2016

25 years of advances in the definition, classification and treatment of status epilepticus

Trinka Eugen

Elsevier BV

Accepted Manuscript

Title: 25 Years of Advances in Definition, Classification and Treatment of Status Epilepticus

Author: Eugen Trinka Reetta Kälviäinen

Please cite this article as: Trinka Eugen, Kälviäinen Reetta.25 Years of Advances in Definition, Classification and Treatment of Status Epilepticus.*SEIZURE: European Journal of Epilepsy* http://dx.doi.org/10.1016/j.seizure.2016.11.001

25 Years of Advances in Definition, Classification and Treatment of Status Epilepticus

Eugen Trinka [1,2,3,], Reetta Kälviäinen[4,5]

1: Department of Neurology, Paracelsus Medical University Salzburg, and Christian Doppler Medical Centre, Salzburg, AUSTRIA

2: Centre for Cognitive Neurosciences Salzburg, Salzburg, AUSTRIA

3: University for Medical Informatics and Health Technology, UMIT, Hall in Tirol, AUSTRIA

4: Epilepsy Center, Neurocenter, Kuopio University Hospital, Kuopio, FINLAND

5: Institute of Clinical Medicine, School of Medicine, Faculty of Health Sciences, University of Eastern Finland, Kuopio, FINLAND

Correspondence to:

Univ. Prof. Dr. Mag. Eugen Trinka, FRCP

Department of Neurology, Christian Doppler Klinik

Paracelsus Medical University Salzburg

Centre for Cognitive Neuroscience Salzburg

Ignaz Harrerstrasse 79, A-5020 Salzburg, Austria

Fax: +43(0)5725534899; Mail: e.trinka@salk.at

Highlights:

- Morbidity and mortality of SE correlate with duration of epileptic activity, the rapid identification of the cause of SE, age and comorbidity of the patients

- SE treatment should be started when epileptic seizure is abnormally prolonged (time-point t1 in the new definition), which is at 5 minutes for generalized tonic clonic seizures, and at 10 minutes for focal seizures with or without impairment of consciousness.

- Time-point t2 marks the time at which neuronal damage may begin, and indicates that SE should be controlled latest by that time, which is 30 minutes for generalized tonic clonic seizures.

- Staged protocol dividing diagnostics and therapy to early, established, refractory and super-refractory stages is the hallmark of current SE treatment

Abstract

Background: Status epilepticus (SE) one of the most common neurological emergencies with an estimated incidence of up to 61 per 100,000 per year. It requires not only urgent symptomatic treatment with antiepileptic drugs but also in the same way rapid identification and treatment of its cause. There has been enormous progress in understanding of the mechanisms, identifying new causes, and developing new treatment strategies of SE in the past three decades.

Objectives: This narrative review summarizes the most important advances in classification and treatment of SE.

Methods: Data sources included MEDLINE, EMBASE, ClinicalTrials.gov, and back tracking of references in pertinent studies, reviews, and books.

Results: SE is defined as follows: "Status epilepticus is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures (after time point t1). It is a condition, which can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures." A new diagnostic classification system of SE introduces four axes (i) semiology, (ii) aetiology, (iii) EEG correlates, and (iv) age. This provides a framework for clinical diagnosis, investigation and therapeutic approaches for each patient.

For the acute treatment intravenous benzodiazepines (lorazepam, diazepam, clonazepam) and intramuscular midazolam appear as most effective treatments for early SE. In children, buccal or intranasal midazolam have recently emerged as useful non-intravenous alternatives with similar efficacy and safety to other intravenous or rectal benzodiazepines but being socially more acceptable and easier to administer. In established SE intravenous antiepileptic drugs (phenytoin, valproate, levetiracetam, phenobarbital, and lacosamide) are in use, but there is limited experience with intravenous brivaracetam. There are no double-blind, but six randomized open studies with valproate and two with levetiracetam. A meta-analysis found higher rates of seizure cessation with valproate 75.7 % (95 % CI 63.7–84.8) and phenobarbital 73.6 %, (95 % CI 58.3–84.8) than with levetiracetam (68.5 %, 95 % CI 56.2–78.7) or phenytoin

(50.2 %, 95 % CI 34.2–66.1). Treatment options in refractory SE are intravenous anaesthetics (continuous infusion of midazolam, propofol, or thiopental/pentobarbital), in super-refractory SE ketamine, magnesium, steroids and other drugs have been used with variable outcomes. Evidence supporting the use of these treatments is very sparse, and therapeutic decisions are based on doctors' preferences, patient factors such as age and comorbidity, and cause of SE, if identified.

Key Words: status epilepticus – classification- antiepileptic drugs – benzodiazepines – anaesthetics

1. Introduction

Status epilepticus has an estimated incidence of up to 61 episodes per 100,000 per year and an overall mortality of 20% (range 1.9 - 40%) (1) (2). There has been considerable development in the past 25 years in the understanding of its pathophysiology, causes, clinical features, EEG changes, prognosis and treatment (3, 4). The purpose of this narrative review in the 25-year anniversary issue of "Seizure-the European Epilepsy Journal" is to give an update on definition, classification and therapeutic options for patients in SE.

2. Recent advances in the definition and classification of status epilepticus

Status epilepticus is often referred to the "*maximum expression of epilepsy*", but status is also a severe expression of an acute brain insult or systemic disturbance, which leads to excessive hyperexcitation of nervous tissue. The modern definition and classification of Status epilepticus has its roots back to the 10th Marseilles Colloquium (the 10th European Electroencephalographic Meeting) in 1962, which was completely devoted to status epilepticus. Henry Gastaut and his colleagues proposed a definition, which was consistent with the meaning of the original term *status* in Latin: "*Status epilepticus is a term whenever a seizure that persists for a sufficient length of time or is repeated frequently enough to produce a fixed and enduring condition*" (5-7). Although there was no duration specified in the definition, Gastaut later proposed 60 minutes to define status epilepticus (8). In the revision of 1981, the definition was minimally changed into a "*seizure*" that "*persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur.*"(9) Status was classified under the terms "prolonged or repetitive seizures (status epilepticus)"and was divided into partial (e.g., Jacksonian), or generalized (e.g., absence status or tonic-clonic status). "When very localized motor status occurs, it is referred to as *epilepsia partialis continua*". These concepts, while highly valuable, were imprecise, as they did not define the duration of a seizure that was fixed and enduring "or" sufficient length. In the past, experts suggested that 30 minutes of ongoing seizure activity could be regarded as "fixed and enduring". Over the past two decades the timelines in clinical trials and treatment recommendations were progressively moved to 20 minutes (10) and to 10 minutes (11). Lowenstein and colleagues suggested in 1999 that a generalized tonic clonic seizure that is longer than the usual two to

three minutes is prolonged, and should be treated as SE (12). The time limit for convulsive status consequently set to 5 minutes, which opened the door to change our view on the classical definitions of SE. The Commission of Classification and Terminology of the International League Against Epilepsy and the Commission on Epidemiology charged a Task Force with clinical researchers and epidemiologists to revise the classification of status epilepticus in 2009. The Task force came out in 2015 with the following definition: ***"Status epilepticus is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally prolonged seizures (after time point t1). It is a condition, which can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures"***.(13) This new definition of SE gives a good guidance, when emergency treatment must be considered. In general, time point t1 is the time when treatment should be started, which is at 5 minutes for generalized tonic clonic seizures, and at 10 minutes for focal seizures with or without impairment of consciousness. Time-point t2 marks the time at which neuronal damage or self-perpetuating alteration of neuronal networks may begin, and indicates that SE should be controlled latest by that time; 30 minutes in case of generalized tonic clonic seizures (figure 1).

