



10-2011

## Status Epilepticus in Children: An Update

Nida Akhtar

*Aga Khan University*

Anwarul Haque

*Aga Khan University*

Khalid Ahmed

*Aga Khan University*

Follow this and additional works at: <https://ecommons.aku.edu/pjns>

 Part of the [Neurology Commons](#)

### Recommended Citation

Akhtar, Nida; Haque, Anwarul; and Ahmed, Khalid (2011) "Status Epilepticus in Children: An Update," *Pakistan Journal of Neurological Sciences (PJNS)*: Vol. 6 : Iss. 3 , Article 7.

Available at: <https://ecommons.aku.edu/pjns/vol6/iss3/7>



# STATUS EPILEPTICUS IN CHILDREN: AN UPDATE

Nida Akhtar<sup>1</sup>, Anwarul Haque<sup>2</sup>, Khalid Ahmed<sup>2</sup>

<sup>1</sup>Aga Khan University Hospital, Karachi, Pakistan

<sup>2</sup>Department of Pediatrics and Child Health, Aga Khan University Hospital, Karachi, Pakistan

Correspondence to: Dr. Khalid Ahmed, Department of Pediatrics and Child Health, Aga Khan University Hospital, Karachi, Pakistan. Tel: 3486-4356, Email: ahmed.khalid@aku.edu

Pak J Neurol Sci 2011; 6(3): 26 - 32

## INTRODUCTION

Status Epilepticus (SE) is the most common, life threatening medical emergency associated with significant morbidity and mortality. An established therapeutic plan for prompt seizure termination along with meticulous supportive care is required to limit the detrimental effects of prolonged seizure activity. These effects may be neurological or systemic. Permanent neurologic damage can occur with prolonged SE.<sup>1</sup> This article starts with a brief review of SE, its definition, epidemiology, classification, pathogenesis and etiologies. Finally the authors discuss the strategic therapeutic steps and treatment of GCSE. Then the systemic and neurological effects of seizures and SE discussed.

## DEFINITION

SE is a clinical diagnosis. The International Classification of Epileptic Seizures defines it as "Seizure lasting for more than 30 minutes or intermittent seizures from which the patient did not regain consciousness lasting for more than 30 minutes".<sup>2</sup>

Although the definition is time based, exact duration of seizure activity is usually difficult to determine; and so treatment cannot be withheld until the 'time-definition' is fulfilled. Based on the recent understanding of the pathophysiology, it is now considered that any seizure lasting for more than 5 minutes needs to be treated as SE.<sup>1</sup>

Numerous clinical studies have demonstrated a relation between seizure duration and mortality. When confronted with a patient with continuous seizures, one cannot wait for 30 minutes, before initiating therapy as the seizure may become refractory and difficult to

control if treatment is delayed. Lowenstein et al.<sup>3</sup> have proposed that SE be defined as a continuous, generalized, convulsive seizure lasting for more than 5 minutes, or two or more seizures during which the patient does not return to baseline consciousness. Probably, any convulsive seizure that lasts more than 2 minutes deserves to be managed as SE.

In some children with SE, seizures persist despite treatment with adequate doses of initial two or three anticonvulsant medications, and this condition constitutes refractory SE. The exact definition is still unclear, with different studies defining refractory SE with varying durations (no time criteria, 30 minutes, 1 hour, 2 hours) and a lack of response to different numbers (two or more) and types of medications. Refractory SE is associated with high morbidity and mortality. In a subgroup of patients, refractory SE may last for weeks or months, despite treatment with multiple anticonvulsants and coma-inducing medications. This is referred to as malignant, refractory SE. Malignant refractory SE is associated with encephalitic etiology, younger age, previous good health and high morbidity and mortality. It remains unclear whether this condition represents a specific disease entity, or simply a particularly severe variant of refractory SE because of certain etiologies.<sup>4</sup>

## EPIDEMIOLOGY

The greatest numbers of cases occur in children, with the average age being 3 years. In 50-86% of children with SE, it may be the initial or only presentation of seizure disorder. Mortality rates have decreased (3-6%) worldwide and this is due to more effective management of SE. Mortality and morbidity is related



to the underlying cause and the duration of SE. If under treated or inappropriately treated it may result in significant brain injury and even death. Neurological sequelae of SE be it motor delay or cognitive impairment, range from 9-29%. Subsequent epilepsy is seen in 30% of individuals. SE has been reported to be more common in boys. At our institute, the mortality has been reported to be as high as 25%.<sup>5</sup>

## CLASSIFICATION

SE is commonly classified by seizure type. Based on the electroclinical features, SE may be classified by the presence or absence of motor convulsions as convulsive SE and non-convulsive SE. They may be further divided into SE that affects the whole brain (generalized SE) or only part of the brain (partial SE).

