We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

6,400
Open access books available

174,000
International authors and editors

190M
Downloads

154
Countries delivered to

Our authors are among the

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter

Status Epilepticus in Children

Athanasios Covanis, Kyriakos Garganis,
Boulenouar Mesraoua, Rola Hosni Khodair,
Rasha K.M. Abumustafa and Thahira Thekkumpurath

Abstract

Status epilepticus (SE) is an acute, one of the most common, life threatening emergency condition in children and adolescence. According to the ILAE commission, SE is defined as a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures. Regarding duration, ILAE defines convulsive SE as bilateral tonic–clonic lasting longer that 5 minutes, and absence and focal status epilepticus as exceeding 10 minutes. Children compared to adults are more prone to epileptic seizures and as a consequence to SE, mainly due to age related maturational imbalance between excitatory and inhibitory synaptic mechanisms. The classification into generalised or focal, convulsive and nonconvulsive differ widely in aetiology, management and outcome. Early prehospital intervention with appropriate protective measures and emergency medication of seizure disorder, may prevent perpetuation of seizure recurrence. If first line treatment fails and or event, emergency hospital admission should be provided for more aggressive intravenous therapy, assessment-support.

Keywords: Status Epilepticus, Generalised, Focal, Nonconvulsive, Refractory status

1. Introduction

Status epilepticus (SE) is an acute, life threatening condition in paediatrics and a medical emergency consisting of persistent or recurring seizures. The incidence, is increasing as the detection abilities improve. SE is convulsive (CSE) and non-convulsive (NCSE), with convulsive being the most common neurological emergency in childhood. Prognosis is dependent on prompt emergency treatment of seizures and management of the underlying aetiology.

Status epilepticus was defined as continuous seizure activity or intermittent seizure activity without regaining consciousness, lasting ≥30 minutes [1]. This definition was based on believe that irreversible brain injury may occur after 30 minutes of seizure activity. To improve the defining pitfalls of the GTCS-SE Lowenstein et al. [2] proposed two distinct operational definition: an operational definition and a mechanistic definition. *Operational*: generalised CSE in adults and older children (>5 years old) refers to ≥5 min of (a) continuous seizures or (b) two or more discrete seizures between which there is incomplete recovery of consciousness. *Mechanistic:* Generalised, convulsive SE refers to a condition in which there is a

failure of the "normal" factors that serve to terminate a typical GTCS. This time frame for the generalised convulsive SE has guided towards when emergency treatment should be given. No time frame has been given for the other types of SE. A useful classical monograph on all types of SE in children and adults was written by Shorvon proposing age at presentation to be included based on the relationship with both aetiology and prognosis [3]. In the *report of the ILAE Classification Core Group* status epilepticus is reported as a broad term comprising of all types of epileptic seizures that fail to stop and last for over 30 min [4].

Based on the detailed analysis of more than 100 episodes of SE documented with video-EEG recordings [5] a semiological classification of status epilepticus relying on the same principles as the semiological seizure classification was also proposed.

2. Incidence

Status epilepticus is an acute, life threatening emergency condition that affects about 20 children per 100,000 child population per year [6–9] and remains a major problem in morbidity and mortality.

The North London Status Epilepticus in Childhood Surveillance Study (NLSTEPSS), the incidence of CSE was shown to be greatest in children under 1 year of age (51 per 100 000 per year) compared with those aged 1–4 years (29 per 100 000 per year), 5–9 years (9 per 100 000 per year) and 10–15 years (2 per 100 000 per year) [7]. In another study in Richmond Virginia the incidence of SE was 41 patients per year per 100,000 population and that in infants 156 per 100,000 compared with 38 per 100,000 in children and in the elderly [10].

The highest incidence in infancy and early childhood is mainly due to lower seizure threshold of the immature brain and to acute causes such as febrile illness.

3. Definition

According to the ILAE commission [11], SE is defined as a condition resulting from the failure of mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures (after time point t_1), and a condition that can have long-term consequences (after time point t_2), including *neuronal injury, neuronal death, alteration of neuronal networks and functional deficits*. It also distinguishes CSE from NCSE [11]. Regarding duration, ILAE distinguishes two operational time frame dimensions. *Time frame t1*: bilateral tonic–clonic SE lasting longer that 5 minutes, and absence and focal status epilepticus as exceeding 10 to 15 and 10 minutes respectively [11]. *Time frame t2*: the time when a seizure may cause long- term consequences. For tonic–clonic SE is 30 minutes, for focal SE with impaired consciousness above 60 minutes and for absence SE is unknown [11]. In the case of convulsive (tonic–clonic) SE, both time points (t_1 at 5 min and t_2 at 30 min) are based on animal experiments and clinical research [11]. Time frame t1 for tonic–clonic SE indicates the time an emergency treatment should be given. In addition with the sorter diagnostic time is expected to identify more patient with SE, confirmed in a population-based study in adults [12].

3.1 Refractory status epilepticus

Refractory status epilepticus (RSE) is defined as seizure activity that persists after administration of a first-line benzodiazepine (BZD) and a second-line

antiseizure drug [13]. Of the SE patients, between 10% and 40% develop refractory status epilepticus [9, 14, 15] with a mortality rate of 16–43.5% [16–18].

SE in defined electroclinical syndromes is usually not refractory in the majority of cases and SE in progressive symptomatic aetiologies is more frequently refractory.

3.2 Super-refractory status epilepticus

Super-refractory status epilepticus (SRSE) is defined as SE that continues or recurs 24 hours or more after the onset of anaesthesia, including those cases in which SE recurs on the reduction or withdrawal of anaesthesia [19]. The few epidemiological studies on SRSE are based mainly in adult population [20] indicating that 10–15% of RSE cases progress to SRSE [21, 22] and approximately one-third of RSE and SRSE patients die [21–23]. In children, a retrospective study showed that of 602 convulsive SE episodes, SRSE occurred in 7.14% [24].

Literature on SRSE in children is limited despite the morbidity associated with this disorder. Current clinical practice is challenged by the heterogeneous aetiologies and multiple factors involved in the progression from SE to RSE and SRSE. For this multicentre and multinational collaborative effort is desirable to evaluate epidemiological data on paediatric RSE/SRSE [25].

4. Diagnosis

Detail history should include information preceding, during and after the event. Other general relevant information. Previous drug administration. Detail examination, differential diagnosis, routine investigations, and management.

Prompt recognition, and diagnostic evaluation of the child in SE will help identify causes, which may require specific treatment, and help in the management of this life-threatening condition. It is important to treat the precipitating cause in order to control SE, with symptomatic SE more common in younger children and infants. Routine haematological and biochemical profile is important. Assessing blood levels for commonly used anti-seizure medication may help to identify cases with epilepsy, where there is no available history, and blood levels are very low. Indeed noncompliance with treatment is one of the most frequent cause of SE in children with epilepsy. Another common aetiology of SE in children is neuro-infection. Laboratory work (haematological and biochemical profile), a CT for structural lesion following the emergency and aggressive treatment, electroencephalogram or continuous video electroencephalogram, lumbar puncture, MRI at a later stage if necessary, and even genetic testing may be considered in the evaluation of the child in status epilepticus.

4.1 Electroencephalography

The EEG is useful for the diagnosis of subtle status as in cases with focal impaired awareness, absence status and for any case presenting with altered consciousness without obvious cause. In addition continuous EEG monitoring helps to monitor response to treatment. In a study of 64 patients who were clinically controlled the EEG demonstrated persistent seizures in 48%, and 14% of these patients had NCSE, predominantly of the complex partial type [10, 26]. In comatose cases EEG can show a variety of rhythmic of periodic patterns, some of which are of unclear significance. Continuous-EEG (C-EEG) in children with acute encephalopathy and Status Epilepticus, in the Paediatric Intensive Care Unit (PICU), is

strongly recommended as a standard diagnostic approach, although its applicability depends much on available resources and practices, which differ among institutions [27, 28]. Available data indicate that an increasing number of critically ill children with acute encephalopathy undergo C-EEG in large hospitals, and more physicians are ready to utilise multidrug regimes and anaesthetics in order to abolish Electrographic Status Epilepticus and Electrographic Seizures [27, 29, 30]. Those Electrographic Seizures that are accompanied by overt, or, subtle clinical manifestations are labelled as *Electroclinical,* whereas those without clinical manifestations as *Subclinical.* The aims of Continuous -EEG in this particular setting are several-fold [28]:

a. Confirmation of epileptiform activity, providing necessary proof of an implicated epileptogenic process.

b. Monitoring not only for the presence of Status Epilepticus but also for Electrographic ones (either Electroclinical, or, Subclinical according to previous definitions). Also, to confirm the nature of clinical signs of uncertain significance, such as tonic phenomena, myoclonus, changes in autonomic function, etc.

c. Guide antiepileptic drug-treatment depending on clinical and electrographic response obtained after each intervention.

d. Confirm resolution of Status Epilepticus /Electrographic Seizures and concomitant encephalopathy.

