



REVIEW ARTICLE

Management protocols for status epilepticus in the pediatric emergency room: systematic review article[☆]



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Received 7 June 2017; accepted 23 July 2017

Available online 21 September 2017

KEYWORDS

Status epilepticus;
Seizure;
Protocol;
Guideline

Abstract

Objective: This systematic review of national or regional guidelines published in English aimed to better understand variance in pre-hospital and emergency department treatment of status epilepticus.

Sources: Systematic search of national or regional guidelines (January 2000 to February 2017) contained within PubMed and Google Scholar databases, and article reference lists. The search keywords were status epilepticus, prolonged seizure, treatment, and guideline.

Summary of findings: 356 articles were retrieved and 13 were selected according to the inclusion criteria. In all six pre-hospital guidelines, the preferred route of medication administration was to use alternatives to the intravenous route: all recommended buccal and intranasal midazolam; three also recommended intramuscular midazolam, and five recommended using rectal diazepam. All 11 emergency department guidelines described three phases in therapy. Intravenous medication, by phase, was indicated as such: initial phase – ten/11 guidelines recommended lorazepam, and eight/11 recommended diazepam; second phase – most (ten/11) guidelines recommended phenytoin, but other options were phenobarbital (nine/11), valproic acid (six/11), and either fosphenytoin or levetiracetam (each four/11); third phase – four/11 guidelines included the choice of repeating second phase therapy, whereas the other guidelines recommended using a variety of intravenous anesthetic agents (thiopental, midazolam, propofol, and pentobarbital).

Conclusions: All of the guidelines share a similar framework for management of status epilepticus. The choice in route of administration and drug type varied across guidelines. Hence, the

[☆] Please cite this article as: Au CC, Branco RG, Tasker RC. Management protocols for status epilepticus in the pediatric emergency room: systematic review article. J Pediatr (Rio J). 2017;93:84–94.

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PALAVRAS-CHAVE

Estado de mal
epiléptico;
Convulsão;
Protocolo;
Diretriz

adoption of a particular guideline should take account of local practice options in health service delivery.

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Protocolos de manejo de estado de mal epiléptico no pronto socorro pediátrico: análise sistemática

Resumo

Objetivo: Esta análise sistemática de diretrizes nacionais ou regionais publicadas em inglês tem como objetivo entender melhor a diferença no tratamento do estado de mal epiléptico pré-hospitalar e no departamento de emergência.

Fontes: Pesquisa sistemática de diretrizes nacionais ou regionais (janeiro de 2000 a fevereiro de 2017) contidas nas base de dados do Pubmed e do Google Acadêmico e listas de referência de artigos. As palavras-chave da busca foram estado de mal epiléptico, convulsão prolongada, tratamento e diretriz.

Resumo do achados: 356 artigos foram identificados, e 13 foram selecionados de acordo com os critérios de inclusão. Em todas as seis diretrizes pré-hospitalares, o caminho preferencial de administração da medicação foi utilizar alternativas à via intravenosa: todas recomendaram midazolam bucal e intranasal; três também recomendaram midazolam intramuscular; e cinco recomendaram utilizar o diazepam via retal. Todas as 11 diretrizes de departamento de emergência descreveram três fases na terapia. No que diz respeito à medicação intravenosa, por fase, temos: fase inicial – 10/11 diretrizes recomendaram lorazepam e 8/11 recomendaram diazepam; segunda fase – a maioria (10/11) das diretrizes recomendou fenitoína, porém outras opções foram fenobarbital (9/11), ácido valpróico (6/11) e fosfenitoína ou levetiracetam (individualmente, 4/11); terceira fase – 4/11 diretrizes incluíram a opção de repetir a terapia da segunda fase, ao passo que as outras diretrizes recomendaram utilizar diversos agentes anestésicos intravenosos (tiopental, midazolam, propofol e pentobarbital).

Conclusões: Todas as diretrizes compartilham uma estrutura semelhante para manejo do estado de mal epiléptico. A escolha da via de administração e do tipo de medicamento variou em todas as diretrizes. Assim, a adoção de uma diretriz específica deve levar em consideração as opções da prática local na prestação de serviços de saúde.

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Introduction

Status epilepticus (SE) is defined as “a condition resulting either from the failure of mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures (after time point t_1), and a condition that can have long-term consequences (after time point t_2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures, etc. In the case of convulsive (tonic-clonic) SE, both time points (t_1 at 5 min and t_2 at 30 min) are based on animal experiments and clinical research”.¹

Therefore, in children, there are two subgroups of patients presenting with a seizure: those with brief episodes <5 min duration (before t_1) that are highly likely to resolve without treatment; and those with episodes >7 min, who are more likely to progress to prolonged episodes necessitating acute treatment to stop the seizure. The consensus of the International League Against Epilepsy (ILAE) task force on the classification of SE is that treatment of convulsive seizures should therefore be initiated at around 5 min.¹

This article discusses some of the issues related to emergency anticonvulsant treatment of acute, prolonged seizures and SE in children with particular emphases on pre-hospital, emergency medical services (EMS), and emergency department (ED) guidelines, as well as protocols used by national and regional societies, organizations, and authorities. The reader interested in other management, investigations, and subsequent clinical follow-up in the outpatient department or by the primary care practitioner should review recent practice reviews and the American Academy of Neurology recommendations.^{2,3}

Methods

Source of data

A systematic review of articles available in the PubMed and Google Scholar databases was carried out. Reference lists of articles identified were also checked. The search strategy included the combination of the following keywords in

English: status epilepticus, prolonged seizure, treatment, and guideline.

