MATERIAL DIDACTIC

STATUS EPILEPTICUS. ADVANCES IN THE TREATMENT

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Summary
Status epilepticus is a major medical emergency that is fatal in 7.6-22% of cases. The incidence per 100,000 population has been estimated at 9.9 episodes in Europe and 41 episodes in the USA. Status epilepticus may be convulsive, i.e., accompanied by motor, activity, or nonconvulsive. There is a consensus that seizures lasting longer than 30 min. constitute established status epilepticus. A useful strategy focuses on imminent convulsive status epilepticus, defined as continuous seizures for longer than 5 min. or three seizures not separated by recovery of normal consciousness or of the level of consciousness present before the seizures. Members of an international workshop held by the Epilepsy Research Foundation agreed on a somewhat vague definition of non-convulsive status epilepticus as “a range of conditions in which electrographic seizure activity is prolonged and results in non-convulsive clinical symptoms”. The immediate treatment goals in patients with generalized convulsive status epilepticus are cessation of the clinical seizures and prevention of subtle status epilepticus. Intravenous lorazepam is the first-line treatment for generalized convulsive status epilepticus. If the seizure persists, a second injection can be given 10 minutes later. Phenytoin or fosphenytoin is a good choice when lorazepam fails. Administration of an additional lorazepam dose can be considered. Anesthesia with propofol, thiopental, or midazolam is the cornerstone of the management of refractory status epilepticus. Regardless of the drug used, the dose should be titrated at 3 to 5 min. intervals under EEG monitoring with the goal of obtaining a burst-suppression pattern with suppression for 5 to 10 seconds.
Key words: advances, treatment, status epilepticus

Rezumat. Statusul epileptic. Progres în tratament
Statusul epileptic constituie o urgenţă neurologică majoră cu o letalitate de 7,6-22% din cazuri. Incidenţa statusului epileptic la 100000 populaţie este estimat la 9,9 cazuri în Europa şi 41 cazuri în SUA. Statusul epileptic poate fi convulsivant însoţit de crize tonicoclonice sau nonconvulsivante. Este stabilit un consens care atribuie la status epileptic activitatea convulsivantă care persistă mai mult de 30 de minute. Trei crize convulsive subintrante care se continuă una după alta fără o perioadă eficientă de recuperare sau crize care durează mai mult de 5 minute sunt indicatori ai iminenţei statusului epileptic şi necesită terapie ţintită. Grupul de lucru al Fundaţiei Internaţionale de Cercetare a Epilepsiei acceptă caracterul vag al noţiunii de status epileptic nonconvulsivant, definiţie bazată pe modificări comportamentale sau mintale şi/sau manifestări EEG de tip epileptiform. Obiectivele imediate ale tratamentului statusului epileptic vizează oprirea crizelor, susţinerea funcţiilor vitale, tratamentul cauzei sau a factorilor declanşatori şi tratamentul complicaţiilor. Tratamentul presupune internare într-o unitate de terapie intensivă şi instituirea imediată a unor măsuri de terapii standardizate, etapizate şi monitorizare electroencefalografică. Administrarea intravenoasă a lorazepamului este obiectivul numărul unu în statusul epileptic convulsivant. În caz de persistenţă a convulsiilor o administrare repetată la 10 minute. Dacă statusul epileptic nu este stopat cu lorazepam se continuă cu fenitoin sau fosfenitoin. În cazul statusului epileptic refractar anestezia generală intravenoasă cu unul din preparate: propofol, thiopental, midazolam pentru stoparea crizelor. Necesită monitorizare funcţiile respiratorie şi cardiacă. Anestezia generală este menţinută până la dispariţia traseului ECG de criză sau maxim 24 ore.
Cuvinte-cheie: progres, tratament, statusul epileptic

Резюме. Эпилептический статус. Достижения в лечении
Эпилептический статус является тяжелым чрезвычайным неврологическим состоянием летальность при котором достигает от 7,6% до 22% случаев. Распространенность эпилептического статуса из расчета на 100000 населения оценивается в 9,9 случаев в Европе и 41 случаев в Соединенных Штатах. Эпилептический статус

может быть представлен судорожными, тонико-клоническими припадками, или сопровождаться конвульсиями. Установлено положение, согласно которому понятие эпилептический статус присваивается конвульсивной деятельности длящийся более 30 минут. Три конвульсивных криза, продолжающиеся один за другим без эффективного восстановления или кризисный период продолжительностью более 5 минут являются индикаторами надвигающегося эпилептического статуса и требуют целенаправленной терапии. Рабочая группа Международного Фонда Исследования Эпилепсии поддерживает концепцию неконвульсивного эпилептического статуса, определяемого на основе характерных изменений поведения, психики и / или наличия эпилептиформного типа ЭЭГ. Задачи проводимой терапии включают прекращение припадков эпилептического статуса, поддержание жизненно важных функций, лечение или устранение причин, а также лечение осложнений. Терапия требует госпитализации в отделение интенсивной терапии и немедленное применение стандартизированных и этапизированых методов лечения, электроэнцефалографической мониторинга. Внутривенное введение лоразепама является мерой номер один при припадках эпилептического статуса. Если судороги сохраняются, повторное введение осуществляется через 10 минут. Если эпилептический статус не купируется после применения лоразепама, вводятся с фенитоином или фосфенитоин. В случае рефрактарного эпилептического статуса, в целях остановки судорог, проводится внутривенная общая анестезии с одним из препаратов: пропофол, тиопентал, мидазолам. Необходим мониторинг дыхательной и сердечной функции. Общая анестезия сохраняется до исчезновения признаков кризиса на ЭКГ, но не более 24 часов.

Ключевые слова: достижения, эпилептический статус, лечение

Introduction

Status epilepticus is a major medical emergency that is fatal in 7.6-22% of cases. The incidence per 100,000 population has been estimated at 9.9 episodes in Europe and 41 episodes in the USA [6,25]. About 5% of adults diagnosed with epilepsy have had at least one episode of status epilepticus, with children higher at 10-25%. Incidence of status epilepticus is U-shaped, with highest incidence in the very young, under 1 year old and the elderly over 60 years old.

Mortality has been reported to be 8% in children and 30% in adults. In addition, 5-10% of people with status epilepticus will be left with permanent disability such as permanent vegetative state or cognitive difficulties.

Status epilepticus may be convulsive, i.e., accompanied by motor, activity, or non-convulsive. Continuous or repeated electrical seizures without recovery of consciousness characterizes both forms of status epilepticus. Morbidity and mortality rates differ between convulsive and non-convulsive status epilepticus, and each requires a specific treatment strategy.

Status epilepticus (SE) is defined as a continuous, generalized, convulsive seizure lasting longer than 5 minutes, or two or more seizures during which the patient does not return to baseline consciousness.

