International Journal of Pediatrics & Neonatal Care
Review Article Open Access

Status Epilepticus: An Update of Classification and Treatment of a Challenging Neurological Emergency

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Abstract

In spite of more than one century of clinical and scientific interest on status epilepticus, further definitions of semiological and etiopathogenetical aspects of this challenging condition are still required. Very recent papers proposed a new mode of classification with the aim to define the operational dimensions of status epilepticus and, of course, an appropriate treatment approach based on clinical and etiopathogenetical criteria. Nevertheless, it remains one of the most common neurological emergencies worldwide, and, its pharmacotherapy still represents an "evidence-free zone" because of lack of controlled trials supporting clinical management. Herein, we reviewed the physiopathology of status epilepticus, from the first descriptions to the more recent data on specific immuno-inflammatory patterns and microglial activation. Moreover, the mostly reported criteria of classification and their pharmacological implications were summarized. Treatment stepwise approaches were also sistematically reviewed.

Publication History:
Received: February 15, 2016
Accepted: May 16, 2016
Published: May 18, 2016

Keywords:
Status epilepticus, Neuronal damage, Classification, Treatment

Abbreviations

SE: Status epilepticus, CSE: convulsive status epilepticus, NCSE: non-convulsive status epilepticus, AV: arterovenous, CO_2: carbon dioxide, HMGB1: High mobility group box 1, BBB: Blood Brain Barrier, BECTS: benign epilepsy with centro-temporal spikes, ESES: Status epilepticus during sleep (ESES), CSWSS: Continuous spikes and waves during slow sleep (CSWSS), NORSE: new onset refractory status epilepticus, RSE: refractory status epilepticus

Introduction

Status epilepticus (SE) is the most common neurological emergency in childhood in developed countries, which can lead to short and long term neuro-cognitive sequels and death [1] After more than 50 years from the first studies, SE continues to be a challenging condition in terms of classification and management.

In 1970 the International League Against Epilepsy (ILAE) defined Status Epilepticus as a "seizure that persists for a sufficient length of time or is repeated frequently enough to produce a fixed and enduring condition" [2].

Minimal changes of the latter definition were made in 1981 revision, in which SE was described as a "…seizure that persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur" [3].

Despite these first attempts to find a proper definition for a clinical seizure, prolonged enough to configure a SE, several years were necessary to figure the question out. The International Italian League Against Epilepsy (ILAE; Commission on Epidemiology & Prognosis, International League Against Epilepsy, 1993) and the Epilepsy Foundation of America (Epilepsy Foundation f America's Working Group on Status Epilepticus, 1993) defined SE as a "condition in which a single attack or more seizures continue for >30 min without recovery of function/consciousness" [4-5]. This timing decided by ILAE and EFA were relied on Meldrum's studies that reported as about 80 minutes of continuous seizure activity can lead to irreversible brain damage [6].

An *ad hoc* committee of the Italian League Against Epilepsy defined SE as " a clinical situation characterized by continuous seizure activity (generalised or partial, with or without motor manifestations) lasting for more than 20 min or seizure recurring at very short intervals (<1 min) establishing a persisting epileptic condition". At least, a shorter time of intervention has been proposed to be 5-10 minutes to define SE and start the treatment [7]. Very recently, the Commission on Classification and Terminology and the Commission on Epidemiology of ILAE constituted a Task Force with the aim to revise concepts of timing and operational dimensions of SE. Based on the short and long term consequences of prolonged critical activity, two different operational dimensions were identified: the first, time point 1, at 5-10 minutes, that represents the shorter time interval required to configure continuous seizure activity, and the second, time point 2, at 30 minutes, that indicates the time requested to induce neuronal damage and consequent long term sequels [8].

Neurophysiopathology

The interest on why and how some patients show a trend to develop prolonged seizures and SE is quite old. The neurophysiopathological mechanisms subsequent to the onset of SE were originally reported by Meldrum et al in 1973 [6].