4.2 Neuroimaging

Neuroimaging is of utmost importance for identifying the aetiology of Status Epilepticus, revealing acute lesions requiring surgical treatment and potentially for prognostication. Computed Tomography (CT) reveals abnormalities (and more reliably haemorrhage, trauma, mass lesions) in 15–33% of patients. Although CT is the most readily available imaging modality in the Emergency Setting, Magnetic Resonance Imaging (MRI) is the modality of choice, being more sensitive than CT in identifying small lesions (inflammation, small tumours, and cortical malformations). Combined CT/MRI studies detect abnormalities in 30–36% of cases. Neuroimaging may lead to urgent interventions in 8.5%, following detection of acute lesions (i.e. haemorrhage and neoplasms) [31].

Periictal MRI abnormalities attributable to Status Epilepticus per se, have been reported in about 11%, of cases; their exact incidence remains uncertain, however, as there may be some overlap with changes of inflammatory and autoimmune aetiology, Status Epilepticus – induced periictal abnormalities appear as T2 & FLAIR increased signal areas, along with high signal in diffusion-weighted (DWI) and low apparent diffusion coefficient (ADC). The changes reflect variable and dependent on MRI timing combinations of cytotoxic (with increased DWI and decreased ADC signal) and vasogenic (increased DWI and T2 without decreased ADC signal) edema [32]. Their incidence ranges between 12 and 50% in retrospective series, depending on timing of the MRI study during the time-course of Status Epilepticus; they are more likely to be detected if the MRI is performed during the course of Status, or shortly after its cessation, compared to more remote time points. In cases of focal Status they appear over the cortical area of ictal activity, thus providing potentially useful localising cues. They also selectively involve particular brain regions and networks, including the medial temporal limbic areas,

pulvinar thalamic nuclei, claustrum, basal ganglia, corpus callosum splenium, insular cortex and cerebellum. In particular, Lateralized Periodic Discharges (LPDs) on the EEG, especially in cases of long-lasting Status Epilepticus, are strongly associated with periictal MRI changes, at the area of LPD localization, along with homolateral pulvinar involvement. Although these MRI changes are often completely reversible, in cases of protracted Status Epilepticus may be followed by permanent structural alterations, such as cortical laminar necrosis, medial temporal sclerosis and cortical atrophy.

CT perfusion, MRI perfusion sequences and Arterial Spin Labeling (ASL) are also useful techniques that may reveal focal hyperpefusion in the areas corresponding to ictal activity, in cases of Non-Convulsive Status Epilepticus (NCSE). ASL sensitivity approaches nearly 100% in one study, while CT shows regional hyperperfusion in NCSE with a sensitivity of 78%, all with good concordance to EEG ictal origin localization, if applied early in the course of Status. The shorter CT Perfusion acquisition time is more preferable in the Emergency setting for critically ill patients, as compared to the longer duration required for an MRI study.

Also ictal/substraction ictal SPECT is a useful test in patients with focal NCSE and in conclusive EEG findings, particularly for patients in whom surgical treatment is being considered [33].

5. Aetiology

Status epilepticus in the paediatric extended period may occur from neonatal (0–30 days), infantile (1 month to 2 years), childhood (2 to 12 years), to adolescent (12 to 18 years) age. The aetiology is relevant to the child's age and is the main factor that determines outcome.

In infancy and early childhood febrile illness is the main cause acting on an immature brain and on a genetically predisposed individual. SE in a previous neurologically normal child aged between 6 months and 5 years can occur, during febrile illness (temperature > 38°C), in the absence of CNS infection. Febrile SE accounts about one third of cases in SE of childhood [21, 34, 35] and neuro-infection is the most common aetiology of SE in childhood. In cases known to have epilepsy noncompliance, inappropriate treatment, abrupt withdrawal of chronically used benzodiazepines, phenobarbitone or discontinuation due to side effects, may trigger SE. There are multiple aetiologies and they differ according to age of the child. A detail age related aetiologies are shown in **Table 1.** In many cases, SE can be the first unprovoked manifestation of a seizure disorder.

As per ILAE report on classification of SE, the aetiology is divided in three categories: known/symptomatic: acute (e.g., stroke, intoxication, malaria, encephalitis, etc.) remote (e.g., posttraumatic, postencephalitic, poststroke, etc.), progressive (e.g., brain tumour, Lafora's disease and other PMEs), SE in defined electroclinical syndromes and unknown/cryptogenic [11]. While in children less than 3 years old, the acute symptomatic aetiology and febrile SE aetiologies are considered as the most common, in most children older than 3 years old the most common aetiology of SE is remote or unknown (**Table 1**). In general about 50% of children with the first episode of CSE may have or may not have pre-existing neurological abnormalities, including epilepsy. Although most studies do not differentiate aetiologies according to seizure types the majority are relevant to GTC-SE.

In 1989 Maytal et al. studied 193 cases with SE, age range one month to 18 years (mean 5.0). The divided aetiology in two groups. Group 1: 137 cases, Idiopathic 46 (24%), remote symptomatic 45 (23%), and febrile 46(24%). Group 2: 56 cases,

Neonatal period/infancy
I. **Acute symptomatic SE**
- Hypoxic-ischaemic encephalopathy
- Perinatal stroke
- Intra-ventricular haemorrhage
- Structural brain abnormalities
- Metabolic disorders
- Febrile illness
- Genetic

In Infancy/childhood/adolescent
- CNS febrile illness (meningitis, encephalitis)
- Hypoxia, anoxia
- Metabolic derangements (diabetic, renal, hepatic, hypoglycaemia, non-ketotic hyperglycaemia, other)
- Traumatic brain injury
- Known case with epilepsy: noncompliance, AED withdrawal (usually abrupt), AED discontinuation for SEs, drug overdose.
- Toxins and poisons
- Acute electrolyte imbalance (hypocalcaemia, hyponatremia, hypomagnesaemia, and other)

II. **Remote symptomatic SE**

Infancy/children
- Cerebral dysgenesis
- Perinatal hypoxic-ischaemic encephalopathy
- First manifestation of an epileptic disorder
- Brain tumour, absence, tuberculosis and malaria common in resource-poor countries

III. **Progressive neurodegenerative disorders**
- Progressive symptomatic SE

IV. **SE in well-defined epileptic syndromes-Idiopathic**

Unknown SE: Status epilepticus that could not be classified into any other group

Table 1.
Aetiology of Status Epilepticus.

acute symptomatic 45(23%) and progressive neurologic 11 (6%). During the 13.2 months follow-up, 7 died within 3 months of having the seizure. All deaths and 15 out of 17 sequalae occurred in the 56 children with acute or progressive neurologic insult (Group II). The rest 2 that sustained new sequalae were from the 137 of Group I. New neurological defects were found in 17 (9.1%) of 186 [36], (**Table 2**).

From a large Richmond SE study [10, 41] the major aetiology in children under 16 years was infection with fever, accounting for 52% of cases, remote symptomatic for 39% and low AED levels for 21% of cases. All other aetiologies represented less than 10% of cases (**Table 2**). In 2004 Chin et al. [37] identified the following aetiologies that require intensive care management during childhood: Prolonged febrile convulsion 31%, acute symptomatic 24%, idiopathic/cryptogenic 24%, remote 11%, acute on remote 8% (SE within a week of an acute neurological insult or in a child with previous neurological abnormality e.g., cerebral palsy, post haemorrhagic hydrocephalus) and 2% unclassified (**Table 2**). In 2019 Specchio et al. [38] retrospectively studied 173 children (mean age 4.43 ± 4.93 years old) treated for SE exceeding 30 minutes acute symptomatic was found in 32.3%, remote symptomatic in 29.5%, progressive symptomatic in 17.3%, unknown in 16.2% and idiopathic (cryptogenic) in 4.6%. Acute symptomatic, the most represented aetiology occurred mostly in the neonatal period, that is, the 51.6% of the SE in the population younger than 12 months of life [38], (**Table 2**). The association between acute symptomatic SE and younger age (under 1 year) has also been reported by others [10, 36, 42–47].

In a recent 2020 retrospective cross-sectional study of 119 patient aged from one month to 15 years [39], the most common aetiologies were acute symptomatic and febrile SE occurred in 32.8% and 22.7% respectively and remote symptomatic in

Aetiology	Maytal et al. [36]	DeLorenzo et al. [10, 41]	Chin et al. [37]	Specchio et al. [38]	Vafaee-Shahi et al. [39]	Das et al. [40]
Infection with fever	24%	52%	31%		22.7%	
Acute symptomatic	23%		24%	32.3%[*]	32.8%	68% (46.80% CNS infection
Remote symptomatic	23%	39%	19%	29.5%	16.8%	
Low AEDs levels		21%				
Idiopathic/ cryptogenic	24%		24%	4.6%		
Progressive/ symptomatic	6%			17.3%		
Unclassified Unknown			2%	16.2%		
Other		10%				
History of seizures						35.1% (42.4% drug default)
SE the 1st episode of seizure						64.9%

[*]*Acute symptomatic occurred mostly in the neonatal period, that is in 51.6% of the SE in the population younger than 12 months of life.*

Table 2.
Aetiology of status epilepticus from neonatal period to childhood.

