokie vaistai nuo traukulių. 3) Siūlomi sprendimai: elektroninės sistemos su svoriu paremtais dozių skaičiavimais, standartizuotos išrašymo formos, praktiniai mokymai, individualizuoti veiksmų planai, mokomoji medžiaga, placebo praktikos ir savitarpio pagalbos tinklai, padėsiantys išvengti dozavimo klaidų ir užtikrinti greitą epilepsinės būklės atpažinimą bei gydymą.

3. KEYWORDS
Status epilepticus, epilepsy, seizure, rescue medication, benzodiazepines, noncompliance with guidelines

## 4. INTRODUCTION

Acute tonic-clonic convulsions represent one of the most critical pediatric neurological emergencies, demanding swift recognition and immediate pharmacological intervention (1,2). These seizures, characterized by sudden onset of generalized motor activity, pose significant risks if inadequately managed, potentially escalating into status epilepticus (SE)—a neurological emergency defined by prolonged or repeated seizures without recovery of consciousness between episodes (1,3–5). Status epilepticus is associated with substantial morbidity and mortality, making timely and precise drug management paramount for favorable patient outcomes (6).

The International League Against Epilepsy (ILAE) provides clear operational time points ($t_1$ and $t_2$) that serve as critical markers for therapeutic intervention (1). Specifically, a generalized tonic-clonic seizure warrants initiation of benzodiazepine (BZD) treatment at five minutes ($t_1$), with prolonged seizure duration beyond thirty minutes ($t_2$) significantly increasing the risk of permanent neuronal injury (1). Despite established international guidelines recommending prompt, weight-based BZD administration, numerous studies worldwide consistently report deviations in both timing and dosage adherence, underscoring global systemic challenges in pediatric seizure management (7–12).

Epidemiologically, status epilepticus exhibits a marked incidence peak within pediatric populations, especially among children under five years of age (13,14). Reports estimate incidence rates ranging from 17 to 82 per 100,000 children annually. In Lithuania specifically, approximately 5% of children under five years experience seizure episodes (13).

In this study, we frame our investigation around a streamlined treatment and care pathway for pediatric SE, organized into four interconnected domains: first, the prescription of rescue medications; second, the delivery of targeted education and hands-on training for parents, caregivers, and frontline medical staff; third, the initiation of interventions during the early phase of SE; and fourth, the escalation of therapeutic strategies for established and refractory SE (Fig. 1). By systematically deconstructing this pathway, we are able to pinpoint critical junctures where delays, knowledge gaps, or suboptimal dosing may compromise clinical outcomes, thereby facilitating targeted improvements and ensuring comprehensive, guideline-concordant care.

(Figure 1) Simplified care and treatment pathway for SE.


This thesis addresses these gaps by evaluating adherence to recommended seizure management protocols at Vilnius University Hospital Santaros Klinikos Pediatric Center. Through a detailed retrospective analysis, we assess actual clinical practices at the institution, identifying specific points of deviation in rescue medication prescriptions, a domain yet to be comprehensively analyzed in existing medical literature. Complementarily, a narrative literature review contextualizes these findings within global trends, highlighting broader systemic issues, such as lack of education of caregivers and medical personel, frequent underdosing, delays in initiating first-line BZD therapy, inadequate escalation to second-line antiseizure medications (ASMs) (10–12,15–19). Such deviations not only prolong seizure durations but also increase risks of refractory seizures, neurodevelopmental delays, and intensified healthcare resource utilization (12,20).

This thesis aims to determine which problems exist in the treatment of pediatric status epilepticus and, if so, to characterize them. The goals are as follows: 1) Present a literature review of the treatment of children's status epilepticus and identify the global challenges in adhering to international Status epilepticus treatment guidelines and discuss the consequences. 2) Investigate, through an retrospective cross-sectional study, whether the recommendations at Vilnius University Hospital Santaros Klinikos Center align with established algorithms, identifying areas of non-adherence. 3) Propose potential solutions to overcome challenges in adhering to treatment guidelines.

# 5. LITERATURE REVIEW

## 5.1 Aims of review

This narrative literature review aims to examine critical issues associated with the management of pediatric SE, focusing on the main domains of SE treatment. Specifically, this review will analyze the following key areas: underdosing of first-line benzodiazepines (BZD), delays in initiating treatment, delays in escalating to second-line antiseizure medications (ASM) and lack of knowledge of SE treatment by caregivers, parents and medical professionals. Each of these factors has significant implications for clinical outcomes, as deviations from evidence-based guidelines are known to compromise patient safety and treatment efficacy. The goal of this review is to identify and highlight gaps in adherence to recommended practices, emphasizing the importance of standardized treatment protocols, timely pharmacological intervention, and adequate caregiver and medical professional education. By addressing these aspects, the literature review seeks to propose pathways to enhance compliance with established guidelines, ultimately improving therapeutic outcomes for children experiencing SE.

## 5.2 Methods

A literature search was performed. To conduct this review, PubMed, Cochrane Library, and Scopus databases were searched. A detailed search strategy can be found in the appendices.

Inclusion Criteria:

- Age: 1 month–18 years, male and female.
- Status epilepticus of various aetiologies.
- Articles accessible through Vilnius University resources or free full text.
- Studies published between 2017–2024.
- Articles in Lithuanian or English.

Exclusion Criteria:

- Studies comparing specific medication efficacy or safety.
- Abstract-only publications.
- Refractory and super-refractory seizures.
- Case reports.
- Animal studies

Data Extraction

Relevant data were extracted based on a structured Population, Intervention, Comparison, and Outcome (PICO) framework:

- Population: Pediatric patients (1–18 years) with acute tonic-clonic seizures.
- Intervention: First-Line treatment.
- Comparison: No treatment or deviations from treatment guidelines.
- Outcome: early SE, SE.

## 5.3 Classification of Status epilepticus

The International League Against Epilepsy (ILAE) Task Force proposes a multidimensional diagnostic framework based on four axes: semeiology, etiology, electroencephalogram (EEG) correlates, and age (1).

### Axis 1: Semiology

This axis refers to the clinical presentation of Status epilepticus (SE) and serves as the backbone of the classification. It is based on two taxonomic criteria: the presence or absence of prominent motor symptoms and the degree of impaired consciousness (1). Forms with prominent motor features include convulsive SE (generalized tonic–clonic, focal evolving into bilateral convulsive, and unknown-onset convulsive SE), myoclonic SE (with or without coma), focal motor seizures (e.g., Jacksonian SE, epilepsia partialis continua), tonic status, and hyperkinetic SE (1). Nonconvulsive SE is subdivided into coma-associated and non-coma–associated patterns (generalized or focal), while indeterminate or "boundary" syndromes (such as epileptic encephalopathies and acute confusional states with epileptiform EEG patterns) form a third category (1).

### Axis 2: Etiology

Etiologic classification distinguishes "known" (symptomatic) from "unknown" (cryptogenic) causes (1). Known causes are further stratified by temporal relationship into acute (e.g., stroke, intoxication, encephalitis), remote (e.g., posttraumatic, postencephalitic, poststroke), and progressive (e.g., brain tumors, progressive myoclonic epilepsies) categories, with an additional subgroup for SE arising within defined electroclinical syndromes (1). Cases lacking an identifiable cause are designated cryptogenic (1).

### Axis 3: EEG Correlates

This axis adopts consensus-derived descriptors to characterize the electrographic patterns of SE, encompassing 05/09/2025 20:50:00:

1. Location: generalized (including bilateral synchronous), lateralized, bilateral independent, or multifocal discharges
2. Pattern name: periodic discharges, rhythmic delta activity, spike-and-wave/sharp-and-wave (with subtypes)
3. Morphology: sharpness, number of phases (e.g., triphasic), amplitude, polarity
4. Time-related features: frequency, duration, onset dynamics (sudden vs. gradual), and temporal indices
5. Modulation: stimulus-induced vs. spontaneous
6. Effect of intervention: changes in EEG following treatment
   Although no formal, evidence-based EEG criteria currently exist, this axis guides diagnostic precision, prognostication, and treatment aggressiveness .

Axis 4: Age

Age stratification recognizes that the semiology, etiology, and prognosis of SE vary across the lifespan. Five age groups are defined (1): neonatal (0–30 days), infancy (1 month–2 years), childhood (> 2–12 years), adolescence and adulthood (> 12–59 years), and elderly (≥ 60 years)

5.4 Drug Management for Acute Tonic-Clonic Convulsions.

The ILAE 2017 operational scheme emphasizes that such events may originate from focal, generalized, or unknown networks and can present with diverse motor or non-motor onsets (2). Although phenomenologically heterogeneous, most isolated convulsive seizures terminate spontaneously within five minutes, revealing a biological line on self-limitation (1). When that line is breached, natural inhibitory mechanisms have failed and the episode is called “abnormally prolonged,” a status that fundamentally alters therapeutic priorities (1).