The task force also came out with a new classification, built on four axes(13): (i) semiology, (ii) etiology, (iii) EEG correlates, and (iv) age. The backbone of the classification is the semiology. The various clinically forms of Status epilepticus are differentiated along two taxonomic criteria: *motor activity* and *impairment of consciousness* falling into two major groups: (1) Status epilepticus with prominent motor symptoms, including all convulsive forms, and (2) those without prominent motor symptoms representing the non-convulsive forms of Status epilepticus (NCSE) (see table 1). Each group can be divided again according to the degree of impairment of consciousness, which is highly clinically relevant. Comatose NCSE represents a life threatening condition that requires urgent and consequent treatment, whereas NCSE proper without coma occurs most often in the form of absence status or focal status with impairment of consciousness (older terms for this conditions were "psychomotor status" or "complex partial Status epilepticus")(13, 14). The etiology of status is divided into two groups: (i) known or symptomatic and (ii) unknown or cryptogenic. The symptomatic group can be subdivided into acute symptomatic, remote symptomatic and progressive symptomatic. The new classification also provides a list of known causes of status as an appendix to the classification, which can be updated periodically as new information emerges. Status epilepticus often occurs in the context of genetic epilepsy syndromes, but there is always a trigger for the status itself, such as fever, electrolyte disturbance or other intrinsic factors (15).

The third axis of the classification comprises EEG correlates of status. In convulsive SE the clinical presentation is most often clear and artefacts obscure the EEG, thus the EEG is of little value. The opposite is true for the non-convulsive forms of Status epilepticus, where a correct diagnosis is often not possible without EEG. In the most extreme forms the patient is in deep coma, and only an EEG can reveal the epileptiform or rhythmic discharges leading to the diagnosis (14, 16). The task force recommends describing the EEG correlate of status in a patient using the following descriptors: name of pattern, morphology, location, time-related features, modulation, and effect of intervention, and use the recently proposed terminology by the American Clinical Neurophysiology Society (17) and the diagnostic "Salzburg EEG criteria for NCSE" (Table 2) (16, 18-20) as a practical guide for diagnosis. In a recent retrospective diagnostic accuracy study using EEG recordings from patients admitted for neurological symptoms or signs of NCSE to three centres (Danish Epilepsy Centre, Dianalund, Denmark; Aarhus University Hospital, Aarhus, Denmark; and Paracelsus Medical University, Salzburg, Austria) in two countries (Austria and Denmark) confirmed the high clinical utility for the "Salzburg EEG criteria for NCSE" (21). The sensitivity was 97.7% (95% CI 87.9-99.6) and specificity was 89.6% (95% CI 80.8-94.6); overall accuracy was 92.5% (95% CI 88.3-97.5). The positive predictive value was 84.0% (95% CI 74.1-91.5) and negative predictive value was 98.6% (95% CI 94.4-100).

The New Classification underwent already a feasibility study: 488 episodes of Status epilepticus were retrospectively assessed and classified according to the clinical tradition and the new classification. 230 (47%) had a generalized convulsive, and 29 (6%) had a nonconvulsive SE in coma; both categories overlapped almost perfectly between the two classifications. However in focal SE, which was markedly heterogeneous, the new classification appears to better reflect the clinical reality, offering more relevant subdivisions, which also differ in mortality rates (22).

2. Recent advances in the treatment of status epilepticus

The management of status epilepticus and its and pharmacological treatment still represents an area with limited evidence derived from high-quality, adequately powered randomized controlled trials (RCTs) to inform clinical practice. However, there have been clear advances in the understanding of the

pathomechanisms, which have led to more effective treatment strategies. The therapeutic principle "time is brain" applies not only for stroke but also for status epilepticus, as the prognosis of SE worsens with increasing duration of seizure activity (23, 24). Indeed, prompt recognition and earliest treatment of status epilepticus is associated with lower morbidity and mortality, fewer drugs required in hospitals, and reduction in seizure duration (25, 26). The cost of status in the refractory stages are high and a recent study in Germany has estimated €1,365/day (27). Nevertheless, there is only limited industry interest to develop new treatments to prevent refractory status.

Until late 1980s there was large variation in patient stabilization procedures, laboratory measures, and sequence of medications in the management of SE (28). In the year 1993, the Epilepsy Foundation of America convened a working group on SE. They published guidelines and a treatment protocol (10), which was based on a literature review and input from experts. Some key treatment principles of this guideline still remain valid. All treatment protocols recognize a staged approach to treatment with different drugs used in early (stage I), established (stage II), refractory (stage III) and super-refractory SE (stage IV) (figure 2) and emphasize prompt recognition and treatment of persisting seizure activity at each stage aiming to reduce morbidity, mortality, and long-term consequences of status epilepticus (beyond t2). Most recent reviews focus on the pharmacotherapy of status, but general measures of neurological emergencies and a thorough search for the causes are equally important (29-31).

Most clinical trials have been performed in the of early stages of status epilepticus, which has been the subject of several RCTs and critical assessment in systematic reviews with meta-analyses (32-37) (34, 35, 38-44) and included in treatment protocols or practical guidelines (29, 30, 45, 46) (31).

The most effective treatment of early status epilepticus are intravenous benzodiazepines, which are able to control status promptly in about two thirds of all patients (3, 42). Benzodiazepines exert their antiepileptic properties by enhancing the inhibitory neurotransmission through increasing channel opening frequency of the GABA-A receptors, with subsequent increased chloride conductance and neuronal hyperpolarization (47). The benzodiazepines commonly used as first-treatment in SE are lorazepam, diazepam, midazolam and clonazepam (figure 3). Intravenous lorazepam is less lipid-soluble (octanol/water partition coefficient for lorazepam is 73 (48)) and hence does not undergo a rapid redistribution into peripheral tissues as diazepam, which should also result in a clinical longer duration of action (47, 49). Previous meta-analyses (33) of all randomised controlled studies (50-52) found lorazepam to be superior. Since the Cochrane Review another large trial was performed in children with status epilepticus (273 patients; 140 randomized to diazepam and 133 to lorazepam), which failed to

show a superiority of lorazepam in terms of seizure control (53). Moreover in this study children who received lorazepam were more often sedated. In a recent systematic review with meta-analysis of randomized controlled trials five RCTs were included, with a total of 656 patients, 320 randomly allocated to IV LZP and 336 to IV DZP. No statistically significant differences were found between IV LZP and IV DZP for clinical seizure cessation (RR 1.09; 95% CI 1.00 to 1.20), continuation of SE requiring a different drug (RR 0.76; 95% CI 0.57 to 1.02), seizure cessation after a single dose of medication (RR 0.96; 95% CI 0.85 to 1.08), need for ventilator support RR 0.93; 95% CI 0.61 to 1.43, and clinically relevant hypotension (40). The authors concluded consequently "Despite its favourable pharmacokinetic profile, a systematic appraisal of the literature does not provide evidence to strongly support the preferential use of IV LZP as first-line treatment of convulsive SE over IV DZP". An overview on the staged treatment approach is given in figure 3.

In the past decades alternative routes of administrations have been explored. A landmark study intramuscular midazolam was compared to intravenous lorazepam as first-line treatment for convulsive status epilepticus in a double blind, randomized, non-inferiority design. This study included 893 children and adults treated by paramedics before admission to hospital (26). Seizures were controlled in 73.4% with intramuscular midazolam, and in 63.4% with intravenous lorazepam (absolute difference 10%; 95% CI: 4.0 to 16.1%; p<0.001 for both non inferiority and superiority). Among patients whose seizures ceased before arrival to the emergency department, the median time to drug administration was significantly shorter in the midazolam group (1.2 minutes vs 4.8 minutes), although clinical seizure cessation occurred earlier after lorazepam administration (1.6 minutes vs. 3.3. minutes) (26).

