# Diagnostic work-up and therapeutic options in management of pediatric status epilepticus

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***Background:*** **Status epilepticus (SE) is a life-threatening neurologic disorder comprising prolonged and unremitting crisis, and two or more series of seizures without complete intercritical recovery.**

***Data sources:*** **We reviewed the literature through a Pubmed/Medline research using key words including status epilepticus, antiepileptic drugs AND children, in order to revise and compare international/national protocols and to examine pediatric guidelines in SE management.**

***Results:*** **Neurologic impairment and SE etiology seem to be the most independent risks for mortality. A deep semiologic evaluation is essential to addressing diagnostic work-up. Ematochemical parameters, plasma levels of antiepileptic drugs and clinically oriented toxic/metabolic screening should be mandatory for investigating both causes and effects of SE. Electroencephalography is clearly helpful to characterize focal from generalized SE and to distinguish epileptic events from pseudoseizures, and it is deal to find nonconvulsive SE. Neuroimaging techniques could detect epileptogenic lesions (such as cortical malformations, tumors, demyelinating disorders or strokes) but are common in practice to find negative or controversial results. Pharmacologic management can be essentially arranged in three stages: benzodiazepines for early SE (lasting less than 30 minutes), phenytoin/fosphenytoin, phenobarbital, valproate, levetiracetam or lacosamide for established SE (30-90 minutes), and anesthetics for refractory SE (more than 90 minutes).**

***Conclusions:*** **Status epilepticus is the most common neurologic emergency in childhood. A systematic diagnostic work-up and a three steps based therapeutic approach is required at this age.**

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***Key words:*** **antiepileptic drugs;**
**children;**
**status epilepticus**

Review article

## Introduction

Status epilepticus (SE) is a neurologic emergency characterized by prolonged and unremitting epileptic seizure or by close, back to back, repetition of short lasting seizures.[1,2] Multifactorial mechanisms, involved in ending up seizures, fail in SE patients, thus resulting in multisystemic failure.[1,2]

In this paper we report controversies concerning pediatric SE in order to guide pediatricians in SE management.

## Classification

Several criteria have been suggested to categorize SE including etiology, cortical involvement and semiology.[3,4] Table 1 summarizes etiologic categorization of SE while Table 2 shows its classification based on seizure semiology.

## Epidemiology

The incidence of SE in pediatric age ranges from 10-17/100 000 to 23-58/100 000 patients per year.[5] There is a higher incidence in infants younger than 1 year (135.2/100 000 and 156/100 000 per year).[6,7] SE represents the first clinical presentation of epilepsy in about 20% of epileptic children and, across five years from the diagnosis, 20% of epileptic children demonstrate an episode of SE.[7,8] Pre-existing epilepsy conditions, history of prolonged febrile/afebrile convulsions, underlying medical etiology, clinical pictures of progressive encephalopathy, specific electroencephalographic patterns, and low plasma antiepileptic drugs (AEDs) levels are common risk

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**Table 1.** Etiologic classification of pediatric status epilepticus