To harmonise bedside action with neurobiology, the ILAE introduced two operational time-points: $t_1$, the moment an ongoing seizure should trigger emergency treatment, and $t_2$, the duration beyond which long-term injury becomes probable (1). For generalised tonic-clonic seizures, $t_1$ is five minutes and $t_2$ thirty minutes; for focal seizures with impaired awareness, the corresponding thresholds are ten and sixty minutes, while absence status epilepticus carries a tentative $t_1$ of ten to fifteen minutes and an undefined $t_2$ (21). These cut-offs are echoed in contemporary paediatric algorithms that recommend immediate BZD delivery once a tonic-clonic convulsion reaches five minutes or a focal impaired-awareness episode lasts ten minutes (3). The guidelines recommend dosages for BZD use, which can be found in table 2. Accordingly, the seizures that

unequivocally warrant drug therapy in children are: 1) any generalised tonic-clonic event persisting ≥ 5 min; 2) any focal seizure with impaired awareness persisting ≥ 10 min; 3) any absence or other clearly non-convulsive seizure continuing ≥ 10-15 min; and 4) any clustering of seizures without full interictal recovery that signals impending status epilepticus (Tab. 1) (3).

(Table 1) Time to treatment of SE.

| SE type | $T_1$ | $T_2$ |
|---|---|---|
| Tonic-clonic | 5 min | 30 min |
| Focal with loss of consciousness | 10 min | More than 60 min |
| Absence | 10-15 min | - |

(Table 2) Recommended dosage of SE treatment.

| | American Epilepsy Society (22) | Resuscitation Council UK (4) | Advanced Paediatric Life Support (23) | Sveikatos Apsaugos Ministerija (13) | Canadian Pediatric Society (24) |
|---|---|---|---|---|---|
| Intramuscular midazolam | (10 mg for > 40 kg, 5 mg for 13-40 kg, single dose, | | | 0,15-0,3 mg/kg | 0.2 mg/kg |
| Intranasal midazolam | 0.2 mg/kg | | | | 0,2 mg/kg |
| buccal midazolam | 0.2 mg/kg | 0.3-0.5 mg/kg | 0,3 mg/kg (max 10mg) | 0,15-0,3 mg/kg | 0,5 mg/kg |
| Intravenous diazepam | (0.15-0.2 mg/kg/dose, max: 10 mg/dose, may repeat dose | | | 0,2-0,5 mg/kg | 0,1 mg/kg |
| Rectal diazepam | (0.2-0.5 mg/kg, max: 20 mg/dose, | | 0,5 mg/kg (max 20mg) | 0,5 mg/ kg | 0,5 mg/kg |

Episodes that conclude before these limits, such as brief focal aware twitches, single myoclonic jerks, or isolated atonic drops, rarely changes systemic stability or evolve into status epilepticus and therefore does not need acute therapeutic treatment (2). Early or impending status epilepticus is

declared once $t_1$ is passed, even though $t_2$ has not yet been reached, underscoring a window in which BZD sensitivity remains high and escalation can still be averted (21). Failure to terminate ictal activity after an adequately dosed first-line agent defines established status epilepticus, while persistence despite two antiseizure medications marks the refractory stage (21). Continuation for more than twenty-four hours or recurrence during anaesthetic weaning then qualifies as super-refractory SE, a phase associated with escalating morbidity and mortality (21).

At the cellular level, prolonged seizures internalise synaptic GABA A receptors, up-regulate NMDA receptors, and promote intracellular chloride accumulation through KCC2 dysfunction, progressively converting inhibitory signaling into paradoxical excitation (21). As GABA sensitivity decreases with time, delays in treatment not only lengthen seizures but also necessitate higher-risk second- and third-line therapies, amplifying systemic complications (21). Clinical studies underscore that every additional minute before definitive medication correlates with longer overall seizure duration and poorer neurological outcomes (5). Conversely, strict protocol adherence, starting timer at onset, giving weight-based BZD within the $t_1$ window, and escalating in a predefined sequence shortens seizures, reduces intensive-care exposure, and improves functional recovery (5). These observations link the abstract $t_1/t_2$ construct to tangible patient trajectories, demonstrating that timely intervention can forestall both pharmacoresistance and excitotoxic injury (3).

### 5.5 Status Epilepticus Epidemiology

SE frequently occurs in children, with the highest incidence occurring during the early years of life, particularly in those younger than five (13,20). Epidemiological studies have reported rates of 17–23 cases per 100,000 children annually (25). Other studies show higher numbers, new cases per year are estimated to be 33.3–82/100,000 (14,26).

According to data from the Lithuanian Ministry of Health, up to 5% of all children under the age of 5 experience epileptic seizures, with half of these being febrile seizures (13). Acute symptomatic seizures occur in about 3-4% of children, and 2-3% of children later experience recurrent unprovoked epileptic seizures (13). Various etiologies of SE affect 18-40 per 100,000 people annually, with 60% of these cases occurring in children under 5 years old and 20% in children under 1 year old (156 per 100,000 annually) (13). About 50% of SE cases occur unexpectedly, while for the rest, it is a complication of epilepsy, and 20-25% of cases are associated with febrile (13). These statistics emphasize the need for early recognition and consistent application of treatment guidelines for this vulnerable population.

## 5.6 Underdosing

Data from the Established Status Epilepticus Treatment Trial (ESETT), a multicenter, randomized, double-blind clinical trial, which enrolled subjects from 41 U.S. academic and community hospitals, providing extensive insights into SE treatment practices. Two separate analyses of ESETT data highlighted the prevalence of underdosing among SE patients (10,11).

To account for variations in BZD potencies, cumulative doses were calculated using lorazepam (LZP) equivalents. This approach revealed significant deviations from recommended dosing practices (10). For instance, guideline-recommended first doses for LZP and midazolam (MDZ) were administered in only 41.9% and 12.5% of cases, respectively, among children weighing less than 40 kg (10). Further cumulative dose analysis in 68 children weighing less than 32 kg showed that doses were <0.1 mg/kg in 18%, 0.1–<0.2 mg/kg in 44%, 0.2–<0.3 mg/kg in 28%, and >0.3 mg/kg in only 10% of subjects (10).

The findings underscored that many SE patients failing BZD therapy did not receive the recommended first doses, deviating from evidence-based guidelines (10,11). The study observed a pattern of administering small, repeated doses, with approximately 70% of patients receiving less than the guideline-recommended dose initially. Excluding rectal diazepam (DZP), the first doses of MDZ and LZP, primarily administered by emergency medical services (EMS) and emergency department personnel, were below recommendations in 80% of cases. Subsequent doses continued to follow this pattern of underdosing (10). Among DZP recipients and 93.9% of those weighing <66.7 kg received the guideline-recommended doses (11). Analysis of 460 patients enrolled in ESETT showed that initial BZD doses were below guideline recommendations in more than 80% of MDZ cases and over 75% of LZP cases (11).

In a study examining children transferred to tertiary care centers for SE, nonadherence to treatment guidelines, including BZD underdosing, was a significant issue (18). Of 184 cases, 76% involved inadequate dosing of medications. This noncompliance was consistent across a three-year period from 2017 to 2019, with adherence rates remaining below 30% (18).

Another pediatric study found that while benzodiazepines were administered as first-line therapy in 96.2% of cases, the initial doses were subtherapeutic in more than half of the children (27). Notably, SE durations were significantly more common among children receiving low BZD doses (median 4.1 hours) compared to those receiving adequate doses (median 2.7 hours; p=0.023) (27).

A study in a pediatric emergency department reviewed 117 cases and found that nearly half involved infra-therapeutic drug doses. Among these, 49.6% presented with early SE episodes, and 6.8% required intensive care (28). Noncompliance with established protocols was strongly associated with the need for multiple antiepileptic drugs and early SE seizure durations (28). These findings emphasize the urgent need for consistent application of evidence-based dosing guidelines to optimize outcomes and minimize complications.

### 5.7 Treatment delay

Current treatment guidelines of SE indicate that the first dose of BZD should be administered 5-10 min and a repeated dose after 10 minutes (22).

