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Timing in the treatment of status epilepticus: From basics to the clinic

Marina Gaínza-Lein[a,b], Iván Sánchez Fernández[a,c], Adriana Ulate-Campos[d], Tobias Loddenkemper[a], Adam P. Ostendorf[e,*]

[a] Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA
[b] Facultad de Medicina, Universidad Austral de Chile, Valdivia, Chile
[c] Department of Child Neurology, Hospital Sant Joan de Déu, Universidad de Barcelona, Spain
[d] Department of Neurology, National Children's Hospital "Dr. Carlos Saenz Herrera", San José, Costa Rica
[e] Neurology Division, Department of Pediatrics, The Ohio State University and Nationwide Children's Hospital, Columbus, OH, USA

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ABSTRACT

Objective: Describe basic science, animal models and clinical data related to timing of treatment in status epilepticus (SE).

Methods: We summarized the results of 15 studies that reported time to treatment in SE, and reviewed basic and clinical literature.

Results: SE is a life-threatening and time-sensitive emergency that requires immediate treatment. Current guidelines recommend escalation of anti-seizure medications (ASM) within specified time frames. Prolonged seizures may lead to changes in the composition and location of gamma-aminobutyric acid A receptors ($GABA_AR$) and N-Methyl-D-aspartic acid receptors (NMDAR), leading to loss of inhibition and increased excitation. These biochemical changes are apparent in specific animal models having progressive resistance to benzodiazepines (BZD) with longer seizures.

Later treatments lead to decreased response to BZD, longer seizures, greater need of continuous infusions, potential brain injury and increased in-hospital mortality. Despite mounting evidence that early treatment of SE is more effective and safer, treatment and ASM escalation is often delayed compared to protocols. Literature review of 2212 patients with SE showed an average time to treatment of 42.4 min and time to hospital arrival of 56 min. Also, only 51.8% of patients received treatment by emergency medical services and 12.8% by their families, including patients with a previous diagnosis of epilepsy or with prior SE.

Conclusions: Morbidity and mortality may be avoided with rapid, effective treatment of SE. Treatment application and escalation remains delayed especially in outpatient settings, potentially leading to suboptimal outcomes. Implementation techniques and quality improvement methodologies may provide avenues for improving outcomes in SE.

1. Introduction

Status epilepticus (SE) is one of the most common neurological emergencies in childhood and is a major cause of morbidity, mortality and economic burden [1]. It has an overall incidence of 6.8–41/100.000 per year [2], half of whom are children [3], and is most common in infants (135–156/100 000 per year) [2,4,5]. Adults have a short-term (30 days) mortality of 7.6% to 22% and 43% thereafter [2]. Mortality is lower in children: 3–9% within 30 days and 7% in the long-term [2]. Beyond mortality, SE is also related to significant morbidities, such as developmental impairments, epilepsy, and recurrent SE [6,7]. Additionally, the economic burden of SE for the U.S. health care system is approximately $4 billion per year, which is higher than most other comparable emergencies (e.g. acute myocardial infarction) [8].

Several guidelines have been developed to improve SE management, albeit on imperfect evidence. Current SE treatment guidelines recommend a stepwise anti-seizure medication (ASM) treatment with up to 2 doses of benzodiazepines (BZD) within the first 5 to 10 min of SE onset, followed by non-BZD ASM after 10 min [9,10]. If SE is not controlled, continuous infusions of IV anesthetics may be initiated within 30–70 min of seizure onset [9,10]. The American Epilepsy Society guidelines recommend 20, 40 and 60 min' cut-offs for the three different lines [11]. An American Academy of Neurology (AAN) quality measure recommends third-line ASM should be administered within

* Corresponding author at: Neurology Division, Department of Pediatrics, Nationwide Children's Hospital, 700 Children's Drive, Columbus, OH 43205, USA.
E-mail addresses: m.gainzalein@gmail.com (M. Gaínza-Lein), ivan.fernandez@childrens.harvard.edu (I.S. Fernández), adrianaulate@hotmail.com (A. Ulate-Campos), tobias.loddenkemper@childrens.harvard.edu (T. Loddenkemper), Adam.Ostendorf@nationwidechildrens.org (A.P. Ostendorf).

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60 min of in-hospital seizure or emergency department arrival [12]. However, these recommendations are largely based on expert opinion, lack high-quality evidence, and substantial variation exists between guidelines.

This review aims to describe basic science and clinical data underlining the importance of timing in the treatment of SE and highlights methods of improving outcomes in SE.

2. Methods

2.1. Literature search strategy

We searched the PubMed database up to January 2018 for studies in the English language with a variable combination of the following terms: “status epilepticus”, “time”, “time- to-treatment”, “anticonvulsants”, “benzodiazepines”, “reaction time”, “delay”, “epidemiology”, “emergency medical services”, “treatment delay”, “drug therapy”, “treatment failure”, “therapy”, and “therapeutics”. Subsequently, we added relevant studies not identified by our search from the reference lists of initially identified studies. Lastly, we selected studies that reported the time to initial treatment in patients with SE, or other relevant timings, such as time to emergency medical services (EMS) or hospital arrival.

2.2. Statistical analysis

Our primary outcome was the time to treatment in SE. We also analyzed drug choices and secondary outcomes, such as the presence of prehospital treatment. We used descriptive statistics available in the original manuscripts to summarize results, and calculated proportions and averages by weighting the number of patients reported by each study. As SE was defined differently depending on the study, we provide the definitions used by the authors in Table 1.

3. Definitions

The definition of SE has varied over time. In 1981 the International League Against Epilepsy (ILAE) described SE as a “seizure that persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur” [13]. Subsequent definitions included a time threshold of 60 min, but in 1993 the American Epilepsy Society defined a time threshold of 30 min that since then became widely used [14]. This classical SE definition with a 30 min’ cut-off reflects the loss of auto-regulatory mechanisms, metabolic decompensation, and often irreversible neuronal damage that occurs with prolonged convulsive seizures, as demonstrated in previously healthy primate models [15]. However, the previously-defined times failed to account for seizures that last longer than 5–10 min, which are unlikely to stop spontaneously [16]. Therefore, in 2015, the ILAE updated the definition of SE to reflect these concepts with an operational definition of an initial time point (t_1) when a seizure is less likely to stop spontaneously, leading to protracted seizures which may have long-term consequences after a second-time point (t_2) [17]. For convulsive seizures, t_1 is 5 min and t_2 is 30 min. SE can be further classified into convulsive SE (CSE) and non-convulsive SE (NCSE).