Since three decades it has been described as the injection of substances such as GABA antagonist bicuculline and L-allyglycine may induce SE in rats and baboons lasting for hours. These studies showed the changes that the normal vascular brain physiology undergoes with the onset of prolonged epileptic activity. In a first phase, just next to the beginning of the critical activity, crucial hemodynamic changes were showed with a marked increase of the arterial and venous

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Citation: Parisi E, Biasone V, Munafò GI, Isgrò AR, Nicotera A, et al. (2016) Status Epilepticus: An Update of Classification and Treatment of a Challenging Neurological Emergency. Int J Pediatr Neonat Care 2: 115. doi: https://doi.org/10.15344/2455-2364/2016/115

cerebral blood pressure, severe metabolic and respiratory acidosis, hyperglycemia, and an abnormal cerebral arteriovenous (AV) oxygen (O_2) and carbon dioxide (CO_2) ratio. In the second phase of the critical activity (+25 to +300 minutes) a normal or low arterial blood pressure was recorded, an improvement of the cerebral AV O_2 and CO_2 ratio, but the O_2 tension of the cerebral venous system was not critically reduced. Moreover, a severe increase of the body temperature, hyperkalemia, and sometimes hypoglycemia could be observed [6]. Indeed, after two hours of critical activity several brain istochemical changes appear. Neurons are involved according to different degrees: Grade I (less severe): neuronal cytoplasm slightly darker than usual; Grade II: usually dark or condensed neurons with microvacuoles; Grade III: classic ischemic changes of cytoplasm and karyoplasm which become dark and wrinkled, with or without microvacuoles. Many of microvacuoles originate from mitochondria. Mitochondrial damage is characterized by swelling and altered calcium influx. An abnormal morphology can be also observed in the pyramidal cell bodies and in basal dendrites of CA3 and CA1 portions of hippocampal neurons. The high calcium enrichment of synaptic vesicles within this regions, mitochondria and Golgi apparatus of pyramidal neurons and dentate granule cells make them particularly vulnerable to hypoxic insults. (6) SE produces a rapid and intense inflammatory reaction cascade: already after 30-60 minutes, high levels of IL-1 beta, TNF-alpha, IL-6, CD68 + macrophages and reduced T lymphocytes CD3 are detected, as well as an increased level of cyclooxygenase-2 (COX-2). The mRNA expression of IL-1 beta, TNF-alpha and IL-6 are increased in rodents after 30 minutes from the seizures' onset, with subsequent decline within 48–72 h. IL-1β is still upregulated in the brain 60 days after SE. Notably, the same inflammatory pathways are usually activated during a fever that constitutes a frequent trigger of SE in childhood. The increased expression of high mobility group box 1 (HMGB1), a nuclear protein secreted into the interstitial space during infection and/or systemic inflammatory conditions, contributes to trigger the inflammatory cascade. (9) HMGB1 is highly expressed in human epileptogenic brain, and HMGB1 blocking therapy has been shown to exert neuroprotective effects during the early phase of kainic-induced SE in juvenile rats [10].

A critical role within the pathophysiology of SE is played by blood-brain barrier (BBB) that results to be structurally and functionally impaired during prolonged seizures. The BBB plays a protective role in CNS by its non-fenestrated epithelium that avoid the immune cells and other agents to enter into the brain. When acute or chronic insults such as seizures, stroke, trauma, infections, hypoxia occur, an inflammatory response is generated, whose causes are not completely understood yet. In these conditions, BBB permeability is modified and an intrathecal inflammatory reaction is triggered. Leukocytes can penetrate into the CSF through several ways: fenestrated endothelium, Virchow-Robin perivascular spaces or brain parenchyma [11].

An increased secretion of corticotroph hormone during prolonged seizures has been detected, which in its turn stimulates the release of IL-1, IL-6, and TNF-alpha. CRH regulates processes of differentiation of CD4 + T cells into their two phenotypes: T helper (Th)1 and Th2. To date, Th1 cells regulate cellular immunity (CD8+ T-cytotoxic cells, natural killer cells, and activated macrophages) by primarily secreting type 1 cytokines: interferon (IFN)-γ , IL-2, and TNF-beta , whereas, Th2 cells secrete primarily type 2 cytokines, such as IL-4, IL-10, and IL-13, which promote humoral immunity (mast cells, eosinophils, B cells). (11) Brain cytokine synthesis has been also attributed to microglia and astrocytes, although subsets of hippocampal neurons can express IL-1β in spontaneously epileptic rats. Cytokine receptors in the CNS are expressed by neurons, microglia, and astrocytes, being them rapidly upregulated during seizures for several hours. Cytokines acting on glial cells receptors can induce the production and release of either cytotoxic or neurotrophic molecules, which may contribute to determine whether cells survive or degenerate in hostile conditions. A predominant role is played by microglia due to its dynamic properties. Infact, in response to an acute injury, microglia rapidly projects its processes towards the sites of danger signals and phagocytes cytokines, prostaglandins and immune cells. After a CNS injury, such as SE, long-term modifications of the microglia have been specifically collected under the term 'microglial activation' whose pattern was investigated in murine models of kainate-induced SE. [11] Nor the basal velocity or directional motility of the microglial processes resulted to be affected under these conditions, in contrast, the size of the territory scanned by a single microglial process during basal motility and an elevated directional velocity towards a potential danger signal, such as a source of ATP, resulted to be significantly higher' [11]. This finding was suggestive of a state of heightened vigilance played by microglia under SE-induced pathological state. [11-12].