Delays in initiating treatment for SE are widely reported across different populations and settings (29). An open-label, non-randomized prospective observational study involving 40 children aged 1 month to 14 years found that the median time for administering first-line BZD was 11 minutes (interquartile range (IQR) 8–15) (20). Continuous infusion therapy was initiated later, with a median delay of 57 minutes (IQR 45–69). Compliance with the SE management protocol was seen in only 60% of cases, highlighting significant gaps in guideline adherence (20).

Another study of 141 pediatric patients reported that the median time to administer the first anti-seizure medication ASM was 25 minutes (IQR 7–56), regardless of whether it was given by parents, emergency medical teams, or in the emergency department (ED) (30). The majority of patients (92%) received a BZD as the first ASM, and 95% received it as the second ASM. Treatment timing had a strong influence on seizure duration; patients treated within 5 minutes experienced a median seizure duration of 59.5 minutes, compared to 151.5 minutes for those treated after 60 minutes ($p<0.01$). Despite these findings, the first ASM successfully terminated SE in only 32% of cases (30).

An Australian study highlighted similar delays, where the median time from seizure onset to ED arrival was 22 minutes (IQR 15–40) (7). First-line BZD administration occurred at a median of 15 minutes (IQR 8–25), exceeding the guideline-recommended time of 5 minutes. Non-adherence to clinical practice guidelines was observed in 93.2% of cases (7). Moreover, 38 out of 59 patients received excessive BZD doses, and two required intubation prior to the administration of second-line agents (7).

A study of 219 pediatric patients with refractory SE (rSE) showed significant delays in treatment. The median times were 16 minutes (IQR 5–45) for first-line BZDs. Delays in first BZD administration were linked to intermittent rSE and out-of-hospital onset. Similarly, delays in non-BZD ASM administration were associated with intermittent rSE and out-of-hospital onset (8).

In another review, delays exceeding 30 minutes for first-line treatment were observed in 17% to 64% of patients, with median times ranging from 30 to 70 minutes (29). Delays were attributed to slow paramedic response times, difficulties in administering rectal medications, and diagnostic uncertainties, particularly for third-line therapies (29).

A systematic literature review of 2212 SE cases summarizes prehospital care gaps. Only 51.8% of patients received treatment through emergency medical services, while 12.8% were treated by family members (31). Prehospital care was associated with shorter SE durations, fewer recurrent seizures, and reduced electroencephalographic evidence of ongoing SE. However, prehospital treatment remains underutilized, and delays in emergency medical service (EMS) response and ASM administration continue to hinder outcomes (31).

These studies collectively underscore the systemic issues in SE treatment, including significant delays in administering critical therapies. Solutions must prioritize adherence to guidelines, enhancement of prehospital care systems, and improvements in rapid ASM delivery (7,8,20,29–31).

### 5.8 Delayed escalation to second-line treatment

The treatment of pediatric SE often deviates from recommended protocols, particularly in the timing and escalation of ASMs (32). Current guidelines advise administering the first BZD within 5–10 minutes of seizure onset and transitioning to second-line treatment / non-BZD ASMs 20 minutes if the seizure persists (22). However, delays are common, as evidenced by a multicenter study involving 293 children, which found that over half received BZDs beyond 30 minutes of seizure onset (19). Additionally, a cohort of 81 children reported a median time of 69 minutes (IQR, 40–120 minutes) for the first non-BZD ASM and 120 minutes (IQR, 75–296 minutes) for the second dose (32), which deviate from the international guidelines significantly.

For example, a prospective study of 52 patients reported median times of 68 minutes (IQR, 48–79 minutes) and 105 minutes (IQR, 100–135 minutes) to administer second- and third-line therapies, respectively (33). Similarly, a study of 64 children observed that 95% received excessive BZD doses, with delays in transitioning to second-line agents in 86% of cases (31).

The time-dependent decrease in BZD efficacy highlights the importance of prompt transition to non-BZD ASMs. Timely intervention is critical, as delays in switching to non-BZD therapies increase the risk of eSE seizures and poor outcomes (30,32).

### 5.9 Education and training on Status epilepticus

Pediatric SE is a medical emergency demanding rapid recognition and treatment to avert serious morbidity and mortality (16). Despite its critical nature, substantial knowledge deficits have been documented among parents and caregivers of affected children (34).

Only one third of parents and caregivers correctly understood that epilepsy is not a psychiatric illness (34). Approximately 46.6% of respondents considered alternative medicine capable of curing epilepsy, indicating pervasive misconceptions about treatment (34).

In a Sudanese cohort, only 1% of caregivers answered all epilepsy knowledge questions correctly, while 38.3% achieved a "good" knowledge level and 58.9% "fair," with a median score of 66.7%, underscoring widespread informational gaps (15).

Knowledge shortfalls are also evident among medical professionals: in Saudi Arabia, 57% of pediatric emergency physicians reported being unaware of the national convulsive SE management guidelines, and only 20% demonstrated full adherence to all recommended components (35). Furthermore, 23% of these physicians underdosed benzodiazepines and 6% failed to select benzodiazepines as the first-line agent when intravenous access was available, indicating insufficient familiarity with critical treatment protocols (36). In simulation assessments, emergency staff exhibited a median pre-training performance of only 40% in SE management skills, highlighting inadequate baseline proficiency (16).

## 6. RETROSPECTIVE STUDY

### 6.1 Aims of the study

The aim of our retrospective study conducted at Vilnius University Hospital Santaros Klinikos Pediatric Center was to evaluate rescue medication prescription practices for acute tonic-clonic convulsions in children. Our study specifically analyzed the first of four pillars in the simplified care pathway for prolonged acute convulsive seizure management: physicians' recommendations and prescriptions for rescue medications. Given that the initial phase of ASM prescription for early

prehospital intervention has been undocumented in current literature, this study focused on mapping and analyzing local ASM prescribing practices, identifying deviations from international guidelines, and addressing this previously unreported gap in paediatric SE treatment.

## 6.2 Materials and methods

Single-center retrospective cross-sectional study data were collected from November 2020 to November 2023 at the Vilnius University Hospital Santaros Klinikos Pediatric Center, which consists of 3 departments. This study was approved by the Vilnius Regional Biomedical Research Ethics Committee and conducted under the principles of the World Medical Association Helsinki Declaration and local law; the need for consent to participate was deemed unnecessary according to national regulations, as the authors received an encrypted database and therefore did not have access to information that could identify individual participants during or after data collection (No. 158200-15-797-309).

The inclusion criteria were as follows: patients (one month 18 years) diagnosed with epilepsy, status epilepticus, or any acute seizure type (G40.00, G40.01, G40.10, G40.11, G40.20, G40.21, G40.30, G40.31, G40.40, G40.41, G40.50, G40.51, G40.80, G40.81, G40.90, G40.91, G41.0, G41.1, G41.2, G41.8, G41.9, R56.8, or R56.0 according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10)) if data from hospital discharge summaries were available.

Biostatisticians obtained data from the electronic medical records of the patients (hospital discharge summaries): age, weight, main and underlying diagnoses according to the inclusion criteria, treatment received, and recommendations for further treatment.

The authors received an encrypted database on 29 March 2024 and did not have access to information that could identify individual participants during or after data collection.
If weight data were not specified in the hospital discharge summaries and if it was impossible to calculate the dose per kilogram of body weight, we excluded these patients from further analysis.
Our primary outcome was noncompliance with the guidelines (see Table X for summarized guidelines).

We analyzed and considered the prescribed dose ranges for the MDZ buccal and DZP rectal groups on the basis of patient weight:

1. If the patient's weight was ≥ 32 kg, a 10 mg dose was considered to be in line with the guidelines (for those whose weight was 32 kg, the dosage was 0.3 mg/kg).

2. If the patient's weight was <32 kg, a DZP dose of 0.3–0.5 mg/kg was considered to be in line with the guidelines; doses <0.3 mg/kg were considered too low, and doses >0.5 mg/kg were considered too high.

3. If the patient's weight was <32 kg, an MDZ dose of 0.2–0.5 mg/kg was considered to be in line with the guidelines; doses <0.2 mg/kg were considered too low, and doses >0.5 mg/kg were considered too high.

4. If the dose was too low or too high, the administration method was not specified/incorrectly specified; we marked the outcome as Noncompliance with guidelines.