4. Basic science

4.1. Neurotransmitter receptor trafficking

Alterations in neurotransmission occur during SE and may contribute to treatment resistance as SE progresses [18,19]. BZDs, the initial treatment for SE, act on gamma-aminobutyric acid A ($GABA_A$) receptors ($GABA_AR$) [20]. Although BZD are effective during the early course of SE, their efficacy decreases the longer seizures persists, at least in part potentially due to diminished $GABA_A$-mediated inhibition [21–25]. Two studies using in-vitro models of status epilepticus demonstrated prolonged epileptiform bursting and reduced $GABA_A$-mediated synaptic inhibition due to $GABA_AR$ internalization after one hour [18,26]. Changes in neurotransmitter receptor (NTR) localization may be etiologically dependent. A recent study comparing status epilepticus in rats due to either kainic acid (KA-SE) or lithium-pilocarpine (LiPilo-SE)_demonstrated increased $GABA_AR$ internalization in the Li-Pilo-SE model compared to the KA-SE animals, in addition to differential surface expression of Kv4.2 potassium channels [27]. Therefore, internalization of $GABA_AR$ may, at least in part, contribute to progressive pharmaco-resistance to BZD during SE [18,24–26] (Fig. 1).

Self-sustaining seizures depend not only on the loss of GABAergic inhibition, but also on increased glutamatergic excitation [19,28,29]. N-Methyl-D-aspartic acid receptors (NMDAR) facilitate neuronal depolarization in the presence of glutamate through a cellular influx of cations. Prolonged seizures induce NMDAR to move from the cell interior to the synaptic and extra-synaptic cell wall sites, increasing neuronal excitability [30] (Fig. 1). Furthermore, NMDAR activation may indirectly lead to GABA resistance through an increase in intracellular Ca^2, which activates the phosphatase calcineurin, leading to a decrease in the number of $GABA_ARs$ in the soma [31]. This mechanism was reinforced by another study where pretreatment with phosphatase inhibitors maintained the expression of the $GABA_AR$ γ2 subunit in SE slices similar to controls due to an increase in receptor stability [32]. Calcineurin and other phosphatases may therefore act as mediators of BZD resistance in prolonged seizures, and could be a potential target for treatment in SE [31]. While GABAergic drugs lose potency during SE, NMDA antagonists are frequently therapeutically effective in terminating prolonged SE [29,33,34].

4.2. Neurotransmitter receptor composition

While $GABA_A$ and NMDA NTR relocate during SE, the subunit composition of several NTR may also change during prolonged seizures. Sustained or repeated epileptiform activity modifies the subunit composition of $GABA_A$ and glutamate receptors, mimicking subunit compositions of the immature brain [35–38]. In the rapidly developing brain of newborns, infants, and small children, neuronal excitation predominates over inhibition and facilitates learning [36]. However, an imbalance towards hyperexcitability also makes the immature brain more susceptible to seizures and epileptogenesis, similar to later stages of SE in older children and adults [39,40].

Studies on changes in human NTR subunit composition have been possible through the use of samples collected during epilepsy surgery or autopsy. They have revealed GABA and glutamate receptor subunit composition similar to immature brains and animal models of SE: increased alpha2/alpha1 ratio in GABAR, increased NMDAR GluN2B/GluN2A ratio, and increased alpha-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid receptor (AMPAR) GluA1/GluA2 ratio [26]. Changes were independent of the epileptic syndrome [26] and were similar to changes in NTR composition in patients with tuberous sclerosis and cortical dysplasia [31,32,41]. These findings suggest a common pathway of response to chronic epileptiform activity, although it is currently unknown whether these changes in subunit composition occur in acute SE.

Molecular mechanisms may in part explain why synaptic GABAergic agonist ASM lose efficacy early during SE [22,25], while NMDA receptor blockers continue to work in prolonged SE [29,33,34]. Thus, NMDA receptor blockers were proposed as treatment for refractory SE [29], with promising results to date in selected patients [34,42,43]. In the future, a better understanding of the molecular changes during prolonged seizures may allow targeting specific molecules during SE treatment [36]. During the early seizure presentation, a crucial time window for optimal BZD effects exists. After seizures become more refractory to BZDs, a rapid switch to other second and third line treatments is necessary [26].

Table 1
Summary of studies on time to treatment in SE.

Author	Year	Population	SE type	Age mean (years)	Sex male%	SE duration median (min)	SE duration range (min)	RSE%	SE definition (min)	N (pts-episodes)	Study type
Gaínza-Lein, et al.	2018	Children (< 21)	CSE	4	53.2% (116/218)	91 (74 timely pts), 139.5 (144 untimely pts). Average: 123	50–360[b]	100% (218/218)	5	218 − 218	Multicenter prospective
Kamppi et al.	2018	Adults (> 16)	CSE	54.3	50% (35/70)	315 (70 pts)	26–31995	88.6% (62/70)	30	70 − 70	Retrospective
Cheng	2016	Adults (> 18)	CSE (97 pts) NCSE (54 pts)	59.1	45% (68/151)	1470 (144 pts)	10–50400	–	5	151 − 151	Retrospective
Sánchez Fernández et al.	2015	Children (< 21)	CSE	3.6	54.3% (44/81)	137 (81 pts)	80–300[b]	100% (81/81)	–	81 − 81	Multicenter prospective
Alvarez et al.	2015	Adults (> 16)	CSE (168) NCSE (9 pts)	56.8	51.4% (91/177)	1668 (177 pts)	0 − 24480	61% (108/177)	5	238	Multicenter prospective
Seinfeld et al.	2014	Children	Febrile SE	—	–	68 (75 pts with PHT)	–	–	30	199 (179 required ASM)-199	Multicenter prospective
Kamppi et al.	2013	Adults (> 16)	CSE (74 pts) NCSE (8 pts)	55	51% (42/82)	352 (CSE) (74 pts)	26–31995 (GCSE)	86.6% (71/82)	30	82 − 82	Retrospective
Hillman et al.	2013	Adults (> 17)	CSE	62.6	55% (60/109)	–	–	–	30	100–109	Retrospective
Aranda et al.	2010	Adults (> 18)	CSE (101) NCSE (17)	56 (101 pts)	53% (54/101)	180 (101 pts)	77–400	27% (27/101)	5	111–118	Prospective
Lewena et al.	2009	Children (< 21)	CSE	3[a]	51% (277/542)	79 (539 pts)	51–110[b]	22% (120/542)	10	467–542	Multicenter retrospective
Chin et al.	2008	Children (< 16)	CSE	3.2[a]	48% (88/182)	70 (182 pts)	30–975	–	30	182–240	Prospective
Lewena et al.	2006	Children (< 18)	CSE	3.7	43% (16/37)	–	10–130	70% (21/37)	10	37 − 37	Retrospective
Alldredge et al. (LZP)	2001	Adults (> 18)	CSE	49.9 (66 pts)	69.7% (46/66)	–	–	–	5	66–91 (with LZP), 258–567 (all)	RCT, double blind
Coeytaux et al.	2000	Adults, children	CSE NCSE	–	59% (102/172)	5472	–	68% (117/172)	30	172 − 172	Prospective
Alldredge et al.	1995	Children (< 18)	CSE	6.1	60.5% (23/38)	31.7 (19 pts PHT), 59.7 (26 pts no PHT). Average 47.8	–	–	15	38–45	Retrospective
Total	–	–	–	**26.0 (1770 pts)**	**52.4% (1062/2026)**	**862.9 (1871 pts), 122.8 (1340 CSE pst only)**	**0-50400 (all pts), 0–31995 (CSE only)**	**55.7% (825/1480)**	–	**2212–2393**	–

Legend: [a]A median was reported instead of mean. [b]An IQR was reported instead of a range.
Summary of studies on time to treatment in SE. Total percentages or averages were weighted by the number of patients reported by each study. All timings are in minutes.
SE: status epilepticus. **RSE**: refractory status epilepticus. **N**: number. **LZP**: lorazepam group. **CSE**: convulsive status epilepticus. **NCSE**: non-convulsive status epilepticus. **RCT**: randomized controlled trial. **Pts**: patients. **ASM**: anti-seizure medication. **PHT:** pre-hospital treatment.
*The study from Alldredge et al. (2001) was a randomized control trial with 3 treatment groups (lorazepam, clonazepam and placebo) [61]. To be able to compare this trial's timing with other studies we only utilized information from the lorazepam group, which had largest patient numbers.

