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**Title:** Epilepsy in children: from diagnosis to treatment

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**Abstract:** Seizures are defined as a transient occurrence of signs and symptoms due to the abnormal, excessive or synchronous neuronal activity in the brain characterized by an abrupt and involuntary skeletal muscles activity. An early diagnosis, treatment and specific medical support must be performed to prevent Status Epilepticus (SE). Seizures' onset, especially in children population, is related to specific risk factors like positive family history, fever, infections, neurological comorbidity, premature birth, mother's alcohol abuse and smoke in pregnancy. Early death risk in children without neurological comorbidity is similar to the general population. Diagnosis is generally based on the identification of continuous or recurrent seizures but EEG evaluation could be useful if SE condition in suspected. The main goal of therapy is to contrast pathological mechanism which occurs in SE before neural cells are irreversibly damaged. According to latest International Guidelines and Recommendations of seizures' related diseases, it is proposed a schematic and multi-stage pharmacological and diagnostic approach especially in the management of SE and its related causes in children. First measures should focus on early and appropriate drugs administration at adequate dosage, airway management, monitoring vital signs, PICU admission and management of parents' anxiety

**Keywords:** seizures, status epilepticus, children

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## INTRODUCTION

Emergency department generally is the place where children affected by seizures receive first treatments and medical support. Proper skills of physicians are essential for an early diagnosis, treatment and an adequate communication with the parents.

Seizures are defined as a transient occurrence of signs and symptoms due to the abnormal, excessive or synchronous neuronal activity in the brain characterized by an abrupt and involuntary skeletal muscles activity. The adjective "transient" in the definition, indicates a time frame with a clear onset and remission [1]. Status epilepticus (SE) is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanism, which lead to abnormally, prolonged seizures (for a time period of 5 minutes or more). It is a condition, which can have long-term consequences (especially if its duration is more than 30 minutes) including neuronal death, neuronal injury and alteration of neuronal network, depending on the type and duration of seizures [1]. Febrile seizures are defined as critical seizures which occurs in children aged between 1 month and 6 years with temperature rise over 38°C and without signs of infectious disease of central nervous system (CNS) [2].

The incidence of epilepsy varies between industrialized countries and developing ones. In Western countries, new cases per year are estimated to be 33.3-82/100.000, [3] in contrast to the maximum incidence of 187/100.000 estimated in developing countries [3, 4]. In particular, recent studies showed that the maximum incidence occurs in the first year of age with a rate of 102/100.000 cases per year, just like the age range from 1 to 12 [3]; in children from 11 to 17 years old incidence is 21-24/100.000 cases [3, 4]. Previous studies suggest that total incidence of epilepsy is constant from 25 years, showing a slight increase in males [3].

In Italy, epilepsy incidence is 48.35/100.000 new cases per year and it is comparable with data recorded in the other industrialized Countries. Peak of incidence occurs in children younger than 15 years old (50.14/100.000 new cases per year) and especially in the first year of life with an incidence of 92.8/100.000 new cases per year. To this regard, it should be taken into due account that children's

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immature CNS is more susceptible to seizures and at the same time refractory to the consequences of an acute attack. Finally, incidence is higher in males than in females [5].

Most common causes of SE in children are fever and infections of CNS. Other causes include hyponatremia, accidental ingestion of toxic agents, abnormalities of CNS, genetic and metabolic disorders (phenylketonuria, hypocalcemia, hypoglycemia, hypomagnesemia).

Physiopathologic course of SE in children depends on the absent of anatomical abnormalities and preexisting predisposing conditions of CNS.

*Classification of SE*

Status Epilepticus is classified according to International League Against Epilepsy (ILAE) guidelines [1] into four categories: semiologic (Table 1), etiologic (Table 2), EEG pattern (Table 3), age-related (Table 4).

**Table 1.** Semeiologic classification of SE.

| | | | |
|---|---|---|---|
| Prominent motor symptoms | Convulsive SE | Generalized convulsive | |
| | | Focal onset evolving into bilateral convulsive SE | |
| | | Unknown whether focal or generalized | |
| | Myoclonic SE | With coma | |
| | | Without coma | |
| | Focal motor | Repeated focal motor seizures (Jacksonian) | |
| | | Epilepsia partialis continua EPC | |
| | | Adversive status | |
| | | Oculoclonic status | |
| | | Ictal paresis | |
| | Tonic status | | |
| | Hyperkinetic SE | | |
| Without prominent motor symptoms or non-convulsive status epilepticus (NCSE) | NCSE with coma | | |
| | NCSE without coma | Generalized | Typical absence status |
| | | | Atypical absence status |

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| | | | |
|---|---|---|---|
| | | | Myoclonic absence status |
| | | Focal | Without impairment of consciousness |
| | | | Aphasic status |
| | | | With impairment of consciousness |
| | | Unknown whether focal or generalized | Autonomic SE |