5. If the rescue medicine was not intended, we marked the outcome as Non-prescribed rescue medication.

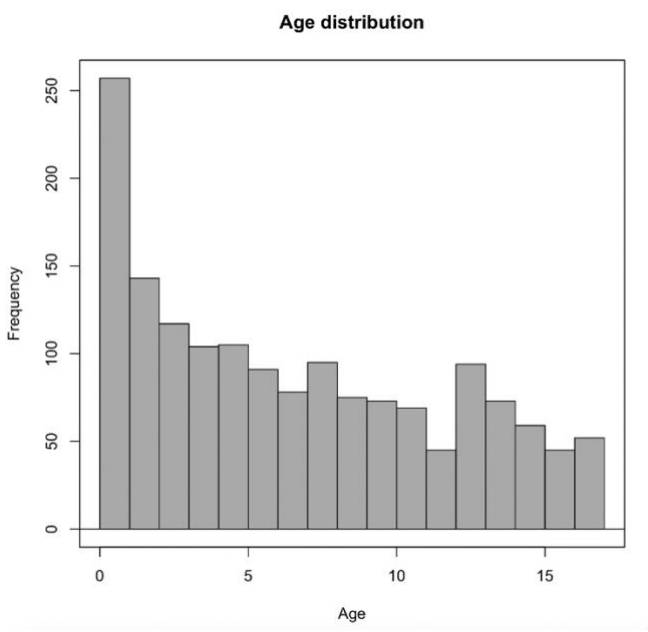
Statistical analyses were performed with R Commander Software for the calculations of median age and median weight (version XQuartz 2.8.5). Categorical data are presented as frequencies and percentages and were analyzed via Excel.

## 6.3 Results

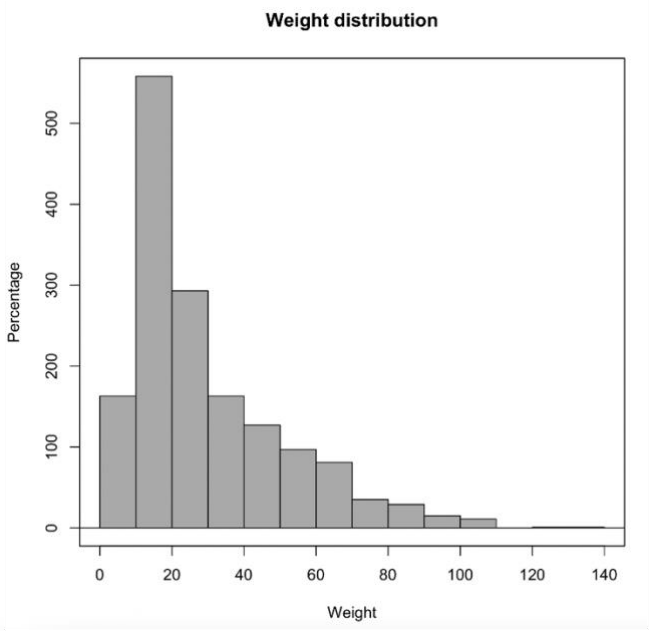
The encrypted Excel database file used in this analysis contained detailed information about a total of 2,661 individual pediatric patients. However, data specifically related to patient weight and corresponding calculations of medication dosage per kilogram of body weight were only available for 1,540 of these patients. Therefore, this study focused solely on the discharge summaries of these 1,540 patients. It is important to note that gender was not found to be a significant differentiating factor in this study and was therefore not considered further in the analysis.

The ages of the included patients spanned from newborns up to individuals who were 18 years old. The median age of this population was 6 years, with an interquartile range (25th–75th percentile) from 2 to 11 years (Fig. 2). In terms of weight, the median patient weight was calculated at 22.00 kilograms, with the interquartile range stretching from 14.8 to 40.1 kilograms (Fig. 3).

(Figure 2)




(Figure 3)




When examining the diagnoses of the 1,540 patients included in the study, it was observed that 381 (24.7%) patients had a primary diagnosis coded as either "other and unspecified convulsions" (ICD code R56.8) or "febrile convulsions" (ICD code R56.0). Additionally, 42 patients (2.7%) were identified as having status epilepticus either as a primary or secondary diagnosis, with diagnostic codes including G41.0, G41.1, G41.2, G41.8, or G41.9. The remaining majority of patients in the study had various forms of epilepsy as their primary diagnosis.

Noncompliance with Guidelines

Out of the 1,540 discharge summaries analyzed, medication was specifically recommended in 890 cases, which corresponds to 57.8% of all cases. Detailed information regarding the prescribed doses and the administration methods, broken down by weight category and dosage group, can be found in Table 3. Overall, the rate of noncompliance with established treatment guidelines was calculated to be 13.5%.

Within the 890 cases where medication recommendations were made, 770 (86.5%) summaries provided dosage information that was in accordance with current guidelines. In 30 (3.4%) of these summaries, the method of drug administration was either not specified, or the dosage itself was missing. Additionally, 90 summaries (10.1%) contained medication recommendations that did not adhere to the appropriate dosage guidelines either by underdosing or overdosing. Specifically, underdosing was observed in 77/890 (8.7%) of these cases.

MDZ emerged as the most frequently recommended rescue medication, accounting for 71.3% of all drug recommendations. The correct dosage of MDZ was provided in 89.6% of the summaries in which it was recommended. In contrast, DZP was recommended with the correct dosage in only 66.2% of the respective discharge summaries. An analysis of incorrect dosages revealed that 7.6% of MDZ prescriptions involved dosages that were too low, while low dosages were also observed in 10.3% of DZP prescriptions. Furthermore, in the case of DZP, a dosage that exceeded recommended levels was advised in also 10.3% of prescriptions.

In a subgroup of 187 patients, both midazolam and diazepam were presented as interchangeable options for use as rescue medication. Within this subgroup, 11.8% of patients received a dosage recommendation that was considered too low, regardless of the drug chosen. A summary of the results can be found in table 3.

(Table 3) Recommended medication dose accuracy.

| **Medication** | **Patient N** | **Dose in line with guidelines N (%)** | **Too low dose N (%)** | **Too high dose N (%)** | **Administration method was not specified/incorrect N (%)** | **Dosage was not specified/incorrect N (%)** |
|---|---|---|---|---|---|---|
| Midazolam (MDZ) | 635 | 569 (89.6) | 48 (7.5) | 2 (0.3) | 3 (0.5) | 13 (2) |
| Diazepam (DZP) | 68 | 45 (66.2) | 7 (10.3) | 7 (10.3) | 2 (2.9) | 7 (10.3) |
| Optional (MDZ/DZP) | 187 | 156 (83.4) | 22 (11.8) | 4 (2.1) | 0 (0) | 5 (2.7) |

Abbreviations: MDZ = midazolam, DZP = diazepam.

In a notable proportion of the total 1,540 discharge summaries, the rescue medication was not specified at all. This occurred in 42.2% of all cases. When this subgroup was examined more closely, it was found that in patients diagnosed with SE, the rescue medication was not prescribed or intended in 21.4% of these cases. Among patients whose primary diagnosis was other or unspecified convulsions or febrile convulsions, the rescue medication was omitted in 170 of 381 cases (44.6%).

### 6.4 Limitations

Our study has several limitations that should be acknowledged. First, we conducted a retrospective observational study, which inherently carries risks of bias and incomplete data due to reliance on previously recorded discharge summaries.

Second, while the dataset included anonymized patient information, we lacked longitudinal data to confirm whether patients had multiple admissions or revisitations during the study period. Repeated hospital visits for the same patient could have introduced redundancy, potentially influencing the results and overestimating or underestimating trends in prescription practices.

Despite these limitations, our study provides valuable insights into the patterns of MDZ and DZP prescription practices in the treatment of pediatric SE and highlights areas where adherence to international guidelines may be improved. Future studies, particularly prospective investigations, are needed to address these limitations and validate our findings in broader clinical settings.

## 7. DISCUSSION

Pediatric SE is one of the most critical neurological emergencies encountered in pediatric practice, characterized by prolonged or repeated seizures without recovery of consciousness between episodes (1). It is associated with significant morbidity and mortality, and its management requires immediate, accurate, and well-coordinated interventions (3). Failure to rapidly control seizures can lead to irreversible neuronal damage, developmental setbacks, cognitive impairments, and in severe cases, death (37). Therefore understanding and implementing effective SE management strategies is paramount for optimizing patient outcomes.

The management of pediatric SE relies heavily on four key domains (Fig. 1): 1) physicians' recommendations and prescriptions for rescue medications; 2) parents'/caregivers'/medical professionals' education/training; 3) intervention during early SE; and 4) intervention during established SE and refractory SE.