Intranasal and buccal administration of benzodiazepines has been studies extensively over the past years. The water-soluble midazolam offers pharmacological advantages over the lipophilic lorazepam and diazepam. In a comprehensive meta-analysis the efficacy and safety of non-intravenous midazolam in adults and children was compared to rectal or intravenous diazepam. Nineteen studies with 1933 seizures in 1602 patients were included. For seizure cessation, non-IV midazolam was as effective as diazepam (any route) (1933 seizures; RR: 1.03; 95% CIs: 0.98 to 1.08). No difference in adverse effects was found between non-IM midazolam and diazepam by any route (1933 seizures; RR: 0.87; 95% CIs: 0.50 to 1.50) (35). A common reference based meta-analysis compared intranasal to buccal administration midazolam (34). Intravenous or rectal diazepam or intravenous lorazepam served as the reference for indirect comparisons. The authors did not find a difference in efficacy between intranasal and buccal midazolam, but found a large width and asymmetrical distribution of confidence intervals around the obtained OR of 2.81 (95% CI 0.39-20.12) comparing intranasal midazolam with rectal

diazepam for serious adverse effects (34). However, overall, these data indicate that midazolam administered by non-intravenous routes represents a practical, rapid, reasonably safe and effective alternative to either intravenous lorazepam or intravenous/rectal diazepam as first-line treatment of early status epilepticus in out of hospital settings (figure 4).

Approximately 40% of patients with generalized convulsive SE (GCSE) are refractory to benzodiazepine treatment (11, 26, 52). This ongoing seizure activity is referred to as established SE (or stage II). In established SE, intravenous antiepileptic drugs (phenytoin/fosphenytoin, valproate, levetiracetam, phenobarbital, and lacosamide) are most commonly used, but there is no class I evidence for choosing one over the other. This unsatisfactory situation has several consequences: firstly most patients are treated off label. Recent data from a registry in Germany, Austria, and Switzerland (54) and a global audit (55) suggests that 34% of patients in the early stages and 91% in the later stages receive off label treatment. Secondly, status epilepticus, with its high mortality and severe morbidity is a shaky ground for the pharma industry to embark in high-class trials with unknown return of investments. And thirdly, there are no well-defined regulatory pathways for drugs to treat later stages of status epilepticus. This leaves the clinicians uninformed about the best choice in the established stage of status epilepticus and they have to take decisions under uncertainty, with all the medico-legal consequences. Guidelines, which are based on currently available evidence are only a weak remedy, because the evidence they are based on is weak. There are several comprehensive narrative reviews on the pharmacologic treatment ot status (3, 42, 43), summarising the current evidence. The succus is, that there are no double-blind, but six randomized open studies with valproate and two with levetiracetam. A meta-analysis found higher rates of seizure cessation with valproate 75.7% (95% CI 63.7–84.8) and phenobarbital 73.6%, (95% CI 58.3–84.8) than with levetiracetam (68.5%, 95% CI 56.2–78.7) or phenytoin (50.2%, 95% CI 34.2–66.1). Based on the favourable tolerability profile of levetiracetam and valproate, the authors prefer these drugs in established SE over phenytoin/fosphenytoin (Figure 3). Currently a large NIH funded trial (Established Status Epilepticus Trial, ESET) is on the way, which is designed as a multicenter, randomized, blinded, comparative effectiveness study of fosphenytoin, valproic acid, or levetiracetam in the emergency department treatment of patients with benzodiazepine-refractory status epilepticus [ClinicalTrials.gov Identifier: NCT01960075] (56, 57). The trial is currently recruiting and first results can be expected in 2017. Until the results of this trial are available, newer drugs such as lacosamide will be used extensively in established and refractory status epilepticus (58, 59).

10

In a review of 136 patients with refractory SE (50% non-convulsive SE, 31% focal SE, and 19% convulsive SE) treated with lacosamide an overall success rate of 56% was reported with adverse events observed in 25% (mostly mild sedation) (59). These findings have been confirmed by a subsequent cohort study (60) and by a case series conducted in 55 patients with SE and 43 patients with acute repetitive seizures (61). The most commonly used bolus dose was 400 mg, followed by a daily dose of 200-400 mg lacosamide leading to abrogation of seizures in 56% (76/136) (59). Intravenous brivaracetam is already on the market and experts feel that there is a certain potential for this drug in status epilepticus, but so far no reports in humans have been published.

In 31-43% of patients in established status epilepticus are not controlled with antiepileptic drugs (62, 63). In this stage, also called refractory status epilepticus, intravenous anesthetic drugs (thiopental/pentobarbital, midazolam, or propofol) have been, and still are, commonly used in the past 30 years (figure 3). In a global audit of 488 episodes of RSE, continuous midazolam infusion was the most widely used anaesthetic in (59%) followed by propofol (32%) and barbiturates (8%) (55). In two systemic reviews none of the treatments currently available was superior to another (64, 65). Propofol may be associated with metabolic acidosis, rhabdomyolysis, renal failure and heart failure (66). This propofol infusion syndrome occurs less likely, when treatment duration is less than 48 hours and doses not exceed 5 mg/kg/hours. Midazolam seems to be the safest drug at this stage with the lowest rate of cardiovascular and metabolic complication, while barbiturates seem to be most often associated with cardiovascular complications, severe immunosuppression, and infections in the (64, 65). The use of anesthetics in refractory and super-refractory SE was associated with more infections during status epilepticus (43% vs 11%; p <0.0001) and a 2.9-fold relative risk for death (2.88; 95% confidence interval 1.45–5.73) in a 6-year prospective cohort study including 171 patients (63 of them received intravenous anesthetics) (67).

These findings fueled the search for more efficacious and better tolerated treatments in refractory and super-refractory status. Ketamine has gained much interest, due to its pharmacological properties. It strong antagonistic effect on the N-methyl-D-aspartate (NMDA) – glutamate receptors (68), which play a ley role in the advanced forms of status epilepticus (69-71). There are three retrospective case series to date (72-74) and 10 case reports (75-84) reporting 94 episodes of refractory status epilepticus in adults treated with ketamine leading to successful termination of status epilepticus in 63% (43). Ketamine is a racemic mixture containing equal amounts of two enantiomers, (S)- and (R)-ketamine. Ketamine is extensively metabolized by N-demethylation producing norketamine, a non-competitive NMDA receptor antagonist that may also exhibit enantioselective pharmacological activity. (S)-ketamine has different

pharmacodynamic activities and is a two to threefold more potent analgesic agent than (R)- ketamine. (S)- ketamine administered alone has a higher clearance than in the racemic mixture resulting in quicker elimination, shorter duration of action and a faster recovery from anesthesia (85). The S-enantiomer was also associated with a more rapid recovery of psychomotor skills than the racemic mixture (86). Thus the use of (s)-ketamine in refractory and super-refractory status should have clinically relevant advantages. One large single centre study from Austria reported on 42 patients who were treated with (s)-ketamine. The median duration of status epilepticus was 10 days; the median latency from SE onset to the first administration of (s)-ketamine was 3 days. In 64 % of patients (s)-ketamine was the last drug before cessation of status. However, in five patients, it was given with propofol at the same time, so a definite causal inference could not be drawn. Median duration of administration was 4 days. Overall (s)-ketamine treatment was well tolerated, adverse effects were not observed, and overall mortality was 45.2 % (87)..

The new antiepileptic drug perampanel also exerts its mechanism on the antiglutamatergic pathways. Unlike ketamine it does not act, even at high doses on the NMDA receptors, but is a non-competitive antagonist at the Alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor (88, 89). Perampanel was administered via nasogastric tube in 22 cases. The initial median dose was 4 mg, which was uptitrated to median 12 mg) (90-92). The patient numbers in these case series are low (largest single centre experience with 12 cases) and patients too heterogeneous to draw valid conclusions on efficacy.