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|---|
| **Status epilepticus with unknown causes** |
| Convulsive status epilepticus with unknown causes (see Table 2) |
| Non-convulsive status epilepticus with unknown causes (see Table 2) |
| **Status epilepticus with acute causes** |
| Meningo-encephalitis or sepsis |
| Febrile infections (i.e., FIRES) |
| Childhood vaccinations |
| Electrolyte dysfunctions |
| Hypoglycemia |
| Perinatal hypoxic-ischemia |
| Stroke |
| Demyelinating diseases |
| Trauma |
| Intoxication |
| **Status epilepticus with non acute causes** |
| Cortical malformations (focal cortical dysplasia, polymicrogyria, subcortical band heterotopia, periventricular nodular heterotopias, lissencephaly, schizencephaly) |
| Neurocutaneous syndromes (tuberous sclerosis, Sturge Weber syndrome, dysembrioplastic neuroepithelial tumors) |
| Brain tumors |
| Autoimmune disorders (i.e., Rasmussen syndrome, cerebral vasculitis and other connetivopathies, multiple sclerosis) |
| Monogenic epileptic encephalopathies (*ARX, CDKL5, STXBP1, SLC25A22, PLC-β1, MeCP2, MAGI 2, PCDH19, SCN1A*) |
| Chromosomal abnormalities (1p36 monosomy, Wolf-Hirschhorn syndrome, 18q-syndrome, Angelman syndrome, ring chromosome 20 syndrome, Down syndrome) |
| Metabolic diseases |
| 1) Mitochondrial diseases (i.e., MERFF, Alpers syndrome, pyruvate dehydrogenase complex deficiency, SUCLA and SUCLG1 related syndrome) |
| 2) Lipid storage disorders (Tay Sachs-Sandhoff disease, Krabbe disease, neonatal adrenoleukodystrophy, Zellweger syndrome, infantile Refsum disease, punctuate rhyzomelic chondrodysplasia, Niemann-Pick disease type A and C, Neuronal ceroid lipofuscinosis) |
| 3) Aminoacidopathies (serine metabolism disorders, hyperpolinemia type II, untreated phenylketonuria, Maple urine syrup diseases, congenital glutamine deficiency, Nonketotic hyperglycinemia) |
| 4) Organic acidopathies (propionic, methylmalonic, D-2-hydroxyglutaric and isovaleric acidurias, 2-methyl-3-hydroxybutyril-CoA dehydrogenase deficiency) |
| 5) Other diseases (vitamine dependant epilepsies, creatine metabolism dysfunctions, Menkes disease, disorders of purine and pyrimidine metabolism) |

FIRES: febrile infection-related epilepsy syndrome; *ARX*: aristaless-related homeobox gene; *CDKL5*: cyclin-dependent kinase-like 5; *STXBP1*: syntaxin binding protein 1; *SLC25A22*: solute carrier family 25, member 22; *PLC-β1*: phospholipase cb1; *MeCP2*: methyl-cpg-binding protein 2; *MAGI 2*: membrane-associated guanylate kinase inverted-2; *PCDH19*: protocadherin 19; *SCN1A*: sodium channel neuronal type 1a subunit; MERFF: myoclonic epilepsy with ragged red fibers; SUCLA: succinate-coenzyme A ligase A; SUCLG2: succinate-coenzyme A ligase A gdp-forming, beta subunit.

**Table 2.** Semiologic classification of pediatric status epilepticus

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|---|
| **Non-convulsive epilepticus** |
| Absences (typical/atypical) |
| Focal status epilepticus with sensorial symptoms |
| Autonomic or focal status epilepticus with affective symptoms |
| Focal status epilepticus with autonomic symptoms (panayiotopoulos syndrome) |
| Complex-partial status epilepticus |
| Continuous spike and wave during slow sleep |
| **Convulsive status epilepticus** |
| Focal |
| Focal motorial |
| Focale motorial with secondary generalization |
| Epilepsia partialis continua |
| Generalized |
| Myoclonic |
| Clonic |
| Tonic |
| Tonic-clonic |

factors for higher morbidity but not for life-threatening SE.[9-11] The incidence of fatal pediatric SE ranges from 3% to 15%.[9-12] A recent population-based study in 226 children who experienced an episode of convulsive SE demonstrated that a previous neurologic impairment is the only independent risk factor for mortality within 8 years of age.[11] Moreover, death risk does not correlate with other demographic (gender, age, ethnicity, socio-economic status) or clinical features (febrile SE, convulsive *vs*. nonconvulsive SE, SE occurrence, seizure type, semiology and duration).[11] Another study revealed 302 children treated in intensive care units defined two independent risk factors for mortality: prior neurologic status and underlying SE etiology.[10]

The term "new-onset refractory status epilepticus" (NORSE) syndrome has been used to describe an extremely severe and prolonged SE occurring both in young adult and children with previous good health conditions (referring to an extensive clinic and laboratory work-up, including neuropathology) and a poor prognosis.[13] Recently, the NORSE syndrome as a distinct clinical feature has been questioned.[14]