The first domain, physicians' recommendations and prescriptions for rescue medications, is fundamental as it directly influences the timeliness and effectiveness of initial interventions. Accurate prescribing practices, including correct drug selection and precise dosing, significantly impact patient prognosis and seizure management efficacy (3).

The second domain emphasizes the education and training of caregivers, parents, and healthcare professionals. The capability of caregivers and first responders to recognize seizure activity

promptly and administer appropriate treatments is crucial for preventing progression to refractory SE.

The third domain pertains to timely and correct intervention during early SE. Delays and deviations from dosage recommendations in administering first-line benzodiazepines significantly reduce their effectiveness (7,9–11).

Finally, the fourth domain involves the appropriate and timely escalation to second-line treatments during established or refractory SE. Clinical guidelines advocate for rapid escalation if initial interventions fail (19,38,39).

In this detailed discussion, we delve into each pillar, examining current practices, identifying systemic challenges, and exploring practical solutions to enhance compliance with established guidelines. Through evidence-based analysis and international comparisons, this discussion underscores the necessity of a coordinated, multifaceted approach to pediatric SE management, aiming to achieve optimal clinical outcomes and ensure a consistently high standard of care.

7.1 Physicians' recommendations and prescriptions for rescue medications (retrospective study)

In our retrospective study, conducted at Vilnius University Hospital Santaros Klinikos Pediatric Center, we specifically addressed the first pillar of pediatric status epilepticus treatment: physicians' recommendations and prescriptions for rescue medications. This element is critical, as accurate drug administration is essential for effective seizure management and minimizing complications in children experiencing acute tonic-clonic convulsions (3).

Our hospital's internal protocol is in line with internationally accepted guidelines regarding MDZ and DZP dosage recommendations. The dosage limits used in this study were defined based on both the hospital protocol and the protocols listed in the Table 2. Therefore, observed deviations from the recommended dosages reflect true nonadherence to these standards, and the results can be reliably compared to international guidelines.

Our comprehensive analysis focused on 1,540 pediatric patients who met the inclusion criteria. Within this cohort, medication prescriptions and recommendations were only documented in 890 cases, representing 57.8% of the total analyzed patient records. A notable observation from the data was a significant rate of noncompliance with established international guidelines, documented at 13.5% of all cases where rescue medication was recommended.

Among prescribed medications, MDZ was the predominant choice, recommended in 71.3% of cases. It exhibited relatively high adherence to dosing guidelines. In our study correct dosage was found in 89.6% of prescriptions, whereas a cross-sectional study conducted at Boston Children's Hospital revealed 87% of pediatric epilepsy patients having a prescribed RM (40). Conversely, DZP demonstrated lower adherence, with correct dosage prescribed in only 66.2% of cases. This discrepancy between MDZ and DZP prescription accuracy could be indicative of differing levels of physician familiarity or confidence with these drugs, highlighting potential areas for targeted educational interventions or clinical guideline reinforcement.

An in-depth examination revealed that underdosing was a more frequent error than overdosing across both medications, noted particularly in 7.5% of MDZ and 10.3% of DZP cases. Although published data on the prescription of RM remain limited, our findings on RM underdosing can be indirectly compared with the underdosing rates observed during the acute phase of SE treatment. For instance, Sathe et al. reported initial midazolam underdosing in 76% of cases, while Pais-Cunha et al. observed underdosing in 48.7% of cases (28)(10). These figures indicate that underdosing is approximately 5 to 7 times more prevalent during the acute phase of SE management than in our cohort. This pattern might stem from physicians' concerns regarding potential adverse effects, leading to overly cautious dosing. While conservative dosing may minimize immediate adverse reactions, suboptimal dosing risks insufficient seizure control, thereby potentially exacerbating patient outcomes (10,11).

Furthermore, in 3.4% of prescriptions, crucial information about drug administration methods was either missing or incorrect. The absence of clear instructions is concerning, given that precise administration is crucial for the effectiveness of rescue medications, particularly in prehospital or home settings where caregivers rather than medical professionals may administer these treatments.

The subgroup analysis of 187 patients who were offered both MDZ and DZP as interchangeable rescue options provides additional insight. Within this subgroup, the rate of underdosing increased to 11.8%. The presence of multiple therapeutic options without clear guidelines or adequate training may lead physicians toward overly cautious dosing strategies, reflecting uncertainty or insufficient clarity in current recommendations or guidelines. This finding underscores the necessity for clearer, standardized guidelines and thorough educational programs for prescribing physicians.

A significant and concerning finding was the total absence of prescribed rescue medication in 42.2% of the analyzed discharge summaries. Of particular note, within patients diagnosed with status epilepticus, an alarming 21.4% had no rescue medication recommended or prescribed.

Similarly, among patients with primary diagnoses of unspecified convulsions or febrile convulsions, rescue medications were omitted in 44.6% of cases. Such omissions significantly deviate from established best practices and international guidelines, representing a critical gap in patient management that necessitates immediate attention through guideline dissemination, physician training, and systems-level improvements to ensure comprehensive patient care.

The omission of rescue medication prescriptions and deviations from recommended dosing guidelines bear significant clinical implications (22). These oversights not only increase the risk of prolonged seizures and subsequent neurological damage but also impact overall patient safety and outcomes (22).

When discussing our findings, it is crucial to compare our data with existing studies to contextualize prescription patterns of RM. Notably, a cross-sectional study conducted at Boston Children's Hospital revealed that despite 87% of pediatric epilepsy patients having a prescribed RM (40). To our knowledge, comprehensive analyses examining physician prescription behavior and adherence to recommended RM dosages specifically from a clinician's perspective are relatively scarce in the literature. While previous surveys have evaluated pediatric emergency physicians' knowledge in Saudi Arabia and China, these studies primarily targeted clinical knowledge gaps from a physician awareness perspective, contrasting partially with our focus on prescription adherence and dosing accuracy. This suggests that the observed nonadherence in our study might stem from physicians' insufficient awareness of recommended doses or uncertainties surrounding RM prescription protocols, indicating a potential need for targeted educational interventions.

In conclusion, our retrospective analysis clearly identifies significant deviations from international recommendations in the prescription of rescue medications for pediatric patients experiencing acute tonic-clonic seizures. These findings underscore the urgent need for interventions aimed at improving adherence to established guidelines to enhance patient outcomes and ensure consistent, high-quality care for pediatric SE patients.

### 7.2 Parents'/caregivers'/medical professionals' education/training

A critical barrier to effective pediatric SE management is the profound lack of knowledge observed among caregivers and healthcare professionals (15,16,35). This knowledge gap has consistently emerged across diverse geographic regions, underscoring a widespread deficiency in critical understanding necessary for optimal SE care (15,16,35).

In Saudi Arabia, adherence to established pediatric SE management guidelines revealed significant knowledge deficiencies among healthcare providers (35). A cross-sectional study involving pediatric emergency physicians showed that a mere 20% adhered fully to all guideline components, and notably, 57% were entirely unaware of the existence of published guidelines (35). Despite SE being a common pediatric emergency, a substantial proportion of physicians managing such cases lacked essential protocol awareness, directly undermining guideline adherence and potentially jeopardizing patient outcomes (35).

Similar trends are evident in other regions as well. A study conducted among 60 emergency department physicians and nurses in China, indicated initial SE knowledge levels were remarkably low, with performance scores averaging around 40% during initial evaluations (16). These results point toward a widespread foundational knowledge deficit, severely limiting effective SE recognition and early management, crucial elements that significantly impact morbidity and mortality rates (16).

Parents and caregivers also display significant gaps in knowledge, directly affecting pediatric SE outcomes (34). In a recent study encompassing 418 parents or caregivers, approximately 69.4% inaccurately classified epilepsy as a psychiatric illness, and around 46.6% erroneously believed that alternative medicines could cure epilepsy (34). These misconceptions contribute to improper management practices and delayed medical interventions, further complicating SE scenarios and exacerbating associated risks.

The situation in Sudan similarly highlights critical knowledge deficits among caregivers (15). A study involving 107 caregivers showed that only 41.1% correctly rejected supernatural causes for epilepsy, while over a third engaged in harmful practices such as sprinkling water during seizures (15). Such practices illustrate the profound misunderstanding prevalent among caregivers, severely impeding proper seizure management.