Another new strategy in the treatment of super-refractory status epilepticus involved neurosteroid. As status evolves over time, synaptic GABA-A receptors are internalized from the synaptic membrane to the cytosol leading to a lack of efficacy of benzodiazepines in later stages of SE, while extrasynaptic GABA-A receptors do not undergo internalization (93, 94). The neuroactive steroid allopregnanolon acts as a positive allosteric modulator of synaptic and extrasynaptic GABA-A receptors (95). In animal models the efficacy of allopregnanolon in cessation of established SE was observed. The evidence in humans is limited to only three patients (one adult, two children) with super-refractory SE reported to date. In all reported cases, allopregnanolon led to control of SE allowing the general anesthetics to be weaned (96). Following successful completion of a phase I/II study (ClinicalTrials.gov Identifier: NCT02052739; results not in the public domain) in superrefractory status epilepticus, an US based company is currently conducting a large multicenter phase III trial with the neuroactive steroid (ClinicalTrials.gov Identifier: NCT02477618). The aims of the trial are very ambitious and irrespective, whether the trial meets the endpoint, important data on the causes, clinical presentations and EEG in superrefractory status will be gathered.

Other treatments than the intravenous anaesthetics (thiopental, pentobarbital, midazolam, propofol, ketamine,) including non-pharmacologic therapies were used in this stage of status epilepticus (inhalational anaesthetics, topiramate, lacosamide, pregabaline, levetiracetam, magnesium, pyridoxine, immunotherapy) and non-pharmacological treatments (hypothermia, ketogenic diet, emergency neurosurgery, electroconvulsive therapy, cerebrospinal fluid drainage, vagal nerve stimulation and deep brain stimulation) (65). Ferlisi and Shorvon have reviewed these treatments and their outcomes (65, 97).

There is growing evidence of inflammation as an important factor in epileptogenesis, as well as the increasing discovery of antibodies against neural targets as underlying cause of some forms of encephalopathies presenting with seizures and refractory status epilepticus (98). Therefore, anti-inflammatory agents like steroids and immunoglobulines as well as plasma exchange in super-refractory SE becomes more frequent despite any evidence supporting its use without a proven or suspected underlying immunological disorder (97). There are potential side effects associated with immunosuppression, such as severe infections and metabolic disturbances, which have to be taken into account when a trial with anti-inflammatory drugs in super-refractory SE is considered. The recently published clinical algorithm is helpful in making the decision for a potentially harmful treatment (99).

Conclusion:

There have been major advances in the clinical field with a new definition and classification, which gives clinicians a better guidance as to when to treat, how aggressive to treat, and how to avoid over- or under-treatment of this condition. In the treatment arena new small companies embark in the development of niche products, such as neurosteroids in super refractory status epilepticus or new alternative methods of application. The increased interest in status epilepticus has alerted clinicians to treat early and more appropriate and search consequently for the causes of status in each patient. Despite these achievements there are many unmet needs, beginning with identification of cause directed treatments not only to prevent status recurrence but also to protect the brain from the consequences of status and the development of epilepsy to the better delineation of the subtypes of status. This can only be achieved through better understand the mechanisms of status in different causes and major efforts to bridge the gap between preclinical knowledge to human applications.

5. References:

1.   Betjemann JP, Lowenstein DH. Status epilepticus in adults. Lancet neurology. 2015 Jun;14(6):615-24. PubMed PMID: 25908090.

2.   Kantanen AM, Reinikainen M, Parviainen I, Ruokonen E, Ala-Peijari M, Backlund T, et al. Incidence and mortality of super-refractory status epilepticus in adults. Epilepsy & behavior : E&B. 2015 Aug;49:131-4. PubMed PMID: 26141934.

3.   Trinka E, Brigo F, Shorvon S. Recent advances in status epilepticus. Current opinion in neurology. 2016 Apr;29(2):189-98. PubMed PMID: 26886360.

4.   Shorvon S, Trinka E. The 5th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures. Epilepsy & behavior : E&B. 2015 Aug;49:1-3. PubMed PMID: 26052077.

5.   Gastaut H. Clinical and electroencephalographical classification of epileptic seizures. Epilepsia. 1970;11 102-13.

6.   Gastaut H. A propos d'une classification symptomatologique des Çtats de mal Çpileptiques. In: H.Gastaut, J.Roger, H.Lob, editors. Les Çtats de mal Çpileptiques Paris: Masson; 1967. p. 1-8.

7.   Gastaut H. Clinical and electroencephalographical classification of epileptic seizures. Epilepsia. 1969;10 (suppl.):S2-S13.

8.   Gastaut H. Classification of status epilepticus. In: Escueta AVD, C.G.Wasterlain, D.M.Treiman, R.J.Porter, editors. Status epilepticus Mechanisms of brain damage and treatment Advances in Neurology, vol 34. New York: Raven Press; 1983. p. 15-35.

9.   Commission on C, Terminology of the International League Against E. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia. 1981;22 489-501.

10.   Treatment of convulsive status epilepticus. Recommendations of the Epilepsy Foundation of America's Working Group on Status Epilepticus. JAMA. 1993;270(7):854-9.

11.   Treiman DM, Meyers PD, Walton NY, Collins JF, Colling C, Rowan AJ, et al. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. NEnglJMed. 1998;339(12):792-8.

12.   Lowenstein DH, Bleck T, Macdonald RL. It's time to revise the definition of status epilepticus. Epilepsia. 1999;40(1):120-2.

13.   Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, et al. A definition and classification of status epilepticus--Report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia. 2015 Oct;56(10):1515-23. PubMed PMID: 26336950.

14.   Bauer G, Trinka E. Nonconvulsive status epilepticus and coma. Epilepsia. 2010 Feb;51(2):177-90. PubMed PMID: 19744116.

15.   Trinka E, Hofler J, Zerbs A. Causes of status epilepticus. Epilepsia. 2012 Sep;53 Suppl 4:127-38. PubMed PMID: 22946730.

16.   Trinka E, Leitinger M. Which EEG patterns in coma are nonconvulsive status epilepticus? Epilepsy & behavior : E&B. 2015 Aug;49:203-22. PubMed PMID: 26148985.

17.   Hirsch LJ, LaRoche SM, Gaspard N, Gerard E, Svoronos A, Herman ST, et al. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2012 version. Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society. 2013 Feb;30(1):1-27. PubMed PMID: 23377439.

18.   Beniczky S, Hirsch LJ, Kaplan PW, Pressler R, Bauer G, Aurlien H, et al. Unified EEG terminology and criteria for nonconvulsive status epilepticus. Epilepsia. 2013 Sep;54 Suppl 6:28-9. PubMed PMID: 24001066.

19.   Kaplan PW. EEG criteria for nonconvulsive status epilepticus. Epilepsia. 2007;48 Suppl 8:39-41. PubMed PMID: 18329995.

20.   Leitinger M, Beniczky S, Rohracher A, Gardella E, Kalss G, Qerama E, et al. Salzburg Consensus Criteria for Non-Convulsive Status Epilepticus - approach to clinical application. Epilepsy & behavior : E&B. 2015 Aug;49:158-63. PubMed PMID: 26092326.

21.   Leitinger M, Trinka E, Gardella E, Rohracher A, Kalss G, Qerama E, et al. Diagnostic accuracy of the Salzburg EEG criteria for non-convulsive status epilepticus: a retrospective study. Lancet neurology. 2016 Sep;15(10):1054-62. PubMed PMID: 27571157.

22.   Rossetti AO, Trinka E, Stahli C, Novy J. New ILAE versus previous clinical status epilepticus semiologic classification: Analysis of a hospital-based cohort. Epilepsia. 2016 Jun 1. PubMed PMID: 27249322.

23.   Madzar D, Geyer A, Knappe RU, Gollwitzer S, Kuramatsu JB, Gerner ST, et al. Association of seizure duration and outcome in refractory status epilepticus. J Neurol. 2016 Mar;263(3):485-91. PubMed PMID: 26725091.

24.   Towne AR, Pellock JM, Ko D, DeLorenzo RJ. Determinants of mortality in status epilepticus. Epilepsia. 1994;35(1):27-34.

