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Timing and selection of first antiseizure medication in patients with pediatric status epilepticus

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ABSTRACT

Objective: Pediatric status epilepticus (SE) may be associated with significant morbidity. We sought to evaluate timing and selection of antiseizure medications (ASM) in patients presenting in SE to a pediatric emergency department (ED). We hypothesized that delays in initial treatment are associated with longer overall duration of SE.

Methods: We identified patients with SE presenting to a single urban, academic pediatric hospital ED from 2009-2015. Patients were included in the study population with physician-documented ICD-9 code of SE. Medical record reviews were used to verify timing of seizure onset, ASM dosing, route, and timing.

Results: 141 patients had complete documentation to determine medication dosing and timing related to seizure onset. There were 75 boys and 66 girls. Median age was 45 months (IQR 20-97.5 months). Median overall duration of SE was 61.5 min (IQR 36–120 min). Median time to first ASM dose (whether given by parent, EMT or in ED) was 25 min (IQR 7–56 min). First dose ASM was a benzodiazepine (BDZ) in 92% of patients (130/141) and second-dose ASM was a BDZ in 95% of patients (90/95). Median seizure duration was 59.5 min and 151.5 min in patients who received first dose ASM in under 5 min and 60 min or more after seizure onset, respectively ($p < 0.01$). SE was stopped by first dose ASM in 32% of patients.

Significance: Our data suggest that there are delays in first dose ASM in patients presenting to our ED with SE. These results support the view that delays in initial ASM administration are associated with prolonged SE in some patients. A group of patients with prolonged SE had complete resolution after single dose of benzodiazepine, indicating that not all prolonged seizures become refractory.

1. Introduction

Pediatric status epilepticus (SE) is a life-threatening, neurological emergency that is often under-appreciated. The International League Against Epilepsy recently proposed a consensus definition of SE as prolonged seizures with varying clinical subtypes (Trinka et al., 2015). A seizure lasting greater than 5 min has a strong tendency to last greater than 30 min (Trinka et al., 2015; Freilich et al., 2014; Eriksson et al., 2005). Prolonged seizures are associated with morbidity and mortality thought to be related to dysfunction of cerebral auto-regulation, and ensuing neuronal damage (Trinka et al., 2015; Eriksson et al., 2005). Mortality and morbidity from status epilepticus in children is primarily a consequence of etiology (Berg et al., 2004). The timing of administration of anti-seizure medications is considered an important variable in preventing seizure-related brain injury from excitotoxicity and neuronal cell death.

Current guidelines recommend a first dose of benzodiazepine (BDZ) within 5–20 min of seizure onset (typically first dose at 5–10 min, second BDZ dose at 10–15 min), a dose of non-BDZ at 20–40 min, a second non-BDZ by 40–60 minutes, with general anesthetic dosing after 60 min of onset (Glauser et al., 2016; De Waele et al., 2013; Capovilla et al., 2013). For convulsive SE, some recommend more aggressive therapy, with general anesthesia induction by 30 min, because of presumed appreciable risks of neuronal damage after 30 min (Trinka et al., 2015). Despite the recognition of the need for urgent administration of ASMs in SE, the timing to drug administration remains a significant barrier to successful treatment of SE (Sanchez Fernandez et al., 2017a). In a recent study of children with refractory SE, the first BDZ, second

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BDZ and third (first non-BDZ) doses of ASMs were administered at 28 min, 40 min and 59 min median time, respectively, after seizure onset- all longer than the recommended approach (Sanchez Fernandez et al., 2015).

We aimed to evaluate the timing and selection of ASM administration for SE at a major, metropolitan, academic institution in children treated for status epilepticus or pending status epilepticus to evaluate adherence to guidelines. We also aimed to determine if delays in treatment were associated with prolonged duration of seizures, and if treatment delays were associated with adverse patient outcomes.

2. Methods

We conducted a retrospective chart review to study the characteristics of patients presenting with SE over a six year period.