**Convulsive SE (CSE):** CSE can further be divided into tonic, clonic or tonic-clonic. Generalized tonic-clonic SE (GCSE) constitutes 73–98% of pediatric SE and involves all extremities. In primary GCSE, seizure onset cannot be localized to one brain region by either clinical or EEG findings. In secondary GCSE, which is more common, seizures begin focally but spread to involve the entire brain. Consciousness is usually impaired.

Focal motor SE, also called simple complex SE, somatomotor SE or epilepsy partialis continua<sup>6</sup>, is characterized by involvement of a single limb or side of the face. This is less common than GCSE and is frequently associated with focal brain pathology.

Myoclonic SE is characterized by irregular, asynchronous, small-amplitude, repetitive myoclonic jerking of the face or limbs. It is more common in comatose patients and is associated with several specific conditions e.g. anoxia or cardiac arrest.

**Non-convulsive SE (NCSE):** NCSE refers to continuous, non-motor seizures and requires EEG confirmation for diagnosis. It may occur in ambulatory or comatose patients. It is characterized by abnormal mental status, unresponsiveness, ocular motor abnormalities, persistent electrographic seizures and possible response to anticonvulsants.<sup>7</sup> NCSE has been divided into two main categories.

**Absence SE (ASE):** ASE is characterized by altered consciousness and a characteristic 3Hz symmetric spike and wave pattern on EEG. ASE is usually easier to treat and may not be associated with significant

neuronal damage.

**Complex partial SE (CPSE):** CPSE is marked by altered consciousness and focal activity on EEG usually involving the temporal lobe. Several investigators have shown that CPSE is more common than previously thought and that many cases of ASE are actually cases of CPSE that have generalized.<sup>8</sup>

## PATHOPHYSIOLOGY

Failure of mechanisms that normally abort an isolated seizure is the fundamental pathophysiology of SE. This failure can arise from abnormal, persistent, excessive excitation or ineffective recruitment of inhibition.<sup>3</sup>

GABA is the major inhibitory neurotransmitter in the CNS. GABA receptor mediated inhibition may be responsible for the normal termination of a seizure.<sup>9</sup>

Glutamate, a prominent excitatory amino acid is important in its ability to excite neurons and in some circumstances destroy them. Glutamate can activate the NMDA receptor and be responsible for the propagation of seizure activity.<sup>9</sup> The activation of NMDA receptors results in increased levels of intracellular calcium, which can be responsible for the nerve cell injury seen in patients with SE.<sup>10-12</sup> A growing body of basic science and clinical observation believes that SE becomes more difficult to control as its duration increases.<sup>13-15</sup> It has been postulated that this may be due to a mechanistic shift from inadequate GABAergic inhibitory receptor mediated transmission to excessive NMDA excitatory receptor mediated transmission.<sup>16-21</sup>

Sustained seizures can cause neuronal loss, especially in vulnerable regions of the limbic structures e.g. hippocampus.<sup>22, 23</sup> Neuron specific enolase, a marker for acute neurological injury, has been demonstrated to be increased in patients with NCSE who did not have preceding or co-existent cerebral injury.<sup>24-27</sup> The degree of neuronal injury is closely related to the duration of seizures, highlighting the importance of rapid control of SE.<sup>23,28</sup> This damage is partly a consequence of glutamate mediated excitotoxicity and does not appear to be primarily due to an excessive metabolic demand imposed by repetitive neuronal firing [3]. Mikati and co-authors have demonstrated that increased NMDA activation results in increased ceramide levels followed by programmed cell death.<sup>29</sup> The superimposition of systemic stresses such as hyperthermia, hypoxia or hypotension, exacerbates the degree of neuronal injury in animal models of SE, a finding co-existent with empirical observations in



in humans.<sup>30, 31</sup>

## ETIOLOGY

A broad differential and ensuing evaluation is important in the assessment of etiology of SE. Etiologies are highly dependent on the age of the patient, in children younger than two years, acute causes are more common than remote etiologies (e.g. prior history of stroke, meningitis, brain tumor and hypoxic insult), whereas this is reversed in older patients.<sup>32</sup>