Selection criteria

In this qualitative review, articles were selected for consideration using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) group 2009 statement.⁴ Published articles were included in the review when they met the following criteria: (1) protocol or guideline on the use of anticonvulsant drug treatment for prolonged seizure or SE published January 1st, 2000 to February 28th, 2017; (2) publication that featured a national or regional guideline for the pediatric population in the EMS or ED setting; and (3) when more than one article was identified from the same organization or society, the most recent publication was included.

All articles that met the inclusion criteria were submitted to data extraction and critical evaluation by each author. The main characteristics were summarized following data extraction: authorship; period of management; EMS or ED; time course of treatment; and recommended medication and administration route.

Data synthesis/analysis

The search strategy of the databases identified a total of 356 listed titles. Each abstract was screened and 344 were excluded because they did not meet the inclusion criteria. Twelve articles were eligible for full review, and their reference lists identified one further article. A total of 13 articles were therefore included in the qualitative synthesis, and their findings were descriptively analyzed.⁵⁻¹⁷

Results and discussion

Table 1 describes the characteristics of the treatment guidelines. Table 2 presents use of immediate ("STAT" or *statim* [Latin]) anticonvulsant drug by type, dosing and route of administration covered in the guidelines. It is evident that the guidelines do not recommend exactly the same dosing for each anticonvulsant drug. However, these differences may be due to regional preference, history, or experience. Developers of new guidelines should take into account the spread in dosing and the maxima recommended, as well as any new clinical drug studies that are published after 2017.

Pre-hospital management

Six guidelines focused on EMS management.^{7,10-14} Fig. 1 presents the algorithm by the Emergency Medical Services for Children (EMSC) for comparison.¹¹ This guideline should be applied to children with a witnessed seizure that was not due to trauma, and was ongoing at the time of arrival of the EMS.

Overall, all six guidelines recommended buccal midazolam or intranasal midazolam, and three recommended intramuscular midazolam.^{10,11,14} Five guidelines recommended rectal diazepam as an option.^{7,10,12-14} A second dose of benzodiazepine was recommended in two of the

guidelines, one at 5 min¹¹ and the other at 10 min.¹³ All of the guidelines stated a preference for alternative non-intravenous routes of administration rather than gain intravenous access on arrival. Two of the guidelines^{11,13} recommended attempting to place either intravenous or intraosseous access in specific situations. Finally, only one of the guidelines provided criteria for patient transfer to ED.¹³

Comment on pre-hospital EMS guidelines

Midazolam through the buccal or intranasal route was recommended in the six pre-hospital guidelines. This guidance likely reflects the efficacy of midazolam *versus* diazepam, and the ease of administration by these access routes. However, rectal diazepam was still present in most of the pre-hospital guidelines. Buccal midazolam is more effective than rectal diazepam for stopping seizures and reducing their recurrence within 1 h of onset, and as safe as rectal diazepam in relation to the incidence of respiratory depression.¹⁸ The effectiveness of intranasal midazolam is similar to, or more effective than rectal diazepam. Intranasal midazolam also has a shorter drug administration time and faster action to seizure cessation than rectal diazepam. Intranasal midazolam is easy to administer, but it has a short-lasting nasal irritant effect. A systematic review demonstrated that midazolam, by any route, is superior in seizure cessation than diazepam, by any route.¹⁹

Besides efficacy and ease of administration, the choice of non-intravenous benzodiazepines depends on local availability, expertise, and preference. For example, according to Osborne et al.,¹³ ambulances in the United Kingdom did not carry midazolam, and so EMS staff would administer the patient's own buccal or intranasal midazolam, if available; otherwise, rectal diazepam would be used because of the difficulty gaining intravenous access in children. For similar reasons, rectal diazepam was commonly available and recommended in the Italian League Against Epilepsy pre-hospital guideline.¹⁰ The World Health Organization (WHO) pediatric emergency triage assessment and treatment (ETAT) guideline¹⁴ recommends that, when oral and intranasal preparations of midazolam and lorazepam are not readily available, especially in resource-limited settings, the available intravenous preparations could be administered through the oral or intranasal routes. Last, intramuscular midazolam was recommended in three of the six guidelines.^{10,11,14} Such administration requires additional expertise, and it is effective and safe. For example, in the Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART), intramuscular midazolam was as effective as intravenous lorazepam in the pre-hospital setting.²⁰ Similar rates of endotracheal intubation and recurrence of seizures were observed in both the midazolam and lorazepam groups. Considered together, all of the guidelines recommended the non-intravenous route of administration.