The study population was identified by evaluating an ED database from aggregated reports of every patient visit at our main emergency department (ED) and our affiliated satellite ED. We collected data from January 1, 2009 until November 1, 2015. Patients were identified by discharge diagnosis of seizure or SE with a concomitant pharmacy record of midazolam, lorazepam, diazepam, or fosphenytoin. Patients were included if aged 1 month to 21-years-old, had documented seizure duration greater than or equal to 5 min (pending SE (1,2,3)), physician documented SE, and any patient who required a rescue medication. The majority of patients were transported from the District of Columbia (40%) and Maryland (52%) while 8% came from Virginia. Prehospital treatment guidelines of SE recommend first dose ASM at 5 min of seizure in DC and by 10 min of seizure in Maryland. Patients were excluded if age < 1 month (neonate), seizures were related to head trauma, or documentation of seizure and/or medication timing was inadequate.

The primary study outcome was time to treatment with ASMs in patients with status epilepticus. We reviewed ED records to determine time of seizure onset (if known), time of first seizure recognition (if onset was not witnessed), time to suppression of status (based on clinical report), ASM selection, dosage, and timing relative to time of seizure onset. Inclusion in the final analysis required documentation of continuous seizure activity or intermittent seizure activity without recovery of consciousness between episodes. In cases where seizure onset was unknown, we used the time of seizure recognition as a conservative estimate of the time of seizure onset.

Statistical analysis was performed using Kruskal-Wallis rank sum test for independent samples.

The study was approved by the Institutional Review Board.

3. Results

Our initial screen using ICD-9 codes and medication administration identified 247 patients with possible SE. Of these, 141 (58% of 247) had complete documentation to determine medication dosing and timing related to seizure-onset (Table 1); 106 patients were excluded due to incomplete documentation. Median age was 45 months (interquartile range 20–97.5 months). 100 patients (71%) of patients had a prior diagnosis of epilepsy; 14 patients (9%) had a prior diagnosis of febrile seizure. 19% (27/141) had first-time seizure: of these patients, 21 patients were afebrile and 6 were febrile seizures. Of patients with known epilepsy: 46 patients had genetic epilepsies; 44 patients had known brain structural abnormalities; 4 patients had history of infectious meningoencephalitis; 3 patients had unknown etiologies; and 3 patients had other etiologies. Only 10% of patients were transferred from other emergency departments (14/141). 106 patients (75%) were brought by EMS (ambulance or air ambulance). 39 of 141 patients (28%) received first dose ASM in less than 10 min; of these patients, 51% (20/39) received diastat, 33% lorazepam IV and 16% other medications. Although 81% of patients in this study had prior seizures (114/141), only 20% received home rescue diastat (29/141).

Table 1
Patient characteristics.

Age (months)		45 (20 - 97.5)
Sex		
	Male	75 (53%)
	Female	66 (47%)
First-time seizure		27 (19%)
	Unprovoked	21 (15%)
	Febrile	6 (4%)
Diagnosis		
	Epilepsy	100 (71%)
	First-time seizure	27 (19%)
	History of febrile seizure	14 (10%)
Transferred		14 (10%)

Data expressed as number of patients (*n*) and interquartile range or % of total study population.

The total duration of SE divided by time frame is shown in Fig. 1. The median overall duration of SE was 61.5 min (IQR 36–120 min). The timing to first dose ASM is shown in Fig. 2. The median time to first ASM dose (whether given by parent, EMT or in ED) was 25 min (IQR 7–56 min). Status was extinguished by first dose ASM in 46 patients (32% of all patients). In patients requiring a second dose, median time to second dose was 44 min (IQR, 21–87.5 min). Status was extinguished by the second dose ASM in 36 patients (25% of all patients). The median time to third dose ASM was 65.5 min (IQR, 37–110 min). Third dose ASM extinguished status in 23 patients, or 16% of all patients. 36 patients required four or more doses of ASMs (26% of all patients) to abort SE.

Fig. 3 shows the duration of seizure as a function of number of ASM doses required to stop SE. Of patients whose SE was extinguished by first dose ASM, median time to first ASM dose was 38 min with median duration of seizure 45 min. Of patients whose PSE was stopped by second dose ASM, median time to first ASM dose was 21 min with median duration of seizure 45.5 min. Of patients whose SE was stopped by third dose ASM, median time to first ASM dose was 17 min with median duration of seizure 72 min. And of patients whose SE was stopped by fourth or greater dose of ASM, median time to first ASM dose was 16 min with median duration of seizure 85.5 min. Of patients whose SE was stopped by two or more doses of ASM, median time to first ASM dose was 38 min with median duration of seizure 70 min. Only 20% (12/58 patients) who required three or more doses of ASM had home rectal diazepam.