Generalized convulsive status epilepticus (GCSE)

The working (operational) definition of convulsive status epilepticus proposed by Lowenstein et al. in 1999 remains widely accepted, despite some degree of controversy [22]. Video-electroencephalographic (EEG) recordings have established that simple convulsive seizures have a mean duration of only 2 minutes, although longer durations of up to 11 minutes are observed occasionally [17]. Seizures longer than 30 min. are associated with a high rate of refractoriness to antiepileptic drugs and with the development of neuronal damage [14]. Therefore, a key treatment objective is to achieve seizure resolution within 30 minutes. There is a consensus that seizures lasting longer than 30 min. constitute established status epilepticus [5]. A useful strategy focuses on imminent convulsive status epilepticus, defined as continuous seizures for longer than 5 min. or three seizures not separated by recovery of normal consciousness or of the level of consciousness present before the seizures [25].

Generalized convulsive status epilepticus (GCSE) involves generalized convulsions with impaired consciousness which may progress to minimal or no apparent motor activity but still show seizure activity on EEG. GCSE is diagnosed clinically by tonic-clonic seizures, loss of consciousness, urinary incontinence and tongue biting. Differential diagnosis includes myoclonic jerks, septic rigors, dystonia and pseudostatus epilepticus.

Non-convulsive status epilepticus

The definition of non-convulsive status epilepticus is actively debated. Members of an international workshop held by the Epilepsy Research Foundation agreed on a somewhat vague definition of non-convulsive status epilepticus as “a range of conditions in which electrographic seizure activity is prolonged and results in non-convulsive clinical symptoms” [45]. The electrographic seizure activity must meet complex electrophysiological criteria, among which some are defined clearly and others must be interpreted according to the clinical setting [18]. Because a working definition was needed, the workshop mem-

bers agreed to include electrographic seizure activity for 30 min. in the definition of non-convulsive status epilepticus.

Non-convulsive status epilepticus (NSCE) can have a variety of presentations including coma, confusion, somnolence, aphasia, altered affect and also uncommon manifestations such as delusions, hallucinations and paranoia. This can be further divided into generalized, focal or other. NSCE should be an important differential diagnosis of coma as studies have found that up to 8% of patients in coma can be found to be in NSCE.

Classification

The most widely accepted classification scheme distinguishes between convulsive status epilepticus, which is usually easy to recognize on clinical grounds, and non-convulsive status epilepticus, in which the symptoms may be minimal and the role for EEG is preponderant (**table 1**) [44]. Subgroups are described within each of these two main categories. Thus, the motor activity in convulsive status epilepticus may consist of partial tonic-clonic seizures or of generalized seizures with tonic-clonic, tonic, clonic, or myoclonic activity (**figure 1**). Patterns of nonconvulsive status epilepticus include absence status epilepticus, complex partial status epilepticus, and electrical status epilepticus (including subtle status epilepticus) (**figure 2**).

Table 1

Clinical classification of status epilepticus

1. Generalized seizures
A. Generalized convulsive status epilepticus
i. Primary generalized status epilepticus
a. Tonic-clonic status epilepticus
b. Myoclonic status epilepticus
c. Clonic-fonic-clonic status epilepticus
ii. Secondary generalized status epilepticus
a. Partial seizures with secondary generalization
b. Tonic status epilepticus
B. non-convulsive status epilepticus
i. Absence status epilepticus (petit mal status)
ii. A typical absence status epilepticus (e.g., in the Lennox-Gastaut syndrome)
iii. Antonic status epilepticus
iv. Nonconvulsive status epilepticus as a sequel of partially treated generalized convulsive status epilepticus
2. Partial status epilepticus
A. simple partial status epilepticus
i. Typical
ii. Epilepsia partialis continus
B. Complex partial status epilepticus
3. Neonatal status epilepticus

Note: **Adapted from Lothman EW. The biochemical basis and pathophysiology of status epilepticus. Neurology 1990; 40:13-23**.

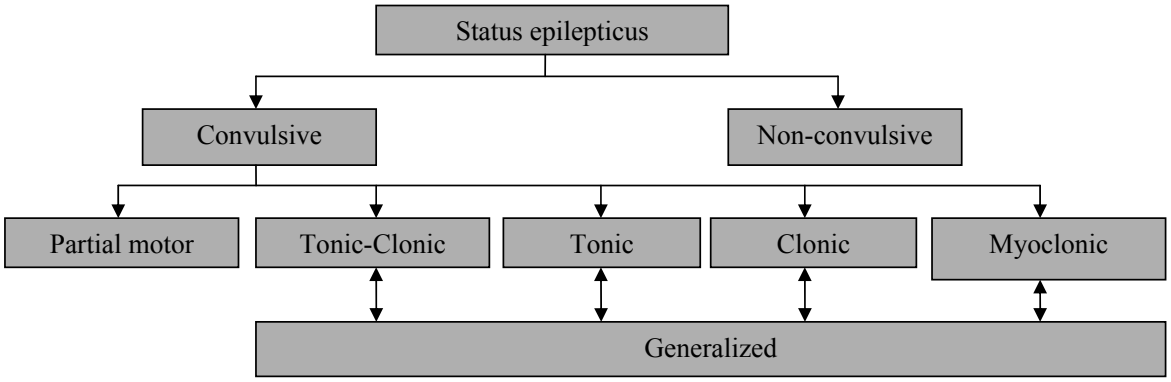

Figure 1. *Classification of convulsive status epilepticus*

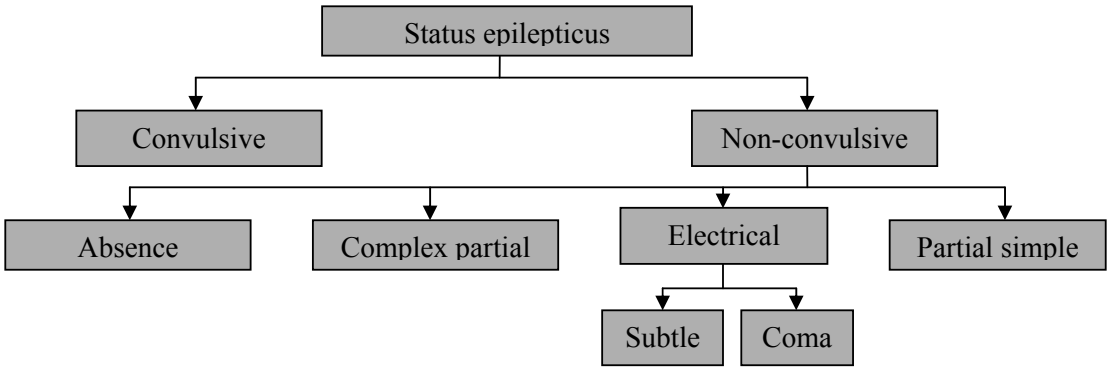

Figure 2. *Classification of non-convulsive status epilepticus*

Aetiology

In children 51% of status epilepticus cases are secondary to infections. In adults, the causes are more diverse and can include drug misuse and cerebral pathologies (**table 2**).