A brief history should be obtained when possible as it often gives clues to the underlying etiology. Laboratory and radiologic studies should be tailored to the patient and based on history and physical examination findings. Anticonvulsant levels should be drawn on all patients with known epilepsy. Likewise, cervical spine evaluation and precautions should be utilized on any patient where trauma is a possibility.

The most common etiology of acute symptomatic SE is febrile seizure. Febrile SE accounts for approximately 5% of febrile seizures and one third of all episodes of SE in children.<sup>33</sup> The diagnosis of febrile SE remains essentially as one of exclusion. The most important etiology to be excluded is one of a CNS infection.

Another common cause of SE is medication non-compliance. Children with usually well-controlled epilepsy can experience prolonged seizures after missing doses of their medications. A careful medication history can be helpful in discerning this as can anticonvulsant levels if available.

Infections of the CNS can often present with SE. In the setting of SE and a fever at any age, analysis of CSF is warranted unless another etiology is clearly identified. This is because the presence or absence of meningeal signs is often hard to interpret in the light of decreased sensorium. Likewise, empiric treatment with antibiotics and acyclovir should be considered unless CSF analysis excludes herpes simplex virus encephalitis or bacterial meningitis as a possibility.

Electrolyte disturbances can also present with SE, usually in the setting of concurrent altered mental status or encephalopathy. The most common electrolyte abnormalities include hyperglycemia, hypoglycemia and hyponatremia. Hypocalcemia is a common cause in the neonate. Electrolyte abnormalities are notorious for inducing SE that is refractory to appropriate anti-epileptic drug (AED) treatment. In this setting,

seizures may continue until the underlying abnormalities are corrected.

Another important etiology of SE is trauma, often associated with non-accidental injuries, including the shaken baby syndrome. Seizures and SE can often be the presenting and only symptom of child abuse, especially, in the absence of any external manifestations or a suggestive history. In the setting of SE without another clear etiology, CT of the head should be considered when the child is clinically stabilized.

Stroke may present with SE, usually in the presence of a known congenital heart lesion, but can occur without such a history too. CT may often be helpful in identifying a new stroke. A persistent new focal finding on neurological examination should be considered a stroke until proven otherwise.

Occult structural abnormalities including cortical dysplasia, CNS tumors, CNS autoimmune processes and vascular malformations may also present with SE, although the diagnosis of these etiologies is somewhat less urgent and may require MRI or serological evaluation not undertaken in the emergency setting.

## TREATMENT

There is no consensus as to treatment approach to SE with respect to medication selection and dosages. Our protocol for treatment of status epilepticus is summarized in Figure 1. The management may be divided into 3 main components:- assessment of airway, breathing and circulation, controlling the seizure activity, and identifying and appropriately managing the underlying etiology. In the evaluation and treatment of SE, evaluation of the patients' vital signs and an assessment of airway, breathing and circulation (with appropriate interventions) should precede anticonvulsant treatment. Simple non-invasive airway maneuvers (e.g. midline positioning of the head and neck, jaw thrust or chin lift), suctioning of excess secretions and the provision of supplemental oxygen should benefit most actively seizing children and should therefore precede efforts to obtain vascular access.<sup>34</sup>

Guiding principles in the medical treatment of SE with AEDs include the rapid administration of appropriate medications at appropriate dosage. Common errors include medication under-dosing, excessive intervals between medications and inappropriate medication choices and routes of administration. For every minute delay between the seizure onset and emergency room



arrival, there is a 5% cumulative increase in the risk of having SE lasting more than 60 minutes [35]. One explanation of this finding may be that with the increasing duration of SE, inhibitory GABA receptors are internalized, making benzodiazepines (BDZ) less effective. BDZ including diazepam and lorazepam are the most commonly used first line AEDs for SE. Intravenous or rectal routes of administration are usually performed for these two drugs given their fast rectal absorption and the more rapid onset of action. Lorazepam is equally or more effective than diazepam but with possibly less respiratory depression.<sup>36-39</sup>