Two of the guidelines recommend attempting intravenous or intraosseous access only in specific situations.^{11,13} The EMSC algorithm¹¹ in the United States considers obtaining intravenous or intraosseous access when the expected transport time was long, or when it would be required for other aspects of patient care such as intravenous fluid or other medications. The United Kingdom Joint Royal Colleges

Table 1 Guideline or protocol characteristics.

Year, Ref #	Country or Region	Endorsed by	Population (A, P)	Scope	
				EMS	ED
2014, ¹¹	USA	Emergency Medical Services for Children	P	Y	–
2015, ¹³	UK	Joint Royal Colleges Ambulance Liaison Committee	A, P	Y	–
2011, ⁷	Canada	Canadian Paediatric Society Acute Care Committee	P	Y	Y
2013, ¹⁰	Italy	Italian League Against Epilepsy	P	Y	Y
2014, ¹²	India	Association of Child Neurology (Indian)	P	Y	Y
2016, ¹⁴	Global	World Health Organization ETAT	P	Y	Y
2000, ⁵	UK	British Paediatric Neurology Association	P	–	Y
2009, ⁶	Aus/NZ	Paediatric Research in EDs International Collaborative	P	–	Y
2012, ⁸	USA	Neurocritical Care Society	A, P	–	Y
2012, ⁹	UK	NHS National Institute of Health and Care Excellence	A, P	–	Y
2016, ¹⁵	USA	American Epilepsy Society	A, P	–	Y
2016, ¹⁶	Spain	Spanish Society of Neurology	A, P	–	Y
2017, ¹⁷	Hong Kong	Hong Kong Epilepsy Society	A, P	–	Y

A, adult; P, pediatric; Aus/NZ, Australia and New Zealand; ED, Emergency Department; EMS, Emergency Medical Services; ETAT, pediatric emergency triage assessment and treatment; NHS, National Health Service; UK, United Kingdom; USA, United States of America; Y, yes.

Ambulance Liaison Committee (JRCALC) algorithm¹³ recommends a second dose of diazepam if the seizure continues after rectal diazepam, and that must be given via the intravenous or intraosseous route. Establishing intravenous access could be difficult, however, in a child with an ongoing seizure in the pre-hospital setting. It requires trained EMS providers and equipment, which may be lacking in resource-limited settings (see ETAT guideline¹⁴). Furthermore, the seizure may stop before intravenous access is obtained, making the procedure unnecessary¹¹; the time needed to set-up intravenous access may prolong the time at the scene and delay drug administration.¹³

Two of the guidelines recommended administering a second dose of benzodiazepines in the pre-hospital setting.^{11,13} The other four guidelines did not include this option. Maintaining adequate airway, breathing, and circulation while the patient is transferred to the ED,^{7,10,12,13} as well as communicating with the medical control center for advice, are recommended.¹¹ One guideline provided guidance on criteria for transfer to hospital. The JRCALC guideline¹³ recommends transfer to hospital for children under 1 year of age, cases with their first seizure or first febrile convulsion, and cases with serial seizures or difficulty monitoring. The JRCALC guideline¹³ also recommends a time-critical transfer to the hospital if any of the following are present: difficulty with airway, breathing, circulation, or disability problems; serious head injury; SE after failed treatment; or, underlying infection.

Emergency department management

Eleven guidelines focused on ED management.^{5–10,12,14–17} For comparison, the authors have selected the American Epilepsy Society (AES) algorithm for convulsive seizure lasting at least 5 min.¹⁵ The structure of this algorithm follows three phases of therapy (Figs. 2–4, and Table 3). The first phase of therapy is initial stabilization and the administration of a benzodiazepine. The second phase of therapy is the administration of a non-benzodiazepine

second anticonvulsant drug, when benzodiazepines have failed. The third phase of therapy is the administration of a general anesthetic drug under intensive care support when SE has become refractory to at least two anticonvulsant drugs from the first and second therapy phases.

The time to starting each phase of therapy was similar across the guidelines. In the initial phase of therapy, nine of the guidelines reported a start time equal to, or earlier than the AES algorithm.^{5–7,9,10,12,15–17} The onset of the second and third phases of therapy were equal to, or earlier than, the AES start times in five of the guidelines that stated the start time.^{5–7,12,15} Endotracheal intubation was considered in the stabilization phase in two of the guidelines,^{8,15} and in the context of rapid sequence intubation in four of the guidelines.^{5–7,9}

In regard to the route of anticonvulsant drug administration, intravenous access may be available after the pre-hospital stage of therapy (Fig. 1). When there is no intravenous access at the start of the ED stage of treatment, the guidelines recommend intraosseous access in the initial ($n=1$)⁶ or second phase of treatment ($n=2$).^{5,7} In both of these phases, benzodiazepines and phenytoin could be administered through the intraosseous route.

Comment on ED time course

No significant discrepancies were observed among the guidelines in regard to the timing for starting each phase of anticonvulsant drug therapy. All guidelines recommended “starting the clock” when a seizure lasts longer than 5 min, which can be assumed to be whenever an actively seizing patient arrives in the ED. This time point is also consistent with the new ILAE definition and classification of SE.¹ A minor difference in timing in the guidelines is observed in the period needed for a stabilization phase, and the different intervals between administering the options in anticonvulsant drugs.

