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Review

The burden of pediatric status epilepticus: Epidemiology, morbidity, mortality, and costs

Kevin Gurcharran[a,b], Zachary M. Grinspan[a,b,c,*]

[a] Department of Pediatrics, Weill Cornell Medicine, New York, NY, United States
[b] New-York Presbyterian Hospital, New York, NY, United States
[c] Department of Healthcare Policy & Research, Weill Cornell Medicine, New York, NY, United States

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ABSTRACT

Purpose: To summarize the epidemiology, morbidity, mortality, and costs of status epilepticus (SE) in the pediatric population.
Method: Review of the medical literature.
Results: The overall incidence of pediatric SE is roughly 20 per 100,000 children per year, with overall mortality of 3%. Underlying etiology is the biggest risk factor for SE, with symptomatic (acute > remote) etiologies associated with worse outcomes. The most common cause of SE in children is febrile SE, though this entity occurs primarily in early childhood. After a first episode, the risk of recurrence is similar to the risk after a first unprovoked seizure (25–40%). SE is expensive, regularly costing more than $10,000 per episode and often more than $100,000 for refractory cases.
Conclusion: SE is not an uncommon neurologic emergency and depending on the associated etiology can carry significant morbidity, mortality, and cost especially if treatment is not performed in a timely manner.

1. Introduction

Status epilepticus (SE) is among the most common neurologic emergencies in pediatrics. An understanding of the epidemiology of SE can guide management and help clinicians counsel children and families. In this section, we aim to describe the epidemiology of pediatric SE and its subtypes while also examining the associated mortality and morbidity.

2. Incidence

The overall incidence of pediatric SE ranges between 3–42 episodes per 100,000 population per year worldwide [1–6] based on several population-based studies, summarized in Table 1. Studies that include *all* cases of SE [1–4] tend to report higher rates. Studies reporting only convulsive status epilepticus (CSE) [5,6] and studies relying on hospital discharge data [5] tend to report lower rates. A consistent finding across multiple studies is that the highest incidence of SE and refractory SE (RSE) is among children under 2 years of age. [1,6–10] This may be due to a higher rate of symptomatic causes of SE, the natural course of genetic/metabolic diseases, or an increased susceptibility to seizures in the developing brain [11,12].

3. Semiology

Broadly, the semiology of SE can be divided into convulsive and non-convulsive. The majority of SE in children is convulsive (i.e., CSE), [1,3] a neurological emergency that requires rapid treatment to minimize morbidity and mortality. Roughly half begin as focal seizures that subsequently generalize; the other half are generalized from onset [1]. A substantial minority of SE presents as partial seizures only, with or without alteration of consciousness, (11–29%). [1,3] Absence status is rare among children in population based studies (0–3%), [1,3] though case series data suggest that tertiary care centers may treat several such cases per year [13].

Of importance, there are settings and populations in which non-convulsive seizures other than absence status are common. For example, a large multicenter study of 550 children in the pediatric intensive care unit who had received EEG monitoring found one in ten had NCSE (30% of the cohort had at least one nonconvulsive electrographic seizure, and 33% of those with nonconvulsive seizures also had NCSE). [14] Independent risk factors for electrographic seizures included younger age, clinical seizures prior to EEG monitoring, an abnormal initial EEG background, interictal epileptiform discharges, and a prior diagnosis of epilepsy [14,15]. Among children with CSE, NCSE

* Corresponding author at: Room LA 220, 402 East 67th Street, New York, NY, 10065, United States.
E-mail address: zag9005@med.cornell.edu (Z.M. Grinspan).

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Table 1
Population Based Studies of Status Epilepticus in Children.