Epidemiology

The annual incidence of SE was mostly reported by Chin et al (2006) to be 17 to 23 episodes for 100,000 children, being significantly higher than in adult populations (6.4 for 100,000 adults) [13]. The number of annual SE also varies according to different age ranges. In children under the first year of life, the incidence is 51/100000 children / year), from 1 to 4 years of 29/100000 children / year; 5 to 9 years of 9/100000children/year and 10 to 15 years of 2/100000 children/ year) [13].

The highest incidence within the first year of life has been attributed to a lower brain adaptation to acute stressors such diselettrolitemia, infections and fever. Febrile SE is the major cause of SE in the first year of life [14]. More than half (55%) of the SE occurred in febrile diseases and focal seizures were present in 61%. The maturation of excitatory synapses earlier than inhibitory, the increased susceptibility and concentration of receptors for excitatory neurotransmitters, the peculiar composition of the receptor subunits (such as to make it less quick and effective the inhibitory response) cause a high incidence of SE in younger children [15]. Bast et al. [15-16] reported that the most important risk factor for relapsing SE is clinical history of a previous prolonged seizure supporting the assumption that the longer a patient stays without SE, the lower will be the risk for further SE. Moreover, the different type of epilepsy is a risk factor for the greater or lesser occurrence of SE. Infact, SE occurs much less frequently in idiopathic generalized epilepsies (absences, juvenile myoclonic epilepsy) than in epilepsy with symptomatic or cryptogenic etiology. Among the idiopathic epilepsies it was found a lower risk for SE in children with Benign Epilepsy with Centro-Temporal Spikes (BECTS) rather than in patients with Panayiotopoulos syndrome, in which the occurrence of SE becomes quite a rule.

Racial, socio-economic and environmental factors may influence the prevalence of SE (8-17-18). Kariuki et al. [17] reported that the major risk factors for SE in Africa were represented by neurological impairments, acute encephalopathy and the presence of antibodies against Plasmodium Falciparum and HIV. Other frequent associations occurred between SE and burns (15%), illiteracy (49%), being single (77%) and unemployment (78%).

In addition, Chin et al described a higher incidence of SE in non-white children (mainly Asian) if compared to Caucasians, and social and economic level as determinant risk factors for SE [18].