Table 2 Commonly used immediate anticonvulsant drug, administration route and dose.

Drug	Administration route			
	Rectal	Buccal (B)/Intranasal (N)	Intraosseous (IO)/Intramuscular (IM)	Intravenous
Diazepam	Bolus 0.2–0.5 mg/kg/dose ^{15,17} 0.5 mg/kg/dose ^{5,6} 0.5 mg/kg × 2 doses ⁷ Maximum dose 10 mg ⁶ ; 20 mg ^{15,17}		Bolus IO: 0.25 mg/kg × 2 doses ⁶	Bolus 0.15–0.2 mg/kg × 2 doses ^{15,17} 0.2–0.3 mg/kg × 2 doses ¹² 0.25 mg/kg × 2 doses ⁶ 0.3 mg/kg × 2 dose ⁷ 0.5 mg/kg ¹⁰ Maximum dose <5 year, 5 mg ⁷ ; ≥5 year, 10 mg ⁷ ; 10 mg ^{10,12,15,17}
Lorazepam	Bolus 0.1 mg/kg × 2 doses ⁷ Maximum dose 4 mg ⁷	Bolus B: 0.1 mg/kg × 2 doses ^{7,10} Maximum dose B: 2.5 mg ¹⁰ ; 4 mg ⁷		Bolus 0.1 mg/kg × 2 doses ^{5,7,10,12,15,17} Maximum dose 4 mg ^{5,7,10,12,15,17}
Midazolam		Bolus B: 5–10 mg ¹⁷ IN: 0.2 mg/kg ⁷ Maximum dose IN: 5 mg/nostril ⁷	Bolus IO: 0.15 mg/kg × 2 doses ⁶ IM: 0.15 mg/kg × 2 doses ⁶ IM: 0.2 mg/kg × 2 doses ^{7,10} Maximum dose IM: 5 mg ¹⁰ ; 13–40 kg, 5 mg ¹⁵ ; >40 kg, 10 mg ¹⁵ ; 10 mg ¹⁷	Bolus 0.15 mg/kg × 2 doses ⁶ 0.15 to 0.2 mg/kg × 2 doses ¹² 0.2 mg/kg × 2 doses ¹⁰
Fosphenytoin (PE, phenytoin equivalents)			Bolus IM: 20 mg PE/kg ⁷ Maximum dose IM: 1000 mg PE ⁷	Bolus 20 mg PE/kg ^{7,12,15} Maximum dose 1000 mg PE ⁷ ; 1500 mg PE ¹⁵
Phenytoin			Bolus IO: 20 mg/kg ⁶ Maximum dose IO: 1000 mg ⁷	Bolus 15–20 mg/kg ^{16,17} 18 mg/kg ⁵ 18–20 mg/kg ¹⁰ 20 mg/kg ^{6,7,12} Maximum dose 1000 mg ^{11,16}
Phenobarbital				Bolus 10–20 mg/kg ¹⁶ 15 mg/kg/dose ^{15,17} 15–20 mg/kg ¹⁰ 20 mg/kg ^{6,12} Maximum dose 1000 mg ¹⁰

Table 2 (Continued)

Drug	Administration route			
	Rectal	Buccal (B)/Intranasal (N)	Intraosseous (IO)/Intramuscular (IM)	Intravenous
Valproic acid				Bolus 20 mg/kg ¹² 25–45 mg/kg ¹⁶ 30–45 mg/kg ¹⁰ 40 mg/kg ^{15,17} Maximum dose 1500 mg ¹⁰ ; 3000 mg ^{15,17}
Levetiracetam				Bolus 20 mg/kg ¹⁶ 20–30 mg/kg ¹² 60 mg/kg ^{15,17} Maximum dose 4500 mg ^{15,17}

ED first phase anticonvulsant therapy

In regard to the choice of anticonvulsant drug treatment, a benzodiazepine was universally recommended in the initial phase of therapy (Fig. 2 and Table 3). Intravenous lorazepam was recommended in ten of the guidelines,^{5–10,12,14,15,17} followed by intravenous diazepam in eight of the guidelines.^{6,7,10,12,14–17} If no intravenous access was available, the most commonly recommended anticonvulsant drug was midazolam: intramuscular midazolam ($n=8$),^{6–8,10,12,15–17} buccal midazolam ($n=8$),^{6,7,9,10,12,15–17} or intranasal midazolam ($n=5$).^{6,7,12,15,16} As an alternative, rectal diazepam ($n=7$) was commonly recommended.^{5,7,8,12,15–17} A repeated dose of benzodiazepine was recommended in five guidelines; four of them considered the pre-hospital dose received,^{6,7,9,10} while the other excluded the pre-hospital dose.⁵ Intravenous phenobarbital was recommended as a non-benzodiazepine alternative in two of the guidelines.^{8,15}