	Richmond, Virginia [1]	Minnesota [2]	Japan [3]	Switzerland [4]	California [5]	London [6]
Status Subtype	All	All	All	All	Convulsive only	Convulsive only
Age Categories	Adults and Children	Adults and Children	Children only	Children only	Adults and Children	Children Only
Study Design	Prospective	Retrospective	Retrospective	Prospective	Retrospective	Prospective
Overall Incidence (episodes per 100,000 residents per year)	41	18.3 (48% convulsive)	–	9.9 (44% convulsive)	6.18	–
Pediatric Incidence	38 (71% convulsive)	19.8	42 (86% convulsive)	0–4: 38.7 5–14: 10.9	3.86	18–20
Peak Age of Incidence (years)	< 1 and > 60	< 1 and > 60	< 2	0–4	< 5 and > 60	< 1
Male:Female	1.2:1	2:1	1.4:1	1.6:1	1:1	1.2:1
Pediatric Mortality	3%	< 1yo: 17% 1–19: 5%	< 1%	6.2%	Under 5: 1.4%	3%
Years of Study	1989–91	1965–84	2003–5	1998	1991–98	2002–2004

is often a sequelae. One third of children initially presenting with CSE subsequently have electrographic seizures without a clinical correlate [16]. Risk factors associated with the development of electrographic seizures after CSE included a prior diagnosis of epilepsy and the presence of interictal epileptiform discharges [16].

Although epileptic encephalopathies are not typically conceptualized as NCSE, they are important disorders in which frequent or continuous epileptic activity impairs cognition and development. There are population based epidemiological estimates for some epileptic encephalopathies. Infantile spasms occur in 1 in 3300 live births. [17] The Lennox-Gastaut syndrome has an incidence of 2 in 100,000 children per year and a prevalence 1 per 4000 children under 10 [18,19].

For others, the epidemiology can be coarsely estimated from hospital-based studies. For example, neonatal epileptic encephalopathy occurred in 35 of a cohort of 611 newborns with seizures [20]. Seizures occur in 95 per 100,000 live births [21], suggesting neonatal epileptic encephalopathy has an incidence of 1 in 18,000 live births.

Continuous spike-and-wave during sleep (CSWS) and the Landau Kleffner Syndrome (LKS) have been described through several hundred published cases, though most were hospital based. [22,23] A back-of-the-envelope calculation can be made using a study of 440 children with epilepsy followed in an outpatient clinic, which found only a single case with CSWS / LKS [24]. The prevalence of epilepsy is 6 per 1000 children [25], suggesting the prevalence of CSWS / LKS is 1–2 per 100,000 children. This may be a lower limit – tertiary care centers regularly care for children with these disorders. Reports suggest the EEG signature of CSWS/LKS occur in 1%–7% of children admitted for epilepsy monitoring and evaluation [26,27].

4. Response to treatment

When children with SE continue to have seizures despite two appropriate antiepileptic drugs, it is called refractory SE (RSE), which is covered in depth elsewhere in this volume [83]. The incidence of RSE ranges from 12 to 40% of all cases of SE [9,28] RSE that continues for 24 h or more after hospitalization is often called “super refractory SE” [28] or “malignant SE” [29]. Super refractory SE is uncommon, occurring in 10–15% of all cases of SE admitted to the hospital [28]. In children, an analysis of a database including roughly 20% of pediatric admissions in the US found that over five years, there were 678 children admitted to an ICU for SE who received pentobarbital, presumably for iatrogenic coma [30]. These data roughly suggest that RSE occurs in 2.5–8 per 100,000 children per year, and super RSE occurs roughly once per 100,000 children per year. In a retrospective study that examined all cases of SE between 1994 and 2004 and compared aborted SE versus RSE, epilepsy related risk factors for RSE include a first degree relative with seizures, use of 5 antiepileptic medications, and multiple seizures per week despite adequate treatment [10].