Midazolam administered by either the buccal or the nasal route has been shown to be effective and safe.<sup>40-42</sup> However, its role in the emergency department and the effective dose has not yet been completely evaluated.<sup>43</sup>

Dosing recommendations are highly variable, as are the number of repeated doses, although most recommend giving 2 or 3 doses of BDZ before considering of other AEDs. A general principle governing the use of BDZ for SE is that administration should be rapid (pushed or infused over a few minutes) and the administered dose should be sufficient. Both low and high dosing can cause problems. High dosing is problematic and often occurs when pre-hospital doses are not considered. Several studies show that extra doses may be associated with increases risk for respiratory depression. Low dosing may not terminate the SE. Frequent dosing of small or inadequate doses should be avoided because this prolongs the time for achieving the therapeutic level of AED. Rather high individual doses should be used once or twice to allow for more timely institution of a second AED if needed.<sup>34</sup>

Most practitioners now regard fosphenytoin as the second choice AED. The pro-drug- fosphenytoin converts to phenytoin within 15 minutes of infusion. A standard initial loading dose for SE is 20 mg/kg PE, although some advocate using lower doses. Advantages of fosphenytoin over phenytoin include lower risk of cardiac dysfunction with acute infusion, lower rates of phlebitis and less severe tissue necrosis if the medicine extravasates from the vein during infusion. A loading dose of 20 PE units should provide a serum phenytoin level of around 20  $\mu\text{g}/\text{ml}$ . A second dose of 10 micro units/kg is often given if the first loading dose fails to stop clinical seizures.<sup>34</sup>

If appropriate doses of two standard anticonvulsant drugs fail to stop clinical and electrographic seizures, SE is considered refractory.<sup>44</sup> At this point a neurolo-

-gist should be consulted, if available and considering intensive care unit placement is appropriate. This is because the alternative medications can potentially depress respiration; therefore, respiratory monitoring is mandatory. This is best achieved in the PICU, where there is high level of nursing input and sophisticated technology for continuous monitoring of physiologic parameters.<sup>45</sup>

A more detailed review of potential acute symptomatic etiologies should be undertaken at this time. Electrolyte derangements such as hyponatremia or hypoglycemia are notorious for inducing SE that is unremitting in the face of AED treatment. Also, infections of the CNS and trauma should be considered. Other routine AEDs recommended at this point include IV phenobarbital, valproic acid, midazolam or pentobarbital continuous infusion, levetiracetam and topiramate.

Phenobarbital is commonly chosen as the next AED for refractory SE. Its main advantages are its powerful antiepileptic action, long duration of action and possible neuroprotective properties. However, it is a powerful sedative, has a long half-life and may cause respiratory depression and hypotension especially after BDZ are given, often requiring ventilatory support. It is given via IV infusion at an initial loading dose of 20 mg/kg. It has a greater intrinsic anticonvulsant action than other barbiturates which may be related to its cerebral distribution, high concentration in the motor cortex or specific physiochemical membrane stabilizing action. Children frequently develop acute tolerance to the respiratory depressing and sedative effects of phenobarbital, but not to its anti-seizure effects. Its half-life of 24-72 hours makes the ongoing assessment of clinical and neurological function difficult for a prolonged time. So, many clinicians are now avoiding its use in refractory SE.