First choice ASM is listed in Fig. 4: BDZ 92% (130/141) (3 BDZ, 9 formulations); fosphenytoin 3.5% (5/141); phenobarbital 2.1% (3/141); and levetiracetam 1.4% (2/141). Of patients requiring dose escalation, second dose ASM was a BDZ in 95% (90/95); non-BDZ in 4% (5/95) and unknown in one patient. Phenobarbital was initial drug for patients ages 48, 72 and 212 months. Of 53 patients requiring three or more doses to extinguish SE, third dose ASM was a BDZ in 36% (19/53); non-BDZ in 42% (23/53; of which 83% received fosphenytoin) and unknown in one patient.

There was a difference between time to first dose ASM and total duration of seizure, shown in Fig. 5 and summarized in Table 2. Median duration of seizure was 59.5 min in patients who received first dose ASM at less than 5 min compared to 151.5 min in patients who received first dose ASM 60 min or more after seizure onset ($p < 0.01$).

There was noted morbidity in our case series. While 73 patients (52%) were admitted to ward service, 68 patients (48%) were escalated to the intensive care unit (ICU). 37 patients (26%) required airway support, including 28 patients (20%) who were intubated. Table 2 demonstrates that longer time to first dose ASM is associated with increased risk of intubation and need for ICU level care. Table 3 shows the outcomes in SE that was responsive (requiring ≤ two doses ASM to cease) versus refractory (seizures requiring more than two doses of medication with different mechanisms of action (Sanchez Fernandez

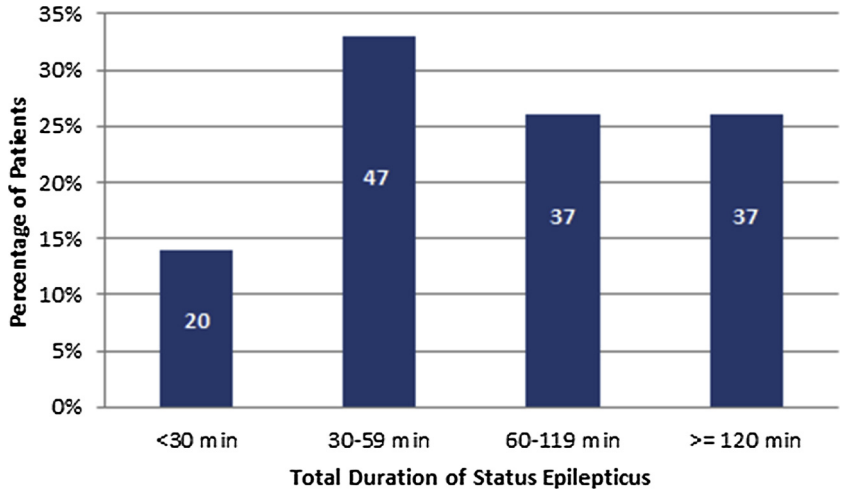

Fig. 1. Total duration of status epilepticus.
Duration of seizures from onset to reported termination of status epilepticus. The total number of patients per group is shown on each bar.

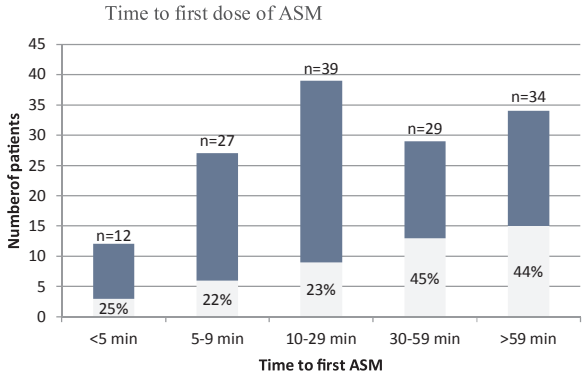

Fig. 2. Time to first dose of ASM.
Bar graph showing the relative time from documented seizure onset to first dose of ASM. Total number of patients per group on bar. Blue bar shows total patients that received first dose ASM at given time; gray shade shows relative percentage of patients within that group whose seizures ceased after first dose ASM.