25.   Alldredge BK, Wall DB, Ferriero DM. Effect of prehospital treatment on the outcome of status epilepticus in children. Pediatr Neurol. 1995 Apr;12(3):213-6. PubMed PMID: 7619187.

26.   Silbergleit R, Durkalski V, Lowenstein D, Conwit R, Pancioli A, Palesch Y, et al. Intramuscular versus intravenous therapy for prehospital status epilepticus. The New England journal of medicine. 2012 Feb 16;366(7):591-600. PubMed PMID: 22335736. Pubmed Central PMCID: 3307101.

27.   Kortland LM, Alfter A, Bahr O, Carl B, Dodel R, Freiman TM, et al. Costs and cost-driving factors for acute treatment of adults with status epilepticus: A multicenter cohort study from Germany. Epilepsia. 2016 Oct 18. PubMed PMID: 27753082.

28. Kalviainen R. Status epilepticus treatment guidelines. Epilepsia. 2007;48 Suppl 8:99-102. PubMed PMID: 18330014.

29. Shorvon S, Baulac M, Cross H, Trinka E, Walker M. The drug treatment of status epilepticus in Europe: consensus document from a workshop at the first London Colloquium on Status Epilepticus. Epilepsia. 2008;49(7):1277-85.

30. Brophy GM, Bell R, Claassen J, Alldredge B, Bleck TP, Glauser T, et al. Guidelines for the evaluation and management of status epilepticus. Neurocritical care. 2012 Aug;17(1):3-23. PubMed PMID: 22528274.

31. Jones S, Pahl C, Trinka E, Nashef L. A protocol for the inhospital emergency drug management of convulsive status epilepticus in adults. Practical neurology. 2014 Jun;14(3):194-7. PubMed PMID: 24810377.

32. Prasad K, Krishnan PR, Al Roomi K, Sequeira R. Anticonvulsant therapy for status epilepticus. BrJClinPharmacol. 2007;63(6):640-7.

33. Prasad M, Krishnan PR, Sequeira R, Al-Roomi K. Anticonvulsant therapy for status epilepticus. The Cochrane database of systematic reviews. 2014;9:CD003723. PubMed PMID: 25207925.

34. Brigo F, Nardone R, Tezzon F, Trinka E. A Common Reference-Based Indirect Comparison Meta-Analysis of Buccal versus Intranasal Midazolam for Early Status Epilepticus. CNS drugs. 2015 Aug 21. PubMed PMID: 26293745.

35. Brigo F, Nardone R, Tezzon F, Trinka E. Nonintravenous midazolam versus intravenous or rectal diazepam for the treatment of early status epilepticus: A systematic review with meta-analysis. Epilepsy & behavior : E&B. 2015 Aug;49:325-36. PubMed PMID: 25817929.

36. McMullan J, Sasson C, Pancioli A, Silbergleit R. Midazolam versus diazepam for the treatment of status epilepticus in children and young adults: a meta-analysis. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine. 2010 Jun;17(6):575-82. PubMed PMID: 20624136.

37. Sofou K, Kristjansdottir R, Papachatzakis NE, Ahmadzadeh A, Uvebrant P. Management of prolonged seizures and status epilepticus in childhood: a systematic review. J Child Neurol. 2009 Aug;24(8):918-26. PubMed PMID: 19332572.

38. Brigo F, Storti M, Del Felice A, Fiaschi A, Bongiovanni LG. IV Valproate in generalized convulsive status epilepticus: a systematic review. European journal of neurology : the official journal of the European Federation of Neurological Societies. 2012 Sep;19(9):1180-91. PubMed PMID: 22182304.

39.   Brigo F, Bragazzi N, Nardone R, Trinka E. Direct and indirect comparison meta-analysis of levetiracetam versus phenytoin or valproate for convulsive status epilepticus. Epilepsy & behavior : E&B. 2016 Oct 10;64(Pt A):110-5. PubMed PMID: 27736657.

40.   Brigo F, Bragazzi NL, Bacigaluppi S, Nardone R, Trinka E. Is intravenous lorazepam really more effective and safe than intravenous diazepam as first-line treatment for convulsive status epilepticus? A systematic review with meta-analysis of randomized controlled trials. Epilepsy & behavior : E&B. 2016 Oct 9;64(Pt A):29-36. PubMed PMID: 27732915.

41.   Brigo F, Igwe SC, Nardone R, Tezzon F, Bongiovanni LG, Trinka E. A common reference-based indirect comparison meta-analysis of intravenous valproate versus intravenous phenobarbitone for convulsive status epilepticus. Epileptic disorders : international epilepsy journal with videotape. 2013 Sep;15(3):314-23. PubMed PMID: 23981687.

42.   Trinka E, Hofler J, Leitinger M, Brigo F. Pharmacotherapy for Status Epilepticus. Drugs. 2015 Aug 27. PubMed PMID: 26310189.

43.   Trinka E, Hofler J, Leitinger M, Rohracher A, Kalss G, Brigo F. Pharmacologic treatment of status epilepticus. Expert opinion on pharmacotherapy. 2016 Mar;17(4):513-34. PubMed PMID: 26629986.

44.   Trinka E, Hofler J, Zerbs A, Brigo F. Efficacy and Safety of Intravenous Valproate for Status Epilepticus: A Systematic Review. CNS drugs. 2014 May 8. PubMed PMID: 24806973.

45.   Meierkord H, Boon P, Engelsen B, Gocke K, Shorvon S, Tinuper P, et al. EFNS guideline on the management of status epilepticus in adults. European journal of neurology : the official journal of the European Federation of Neurological Societies. 2010 Mar;17(3):348-55. PubMed PMID: 20050893.

46.   Capovilla G, Beccaria F, Beghi E, Minicucci F, Sartori S, Vecchi M. Treatment of convulsive status epilepticus in childhood: recommendations of the Italian League Against Epilepsy. Epilepsia. 2013 Oct;54 Suppl 7:23-34. PubMed PMID: 24099053.

47.   Trinka EB, F.;. Benzodiazepines used in the treatment of epilepsy. In: Shorvon SP, E.; Engel, J.; , editor. The Treatment of Epilepsy. 4th ed. Chichester, UK: Wyley; 2015. p. 398-417.

48.   Schütz H. Benzodiazepines II. A Handbook. Basic Data, Analytical Methods, Pharmacokonetics, and Comprehensive Literature. Heidelberg, New York: Springer; 1989.

49.   Greenblatt DJ, Divoll M. Diazepam versus lorazepam: relationship of drug distribution to duration of clinical action. In: Escueta AVD, C.G.Wasterlain, D.M.Treiman, R.J.Porter, editors. Status epileptics Mechanisms of brain damage and treatment Advances in Neruology, vol 34. New Yrok: Raven Press; 1983. p. 487-91.

50.   Leppik IE, Derivan AT, Homan RW, Walker J, Ramsay RE, Patrick B. Double-blind study of lorazepam and diazepam in status epilepticus. Journal of American Medical Association. 1983;249 1452-4.

51.   Appleton R, Sweeney A, Choonara I, Robson J, Molyneux E. Lorazepam versus diazepam in the acute treatment of epileptic seizures and status epilepticus. DevMedChild Neurol. 1995;37(8):682-8.

52.   Alldredge BK, Gelb AM, Isaacs SM, Corry MD, Allen F, Ulrich S, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. NEnglJMed. 2001;345(9):631-7.

53.   Chamberlain JM, Okada P, Holsti M, Mahajan P, Brown KM, Vance C, et al. Lorazepam vs diazepam for pediatric status epilepticus: a randomized clinical trial. JAMA. 2014 Apr 23-30;311(16):1652-60. PubMed PMID: 24756515.

54.   Kellinghaus C, Lang N, Rossetti AO, Ruegg S, Tilz C, Trinka E, et al. Making SENSE--Sustained Effort Network for treatment of Status Epilepticus as a multicenter prospective registry. BMC neurology. 2015 Nov 10;15:230. PubMed PMID: 26554812. Pubmed Central PMCID: 4641362.