## Pathophysiology

Several studies, based on seizure animal models, have revealed the picture of multiple alternative or incoming pathomechanisms for SE. The picture includes complex network dysfunction, increased proconvulsivants release (for instance subunits of AMPA and NMDA receptors, tachykinins, P substance and neurokinin B), and relapse of lowering inhibitory factors (GABAA receptors, dynorphin, galanin, somatostatin and neuropeptide Y). Neuronal cell death, due to excitotoxicity, in particular seems to dress up the role of a converging pathway.[14-16] *In vitro* models have demonstrated that both convulsive and non-convulsive SE (such as partial complex SE) bring to excitotoxic neuronal injury through an increased recruitment of glutamate receptors [for instance N-methyl-D-aspartate (NMDA) glutamate receptor]. Glutamate, for its part, increases intracellular calcium levels, leading to acute necrosis and, afterwards, delayed apoptotic cell death.[11] On the contrary, the administration of NMDA receptor antagonist drives to a clear hippocampal cell-death decrease in experimental mice models of SE.[17] Less encouraging results were obtained using AMPA glutamate receptor antagonists.[17] Metabotropic glutamate receptor is involved in thalamocortical excitatory and inhibitory networks and represents a future target for pharmacologic management of absence status epilepticus.[18]

Dysregulation of cell-cycle modulators is probably

another basic mechanism in the evolution of SE-mediated brain damage.[19] Protein p53, acting as an important regulator of apoptosis, has been involved in seizure-induced *in vivo* neuronal death while mice models of prolonged electro-clinical SE and severe chronic epileptic phenotypes are ascribed to p53 deficiency.[20] These data underline that the use of pharmacologic p53 blockers could be extremely deleterious.[19,20] A promising target could be protein Puma, a p53-dependent pro-apoptotic protein.[20] Genetic silencing of Puma seems to play a protecting role for hippocampal neurons in mice model of prolonged SE.[20]

SE induced drug-resistance is another research topic. Drug-resistance should be ascribed to increased brain expression, after prolonged seizures, of drug efflux transporter genes and proteins [such as P-glycoprotein (Pgp) and multidrug resistance proteins (MRP) family] which decrease antiepileptic drug levels in the brain.[21] The expression of efflux transporter genes is also strictly time related.[22,23] *In vitro* models have demonstrated that this process is negatively modulated by several proinflammatory cytokines which suppress the expression of Mdr1/Pgp and other drug efflux transporters.[21-23] In the early stage of SE, the expression of efflux transporter genes decreases because of an increased release of proinflammatory cytokine such as interleukin-beta 1, interleukin 6 and tumor necrosis factor alpha.[21-23] On the contrary, in later stages this mutual dependence is reversed and drug-resistance is far more important.[21-23]

## Diagnostic approach

### Clinical evaluation

The diagnostic work-up in children with SE should be etiologically oriented (Table 1). A comprehensive and detailed history concerning seizures semiology, developmental characteristics, neurologic or other diseases in the patient or in his family are essential to guiding the investigation of epilepsy through electroencephalography (EEG) and/or neuroimaging.[6]

SE is often associated with several acute life-threatening conditions such as cerebral edema, trauma, hyperthermia, fluid/electrolyte/metabolic disturbances, pulmonary edema, cardiac arrhythmias, and cardiovascular collapse.[24,25] SE can also progress in epilepsy or epileptic encephalopathy with severe cognitive impairments and focal neurologic deficits, which obviously may deteriorate long-term neurologic outcomes.[25] Seizure-related cerebral edema does not routinely require aggressive therapies.[25] Craniofacial injuries are characterized by oral trauma (such as biting the tongue or oral mucosa, hitting the lips) and closed head or facial injuries during clonic phase of seizures.[25] Fluid/electrolyte/metabolic complications include lactic acidosis, dehydration, hypovolemia and hypotension.[25] Myoglobinuria, due to muscle breakdown during seizure, may result in renal failure.[25] Pulmonary edema and cardiac arrhythmia may complicate both SE and its treatment.[25] Disseminated intravascular coagulation is rarely observed in children with SE and no sepsis or central nervous system infection signs.[25] This event is likely related to a widespread endothelial damage secondary to seizure-induced hyperpyrexia.[25] Hence body temperature should be closely monitored in patients with prolonged seizures.[25]