IV valproic acid has some formal evidence for its efficacy in SE. The exact mechanism of action of this commonly used antiepileptic drug is unknown, but it is thought to have GABAergic actions and blocks sodium ion channels. It is considered a broad spectrum anticonvulsant. It is also less sedating than the other AEDs, allowing for more precise ongoing neurological examination and does not cause arrhythmias, bradycardias or hypotension [46]. Although, valproic acid is often loaded slowly (< 20mg/min), recent studies have shown that faster infusion rates may be safe. Valproic acid rarely causes thrombocytopenia or hepatotoxicity, but this has not been reported after first loading dose.<sup>47</sup>



Midazolam is an injectable BDZ, used primarily as a premedicant, sedative and anesthetic agent. It causes little, if any, local discomfort after administration and has shown to have a wide safety margin with a broad therapeutic index. It also diffuses rapidly across the capillary walls into the CNS and can be mixed with saline or glucose solutions, thereby facilitating its administration as a continuous infusion. Midazolam continuous infusions are usually started at 50-100  $\mu\text{g}/\text{kg}/\text{hr}$  and titrated upwards to a range of 600-1200  $\mu\text{g}/\text{kg}/\text{hr}$ . To avoid tachyphylaxis, the infusion rate increments should be small, reaching maximal dose a few hours after initiation at most. Hypotension can occur with midazolam. Hypoxia associated with respiratory depression and increased pharyngeal secretions has also been seen.

Pentobarbital has been the preferred barbiturate in the US for the treatment of refractory SE, though there is little published experience with children. Although it is similar to thiopentone, phenobarbital has theoretical advantages over thiopentone, including a shorter elimination half-life, non-saturable kinetics and GABAergic activity that may enhance neuroprotection. And it is less cardiotoxic in high doses. However, in practice the use of pentobarbital has been associated with a poor outcome. Pentobarbital can be administered as a continuous infusion for refractory SE. It is usually initiated with a loading dose of 5-8 mg/kg followed by a continuing infusion at a rate of 0.5-1 mg/kg/hr and then increased as needed to 3-5 mg/kg/hr. Pentobarbital, like phenobarbital, is extremely sedating and has a higher associated rate of hypotension than does midazolam, often requiring pressor support for blood pressure management.

Levetiracetam is an anti-convulsant medication, thought to have multiple sites of action including calcium channels, glutamate receptors and GABA modulation. It is available as IV and oral preparations, but the IV form is not approved for use in children. Refractory SE is often associated with systemic disorders such as coagulopathy, liver failure and hypotension, which could be complicated by traditional anticonvulsants. IV Levetiracetam may provide an alternative because it is not metabolized by the liver, has low protein binding, is renally excreted and exhibits few drug interactions. It is administered at 20-30 mg/kg and IV at 5 mg/kg/min (maximum 3 g).

Topiramate exhibits several mechanisms of action, including blockage of the voltage-sensitive sodium and calcium channels, enhancement of GABA activity via modulation of GABA type A receptor and modulation of

glutamate receptors. Because it exhibits mechanism independent of GABA receptors, topiramate may be effective later in refractory SE after GABA receptors have been targeted by other agents. Studies suggest that rapid titration is safe.

Termination of motor manifestations of CSE does not necessarily imply that the abnormal brain electrical activity has also stopped. Such electromechanical dissociation is associated with a worsened prognosis and it is important not to miss it. So, paralyzing drugs should be used cautiously in children with CSE. The only way to identify electromechanical dissociation is to obtain an EEG after termination of motor manifestations. A potential pitfall is overtreating children with long standing frequent EEG abnormalities, who have an episode of CSE, in order to try and remove all epileptic discharges from the EEG.

## COMPLICATIONS

Patients with SE are prone to several medical complications. Prolonged seizures can lead to multiple organs' dysfunction. Medications, such as phenobarbital, may depress the immune response of the patient and therefore predispose them to infections. Non-neurological complications include nosocomial and ventilator associated pneumonia, atelectasis, respiratory distress syndrome, neurogenic pulmonary edema, pulmonary embolism, hypovolemia, myocardial dysfunction, hypertension, arrhythmias, stress ulcers, gastrointestinal bleed, constipation, diarrhea, paralytic ileus, renal dysfunction, urinary tract infection and vascular catheter related sepsis. It is important to watch for these complications, so as to detect them as early as possible and institute prompt treatment.