55.   Ferlisi M, Hocker S, Grade M, Trinka E, Shorvon S, International Steering Committee of the StEp A. Preliminary results of the global audit of treatment of refractory status epilepticus. Epilepsy & behavior : E&B. 2015 Aug;49:318-24. PubMed PMID: 25952268.

56.   Cock HR, Group E. Established status epilepticus treatment trial (ESETT). Epilepsia. 2011 Oct;52 Suppl 8:50-2. PubMed PMID: 21967363.

57.   Bleck T, Cock H, Chamberlain J, Cloyd J, Connor J, Elm J, et al. The established status epilepticus trial 2013. Epilepsia. 2013 Sep;54 Suppl 6:89-92. PubMed PMID: 24001084.

58.   Lang N, Lange M, Schmitt FC, Bos M, Weber Y, Evers S, et al. Intravenous lacosamide in clinical practice-Results from an independent registry. Seizure : the journal of the British Epilepsy Association. 2016 Jul;39:5-9. PubMed PMID: 27161669.

59.   Hofler J, Trinka E. Lacosamide as a new treatment option in status epilepticus. Epilepsia. 2013 Mar;54(3):393-404. PubMed PMID: 23293881.

60.   Sutter R, Marsch S, Ruegg S. Safety and efficacy of intravenous lacosamide for adjunctive treatment of refractory status epilepticus: a comparative cohort study. CNS drugs. 2013 Apr;27(4):321-9. PubMed PMID: 23533010.

61.   Garces M, Villanueva V, Mauri JA, Suller A, Garcia C, Lopez Gonzalez FJ, et al. Factors influencing response to intravenous lacosamide in emergency situations: LACO-IV study. Epilepsy & behavior : E&B. 2014 Jul;36:144-52. PubMed PMID: 24922617.

62.   Mayer SA, Claassen J, Lokin J, Mendelsohn F, Dennis LJ, Fitzsimmons BF. Refractory status epilepticus: frequency, risk factors, and impact on outcome. ArchNeurol. 2002;59(2):205-10.

63.   Holtkamp M, Othman J, Buchheim K, Meierkord H. Predictors and prognosis of refractory status epilepticus treated in a neurological intensive care unit. JNeurolNeurosurgPsychiatry. 2005;76(4):534-9.

64.   Claassen J, Hirsch LJ, Emerson RG, Mayer SA. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. Epilepsia. 2002;43(2):146-53.

65.   Ferlisi M, Shorvon S. The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy. Brain. 2012 Aug;135(Pt 8):2314-28. PubMed PMID: 22577217.

66.   Niermeijer JM, Uiterwaal CS, Van Donselaar CA. Propofol in status epilepticus: little evidence, many dangers? JNeurol. 2003;250(10):1237-40.

67.   Sutter R, Marsch S, Fuhr P, Kaplan PW, Ruegg S. Anesthetic drugs in status epilepticus: risk or rescue? A 6-year cohort study. Neurology. 2014 Feb 25;82(8):656-64. PubMed PMID: 24319039. Pubmed Central PMCID: 3945664.

68.   Fujikawa DG. Neuroprotective effect of ketamine administered after status epilepticus onset. Epilepsia. 1995;36(2):186-95.

69.   Borris DJ, Bertram EH, Kapur J. Ketamine controls prolonged status epilepticus. Epilepsy Res. 2000;42(2-3):117-22.

70.   Kapur J, Coulter DA. Experimental status epilepticus alters gamma-aminobutyric acid type A receptor function in CA1 pyramidal neurons. AnnNeurol. 1995;38(6):893-900.

71.   Mazarati AM, Wasterlain CG. N-methyl-D-asparate receptor antagonists abolish the maintenance phase of self-sustaining status epilepticus in rat. NeurosciLett. 1999;265(3):187-90.

72.   Gaspard N, Foreman B, Judd LM, Brenton JN, Nathan BR, McCoy BM, et al. Intravenous ketamine for the treatment of refractory status epilepticus: a retrospective multicenter study. Epilepsia. 2013 Aug;54(8):1498-503. PubMed PMID: 23758557. Pubmed Central PMCID: 3731413.

73.   Synowiec AS, Singh DS, Yenugadhati V, Valeriano JP, Schramke CJ, Kelly KM. Ketamine use in the treatment of refractory status epilepticus. Epilepsy Res. 2013 Jul;105(1-2):183-8. PubMed PMID: 23369676.

74.   Basha MM, Alqallaf A, Shah AK. Drug-induced EEG pattern predicts effectiveness of ketamine in treating refractory status epilepticus. Epilepsia. 2015 Apr;56(4):e44-8. PubMed PMID: 25759241.

75.   Walker MC, Howard RS, Smith SJ, Miller DH, Shorvon SD, Hirsch NP. Diagnosis and treatment of status epilepticus on a neurological intensive care unit. QJM. 1996;89(12):913-20.

76.   Kofke WA, Bloom MJ, Van Cott A, Brenner RP. Electrographic tachyphylaxis to etomidate and ketamine used for refractory status epilepticus controlled with isoflurane. Journal of neurosurgical anesthesiology. 1997 Jul;9(3):269-72. PubMed PMID: 9239591.

77.   Ubogu EE, Sagar SM, Lerner AJ, Maddux BN, Suarez JI, Werz MA. Ketamine for refractory status epilepticus: a case of possible ketamine-induced neurotoxicity. Epilepsy Behav. 2003;4(1):70-5.

78.   Robakis TK, Hirsch LJ. Literature review, case report, and expert discussion of prolonged refractory status epilepticus. NeurocritCare. 2006;4(1):35-46.

79.   Pruss H, Holtkamp M. Ketamine successfully terminates malignant status epilepticus. Epilepsy Res. 2008 Dec;82(2-3):219-22. PubMed PMID: 18804344.

80.   Yeh PS, Shen HN, Chen TY. Oral ketamine controlled refractory nonconvulsive status epilepticus in an elderly patient. Seizure : the journal of the British Epilepsy Association. 2011 Nov;20(9):723-6. PubMed PMID: 21724423.

81.   Kramer AH. Early ketamine to treat refractory status epilepticus. Neurocritical care. 2012 Apr;16(2):299-305. PubMed PMID: 22237581.

82.   Zeiler FA, Kaufmann AM, Gillman LM, West M, Silvaggio J. Ketamine for medically refractory status epilepticus after elective aneurysm clipping. Neurocritical care. 2013 Aug;19(1):119-24. PubMed PMID: 23702695.

83.   Shrestha GS, Joshi P, Chhetri S, Karn R, Acharya SP. Intravenous ketamine for treatment of super-refractory convulsive status epilepticus with septic shock: A report of two cases. Indian journal of critical care medicine : peer-

reviewed, official publication of Indian Society of Critical Care Medicine. 2015 May;19(5):283-5. PubMed PMID: 25983437. Pubmed Central PMCID: 4430749.

84.   Hsieh CY, Sung PS, Tsai JJ, Huang CW. Terminating prolonged refractory status epilepticus using ketamine. Clin Neuropharmacol. 2010 May;33(3):165-7. PubMed PMID: 20098301.

85.   White PF, Schuttler J, Shafer A, Stanski DR, Horai Y, Trevor AJ. Comparative pharmacology of the ketamine isomers. Studies in volunteers. British journal of anaesthesia. 1985 Feb;57(2):197-203. PubMed PMID: 3970799.

86.   Engelhardt W, Stahl K, Marouche A, Hartung E. [Recovery time after (S)-ketamine or ketamine racemate. Recovery time after short anesthesia in volunteers]. Anaesthesist. 1998 Mar;47(3):184-92. PubMed PMID: 9567151. Aufwachzeit nach (S)-Ketamin- oder Ketamin-Razemat. Aufwachzeit nach Kurznarkosen bei Probanden.