**Table 2.** Etiologic classification of SE.

| | | |
|---|---|---|
| Known | Acute | Stroke, Intoxication, Malaria, Encephalitis, Etc. |
| | Remote | Post traumatic, Post encephalitic, Post stroke, Etc. |
| | Progressive | Brain tumors, Lafora's desease, Dementias |
| | SE in defined electro clinical syndromes | |
| Unknown | Cryptogenetic | |

**Table 3**. EEG related SE classification.

| | |
|---|---|
| Location | Generalized |
| | Lateralized |
| | Bilateral independent |
| | Multifocal |
| Pattern | Periodic discharges |
| | Number of phases |
| | Spike-and-wave/sharp-and-wave plus subtypes. |
| Morphology | Sharpness |
| | Number of phases |
| | Absolute and relative amplitude |
| | Polarity |

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| | |
|---|---|
| Time related features | Prevalence |
| | Frequency |
| | Duration |
| | Onset |
| | Dynamics |
| Modulation | Stimulus-induced vs. spontaneous |
| | |
| Effect of intervention on EEG | |

**Table 4.** Seizures age-related classification.

| | |
|---|---|
| SE occurring in neonatal and infantile-onset epilepsy syndromes | Tonic status (Ohtahara's Syndrome, West's syndrome) |
| | Myoclonic status in Dravet syndrome |
| | Focal status |
| | Febrile SE |
| SE occurring mainly in childhood and adolescent | Autonomic in early onset benign childhood occipital epilepsy Panayiotopoulos Syndrome) |
| | NCSE in specific childhood epilepsy syndromes and etiologys (Ring Cromosome 20, Angelman Syndrome) |
| | Tonic status in Lennox-Gastaut syndrome |
| | Myoclonic status in progressive myoclonus epilepsies |
| | Electrical status epilepticus in slow wave sleep (ESES) |
| | Aphasic status in Landau-Kleffner Syndrome |
| SE occurring mainly in adolescents and adulthood | Myoclonic status in juvenile myoclonic epilepsy |
| | Absence status in juvenile myoclonic epilepsy |
| | Myoclonic status in Down syndrome |
| SE occurring mainly in the elderly | Myoclonic status in Alzhaimer's disease |
| | NCSE in Creutzfeldt-Jakob desease |
| | De novo (or relapsing) absence status of later life |

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*Risk factors*

The principal risk factors for seizures in children are correlated with: positive family history [6], high temperature [7], mental disability [8], delayed discharge from NICU or premature birth [6], mother's alcohol abuse and smoke in pregnancy doubles risk of seizures incidence [9]. Moreover in 30% of children in which occurs the first episode of seizures, the probability of recurrent episodes is increased.

Instead risks factors of recurrent febrile seizures include: small age and duration of first episode of seizures, low temperature during the first episode, positive familiar history for febrile seizures in a first degree relative, short timeframe from temperature elevation and seizures onset [6].

Patients with all these risk factors show more than 70% of probability of a recurrent episode of seizures; in contrast patients with none of them have a probability of a recurrent episode of seizure lower than 20% [10, 11].

*Mortality*

Mortality rate in people affected by epilepsy are 2-4 times higher than the rest of population, and 5-10 times higher in children.

Early death risk in children without neurological comorbidity is similar to the general population and lots of death are not related to seizures themselves but to the neurological preexisting disability.

This risk increase is a consequence of: lethal neuro-metabolic alterations, systemic complications (consequence of neuro-disability), death directly related to seizures.

This group includes sudden unexpected death in epilepsy (SUDEP), that represents the most common cause of death related to epilepsy in children: it is uncommon but death risk increases if epilepsy persist until the young-adult age [8, 9].

Other causes of death could be: seizures-related (ab-ingestis), natural causes-related (brain tumors), non- natural causes (suicide or accidental death).

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Global mortality rates are between 2.7 and 6.9 death per 1000 children every year; SUDEP related mortality in children is about 1.1-2 cases/10.000 children per year [9].

*Pathophysiology*

The exact mechanism of seizures onset is unknown. There could be either a deficit of neuronal inhibition or an excess of excitatory stimuli. Most of Authors suggests that the onset of seizures depends on a deficit in the neuronal inhibition, in particular GABA deficit [12], the most important neurotransmitter of CNS; alternatively it depends on the alteration of GABA function that determines a prolonged and high intensity stimulation.

Other Studies, in experimental animal models, demonstrated that NMDA and alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid, both Glutamate receptors, the most important excitatory receptor of CNS, are involved in seizures physiopathology [12]. Febrile seizures occur in young children whose convulsive threshold is lower.

Children are more exposed to frequent infections like: respiratory high tract infections, otitis media, viral infection. When children presents high temperature [13,14]. Animal models suggest the central role of inflammatory mediators like IL-1 that could cause an increase in neuronal stimulation and the onset of febrile seizures [13].