5. Etiology

As per recommendations by the International League Against Epilepsy, the etiology of SE can be divided into three categories, (1) known/symptomatic, (2) SE in defined electroclinical syndromes, and (3) unknown/cryptogenic. Symptomatic causes are then subdivided into acute, remote, and progressive (Fig. 1). [31] Febrile status epilepticus (FSE) is the most common cause of pediatric SE overall, accounting for about a third of cases [3,5,6,8,32] though limited to early childhood. For older children, cryptogenic and remote symptomatic causes are more common [6,8,9,33].

5.1. Known symptomatic

FSE occurs in young children (6 months–five years) with fever and seizures (continuous or intermittent without return to baseline) that last 30 min or longer, with no evidence of a central nervous system infection, explanatory metabolic abnormality, nor history of seizures without fever. FSE has been well characterized via an ongoing multicenter prospective cohort (The Consequences of Prolonged Febrile Seizures in Childhood; FEBSTAT study). The majority (75%) had FSE as the initial febrile seizure. Several viruses are associated with febrile seizures in children, though HHV-6 and/or HHV-7 (38% of FSE in the FEBSTAT study [34]) and influenza are the most common [35]. Seizures are typically convulsive, though two thirds begin with focal features that generalize. Interestingly, 25% of the patients had a first degree relative with a history of febrile seizures, suggesting a genetic predisposition [36,37]. Of importance, it may be difficult to clinically distinguish febrile status epilepticus from seizures due to a central nervous infection [81,82], and thus a full evaluation including lumbar puncture is often indicated.

Other common causes of SE in children appear in Table 2. In a retrospective study of patients who had epilepsy due to a symptomatic cause there was an increased risk of SE if there were focal background EEG abnormalities, partial seizures with secondary generalization, or generalized abnormalities on neuroimaging [38].

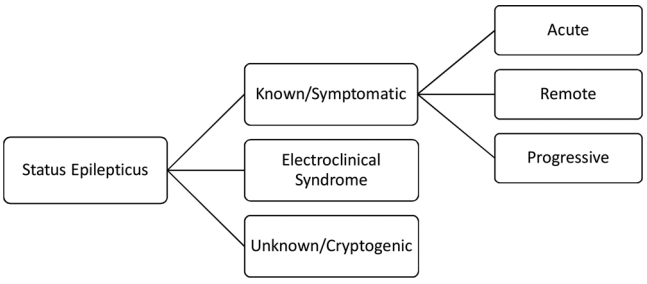

Fig. 1. Etiologies in Status Epilepticus (per Trinka et al. [31]).

Table 2
Selected Examples of Symptomatic Etiologies of Status Epilepticus.

Remote Symptomatic	Acute Symptomatic	Progressive
Hypoxic Ischemic Injury	Febrile seizures	Inborn errors of metabolism
Tumor	Central nervous system infection	Progressive myoclonic epilepsies
Congenital brain malformation	Stroke	Leukodystrophies
	Traumatic brain injury	
	Drug/poison	
	Electrolyte abnormality	
	Hypoxia/anoxia	

5.2. Epilepsy and electroclinical syndromes

10% of children with epilepsy have their first seizure present as SE [32], and as many as a quarter of people with epilepsy will experience SE at some point [7,39]. Among people with epilepsy, several factors have been associated with an increased risk for SE. These include age of onset < 1 year old, symptomatic etiology, and history of prior SE [39]. There are several epilepsy syndromes that have been associated with SE, summarized in Table 3.

5.3. Unknown

10% of children with epilepsy have their first seizure present as SE [32]. Furthermore, almost 60% of children have no history of neurological deficits prior to their episode of SE [1,6]. An identifiable etiology is often not found for children with SE (7–10% [3,6]). A particularly difficult to treat form of SE with unknown etiology is febrile infection-related epilepsy syndrome (FIRES) which has an estimated incidence 1/1,000,000 [40]. This severe subtype of RSE has a high mortality rate (~10%) and frequent neurological sequelae including refractory epilepsy, cognitive impairment, brain atrophy, and vegetative state [40,41].