87.   Hofler J, Rohracher A, Kalss G, Zimmermann G, Dobesberger J, Pilz G, et al. (S)-Ketamine in Refractory and Super-Refractory Status Epilepticus: A Retrospective Study. CNS drugs. 2016 Sep;30(9):869-76. PubMed PMID: 27465262. Pubmed Central PMCID: 4996879.

88.   Hanada T, Hashizume Y, Tokuhara N, Takenaka O, Kohmura N, Ogasawara A, et al. Perampanel: a novel, orally active, noncompetitive AMPA-receptor antagonist that reduces seizure activity in rodent models of epilepsy. Epilepsia. 2011 Jul;52(7):1331-40. PubMed PMID: 21635236.

89.   Rogawski MA, Hanada T. Preclinical pharmacology of perampanel, a selective non-competitive AMPA receptor antagonist. Acta neurologica Scandinavica Supplementum. 2013 (197):19-24. PubMed PMID: 23480152. Pubmed Central PMCID: 4506647.

90.   Rohracher A, Hofler J, Kalss G, Leitinger M, Kuchukhidze G, Deak I, et al. Perampanel in patients with refractory and super-refractory status epilepticus in a neurological intensive care unit. Epilepsy & behavior : E&B. 2015 Aug;49:354-8. PubMed PMID: 25962657.

91.   Redecker J, Wittstock M, Benecke R, Rosche J. Efficacy of perampanel in refractory nonconvulsive status epilepticus and simple partial status epilepticus. Epilepsy & behavior : E&B. 2015 Apr;45:176-9. PubMed PMID: 25819947.

92.   Rosche J, Kampf C, Benecke R. Possible effect of perampanel on focal status epilepticus after generalized tonic-clonic status epilepticus. Acta neurologica Belgica. 2014 Sep;114(3):243-4. PubMed PMID: 23801431.

93.   Naylor DE, Liu H, Wasterlain CG. Trafficking of GABA(A) receptors, loss of inhibition, and a mechanism for pharmacoresistance in status epilepticus. JNeurosci. 2005;25(34):7724-33.

94.   Naylor DE, Wasterlain CG. GABA synapses and the rapid loss of inhibition to dentate gyrus granule cells after brief perforant-path stimulation. Epilepsia. 2005;46 Suppl 5:142-7.

95.   Rogawski MA, Loya CM, Reddy K, Zolkowska D, Lossin C. Neuroactive steroids for the treatment of status epilepticus. Epilepsia. 2013 Sep;54 Suppl 6:93-8. PubMed PMID: 24001085. Pubmed Central PMCID: 3772544.

96.   Broomall E, Natale JE, Grimason M, Goldstein J, Smith CM, Chang C, et al. Pediatric super-refractory status epilepticus treated with allopregnanolone. Ann Neurol. 2014 Dec;76(6):911-5. PubMed PMID: 25363147. Pubmed Central PMCID: 4534165.

97.   Shorvon S, Ferlisi M. The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. Brain. 2011 Oct;134(Pt 10):2802-18. PubMed PMID: 21914716.

98.   Vezzani A, Ruegg S. The pivotal role of immunity and inflammatory processes in epilepsy is increasingly recognized: introduction. Epilepsia. 2011 May;52 Suppl 3:1-4. PubMed PMID: 21542838.

99.   Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet neurology. 2016 Apr;15(4):391-404. PubMed PMID: 26906964. Pubmed Central PMCID: 5066574.

Figure Legends:

Figure1: Operational dimensions with t1 indicating the time that emergency treatment of SE should be started and t2 denoting the time at which long term consequences may be expected. Time (t_1), when a seizure is likely to be prolonged leading to continuous seizure activity. Time (t2), when a seizure may cause long-term consequences (including neuronal injury, neuronal death, alteration of neuronal networks and functional deficits). For generalized tonic clonic status the stages have been added (stage I 5-10 minutes; stage II 10-30 minutes; stage III 30-30 min) (13)
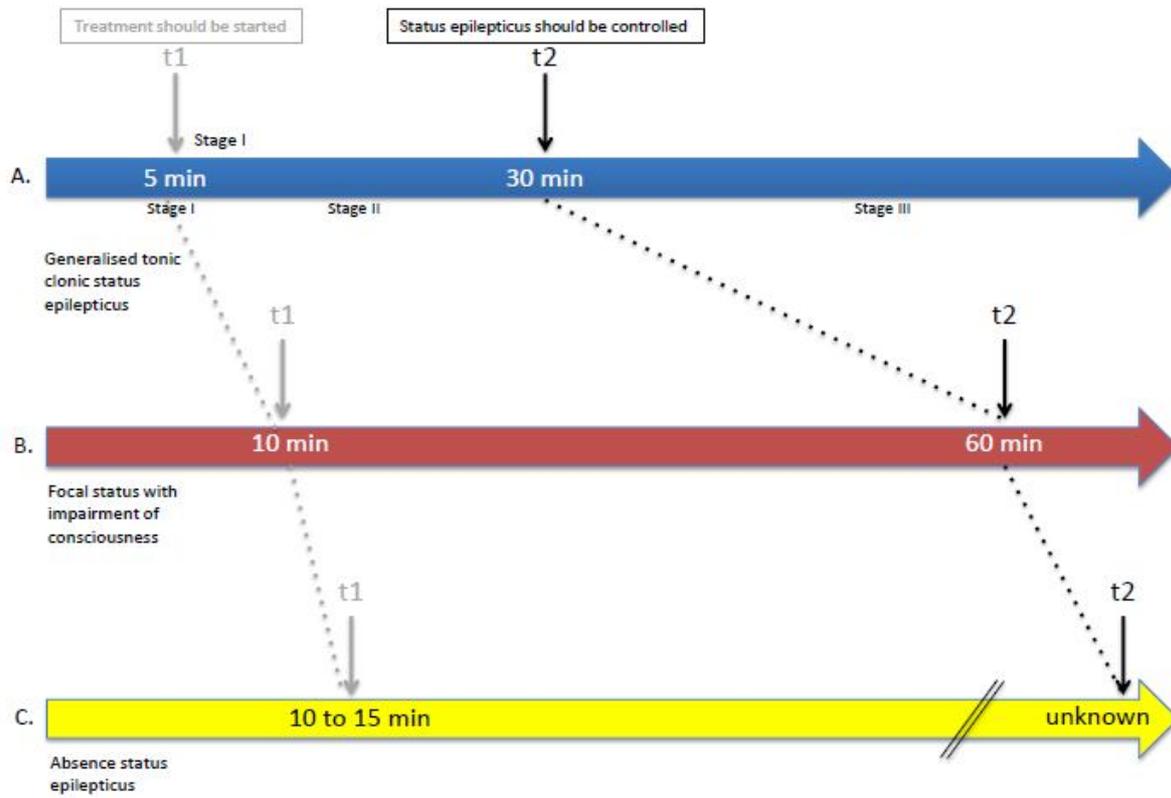
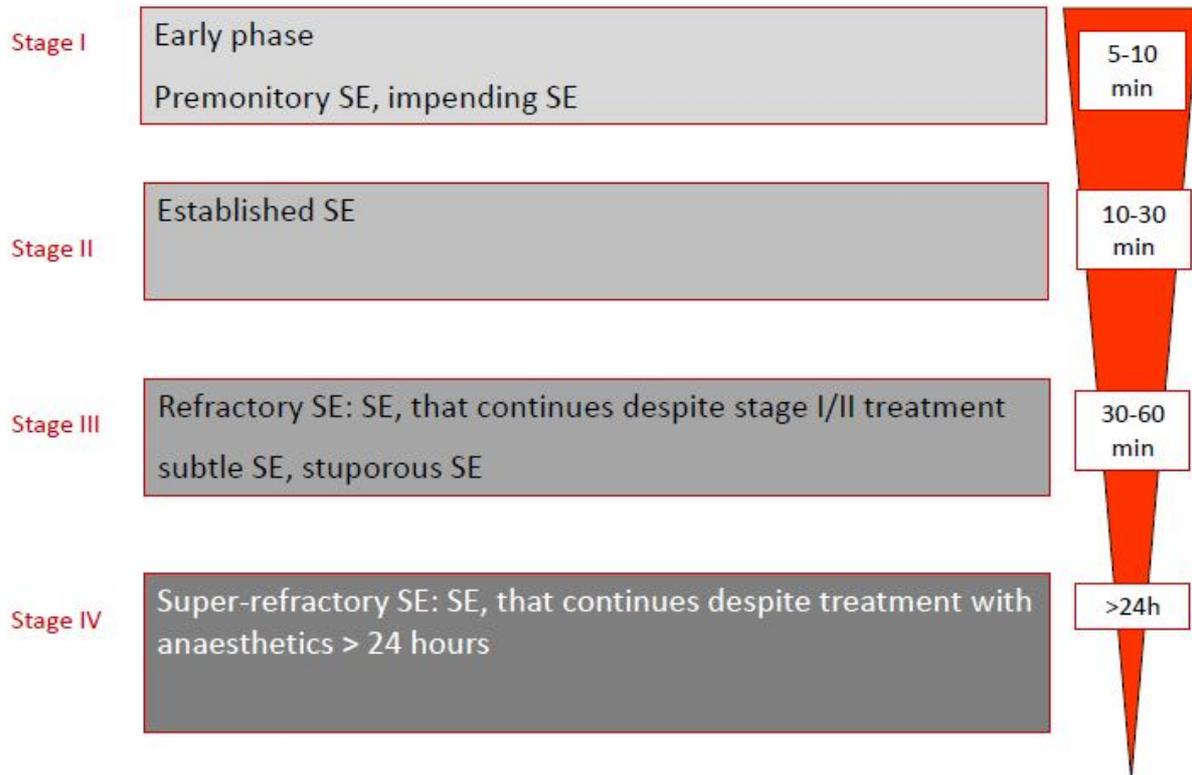*Figure 2:* Clinical course of convulsive status epilepticus (Figure 1 from reference (42))