## REFERENCES

1. Status Epilepticus. Ajith cherian, Sanjeev V. Thomas. Annals of Indian Academy of Neurology. July-Sept 2009.
2. Classification of status epilepticus. Gastaut H. Adv Neurol 1983;34:15-35.
3. Status Epilepticus. Lowenstein DH, Alldredge BK. N Engl J Med. 1998;338:970-6.
4. Treatment of Refractory Status Epilepticus: Literature review and a Proposed Protocol. Nicholas S. Abend, Dennis J. Dlugos. Pediatr Neurol 2008;38:377-390.
5. Status Epilepticus in Children: A 5-year Experience at Aga Khan University Hospital. S. II.



- Ibrahim, M. A. Yezdan, S. Q. Nizami. *JPMA* 53:597:2003
6. International League against Epilepsy: Proposal for revised Clinical and electrographic classification of epileptic Seizures. *Epilepsia* 22; 489,1981
  7. Status Epilepticus: Its Clinical Features and Treatment in children and Adults. Shorvon S. Cambridge, England: Cambridge University Press; 1994. P. 201e.
  8. Long Term Mortality after a first episode of Status Epilepticus. Logroscino G, Hesdorffer DC, Cascino GD, Annegers JF, Bagiella E, Hauser WA. *Neurology* 2002; 58:537-41.
  9. The management of status Epilepticus. Paul E Marik, Joseph Varon. *Chest* 2004; 126:582-591.
  10. Analysis of Electrocardiographic changes in Status epilepticus. Boggs JG, Painter JA, DeLorenzo RJ. *Epilepsy res* 1993; 14:87-94.
  11. NMDA receptor activation during status epilepticus is required for the development of epilepsy. Rice AC, DeLorenzo RJ. *Brain Res* 1998; 782:240-247
  12. In vitro status epilepticus causes sustained elevation of intracellular calcium levels in hippocampal neurons. Pal S, Sombati S, Limbrick DD Jr, et al. *Brain Res* 1999; 851: 20-31
  13. Response of status epilepticus induced by lithium and pilocarpine to treatment with diazepam. Walton NY, Treiman DM. *Exp Neurol* 1988; 101:267-275
  14. Refractory status epilepticus: frequency, risk factors, and impact on outcome. Mayer SA, Claassen J, Lokin J, et al. *Arch Neurol* 2002; 59:205-210
  15. A comparison of four treatments for generalized convulsive status epilepticus: Veterans Affairs Status Epilepticus Cooperative Study Group. Treiman DM, Meyers PD, Walton NY. *N Engl J Med* 1998; 339:792-798
  16. Refractory status epilepticus in 2001. Bleck TP. *Arch Neurol* 2002; 59:188-189
  17. Evidence that repetitive seizures in the hippocampus cause a lasting reduction of GABAergic inhibition. Kapur J, Stringer JL, Lothman EW. *J Neurophysiol* 1989; 61:417-426
  18. Loss of inhibition precedes delayed spontaneous seizures in the hippocampus after tetanic electrical stimulation. Kapur J, Lothman EW. *J Neurophysiol* 1989; 61:427-434
  19. Rapid seizure-induced reduction of benzodiazepine and Zn<sup>2+</sup> sensitivity of hippocampal dentate granule cell GABA<sub>A</sub> receptors. Kapur J, Macdonald RL. *J Neurosci* 1997; 17: 7532-7540
  20. Motor and electroencephalographic response of refractory experimental status epilepticus in rats to treatment with MK-801, diazepam, or MK-801 plus diazepam. Walton NY, Treiman DM. *Brain Res* 1991; 553:97-104
  21. Ketamine controls prolonged status epilepticus. Borris DJ, Bertram EH, Kapur J. *Epilepsy Res* 2000; 42:117-122
  22. Extracellular hippocampal glutamate and spontaneous seizure in the conscious human brain. During MJ, Spencer DD. *Lancet* 1993; 341:1607-1610
  23. The pattern of 72-kDa heat shock protein-like immunoreactivity in the rat brain following flurothyl-induced status epilepticus. Lowenstein DH, Simon RP, Sharp FR. *Brain Res* 1990; 531:173-182
  24. Neuronspecific enolase, a marker of acute neuronal injury, is increased in complex partial status epilepticus. DeGiorgio CM, Gott PS, Rabinowicz AL, et al. *Epilepsia* 1996; 37:606-609
  25. Neuron specific enolase is increased after non-convulsive status epilepticus. Rabinowicz AL, Correale JD, Bracht KA, et al. *Epilepsia* 1995; 36:475-479
  26. CSF neuron-specific enolase after methohexital activation during electrocorticography. Rabinowicz AL, Correale JD, Couldwell WT, et al. *Neurology* 1994; 44:1167-1169
  27. Serum neuron specific enolase in status epilepticus [abstract]. DeGiorgio CM, Correale JD, Ginsburg DL. *Neurology* 1994; 44(suppl):205
  28. The role of excitatory neurotransmitters in seizure-induced neuronal injury in rats. Tanaka K, Graham SH, Simon RP. *Brain Res* 1996; 737:59-63
  29. Hippocampal programmed cell death after status epilepticus: evidence for NMDA-receptor and ceramide-mediated mechanisms. Mikati MA, Abi-Habib RJ, El Sabban ME, et al. *Epilepsia* 2003; 44:282-291
  30. Prolonged epileptic seizures in primates: ischemic cell change and its relation to ictal physiological events. Meldrum BS, Brierley JB. *Arch Neurol* 1973;28:10-7.
  31. Systemic factors and epileptic brain damage: prolonged seizures in paralyzed, artificially ventilated baboons. Meldrum BS, Vigouroux RA, Brierley JB. *Arch Neurol* 1973;29:82-7.
  32. In whom does status epilepticus occur: age related differences in children. Shinnar S, Pellock JM, Moshe SL, et al. *Epilepsia* 1997;