6. Cost

An appreciation of the monetary costs associated with caring children with epilepsy highlights the economic burden of the disease. A 15-year U.S study of the cost for any epilepsy admission between 1993 and 2008 saw the cost per day of admission rise from $1703 to $6131 with the average hospital stay cost rising from $10,050 to $23,909 [42].

A United States study from 1993 to 1994 and a German study from 2008 examined the cost of SE. The estimated mean inpatient costs were $18,834 in the USA and to €8347 (US $10,071) in Germany per admission [43,44]. The mean annual direct costs for SE was estimated at US$4 billion in the USA and at €83 million (adults only) in Germany [45].

A recent multicenter study in the US involving pediatric patients with SE included information about hospital costs. In children with RSE who received pentobarbital for iatrogenic coma, the average length of stay was 30 days, with a daily hospital cost of about $5000 per day and an average hospital stay cost of $148,000. In a smaller group who received pentobarbital and ketamine (i.e., suggesting a more refractory phenotype) the average hospital stay was 51 days, average daily cost of $6,000, and average cost of stay was $298,000 [30].

7. Morbidity

7.1. Immediate complications

The immediate consequences of SE can be severe, and may include tachycardia, hypertension, respiratory failure, metabolic and/or respiratory acidosis, increased intracranial pressure, cerebral edema, electrolyte abnormalities, rhabdomyolysis, and renal failure [46].

7.2. Neurologic disability

Survivors of SE are at risk of remote neurologic disability including focal neurologic deficits (ie diplegia, extrapyramidal syndromes, cerebellar syndrome), cognitive impairment, seizure recurrence/epilepsy, and behavioral problems. Neurologic morbidities may occur in less than

Table 3
Status Epilepticus in Selected Epilepsies.

Epilepsy	Epidemiology	Notes
Absence Epilepsy (Childhood or Juvenile)	*Prevalence*: 36 per 100,000 children 3–13 [63]	Absence SE very rare in younger children, uncommon in older children and adults [13,64]
Juvenile Myoclonic Epilepsy	*Prevalence*: 6 per 100,000 children 0–15 [65]; 18 per 100,000 population [66]	SE rare (3%), often myoclonic SE, more likely in adults [67,68]
Dravet Syndrome	*Prevalence*: 4 per 100,000 children 3–13 [63]	SE Common (as high as 90% [69]) with multiple forms, including hemiclonic febrile SE, and NCSE [70]
Angelman Syndrome	*Birth incidence:* 4 per 100,000 [71]	Myoclonic SE common [72,73]
Rasmussen's Encephalitis	*Prevalence*: < 1 per 100,000 children 3–13 [63]	Epilepsia partialis continua common [74]
Ring chromosome 20	Very rare	Repeated episodes of NCSE [75]
Lennox Gastaut Syndrome	*Prevalence*: 1 in 4000 in children under 10 [76]	NCSE common (50–75%) [77]
Continuous spike-and-wave during sleep (CSWS) and the Landau Kleffner Syndrome (LKS)	*Prevalence:* 1–2 per 100,000 children [24,25],	More common in hospital based cohorts. [26,27]
Neonatal Epileptic Encephalopathy	*Birth Incidence:* 1 per 18,000 live births [20,21],	Only a minority with classic neonatal epilepsy syndromes. Of 35 with neonatal encephalopathy, four had Ohtahara syndrome and one early myoclonic encephalopathy [20].
Febrile Infection Related Epilepsy Syndrome (FIRES)	*Incidence*: 1 per 1,000,000 children and adolescents [40]	Recent consensus definition: new onset refractory SE in a child without prior neurologic condition with no clear acute cause. Fever must have been present for 24 h–2 weeks prior to seizures, making FIRES distinct from febrile SE. [78]

SE: Status epilepticus, NCSE: Nonconvulsive status epilepticus, FIRES: Febrile infection related epilepsy syndrome.

15%, [47], though they are more common among children with symptomatic etiology [1,5,32,47–49].