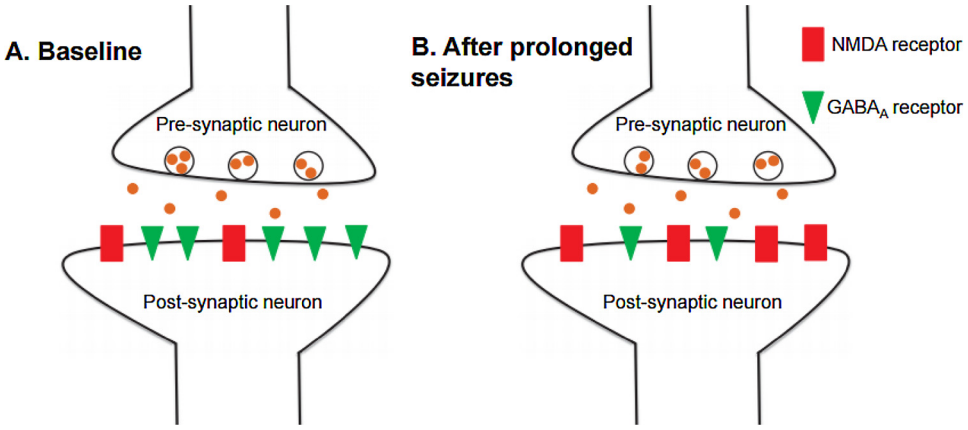

Fig. 1. Changes in neurotransmitter receptor concentrations at baseline and during prolonged seizures. A. At baseline, GABA (inhibitory) neurotransmission predominates over NMDA (excitatory) neurotransmission. **B.** During seizures, GABA receptors are internalized and NMDA receptors accumulate in the postsynaptic membrane. These changes favor self-sustaining seizures and resistance to antiepileptic drugs with a GABAergic mechanism, like benzodiazepines. **Legend: GABA:** Gamma-amino-butyric acid. **NMDA:** N-methyl-D-aspartate.

5. Animal models

Multiple animal models have demonstrated progressive resistance to BZDs and phenytoin with longer seizure duration [19,21,22,25]. In a rat model of SE, all animals responded to diazepam administered within 5 min from seizure onset and rarely when treatment was given after 15 min [25]. In another study, all seizures were terminated when treated after 10 min (3/3), but not after 45 min of SE (0/3) [21]. In contrast, a comparative study of KA-SE and LiPilo-SE in a rat model of SE demonstrated preserved efficacy of BZD after 3 h in the KA-SE model where GABAR surface expression was preserved compared to the LiPilo-SE animals, which developed BZD resistance associated with decreased surface expression of GABAR [27]. These animal models support the development of progressive pharmaco-resistance with longer seizures duration, which may be etiologically-dependent.

But what are the consequences of longer seizures? In 1973, a study on previously healthy monkeys observed physiological changes during SE and described loss of auto-regulatory mechanisms and metabolic decompensation in the later phases of SE [15,44]. These authors also discovered irreversible neuronal damage in primates that had prolonged convulsive seizures lasting 82–299 min [15]. Further, animal models of prolonged seizures or SE demonstrated that brain damage is age dependent [45,46]. The immature brain may be less vulnerable to neuronal loss with prolonged seizures [47,48] but also has a lower seizure threshold [46,49].

Neurocognitive sequelae of SE, such as learning, memory and behavior deficits, are furthermore age dependent in animal studies [50,51]. Both adult and young rats demonstrate learning deficits after SE, but these were more severe in adults [50]. Rats that underwent kainic acid-induced SE during early development demonstrated impairment in short- and long-term spatial learning at all ages and increased anxiety compared to controls [52].

Additionally, seizures in early life predispose to subsequent neuronal damage [53]. In a kainate seizure model, older rats (postnatal day 45) suffered more extensive neuronal injury and demonstrated decreased spatial learning performance if they had a history of seizures induced as young pups (postnatal day 15) [53]. Young rats with SE are also more prone to developing chronic epilepsy [54]. These animal data suggest neurologic consequences are age dependent and prompt treatment is more likely to stop seizures.

6. Clinical data

Clinical data reinforce basic science and animal models, and suggest that later treatment is associated with worse response [55,56]. In a study of 157 patients with SE, a treatment delay of more than 30 min was associated with longer seizure duration [55]. Similarly, time to administration of the first 3 ASM correlated with prolonged seizure duration [56]. In a series of 182 children with SE, lack of prehospital treatment and more than two doses of BZD were associated with SE episodes lasting longer than 60 min [57]. For every minute of delay from CSE onset to the arrival at the emergency department, there was a 5% cumulative increase in risk of having a SE episode that lasted longer than one hour [57]. Intervention less than 30 min from seizure onset was associated with an 80% response to first-line medications. In comparison, less than 40% responded when treated after 2 h [58]. Furthermore, prehospital treatment has been shown to reduce seizure duration in children [59] and in adults [60]. Jointly, these studies support the notion that prompt treatment may improve response.

If we treat patients more rapidly, SE episodes are shorter. But does earlier treatment improve SE outcomes? A recent multicenter study of 218 patients with refractory SE demonstrated an independent association between an untimely first BZD (administered after 10 min) and in-hospital mortality after adjusting for confounders [61]. Untimely treatment was also associated with a greater need of continuous infusions, longer convulsive seizure duration and more frequent hypotension [61]. The time to initial treatment was also associated with the timing of later ASM, which was interpreted as a subsequent workflow delay [61].

A different study also highlighted the significance of workflow delay. In this study of 70 adults, univariate analysis showed an association between delays in diagnosis, time to second-line medication, time to consciousness and long anesthetic treatments with negative cognitive outcomes (GOS score < 3) [62]. Univariate analysis also showed an association between delay in reaching a tertiary hospital and functional deterioration at discharge [62]. Although multivariate analysis did not identify an independent predictor of outcome, the authors hypothesized the accumulation of different delays in this treatment chain may be influencing outcomes [62]. In a different study including 100 adults, a good recovery (defined as no significant disability in a modified Rankin Scale) occurred in 82% of patients treated within 1 h of seizure onset, and in 46% of patients treated after 1 h [63].