Further emphasizing the urgent need for structured education, a study conducted at Boston Children's Hospital revealed that despite 87% of pediatric epilepsy patients having a prescribed rescue medication, only 61% of families reported receiving training on its use (40). Alarmingly, 12% of caregivers could not name the medication, and over a third were unaware of the correct administration timing (40). These gaps significantly compromise the efficacy of early intervention, especially in pre-hospital settings where prompt administration is critical. The study also highlighted that families who had a seizure action plan were significantly more likely to know the medication name and timing, and to involve schools in care coordination (40). These findings

underscore that merely prescribing rescue medications is insufficient - effective training and comprehensive seizure action planning must be integrated into care protocols to ensure caregivers are equipped to respond appropriately during emergencies.

These combined findings underscore an alarming global issue: inadequate knowledge significantly hampers effective pediatric SE management (15,16,35). These deficiencies are notably prevalent among both healthcare providers and caregivers, revealing an urgent need for targeted education and training interventions. Without substantial improvements in fundamental understanding among those responsible for initial SE management, efforts to mitigate associated morbidity and mortality will continue to be severely compromised.

The extensive documentation of knowledge gaps across multiple studies clearly indicates the critical nature of this issue. Addressing these deficits must therefore become a foundational priority in global pediatric epilepsy care strategies. Comprehensive education initiatives aimed at bridging these gaps will be indispensable for improving pediatric SE outcomes worldwide.

### 7.3 Intervention during early Status epilepticus

The effective management of pediatric SE hinges on the timely and adequate administration of first-line BZDs. Despite clear and evidence-based guidelines, two critical issues continue to compromise treatment efficacy across clinical settings: delays in drug administration and the widespread underdosing of BZDs (7–11).

#### 7.4.1 Underdosing

Underdosing of BZDs remains a significant concern in pediatric SE management, with various studies highlighting frequent deviation from established treatment guidelines (3,10). Despite clear recommendations provided by authoritative bodies such as the Neurocritical Care Society, ILAE, American Epilepsy Society, and European Federation of Neurological Societies, adherence remains suboptimal (11).

An analysis of benzodiazepine administration patterns revealed widespread underdosing across different clinical settings. A large-scale investigation involving 460 patients documented 1170 benzodiazepine doses, finding that 76% of initial midazolam doses and 81% of initial lorazepam doses were below guideline recommendations (11). Furthermore, an additional assessment demonstrated that overall benzodiazepine administration was inadequate in over 85% of midazolam and over 76% of lorazepam cases, highlighting a systemic trend of underdosing (11).

The significance of benzodiazepine underdosing is underscored by its direct association with poorer clinical outcomes (10–12). Low cumulative benzodiazepine dosing has been correlated with decreased likelihood of seizure cessation, with multivariate analysis confirming this relationship (27). Specifically, pediatric patients receiving lower-than-recommended total benzodiazepine doses exhibited significantly reduced chances of achieving seizure control, reflected in a hazard ratio of 0.7 (95% CI 0.57–0.95) (27).

Further complicating this issue, a retrospective review conducted at a tertiary pediatric emergency department found infra-therapeutic dosing in 48.7% of cases (28). This misuse was significantly associated with prolonged status epilepticus episodes and increased requirements for additional antiepileptic drug administrations (28). Consequently, nearly half of the pediatric patients presented prolonged seizures, and 6.8% required intensive care management, highlighting the severe clinical implications associated with underdosing (28).

Multiple factors contribute to the widespread practice of benzodiazepine underdosing. One explanation is related to EMS protocols that often recommend initial doses below guidelines. For example, Betjemann et al. (2021) highlighted that many EMS protocols in California suggested midazolam initial doses significantly below established recommendations (41).

In conclusion, benzodiazepine underdosing in pediatric status epilepticus is prevalent and significantly associated with adverse clinical outcomes. Despite well-established guidelines, persistent underdosing, inappropriate administration routes, and treatment delays continue to compromise patient care (8–12,17,18). These findings underscore the need for increased awareness and stringent adherence to evidence-based benzodiazepine dosing recommendations to mitigate the risks associated with pediatric status epilepticus

### 7.4.2 Delayed Treatment

Delayed administration of first-line BZDs in pediatric SE remains a pervasive and multifactorial problem, as demonstrated by numerous studies which show, that treatment delays are not only common but are also quantitatively significant, with critical clinical implications (7,8).

In pediatric patients with convulsive SE, the median time from seizure onset to first-line BZD administration has been reported to be as prolonged as 16 minutes in some multicenter investigations, which starkly contrasts with guideline recommendations advocating that treatment should ideally begin within 5 to 10 minutes (8,30). These prolonged delays are not trivial; even minor postponements in administering the initial dose can set off a cascade of physiological

changes that reduce drug efficacy, ultimately lengthening the seizure itself and increasing the risk of neuronal injury (29,37).

A principal factor underpinning these treatment delays is the nature of seizure onset. Specifically, studies have shown that when SE begins outside the hospital, the delay to first-line intervention is considerably prolonged compared to in-hospital onset, with out-of-hospital cases exhibiting a significant time lag that is attributable to pre-hospital factors such as recognition delay and variability in emergency response times (7,8). For example, Sanchez et al. reported that intermittent seizure activity and out-of-hospital onset were independently associated with a delay in the administration of BZD, with a median delay of 16 minutes from seizure onset (8). Similarly, Uppal et al. (2021) found that even when pre-hospital administration was attempted, with 81.4% of cases receiving MDZ prior to emergency department arrival, the overall system delays still resulted in a median time to first-line therapy of 15 minutes, exceeding the optimal window (7).

Beyond the setting of seizure initiation, inter-institutional variability further compounds the problem. In some pediatric centers, median treatment times vary from 11 minutes to nearly 25 minutes, an inconsistency that suggests systemic deficiencies in the rapid mobilization of emergency care (30,33). Srivastava et al. observed that even in centers where protocols were strictly implemented, the median time to BZD administration remained above 10 minutes, highlighting the inherent difficulties in adhering to a rigid treatment timeline in real-world practice (20). This variability indicates that while guidelines are clear in their recommendations, the translation into clinical practice is subject to numerous delays.

The pathophysiological consequences of these delays are grounded in well-established neurobiological processes. Studies have revealed that prolonged seizure activity leads to significant receptor alterations at the synaptic level (42). In particular, there is a rapid internalization of GABA_A receptors during ongoing seizure activity, which diminishes the inhibitory effects of BZDs as time elapses (42). Such receptor trafficking begins within minutes and is increasingly prominent beyond the 10-minute mark after seizure onset, rendering the central nervous system progressively less responsive to standard BZD therapy (30,37). The resulting decrease in effective inhibitory neurotransmission not only prolongs the duration of the seizure but also sets the stage for further excitotoxic injury, thereby amplifying the risk of irreversible neuronal damage (9,30).

Delays in treating SE significantly affect outcomes, as later BZD administration decreases responsiveness, prolonging seizures and increasing the need for continuous infusions (37). eSE

seizure activity has been linked to brain damage and heightened in-hospital mortality (31,43). Furthermore, each minute of treatment delay in pediatric SE adds a 5% cumulative risk of seizures lasting over an hour (43). Patients treated promptly, such as within 10 minutes of seizure onset, had no recorded deaths, whereas those treated later showed a 5% mortality rate (43).

Functional and clinical outcomes deteriorate with treatment delays. A study comparing adherence to SE management time frames found that compliant patients had significantly shorter hospital stays (median 4 vs. 9 days, p=0.0008) (20). In the non-compliant group, 50% progressed to refractory SE, and 18.7% developed super-refractory SE, while none of the compliant patients reached the super-refractory SE stage (20). Early treatment not only reduced SE duration but also improved discharge outcomes, with 79% of compliant patients returning to their functional baseline compared to only 44% of non-compliant ones (20).

SE duration and its adverse effects increase when treatment is delayed beyond 30 minutes (37). Delays greater than this threshold were associated with a twofold increase in mortality and poor functional outcomes (6). Adjustments for SE duration and nonconvulsive seizures confirmed these risks, emphasizing the importance of immediate intervention (6). Pediatric patients, in particular, demonstrated significant reductions in SE duration when treated in outpatient settings before hospital arrival compared to those who were untreated until reaching the emergency department (43).

Moreover, non-cardiac acute symptomatic SE treated after 60 minutes showed an even greater risk of poor functional prognosis, further underscoring the urgency for rapid treatment escalation (6).

Studies have quantified the relationship between delayed treatment and seizure duration. For instance, Cohen et al. documented that patients receiving the ASM within 5 minutes had a median seizure duration of roughly 59.5 minutes, whereas those who experienced delays beyond 60 minutes had a median duration extending to 151.5 minutes, a nearly threefold increase (30). This quantitative association underscores the direct impact that each incremental minute of delay has on the prolongation of SE, and it reinforces the concept that even minor delays can have dramatic clinical repercussions (29,30).