Comment on ED first phase anticonvulsant therapy

Intravenous lorazepam and diazepam were the most commonly recommended intravenous benzodiazepines in the first phase of therapy. All except for one guideline (from the Spanish Society of Neurology) recommended intravenous lorazepam.¹⁶ In Spain, in 2016, intravenous lorazepam was not available; thus, intravenous clonazepam is recommended instead. Intravenous lorazepam or diazepam are efficacious and safe to use. For example, in one randomized controlled trial²¹ comparing intravenous lorazepam and intravenous diazepam, 72.9% of the lorazepam group and 72.1% of the diazepam group had cessation of SE within 10 min without recurrence within 30 min, with similar rates of assisted ventilation (17.6% in the lorazepam group and 16.0% in the diazepam group). In the resource-limited setting, one additional consideration with lorazepam use is the need for refrigeration of the drug, because of its degradation at high temperature. Although both intravenous lorazepam and diazepam are included in the WHO model list of essential

medicines for children, the ETAT guideline recommends intravenous diazepam in high temperature regions with no refrigeration facility.¹⁴

When a repeat dose of benzodiazepine is required because of an ongoing seizure, four of the 11 guidelines^{6,7,9,10} recommended taking account of whether any pre-hospital benzodiazepine dose(s) had been administered, since EMS dosing would affect the choice of next anticonvulsant drug. Interestingly, these four guidelines were published after 2008, which is when Chin et al.²² showed that in community-onset childhood convulsive SE there was an association between no pre-hospital anticonvulsant drug treatment, or use of more than two doses of benzodiazepines, and SE lasting more than 60 min. Moreover, their study demonstrated that treatment with more than two doses of benzodiazepines was associated with respiratory depression. Only one guideline, from 2000, recommended excluding consideration of prior EMS treatment,⁵ and that was on the basis of possible variability in pre-hospital dosing.

ED second phase anticonvulsant therapy

In the second phase of therapy (Fig. 3 and Table 3), guideline recommendations for intravenous medications included: phenytoin ($n=10$),^{5–10,12,14,16,17} phenobarbital ($n=9$),^{6–10,14–17} valproic acid ($n=6$),^{8,10,14–17} fosphenytoin ($n=4$),^{7,12,14,15} and levetiracetam ($n=4$).^{8,15–17} If no intravenous access was available, intraosseous phenytoin was recommended in three guidelines,^{5–7} and the other options presented were intramuscular fosphenytoin,⁷ phenobarbital,¹⁴ and rectal paraldehyde.^{5,7}

Comment on ED second phase anticonvulsant therapy

Intravenous phenytoin was the most commonly recommended therapy for benzodiazepine-refractory SE. Together with intravenous fosphenytoin (the prodrug of phenytoin), they were the second phase therapy of choice in all

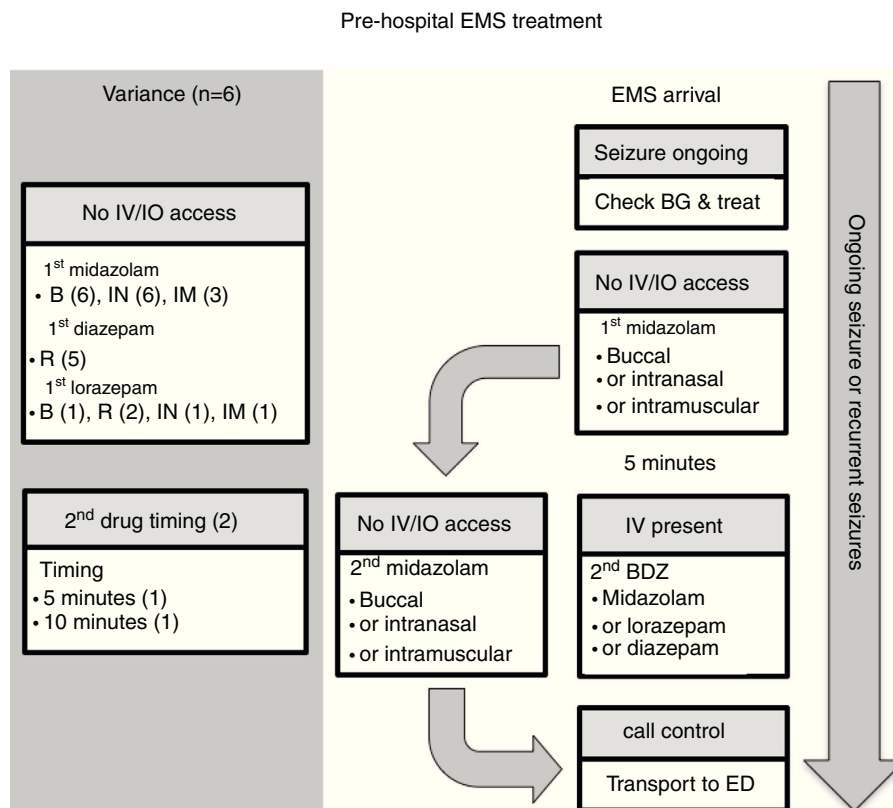


Figure 1 Pre-hospital EMS treatment. B, buccal; BDZ, benzodiazepine; BG, blood glucose; ED, emergency department; EMS, emergency medical system; IO, intraosseous; IN, intranasal; IM, intramuscular; IV, intravenous; R, rectal. *Note:* the number in parentheses is guidelines-out-of-six in this category (see text for details).