Prolonged SE is more common in the presence of treatment delays and increases morbidity and mortality. In a series of 228 adult and pediatric patients, patients with seizures lasting longer than 30 min had a mortality of 19%, compared with 3% mortality in patients with seizures lasting 10 to 29 min [64]. Another series of 184 adults and children demonstrated that patients with SE lasting longer than 24 h had increased mortality compared to patients with episodes of less than 2 h [65]. Longer SE episodes also correlated with more frequent medical complications, longer hospital stays, increased functional disability at discharge [58], and brain damage [66]. Further, biomarkers provide evidence of brain injury in prolonged seizures. Levels of serum neuron-specific enolase, a marker of acute brain injury and blood-brain barrier dysfunction [66,67], were elevated and levels correlated with seizure duration [66].

Seizures are also more likely to recur after delayed treatment and prolonged SE [59]. Prehospital therapy significantly shortened duration

of SE (32 min vs 60 min) and reduced the seizure recurrence rate (58% vs 85%) in children who received diazepam compared to children untreated in the prehospital setting [59]. Treatment timing and SE duration are not the only influences of outcomes in SE, which may be influenced by age and etiology [55,65,68]. However, the timing of treatment and SE duration can be more easily modified, and thus provide optimal initial targets to improve SE outcomes.

6.1. Literature review results

Our search identified 15 studies that reported results regarding time in SE treatment (Table 1) [56,57,59–63,69–76]. Seven focused on children, seven on adults, and one on both. These studies reported a total of 2212 patients, with a mean age of 26 years, and 52.4% of males. Fifty-six percent of patients had refractory SE, 43.3% (802/1854) of patients had a prior epilepsy diagnosis and 22.2% (151/681) had prior SE episodes.

The mean of all reported SE durations was 862.9 min (when considering a total of 1871 reported patients) and 122.8 min, when considering 1340 patients with convulsive SE only. Although these studies encompassed different patient populations and designs, we summarized main results to provide an overview on the timing in SE treatment (Table 2). The median time to the first ASM reported by ten studies and 1134 patients was 42.4 min, and 40.2 min when considering 902 patients who only had CSE. The mean time from SE onset to EMS arrival was 22 min (427 patients); and the mean time from SE to hospital arrival was 56 min (1391 patients). Two studies also reported mean time from in-hospital SE onset to treatment, with overlapping populations, with a total of 8 min (IQR 4–24) [56,61]. In 86% (1182/1374) of cases, BZD was the first choice when treating SE (Table 3), and diazepam was the most commonly administered drug in the pre-hospital setting [57.6% (624/1083)], followed by lorazepam [34.4% (181/526)].

These data reveal prehospital treatment occurred often later than commonly recommended, and delays were multifactorial. First, the time from SE onset to EMS arrival exceeds the time interval recommended for first line BZD administration (Table 2). Second, prehospital treatment was not ubiquitous, even when considering patients with a previous diagnosis of epilepsy or with prior SE episodes. Among patients treated in the prehospital setting, 12.8% (62/483) were treated by their families, and 51.8% (790/1524) were treated by EMS. Furthermore, 66.7% (38/57) of patients with prior SE episodes were treated by their families (Table 3).

6.2. Timing of prehospital status epilepticus treatment

Many patients did not receive any pre-hospital treatment, despite its association with improved outcomes. Prehospital treatment is associated with shorter SE duration [59,74], fewer recurrent seizures in the emergency department [59], and a decreased amount of electroencephalographic SE on EEG [74]. Similarly, lack of prehospital treatment and application of more than 2 BZD doses were associated with SE episodes lasting longer than 1 h [57]. Additionally, initial ASM administration was delayed compared to recommendations. Patients with a prior diagnosis of epilepsy received the first non-BZD ASM later than patients without prior diagnosis [77]. Also, patients with a prior history of SE received an earlier first BZD, and having an intermittent RSE was associated with delays in the second line treatment [78].

Although data support prehospital treatment, administration may be challenging. Family members or caregivers may not have had education on how to administer rescue medications or may not feel confident about application of medication. A survey of 100 families of patients with epilepsy revealed most of them (87%) had a rescue medication prescription but only 61% reported receiving training on how to use it [79]. Also, EMS may not have authorization to give ASM or training on the need for rapid SE treatment [2].

Prehospital treatment should also include adequate dosing of ASM, which is more likley to result in seizure termination [80]. However, acutal doses were frequently lower than recommended [71,80]. Prehospital administration of BZD may also intermittently be overlooked during ASM escalation after hospital arrival, as patients repeateadly tend to receive BZDs at the hospital that had already failed [56], suggesting lack of hand offs or care coordination between the out-of-hospital and in-hospital treatment. The route of drug administration may also influence time to treatment. For example, the time to administration of intravenous BZD was longer than the time needed to administer rectal BZD [57]. In a randomized clinical trial, the median time to administer intramuscular midazolam was 1.2 min vs 4.8 min in the intravenous lorazepam group, and was similar in terms of safety and efficacy [81]. Nevertheless, EMS frequently continue to administer BZD intravenously, even though faster routes may be available [82].

7. Outlook: future directions

We highlight several areas of opporunity to improve SE time to treatment and outcomes.

7.1. ASM choices

Current SE treatment algorithms recommend a stepwise approach with BZD, a second-line IV antiseizure medication such as phenytoin, phenobarbital, levetiracetam or valproic acid, and eventually anesthetic therapies [9,11,83]. The American Epilepsy Society analyzed the available literature and published a guideline on the treatment of SE [11]. Only the first line treatment with BZD is supported by high-level evidence, with no strong evidence for second and third line treatment strategies [11]. Phenytoin and phenobarbital have been available for much longer than any new ASM and therefore, have a larger body of literature on their efficacy. However, a *meta*-analysis that compared phenytoin, phenobarbital, valproate, and levetiracetam in SE treatment yielded the following efficacy rates: phenytoin 50% (95% CI: 43%-66%), phenobarbital 74% (95% CI: 58%-85%), valproate 76% (95% CI: 64%-85%), and levetiracetam 69% (95% CI: 56%-79%) [84]. Therefore, large randomized trials comparing the efficacy of non-benzodiazepine ASM are urgently needed. Several multicenter studies are currently underway to examine second-line ASM. The Established Status Epilepticus Treatment Trial (ESETT) is in the process of comparing valproate, levetiracetam, and phenytoin (or fosphenytoin) for the treatment of SE refractory to BZD, although final data are not yet available [84]. The TRENdS trial delivered preliminary demographic and enrollment data on the comparison between lacosamide and fosphenytoin, although efficacy data have not been reported [85]. Two additional trials are in the process of comparing levetiracetam and phenytoin as second-line treatment in children with SE, the EcLIPSE study [86] and the ConSEPT study from the PREDICT group [87]. The pediatric Status Epilepticus Research Group (pSERG) is using comparative effectiveness approach [88]. We anticipate these studies will soon provide higher level evidence for medical management steps of SE.

7.2. Early polytherapy

The recommended treatment of SE follows a stepwise approach: a new ASM is tried after the prior ASM has failed to stop seizures, partially to minimize adverse effects of ASM. However, morbidity and mortality in SE are high and the risks associated with ongoing SE may be greater than the risks associated with overtreatment [60]. Early polytherapy may potentially be more effective and less toxic than monotherapy, at least in some types of SE [89]. Catch-up dosing or combined dosing of first and second line medications may be considered during delayed initial therapy due to the increased likelihood of treatment resistance.