Clinical Features

From a taxonomical point of view, SE is a very heterogeneous condition that has been classified according to different criteria (table 1, Supplementary File). A recent mode of classification of SE was based on four diagnostic axes defined by: 1. Semiology; 2. Etiology; 3. EEG correlates 4. Age. According to the semiology, SE could be classified based on the presence of predominant motor symptoms in convulsive (CSE) and non-convulsive (NCSE), with partial or generalised localization. As opposite, NCSE is a persistent change (> 30 minutes) in behavior and/or mental processes from baseline associated with continuous epileptiform EEG changes but without major motor signs. The NCSE, can be divided into absence SE, or primary generalised NCSE and complex partial SE, or secondary generalised NCSE. However, beyond the mere clinical features, CSE e NCSE underlie different physiopathological mechanisms, timing of intervention and prognostic implications, less defined in NCSE compared to CSE. According to the etiological criterium (table 2, Supplementary File), SE may be associated to known and unknown causes. The first group includes the SE caused by acute (stroke, toxic factors, encephalitis) and remote brain injuries (infections, trauma, stroke), and progressive CNS diseases (brain tumors, neurodegenerative disorders). Some structural brain abnormalities or malformations have been specifically associated to prolonged seizures or SE. Miller et al. [19] showed how infants with a damage to the thalami and basal ganglia presented with severe epileptic phenotype and neurocognitive impairment. Fortini 2013 reported that partial-onset seizures with or without secondary generalisation were the first epileptic manifestations in children with shunted hydrocephalus, porencephalic cysts associated with polymicrogyria, unilateral polymicrogyria or thalamic lesions with subsequent appearance of hemi-status epilepticus during sleep (ESES) or hemi-continuous spikes and waves during slow sleep (CSWSS) syndrome. Thalamic functional rather than structural impairment has been associated to CSWSS pattern [20]. An abnormal thalamic glucose metabolism was detected by using F-18-fluorodeoxyglucose-positron emission tomography (FDG-PET) in patients with CSWSS and normal thalami at brain MRI scan [21]. A peculiar malrotation of the left hippocampal portion has been reported as a brain structural abnormality associated to febrile CSE, expecially in males [22]. Although this pattern has been considered as an atypical variant of hippocampal development, in the light of these evidences, it could indeed play as a pathological brain structure. Conversely, several well-defined electroclinical syndromes, even though they are not necessarily associated to specific structural brain abnormalities, may present with SE (e.g. chromosomal disorders such as Down or X-fragile syndromes, Rett syndrome). The second group including SE with a unknown cause [8] is summarized in table 2 and include all those conditions without significant structural neuroradiological abnormalities or cryptogenic epileptic syndromes [23]. Brain inflammation can represent a cause of SE and may originate from several viral or bacterial infections. This group encompasses the 3-35% of SE cases. An autoimmune process has been reported in 2-3% of cases of SE [24] and need to be confirmed by detection of specific neural autoantibodies in CSF [25] Autoimmune or paraneoplastic encephalitis are common cause of refractory SE mainly when antibodies anti-NMDA, anti-Hu, anti-Ma2, anti GluR3 or anti GluR5 are detected in patients' sera. Autoimmune etiology has been also associated to new onset refractory status epilepticus (NORSE), a challenging condition, characterized by the occurrence of a prolonged period of refractory seizures with often no readily identifiable cause in otherwise healthy individuals. The literature reports that 18% of cases show a paraneoplastic autoimmune cause whereas 19% a non-paraneoplastic autoimmune one. Conversely, a high rate of patients do not present significant findings in CSF. Anti-NMDA autoantibodies are those mostly detected in NORSE. The assessment of the specific class of autoantibodies provides crucial prognostic cues with a better outcome associated to detection of anti-NMDA or VGKCC antibodies if compared to the others [26,27].

Treatment of SE

After the first approach to a patient with SE including vital signs evaluation (ABC model), consciousness status, laboratory and neurophysiological investigations, pharmacological treatment can be started [15]. If intravenous route is difficult to be gained two main treatment options can be available: oromucosal midazolam and rectal diazepam. In a prospective randomized trial, oromucosal midazolam was found to be more effective than rectal diazepam in children with convulsive febrile seizures. Moreover, IM midazolam can be an easy, safe and effective alternative to IV lorazepam for the treatment of prolonged seizures in prehospital settings (table 3, Supplementary File).

Stage I: Early phase (duration from 5 to 10 minutes)

The AEDs commonly used as first-line treatment in SE include IV Lorazepam or IM Midazolam, able to control seizures in approximately 63–73% of patients. The two drugs were compared according to their safety and efficacy within SE: lorazepam showed longer initial duration of action than diazepam, it is less lipid-soluble and does not undergo the rapid redistribution into peripheral tissues. There was no statistically significant difference between lorazepam and diazepam administered intravenously in terms of respiratory failure/depression, or hypotension. Diazepam is highly lipophilic, it rapidly enters into the brain but is redistributed into peripheral tissues. Diazepam can be administered either intravenously or rectally, with demonstrated significantly higher efficacy over placebo in terms of controlling acute repetitive convulsive seizures in adults and children for both route of administration. Another choice is given by clonazepam with a rapid onset of action and a half-life of 17–55 hours that make it an attractive agent for SE treatment [28].

STAGE II: Established Status Epilepticus (duration from 10 to 30 minutes)

In established SE, IV AEDs (phenytoin/fosphenytoin, valproate, levetiracetam, phenobarbital) are most commonly used, but there is no class I evidence for choosing one over the others. However, the central depressive effect of phenobarbital, especially following the use of benzodiazepines, limits its clinical utility, when alternatives are available. Valproate and levetiracetam represent safe and effective alternatives to both phenobarbital and phenytoin, furthermore, many authors believe that these drugs should be used as first-line drugs in benzodiazepine-resistant SE. Another potential alternative is lacosamide, but current evidences are too sparse to give recommendations [28].