In intensive care units, other non-neurologic complications such as nosocomial and ventilator-associated pneumonia, neurogenic pulmonary embolism, myocardial dysfunction, hypertension, stress ulcer, gastrointestinal bleeding, constipation, diarrhea, paralytic ileus, renal distress, urinary tract infections and vascular catheter-related sepsis should also be monitored.[24,25]

SE differential diagnosis includes psychogenic SE, prolonged syncope, decerebrate spasms, tetanus, malignant hyperthermia, malignant neuroleptic syndrome, paroxysmal dyskinesia, acute chorea, ballismus, and dystonia.[24,25] Among these disorders, psychogenic SE is the most struggling diagnostic challenge due to its ambiguous symptoms (such as subtle writhing, in-phase limb movements, unresponsive behaviours or confusional state) and frequent comorbidity with epileptic seizures.[24,25]

### Laboratory investigations

Blood tests, inflammatory indexes, nutritional, hepatic and renal functionality markers, coagulation, electrolytes tests and hemogasanalysis are commonly used in evaluating both causes and effects of SE.[26,27]

Plasma levels of AEDs should always be measured in children under treatment.[26] Frequently low plasma AED levels reveal inadequate dosing based on patient weight, noncompliance, therapeutic unresponsiveness or drug withdrawal, which results in SE episodes.[26-28]

All infants with SE under 6 months of age should undergo a lumbar puncture to exclude central nervous system infection even if no clinical signs are evident.[29] Lumbar puncture should also be made to detect metabolic and demyelinating disorders.[30-32] Cefalospinal fluid pleocytosis is often observed etiologically because there is a specific inflammatory reaction possibly caused by seizures.[29] Blood culture should be made in children with signs of systemic infection.[30]

Serum or urine toxicological screening should be carried out if there are clinical findings suggestive

of the disease.[30,31] Inborn errors of metabolism including aminoacidopathies, urea cycle disorders, organic acidopathies, creatine metabolism disorders, mitochondrial and peroxisomal disorders should be investigated in unexplained neonatal encephalopathy, developmental delay, acidosis, coma, recurrent and specific food intolerance, frequent eating to prevent lethargy, unfair dehydration during acute illness.[32]

### Electroencephalogram

In the evaluation of SE, EEG can distinguish focal from generalized SE and epileptic events from pseudoseizures.[33] The effects of drug administration on epileptic traces should also be evaluated in the emergency department.[34,35]

EEG is also useful in assessing nonconvulsive SE.[33,34] EEG patterns of nonconvulsive SE include: 1) generalized or focal spikes, slow spikes, spikes and slow waves with a frequency ≥3 Hz; 2) generalized or focal spikes, slow spikes, spikes and slow waves with a frequency ≤3 Hz associated with electroclinical responsiveness to intravenous administration of antiepileptic drugs; 3) rhythmic, periodic or semi-periodic discharges with a frequency of below 1 Hz and an undoubted evolution of its frequency, morphology and localization.[34,35]

Peculiar and mostly sleep-related non-convulsive SE occurs together with autonomic symptoms, for instance nocturnal vomiting in patients with panayotopoulos syndrome, and it can be sampled by nocturnal video-EEG recording.[36]

EEG also plays an important role in electrical status epilepticus during sleeping (ESES). ESES is a specific SE that has been described in two distinct but partially overlapping syndromes: continuous spikes and waves in slow wave sleep (CSWS) and Landau-Kleffner syndrome (LKS). Regression of cognitive, language and motor skills is more evident than seizures in CSWS and LKS.[37] For these reasons, EEG recordings showing typical sub-continuous epileptiform discharges in sleep often represent the only diagnostic clue.[37]

### Neuroimaging

Magnetic resonance of the brain helps to detect different epileptogenic lesions such as cortical malformations, tumors or strokes in case of focal SE. Neuroimaging investigation should never be performed before stabilization of patients and complete control of seizures.[38]

## Therapeutic options

Out-of-hospital rescue of SE patients starts with a basic pediatric life support.[28] Airways preservation, oxygen administration, venous access availability and cervical column immobilization are essential.[28] Rescuers should eventually administer rectal diazepam (0.5 mg/kg) or buccal/intranasal midazolam (0.1-0.2 mg/kg, maximum 10 mg).[28] In the emergency room, at least three operators are required to ensure a complete advanced pediatric life support and to administer intravenously appropriate antiepileptic drugs.[28] If a peripheral venous access is not available, a bony one is necessary.[28]

Drug treatment of SE (Figs. 1-3) can be divided into three stages: early (0-30 minutes), established (30-90 minutes) and refractory (>90 minutes) SE.