Table 2
Time in the treatment of SE.

Author	Year	SE type	Time to first treatment		Prehospital time to first treatment	Epilepsy history	SE history	Time to EMS arrival		Time to hospital arrival	
			Median	Range	Median (range)	%	%	Mean	Range	Mean	Range
Gaínza-Lein, et al.	2018	CSE	17 (218 pts)	5–45[b]	25 (10–60)[b] (139 pts)	51.4% (112/218)	21.6% (47/218)	16 (63 pts)	10–25[b]	45[a] (106 pts)	30–80[b]
Kamppi et al.	2018	CSE	30 (67 pts)	0 − 485	–	65.7% (46/70)	–	–	–	145[a] (70 pts)	37–16660[c]
Cheng	2016	CSE (97 pts) NCSE (54 pts)	60 (151 pts)	0–10080	–	33% (49/149)	–	–	–	–	–
Sánchez Fernández et al.	2015	CSE	28 (81 pts)	6–67	30 (12–60)[b] (64 pts)	46.9% (38/81)	17.3% (14/81)	49.4 (26 pts)	2–875	81.8 (50 pts)	11–920
Alvarez et al.	2015	CSE (168) NCSE (9 pts)	45 (99 CSE pts)	5–2880 (99 CSE pts)	–	–	–	–	–	–	–
Seinfeld et al.	2014	Febrile SE	30 (161 pts)	1–175	22.3 (12.5 min + 9.8 min) (161 pts)	–	–	20 (161 pts)	0–95	38 (161 pts)	0–239
Kamppi et al.	2013	CSE (74 pts) NCSE (8 pts)	35 (81 pts)	0 − 4625	–	62.2% (51/82)	–	9 (68 pts)	0 − 45	69 (68 pts)	10–182
Hillman et al.	2013	CSE	70[a] (109 pts)	–	70[a] (109 pts)	43% (47/109)	32% (35/109)	30[a] (109 pts)	–	105[a] (109 pts)	–
Aranda et al.	2010	CSE (101) NCSE (17)	90 (101 CSE pts)	50–187	–	60% (61/101)	19% (19/101)	–	–	–	–
Lewena et al.	2009	CSE	–	–	–	35% (190/542)	–	–	–	45[a] (542 pts)	3–3960
Chin et al.	2008	CSE	–	–	–	24% (44/182)	–	–	–	39[a] (182 pts)	5–514
Lewena et al.	2006	CSE	–	–	–	65%[d] (24/37)	–	–	–	48 (37 pts)	–
Alldredge et al. (LZP)	2001	CSE	34 (mean) (66 pts)	17.8 (SD)	–	54.6%[d] (36/66)	–	–	–	50.2 (66 pts)	–
Coeytaux et al.	2000	CSE NCSE	–	–	–	42.4% (74/172)	20.9% (36/172)	–	–	–	–
Alldredge et al.	1995	CSE	–	–	–	66.7% (30/45)[d]	–	–	–	–	–
Total	–	–	**42.4 (1134 all pts), 40.2 (902 CSE pts)**	**0-10080 (all pts), 0–485 (CSE pts)**	**35.1 (473 CSE pts)**	**43.3% (802/1854)**	**22.2% (151/681)**	**22.0 (427 pts)**	**0 − 875**	**56.0 (1391 pts)**	**0 − 16660**

Legend: Time to treatment reported in different studies on SE. Total percentages or averages were weighted by the number of patients reported by each study. All timings are in minutes. [a]A median was reported instead of mean. [b]An IQR was reported instead of a range. [c] time to tertiary hospital. [d] prior seizures.
SE: status epilepticus. **SE**: status epilepticus. **LZP**: lorazepam group. **EMS**: emergency medical services. **Pts**: patients. **CSE**: convulsive status epilepticus. **NCSE**: non-convulsive status epilepticus.

Table 3
Drug administration in the pre-hospital setting.

Author	Year	Prehospital treatment			First line drug choices				
		Drug by EMS%	Drug by family%	Pts with prior SE treated by family%	Any BZD	DZP	LZP	MDZ	CLZ
Kamppi et al.	2018	87.1% (61/70)	–	–	98.6% (69/70)	80% (56/70)	18.6% (13/70)	0% (0/70)	0% (0/70)
Sánchez Fernández et al.	2015	35.9% (23/64)	9.4% (6/64)	33.3% (3/9)	96.3% (78/81)	–	–	–	–
Alvarez et al.	2015	–	–	–	74.5% (177/238)	–	46.3% (82/177)	13.0% (23/177)	40.6% (72/177)
Seinfeld et al.	2014	41% (73/179)	1% (2/179)	–	96.1% (172/179)	46.4% (83/179)	46.4% (83/179)	3.4% (6/179)	–
Kamppi et al.	2013	91.5% (75/82)	–	–	96.3% (78/82)	–	–	–	–
Aranda et al.	2010	71% (66/93)	–	–	60% (60/100)	26% (26/100)	3% (3/100)	0% (0/100)	31% (31/100)
Lewena et al.	2009	48% (260/542)	–	–	94% (510/542)	55% (299/542)	–	39% (211/542)	–
Chin et al.	2008	38.8% (93/240)	22.5% (54/240)	72.9% (35/48)	–	96% (141/147)	–	–	–
Lewena et al.	2006	51% (19/37)	–	–	51% (19/37)	–	–	–	–
Coeytaux et al.	2000	58.7% (101/172)	–	–	–	–	–	–	–
Alldredge et al.	1995	42.2% (19/45)	–	–	42.2% (19/45)	42.2% (19/45)	–	–	–
Total	–	**51.8% (790/1524)**	**12.8% (62/483)**	**66.7% (38/57)**	**86.0% (1182/1374)**	**57.6% (624/1083)**	**34.4% (181/526)**	**22.5% (240/1068)**	**29.7% (103/347)**

Legend: only studies with available information (complete or partial) on the pre-hospital drug administration in patients with SE were included in this table. Total percentages were weighted by the number of patients reported by each study.
SE: status epilepticus. **EMS**: emergency medical services. **BZD**: benzodiazepine drug. **DZP**: diazepam. **LZP**: lorazepam. **MDZ**: midazolam. **CLZ**: clonazepam.

7.3. Targeted therapies

ASM management for established SE may be guided by insight into the physiologic changes in NTR during prolonged seizures described earlier (Fig. 1). These mechanisms may partially explain why some animal models become more resistant to BZD, phenytoin, and phenobarbital [22,90] during longer seizures, while seizures often continue to respond to glutamate receptor antagonists [90]. The progressive resistance to initial ASM is also described in the clinical literature [73,91], and hence ASM targeted at the NMDA receptors—such as ketamine—have also been suggested for treatment of prolonged status epilepticus [34].