16.8% aetiologies were the most common underlying causes of S.E. While in children less than 3 years old, the acute symptomatic aetiology and febrile status SE aetiologies were estimated as the most common, in most patients older than 3 years old the most common aetiology of SE was unknown. Furthermore, aetiology appears an important predictor of mortality and morbidity [39], (**Table 2**).

In another 2020 prospective cohort, children aged 1 month to 14 years with SE, as per new ILAE's guideline, 94 cases were assessed regarding clinical profile, treatment and outcome [40]. The majority of children, 60 (63.82%), were less than five years of age. Prior history of seizures was present in 33 (35.1%) cases, whereas 61 (64.9%) cases presented with SE as the first episode of seizure. In 14 (42.4%) previous seizure cases, SE was due to drug default. No response to first-line antiepileptic drug (AED) was seen in 84 (89.37%) cases. Acute symptomatic aetiology was the commonest aetiology of SE in 64 (68%) cases, of which neuro-infections accounted for 44 (46.80%) cases. Longer duration (>60 minutes) of status (p < 0.01), ventilator support (p < 0.0001), and circulatory impairment (p < 0.0001) were attributable risk factors for mortality. A total of 28 children died (mortality rate, 29.8%), and 11 showed the persistence of their neuro-deficit **Table 2**, [40].

6. Classification of status epilepticus

Status epilepticus is semiologically classified for the prominent motor symptoms or convulsive (bilateral tonic–clonic, focal motor, myoclonic, tonic, and

hyperkinetic SE) and SE without prominent motor symptoms or nonconvulsive SE (NCSE). The majority of SE in children is convulsive, generalised or focal secondary generalised (impaired awareness) [10, 21].

6.1 With prominent motor symptoms

6.1.1 Generalised tonic–clonic status epilepticus (GTC-SE)

A GTC seizure becomes a GTC-SE when it fails to terminate spontaneously within 5 minutes without the use of medication. In accordance with the recent guidelines from the International League Against Epilepsy [11] a GTC seizure becomes a GTC-SE when it lasts more than 5 minutes (time point t1) entering into a self-perpetuating, self-sustaining phase either continuously or intermittently without full recovery between the seizures. Time point one is the suggested time at which emergency treatment should be given. When GTC seizures last 30 minutes (time point t2) or more may cause long term consequences including neuronal injury, neuronal death, alteration of neuronal networks and functional deficits [11]. Therefore, prolonged seizures of SE result from failure of mechanisms of seizure termination or activation of mechanisms that sustain seizures. SE is a condition that can have, after time point t2, long term consequences such as neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures [11]. Although the mechanisms that self-perpetuate prolonged seizures are not known, a hypothesis that enhanced alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor transmission plays an important role in sustaining SE is proposed [48]. GTC-SE is the most dangerous type due to the underlying cardiac arrhythmias, blood pressure changes, and breathing and oxygenation difficulties. GTC-SE can be an acute symptomatic event, primarily GTC-SE in idiopathic or symptomatic generalised epilepsies and commonly secondarily GTC-SE in focal epilepsies [4]. Occasionally the clinical manifestation can be unilateral [4]. The Initial violent convulsions progressively reduce in frequency and intensity and transform to a tonic state followed by irregular jerking which may become subtle mild facial clonic or jerking. Subtle electroclinical features may continue longer than the overt GTC-SE symptoms or even may be subtle from start in comatose patients [49].

The pathophysiological changes of GTC-SE can be divided into *compensatory phase* most likely begins 5–7 min after onset and lasts around 30 minutes. During this period compensatory mechanisms prevent brain damage from hypoxia or metabolic aberrations [50].The *refractory stage or established phase* starts approximately 30 minutes after the onset of the compensatory phase [50] although this time may vary [2]. During this stage the cerebral metabolic demands cannot be met resulting in hypoxia, cerebral autoregulation fails, cerebral blood flow drops and a reduction of brain oxygen, glucose and lactate. Intracranial hypertension and oedema will follow. Systemic and metabolic changes involve hypoglycaemia, hyponatraemia, hypo or hyperkalaemia, metabolic and respiratory acidosis. Hepatic, renal and cardiorespiratory dysfunction and failure, systemic hypoxia, falling blood pressure and cardiac output ensue. In more than 10% of patient treated for GTC-SE, clinical symptoms stop or become subtle while electrical seizures continue [26]. During prolonged GTC-SE the electroclinical features become subtle though the prognosis is worse than any other stage of GTC-SE [51]. Pharmacoresistance during GTC-SE is progressive and time-dependant. Benzodiazepines within the first 30 minutes of status, lose their efficacy [52] while this for phenytoin and phenobarbitone is slower and usually drives to higher doses and toxicity. Alternative N-methyl-D-aspartate (NMDA) blockers such as ketamine are effective in stopping GTC-SE [53].

6.1.2 Generalised tonic status epilepticus

A tonic seizure is sustained increased in muscle contraction lasting a few seconds to minutes. A characteristic tonic seizure: the neck and head is flexed and the arms are flexed at the elbow and slightly elevated. Such episodes are usually brief or may continue at brief intervals for hours (tonic SE). Generalised tonic SE is a rare event that occurs predominantly in children and adolescents though has been reported in adults.

Aetiologically is connected to symptomatic epilepsies, particularly epileptic encephalopathies in the Lennox–Gastaut syndrome (LGS).The interictal EEG in children with LGS will show typical high amplitude spike–wave pattern <2.5 Hz or generalised fast activity >10 Hz condensed during sleep. The ictal EEG is characterised by voltage suppression or desynchronization patterns intermixed with fast activity. Pathophysiology, brain changes, and management, is not particularly different from GTC-SE.

6.1.3 Generalised myoclonic status epilepticus

Myoclonic seizures are brief, sudden, involuntary muscle contractions (< 100 ms) that may involve the whole body or part of the body (focal, segmental) and may be single, or repetitive, rhythmic or arrhythmic, unilateral or bilateral (massive), symmetrical or asymmetrical. Myoclonic status epilepticus (MSE) consists of irregular, usually bilateral or generalised myoclonic jerks without interference with consciousness. Duration may be up to many hours. Most often is seen in uncontrolled juvenile myoclonic epilepsy, Dravet syndrome and MSE in nonprogressive encephalopathies, particularly Angelman syndrome. Like the myoclonic seizures, MSE can be generalised or focal, idiopathic, unknown or symptomatic.

In idiopathic generalised epilepsies myoclonic SE is usually triggered by misusing precipitating factors and the use of inappropriate AEDs. It can be seen most commonly in juvenile myoclonic epilepsy where mental status is usually unaffected. Myoclonic SE is rarely seen in myoclonic-atonic seizures (Doose syndrome), Facial (perioral) myoclonia with absences, epilepsy with myoclonic absences and eyelid myoclonia and absences (Jeavons syndrome). During the prolonged MSE the patient may become mildly impaired and incapacitated by the frequent jerks.

Symptomatic /unknown myoclonic SE is commonly seen in progressive myoclonic epilepsies, epilepsy with myoclonic-atonic seizures (the symptomatic forms), infectious/inflammatory diseases, toxic-metabolic encephalopathies and anoxic-ischaemic injuries.

Prognosis of MSE is dependent on the underlying aetiology. The outcome is good in idiopathic group and variable in the symptomatic MSE. In symptomatic group the prognosis is good if the aetiology is reversible (e.g. drug intoxication) and almost always poor in degenerative conditions and in anoxic brain injury.

6.1.4 Febrile status epilepticus

Febrile seizures are seizures associated with febrile illness (temperature > 38°C) without of an intracranial cause (infection, trauma) or another definable cause of seizure (e.g. electrolyte imbalance, hypoglycaemia, drug use, or drug withdrawal), and without a history of prior afebrile seizures [54–58].

Febrile seizures (FS) are classified as simple when they are brief, generalised and isolated and as complex if they are prolonged (>10 minutes), focal or multiple.

Febrile-SE (≥ 30 minutes) is considered the extreme end of the complex FS spectrum [57, 59].

Febrile seizures are common in children aged 6 months to 5 years, affecting 2–8% of children [60, 61]. Up to 10% of children with FS develop FSE, which accounts for 25% of all childhood SE and more than two thirds of SE in the second year of life [62]. Febrile status is the commonest cause of CSE in childhood. The peak incidence is between 12 and 24 months and is rare in children over the age of 5 years [63]. Furthermore, CSE in childhood is associated with fever in 54% of patients (8). In children older than 5 years febrile CSE may be part of the epilepsy syndromes such as Dravet syndrome or generalised epilepsy FS plus. Viral infection is the cause of fever in approximately 80% of cases of FS [64].

It is important for the correct diagnosis a detailed and accurate history completed with a detailed neurological and clinical assessment. The clinical evaluation should focus primarily on identifying the causing the fever, aetiology and treat appropriately. If the child is still convulsing emergency stabilisation of vital signs providing respiratory support should take place in parallel to emergency investigations and treatment. Computed tomography (CT), MRI, electroencephalography (EEG), or a combination of these may be considered in children with prolonged SE or recurrent FS or who present with neurological abnormalities to rule out the presence of neurologic conditions.