The heterogeneity observed in the timing data across different studies further elucidates the multifactorial origins of these delays. For example, Srivastava et al. reported that variations in adherence to established protocols contributed significantly to treatment delays, even within systems that had adopted recommended management pathways (20). This discrepancy points to the

influence of local emergency medical protocols, staff training levels, and the operational readiness of pre-hospital services,all factors that conspire to delay the initiation of critical treatment (7,33). In parallel, research conducted by Cohen et al. in the context of pediatric SE emphasizes that system-level issues, such as the route and timing of ASM administration, can markedly alter the time-to-treatment profile, thereby affecting the clinical trajectory of SE (30).

Notably, these studies collectively reinforce the idea that the delay in first-line treatment is not solely an isolated metric but rather a marker of a broader failure within the emergency response system to meet the narrow therapeutic window required for optimal outcomes (8,31).

Furthermore, the integration of pre-hospital care dynamics with in-hospital processes provides a comprehensive view of the challenges in timely SE management. Uppal et al. revealed that even when caregivers or EMS administer pre-hospital midazolam, the transition to hospital-based care is fraught with additional delays that cumulatively extend the time to definitive intervention (7). This continuum of delay, from the initial recognition of prolonged seizure activity by a caregiver, through dispatch and arrival of emergency services, to in-hospital management,highlights a multi-tiered failure in achieving the guideline-recommended timeframe for first-line therapy (8).

The quantitative data extracted from these studies, which span diverse healthcare systems and geographic regions, consistently demonstrate that the median delays for first-line treatment typically range between 11 and 25 minutes, with interquartile ranges often extending beyond these medians (30,33). Such variability underscores the influence of extrinsic factors such as local emergency response protocols, differences in pre-hospital care infrastructure, and the inherent challenges faced by clinicians when managing pediatric emergencies under high-stress conditions (7,8).

The profound impact of these delays is further illustrated by the association between extended time-to-treatment and increased seizure duration. In quantitative terms, a delay in initiating first-line therapy appears to correlate with a proportional increase in the overall duration of the seizure, thereby creating a self-reinforcing cycle of worsening pharmacoresistance and neuronal injury (29,30). This is of particular concern in pediatric patients, whose developing neural networks are highly susceptible to excitotoxic damage during prolonged periods of uncontrolled seizure activity (9,31).

In synthesizing the evidence, it becomes apparent that the delay in administering first-line BZD therapy in pediatric SE is not a result of a single, isolated failure but rather a convergence of

multiple systemic and biological factors that interact synergistically to extend the duration of seizures (8,30). The data from multiple centers indicate that although some institutions may achieve shorter median treatment times, the overall pattern remains suboptimal when compared to the ideal benchmark, thereby consistently exposing patients to extended periods of excitotoxic injury (7,33).

It is also critical to consider the implications of these treatment delays for the overall clinical outcomes of pediatric SE. While the immediate focus is on the duration of the seizure itself, prolonged SE is intrinsically linked to both short-term and long-term morbidity, as extended periods of seizure activity are associated with a higher risk of subsequent neurological deficits, cognitive impairments, and even mortality (9,29). In this context, the delay in first-line therapy emerges as not only a surrogate marker for poor process adherence but also as an independent contributor to adverse clinical outcomes (8,30).

The convergence of these findings across multiple studies emphasizes that the problem of delayed time-to-treatment in pediatric SE is deeply entrenched in the realities of clinical practice. It is a phenomenon that persists despite clear guideline recommendations and is further exacerbated by the complex interplay of pre-hospital and in-hospital factors (7,33). The consistent observation that treatment times exceed the optimal window,even in settings where protocols are well established, highlights the inherent challenges in rapidly mobilizing an effective response in pediatric emergencies (8,29).

In addition, systemic issues related to pre-hospital care, emergency department processes, and inherent variability among institutions contribute further to these delays, creating a scenario in which the critical therapeutic window is rarely achieved in clinical practice (7,33). In summary, the evidence clearly demonstrates that the delayed administration of first-line benzodiazepines in pediatric SE constitutes a critical and multifaceted problem. The delay, which has been quantified in several studies as extending the time to treatment well beyond the recommended 5- to 10-minute window, directly correlates with prolonged seizure duration and is associated with neurobiological changes that diminish drug efficacy (8,30).

### 7.5 Intervention during established SE and refractory SE

#### Transition to second-line treatment

Guidelines recommend escalation to a non-BZD antiseizure medication within 20–40 min of convulsive status epilepticus onset, yet every contemporary pediatric series demonstrates that this transition is routinely violated (33).

Escalation to second-line therapy in pediatric SE is consistently delayed across continents, but the pattern of delay is neither random nor benign. In three prospectively collected cohorts the median interval from seizure onset to the first non-BZD ASM ranged from 68 min in India to 69 min in the United States and 45 min in Australia, underscoring a reproducible failure to meet 20-min guideline targets (17,32,33). 62.5 % of North-American children and 46.8 % of those in a multinational rSE registry reached hospital without any ASM, despite prior epilepsy in roughly half of cases (19,32). EMS rarely progress beyond repeated BZDs because regulatory protocols or lack of intravenous access restrict access to second-line drugs, resulting in an algorithm that restarts on arrival and adds even more first-line doses (19).

Once in hospital, therapeutic deviations persists: 96.8 % of New South Wales children received at least three in-hospital BZDs, with a median of seven doses, before escalation (17). Multicenter data confirm that 57.3 % of refractory cases are still exposed to BZDs beyond 30 min, and 36.2 % exceed the two-dose threshold entirely, particularly after out-of-hospital onset or when seizures present intermittently rather than continuously (19). These observations suggest that clinicians confronted with fluctuating motor activity misinterpret transient pauses as treatment response, opting to repeat the familiar agent instead of advancing therapy (19).

Each additional BZD doubled the odds of intubation in the Australian cohort and ≥5 doses increased that risk twenty times while prolonging intensive car unite (ICU) stay by two days (17). Parallel findings in Pediatric Status Epilepticus Research Group (pSERG) (pSERG) show that initiation of the second non-BZD ASM at 120 min correlated with longer ICU stay, whereas the timing of early BZD doses did not, highlighting the decisive influence of timely escalation rather than initial administration alone (32).

Finally, system-level heterogeneity magnifies these challenges. A global review encompassing 2 212 patients calculated an average treatment initiation of 42.4 min, with only 51.8 % of cases receiving any EMS therapy and a strikingly low 12.8 % treated by caregivers (31).

Such variability reflects differences in EMS scope of practice, drug availability, and transfer pathways, but it converges on the same clinical reality: the journey from first to second line is routinely too slow. Understanding these interconnected logistical, cognitive, and pharmacologic barriers is essential for interpreting outcome data and framing future quality-improvement priorities.

## 7.6 Solutions to Deviations in the Treatment of Pediatric Status Epilepticus

Despite detailed international algorithms, real-world management of paediatric SE often diverges from recommended timelines and drug doses (44). Deviation begins before the child reaches hospital and persists across the emergency continuum, reflecting structural, cognitive, and educational deficits in the acute seizure pathway (45). Consequently, effective solutions must operate at multiple places like: community, pre-hospital, emergency department, and inpatient units to compress treatment latency and optimise dosing (46). The following discussion synthesises evidence from recent interventional and observational work to propose pragmatic recommendations that address the root drivers of non-adherence and promote sustainable guideline-concordant care (16).

First, mastery of guidelines cannot be presumed and should be systematically cultivated through deliberate practice in high-fidelity scenarios that reproduce the temporal stress of convulsive SE (16). Curriculum learning coupled with in-situ simulation tripled technical performance scores and significantly upgraded teamwork among mixed physician and nurse groups (16). Hospitals should be implemented with recurrent simulation cycles, ideally every 2-3 months, to guard against skill decay (16).

Such programmes must be multiprofessional, scenario-based, and immediately debriefed to consolidate cognitive frames that favour early BZDdelivery and program non-BZDescalation pathways (44). Moreover, simulation drills create a psychologically safe venue where latent system flaws, for example unavailable drug concentrations or alarm fatigue, could be uncovered before real patients are involved (16). Regular post-drill  sessions should be calculated and translated into actionable tasks assigned to accountable owners (38).