STAGE III: Refractory Status Epilepticus (Refractory GCSE) (duration from 30 to 60 minutes)

The definition of refractory generalized CSE (GCSE) is based on the

number of anticonvulsants used. A patient is considered to have refractory SE when seizures continue despite first- and second-line treatments and the seizures duration is greater than 1 hour or there is a need for general anesthesia. In this stage the anesthetics are the most commonly used drugs. When treating refractory GCSE with an anesthetic, continuous-EEG is needed to help guide therapy. The goal is to achieve electrographic seizure suppression and potentially a burst-suppression EEG pattern. No definitive data exist to determine what adequate burst-suppression entails and how long it should be maintained. According to convention, 1 to 2 seconds of cerebral activity with 10-second interburst intervals of background suppression for a total of 24 to 48 hours is required before attempting to lighten sedation. This period of electrographic suppression also provides an opportunity to add on maintenance AEDs and quickly bring them to therapeutic levels After seizure control has been achieved for at least 12 h, the drug dosage should be slowly reduced over a further 12 h. If seizures recur, the anesthetic agent should be replaced for another 12 h, and then, withdrawal will be attempted again. This cycle may need to be repeated every 24 h until achievement of seizure control. Continuous EEG monitoring is indicated to assess level of anesthesia (burst-suppression pattern) and abolition of ictal discharges after drug withdrawal [27,29].

Stage IV: Super refractory status epilepticus (duration > 24 hours)

When treatment with an IV anesthetic for more than 24 h is not successful in controlling SE, the condition can be termed super-refractory SE or malignant SE. No randomized, controlled trials are available in the literature to assess the use of any drug in the treatment of super-refractory status epilepticus. In general, the treatment goals for SE include primarily control of seizures and therefore avoidance of excitotoxicity, their recurrence, and systemic complications. The first-line therapy includes maintaining the use of anesthetic drugs used in Phase III although other drugs have been reported with uncertain outcomes such as ketamine, enteral topiramate, perampanel and bumetanide [30]. Other therapeutic options included hypothermia, magnesium infusion, pyridoxine infusion, ketogenic diet and immunologic therapy. In rare cases emergency neurosurgery including focal resection, multiple subpial transection, corpus callosotomy, and hemispherectomy, were applied [28].

Competing Interests

The authors declare that they have no competing interests.

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Citation: Parisi E, Biasone V, Munafò GI, Isgrò AR, Nicotera A, et al. (2016) Status Epilepticus: An Update of Classification and Treatment of a Challenging Neurological Emergency. Int J Pediatr Neonat Care 2: 115. doi: https://doi.org/10.15344/2455-2364/2016/115

Supplementary File

SEMEIOLOGY	• **With prominent motor symptoms:** ° Convulsive SE (generalised convulsive, focal onset evolving into bilateral convulsive SE, unknown whether focal or generalized) ° Myoclonic SE (with coma or without coma) ° Focal motor (repeated focal motor seizures, epilepsia partialis continua, adversive status, ictal paresis) ° Tonic status ° Hyperkinetic SE • **Without prominent motor symptoms (non-convulsive SE, NCSE)** ° NCSE with coma ° NCSE without coma ° Generalized (typical absence status, atypical absence status,myoclonic absence status) ° Focal (without impairment of consciousness, aphasic staus, with impaired consciousness) ° With impaired consciousness ° Unknown whether focal or generalized ° Autonomic SE
ETIOLOGY	• **Known (symptomatic)** ° Acute (stroke, toxic factors, encephalitis, etc.) ° Remote (infections, trauma, stroke, etc.) ° Progressive (brain tumors, neurodegenerative disorders, etc.) ° SE in defined electroclinical syndromes • **Unknown (cryptogenic)**
(interval between the onset of SE and the first EEG without epileptic activity and clinical manifestations)	**Initial** (duration <20-30 min) **Defined** (duration 30-60 min) **Refractory** (60-120 min) **Super refractory** (>24h)
EEG CORRELATES	• **Location** ° Generalized ° Lateralized ° Bilateral independent ° Multifocal • **Name of the pattern** ° Periodic discharges ° rhythmic delta activity ° spike-and-wape/sharp-and-wave plus subtypes • **Morphology** ° Sharpness ° Number of phases ° Absolute and relative amplitude ° Polarity • **Time-related features** ° Prevalence ° Frequency ° Duration ° Daily pattern duration and index ° Onset ° Dynamics • **Modulation** • **Effect of intervention on EEG**
	Neonatal (0 to 30 days) and infancy (1 month to 2 years) ° Tonic status (Ohtahara syndrome or West syndrome) ° Myoclonic status in Dravet syndrome ° Focal status ° Febrile SE • **Childhood (>2 to 12 years)** ° Autonomic SE in early-onset benign childhood occipital epilepsy (Panayiotopoulos syndrome) ° NCSE in specific childhood epilepsy sindromes and etiologies (ring chromosome 20 and other karyotype abnormalities e.g. Angelman syndrome, epilepsy with myoclonic-atonic seizures, etc) ° Tonic status in Lennox-Gastaut syndrome ° Myoclonic status in progressive myoclonus epilepsies ° Electrical status epilepticus in slow wave sleep (ESES) ° Aphasic status epilepticus in Landau-Kleffner syndrome • **Adolescence and adulthood (>12 to 59 years)** ° Myoclonic status in juvenile myoclonic epilepsy ° Absence status in juvenile absence epilepsy ° Myoclonic status in Down syndrome • **Elderly (>60 years)** ° Myoclonic status in Alzheimer's disease ° NCSE in Creutzfeldt-Jakob disease ° De novo (or relapsing) absence of later life