7.3. Risk of epilepsy

The risk of subsequent unprovoked seizures two years after a first-ever unprovoked episode of SE is 25–40%, which is similar to the risk of recurrence after first self-limited unprovoked seizure [46,47,50,79]. However, children with acute symptomatic causes, previous neurological abnormalities, or unclassified causes are at particularly high risk: half these children may develop epilepsy after a first episode of convulsive SE [47].

7.4. Recurrent SE

The estimated overall recurrence of convulsive SE is 20% after 4 years. When SE recurs, most (69%) recurrences occur within 1 year of the first episode of SE. Etiology is again the most important risk factor: the recurrence risk for SE is roughly 3% for febrile SE, 4% for SE of unknown etiology, 11% for acute symptomatic etiologies, 44% for remote symptomatic etiologies, and 67% for progressive symptomatic etiologies [50].

7.5. Developmental and psychiatric outcomes

Children with nonfebrile CSE often have developmental scores 1–2 standard deviations lower than a reference group of normal children in multiple domains (motor, language, and cognition) [51]. For children with FSE, developmental scores are often 0.5–1 standard deviation lower than the reference mean [51,52]. A retrospective analysis of 460 patients with new onset SE found that children with symptomatic etiology had greater odds of cognitive and behavioral problems compared with children with unknown etiology [53]. Of importance, however, it is unclear if these developmental differences are due to the underlying etiology of the SE, or a sequelae of the SE itself. The population-based North London Convulsive Status Epilepticus in Childhood Surveillance Study examined the long-term developmental and psychiatric outcomes of 134 of 203 children with CSE in their cohort. After a mean of 8 years, 37% had behavioral problems and 28% had a psychiatric disorder that met criteria in the Diagnostic and Statistical Manual mental disorder IV (DSM-IV), including autism, attention deficit disorder, pervasive developmental disorder not otherwise specified, and developmental coordination disorder. Seizures before CSE (AOR 2.9) and recurrent CSE (AOR 1.9) increased the risk. These data indicate that patients with CSE often have behavioral and psychiatric manifestations several years after an event and require screening [54].

7.6. Quality of life

A multicenter Canadian study followed children with new onset epilepsy and found that convulsive SE was independently associated with a significantly worse quality of life as evidenced by scores on the Quality of Life in Childhood Epilepsy Questionnaire (QOLCE) [55]. The QOLCE Questionnaire offers assessment of health related quality of life in a broad age group of children and several functional domains including physical function, social function, emotional well-being, behavior, and cognition [56].

7.7. Refractory SE and morbidity

Refractory and super refractory SE carry higher mortality and morbidity rates compared to SE that responds to treatment [10]. Risk factors for worse outcome include long seizure duration (>120 min), acute symptomatic etiology, NCSE, and age at admission <5 years [10].

7.8. Electrographic SE and morbidity

The long-term effects of electrographic SE are still being determined. Among children with acute neurologic disorders who were reported to be neurodevelopmentally normal before PICU admission, electrographic SE (but not electrographic seizures) was associated with an increased risk of unfavorable global outcome, lower health-related quality of life scores, and an increased risk of subsequently diagnosed epilepsy [15]. A study of the effect of electrographic seizure burden on outcome found that the odds of neurological decline increased by 1.13 for every 1% increase in the maximum hourly seizure burden [16].

8. Mortality

Mortality after SE in children is 3–11%. Deaths occur either due to the underlying cause or due to the complications of SE itself. Etiology is the most important predictor of outcome; symptomatic etiologies have the highest risk [1,6,10,49,57]. In one study with a mortality of 4%, all deaths were among children with a symptomatic causes of SE [49].