Because over three-quarters of paediatric SE cases receive their first intervention from emergency medical services, optimising pre-hospital care is essential (46). Implementation of the colour-coded Medic One Paediatric cards reduced BZD underdosing from 52 % to 6 %, underscoring how cognitive off-loading tools can correct dosing mistakes in dynamic field conditions (46). Agencies should therefore implement calculation aids into standard equipment, mandate annual competency sessions, and conduct feedback questionnaires to reinforce appropriate first-line therapy (46). To cement uptake, regional medical directors can integrate dosing-card competencies into credentialing examinations (46). Future iterations could leverage smartphone applications that autocalculate dosage once a measurement is entered, reducing cognitive load even further (46). Parallel dissemination of seizure action plans to caregivers and school personnel can further improve

out-of-hospital treatment by clarifying when to activate EMS and how to administer home rescue medication (40).

Within the emergency department, structured treatment pathways shorten drug-delivery times and reduce practice variability (39). A paper-based protocol decreased median time to second-line fosphenytoin from forty to twenty-five minutes among children seizing on arrival, highlighting the power of simple visual algorithms in high-noise environments (39).

Quality-improvement methodology can extend these gains; iterative Plan-Do-Study-Act cycles halved the delay between BZD failure and fosphenytoin initiation, sustaining an eleven-minute median over six years (38). Key drivers included real-time pharmacy batching, predefined drug carts, and scripted communication—elements that are readily portable to other institutions regardless of resource level (38). Embedding these protocols into electronic order sets with forced weight-based calculations may further prevent dosing errors while preserving situational awareness (39).

Although non-hospital caregivers play a crucial role, only 61 % of families report receiving training on rescue therapies, and more than one-third cannot recall the correct timing of administration, revealing a substantial adherence gap. (40). Provision of tailored education sessions, simulation with placebo devices, and bilingual instructional media can heighten caregiver confidence and promote timely intranasal or buccal midazolam usage at home (40).

Institutions should formalise seizure action plans that travel with the child across home, school, and respite settings to ensure continuity and legal clarity around medication administration (45). Process mapping of the paediatric seizure journey revealed twenty-nine discrete barriers, many remediable through integrated digital diaries, closed-loop communication, and outreach to community nurses (45). Accordingly, solutions must transcend the hospital wall and address documentation, follow-up, and prescription fulfilment to reinforce adherence along the entire care continuum (45).

Schools often cite legal ambiguity and insufficient training as barriers to administering rescue medication, challenges that can be addressed through nurse-led workshops and standing delegation orders (40). Because parental anxiety frequently impedes early activation of rescue plans, psychosocial support and peer-to-peer mentoring should accompany technical instruction (45).

When pre-emptive strategies fail and refractory seizures persist, rapid-response models analogous to trauma codes can compress escalation intervals (44). The proposed “Seizure Code” mobilises a multidisciplinary team equipped with checklist-driven algorithms, dedicated drug boxes, and

weight-based calculators, thereby reducing ambiguity and synchronising actions under a shared mental model (44). Hospitals should define clear activation criteria—such as five minutes of ongoing convulsions or two failed benzodiazepines—and empower nursing staff to trigger the code without hierarchical delay (44). Simulation data indicate that code activation can reduce door-to-drug times by streamlining parallel workflows such as vascular access, pharmacy preparation, and airway assessment (44). Adaptation of this model to smaller hospitals may involve telemedicine support from tertiary centres, ensuring equitable access to specialist input (44). Outcome metrics, including seizure duration, intensive-care admission, and ventilation rates, should be continuously monitored to guide iterative refinements and maintain executive support (38).

Collectively, the evidence points toward an interlocking suite of educational, cognitive, and system-redesign interventions that, when orchestrated together, can markedly elevate adherence to international standards (16). Key recommendations include quarterly simulation for all acute-care personnel, universal use of pre-hospital weight-based dosing cards, mandatory emergency-department protocols embedded in electronic health records, and clear seizure action plans extending into community domains (39,40,46).

## 8. RECOMMENDATIONS

To improve guideline adherence, we recommend deploying an AI-supported clinical-decision plug-in that sits directly inside the hospital's electronic medical-record system. The hypothetical module could automatically import the child's most recent weight, calculate the guideline-conforming buccal MDZ or rectal DZP dose, and surface it as a single-click order.

If a physician attempts to enter a dose <0.2 mg/kg or >0.5 mg/kg for MDZ, or <0.3 mg/kg or >0.5 mg/kg for DZP, the plug-in would issue a real-time "underdose/overdose" warning; similar alerts would fire whenever rescue ASM is omitted, a scenario that occurred in 42 % of our studies discharge summaries and contributed most to overall guideline deviation

Context-aware remindere, for example: a pop-up when the ICD-10 codes G41.x or R56.x are entered without a linked ASM order, could further reduce the 13.5 % of prescriptions that were outside dosing limits in Type 1 non-compliance.

Because the algorithm is embedded in the existing workflow, it minimizes extra clicks while providing an auditable log of overridden alerts for quality-improvement meetings. Periodic model updates, like incorporating new weight-band recommendations or additional rescue options and

brief quarterly feedback dashboards would close the loop, reinforcing best practice and driving sustainable gains in compliance.

Regular, high-fidelity simulation exercises are critical for instilling proficiency under time pressure (16). Multidisciplinary teams comprising physicians and nurses should engage in scenario-based drills every two to three months, followed by structured debriefings that reinforce rapid benzodiazepine administration and clear escalation pathways (16). Prehospital providers benefit equally from cognitive off-loading tools: color-coded pediatric dosing cards have demonstrated a reduction in benzodiazepine underdosing from approximately 52 % to 6 % (46). Complementary smartphone applications that auto-calculate doses upon entry of weight data can further minimize calculation errors (46). Concurrently, tailored seizure action plans, distributed across home, school, and respite settings, together with bilingual instructional media, placebo-device practice sessions, and peer-support networks, will empower caregivers and school personnel to recognize status epilepticus promptly and administer rescue therapy effectively (16,40,46).

Optimizing the prehospital and emergency department continuum hinges on structured protocols and streamlined workflows (38,39). Emergency medical services should incorporate annual competency assessments in pediatric dosing and integrate dosing cards or apps into standard equipment, with regional credentialing bodies including these competencies in certification requirements (38). Within the emergency department, visual algorithms (either paper-based or embedded in electronic order sets) can halve the time to second-line anticonvulsant administration (39). Pre-stocked, weight-segmented drug carts, coupled with real-time pharmacy batching and scripted interprofessional communication, maintain this performance; iterative Plan-Do-Study-Act cycles ensure sustainability, preserving a median benzodiazepine-to-second-line interval of approximately 11 minutes (38).

## 9. CONCLUSIONS

1. The management of pediatric SE is guided by evidence-based international algorithms, which define critical timepoints for intervention. First-line treatment with BZDs should be initiated within five minutes of convulsive seizure onset ($t_1$), and if seizures persist, escalation to a non-benzodiazepine ASM is recommended at or before twenty minutes ($t_2$). Our narrative literature review revealed that there are widespread knowledge gaps among both caregivers and healthcare providers, undermining timely recognition of SE and proper use of rescue medications. Early SE interventions likewise suffer from pervasive underdosing of benzodiazepines and delays in administration that exceed the recommended 5–10-minute window, allowing receptor changes to

diminish drug efficacy. Finally, transition to second-line therapy is routinely postponed well beyond guideline targets, with repeated benzodiazepine redosing rather than prompt escalation, thereby prolonging seizures and increasing the risk of intensive care interventions.

2. Our single-center, retrospective cros-sectional analysis indicate that only 57.8% of children were discharged with any rescue medication. Of the patients diagnosed with SE, 21.4% were not prescribed any RM. Among  prescriptions, 13.5% deviated from guideline-based dosing recommendations, with underdosing being the most frequent error.

3. Potential solutions could be: integration of a weight-sensitive decision-support module into the EMR can automatically retrieve patient weight, compute target antiseizure doses, flag out-of-range entries or missing rescue medications, and offer one-click ordering, while standardized weight-based discharge aids eliminate omission rates and dosing errors. Regular, multidisciplinary, high-fidelity simulation drills sharpen rapid benzodiazepine administration under time pressure. Tailored seizure action plans, bilingual instructional media, placebo-device practice sessions, and peer-support networks empower caregivers and school personnel to recognize and treat status epilepticus promptly.

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# 11. APPENDICES

## PubMed:

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Cochrane:

"epilepsy" in Title Abstract Keyword AND "Child" in Title Abstract Keyword AND "treatment" in Title Abstract Keyword

Scopus:

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## Ethical Considerations

The study adhered to ethical standards and guidelines. All patient data were anonymized and analyzed without direct identifiers.