Febrile seizures result from the age dependant response of the immature brain to fever in combination with an underlying genetic predisposition and environmental factors [57, 65]. During the maturation process, there is an enhanced neuronal excitability that predisposes the child to febrile seizures [66]. As such, febrile seizures occur mainly in children before the age of 3 years when the seizure threshold is low [66]. The genetic predisposition is supported with the positive family history. The risk for febrile seizure for a child is about 20% with an affected sibling and about 33% with affected parents [55].The concordance rate is about 35–69% and 14–20% in monozygotic twins and dizygotic twins, respectively [55]. Several genes have been reported that might increase the risk for a febrile seizure. These genes have been mapped to following loci of chromosomes: 1q31, 2q23-34, 3p24.2-23, 3q26.2-26.33, 5q14-15, 5q34, 6q22-24, 8q13-21, 18p11.2, 19p13.3, 19q, and 21q22 [67] *and* emphasise the genetic heterogeneity of febrile seizures. Recurrent and prolonged FS are associated with Dravet syndrome and GE-FS plus. Children with these two syndromes often present with recurrent seizures with fever including febrile CSE, which on initial presentation may be indistinguishable from febrile convulsions. It is often only later, with the emergence of afebrile seizures or continuation past the age for febrile convulsions that the diagnosis is made. As a consequence of FSE overt or subtle changes have been allocated in hippocampus that need longer follow-up to determine the relation of these findings to temporal lobe epilepsy [68]. Focal EEG slowing or attenuation are present in EEGs obtained within 72 hours of FSE in a substantial proportion of children and are highly associated with MRI evidence of acute hippocampal injury. These findings may be a sensitive and readily obtainable marker of acute injury associated with FSE [69]. Furthermore from the same group of authors is reported the involvement of IL-1 system and related cytokines in the development of FSE in children, as well as potential biomarker of patient at risk in developing mesial temporal lobe epilepsy [70].

The presenting seizures of febrile CSE may be tonic, clonic, or tonic–clonic. Up to 35% of febrile CSE has a focal onset [63]. Simple febrile seizures account for about 80–85% of all febrile seizures [55, 56]. Loss of consciousness at the time of seizure is a constant feature and foaming at the mouth, difficult breathing, pallor, or cyanosis may also occur [71].

It is important to differentiate prolonged febrile seizures and brain infection as the morbidity and mortality associated with untreated bacterial meningitis is considerable. In a population based study up to 20% of children with CSE and fever have been shown to have brain infection [6, 8]. The proportion of children who have short seizures associated with fever that are subsequently diagnosed with brain infection is 1–2% and therefore the presence of SE dramatically increases the risk [72]. This been the case brain infection should be considered in all children with CSE associated with fever. In a prospective cohort study [47] it was suggested that previously neurologically intact children presenting with an acute febrile illness or acute symptomatic cause of convulsive SE who survive, have a low risk of developing new, long-term neurological morbidity.

6.1.5 Focal status epilepticus

A focal seizure becomes focal Status Epilepticus with impaired awareness when it last more than 10 minutes (time point t1) and may cause long term consequences when exceeds 60 minutes (time point t2)[11]. A percentage of 11–29% of SE children present as focal seizures only with or without alteration of consciousness [10]. Repeated focal motor seizures (Jacksonian) and Epilepsia partialis continua are characteristic examples of prolonged-repeated focal seizures.

6.2 Nonconvulsive status epilepticus

Nonconvulsive status epilepticus (NCSE) is a heterogenous disorder, more common in children, elderly and the critically ill. NCSE, particularly in children has high potential for comorbidity, is underdiagnosed, and as yet do not exist specific guidelines regarding diagnosis, management and prognosis. According to the ILAE commission NCSE is a SE without motor symptoms and is divided in NCSE with coma (including subtle SE) and NCSE without coma [11]. The latter is further divided into generalised (typical absence SE, atypical SE, myoclonic absence SE), Focal (without impairment of consciousness, aphasic status, with impaired consciousness) and unknown whether focal or generalised e.g., autonomic SE [11]. In paediatric ICU 550 children who had received intensive EEG monitoring, one in ten, found to have NCSE (30% of the cohort had at least one nonconvulsive electrographic seizure, and 33% of those with nonconvulsive seizures also had NCSE) [30]. Furthermore, those cases with convulsive SE that evolve to NCSE have a history of epilepsy and the presence of interictal epileptiform discharges in their initial background EEG [73]. NCSE is particularly common in several paediatric syndromes such as malignant migrating focal seizures in infancy, Dravet syndrome and in myoclonic atonic seizures (Doose syndrome), Lennox–Gastaut syndrome, and Panayiotopoulos syndrome. It is also seen in metabolic disorders, in acute cerebral lesions and in some syndromes associate with epilepsy in which NCSE is a common and prominent feature e.g. Angelman syndrome, Ring 20 chromosome syndrome, Wolf-Hirschorn syndrome (4p-), and severe cortical malformation e.g. polymicrogyria/lissencephaly. De novo NCSE is rare in childhood associated with several acute symptomatic etiologies.

A case with NCSE usually presents with an episode or recurrent episodes of alter behaviour, mental state, confusion, lethargy, disturbed fluent communication, agitation, hallucination without overt convulsive movements. Subtle motor signs such as twitching, blinking or eye movement may be observed. The clinical suspicion, neurological assessment and an EEG is necessary to correctly diagnose NCSE, and assess response to treatment and follow-up. If an EEG is not easily available, the event did not follow a GTCS, the child has no epilepsy and the routing

investigations failed to identify a treatable cause a timely therapy of first line benzodiazepine should be introduced and observe for clinical improvement. Even if there is a clinical improvement, an emergency EEG with a restricted electrode placement, is important for the diagnosis NCSE and use a continuous EEG monitoring for assessing the underlying electrical activity and treatment response as per existing guidelines. If the repeat dose of benzodiazepines fails, the second and even third-line treatment should be planned. A timely therapy may help to cease electroclinical activity and prevent neurologic sequelae.

In infancy and early childhood there is a devastating group of epileptic disorder, "epileptic encephalopathies" that although there are not discussed under the heading of NCSE, have many similarities. Epileptic encephalopathies are a heterogenous group of brain disorders occurring at a critical period of brain development in which the frequent abnormal ictal (seizure) and or interictal epileptiform activity is mainly responsible (idiopathic/genetic) or contributes (unknown/cryptogenic) to severe behavioural, psychiatric, cognitive and or motor slowing or regression (mental and neurological decline) [74]. The electrical activity may become persistent, perpetuating hyperexcitactivity and in seizure prone regions altering networks, seizure semiology and response to treatment [75]. Examples of such an epilepsy encephalopathies are: infantile spasms, Lennox–Gastaut syndrome, Landau–Kleffner syndrome (**Figure 1**) and Epileptic encephalopathy with continuous spike-and- wave during sleep. The electrical SE of LGS and the latter two syndromes can be differentiated clinically e.g. focal motor seizures often occur in electrical SE during slow sleep but are rare in LGS and tonic seizures commonly occur in LGS. Clinically in NCSE important deficits involve: consciousness (reduced vigilance, reactivity and orientation), speech, praxis, and cognitive higher functions, such as apraxia, acalculia, alexia, and aphasia with or without memory disturbance. Based on clinical semiology alone, diagnosis is difficult and requires emergent EEG, preferably video-EEG. Our primary aim regarding epileptic encephalopathies is not only to treat the ictal electroclinical events but also the

Figure 1.
Landau–Kleffner syndrome. EEG: A 4 years old boy with a four month history of linguistic, cognitive and behavioural disturbances referred from the psychology department for assessment. The EEG, particularly during NREM sleep-figure revealed subclinical continuous generalised, high amplitude spike-slow wave discharges with no obvious clinical symptoms during EEG.

underlying electrical activity mainly responsive for cognitive dysfunction/regression.

6.2.1 Absence status epilepticus

Typical absence seizures are non-convulsive generalised epileptic seizures characterised by an abrupt onset and termination of a brief, complete or partial loss of consciousness that is accompanied by a generalised, synchronous, bilateral 2.5–4 Hz spike- or polyspike-slow wave discharges in the EEG. Absence status epilepticus (ASE) may occur in 5–16% of cases, with typical absence seizures starting before the age of 10 years [76]. Absence status is rare among children in population based studies (0–3%) [10]. An absence seizure becomes ASE when lasts more than 10 to 15 minutes (time point t1). The time point t2 that may cause long term consequences has not as yet been defined [11].

ASE is a prolonged, generalised, nonconvulsive electroclinical activity characterised by mild, intermittent, moderate or severe impairment of consciousness at times associated with other clinical manifestations such as automatisms or subtle myoclonic, atonic, tonic, automatisms or autonomic components. These symptoms may be continuous or repetitive with no full recovery in-between before complete recovery. An ASE may last for hours or even days characterised by periods of vague looks, unresponsiveness, inappropriate behaviour, or responses, luck of response or appropriate response. ASE may occur in children with idiopathic generalised epilepsies such as childhood absence epilepsy, Juvenile absence epilepsy and in syndromes where absence seizures and myoclonic seizures are the predominant seizures in the phenotype e.g. Eyelid myoclonia and absences (Jeavons syndrome), Facial (perioral) myoclonia with absences, Epilepsy with myoclonic absences (Doose syndrome). The diagnosis of ASE should be suspected in any child who has a prolonged episode of altered responsiveness and should be confirmed by an EEG. The ictal EEG is characterised by generalised SW or (poly)-SW discharges of 1-4 Hz. The background inter-ictal activity may be normal or abnormal relevant to underlying epileptic syndrome idiopathic, symptomatic, or unknown aetiology. Brief or long runs of spikes or spike (poly)-spike–wave discharges maybe recorded.