Table 1: Classification of Status Epilepticus according to clinical and etiological criteria.

Table 2: Principal causes of Status Epilepticus.

• **Cerebrovascular diseases** (e.g. ischemic stroke, intracerebral bleeding, subarachnoid bleeding, subdural hematoma, epidural hematoma)
• **CNS infections** (e.g. bacterial meningitis, viral encephalitis, cerebral toxoplasmosis, tuberculosis, cerebral malaria,)
• **Neurodegenerative diseases** (e.g. Alzheimer's disease, frontotemporal dementia)
• **Intracranial tumors** (e.g. glial tumors, meningioma, metastases, Lymphoma, meningeosis neoplastica)
• **Cortical dysplasias** (e. g. tuberous sclerosis complex, nodular heterotopias, lissencephaly)
• **Head trauma**
• **Alcohol related** (e.g. intoxication, Wernicke encephalopathy)
• **Intoxication** (e.g. drugs, neurotoxins)
• **Withdrawal of or low levels of antiepileptic drugs**
• **Cerebral hypoxia or anoxia**
• **Metabolic disturbances** (e.g. organ failure, acidosis, hepatic encephalopathy, radiation encephalopathy)
• **Autoimmune disorders causing SE** (e.g. multiple sclerosis, paraneoplastic encephalitis, Hashimoto's encephalopathy, Rasmussen encephalitis, Goodpasture syndrome, cerebral lupus)
• **Mitochondrial diseases causing SE** (e.g. MELAS, MERRF, Leigh syndrome)
• **Chromosomal aberrations and genetic anomalies** (e.g. Angelman syndrome, Wolf-Hirshhorn syndrome, Fragile X syndrome, X-linked mental retardation syndrome)
• **Neurocutaneous syndromes** (e.g. Sturge-Weber syndrome)
• **Metabolic disorders** (e.g. Wilson disease, Adrenoleukodystrophy, Morbus of Gaucher, Porphyria)
• **Others**