- 38:907-14.
33. Outcome of childhood status epilepticus and lengthy febrile convulsion: finding of national cohort study. Verity CM, Ross EM, Golding J. *BMJ* 1993;307:225-8.
  34. Status Epilepticus in the Pediatric emergency department. Joshua Goldstein. *Clinical Pediatric Emergency Medicine* 9:96-100. 2008
  35. Treatment of community-onset, childhood convulsive status epilepticus: a prospective, population based study. Chin RF, Neville BG, Peckham C, et al: *Lancet Neurol* 7:696-703, 2008
  36. Double-blind study of lorazepam and diazepam in status epilepticus. Leppik IE, Derivan AT, Homan R, Walker J, Ramsay RE, Patrick B. *JAMA* 1983;249:1452-4.
  37. Lorazepam vs. diazepam in the treatment of epileptic seizures and status epilepticus. Appleton RE, Sweeney A, Choonara I, Robson J, Molyneux E. *Dev Med Child Neurol* 1995; 37:682-8.
  38. A comparison of four treatments for generalized convulsive status epilepticus. Treiman DM, Meyers PD, Walton NY, et al. *N Engl J Med* 1998;339:792-8.
  39. Respiratory depression in children receiving diazepam for acute seizures: a prospective study. Norris E, Marzouk O, Nunn A, McIntyre J, Choonara I. *Dev Med Child Neurol* 1999;41:340-3.
  40. Nasal rather than rectal benzodiazepines in the management of acute childhood seizures. O'Regan ME, Brown JK, Clarke M. *Dev Med Child Neurol* 1996;38:1037-45
  41. Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence. Scott RC, Besag FMC, Neville BGR. *Lancet* 1999;353:623-6.
  42. Buccal midazolam use in children. Chattopadhyay A, Morris B, Blackburn, Wassmer E, White house W. *Lancet* 1999;353:1798.
  43. The Treatment of convulsive Status Epilepticus in children. The status epilepticus working party. *Arch Dis Child* 2000 83: 415-419
  44. Status Epilepticus and Acute Serial Seizures in Children. Wendy G. Mitchell. *J Child Neurol* 2002; 17:S36-S43.
  45. Status Epilepticus. Richard F.M. chin, Rod C. Scott. *The Central Nervous System in Pediatric Critical Illness and Injury*. Chapter 11.
  46. Safety of rapid intravenous valproate infusion in pediatric patients. Morton LD, O'Hara KA, Coots BP, et al: *Pediatr Neurol* 36:81-83, 2007
  47. Valproic acid hepatic fatalities. III. U.S. experience since 1986. Bryant AE, Dreifuss FE: *Neurol-*