### Early SE

Benzodiazepines (diazepam, lorazepam or midazolam)

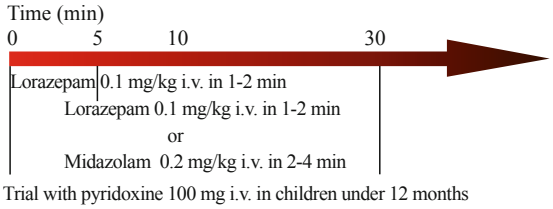


**Fig. 1.** Pharmacologic options for the treatment of early status epilepticus (lasting less than 30 minutes). Emergency department approaches, with the dosages, the way and the timing of administration of benzodiazepines and pyridoxine.

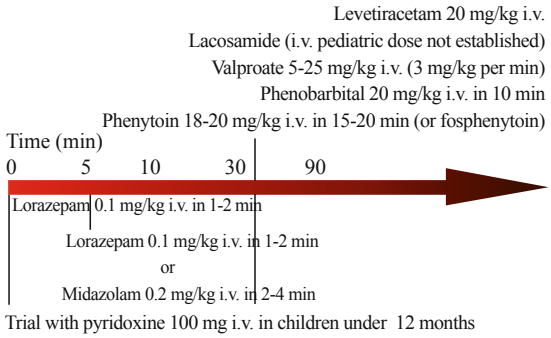


**Fig. 2.** Pharmacologic options for the treatment of established status epilepticus (lasting between 30 and 90 minutes). The dosages and the timing of administration of phenytoin, phenobarbital, valproate and levetiracetam are indicated. For lacosamide, a pediatric intravenous dose has not been established.

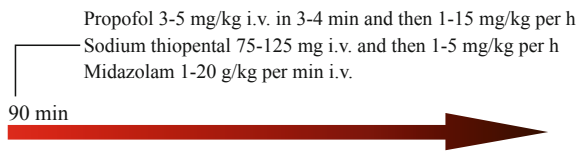


**Fig. 3.** Pharmacologic options for the treatment of refractory status epilepticus (lasting more than 90 minutes, Pediatric Intensive Care Unit). The dosages and the timing of administration of propofol, sodium thiopental and midazolam are indicated.

are the first-line treatment for pediatric SE in both out-of-hospital rescue and emergency room (Fig. 1).[39-44] Benzodiazepines can be readministered five minutes later.[39,40] Further administration should be avoided because of decreased therapeutic effect and increased risk of respiratory depression.[39,40] The intravenous dose of diazepam is 0.3 mg/kg (maximum 10 mg) and its half-life is about 24 hours.[40,42-44] The high distribution of diazepam in adipose tissues 15-20 minutes after its administration leads to half-life and decreased efficacy.[40,42-44] Moreover, there is an increased risk of respiratory impairment after drug storage.[40,42-44] The effect of diazepam is limited by unavailability of drug towards fecal obstacles and by the accuracy of the administration.[40,41-43]

Lorazepam, which is less lipophile than diazepam, has a shorter half-life (3 hours *vs.* 15 hours). Its dosage is 0.1 mg/kg (maximum 4 mg/dose).[40,41] Intravenous lorazepam seems to be as effective as diazepam in the treatment of acute tonic clonic seizures and it is also better tolerated.[41]

Midazolam has a very short half-life (1-2 hours) and a highest lipophile profile with a fast blood-brain barrier crossing. Oral midazolam is more effective than rectal diazepam in treating acute tonic-clonic seizures, but intranasal midazolam is less effective than intravenous diazepam.[42-44] In children under 12 months of age, 100 mg of pyridoxine should be administered intravenously in the treatment of pyridoxine-dependant seizures.[45]