guidelines. There are a number of reasons why fosphenytoin should be recommended in preference to phenytoin: it does not require the excipient propylene glycol; it has less risk of hypotension and cardiac dysrhythmia; it does not cause the serious extravasation reaction, purple glove syndrome; and, it can be administered via the intramuscular route when intravenous access is not available.⁷

Intravenous phenobarbital was recommended in nine of the 11 guidelines.^{6-10,14-17} Of note, two guidelines recommended phenobarbital only if the patient had received phenytoin,^{9,16} the reasoning being that phenobarbital has more depressant side effects than phenytoin (e.g., respiratory depression and sedation), especially when benzodiazepines have already been used. The evidence for using intramuscular phenobarbital is based on pediatric practice in cerebral malaria.²³ For example, an intramuscular dose of 20 mg/kg reduces seizure frequency, but it causes an increased risk of respiratory depression and mortality, especially in those who have already received multiple doses of diazepam.²³

Valproic acid was recommended in six of the 11 guidelines.^{8,10,14-17} Valproic acid may be hepatotoxic and may lead to hyperammonemia. Three of the guidelines point out that it should be avoided or used with caution in liver disease (or suspected metabolic disease) and in children younger than 2–3 years with uncertain seizure etiology.^{10,12,14} Valproic acid causes less hypotension or respiratory depression when compared with phenytoin or

phenobarbital. For example, in a randomized controlled trial, although rapid intravenous loading of valproic acid stopped seizures in a comparable rate to intravenous phenobarbital (90% versus 77%, no statistical difference), the rate of adverse effects were lower (24% versus 74%); the phenobarbital group experienced more lethargy, vomiting, or respiratory depression.²⁴ In comparison with intravenous phenytoin, valproic acid is as effective in seizure control, and better tolerated in regard to risk of hypotension and respiratory depression, but it does cause mild elevation of liver enzymes.²⁵ Taken together, valproic acid can be considered an effective option for second phase anticonvulsant drug therapy.

Levetiracetam was recommended in four of the 11 guidelines.^{8,15-17} It has the advantages of good tolerability, intravenous administration over relatively short time, and absence of hemodynamic and sedative effects.¹⁰ Nonetheless, no randomized controlled trials of levetiracetam in pediatric convulsive SE have been conducted. A randomized, pilot open study has demonstrated equivalence of effectiveness in seizure control with lorazepam, and it has less associated respiratory depression and hypotension.²⁶

Lastly, of relevance to the future of second phase anticonvulsant drug treatment, there is an on-going multicenter randomized comparative effectiveness study, the Established Status Epilepticus Treatment Trial (ESETT; ClinicalTrials.gov: NCT01960075; due to be completed on December 2019), which aims to determine the most effective ED treatment out of fosphenytoin, levetiracetam, and

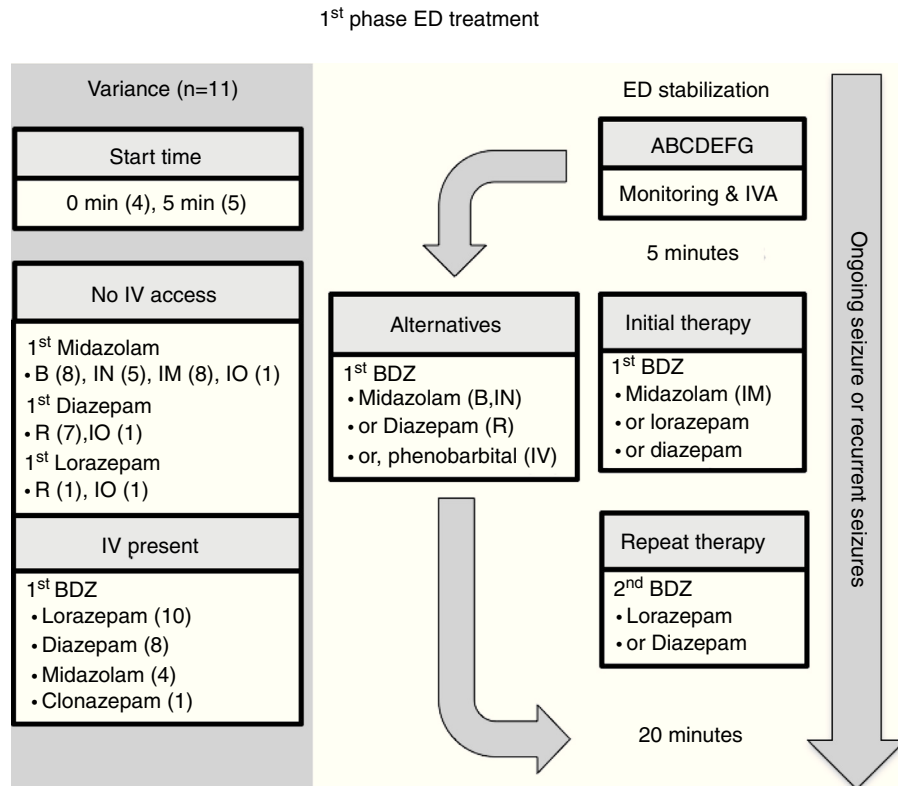


Figure 2 First-phase ED treatment. ABCDEFG, stabilization support with intervention for Airway, Breathing, Circulation, Dextrose, Essential neurology, Fluids, Global picture; BDZ, benzodiazepine; ED, emergency department; EMS, emergency medical system; IO, intraosseous; IN, intranasal; IM, intramuscular; IV, intravenous; IVA, intravenous access; R, rectal. *Note:* the number in parentheses is guidelines-out-of-11 in this category (see text for details).

valproic acid for benzodiazepine-refractory SE, and provide information on effectiveness and safety in children.