Another potential target for SE treatment that works through both synaptic and extrasynaptic $GABA_A$ receptors is allopregnanolone, a neuroactive steroid derived from progesterone [92]. Preliminary case data based on these neuro-steroids demonstrated good antiseizure efficacy in animal models [92] and has been used to stopped super-refractory SE in humans [18,93]. A phase 1/2 trial on 25 patients with super RSE showed that brexanolone was safe and tolerable [94]. However, a double-blinded, placebo-controlled phase 3 study of 132 patients did not show significant superiority versus placebo [95].

Other treatments are under investigation to treat SE, including flupirtine, a potassium channel modulator that facilitates $GABA_AR$ function. In one study, three rodent models of SE were used to evaluate flupirtine effectiveness: induced by administration of lithium and pilocarpine, by electrical stimulation of the hippocampus or by diisopropylfluorophosphate [96]. SE was controlled within 60 min by the combination flupirtine and diazepam in the 3 models, shortening the duration of the SE. This provides evidence that SE is terminated faster with a combination of synergistic drugs [96].

Neurosteroids and flupirtine represent ASM candidates under current study, among many others, and we anticipate more future candidates based on the increasing utilization of genetic anlysis. Seizures stop spontaneously in most patients, and may continue in few patients [16]. Further, seizure duration tends to be relatively homogeneous in each individual [16], suggesting that there may be a genetic predisposition to prolonged seizures. If the mechanism leading to seizure termination is elucidated, it is reasonable to speculate that treatments targeting this pathway may reduce seizure duration. This may prove a promising pathway to an era of personalized medicine for SE.

7.4. Quality improvement

While ASM choice may affect SE treatment efficacy, it is possible that changes in second-line treatment trials to date may have been confounded by time to treatment. Delays in ASM administration are frequent in published series [56,60,61,75] and escalation from one ASM to another is slow [56,61,72]. A recent AAN quality measure has indentified third-line ASM administration within 60 min of in-hospital seizure or emergency department arrival as a method for improving care in SE [12]. These areas provide opportunities for improving outcomes in SE.

Seizure diagnosis and pre-hospital treatment are often delayed. Seizure detection devices may help identify seizures early and, in the future, may, to a certain extent, even operate as closed-loop treatment systems [97,98]. Furthremore, education of families and EMS on the importance of early treatment may help increase the proportion of patients who receive treatment in the prehospital setting [56]. A study on 100 families of patients with epilepsy showed that families who had a seizure action plan were more knowledgeable about the rescue medication indications, and the schools were also more involved [79]. The concept that convulsive SE is a life-threatening, time-sensitive emergency may require further education of patients, families, care providers and of additional stake holders, such as schools and EMS.

Additionally, further measures of care coordination and integration at crucial times of care hand off, such as between the in-patient and outpatient setting, and more rigorous implementation of current care knowledge through implementation research methodology may provide further improvements [99]. Epileptologists may learn from stroke specialists and related health care system improvements, that, in convulsive status epilepticus, ‘time is brain’, too.

Finally, quality improvement methodologies within the hospital setting could improve the adherence to guidelines and protocols [100] and could reduce direct economic costs and impact quality of life [101].

Preliminary data from a study using quality improvement methodologies demonstrated a significant reduction in critical care utilization and hospital charges after improving the proportion of patients with SE who were treated with a BZD in less than 10 min [102]. The study focused on several areas of intervention, including more rapid initial assessment, utilizing non-IV BZD formulations and other process improvements [101].

8. Conclusions

SE is a life-threatening and time-sensitive emergency that requires immediate treatment. Multiple physiological changes make prolonged seizures more difficult to treat with increasing duration. While treatment guidelines have been established, the evidence on which they are founded remains lower quality, and several well-designed studies are underway to fill this particular knowledge gap. In the future, treatments targeting specific molecular changes during prolonged seizures may further improve efficacy.

While optimization of ASM choices is desirable, the most important gap in SE treatment is time to treatment administration. Literature review of 15 studies reporting 2212 patients with SE showed an average time to treatment of 42.4 min and time to hospital arrival of 56 min. Also, only 51.8% of patients received treatment by EMS and 12.8% by their families. Methods of improving these deficiencies include improved education, care coordination, implementation research, early seizure detection and rapid ASM delivery. Quality improvement methodologies may provide an avenue for addressing these areas and improving outcomes in SE.

Author contributions

Marina Gaínza-Lein participated in study design, performed the literature search, literature revision and interpretation, drafted the manuscript, reviewed, and edited for important intellectual content.

Iván Sánchez Fernández participated in study design, participated in the interpretation of data in the literature, reviewed, and edited the manuscript for important intellectual content.

Adriana Ulate-Campos participated in the interpretation of data in the literature, reviewed, and edited the manuscript for important intellectual content.

Tobias Loddenkemper participated in the interpretation of data in the literature, reviewed, and edited the manuscript for important intellectual content.

Adam P. Ostendorf participated in the interpretation of data in the literature, reviewed, and edited the manuscript for important intellectual content.