Atypical absence status occurs mainly in children with LGS and are characterised by fluctuating impairment of consciousness, often with other ictal symptoms (serial tonic or atonic and segmental or generalised jerks). The onset and termination is gradual. The ictal EEG pattern is slow less than 2.5 Hz of generalised spike–wave or polyspike-wave activity. Most children have moderate to severe cognitive dysfunction.

Misdiagnosis and use inappropriate medication (sodium channel blocker drugs) for idiopathic generalised epilepsy may trigger absence or myoclonic SE [77]. Other trigger factors maybe abrupt withdrawal of certain drugs, electrolyte or metabolic disturbances.

6.2.2 Autonomic status epilepticus

Autonomic SE is a condition lasting at least 30 minutes and characterised by epileptic activity causing altered autonomic function of any type at seizure onset or in which manifestations consistent with altered autonomic function are prominent (quantitatively dominant or clinically important) even if not present at seizure onset [78]. Autonomic seizures and autonomic SE are the hallmark of Panayiotopoulos syndrome and are frequently misdiagnosed and often treated as encephalitis, atypical migraine, cardiogenic syncope, or other unrelated medical conditions such as gastroenteritis [79]. Autonomic seizures in Panayiotopoulos

syndrome consist of episodes of disturbed autonomic function with emesis as the predominant symptom. Other autonomic manifestations include pallor (or, less often, flushing or cyanosis), mydriasis (or, less often, miosis), cardiorespiratory and thermoregulatory alterations, incontinence of urine and/or faeces, hypersalivation, and modifications of intestinal motility [79]. In approximately one fifth of the seizures the child becomes unresponsive and flaccid (ictal syncope) before or often without convulsions. The child, who was initially fully conscious, becomes confused and unresponsive. Eyes turn to one side or gaze widely open. Only half of the seizures end with brief hemiconvulsions or generalised convulsions. Convulsive status epilepticus is extremely rare. Autonomic symptoms may be the only features of the seizures. Half of the seizures in Panayiotopoulos syndrome last for >30 minutes, thus constituting autonomic status epilepticus, which is the more common nonconvulsive status epilepticus and the second in frequency after febrile SE in normal children. Two thirds of seizures occur during sleep [79]. The ictal EEG unequivocally demonstrates the epileptic nature of the autonomic manifestations. These may start long after the onset of the electrical ictal activity and are characterised as breathing irregularities, tachycardia, retching, nausea,vomiting which continue for many minutes and impossible to consider as an epileptic event without an EEG. The seizure discharge is characterised of rhythmic theta or delta activity intermixed with low amplitude spikes. The interictal EEG reveals multifocal, functional, high amplitude, sharp-slow-wave complexes with posterior predominance. The prognosis is remarkably benign (except for the symptomatic cases) with complete recovery after hours [80–82]. Despite the dramatic and long lasting onset of clinical presentation, no immediate or long-term sequelae have been reported in Panayiotopoulos syndrome, a self-limited epileptic syndrome. The EEG characteristics in patients with autonomic seizures, including autonomic SE are relevant to the syndrome than specific to seizure-type.

7. Treatment of CSE

Prolonged seizures of any type are associated with an increased risk of complications, and the time from seizure onset to treatment is critical. Longer seizure duration increases potential risk of short-and long-term morbidity. Indeed prior studies have shown that early treatment of SE by emergency medical services leads to improved outcomes [83–85].

All the treatment guidelines share similar framework of managing SE but there is no standardised treatment protocol suggested for prolonged seizures that all emergency medical services follow. Many differences may reflect of local practice options in health service delivery.

In general children may have a CSE at home, school or in the community. It is therefore, important the community at large to be well informed about epilepsy, epilepsy seizures and the emergency care of any person with epilepsy. Awareness and education is of primary important. For cases that have epilepsy special information should be directed to parents and or carers that ideally should be passed to the school personnel for general and specific emergency treatment.

The goals in the emergency management of SE are to maintain vital functions, stop seizures, and identify and treat any underlined cause [86]. In this way we prevent any neuronal damage caused by systemic and metabolic disturbances and the ictal-interictal continues discharges. The risk for any brain damage is relevant to the duration of seizure and increases if the seizure persists for more than 30 min. Treatment management of seizures particularly convulsive is given in pre-hospital and hospital settings.

7.1 *Pre-hospital management*: early emergency under 10 min of seizure onset

Pre-hospital options include: rectal diazepam, intranasal/buccal midazolam, intranasal/buccal lorazepam. The choice of the preferable emergency pre-hospital route treatment is relevant to availability, affordability and child's age.

The first 5 minutes from seizure onset are occupied to secure protection from injuries and free airways. The treatment objectives are to maintain adequate airway, breathing, circulation and subsequently administer available appropriate medication to terminate the seizure as soon as possible.

Rectal diazepam is the most commonly used medical treatment for infants and early childhood. For late childhood and adolescence, particularly in females, should be used either buccal or preferably intranasal midazolam or even lorazepam at home and or social settings. An easy route and more socially accepted.

Diazepam can be given rectally 0.5 mg/kg for age 2–5 years, 0.3 mg/kg for children 5 to 12 years, and 0.2 mg/kg in adolescent (maximum 20 mg). A second dose, if needed, can be given five minutes after the first dose. The intramuscular route, is not recommended due to slow and erratic absorption. Diazepam has a long elimination half-life but only short lasting anti-seizure effect of 15–20 minutes. Diazepam is a good agent to arrest SE, but should not be used in combination with phenobarbital because of the risk of hypotension and respiratory depression, particularly in infants.

Midazolam buccal/intranasal: 0.3 mg/kg, intramuscular: 0.2 mg/kg. Maximum dose is 10 mg. Midazolam has a rapid onset anti-seizure effect observed within one minute after IV administration. Second dose is recommended if seizures continue five minutes after first dose. The buccal and preferably the nasal routes have replaced rectal diazepam for the management of seizures by the parents and caregivers. Oral absorption is less reliable. Midazolam has a short duration of action and in children who stop convulsing after the initial dose may require a repeat dose to maintain seizure control.

Lorazepam buccal/intranasal: 0.1 mg/kg, maximum 4 mg, is less effective than IV lorazepam as first line treatment for acute seizures but may be useful in children without or with difficult IV access.

7.2 Hospital setting

The aim is to terminate seizure, refractory SE, prevent relapse and to diagnose and treat early underlying aetiologies and biochemical disturbances.

Treatment of CSE in hospital setting is likely to be more effectively successful if a systematic approach is adopted following guidelines. The initial statement should refer to the important assessment of airway, breathing and circulation when the child arrives in the emergency department. Initial assessment should aim to exclude underlying acute symptomatic aetiology e.g. CNS infection associated with fever. It has been reported that 1–2% of children with brief seizures and fever have meningitis, compared with 10% of children with 30 minutes seizures associated with fever [72]. Taking into consideration what treatment was given before arriving to hospital, first-line treatment include: IV diazepam, lorazepam, midazolam, or clonazepam should be given.

Diazepam: 0.1–0.4 mg/kg (maximum 10 mg). Diazepam has a median anti-seizure effect within two minutes of IV administration. The slow IV bolus administration not exceeding 5 mg/min is recommended to avoid respiratory depression.

Lorazepam: 0.05–0.1 mg/kg (maximum 4 mg/dose), administered in slow IV bolus over 2–5 minutes not exceeding 1-2 mg/min. Lorazepam is a preferred benzodiazepine because it has rapid (under 2 minutes) across blood–brain barrier and

relative long half-line with an effective duration of action 4 to 6 hours. It has fewer side effects compared to other benzodiazepines. Repeat dose may be given 10–15 minutes after first dose. Lorazepam is also available as buccal, rectal and intranasal.

Midazolam: 0.1–0.25 mg/kg in slow IV bolus not exceeding 0.15 mg/kg/min or 4 mg/min.

Clonazepam IV: 0.01–0.03 mg/kg in IV bolus not exceeding 1 mg/min.

Second-line anti-seizure drugs are used if seizure continue after two doses of first-line agent, usually after 30 minutes from onset. Second-line drugs are levetiracetam, phenytoin and phenobarbitone. Important: treat underlying cause if present and make sure you are treating an epileptic event. An EEG may not be necessary at this stage if seizures are controlled and not easily available. A CT/MRI is indicated if history of trauma, focal onset seizures or focal neurological signs.

