

# Current treatment of convulsive status epilepticus — a therapeutic protocol and review

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## Abstract

The management of status epilepticus (SE) has changed in recent years. Substantial differences exist regarding the definition and time frame of a seizure, which has been operationally defined as lasting for 5 min. Not only have many new intravenous drugs, such as levetiracetam and lacosamide been introduced but other routes of administration, such as intranasal or buccal administration for midazolam, are also being developed. Optimal and successful therapy initiated at the appropriate moment, adequately tailored to the clinical state of the patient, determines the first step in the normalisation of vital functions and leads to the restoration of the physiological homeostatic mechanisms of the organism.

The aim of this review is to present the current treatment options for the management of convulsive status epilepticus (CSE) that have been widely confirmed as the most effective in clinical trials and approved by the international neurology authorities as the actual therapeutic standards. We also intend to indicate distinct and unequivocal differentiation and therapeutic indications for each phase of CSE, including the precise doses of the related medications, to present practical guidelines for clinicians. The treatment of patients with CSE requires emergency physicians, neurologists and specialists in intensive care to work together to provide optimal care that should be initiated as soon as possible and conducted as a unified procedure to improve neurocritical care in patients who are transferred from the ambulance service, through the emergency department and finally to the neurology department or ICU. Appropriate treatment also involves avoiding mistakes associated with inadequate doses of medications, overdosing a patient or choosing an inappropriate medication.

**Key words:** convulsive status epilepticus, treatment, treatment protocol

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The majority of epileptic seizures, both incidental and seizures occurring in the course of epilepsy, subside spontaneously within several minutes. In patients with status epilepticus (SE), the mechanisms responsible for the seizure's self-termination fail, then the seizure can prolong to a dozen or several dozen minutes, impairing body homeostasis, which constitutes a considerable threat to life. According to the traditional definition established by the International League Against Epilepsy (ILAE) in 1981, SE is defined as the prolonged seizure or recurrent seizures without full recovery between them. It does not indicate a clear time frame. For many years, in the literature it was assumed that SE was a seizure lasting longer than 30 min or at least two seizures without a full regain of consciousness between them.

In a recent years a new, so-called operational definition has been proposed. It assumes that each epileptic seizure lasting more than 5 min requires the same treatment as that used in SE because numerous studies have demonstrated that the probability of self-termination of an epileptic seizure drops considerably in seizures lasting more than 2 min [1–6].

The threat to life and health of patients in SE does not depend only on the seizure duration but also on the direct cause leading to its occurrence [6, 7].

The most severe effects of a long-lasting SE episode include a wide spectrum of symptoms, from a considerable deterioration of neurological condition to death. The deteriorating clinical condition results from disorders of various organs and systems (including respiratory disorders, risk of

secondary aspiration, arrhythmia, symptoms resulting from disturbed homeostasis of metabolic processes or dysfunction of the autonomic nervous system) as well as from direct damage to the brain cells caused by the destructive effect of a release of neurotransmitters. Quick termination of SE in experimental studies protects from permanent damage to the cerebral tissue and is related with a better prognosis in patients under prospective clinical observation. Study findings have revealed that the incidence of admissions to Intensive Care Units (ICUs) was 32% in the cases when the epileptic seizure subsided spontaneously before the arrival of an emergency medical service team, and increased to 73% otherwise [6].

Studies conducted with large groups of patients demonstrated that the overall 30-day mortality rate in patients with generalised convulsive status epilepticus (GCSE) fluctuated between 19 and 27%. A higher rate was related to the cases, in which the seizure lasted for at least 1 hour and in patients above 65 years of age who were previously exposed to hypoxia [6, 8]. Moreover, the mortality seems to be significantly affected by SE aetiology [8]. Prognosis in SE prior to the introduction of treatment may be indirectly assessed using the Status Epilepticus Severity Score (STESS), which is based on the assessment of 4 predictive factors: the severity of consciousness disturbances, the type of epileptic seizure, the age and history of the presence or absence of epileptic seizures [9]. High STESS scores correlate with high mortality. Patients with such results should most likely be treated more aggressively [7].