Table 2

Causes of convulsive status epilepticus

Previous history of epilepsy	Presenting for the first time with status
Withdrawal of anti-epileptoc drug treatment	Cerebrovascular disease
Alcohol (or withdrawal of)	Cerebral tumour
Drug overdose	Intracranial infection
Cerebral trauma	Acute metabolic disturbances
Cerebral tumour	
Intracranial infection	
Acute metabolic disturbances	

Table 2 summarizes the most common causes of status epilepticus in adults in the community. Almost 50% of the cases were attributed to cerebral vascular disease. Garzon and colleagues found antiepileptic drug noncompliance as the main cause of status epilepticus in patients with a prior history of epilepsy, and CNS infection, stroke, and metabolic disturbances predominated in the group without previous seizures.

Three major factors determine outcome in patients with status epilepticus: the type of status epilepticus, its cause, and its duration. Generalized convulsive status epilepticus has the worst prognosis for neurologic recovery; myoclonic status epilepticus following an anoxic episode carries a very poor prognosis for survival. Complex partial status epilepticus can produce limbic system damage, usually manifested as a memory disturbance. Causes associated with increased mortality included anoxia, intracranial hemorrhages, tumors, infections, and trauma. The mortality of patients with nonconvulsive status epilepticus has been reported as high as 33% and correlates with the underlying cause, severe impairment of mental status, and the development of acute complications, especially respiratory failure and infection.

Pathophysiology

GCSE causes a sympathetic overdrive which causes both systemic and cerebral effects, whereas systemic effects are more limited in NCSE (**table 3**).

Table 3

Systemic effects of status epilepticus

Cardiovascular system	Sympathetic overdrive Tachycardia, arrhythmias Initial increase in blood pressure and peripheral vascular resistance, followed by normalization and possible hypotension
Respiratory system	Increased respiratory rate and tidal volume Respiratory acidosis and when combined with metabolic acidosis leads to low pH on arterial blood gases Increased pulmonary vascular resistance and pulmonary oedema illustrated in animal studies
Musculoskeletal system	Anaerobic metabolism, lactic acidosis
Temperature	Increased core temperature

In the early stages of established GCSE, there is an increase in blood pressure, glucose and lactate and a lower plasma pH. After 30 min. and in the second phase, blood pressure and glucose will normalize or even decrease, lactate will normalize, respiratory compensation and hyperthermia will follow. The compensatory mechanisms will result in increased cerebral perfusion but these do not last. By 60-90 min. these compensatory mechanisms will fail, hypotension and loss of cerebral autoregulation will ensue, leading to cerebral hypoperfusion and cerebral damage.

Neurons also suffer damage as a result of complex interplay of multiple factors termed excitotoxic neuronal injury. During this process, the inhibition of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) and excesive action of the excitatory neurotransmitter glutamate. High concentrations of excitatory neurotransmitter open N-methyl-D-aspartate (NMDA) receptor-mediated calcium channels resulting in excessive intracellular calcium, leading to a sequence of events which results in neuronal damage and apoptosis.

Clinical Manifestations

Three problems complicate seizure recognition: the occurrence of complex partial seizures in the setting of impaired awareness, the occurrence of seizures in patients receiving pharmacologically induced paralysis and/or sedation, and misinterpretation of other abnormal movements as seizures (**table 4**).

Table 4

Emergency investigations

Arterial blood gases
Biochemistry – blood glucose, renal, liver function, calcium, magnesium
Haematology – full blood count, clotting profile
AED levels
Venous blood sample and urine sample for toxicology screen
Chest X-ray – aspiration
CT scan/LP

Subtle status epilepticus and partially treated status epilepticus. Subtle status refers to the fact that as SE continues, the clinical and EEG signs of seizure activity may lessen but the condition was critical as frank SE. Partially treated SE is similar in that the clinical signs of the seizure may diminish after treatment for SE with high-dose medications, but the EEG activity persists. Continuous EEG monitoring should thus be performed in all SE patients.

Non-convulsive status epilepticus. Non-convulsive SE presents as altered mental status ranging from a mild behavioral alteration noticeable only to family or friends to frank coma. Other manifestations may include speech arrest, cognitive deficits, delusions, paranoia, hallucinations or psychosis. Because, by definition there is rarely a significant motor component, the diagnosis is often missed, and there are many case reports of these patients initially being diagnosed with a psychiatric illness. Non-convulsive SE has been reported in every age group, can be the initial presentation of a seizure disorder and has been reported to last as long as 8 weeks.

The diagnosis should be suspected in patients with a seizure history who present with a prelonged postictal period or an unusual behavior pattern. Non-convulsive SE should also be considered in patients without a seizure history who present with altered mental status of undetermined etiology. The diagnosis is made by EEG. Treatment is the same as for convulsive SE, beginning with lorazepam, 2 mg/min., until the EEG normalizes or a total of 10 mg in administered. This treatment should be followed by phenytoin loading, although it is questionable whether phenytoin is effective in absence status (**table 5**).

Table 5

Monitoring

Regular neurological observations
Heart rate, ECG, blood pressure measurements
Temperature
Arterial blood das
FBC, clotting, biochemistry
Drug levels
ECG required for refractory status epilepticus

Refractory status epilepticus

Refractory status epilepticus is defined as continued seizures despite the use of two first-line agents. These patients will require intubation and ventilation and possibly pressor support in a critical care setting.

The traditional goal of burst suppression pattern on EEG for initial 12-24 hours has been challenged as there are no data to suggest that burst suppression is needed to control or prevent recurrent seizures. However, EEG monitoring is recommended in refractory status epilepticus to aid the titration of anticonvulsant drugs and ensure suppression of seizure activity (**table 6,7**).

Long-term anti-epileptic drug therapy

Long-term and maintenance AED therapy must be given in tandem with emergency treatment. Choice of medication when commencing new maintenance therapy will depend on previous treatment, the type of epilepsy and clinical setting. Pre-existing AED therapy should be continued at full dose and any recent changes reversed.

Maintenance AEDs should be started after oral loading dose. If phenytoin or phenobarbitone is started as emergency treatment and is to be continued, then it can be given orally or intravenously guided by serum level monitoring. Naso-gastric feed can interfere with absorption of some drugs such as phenytoin. Once the patient has been seizure-free for 12-24 hours and the plasma levels of AEDs are adequate, the general anaesthetic agent should be slowly decreased.