Levetiracetam is preferred in children if failure of DZP or fPHT to control seizures. The IV loading dose is 40 mg/kg (maximum 2.5 g) infused over five minutes may prevent the need for intubation and ventilation. It is easy to administer and can be given as a five-minute infusion with both dextrose and normal saline without the increased risk of serious adverse events (including hypotension, cardiac arrhythmias, extravasation or death) [87, 88]. Furthermore, levetiracetam has limited drug interactions [89].

Phenytoin (PHT) or Fosphenytoin (fPHT) is suitable for children over one year. The IV dose is 15-20 mg/kg (maximum pm 1,500 mg) to be given over a minimum of 20 minutes or slower over sixty minutes if seizures have ceased. Do not exceed rate of 1 mg/kg/min or 50 mg/min. Special watch for side effects such as arrhythmias, respiratory depression is needed. Cardiac monitoring is recommended during infusion period.

Phenobarbitone is used as a second-line for infants up to one year, children already on phenytoin or for those children that phenytoin is contraindicated. Dose IV: 15-20 mg/kg (maximum 1 g) to be administered over a minimum 20 minutes. In order to prevent respiratory and or cardiac side effects, doses above 1 mg/kg/min should be avoided.

Valproate is another alternative second line drug for IV use. Dose 30 mg/kg (maximum 800 mg) by slow IV injection over three to five minutes. Valproate is mainly used for adults for the risk of hepatotoxicity in infants and young children or those with underlying mitochondrial disease.

After the second line medication is given, preparation steps should be taken to secure airway and breathing by intubation if needed. These will facilitate further investigations (e.g. CT), treatment and management underlying causes.

CSE that has failed to second-line therapy (refractory SE, if seizures persist >30 min) will almost certainly require induction of anaesthesia e.g. a barbiturate such as thiopentone or propofol as a bolus dose and even ketamine are alternative agents to be used and in some cases ketogenic diet maybe effective or even VNS. It is important to exist and follow existing locally guidelines. Avoid the use of respiratory depressant drugs in settings with limited resuscitation facilities. Consider also pyridoxine responsive seizures (30 mg/kg by IV or IM injection) or thiamine deficiency IV 100 mg.

When seizures have been controlled for 12 hours, the drug dosage should be slowly reduced over a further 12 hours. If seizures recur repeat the infusion again for 12 hours and try to withdraw again. An EEG may help to identify electroclinical dissociation indicating poor prognosis. EEGs particularly continuous are also useful in long intubated children in order to confirm in cases with no clinical symptoms that the abnormal electrical activity has vanished as well. Subtle underlying electrical activity will require intensive care treatment. A recent position statement

on emergency management of paediatric patients with convulsive status epilepticus is published [90]

8. Outcome-prognosis

Aetiological differences between children and neonates are elucidated in (**Table 1**). In general factors that influence prognosis in childhood SE are age, aetiology, and duration of seizure before successful treatment is given. SE remains a major problem in morbidity and mortality [2, 91]. Morbidity of aggressively treated status epilepticus in children, in the absence of an acute neurologic insult or progressive neurologic disorder, is low. Short-term unfavourable outcomes after SE, such as in-hospital mortality and neurological morbidity at hospital discharge, have been shown across several paediatric cohorts, in both convulsive and non-convulsive *SE* [92, 93]. It has been shown that previously neurologically intact children presenting with an acute febrile illness or acute symptomatic cause of convulsive SE who survive had a low risk of developing new, long-term neurological morbidity [6, 94]. By contrast, children who develop SE in the context of an established neurological disorder are at significantly increased risk for neurological morbidity, including worsening neurological status [6, 94]. There is some evidence that CSE, especially febrile CSE, might cause hippocampal injury, although its role in the development of mesial temporal sclerosis is unknown. Regarding neonates adverse neurological outcomes may occur in up to 66% of neonates with status including cerebral palsy and developmental delay [95] Among infants affected by SE, only 48–53% recover completely, 36–54% develop neuro-developmental sequelae and 10–16% die during the acute episode [96–98]. In children the corresponding figures are 67–71%, 24.7% and 27% [97, 99].

Despite the higher incidence of status epilepticus in children than adults, the overall mortality of status epilepticus is lower in children than in adults [100]. In some studies, age is the only factor in multivariate analysis to predict a better outcome [101]. While mortality was higher in early studies [102], recent studies with prospective measurement in children approximate mortality at 3% [6]. Mortality and morbidity directly from status epilepticus is difficult to distinguish from the underlying cause of the seizure.

9. Conclusion

In conclusion early therapy of a convulsive epileptic seizure may prevent CSE and as a consequence associated morbidity and mortality and also save health system from huge expenses. The prognosis with status epilepticus will depend on the duration of status and co-existing medical problems. The prognosis is good for recovery if status can be stopped in a relatively short period of time (hours) and there are no complications such as infection, active cardiac problems, or other active medical issues. However, prognosis for complete recovery is less favourable as status persists for long periods of time. Some cases may also need psychological and social worker assessment and follow-up maybe needed for rehabilitation and early treatment of associated comorbidities. Longer duration of SE, more lag time for receiving the first AED, respiratory failure, and presence of shock are independent predictors for poor outcome. Hence, cessation of convulsion at the earliest leads to improved outcomes.

Author details

Athanasios Covanis[1]*, Kyriakos Garganis[2], Boulenouar Mesraoua[3],
Rola Hosni Khodair[4], Rasha K.M. Abumustafa[4] and Thahira Thekkumpurath[4]

1 The Children Hospital "Agia Sophia", Athens, Greece

2 Epilepsy Centre, "St. Luke's" Hospital, Thessaloniki, Greece

3 Hamad Medical Corporation and Weill Cornell Medical College-Qatar, Doha, Qatar

4 Hamad Medical Corporation, Doha, Qatar

*Address all correspondence to: dracovanis@gmail.com

IntechOpen

References

[1] Treatment of convulsive status epilepticus. Recommendations of the Epilepsy Foundation of America's Working Group on Status Epilepticus. JAMA 1993; 270: 854–859

[2] Lowenstein DH, Bleck T, Macdonald RL. It's Time to Revise the Definition of Status Epilepticus. Epilepsia 1999; 40(1):120-122.

[3] Shorvon SD. Status epilepticus its clinical features and treatment in children and adults. Cambridge: Cambridge University Press, 1994.

[4] Engel J Jr. Report of the ILAE Classification Core Group. Epilepsia, 2006; 47(9):1558–1568.

[5] Rona S, Rosenow F, Arnold S, Carreño M, Diehl B, Ebner A, Fritsch B, et al A semiological classification of status epilepticus. Epileptic Disord 2005, 7 (1): 5-12.

[6] Chin, R.F., Neville, B.G., Peckham, C., et al. Incidence, Cause, and Short-Term Outcome of Convulsive Status Epilepticus in Childhood: Prospective Population-Based Study. The Lancet, 2006; 368: 222-229. https://doi.org/10.1016/S0140-6736(06)69043-0.

[7] **Novorol,** C.L., Chin, R.F.M. and Scott, R.C. () Outcome of Convulsive Status Epilepticus: A Review. Archives of Disease in Childhood, 2007; 92: 948-951. https://doi.org/10.1136/adc.2006.107516.

[8] Raspall-Chaure M, Chin RF, Neville BG, Bedford H, Scott RC. The epidemiology of convulsive status epilepticus in children: a critical review. Epilepsia 2007; 48:1652–63.

[9] Lewena S, Young S. When benzodiazepines fail: how effective is second line therapy for status epilepticus in children. Emerg Med Australas 2006; 18:45–50.

[10] DeLorenzo RJ, Hauser WA, Towne AR, Boggs JG, Pellock JM, Penberthy L, et al. A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. Neurology, 1996; 46 (4): 1029-35. DOI: https://doi.org/10.1212/WNL.46.4.1029.

[11] Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, Shorvon S, Lowenstein DH. A definition and classification of status epilepticus – Report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia 2015; 56 (10):1515–1523. Doi: 10.1111/epi.13121.

[12] Leitinger M, Trinka E, Giovannini G, Zimmermann G, Florea Cr, Rohracher A et al. Epidemiology of status epilepticus in adults: A population-based study on incidence, causes, and outcomes. Epilepsia. 2019; 60:53–62. DOI: 10.1111/epi.14607.

[13] Falco-Walter J.J., Bleck T. Treatment of established status epilepticus. J Clin Med 2016; 5:49

[14] Eriksson K, Metsaranta P, Huhtala H, Auvinen A, Kuusela AL, Koivikko M. Treatment delay and the risk of prolonged status epilepticus. Neurology 2005; 65:1316–8.

[15] Barzegar M, Mahdavi M, Galegolab Behbehani A, Tabrizi A. Refractory convulsive status epilepticus in children: etiology, associated risk factors and outcome. Iran J Child Neurol 2015; 9: 24–31.

[16] Sahin M, Menache CC, Holmes GL, Riviello JJ. Outcome of severe refractory status epilepticus in children. Epilepsia 2001; 42:1461–7.

[17] Gilbert DL, Gartside PS, Glauser TA. Efficacy and mortality in treatment of refractory generalized convulsive status epilepticus in children: a meta-analysis. J Child Neurol 1999; 14:602–9.