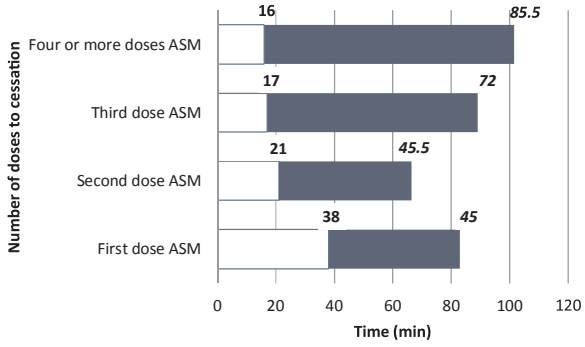

Fig. 3. Timeline of seizure duration as a function of ASM doses required to stop SE.
Seizure start at time 0 min. Median time to first dose ASM (min) labeled above bar on left; median duration of SE (min) in italics above bar on right.

et al., 2015). Refractory SE was associated with an increased risk of intubation and ICU admission compared to responsive SE. When outcomes were analyzed by presenting diagnosis (Table 4), those patients with epilepsy were at lower risk of intubation and need for ICU compared to patients presenting with first time seizure and febrile seizures.

4. Discussion

We observed delays in the timing of the first dose of ASM in patients presenting to the ED with ongoing convulsions. The median time to first dose of ASM was 25 min, a notable delay from current treatment guidelines. There appear to be two separate groups- one that responded to initial treatment (including several who responded regardless of treatment delay), and one that was refractory to treatment (requiring two or more doses of different ASMs). More than half (57%) responded to one or two dosages of ASM despite delays in treatment. One quarter responded poorly to medications; for these patients early aggressive treatment may alter outcomes.

The majority of seizures resolve spontaneously by five minutes; after five minutes seizures are likely to persist without intervention (Trinka et al., 2015). Our data indicate that giving medications early on in SE is associated with shorter overall duration of SE. Patients receiving first dose ASM in any of the time allotments under 60 min had shorter post treatment seizure duration compared to those who received first dose ASM at 60 min and longer. Those patients treated after an hour of continuous seizure may have a physiologic lack of response to benzodiazepine due to modifications in benzodiazepine receptor with prolonged seizure. In animal models, prolonged SE is associated with reuptake/decreased surface expression of the benzodiazepine specific GABA receptor subunit γ2, which suggests that the longer the seizure goes untreated, the more likely the seizure will become benzodiazepine-resistant and require anesthetic doses to abort status (Goodkin et al., 2008). These data support the use of initial treatment at home and by EMT services, which has been demonstrated to shorten duration of SE (Chin et al., 2008; Alldredge et al., 1995).

Our data are in line with other studies demonstrating significant delay in early treatment despite guideline recommendations (Sanchez Fernandez et al., 2015; Chin et al., 2008; Sanchez Fernandez et al., 2014). A 2018 systematic review of adherence to guidelines for treatment of SE (including 13 pediatric specific articles (1323 pediatric SE cases) of the 22 articles) found that all included studies varied from recommended guidelines for treatment. This variability was associated with increased risk of morbidity (ICU admission) and mortality (Uppal et al., 2018). Delayed time to treatment with first dose ASM is especially of concern given that prolonged duration of status may be associated with increased risk of neuronal injury (Trinka et al., 2015; Meldrum and Horton, 1973). A recent study demonstrated correlation between prolonged convulsive SE and cardiac injury (El Amrousy et al., 2017). Convulsive SE is an independent risk factor associated with mortality in children, as is delayed initiation of continuous EEG, suggesting more rapid detection and treatment of SE can be life-saving

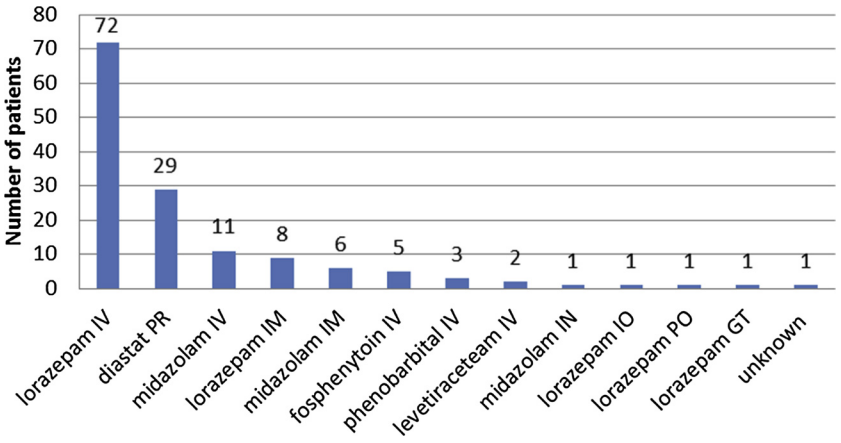

Fig. 4. First choice ASM for pediatric status epilepticus.
Bar graph showing initial ASM selection in patients with SE. Total patients per group listed above each bar.