8.1. Immediate mortality

Short term mortality of SE, defined as up to 30 days post discharge, ranges from 3 to 9%, with symptomatic causes associated with a higher risk of mortality [2,6,7,33,49]. A multicenter review of 12,365 pediatric inpatients (age 0–20 years) with convulsive SE examined causes for mortality in the hospital. Several patient comorbidities corresponded to a greater mortality risk: near drowning, hemorrhagic shock, sepsis, massive aspiration, mechanical ventilation >96 h, transfusion, structural brain lesion, and hypoglycemia [58]. A retrospective observational study of 625 patients found that in critically ill neonates and children, the time from ICU admission to continuous EEG initiation and the presence of electrographic SE were independently associated with increased in-hospital mortality [59].

Electrographic SE is associated with a high risk of in-hospital mortality. In a multicenter retrospective study of 550 pediatric patients, electrographic SE was associated with odds ratio of 2.42 for mortality. In that study, 25% of the children with electrographic SE died. Electrographic seizures themselves were not an independent risk factor for mortality [14].

8.2. Long term mortality

Studies examining long-term mortality have found mixed results with a wide range from 0 to 40% [33,57]. In the Rochester cohort, patients who survived 30 days after the episode of SE were followed until death or the completion of the study. Mortality for patients <1 year old at time of presentation was 16% compared to 3% for those age 1–19 years old. All those who died had a symptomatic etiology [33]. The mortality rate of all patients without a known cause was no different than that of the general population. Analysis of a Finnish cohort of individuals with childhood epilepsy followed prospectively for 30 years found that SE did not affect mortality, after controlling for etiology [80]. Mortality in a London cohort followed for 8 year after CSE found etiology to be the main risk factor for mortality [79]. These population-based studies suggest that SE itself does not confer an increased risk of mortality, rather, similar to the short term mortality, it is the underlying etiology that is most predictive.

Some studies suggest that younger age is associated with increased mortality. In the Richmond cohort, the majority of all pediatric SE deaths occurred in the first year of life, 62% (23 of 37). SE mortality was low after the first year of life at 3% [33,60].

Refractory SE, expectedly, confers a higher risk of mortality with a wide range from 16 to 32%. The presence of generalized or multifocal epileptiform discharges, acute symptomatic etiology, and age <5 years old were risk factors for death [10,61].

8.3. Mortality by age

Mortality in children is much lower as compared to adults, as demonstrated in several studies of SE that included both children and adults. In a California based cohort of convulsive SE case fatality was 1.4% for ages < 5 years old and 2.4% for ages 5–19 years old, compared to 7.6% for 20–54, 16.1% for 55–74, and 19% for > 75 [5]. In the Richmond cohort, the mortality for pediatric patients was 3%, while the mortality of adults was 26%. In the Rochester cohort, short term (within 30 days of SE) the overall mortality was 19%, 84% of which was comprised of adults (age > 19 years old) [33]. The long-term mortality was 82% for patients above 65 years old and 32% between 20–64 years old. On the other hand, mortality was 16% for < 1 year old and 3% in the 1–19 years old group [59].

8.4. Outcomes with respect to time to treatment

A longer time to treatment has been associated with increased morbidity and mortality. In a prospective, observational cohort study of 218 pediatric SE patients, patients were divided into two cohorts: those who received a benzodiazepine within 10 min of seizure onset versus those who reeved a benzodiazepine after 10 min. Patients who received a benzodiazepine after 10 min had longer convulsive seizure duration (adjusted odds ratio (AOR), 2.6), were more likely to require a continuous infusion for treatment (AOR, 1.8), had more frequent hypotension (AOR 2.3), and were more likely to die (AOR 11) [62].

9. Conclusion

SE is among the most common neurologic emergencies in children. FSE is the most common cause of SE. The most important risk and prognostic factor is etiology, with symptomatic causes having worse outcomes. Children who have an acute symptomatic cause have a higher risk of recurrent SE and of developing epilepsy. SE carries significant cost, mortality, and morbidity making prompt diagnosis and treatment critical.

Conflict of interest

There are no conflict of interests to disclose for this paper. The authors alone are responsible for the content and writing of this article.

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