Table 6

Complications of status epilepticus

Central nervous system	Cerebral hypoxia Cerebral oedema Cerebral haemorrhage Cerebral venous thrombosis
Cardiovascular system	Myocardial infarction Hyper/hypotension Arrhythmias Cardiac arrest Cardogenic shock
Respiratory system	Apneea Respiratory failure Pneumonia Pulmonary oedema
Metabolic system	Hyponatraemia Hypoglycaemia Hyperkalaemia Metabolic acidosis Acute tubular necrosis Acute hepatic necrosis Acute pancreatitis
Miscellanous	Disseminated intravscular coagulopathy Rhabdomyolysis Fractures

Table 7

Electrographic-Clinical Correlations in Generalized Convulsive Status Epilepticus

Typical clinical Manifestations	Electroencephalographic Features
Tonic-clonic convulsions; hypertension and hyperglycemia common	Discrete seizures with interictal slowing
Low or medium amplitude clonic activity, with rare convulsions	Waxing and waning of ictal discharges
Slight but frequent clonic activity, often confined to the eyes, face, or hands c	Continuous ictal discharges
Rare episodes of slight clonic activity; hypotension and hypoglycemia become manifested	Continuous ictal discharges punctuated by flat periods
Coma without other manifestations of seizure activity	Periodic epileptiform discharges on a flat background

Note: **Data from Treiman DM. Generalized convulsive status epilepticus in the adult. Epilepsia 1993; 34: S2-11.**

Differential Diagnoses

Pseudo-status epilepticus

Pseudo-epileptic seizure is defined as paroxysmal motor or behavioral symptoms that simulate an epileptic seizure in the absence of detectable electrical seizure activity or brain lesions [1]. The incidence of pseudo-epileptic seizure in patients with known epilepsy is about 15%. Prolonged episodes of pseudo-epileptic seizure define pseudo-status epilepticus, which mimics status epilepticus. Of 25 patients with pseudo-epileptic seizures, 77.6% reported at least one episode of pseudo-status epilepticus > 30 mins., and 27% ICU admission for pseudo-status epilepticus. Distinctive features of pseudo-status epilepticus mimicking generalized convulsive status epilepticus have been identified [33].

Eye opening and closing may be the best clinical feature for differentiating pseudo-status epilepticus from status epilepticus, although most studies focused on seizures as opposed to status. Eye opening is the rule during epileptic seizures (positive predictive value [PPV], 97%), whereas the eyes are closed in most pseudo-epileptic seizures (PPV, 94.3%) [7]. The serum creatine phosphokinase level may be normal in pseudo-status epilepticus, contrasting with the increase from 3 to 36 hours seen in convulsive status epilepticus [16]. Elevated serum prolactin helps to differentiate epilepsy from pseudo-epileptic seizure but remains unproven for separating status epilepticus from pseudo-status epilepticus [4]. In contrast, a normal interictal EEG trace after clinical resolution of the seizure supports pseudo-status epilepticus, as abnormalities are consistently found just after convulsive status epilepticus [13].

Treatment Strategies

A European consensus conference on the management of status epilepticus was held in 2006.

Treatment Goals

The immediate treatment goals in patients with generalized convulsive status epilepticus are cessation of the clinical seizures and prevention of subtle status epilepticus. Subtle status epilepticus has been reported to develop in 14% to 20% of patients with convulsive status epilepticus [41]. The optimal time for obtaining an EEG is not known [11]. In practice, an EEG should be obtained as early as possible and is particularly urgent in patients who fail to recover normal or pre-seizure levels of consciousness after cessation of clinical seizuring [39]. In nonconvulsive status epilepticus, the goal of treatment is resolution of the critical EEG patterns accompanied with a return to normal of the patient's clinical status. When clinical abnormalities persist, their link to epilepsy should be reappraised [25].

According to current recommendations, the immediate treatment objective in patients with refractory status epilepticus is prompt generation of a burst-suppression pattern [16,24]. Resolution of the electrical seizures without a burst-suppression pattern is associated with a higher rate of recurrence than maintenance of a burst-suppression pattern for 12 to 24 h [8]. The desired characteristics and optimal duration of the trace remain debated. It has been suggested that a 1-second burst followed by 10 seconds of suppression may be sufficient, although others have recommended suppression for 15 to 30 seconds [12]. Well-designed trials are not available to prove that this aggressive approach to the management of refractory status epilepticus translates into reduced mortality rates [35].

Regardless of the pattern of status epilepticus, continuous EEG monitoring has emerged as a crucial management tool [49].

General Measures

Patients with status epilepticus require the symptomatic measures usually taken in the ICU. Hemodynamic stability should be ensured, particularly as many of the drugs used to treat status epilepticus can induce hypotension and/or heart failure. Catecholamines are often needed in patients with refractory status epilepticus. The need for upper airway protection should be evaluated continuously while bearing in mind that the primary treatment goal is seizure resolution with recovery of consciousness. Therefore,

an initial phase of coma without life-threatening manifestations is acceptable if not unduly prolonged. If endotracheal intubation is performed, rapid-sequence induction with etomidate and succinylcholine can be used, provided there is no evidence of hyperkalemia. Propofol or thiopental are also good choices, since they have anticonvulsant effects. Neuromuscular agents may transiently mask the seizures. Hypoglycemia should be looked for routinely and corrected. If glucose is given, 100 mg of thiamine should be administered concomitantly, most notably when there is evidence of vitamin B_1 deficiency. Patients should be routinely evaluated for hyperthermia and metabolic disturbances, which require prompt correction. Metabolic and/or respiratory acidosis should be controlled, and tests for acute renal failure with rhabdomyolysis should be performed. Aspiration pneumonia may complicate the initial consciousness disorders [24]. Patients should be evaluated for injuries such as head injury and shoulder dislocation [5]. Antiepileptic treatment, appropriate for the electrical and clinical pattern in the patient, should be initiated on an emergency basis. In addition to these symptomatic measures, the treatment strategy should include investigations for a cause of the status epilepticus, followed by etiological treatment [24].

The National Institute for Clinical Excellence has recommended the following strategy devided into different stages:

1st Stage (0-10 min) Early Status

• Secure airway and resuscitate

• Administer oxygen

• Assess cardiorespiratory function

• Establish intravenous access

2nd Stage (0 -30 min)

• Institute regular monitoring

• Consider possibility of non-epileptic status

• Emergency anti-epileptic drug treatment (AED)

• Emergency investigations

• Administer 50 ml of 50% dextrose and/or intravenous thiamine if there is history of alcohol abuse or poor nutrition

• Correct acidosis if severe with bicarbonate (not necessary in most cases)

3rd Stage (0-60 min) Established Status

• Establish aetiology

• Alert anaesthetist and ITU

• Identify and treat and medical complications

• Pressor therapy if required

4th Stage (30-90 min) Refractory Status

• Transfer to ITU

• Establish intensive care and EEG monitoring

• Initiate intracranial pressure monitoring if there is persistent high intracranial pressure

• Initiate long-term maintenance AED therapy.