[18] Kim SJ, Lee DY, Kim JS. Neurologic outcomes of pediatric epileptic patients with pentobarbital coma. Pediatr Neurol 2001; 25:217–20.

[19] Shorvon S. Super-refractory status epilepticus: An approach to therapy in this difficult clinical situation. Epilepsia 2011; 52(Suppl. 8):53–56. Doi: 10.1111/j.1528-1167.2011.03238.x.

[20] Chateauneuf AL, Moyer JD, Jacq G, Cavelot S, Bedos JP, Legriel S. Super-refractory status epilepticus: epidemiology, early predictors, and outcomes. Intensive Care Med 2017; 43: 1532–4

[21] Novy J, Logroscino G, Rossetti AO. Refractory status epilepticus: a prospective observational study. Epilepsia 2010; 51:251–6.

[22] **Ferlisi M**, Shorvon S. The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy. Brain 2012; 135(8):2314–28.

[23] Hocker SE, Britton JW, Mandrekar JN, Wijdicks EFM, Rabinstein AA. Predictors of outcome in refractory status epilepticus. JAMA Neurol 2013; 70(1):72–7.

[24] Kravljanac R, Djuric M, Jankovic B, Pekmezovic T. Etiology, clinical course and response to the treatment of status epilepticus in children: a 16-year single-center experience based on 602 episodes of status epilepticus. Eur J Paediatr Neurol 2015; 19:584–90.

[25] Vasquez A, Farias-Moeller R, Tatum W. Pediatric refractory and super-refractory status epilepticus. Seizure 2019; 68: 62–71.

[26] DeLorenzo RJ, Waterhouse EJ, Towne AR, Boggs JG, Ko D, DeLorenzo GA et al Persistent nonconvulsive status epilepticus after the control of convulsive status epilepticus. Epilepsia 1998; 39: 833-40.

[27] Sanchez S, Carpenter J, Chapman K et al: Electroencephalography monitoring in critically ill children: current practice and implications for future study design, Epilepsia, 2013; 54: 1419-1427

[28] Payne E. & Hahn C: Continuous electroencphalography for seizures and status epilepticus, Curr. Opin. Pediatr., 2014; 26: 675-681

[29] Abend N, Dlugos D, Hahn C, et al: Use of EEG monitoring and management of non-convulsive seizures in critically ill patients: a survey of neurologists, Neurocrit. Care, 2010; 12: 382-389

[30] Abend N, Arndt D, Carpenter J, et al: Electographic seizures in pediatric ICU patients: cohort study of risk factors and mortality, Neurology, 2013; 81: 383-381

[31] Guerriero R & Gaillard W: Imaging modalities to diagnose and localize status epilepticus. Seizure 2019; 68: 46-51

[32] Giovannini G, Kuchukhidze G, McCoy M et al: Neuoimaging alterations related to status epilepticus in an adult population: Definition of MRI findings and clinical and EEG correlations, Epilepsia, 2018; 59(S2): 120-127

[33] Kutluay E, Beattie J, Passaro EA, et al. Diagnostic and localizing value of ictal SPECT in patients with nonconvulsive status epilepticus. Epilepsy Behav. 2005; 6(2): 212-217.

[34] Shinnar S, Pellock JM, Moshe SL, Maytal J, O'Dell C, Driscoll SM, et al. In whom does status epilepticus occur: age-

related differences in children. Epilepsia 1997; 38:907–14.

[35] Singh RK, Stephens S, Berl MM, Chang T, Brown K, Vezina LG, et al. Prospective study of new-onset seizures presenting as status epilepticus in childhood. Neurology 2010; 74:636–42

[36] Maytal J, Shinnar S, Moshé SL, Alvarez LA, Shinnar S, Mosh SL. Low Morbidity and Mortality of Status epilepticus in Children. Pediatrics, 1989; 83:323-31.

[37] Chin RF, Verhulst L, Neville BG, Peters Mj, Scott RC. Inappropriate emergency management of status epilepticus in children contributes to need for intensive care. J Neurol Neurosurg Psychiatry 2004; 75: 1584-1588.

[38] Specchio N, Pietrafusa N, Bellusci M, Trivisano M Benvenga A, de Palma L, Ferretti A et al. Pediatric status epilepticus: Identification of prognostic factors using the new ILAE classification after 5 years of follow-up. Epilepsia 2019; 60: 2486-2498.

[39] Vafaee-Shahi M, Soltanieh E, Saidi H, Riahi A. Etiology, Risk Factors, Mortality and Morbidity of Status Epilepticus in Children: A Retrospective Cross-Sectional Study in Tehran, Iran. The Open Neurology Journal 2020; 14: 95-102. DOI: 10.2174/1874205X02014010095]

[40] Das K, Das S K, Pradhan S, et al. Clinical Feature and Outcome of Childhood Status Epilepticus in a Teaching Hospital, Odisha, India. Cureus 2020; 12(10): e10927. DOI 10.7759/cureus.10927

[41] DeLorenzo RJ, Towne AR, Pellock JM et al. Status epilepticus in children, adults and the elderly. Epilepsia 1992; 33 (Suppl 4):515-525

[42] Coeytaux A, Jallon P, Galobardes B, Morabia A. Incedense of status epilepticus in French-speaking Swutzerland:EPISTAR. Neurology 2000; 55:693-7.

[43] Metsäranta P, Koivikko M, Peltola J, Eriksson K. Outcome after prolonged convulsive seizure in 186 children: Low morbidity, no mortality. Dev Med Child Neurol 2004; 46:4-8.

[44] Eriksson K, Koivikko M. Status epilepticus in children: aetiology, treatment, and outcome. Dev Med Child Neurol. 1997; 39:652-8.

[45] Trinka E, Kälviänen R. 25 years of advances in the definition, classification and treatment of status epilepticus. Seizure 2017; 44:65-73

[46] Pujar SS, Martinos MM, Cortina-Borja M, et al. Long-term prognosis after childhood convulsive status epilepticus: a prospective cohort study. Lancet Child Adolesc Health 2017; published online Dec 5. http://dx.doi.org/10.1016/S2352-4642(17)30174-8

[47] Nelson-Chaure M, Chin RF, Neville BG, Scott RC. Outcome of paediatric convulsive status epilepticus: a systematic review. Lancet Neurol. 2006; 5:769-79

[48] Joshi S, Kapur J. Mechanisms of status epilepticus: α-Amino-3-hydroxy-methyl-4-isoxazolepropionic acid receptor hypothesis. Epilepsia 2018; 59 (S2):78-81

[49] Treiman DM. Electroclinical features of status epilepticus. J Clin Neurophysiol 1995; 12:343-62.

[50] Shorvon S. The management of Status epilepticus. J Neurol Neurosurg Psychiatry 2001; 70 (Suppl. 2): 1122-7

[51] Treiman DM, Walton NY, Kendrick C. A progressive sequence of electroencephalographic changes during generalized convulsive status epilepticus. Epilepsy Res 1990; 5:49-60.

[52] Goodkin HP, Kapur J. Responsiveness of status epilepticus to treatment with diazepam decreases rapidly as seizure duration increases. Epilepsy Curr 2003; 3:11-2

[53] Chen JW, Wasterlain CG. Status epilepticus pathophysiology and management in adults. Lancet Neurol2006; 5:246-56

[54] Chungath M, Shorvon S. The mortality and morbidity of febrile seizures. Nat Clin Pract Neurol. 2008; 4 (11):610–621. https://doi.org/10.1038/ncpneuro0922

[55] Leung AK, Robson WL. Febrile seizures. J Pediatr Health Care. 2007; 21 (4):250–255. PMID: 17606162

[56] Leung AK. Febrile seizures. In: Leung AK, ed. Common Problems in Ambulatory Pediatrics: Specific Clinical Problems, Volume 1. New York, NY: Nova Science Publishers, Inc.; 2011: 199–206.

[57] Millichap JJ. Clinical features and evaluation of febrile seizures. In: Post TW, ed. UpToDate. Waltham, MA.

[58] Steering Committee on Quality Improvement and Management, Subcommittee on Febrile Seizures American Academy of Pediatrics. Febrile seizures: clinical practice guideline for the long-term management of the child with simple febrile seizures. Pediatrics. 2008; 121(6):1281–1286

[59] Molinero I, Shinnar S. Febrile Status Epilepticus. J Pediatr Epilepsy 2019; 8:79-82.

[60] Graves RC, Oehler K, Tingle LE. Febrile seizures: risks, evaluation, and prognosis. Am Fam Physician. 2012; 85 (2):149–53. Epub 2012/02/18.

[61] Sadleir LG, Scheffer IE. Febrile seizures. BMJ. 2007; 334(7588):307–11. Epub 2007/02/10

[62] Seinfeld S, Shinnar S, Sun S, Hesdorffer DC, Deng X, Shinnar RC, O'Hara K, Nordli Jr DR, Frank LM, Moshé SL, Pellock JM and FEBSTAT study team. Emergency management of febrile status epilepticus: Results of the FEBSTAT study. Epilepsia, 2014; 55(3): 388–395. Doi: 10.1111/epi.12526

[63] Shinnar S, Pellock JM, Berg AT, O'Dell C, Driscoll SM, Maytal J Moshe SL, DeLorenzo RJ. Short-term outcomes of children with febrile status epilepticus. Epilepsia 2001; 42:47-53.