ED third phase anticonvulsant therapy

In the third phase of therapy (Fig. 4 and Table 3), four guidelines included the choice for repeating second phase therapy.^{7,10,12,15} Nine guidelines recommended inducing anesthesia with thiopental^{5-9,12,15-17}; all four of the guidelines which recommended rapid sequence intubation suggested thiopental as the inducing agent.^{5-7,9} Seven of the guidelines recommended using midazolam infusion,^{7,8,10,12,15-17} six recommended propofol infusion,^{6,8,10,15-17} and three recommended pentobarbital infusion.^{7,8,15}

Comment on ED third phase anticonvulsant therapy

At the time of starting the third phase of anticonvulsant drug treatment, four of the 11 guidelines included the choice for repeating second phase therapy.^{7,10,12,15} The Canadian Pediatric Society Acute Care Committee guideline⁷ recommended a combination of using two second-phase drug therapies, each separated by a 5-minute interval, before proceeding to the induction of anesthesia. The Association of Child Neurology (India, 2013)¹² guideline group considered the scenario when no intensive care bed

is available, and recommended the following before a midazolam infusion: either valproic acid and phenobarbital, or levetiracetam. The Italian League Against Epilepsy guideline¹⁰ recommended valproic acid after second phase therapy, if delay or difficulty in endotracheal intubation was expected.

Finally, in regard to the choice of anesthetic agent, the guidelines do not have clear recommendations for preference between thiopental, midazolam, propofol, and pentobarbital. Rather, specific drug selection is deferred to local expertise. It should be noted, however, that although propofol is used in adult practice of refractory SE, the risk of propofol infusion syndrome in children is unacceptable and, therefore, continuous infusion is not recommended in a number of countries. In regard to the other anesthetic agents, the data on intensive care treatment of pediatric refractory SE are of poor quality, yet they show a hierarchy in strategies: early midazolam by continuous infusion, then barbiturates, and then trial of other anesthetic therapies.^{27,28} Recently, a two-year prospective observational study assessed the use of continuous infusion of anesthetic agent in pediatric patients (age range, 1 month to 21 years) with refractory SE not responding to two anticonvulsant drug classes.²⁹ The United States Pediatric SE Research Group found that, in their 11 centers, midazolam and pentobarbital remain the mainstay of continuous infusion therapy.

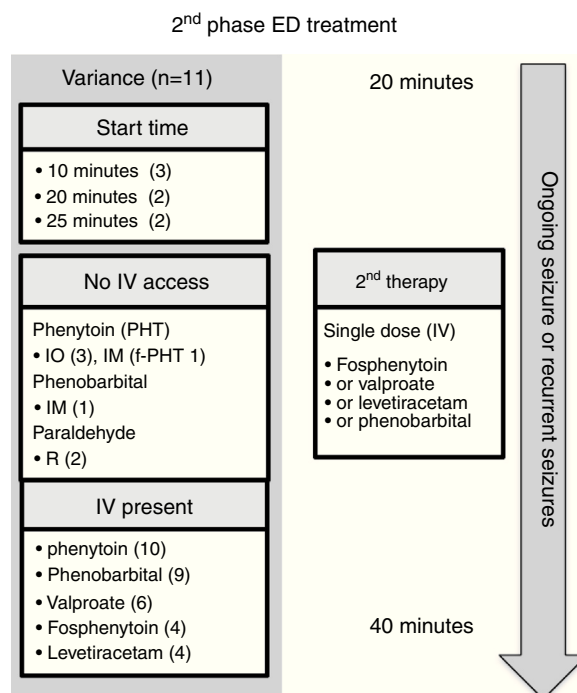


Figure 3 Second-phase ED treatment. ED, emergency department; f-PHT, fosphenytoin; IO, intraosseous; IN, intranasal; IM, intramuscular; IV, intravenous; R, rectal. *Note:* the number in parentheses is guidelines-out-of-11 in this category (see text for details).