Terminating seizure activity (**table 8**) for a summary of emergency AED therapy.

Table 8

Emergency AED therapy for convulsive status epilepticus

Premonitory stage	Diazepam 10-20 mg PR, repeat once 15 min. later or midazolam 10 mg buccal
Early status	Lorazepam 0,1 mg/kg i.v. bolus, repeated once after 10-20 min. Usual AED medication
Established status	One of the folowing: Phenytoin infusion 15-18 mg/kg at rate of 50 mg/min. Fosphenytoin infusion 15-20 mg phenytoin equivalents (PE)/kg at rate of 50-100 mg PE/min. Phenobarbitone bolus 10-15 mg/kg at rate of 100 mg/kg
Refractory status	General anaesthesia with one of the folowing: Propofol 1-2 g/kg bolus, then 2-10 mg per hour Midazolam 0,1-0,2 mg/kg bolus, then 0,05-0,5 mg/kg per hour Thiopentone 3-5 mg/kg bolus, then 3-5 mg/kg per hour (reduce rate after 2-3 days as fat stores deplete) Consider tapering dose after 12-24 hours after last known seizure

Benzodiazepines

Benzodiazepines act by enhancing the neuroinhibitory effects of GABA. All patients given benzodiazepines should be monitored for side effects of respiratory depression and hypotension.

Diazepam

Diazepam can be given rectally (dose of 10-20 mg) in the premonitory stage or as first-line treatment intravenously (10-20 mg at 2 mg/min) during the established stage. Rectal diazepam will successfully terminate seizures in up to 70% of patients, with success by the intravenous route in 60-80% of patients. It is highly lipid soluble and has rapid CNS penetration, achieving sufficient levels at 1 min after intravenous administration and within 20 min by rectal route. Despite its long elimination half-life, when given intravenously diazepam is taken up by fat and muscle rapidly, leading to a redistribution half-life of only 30 min. This results in a rapid fall in plasma levels and the possibility of recurrence of seizures within 2 hours. Repeated boluses can lead to accumulation and

sudden unexpected apnoea, cardio-respiratory collapse and CNS depression.

Lorazepam

Intravenous lorazepam (4 mg at 2 mg/min) is recommended as first-line treatment during the established stage and will terminate status epilepticus in 60-90% of patients. Lorazepam is less lipid soluble than diazepam and plasma levels rise at a slower rate after intravenous injection. In practice, however, diazepam and lorazepam are equally fast-acting. Lorazepam has the advantage of a longer redistribution half-life and smaller chance of recurrent seizures when used alone.

Midazolam

Midazolam can be given buccally (10 mg), sublingually or intranasally during the premonitory stage with a 75% chance of preventing further seizures.

Clinical studies have shown that midazolam bolus (0,1-0,3 mg/kg) followed by the an infusion (0,05-2,0 mg/kg per hour) achieves rapid control of seizures that have been unresponsive to other agents. Prelonged usage is associated with tachyphylaxis and accumulation.

Phenytoin

Phenytoin is commonly used as a second-line treatment after benzodiazepines have failed or as a maintenance anti-seizure treatment after rapid control of seizures by benzodiazepines. About half of the patients who have not responded to initial benzodiazepines will respond to the addition of phenytoin. A loading dose of 15-20 mg/kg should be followed by infusion of 15-18 mg/kg per min. potential side effects are respiratory depression, arrhythmias, hypotension, rash and purple glove syndrome on extravasation.

Fosphenytoin

Fosphenytoin is a water-soluble pro-drug of phenytoin and is converted to phenytoin by endogenous phosphatases. Doses are therefore expressed as phenytoin equivalents (PE). The preparation of fosphenytoin does not contain propylene glycol and as a result it can be given at a higher rate of 150 PE/min. and it does not cause purple glove syndrome.

Barbiturates

Phenobarbitone

Phenobarbitone can be given intravenously (10-20 mg/kg at 100 mg/min.) in established status and gives a 60-70% chance of success in terminating seizures. It is a potent anticonvulsant with a long duration of action, rendering ventilatory and resuscitative support mandatory for its use. Potential side effects are respiratory depression, hypotension and rush.

Thiopentone

Thiopentone is a general anesthetic agent that has been successfully used to treat refractory status epilepticus. An induction dose of 3-5 mg/kg is used for intubation, followed by doses of 0,5-1 mg/kg until seizures are controlled. As thiopentone is rapidly redistributed to fat stores, an infusion of 1-5 mg/kg per hour should be started to maintain seizures control. Once fat stores are saturated, the duration of action will be prolonged due to subsequent plasma redistribution and recovery can take hours or even days. Potential side effects are hypotension, myocardial depression and immunosuppresion.

Propofol

Many studies have demonstrated the efficacity of propofol in the treatment of refractory status epilepticus. Propofol has anticonvulsant properties due to its action in potentiating GABA receptors.

However, its use can still cause significant hypotension and if used long term it can cause hyperlipidaemia and metabolic acidosis and rhabdomyolysis has been reported. Abrupt discontinuation of treatment can lead to recurrence of seizures and doses should be gradually tapered with caution. An initial bolus of 3-5 mg/kg is followed by infusion of 1-15 mg/kg per hour.

Treatment Strategies for Convulsive Status Epilepticus

Generalized convulsive status epilepticus (figure 3)

Intravenous lorazepam is the first-line treatment for generalized convulsive status epilepticus. If the seizure persists, a second injection can be given 10 minutes later.

Phenytoin or fosphenytoin is a good choice when lorazepam fails. Administration of an additional lorazepam dose can be considered.

When lorazepam is not available, a short-acting benzodiazepine such as clonazepam or diazepam should be given in combination with a long-acting antiepileptic drug such as phenobarbital, phenytoin, fosphenytoin, or sodium valproate [20, 21, 26]. Factors that affect the choice of the antiepileptic agent include the spectrum of antiepileptic activity, contraindications, and expected side effects (**table 9**). Patients with persistent seizuring at the end of the infusion can be given an additional dose of the same antiepileptic drug [42].