[64] Yousefichaijan P, Eghbali A, Rafeie M, Sharafkhah M, Zolfi M, Firouzifar M. The relationship between iron deficiency anemia and simple febrile convulsion in children. J Pediatr Neurosci. 2014; 9(2):110–114. https://doi.org/10.4103/1817-1745.139276.

[65] King D, King A. Question 2: should children who have a febrile seizure be screened for iron deficiency? Arch Dis Child. 2014; 99(10):960–964. https://doi.org/10.1136/archdischild-2014-306689.

[66] Sharawat IK, Singh J, Dawman L, Singh A. Evaluation of risk factors associated with first episode febrile seizure. J Clin Diagn Res. 2016;10(5): SC10–13. Doi: 10.7860/JCDR/2016/18635.7853.

[67] Saghazadeh A, Mastrangelo M, Rezaei N. Genetic background of febrile seizures. Rev Neurosci. 2014; 25(1):129–161. https://doi.org/10.1515/revneuro-2013-0053

[68] Lewis DV, Shinnar S, Hesdorffer DC, Bagiella E, Bello JA, Chan S, Xu Y, MacFall J, Gomes WA. Moshé SL et al. Hippocampal Sclerosis after Febrile Status Epilepticus: The FEBSTAT Study. ANN NEUROL 2014; 75:178–185

[69] Nordli DR, Moshé SL, Shinnar S, Hesdorffer DC, Sogawa Y et al. Acute

EEG findings in children with febrile status epilepticus. Results of the FEBSTAT study. Neurology 2012;79: 2180–2186

[70] Gallentine WB, Shinnar S, Hesdorffer DC, Epstein L, Nordli DR Jr, Lewis DV, Frank LM, Seinfeld S, Shinnar RC, Cornett K, Liu B, Moshé SL, Sun S; FEBSTAT Investigator Team. Epilepsia. 2017; 58(6):1102-1111. doi: 10.1111/epi.13750. Epub 2017 Apr 27.

[71] Paul SP, Kirkham EN, Shirt B. Recognition and management of febrile convulsion in children. Nurs Stand. 2015; 29(52):36–43. https://doi.org/10.7748/ns.29.52.36.e9927

[72] Chin RF, Neville BG, Scott RC. Meningitis is a common cause of convulsive status epilepticus with fever. Arch Dis Child 2005; 90:66-69

[73] Sánchez Fernández I, Abend NS, Amengual-Gual M, Anderson A, Arya R, Aguilar CB, Brenton JN et al. Neurology, 2020; 95:e1222-e1235. doi:10.1212/WNL.0000000000010174.

[74] Covanis A. epileptic Encephalopathies (including severe epilepsy syndromes). Epilepsia 2012; 53 (suppl.4):114-126.

[75] Cohen I, Navarro V, Clemenceau S, Baulac M, Miles R. On the origin of interictal activity in human temporal lobe epilepsy in vitro. Science 2002; 298: 1418- 1421.

[76] Dieterich E, Baier WK, Doose H, Tuxhorn I. Long-term follow-up of childhood epilepsy with absences at onset. Neuropediatrics 1985; 16:149-54. PMID 3930988

[77] Thomas P, Valton L, Genton P. Absence and myoclonic status epilepticus precipitated by antiepileptic drugs in idiopathic generalized epilepsy. Brain 2006 129(5):1281-1292; doi: 10.1093/brain/awl047.

[78] Ferrie CD, Caraballo R, Covanis A, Demirbilek V, Dervent A, Fejerman N, Fusco L, Grünewald R et al. Autonomic Status Epilepticus in Panayiotopoulos Syndrome and Other Childhood and Adult Epilepsies: A Consensus View. Epilepsia 2007;48(6):1165-72

[79] Covanis A. Panayiotopoulos syndrome: a benign childhood autonomic epilepsy frequently imitating encephalitis, syncope, migraine, sleep disorders or gastroenteritis. Pediatrics 2006; 118(4):e1237-e1243, doi:10.1542/peds.2006-0623.

[80] Panayiotopoulos CP. Autonomic seizures and autonomic status epilepticus peculiar to childhood: Diagnosis and management. Epilepsy & Behavior 2004; 5(3); 286-95.

[81] Koutroumanidis M, Rowlinson S, Sanders S. recurrent autonomic status epilepticus in Panayiotopoulos syndrome: video/EEG studies. Epilepsy & Behav 2005; 7; 543-547

[82] Covanis A. Panayiotopoulos syndrome. Atlas of Epilepsies, Panayiotopoulos CP (ed), 2010; vol (2): 965-972. DOI 10.1007/978-1-84882-128-6-191.

[83] Pellock JM, Marmarou A, DeLorenzo R. Time to treatment in prolonged seizure episodes. Epilepsy Behav 2004; 5:192–196

[84] Alldredge BK, Wall DB, Ferriero DM. Effect of prehospital treatment on the outcome of status epilepticus in children. Pediatr Neurol 1995; 12:213–216.

[85] Dreifuss FE, Rosman NP, Cloyd JC, et al. A comparison of rectal diazepam gel and placebo for acute repetitive seizures. N Engl J Med 1998; 338:1869–1875.

[86] Fernadez IS, Abend NS, Agadi S, An S, Arya R, Carpenter JL et al. Gaps and opportunities in refractory status

epilepticus research in children. A multicentre approach by the Pediatric Status Epilepticus Research Group (pSERG). Seizure: European Journal of Epilepsy. BEA Trading Ltd: 2014 Feb 1; 23(2):87-97.

[87] Dalziel SR, Furyk J, Bonisch M, Oakley E , Borland M, Neutze J, Donath S 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. BMJ Pediatrics 2017; 17:152. DOI 10.1186/s12887-017-0887-8.

[88] Lyttle, M.D., Gamble, C. and Messahel, S. Emergency Treatment with Levetiracetam or Phenytoin in Status Epilepticus in Children—The EcLiPSE Study: Study Protocol for a Randomised Controlled Trial. Trials, 2017; 18: 283. https://doi.org/10.1186/s13063-017-2010-8.

[89] Loddenkemper T, Goodkin HP. Treatment of pediatric status epilepticus. Curr Treat Options Neurol 2011; 13(6):560–73.

[90] McKenzie KC, Hahn CD, Friedman JN. Emergency management of the paediatric patient with convulsive status epilepticus. Paediatrics & Child Health, 2021, 50–57 doi: 10.1093/pch/pxaa127.

[91] Riviello JJ. Pediatric Status Epilepticus: Initial management and the Special Syndromes of Status Epilepticus in Children. In: Status epilepticus: a clinical perspective. 2nd edn. Drislane FW, Kaplan MBBS, Peter Wolf (eds). Humana Press; 2018: pp333-82.

[92] Topjian AA, Gutierrez-Colina AM, Sanchez SM, et al. Electrographic status epilepticus is associated with mortality and worse short-term outcome in critically ill children. Crit Care Med 2013; 41: 215–23.

[93] Maegaki Y, Kurozawa Y, Tamasaki A, et al. Early predictors of status epilepticus-associated mortality and morbidity in children. Brain Dev 2015; 37: 478–86.

[94] Pujar SS, Martinos MM, Cortina-Borja M, Chong WKK, De Haan M, Gillberg C et al. Long-term prognosis after childhood convulsive status epilepticus: a prospective cohort study. Lancet Child Adolesc Health. 2018; 2: 103-11.

[95] Pisani F, Cerminara C, Fusco C, Sisti L. Neonatal status epilepticus vs recurrent neonatal seizures: Clinical findings and outcome. Neurology 2007; 69:2177-85.

[96] Tabarki B, Yacoub M, Selmi H, Oubich F, Barsaoui S, Essoussi AS. Infantile status epilepticus in Tunisia. Clinical, etiological and prognostic aspects. Seizure 2001;10:365-9.

[97] Battaglia D, Randò T, Deodato F, Bruccini G, Baglio G, Frisone MF, *et al*. Epileptic disorders with onset in the first year of life: Neurological and cognitive outcome. Eur J Paediatr Neurol EJPN off J Eur Paediatr Neurol Soc 1999; 3:95-103.

[98] Datta AN, Wirrell EC. Prognosis of seizures occurring in the first year. Pediatr Neurol 2000;22:386-91.

[99] Vasudevan C, Levene M. Epidemiology and aetiology of neonatal seizures. *Semin Fetal Neonatal Med*. 2013; 18:185–91. [PubMed] [Google Scholar]

[100] Dham, B.S.; Hunter, K.; Rincon, F. The epidemiology of status epilepticus in the United States. Neurocrit. Care 2014, 20, 476–483.

[101] Wu YW, Shek DW, Garcia PA, Zhao S, Johnston SC. Incidence and mortality of generalized convulsive

status epilepticus in California.
Neurology 2002; 58:1070–76.

[102] Aicardi, J; Chevrie, J.J. Convulsive
status epilepticus in infants and
children. A study of 239 cases.
Epilepsia 1970, 11, 187–197.