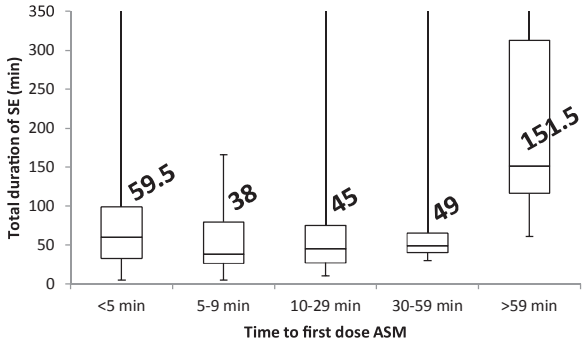

Fig. 5. Duration of pediatric SE as a function of time to first dose ASM.
Box-and-whiskers plot of duration of pediatric SE, separated by time to first dose ASM in minutes (< 5 min, 5–9 min, 10–29 min, 30–59 min, > 59 min). Median duration of SE is shown in bold. Max value whisker intentionally tapered. $p < 0.01$ using Kruskal-Wallis test (< 5 min vs. > 59 min; 5–9 min vs. > 59 min; 10–29 min vs. > 59 min; 30–59 min vs. > 59 min).

(Sanchez Fernandez et al., 2017b).

Our data contain a paradox: patients treated earlier, at less than 60 min, were more likely to have shorter SE, but were also more likely to require more medications; another group responded to a first treatment despite medication administration delays. The group refractory to ASMs (requiring 4 or more doses) received first dose ASM earlier than the group that ceased after first dose ASM; but paradoxically the refractory group had longer total duration of SE than the group that stopped after the first dose ASM (Fig. 3). There may be several explanations for this observation including rapid recognition and escalation in patients with known refractory disease- seizures may be more likely to be noticed in patients who carry a diagnosis of epilepsy, although this comparison is difficult to make given that the majority of patients in the study (100 patients) had a known diagnosis of epilepsy and we did not track those who have medically refractory disease.

Table 3
Outcomes as function of number of ASM doses to stop SE.

# doses to stop SE	*n*	Intubated	ICU
Dose 1	46	6/46 (13%)	12/46 (26%)
Dose 2	36	6/36 (18%)	14/36 (39%)
Refractory (3 or more)	59	16/59 (27%)	42/59 (71%)

n = number of patients per group.
Number of patients intubated and admitted to ICU in rightmost columns (relative percentages in parentheses).

Patients with more severe epilepsy or a given set of underlying etiologies may not respond as well to standard dosing/dose sequence of ASMs. It is possible, but not discernable from our data, that earlier treatment is important for seizure control in this subset of patients. These results suggest that earlier, more aggressive treatment is associated with shorter duration of SE. The efficacy window of non- anesthetic doses of BZP may be longer in children than suggested by animal studies.

A recent study of 218 patients with refractory convulsive SE (pediatric status epilepticus group (pSERG)) showed that delayed initial BDZ dose is associated with increased seizure duration, risk of death, need for continuous drug infusion, and risk for hypotension (Gainza-Lein et al., 2018 Apr). Our results show a similar delay in initial drug dose in SE and subsequent dosing of second, third, and fourth medications as pSERG. pSERG is limited only to patients with refractory SE who were treated both pre-hospital or in-hospital onset. No consistent treatment guideline was followed because of the multicenter nature of this report, whereas our institution had a treatment algorithm for SE. Our data are unique in that we analyzed the entire population of undifferentiated SE patients presenting to our emergency department, including those patients with SE that resolved after single medication dose. Our experience is likely more broadly applicable to pediatric populations.

The majority of patients received an appropriate first-line

Table 2
Median duration of SE as function of time to first dose ASM.