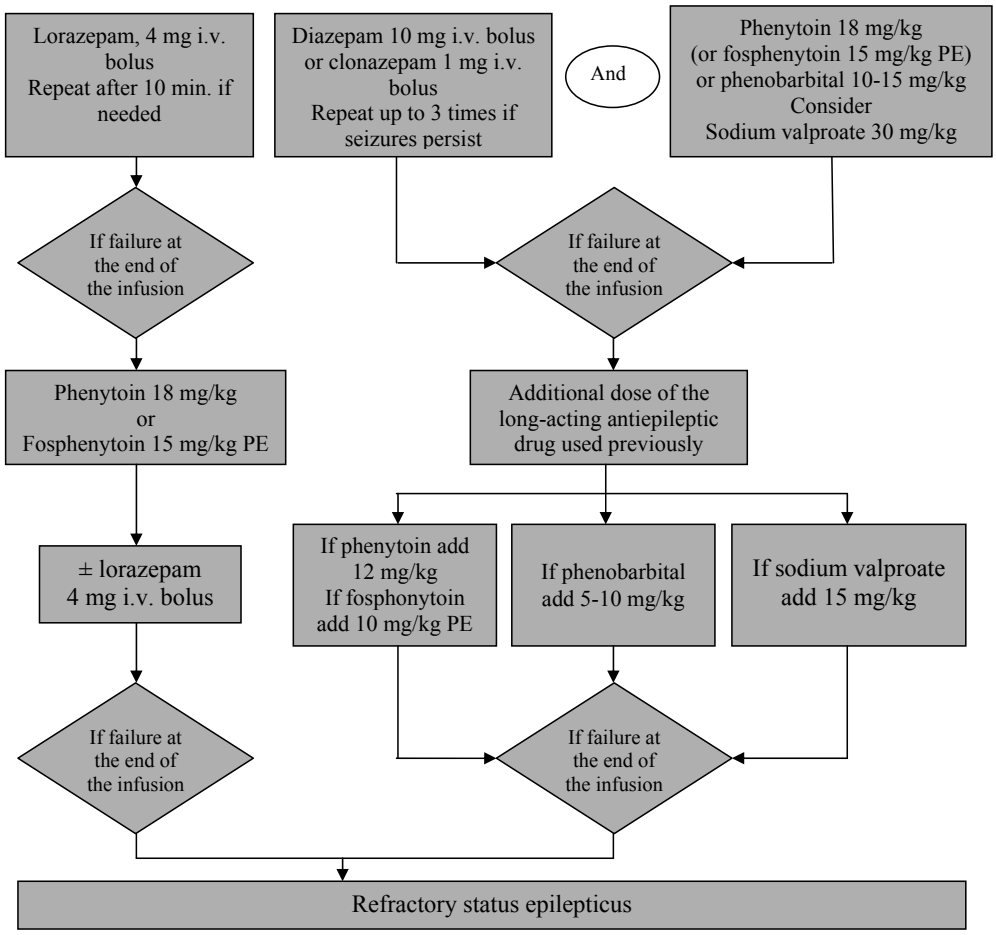

Figure 3. *Treatment strategy for generalized convulsive status epilepticus. PE: phenytoin-equivalent*

Table 9

Rules for using long-acting antiepileptic agents to treat status epilepticus

	Sodium valproate	Phenytoin	Fosphenytoin	Phenobarbital
Contraindications	Hypersensitivity to the drug Acute or chronic hepatitis Family history of acute hepatitis Mefloquine, St John's wort	Hypersensitivity to the drug Several cytotoxic drugs, St John's wort, saquinavir Sinus bradycardia, smoatrial block, Atrioventricular block II and III, Stokes-Adams syndrome		Hypersensitivity to the drug Severe respiratory failure Several cytotoxic drugs St John's wort, saquinavir, voriconazole
Seizure type	All patterns of status epilepticus Particularly myoclonic convulsive status epilepticus	Do not use for myoclonic convulsive status epilepticus or absence nonconvulsive status epitepticus		All patterns of status epilepticus
Loading dose	30 mg/kg	18 mg/kg	15 mg/kg PE	10 to 15 mg/kg
Additional dose	15 mg/kg	12 mg/kg	10 mg/kg PE	5 to 10 mg/kg
Administration	Slow i.v. over 15 min. in 100 ml saline	Slow i.v. 1 mg/kg/ min. Rate no faster than 50 mg/min. in saline (precipitates in glucose solutions, such that the maximum concentration is 5 mg/ml	Slow i.v. 100-150 mg/min. PE, maximum rate 150 mg/min. PE, in 5% glucose or saline so that the maximum concentration is 25 mg PE/ml	Slow i.v. ≤ 100 mg/ min., in 10 ml sterile water for i.v.

Example For a 60-kg patient	1800 mg in 100 ml saline Slow i.v. over 15 min.	1000 mg in 200 ml saline Slow i.v. ≥ 20 min.	900 mg PE in 18 ml saline or 5% glucose, Slow i.v. ≥ 6 min.	600 to 900 mg in 10 ml sterile water for i.v. Slow i.v. over 6 to 9 min.
Monitoring during administration	No CNS, respiratory, or hemodynamic depression	Monitor during the infusion, decrease the rate if bradycardia occurs Induces respiratory and hemodynamic depression		Induces respiratory, CNS, and hemodynamic depression
Continuous pump infusion for maintenance	Routinely, 1 to 5 mg/kg/h To maintain serum level at 75 mg/l then switch to oral route	If enteral route not available 7-10 mg/kg/24 h pump infusion start 6 to 12 h after the loading dose	If enteral route not available 4 to 5 mg/kg/24 h pump infusion or 1 to 2 doses/24 h ≤ 100 mg/min. PE	If enteral route not available 2 to 3 mg/kg/24 h single siow i.v. ≤ 5 mg/min.
Switch to the oral route	20-30 mg/kg/24 h Divided in 2-3 daily doses Start during the maintenance infusion	Phenytoin 2 to 6 mg/kg/24 h Divided in 1 to 2 doses Start within 12 h of the loading dose		Phenobarbital 2 to 3 mg/kg/24 h Once daily, preferably in the evening Start within 12 h after the loading dose
Therapeutic concentration	50-100 mg/l	10-20 μg/ml		15-40 μg/ml

Note: **i.v. – intravenous; PE – phenytoin-equivalent; CNS – central nervous system.**

Refractory status epilepticus is defined as either persistent seizures at the end of this treatment sequence or continuous seizures for 1 hour [24). Anesthetics should be used as the first-line treatment of refractory status epilepticus [41). When there is concern that this aggressive strategy may have limited benefits, for instance in elderly patients, addition of a second long-acting antiepileptic drug may deserve consideration [24).

Partial motor convulsive status epilepticus

The paucity of published data on this form of status epilepticus hinders the development of treatment strategies and probably explains the lack of consensus about the optimal treatment. In patients with altered consciousness, progression to generalized convulsive status epilepticus is common and the risk of progression to refractory status epilepticus high, supporting the use of the treatment strategy designed for generalized convulsive status epilepticus [23). When consciousness is normal, an orally or rectally administered drug can be used initially. Refractoriness should not be diagnosed until several lines of treatment fail *(***figure 4***)*.