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References

[1] Loddenkemper T, Goodkin HP. Treatment of pediatric status epilepticus. Curr Treat Options Neurol 2011;13(6):560–73.
[2] Chin RF, Neville BG, Scott RC. A systematic review of the epidemiology of status epilepticus. Eur J Neurol 2004;11(12):800–10.
[3] Sanchez S, Rincon F. Status epilepticus: epidemiology and public health needs. J Clin Med 2016;5(8).
[4] DeLorenzo RJ, et al. A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. Neurology 1996;46(4):1029–35.
[5] Hesdorffer DC, et al. Incidence of status epilepticus in Rochester, Minnesota, 1965–1984. Neurology 1998;50(3):735–41.
[6] Martinos MM, et al. Early developmental outcomes in children following convulsive status epilepticus: a longitudinal study. Epilepsia 2013;54(6):1012–9.
[7] Raspall-Chaure M, et al. Outcome of paediatric convulsive status epilepticus: a systematic review. Lancet Neurol 2006;5(9):769–79.
[8] Penberthy LT, et al. Estimating the economic burden of status epilepticus to the health care system. Seizure 2005;14(1):46–51.
[9] Brophy GM, et al. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care 2012;17(1):3–23.
[10] Wilkes R, Tasker RC. Pediatric intensive care treatment of uncontrolled status epilepticus. Crit Care Clin 2013;29(2):239–57.
[11] Glauser T, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the guideline committee of the american epilepsy society. Epilepsy Curr 2016;16(1):48–61.
[12] Patel AD, et al. Quality improvement in neurology: child neurology quality measure set: executive summary. Neurology 2018;90(2):67–73.
[13] Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia 1981;22(4):489–501.
[14] Treatment of convulsive status epilepticus. recommendations of the epilepsy foundation of america's working group on status epilepticus. JAMA 1993;270(7):854–9.
[15] Meldrum BS, Brierley JB. Prolonged epileptic seizures in primates. Ischemic cell change and its relation to ictal physiological events. Arch Neurol 1973;28(1):10–7.
[16] Shinnar S, et al. How long do new-onset seizures in children last? Ann Neurol 2001;49(5):659–64.
[17] Trinka E, et al. A definition and classification of status epilepticus–Report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia 2015;56(10):1515–23.
[18] Goodkin HP, Yeh JL, Kapur J. Status epilepticus increases the intracellular accumulation of GABAA receptors. J Neurosci 2005;25(23):5511–20.
[19] Rice AC, DeLorenzo RJ. N-methyl-D-aspartate receptor activation regulates refractoriness of status epilepticus to diazepam. Neuroscience 1999;93(1):117–23.
[20] Kapur J. Prehospital treatment of status epilepticus with benzodiazepines is effective and safe. Epilepsy Curr 2002;2(4):121–4.
[21] Kapur J, Macdonald RL. Rapid seizure-induced reduction of benzodiazepine and Zn2+ sensitivity of hippocampal dentate granule cell GABAA receptors. J Neurosci 1997;17(19):7532–40.
[22] Mazarati AM, et al. Time-dependent decrease in the effectiveness of antiepileptic drugs during the course of self-sustaining status epilepticus. Brain Res 1998;814(1–2):179–85.
[23] Kapur J, Coulter DA. Experimental status epilepticus alters gamma-aminobutyric acid type A receptor function in CA1 pyramidal neurons. Ann Neurol 1995;38(6):893–900.
[24] Jones DM, et al. Characterization of pharmacoresistance to benzodiazepines in the rat Li-pilocarpine model of status epilepticus. Epilepsy Res 2002;50(3):301–12.
[25] Goodkin HP, Liu X, Holmes GL. Diazepam terminates brief but not prolonged seizures in young, naive rats. Epilepsia 2003;44(8):1109–12.
[26] Naylor DE, Liu H, Wasterlain CG. Trafficking of GABA(A) receptors: loss of inhibition, and a mechanism for pharmacoresistance in status epilepticus. J Neurosci 2005;25(34):7724–33.
[27] Joshi S, et al. Status epilepticus: role for etiology in determining response to benzodiazepines. Ann Neurol 2018;83(4):830–41.
[28] Naylor DE. Treating acute seizures with benzodiazepines: does seizure duration matter? Epileptic Disord 2014;16(Suppl. 1):69–83.
[29] Mazarati AM, Wasterlain CG. N-methyl-D-asparate receptor antagonists abolish the maintenance phase of self-sustaining status epilepticus in rat. Neurosci Lett 1999;265(3):187–90.
[30] Naylor DE, et al. Rapid surface accumulation of NMDA receptors increases glutamatergic excitation during status epilepticus. Neurobiol Dis 2013;54:225–38.
[31] Eckel R, et al. Activation of calcineurin underlies altered trafficking of alpha2 subunit containing GABAA receptors during prolonged epileptiform activity.