Figure 3: Staged treatment protocol for early (Stage I), established (Stage II) and refractory (Stage III) convulsive status epilepticus. Timelines for stage I to III given are general approximations and may vary depending on clinical circumstances, cause, and age of the patient. (Figure 1 from reference (43))
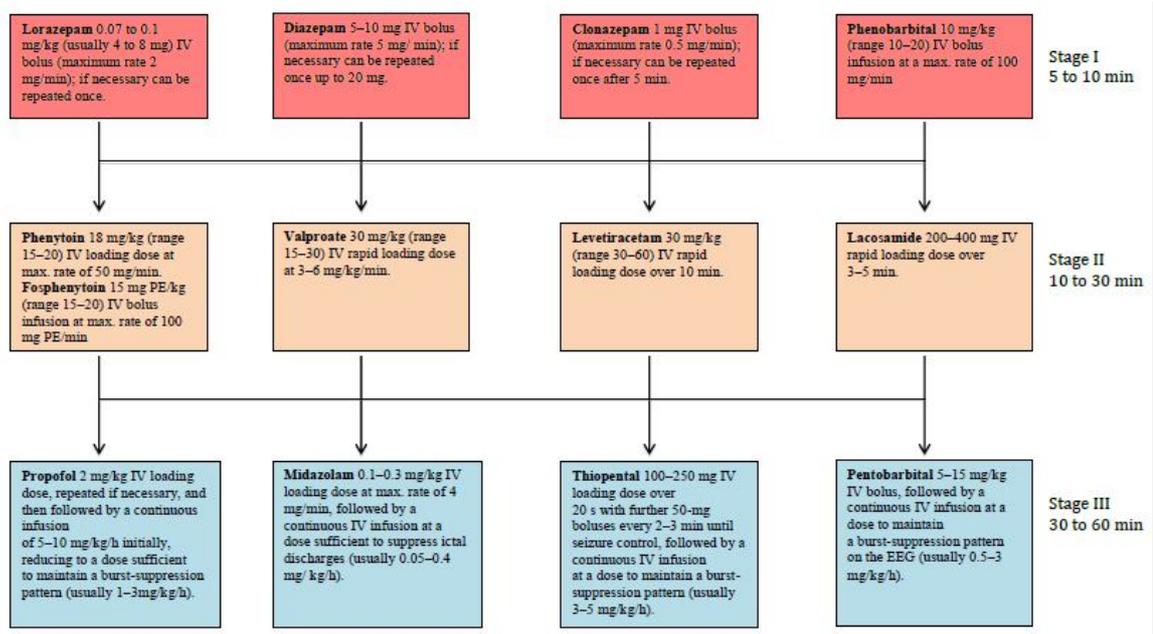
Figure 4: Treatment options for early (Stage I) status epilepticus, when intravenous routes are not available (Figure 2 from reference (43))
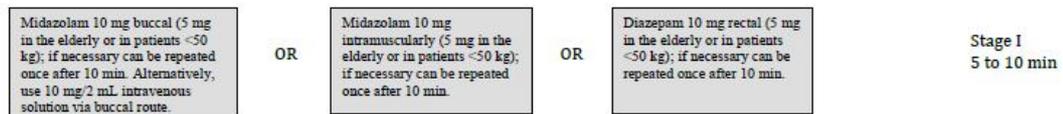
Table 1: Axis 1 of the Classification of Status epilepticus (SE) (13)

A. With prominent motor symptoms

1. **Convulsive SE (CSE, synonym: tonic-clonic SE)**

   a. Generalized convulsive

   b. Focal onset evolving into bilateral convulsive SE

   c. Unknown whether focal or generalized

2. **Myoclonic SE** (prominent epileptic myoclonic jerks)

   a. With coma

   b. Without coma

3. **Focal motor**

   a. Repeated focal motor seizures (Jacksonian)

   b. Epilepsia Partialis Continua (EPC)

   c. Adversive status

   d. Oculoclonic status

   e. Ictal paresis (i.e. focal inhibitory SE)

4. **Tonic status**

5. **Hyperkinetic SE**

B) Without prominent motor symptoms (i.e. Non Convulsive SE, NCSE)

1. **NCSE with coma (including so-called "subtle" SE)**

2. **NCSE without coma**

   a. **Generalized**

      i. *Typical absence status*

      ii. *Atypical absence status*

      iii. *Myoclonic absence status*

   b. Focal

      i. Without impairment of consciousness (aura continua, with autonomic, sensory, visual,

         olfactory, gustatory, emotional/psychic/experiential, or auditory symptoms)

      ii. Aphasic status

      iii. With impaired consciousness

   c. Unknown whether focal or generalized

      i. Autonomic SE

Table 2: Salzburg EEG Consensus Criteria for nonconvulsive status epilepticus (18,20,21)

Patients without known epileptic encephalopathy
- EDs > 2.5 Hz, *or*

- EDs ≤ 2.5 Hz or rhythmic delta/theta activity (>0.5 Hz) AND one of the following:

  - EEG and clinical improvement after IV AED*, *or*

  - Subtle clinical ictal phenomena, *or*

  - Typical spatiotemporal evolution**

Patients with known epileptic encephalopathy
- Increase in prominence or frequency when compared to baseline **with** observable change in clinical state

- Improvement of clinical and EEG* features with IV AEDs

If EEG improvement without clinical improvement, or if fluctuation without definite evolution, this should be considered **possible NCSE.*
**Incrementing onset (increase in voltage and change in frequency), or evolution in pattern (change in frequency >1 Hz or change in location), or decrementing termination (voltage or frequency).
EDs: epileptiform discharges (spikes, polyspikes, sharp-waves, sharp-and-slow-wave complexes)
IV AED: intravenous antiepileptic drugs