Time to first dose ASM	*n*	Median duration of SE	Intubated	ICU
< 5 min	12	59.5 (32.5-98.75)	1/12 (8%)	4/12 (33%)
5-9 min	27	38 (26.5-79.5)	9/27 (33%)	13/27 (48%)
10-29 min	39	45 (27-75)	8/39 (26%)	20/39 (51%)
30-59 min	29	49 (40-65)	6/29 (21%)	13/29 (45%)
> 59 min	34	151.5 (116.25-313)	4/34 (12%)	17/34 (50%)

Median duration of SE in min (interquartile range in parentheses). Columns for number of patients intubated and number of patients requiring ICU admission on right (relative percentages in parentheses).

Table 4
Outcomes as a function of presenting diagnosis.

Diagnosis	*n*	t_1	Median duration SE	Intubated	ICU
Epilepsy	100	23.5 (5-54.25)	59 (32.5-120.5)	14/100 (14%)	44/100 (44%)
History of febrile seizure	14	33 (17.5-62.5)	67 (48.75-87.5)	7/14 (50%)	8/14 (57%)
First time seizure	27	25 (14-45.5)	62 (45-120.5)	7/27 (26%)	16/27 (59%)
Febrile	6	28.5 (12.5-51.5)	115 (89.75-146.25)	2/6 (33%)	4/6 (67%)
Afebrile	21	25 (14-45)	56 (44-99)	5/21 (24%)	12/21 (57%)

n = number of patients per group.
$\mathbf{t_1}$ = .median time to first dose ASM in minutes (interquartile range in parentheses).
Median duration of SE in min (interquartile range in parentheses).
Number of patients intubated and admitted to ICU in rightmost columns (relative percentages in parentheses).

medication (benzodiazepine via IV or per rectum); however, many patients received inappropriate first line ASM treatment. Despite having a system-wide pathway for SE, these differences may be explained by patients having received initial treatment at an outside ED and/or provider/trainee unfamiliarity with pathways (as there are many trainees from the same and other institutions that rotate through the ED). One tenth of patients received non-standard-of-care first dose ASM (including IM lorazepam and phenobarbital). IM lorazepam was given as initial ASM to 6% of the patients in this series (8/141). Phenobarbital was used outside the appropriate age of < 6 months for typical use (Shellhaas et al., 2017). 38 patients received a BDZ as third dose ASM, which varies from guideline recommendations that third dose ASM is nonBDZ. Only one patient with non-standard-of-care first dose ASM was transferred from another facility.

This study has several limitations. Its retrospective nature introduces room for error in terms of accurate reporting of seizure and medication timing and not all possible patients had complete data sets; duration of seizures and time of medications are likely conservative. We were not able to obtain timing of ambulance arrival, duration of transport, and other key prehospital data because these are not maintained in the medical record. Our results may be influenced by initial treatment at outside facilities prior to transfer; however, this effect is likely minimal as 91% of patients presented initially to our hospital. Another limitation is that we did not have EEG confirmation of seizure cessation; rather we relied on clinical report.

There was noticeable morbidity in our population. Half our patients received ICU-level care, a quarter received some form of respiratory support and a fifth were intubated. Longer time to first dose ASM is associated with increased risk of intubation and need for ICU level care. We hypothesize that the level of acuity seen in this series may be a consequence of the hospital being a level 1 trauma and tertiary care center. We did identify a subpopulation of patients with prolonged SE who had termination of seizure after first dose ASM.

There are several potential reasons for treatment delay that may be addressed at system-wide, provider, and family-based levels. Potential areas for improvement may include standardizing SE treatment protocols among county and state emergency medical services, and increased education for physician and allied health recognition of SE and its management. Families should be better informed on rapid detection and treatment of SE- although four fifths of patients in this study had prior seizures, only one fifth received home rescue diastat. These are proposed causes and require further study as targets for intervention.

5. Conclusion

Our data contribute to a growing body of literature that, despite the known risks and consequences of delayed initial treatment of SE, there remains a large proportion of patients who receive postponed or inappropriate initial treatment of their disease. These data, and a growing literature on delays in treatment, may be used to address approaches to recognition and treatment of SE. Future studies should aim to address mechanisms both pre- and intra-hospital to address these discrepancies with the goal of limiting morbidity/mortality from SE. Factors that distinguish medication resistant versus medication responsive status patients, regardless of treatment timing, require further investigation.

Author disclosures

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