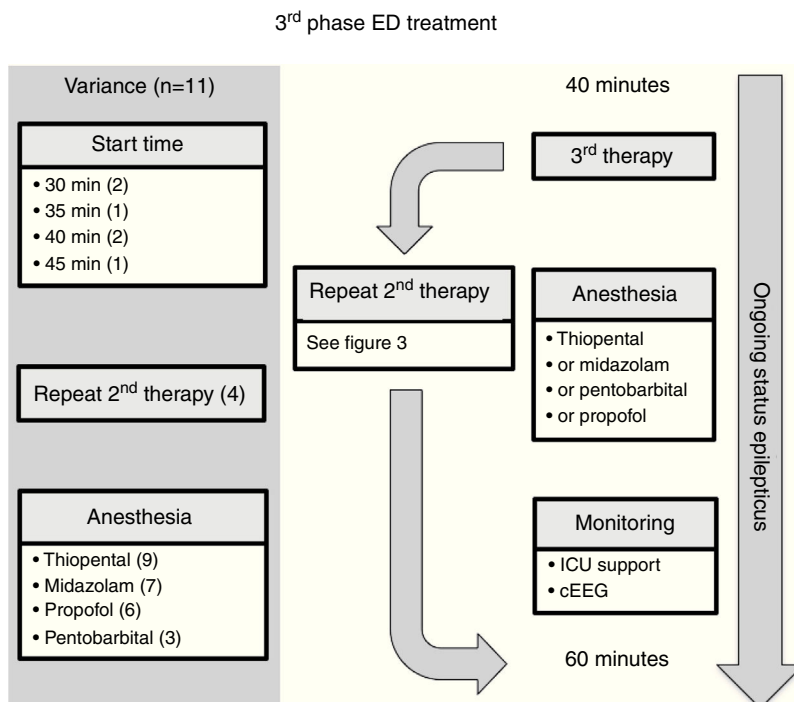


Figure 4 Third-phase ED treatment. cEEG, continuous electroencephalography; ED, emergency department; ICU, intensive care unit. *Note:* the number in parentheses is guidelines-out-of-11 in this category (see text for details).

Conclusion

Managing a child who presents in an emergency with a seizure is a challenge; knowing how to best deal with acute

interventions and follow-up is an important part of pediatric practice.³⁰ Guidelines on anticonvulsant drug therapy for a seizure or SE before and after arrival in the ED serve as important reference documents in acute care. In

Table 3 Comparison of anticonvulsant drugs used in each of the three phases of therapy and their administration routes (see also, Tables 1 and 2).

Year, Ref #	Group	First-phase therapies			Second-phase therapies						Third-phase therapies			
		LZ	DZ	MZ	PHT	f-PHT	PB	VPA	Lev	Par	TH	MZ	Pfl	Pent
2000, ⁵	BPNA	iv	r		iv, io							iv		
2009, ⁶	PREDICT	iv, io	iv, io	im, b, in, io, iv	iv, io		iv					iv	iv	
2011, ⁷	CPS	iv, r	iv, r	im, b, in, iv	iv, io	iv, im	iv			r	iv	iv		iv
2012, ⁸	NCS	iv	r	im	iv	iv	iv	iv	iv		iv	iv	iv	iv
2012, ⁹	NICE	iv		b	iv		iv			r	iv	iv	iv	iv
2013, ¹⁰	LICE	iv	iv	im, b	iv		iv	iv			iv	iv	iv	iv
2014, ¹²	AOCN	iv	iv, r	im, b, in, iv	iv	iv						iv		
2016, ¹⁴	WHO	iv	iv		iv		iv, im	iv						
2016, ¹⁵	AES	iv	iv, r	im, b, in		iv	iv	iv	iv		iv	iv	iv	iv
2016, ¹⁶	SEN		iv, r	im, b, in, iv	iv		iv	iv	iv		iv	iv	iv	iv
2017, ¹⁷	HKES	iv	iv, r	im, b	iv		iv	iv	iv		iv	iv	iv	iv

Groups: AES, American Epilepsy Society; AOCN, Association of Child Neurology (India); BPNA, British Paediatric Neurology Association; CPS, Canadian Paediatric Society; HKES, Hong Kong Epilepsy Society; LICE, Italian League Against Epilepsy; NCS, Neurocritical Care Society; NICE, National Health Service National Institute of Health and Care Excellence; PREDICT, Paediatric Research in Emergency Departments International Collaborative; SEN, Spanish Society of Neurology; WHO, World Health Organization. *Therapies:* DZ, diazepam; Lev, levetiracetam; LZ, lorazepam; MZ, midazolam; Par, paraldehyde; Pent, pentobarbital; PB, phenobarbital; f-PHT, fosphenytoin; PHT, phenytoin; Pfl, propofol; TH, thiopental; VPA, valproic acid. *Routes:* b, buccal; im, intramuscular; in, intranasal; io, intraosseous; iv, intravenous; r, rectal.

this qualitative systematic review of 13 regional/national guidelines, we have found that each share similar frameworks for practice and time points. Different routes of benzodiazepine administration are feasible in the pre-hospital (EMS) and first phase of ED therapy. The choice of benzodiazepines depends on presence of intravenous access, local availability, skills of healthcare providers, and the resource setting. Valproic acid and levetiracetam have better side effect profiles than phenytoin or fosphenytoin. Direct comparison of effectiveness and safety of different second phase therapy for SE awaits further clinical study. Finally, regarding the use of anesthetic agents in children, most of the experience and literature is in using midazolam and then pentobarbital by continuous infusion.

Conflicts of interest

The authors declare no conflicts of interest.

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