• STAGE I: Early Phase • (duration from 5 to 10 minutes)	If the intravenous (IV) route is available: • **Lorazepam** ° Dosage (IV): 0.1 mg/kg (maximum dose 10 mg) over 30-60 sec; if seizure continues in 5 min, give an additional 0.1 mg/kg. • **Diazepam:** ° Dosage (IV): 0.5 mg/kg (maximum dose 10 mg) IV bolus (maximum rate 5 mg/min); if necessary can be repeated once up to 20 mg. • **Clonazepam:** ° Dosage (IV): 1 mg IV bolus (maximum rate 0.5 mg/min); if necessary can be repeated once after 5 min. If IV route is difficult or not possible: • **Midazolam:** ° Dosage (buccal): 0.15-0.5 mg/kg (maximum dose 10 mg). ° Dosage (IM): 0.2 mg/kg (maximum dose 5 mg). • **Diazepam** ° Dosage (rectal): 0.5 mg/kg (2-5 yr); 0.3 mg/kg (6-11 yr); 0.2 mg/kg (≥12 yr.
• STAGE II: Established Status Epilepticus • (duration from 10 to 30 minutes)	• **Phenytoin/Fosphenytoin:** ° Dosage phenytoin (IV): 18-20 mg/kg over 20 min (<1 mg/kg/min; maximum, 50 mg/min); may give an additional 5 mg/kg as needed. ° Dosage fosphenytoin (IV or IM): 18-20 mg phenytoin equivalents/kg (< 3mg phenytoin equivalents/kg/min; max. < 100-150 mg phenytoin equivalents/min). • **Phenobarbital:** ° Dosage (IV): 15-20 mg/kg (maximum dose 1 g) IV bolus infusion at a max. rate of 1 mg/kg/min. • **Valproic Acid:** ° Dosage (IV): 25-30 mg/kg over 5-15 min (<3 mg/kg/min up to 200 mg/min) followed by an infusion of 1-6 mg/kg/hr. • **Levetiracetam:** ° Dosage (IV): 40-60 mg/kg, max. 3 g (administer 2-5 mg/kg/min).
	• **Lacosamide** ° Dosage (IV): 50-400 mg; 200 mg given over 15 min. • **Propofol:** ° Dosage (IV): 2 mg/kg IV bolus infusion, repeated if necessary, and then followed by a continuous infusion of 5–10 mg/kg/h initially, reducing to a dose sufficient to maintain a burst-suppression pattern on the EEG (usually 1–3 mg/kg/h). • **Thiopental** ° Dosage (IV): 100–250 mg IV bolus infusion giver over 20 s with further 50-mg boluses every 2–3 min until seizure control, followed by a continuous IV infusion at a dose sufficient to maintain a burst-suppression pattern on the EEG (usually 3–5 mg/kg/h). • **Pentobarbital** ° Dosage (IV): 5–15 mg/kg IV bolus, followed by a continuous IV infusion at a dose sufficient to maintain a burst-suppression pattern on the EEG (usually 0.5–3 mg/kg/h).
• STAGE IV: Super Refractory Status Epilepticus • (Duration > 24 hours)	The first-line therapy includes maintaining the use of anesthetic drugs used in Phase III, ad in addition to which may be used: • **Ketamine***1–3 mg/kg IV bolus, followed by a continuous IV infusion at a dose sufficient to maintain a burst-suppression pattern on the EEG (usually up to 5 mg/kg/h). • **Topiramate (Enteral)**: The dose of topiramate used in studies ranged between 2 and 25 mg/kg/day in children and up to 1600 mg/day in adults. Metabolic acidosis was the most frequently reported side effect with its use. • **Perampanel:** The initial dose in studies case of refractory & super-refractory status epilepticus is of 4 mg, titrated up to a maximum dose of 12 mg in steps of 2 to 4 mg per day. Data on PER in SE remain anecdotal and are limited to a few cases. Perampanel was used in refractory and super-refractory cases only, and this may explain the low rate of respondents in both studies. (Adam Strzelczyk, Laurent M Willems, Sophia Willig, Felix Rosenow & Sebastian Bauer (2015) Perampanel in the treatment of focal and idiopathic generalized epilepsies and of status epilepticus, Expert Review of Clinical Pharmacology, 8:6, 733-740) As second-line therapy consider: • **Hypothermia*** levels of hypothermia uncertain, usually target temperatures between 32 and 35 °C continued in the first instance for 24–48 h; • **Magnesium infusion***dose of 2–6 g/h to obtain a serum level of 3.5 mmol/L; • **Pyridoxine infusion*** (in young children): 180–300 mg; • **Immunologic therapy*** high-dose steroids (1 g/day in adults) over 3 days and continued at lower doses (1 mg/kg/day) over 1 week; in addition, course of IV immunoglobulin (0.4 g/kg/day) over 5 days or plasma exchange; other like immunomodulatory agents (such as cyclophosphamide or rituximab) or plasma exchange is rarely used, it has been tried. • **Ketogenic diet*** • **Emergency neurosurgery*** (including focal resection, multiple subpial transection, corpus callosotomy, and hemispherectomy, even in combination). As third-line therapy consider: • **Electroconvulsive therapy*;** • **Cerebrospinal fluid drainage*.** *No randomized, controlled trials available in the literature to inform about the use of this drug/procedure in this stage of status epilepticus.

Table 3: Treatment strategies of Status Epilepticus.