Neuropharmacology 2015;88:82–90.
[32] Joshi S, et al. Phosphatase inhibition prevents the activity-dependent trafficking of GABAA receptors during status epilepticus in the young animal. Epilepsia 2015;56(9):1355–65.
[33] Yen W, et al. A comparison of three NMDA receptor antagonists in the treatment of prolonged status epilepticus. Epilepsy Res 2004;59(1):43–50.
[34] Gaspard N, et al. Intravenous ketamine for the treatment of refractory status epilepticus: a retrospective multicenter study. Epilepsia 2013;54(8):1498–503.
[35] Loddenkemper T, et al. Subunit composition of glutamate and gamma-aminobutyric acid receptors in status epilepticus. Epilepsy Res 2014;108(4):605–15.
[36] Sanchez Fernandez I, Loddenkemper T. Subunit composition of neurotransmitter receptors in the immature and in the epileptic brain. Biomed Res Int 2014;2014:301950.
[37] Brooks-Kayal AR, et al. Selective changes in single cell GABA(A) receptor subunit expression and function in temporal lobe epilepsy. Nat Med 1998;4(10):1166–72.
[38] Galanopoulou AS. Developmental patterns in the regulation of chloride homeostasis and GABA(A) receptor signaling by seizures. Epilepsia 2007;48(Suppl. 5):14–28.
[39] Rakhade SN, Jensen FE. Epileptogenesis in the immature brain: emerging mechanisms. Nat Rev Neurol 2009;5(7):380–91.
[40] Sanchez RM, Jensen FE. Maturational aspects of epilepsy mechanisms and consequences for the immature brain. Epilepsia 2001;42(5):577–85.
[41] Talos DM, et al. Cell-specific alterations of glutamate receptor expression in tuberous sclerosis complex cortical tubers. Ann Neurol 2008;63(4):454–65.
[42] Fang Y, Wang X. Ketamine for the treatment of refractory status epilepticus. Seizure 2015;30:14–20.
[43] Keros S, et al. Increasing ketamine use for refractory status epilepticus in US pediatric hospitals. J Child Neurol 2017;32(7):638–46.
[44] Meldrum BS, Horton RW. Physiology of status epilepticus in primates. Arch Neurol 1973;28(1):1–9.
[45] Sankar R, Rho JM. Do seizures affect the developing brain? Lessons from the laboratory. J Child Neurol 2007;22(5 Suppl):21s–9s.
[46] Holmes GL. Effects of seizures on brain development: lessons from the laboratory. Pediatr Neurol 2005;33(1):1–11.
[47] Holmes GL, Thompson JL. Effects of kainic acid on seizure susceptibility in the developing brain. Brain Res 1988;467(1):51–9.
[48] Sankar R, et al. Patterns of status epilepticus-induced neuronal injury during development and long-term consequences. J Neurosci 1998;18(20):8382–93.
[49] Ben-Ari Y, Holmes GL. Effects of seizures on developmental processes in the immature brain. Lancet Neurol 2006;5(12):1055–63.
[50] Liu Z, et al. Long-term behavioral deficits following pilocarpine seizures in immature rats. Epilepsy Res 1994;19(3):191–204.
[51] Stafstrom CE, et al. Age-dependent cognitive and behavioral deficits after kainic acid seizures. Epilepsia 1993;34(3):420–32.
[52] Sayin U, Sutula TP, Stafstrom CE. Seizures in the developing brain cause adverse long-term effects on spatial learning and anxiety. Epilepsia 2004;45(12):1539–48.
[53] Koh S, et al. Early-life seizures in rats increase susceptibility to seizure-induced brain injury in adulthood. Neurology 1999;53(5):915–21.
[54] Sankar R, et al. Epileptogenesis after status epilepticus reflects age- and model-dependent plasticity. Ann Neurol 2000;48(4):580–9.
[55] Eriksson K, Kalviainen R. Pharmacologic management of convulsive status epilepticus in childhood. Expert Rev Neurother 2005;5(6):777–83.
[56] Sanchez Fernandez I, et al. Time from convulsive status epilepticus onset to anticonvulsant administration in children. Neurology 2015;84(23):2304–11.
[57] Chin RF, et al. Treatment of community-onset, childhood convulsive status epilepticus: a prospective, population-based study. Lancet Neurol 2008;7(8):696–703.
[58] Mayer SA, et al. Refractory status epilepticus: frequency, risk factors, and impact on outcome. Arch Neurol 2002;59(2):205–10.
[59] Alldredge BK, Wall DB, Ferriero DM. Effect of prehospital treatment on the outcome of status epilepticus in children. Pediatr Neurol 1995;12(3):213–6.
[60] Alldredge BK, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. N Engl J Med 2001;345(9):631–7.
[61] Gainza-Lein M, et al. Association of time to treatment with short-term outcomes for pediatric patients with refractory convulsive status epilepticus. JAMA Neurol 2018;75(4):410–8.
[62] Kamppi L, et al. The essence of the first 2.5 h in the treatment of generalized convulsive status epilepticus. Seizure 2017;55:9–16.
[63] Hillman J, et al. Clinical significance of treatment delay in status epilepticus. Int J Emerg Med 2013;6(1):p6.
[64] DeLorenzo RJ, et al. Comparison of status epilepticus with prolonged seizure episodes lasting from 10 to 29 minutes. Epilepsia 1999;40(2):164–9.
[65] Logroscino G, et al. Long-term mortality after a first episode of status epilepticus. Neurology 2002;58(4):537–41.
[66] DeGiorgio CM, et al. Serum neuron-specific enolase in the major subtypes of status epilepticus. Neurology 1999;52(4):746–9.
[67] Sankar R, Shin DH, Wasterlain CG. Serum neuron-specific enolase is a marker for neuronal damage following status epilepticus in the rat. Epilepsy Res 1997;28(2):129–36.
[68] Maytal J, et al. Low morbidity and mortality of status epilepticus in children. Pediatrics 1989;83(3):323–31.
[69] Alvarez V, et al. Practice variability and efficacy of clonazepam, lorazepam, and midazolam in status epilepticus: a multicenter comparison. Epilepsia 2015;56(8):1275–85.
[70] Coeytaux A, et al. Incidence of status epilepticus in french-speaking Switzerland: (EPISTAR). Neurology 2000;55(5):693–7.
[71] Seinfeld S, et al. Emergency management of febrile status epilepticus: results of the FEBSTAT study. Epilepsia 2014;55(3):388–95.
[72] Lewena S, et al. Emergency management of pediatric convulsive status epilepticus: a multicenter study of 542 patients. Pediatr Emerg Care 2009;25(2):83–7.
[73] Lewena S, Young S. When benzodiazepines fail: how effective is second line therapy for status epilepticus in children? Emerg Med Australas 2006;18(1):45–50.
[74] Aranda A, et al. Generalized convulsive status epilepticus management in adults: a cohort study with evaluation of professional practice. Epilepsia 2010;51(10):2159–67.
[75] Kamppi L, Mustonen H, Soinila S. Analysis of the delay components in the treatment of status epilepticus. Neurocrit Care 2013;19(1):10–8.
[76] Cheng JY. Latency to treatment of status epilepticus is associated with mortality and functional status. J Neurol Sci 2016;370:290–5.
[77] Sanchez Fernandez I, et al. Refractory status epilepticus in children with and without prior epilepsy or status epilepticus. Neurology 2017;88(4):386–94.
[78] Sanchez Fernandez I, et al. Factors associated with treatment delays in pediatric refractory convulsive status epilepticus. Neurology 2018;90(19). e1692–e1701.
[79] Gainza-Lein M, et al. Rescue medications in epilepsy patients: a family perspective. Seizure 2017;52:188–94.
[80] Cascino GD, et al. Treatment of nonfebrile status epilepticus in Rochester, Minn, from 1965 through 1984. Mayo Clin Proc 2001;76(1):39–41.
[81] Silbergleit R, et al. Intramuscular versus intravenous therapy for prehospital status epilepticus. N Engl J Med 2012;366(7):591–600.
[82] Capovilla G, et al. Treatment of convulsive status epilepticus in childhood: recommendations of the Italian League Against Epilepsy. Epilepsia 2013;54(Suppl. 7):23–34.
[83] Treiman DM, et al. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. N Engl J Med 1998;339(12):p792–8.
[84] Yasiry Z, Shorvon SD. The relative effectiveness of five antiepileptic drugs in treatment of benzodiazepine-resistant convulsive status epilepticus: a meta-analysis of published studies. Seizure 2014;23(3):167–74.
[85] Husain AM. Lacosamide in status epilepticus: update on the TRENdS study. Epilepsy Behav 2015;49:337–9.
[86] Lyttle MD, et al. Emergency treatment with levetiracetam or phenytoin in status epilepticus in children-the EcLiPSE study: study protocol for a randomised controlled trial. Trials 2017;18(1):p283.
[87] Dalziel SR, et al. A multicentre randomised controlled trial of levetiracetam versus phenytoin for convulsive status epilepticus in children (protocol): Convulsive Status Epilepticus Paediatric Trial (ConSEPT) – a PREDICT study. BMC Pediatr 2017;17(1):p152.
[88] Sanchez Fernandez I, et al. Gaps and opportunities in refractory status epilepticus research in children: a multi-center approach by the Pediatric Status Epilepticus Research Group (pSERG). Seizure 2014;23(2):87–97.
[89] Wasterlain CG, et al. Rational polytherapy in the treatment of acute seizures and status epilepticus. Epilepsia 2011;52(Suppl. 8):70–1.
[90] Borris DJ, Bertram EH, Kapur J. Ketamine controls prolonged status epilepticus. Epilepsy Res 2000;42(2–3):117–22.
[91] Eriksson K, et al. Treatment delay and the risk of prolonged status epilepticus. Neurology 2005;65(8):1316–8.
[92] Rogawski MA, et al. Neuroactive steroids for the treatment of status epilepticus. Epilepsia 2013;54(Suppl. 6):93–8.
[93] Vaitkevicius H, et al. First-in-man allopregnanolone use in super-refractory status epilepticus. Ann Clin Transl Neurol 2017;4(6):411–4.
[94] Rosenthal ES, et al. Brexanolone as adjunctive therapy in super-refractory status epilepticus. Ann Neurol 2017;82(3):342–52.
[95] Sage Therapeutics. (2017, September 12). Sage Therapeutics Reports Top-Line Results from Phase 3 STATUS Trial of Brexanolone in Super-Refractory Status Epilepticus [Press release]. Retrieved from http://investor.sagerx.com/news-releases/news-release-details/sage-therapeutics-reports-top-line-results-phase-3-status-trial.
[96] Zhang T, et al. Flupirtine and diazepam combination terminates established status epilepticus: results in three rodent models. Ann Clin Transl Neurol 2017;4(12):888–96.
[97] Ramgopal S, et al. Seizure detection, seizure prediction, and closed-loop warning systems in epilepsy. Epilepsy Behav 2014;37:291–307.
[98] Ulate-Campos A, et al. Automated seizure detection systems and their effectiveness for each type of seizure. Seizure 2016;40:88–101.
[99] Patient- and family-centered care coordination: a framework for integrating care for children and youth across multiple systems. Pediatrics 2014;133(5):e1451–60.
[100] Hill CE, et al. Timing is everything: where status epilepticus treatment fails. Ann Neurol 2017;82(2):155–65.
[101] Ostendorf AP, Gedela S. Effect of epilepsy on families communities, and society. Semin Pediatr Neurol 2017;24(4):340–7.
[102] Ostendorf AP, M.K, Patel AD. Improving timeliness of inpatient seizure treatment utilizing quality improvement methodologies. American Epilepsy Society Annual Meeting. 2016.