Despite advanced studies devoted to discovering causes and the diagnosis and treatment of SE still little is known of the pathophysiological mechanisms leading to the loss of the ability to spontaneous seizure's self-termination. Therefore, doctors, patients and their guardians are often unable to predict the course of the seizure and undertake actions that prevent the development of a prolonged seizure with all its health, socio-psychological and economic consequences. As long as the pathophysiological cause of SE is not established, the working definition, stating that seizures lasting longer than 5 min require immediate medical intervention, should be considered the most appropriate for a number of reasons. According to the traditional definition, a seizure lasting less than 30 min is considered mild, whereas clinical experience indicates that there is no difference between prolonged seizures lasting 25 or 35 min. Nevertheless, according to the traditional definition, the treatment and management in these two cases is completely different. Furthermore, the exact time frame of beginning and termination of the seizure is almost always approximate because it is impossible to estimate the seizure duration, especially in out-of-hospital circumstances. According to analyses based on electroencephalography (EEG), the average mild, self-limiting general-

ized tonic-clonic seizure usually lasts little over 1 min and rarely attains almost 2 min. Therefore, it was assumed that the chances for self-termination of the seizure lasting at least 5 min. are so slight that it requires the same treatment as for seizures lasting at least 30 min. Thus, a new time frame for the diagnosis and introduction of treatment for SE has been published. It is completely different from that in 1–2 min seizures, which self-terminate without the introduction of emergency treatment [6].

One of the reasons for the fact that time frame SE was shortened, for 30 min was that historically after 20 min the first permanent histopathological changes in brain neurons were observed. Although the course of the pathophysiological process leading to neuron damage still remains unclear, owing to modern techniques, it has been confirmed that the histopathological changes begin much earlier and already are present during the first several minutes of the seizure's onset. Therefore, the traditional definition is no longer valid [1, 6].

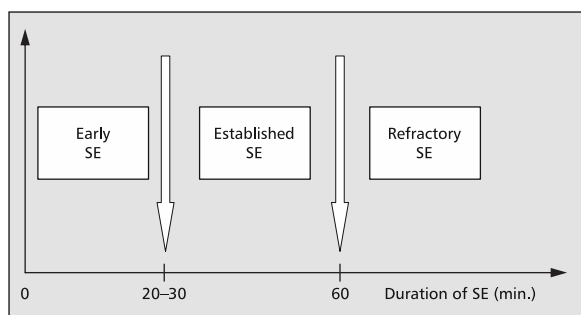
In response to numerous objections regarding the conventional definition of SE, Lowenstein proposed a new definition, officially published in 1999. The definition states that GCSE in adults and children above 5 years of age is a continuous, unremitting seizure lasting at least 5 min or at least two discrete seizures without full normalisation of consciousness between them. Such approach allows us to consider mild, short-lasting seizures to be incidents not requiring emergency treatment, however in prolonged seizures, it enables us to relatively quick introduce the treatment aimed at their termination [5].

Optimal targeted therapy introduced at the proper moment, adequately to the patient's clinical condition, is the first step towards fast and more effective control of the SE, including the normalisation of bodily functions and restoring of natural homeostatic mechanisms. The management of SE includes the maintenance of basic bodily functions, identification and elimination of causal factors, suppression of epileptic seizures and treatment of the accompanying symptoms or those persisting after the seizure termination, including cerebral oedema, headache and others (Fig 1).

This study presents considerations on the effective treatment of SE, involving pre-hospital management (conducted by family members or trained guardians who witness the seizure, as well as rescue therapy administered by the emergency service team) and in-hospital procedures conducted in the emergency department or at the hospital ward.