Treatment Strategies for Non-convulsive Status Epilepticus

Absence or simple partial non-convulsive status epilepticus

A benzodiazepine, such as clonazepam or diazepam, is usually sufficient [38).

Complex partial non-convulsive status epilepticus (figure 4)

The risk of neuronal damage and the high mortality rate associated with complex partial non-convulsive status epilepticus support the use of the treatment strategy designed for generalized convulsive status epilepticus. However, refractory status epilepticus should be defined as failure of the second or even third line of antiepileptic therapy [24).

Subtle status epilepticus and electrical status epilepticus

In the Veterans Affairs study published in 1998, resistance to medication was common in subtle non-convulsive status epilepticus, which carried a high mortality rate [41). These features warrant aggressive first-line treatment using the same strategy as in refractory status epilepticus (**figure 5**).

Treatment Strategies for Refractory Status Epilepticus (figure 5)

Anesthesia with propofol, thiopental, or midazolam is the cornerstone of the management of refractory status epilepticus [16,21). Regardless of the drug used, the dose should be titrated at 3 to 5 min. intervals under EEG monitoring with the goal of obtaining a burst-suppression pattern with suppression for 5 to 10 seconds [28, 29).

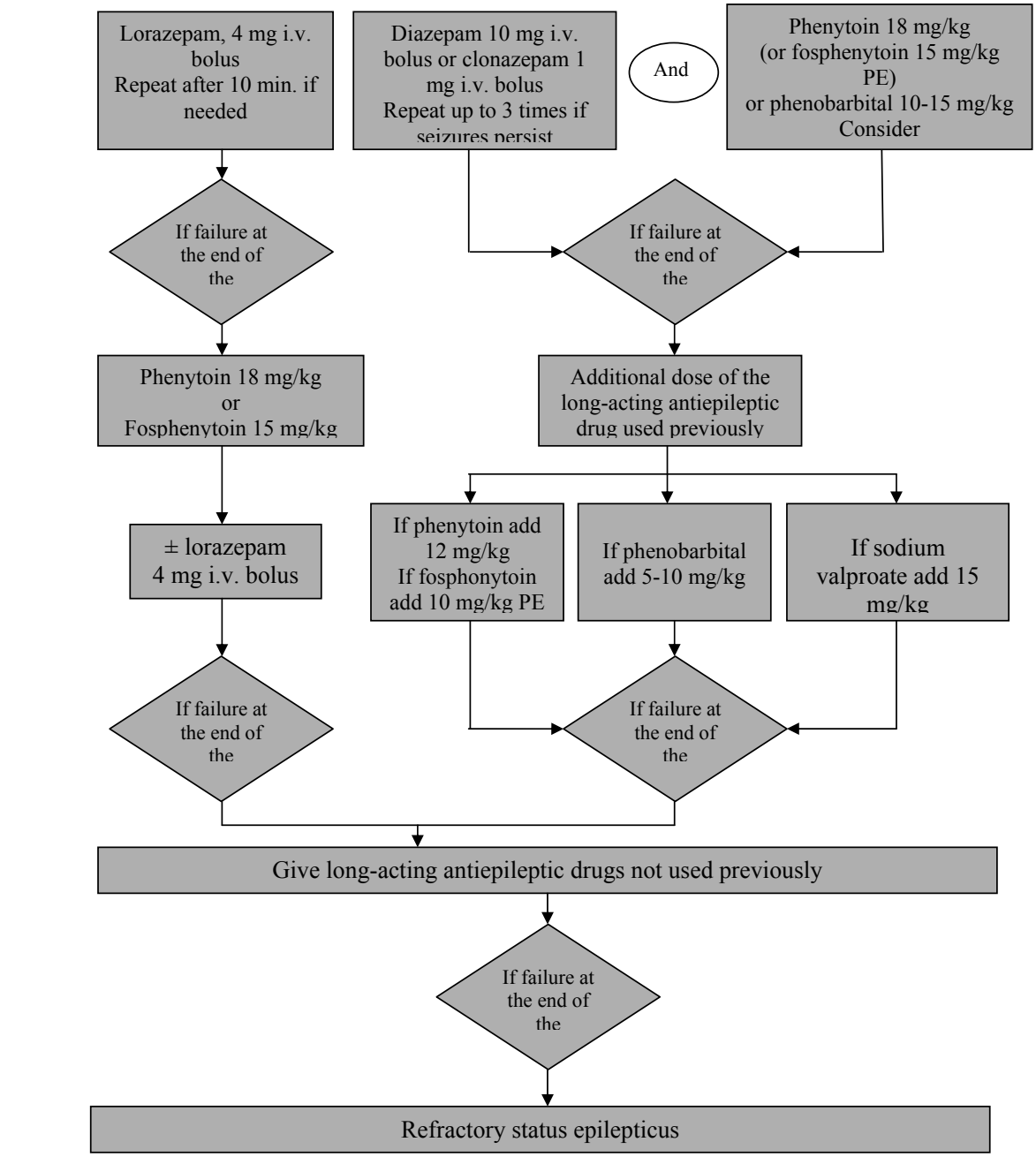

Figure 4. *Treatment strategy for partial convulsive status epilepticus and complex partial nonconvulsive status epilepticus. PE: phenytoin-equivalent*