**Established SE**

Phenytoin or fosphenytoin, phenobarbital, valproate, levetiracetam and lacosamide actually represent second-line drugs for SE (Fig. 2).[28,39] Intravenous phenytoin should be given at a dose of 18-20 mg/kg.[28-39] A slow administration (1 mg/kg per minute) avoids side-effects such as hypotension, arrhythmia, respiratory depression, venous irritation, tissue injury or necrosis, and the so-called "purple glove syndrome" (appearance of limb edema, discoloration and pain 2 to 12 hours after the administration of drugs).[28,39] Therapeutic effectiveness is seen 10-30 minutes after drug administration up to 1-24 hours.[28,39]

Fosphenytoin is prefered to phenytoin mostly in the United States, as it is soluble and can be infused more rapidly than phenytoin.[46] Fosphenytoin must be given as phenytoin (75 mg of fosphenytoin = 50 mg of phenytoin) and its adverse effects are similar to those of phenytoin.[46] It has been underscored that no clear advantages justify the high cost of phosphenytoin.[46]

Phenobarbital is particularly effective in treating patients with febrile SE under 12 months of age. Its intravenous dose is 10-20 mg/kg in 10-15 minutes. The therapeutic plasma level of phenobarbital can be achieved in 15 minutes but its half-life is about 48 hours.[28,39]

Valproate is used in patients with cardiovascular instability presenting absence SE and myoclonic SE, juvenile myoclonic epilepsy and postanoxic myoclonus.[47,48] Its intravenous dose is 15-45 mg/kg (6 mg/kg per minute) followed by infusion of 1 mg/kg per hour. Its half-life is about 12 hours but therapeutic effectiveness is seen in 30 minutes.[49] Side-effects (hypotension, dizziness and thrombocytopenia) appear in less than 10% of the patients and they are infusion-rate independent, with valproate-related acute encephalopathy in only few cases.[49,50]

Levetiracetam can be used to deal with low respiratory and cardiovascular side effects in established and refractory SE.[51] Its intravenous doses range from 15 to 70 mg/kg.[51]

Lacosamide has been recently warned even in the management of early SE stages. In adult patients, the loading intravenous dose was between 200 and 600 mg.[52] Only one case of pediatric SE treated with lacosamide enterally has been reported so far.[53] Headache, dizziness, somnolence and diplopia are the most common symptoms in patients.[52]

Oral topiramate is anecdotally effective and well tolerated in subjects with refractory SE.[54-57] This agent has a broad spectrum of efficacy but unavailability of intravenous medication prevents clinical enforceability.[57]

**Refractory SE**

Refractory SE is managed in pediatric intensive care unit and requires orotracheal intubation and mechanical ventilation. Guidelines for drugs are summarized in Fig. 3.

Propofol is characterized by partial low toxicity associated with a short-term administration, quick effectiveness, and fast recovery after withdrawal.[58] In infants with severe metabolic acidosis and movement disorders, the use of this agent should be reduced due to the risk of side effects induced.[58,59]

Sodium thiopental is characterized by high lipid solubility, fast effectiveness, and rapid metabolic degradation.[59] A EEG burst-suppression pattern is typically seen when its serum level is more than 30-40 mg/L, even if a higher blood level is needed in long treated patients.[59] EEG slowing is usually observed when its plasma level is more than 70 mg/L.[59] Thiopental protein binding, pH-dependent nonionized drug fraction and blood distribution influence effectiveness so that daily thiopental monitoring is required during infusion.[59]

Prolonged SE associated to increased brain Pgp expression suggests the treatment with verapamil,

which acts as a Pgp inhibitor. In two patients, verapamil reversed phenobarbital and phenytoin refractory with clinical improvement.[60,61]

Finally, SE occurring above 24 hours has been defined "super-refractory SE". This event should be managed with not only the abovementioned therapies but interventions including use of intravenous magnesium, pyridoxine, steroids, immunoglobulins, ketogenic diet, hypothermia, neurosurgery, electrical and magnetic stimulation, and cerebrospinal fluid outflow.[14]



## Conclusion

Status epilepticus is the most common neurologic emergency in childhood. A systematic diagnostic work-up and a three steps based therapeutic approach is required at this age. To date, no internationally shared pediatric guidelines are available for therapeutic management and further studies on wide populations are necessary to collect and to compare data about the potentials of the old and the new generation of antiepileptic drugs.

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