Preliminary studies in children seem to confirm this hypothesis but its clinical and pathological meaning is still unknown. Febrile seizures could underline a severe pathological process like meningitis, encephalitis, and cerebral abscess [13].

Viral infections seem to be involved in the pathogenesis of seizures. Recent studies show that HHSV-6 (Human herpes simplex virus-6) and Rubivirus could be found in 20% of patients affected by febrile seizures for the first time [14,15]. Finally, other reports also suggest that Shigella related gastroenteritis have been associated with febrile seizures [16].

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**Diagnosis**

Clinical presentation in status epilepticus is various. It depends on the type of seizures, stage and previous state conditions of the pediatric patient. Diagnosis is based on the identification of continuous or recurrent seizures, and it is easy to recognize during the clinical manifestation.

After persisting status epilepticus, despite of disappearance of motor manifestations, it is difficult to exclude non-epilepticus continuous status.

A complete instrumental evaluation can be requested in case of first clinical presentation of SE, or in case of complicated SE, comorbidity, and during the extreme ages [17].

Literature suggests that in pediatric age routine serologic exams are not justified, since the low frequency of abnormal values. The only abnormal test in more than 20% of patients is hypoglycemia [17].

In patients that status epilepticus and body temperature above 38.5°C, a lumbar puncture could be considered, when infectious etiology is suspected. Temperature, leukocytosis, and pleocytosis in cerebro-spinal fluid may be present in SE even if infections in central nervous system are absent.

AAP guidelines in medical management of pediatric patient with febrile seizures don't suggest to perform diagnostic tests routinely, including lumbar puncture, except it's requested by the state condition [15].

The lumbar puncture is firmly recommended in all patients under one-year age that present temperature and seizures [10].

ACEP guidelines suggest that the lumbar puncture is requested in case of immune-compromission, clinical signs of meningitis, persisting seizures and recent CNS infections [15].

Computerized Tomography (CT) is requested during first clinical presentation of seizures and in clinical conditions that could increase the risk of complications.

An encephalic CT without contrast media is the first test recommended to diagnose neoformations, head injury, hemorrhages and/or cerebral infarcts. A CT with contrast media could be necessary to confirm suspected diagnose of brain tumors or subdural hematoma.

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A study has shown that pediatric patients with complex febrile seizures and normal clinical examination, and pediatric patients with febrile seizures without evident acute cause in anamnesis rarely have a positive CT. So this exam could be postponing [10].

The use of EEG in emergency room is restricted to differential diagnosis. EEG should be considered every time SE is suspected.

Research of SE causes should proceed in parallel with treatment, and good knowledge is requested because optimal treatment includes the prevention of recurrent SE.

**Treatment of SE**

The main goal in therapy during SE is to stop seizures before neural cells are irreversibly damaged. SE is as difficult to control as the duration increases; for this reason, it is important to start an early target pharmacological treatment.

The most important thing in the pharmacological treatment is a rapid implementation of a clear protocol, adjusting doses to the weight of the patient. Therefore, in case of refractory SE the treatment is as fast as possible.

The 2017 ILAE recommendations [18] relate the pharmacological treatment to time. So 3 time-points are described:

- T1 is the period in which the emergency treatment of SE should be start.
- T2 is the period after which seizures could hesitate in neural cell death, modifications in neural networks and functional deficiency.
- T3 is characterized by refractory SE: SE continues despite the treatment. In this case, the hospitalization and PICU admission is recommended.

There is also a period called T4. It is characterized by a super refractory SE, that continue more than 24 hours. In this case, it is necessary an advanced life support.

*General support measures*

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First approach in SE should focus on airway management and adequate ventilation and circulation. It is important to safeguard patient from injuries caused by uncontrolled movement. It is also important to place the patient in lateral position to prevent inhalation, and place a peripheral venous catheter.

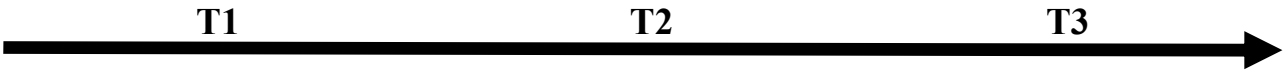
Vital signs monitoring (heart rate, blood pressure, oxygen saturation and temperature) is essential to evaluate the course of SE. A rapid blood test should be done to recognize hypoglycemia or poisoning [19].

Most of drugs used to treat SE suppress respiratory drive. Therefore, it is important take precautions to recognize and treat their side effects.