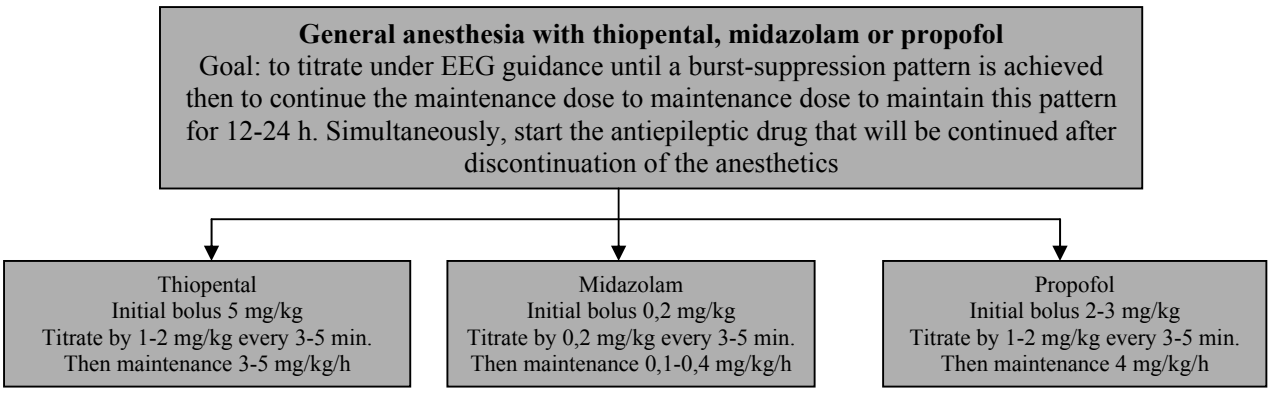

Figure 5. *Strategy for managing refractory status epilepticus*

Table 10

Rules for using anesthetic drugs to treat refractory status epilepticus

	Sodium thiopental Penthotal®	**Midazolam Hypnovel®**	**Propofol Diprivan®**
Loading dose	5 mg/kg slow i.v., 20 sec.	0.2 mg/kg slow i.v.	2-3 mg/kg slow i.v.
Bolus titration under EEG guidance	1-2 mg/kg slow i.v., 20 sec. every 3-5 min.	0.2 mg/kg slow i.v. every 3-5 min.	1-2 mg/kg slow i.v. every 3-5 min.
Maintenance dose, pump infusion	3-5 mg/kg/h ± 1 mg/kg/h	0.1-0.4 mg/kg/h ± 0.1 mg/kg/h	4 mg/kg/h ± 1 mg/kg/h
Administration modalities	Dilute to 2.5% or 5%	No dilution needed	≤ 48 h
Specific effects	Immunosuppressant	Tachyphylaxis	Risk of propofol infusion syndrome

Note: **i.v. – intravenous.**

Once this goal is reached, a continuous infusion is given to maintain the burst-suppression pattern for 12 to 24 h. Boluses should be given if the burst-suppression pattern is lost before the pre-specified time; after the boluses, the continuous-infusion dose should be increased gradually. **Table 10** recapitulates the rules for using these anesthetic agents.

The treatment-discontinuation modalities vary across agents, in relation to the differences in their half-life values. A 20% reduction every 3 h is appropriate with propofol and a 50 % decrease every 3 h with midazolam, whereas thiopental can be stopped with no prior dosage reduction. Should the seizures recur, the same anesthetic agent should be given in the dosage that was effective previously. A loading dose of one or two long-acting antiepileptic agents should be given routinely in combination with the anesthetic agent and continued after anesthesia withdrawal [28, 29).

Treatment strategies for status epilepticus (**figure 6**).

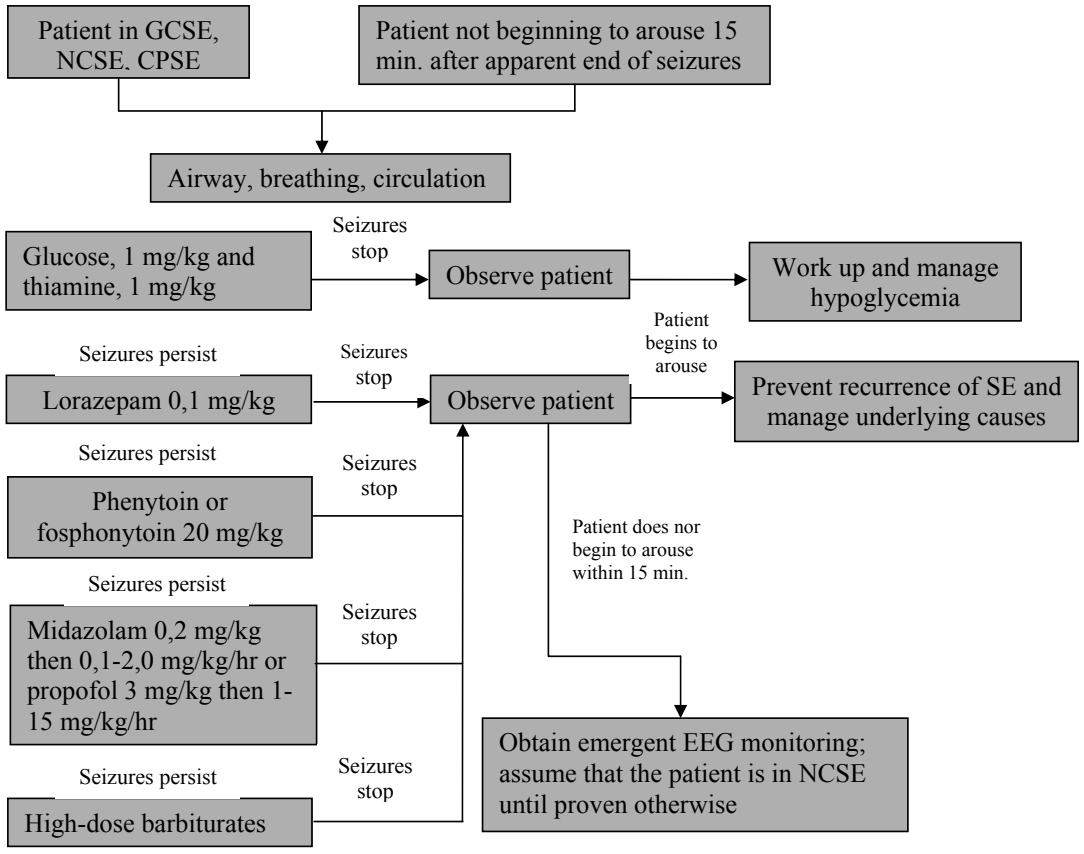

Figure 6. *Management algorithm for status epilepticus*

Note: **CPSE, complex partial status epilepticus; GSCE, generalized convulsive status epilepticus; NCSE, non-convulsive status epilepticus; SE; status epilepticus.**

Conclusion

1. This review highlights recent advances in the diagnosis and treatment of status epilepticus. Knowledge of the classification scheme that separates convulsive and non-convulsive status epilepticus is crucial. Generalized convulsive status epilepticus carries a grim prognosis and requires early diagnosis and treatment. Status epilepticus (SE) is a recognized medical and neurological emergency and is associated with significant morbidity and mortality. SE is also an under-recognized cause of persistent coma on the intensive care unit.

2. In children, most SEs are secondary to infections. In adults, the causes are more diverse and can include drug misuse and cerebral pathologies.

3. The diagnosis of non-convulsive status epilepticus may be difficult, as it requires an EEG. The many diagnostic pitfalls are dominated by pseudo-status epilepticus, which should be considered routinely.

4. Treatment starts with immediate resuscitation with ABC approach and referral to critical care team if in refractory status (more than 90 min of seizure activity).

5. The undeniable treatment advances achieved in recent years have resulted in the development of treatment strategies tailored to the type and severity of status epilepticus. Although old antiepileptic agents are still used, their indications have been refined.

6. Benzodiazepines still remain the first-line treatment of SE with phenytoin as second-line treatment. Barbiturates and propofol have also been used to treat refractory SE successfully.

7. Mortality rates associated with status epilepticus remain high overall, indicating a need for new drugs and for randomized trials of new treatment strategies.

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