*Anticonvulsant drugs in emergency*

Guidelines in treatment of SE give the base to manage optimally SE in emergency room; 80% of patients with simple convulsion respond to initial treatment, including those who will develop a SE. The most important factor is to use effective drugs at the appropriate dosages. Therapy could be optimized choosing the correct sequence of drugs. (table 5)

**Table 5.** Pharmacological therapy.




| **Early phase Status epilepticus** | | **Clear status epilepticus** | | **Refractory status epilepticus Hospitalization in PICU** | |
|---|---|---|---|---|---|
| ***Phase 1 5-10 minutes*** | Lorazepam: 0.1 mg/kg. 4 mg max. If it's necessary, it can be repeated once | ***Phase 2 10-30 minutes*** | Phenytoin: 15 mg/kg IV. 10 mg/kg repeatable after 20 mins(velocity not above 50mg/min) | ***Phase 1 30-60 minutes*** | Propofol: 2-4 mg/kg in bolus. Infusion 3-10 mg/kg/h and titolazione to maintain burst-suppression. |

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| | | | | | |
|---|---|---|---|---|---|
| | Diazepam: 0.5-1mg/kg IV | | Valproic acid: 20 mg/kg (velocity: 5 mg/kg/min) | | Midazolam: 0.2 mg/kg (dose max 5 mg). Continuous infusion 0.1-0.3 mg/kg/h |
| | Clonazepam: 1 mg bolus IV (max 0.5 mg/min). If it's necessary it can be repeated once after 5 minutes | | Levetiracetam: 30 mg/kg (velocity: 5 mg/kg/min) | | Thiopental: 3-5 mg/kg IV. Loading dose in 20 seconds. continuous infusion: 1-3 mg/kg/h with the aim to maintain burst suppression |
| | Fenobarbital: 10 mg/kg (range 10-20) bolus IV. Infusion max dose: 100 mg/min | | Lacosamide (>16 years): loading dose 200 mg. Dose max/die 400 mg repeatable once | | Pentobarbital: 5-15 mg/kg bolus IV. Continuous infusion to maintain burst suppression (0.5-3 mg/kg/h) |

Benzodiazepines are considered the first choice in the initial treatment of seizures and SE in pre-hospital emergency care. They increase inhibition of GABA receptors, have a rapid onset and are effective in 79% of patients in SE.

Barbiturates increase inhibition of GABA receptors. Fenobarbital is one of the most common and used. However, it is difficult to manage because of its long half time.

Phenobarbital and Phenytoin are considered second-class drugs to treat seizures and SE, and they are usually administrated when benzodiazepines fail. Side effects are: sedation, respiratory depression and hypotension. So airway management and cardiovascular should be priory considered [20].

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Phenobarbital is the antiepileptic drug, often used in neonatal seizures, although Phenytoin is equally effective.

Valproic acid is important in refractory SE (stage 2 in 2017 ILAE recommendations) [18].

Propofol is an anesthetic agent with anticonvulsant activity. It is used in refractory SE. Disadvantages are short half-life and rapid metabolism that could get convulsions worse. The main side effects are respiratory depression and hypotension because of myocardial depression [21,22]. High doses of Propofol in continuous rate infusion should be limited to short period, generally no more than 24-48 hours in order to prevent Propofol infusion syndrome [23].

**Remarks about convulsions and pediatric SE**

Pediatric patients with head injury and 3-8 Glasgow Coma Scale (GCS) risk developing seizures and it is recommended to prevent them by prophylaxis. Most of seizures in pediatric patients and teenagers can be treated by oral valproic acid. In particular, juvenile myoclonic epilepsy (JME) take advantage of it. Young adult that do not sleep much and drink alcohol can show generalized seizures in the morning [24]. In these patients, valproic acid is a very good drug to use in emergency [25].

**Parents training for the future**

Parents must be prepared to know what to do if their children show seizures. They should call the emergency number if seizures persist more than 10 minutes, and if the post convulsive state last longer than 30 minutes. Moreover, they should be informed about benign nature of febrile seizures. Infact they are not connected to neurological problems or physical slowed development. Parents must pay attention to their sons, because studies have proved that febrile seizures are inclined to be recurrent in family [26].

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## Conclusions

Pediatric seizures and SE are emergencies that request early and effective treatment. Everybody knows that for all this patients outcome can be improved using antiepileptic drugs at the appropriate dose. Further studies should focus on the management in pediatric patient's convulsions or SE through the improvement of treatment taking into due account that airway management is prior in pediatric patient with seizures or SE; child with febrile seizures in anamnesis must be evaluated through neurological examination and monitoring of mental development, causes of fever must be always investigated and treated, other causes of seizures must be excluded and parent's anxiety must be controlled.

## Author Contributions

C. M., R.M., P.V., F.V., S.P., P.P., M. A., P.M. reviewed the literature, critically discussed various aspects of epilepsy in pediatric patients and read the manuscript; C.M. and P.M. wrote the manuscript and prepared tables.

## Conflicts of Interest

The authors declare no conflict of interest.

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