## **EARLY STATUS EPILEPTICUS FIRST-LINE THERAPY (6–20 MINUTES)**

Status epilepticus requires immediate and effective treatment [1, 12–14]. The emergency treatment system,



**Figure 1.** Division of status epilepticus (SE) according to duration [10, 11]

prior to hospitalisation, should ensure the fastest possible introduction of pharmacological treatment.

The first-line drugs are benzodiazepines, GABA receptor agonists [1, 7, 13], which are preferred mainly due to their rapid onset of action and high effectiveness in seizure termination [15].

In the case of a prolonged convulsive seizure in a patient with diagnosed and treated epilepsy, a family member or trained guardian may administer diazepam in the form of rectal gel before the arrival of the emergency service team. In practice, in Poland, many diagnosed and treated epileptic patients who have a history of prolonged seizures or SE are prescribed diazepam in that form. In Poland, the rectal gel containing diazepam is available in two doses: 5 mg and 10 mg. In adults, the seizure is terminated with a single dose of 20 mg. If it fails and the emergency service team has not yet arrived, an additional dose of 10 mg per rectum can be administered 10 min after the first dose. In children, depending on age and body weight, a dose of 5 mg per rectum is recommended, (body weight > 10 kg, age 1–3 years), and in older children, 10 mg is recommended (body weight > 15 kg, age > 3 years). If necessary, the dose may be repeated, 5 mg in younger children and 10 mg in older ones. The manufacturer does not recommend administration of the drug to infants (< 1 year of age or body weight < 10 kg).

Another drug from the benzodiazepine class, midazolam, is distributed under the trade name Buccolam and is available in autoinjectors with a solution administered orally and absorbed through the internal buccal mucosa. In Poland, this specimen has been approved for use Poland only in children (from 3 months to 18 years of age); however, it is not available on the Polish market. It is possible to import it through targeted import.

On arrival to the patient in a tonic-clonic seizure, the emergency service team should gather information from witnesses or make their own assumptions concerning the most precisely: duration of the seizure with its potential cause, accompanying diseases, including epilepsy, seizure circumstances, provoking factors, medicines used or

discontinued, exposure to toxic and narcotic substances including alcohol, risk of aspiration; and potential injuries preceding or resulting from the seizure.

The procedures carried out simultaneously upon patient arrival include the immediate evaluation of airway patency; cardiopulmonary efficiency, including assessment of SaO<sub>2</sub>, heart rate, and blood pressure, ECG, and the introduction of oxygen therapy. An intravenous access for blood collection and for drug administration to terminate the seizures is necessary.

According to the guidelines of the European Federation of Neurological Societies (EFNS), the first-choice drugs in the treatment of SE are benzodiazepines, especially lorazepam, a drug used for many years in the USA as well as in some European countries. In Poland, intravenous lorazepam has not been approved. Difficulties regarding its approval and widespread availability, even in the countries where it is used, result from the fact that the drug is more expensive and highly heat-labile than other benzodiazepines. Therefore, it is often replaced with diazepam or midazolam, whose half-life at room temperature is longer. The recommended intravenous dose of lorazepam is 0.05–0.1 mg kg<sup>-1</sup> (usually 4–8 mg) for 2–5 min. If the seizure does not subside after 10 minutes, Meierkord [1] recommends the administration of another 4 mg *i.v.* When no improvement is observed, second-line therapy is recommended [1].

Diazepam is an alternative drug commonly used in Poland. Apart from its per rectum dosage form, diazepam can be administered intramuscularly or intravenously in 10–20 mg doses in adults (the dose may be repeated after 30–60 min; a slow intravenous infusion can be introduced in a maximum dose of 3 mg kg<sup>-1</sup> in a 24 hour period) or 0.2–0.3 mg kg<sup>-1</sup> in children (or 1 mg per each year of life) [16, 17]. The administration rate should be slow (2–5 mg min<sup>-1</sup>) [16]. The appropriate concentration in the CNS system is achieved quickly, after approximately 1 minute following *i.v.* administration [17]. The peak concentration of diazepam is reached within 15 min from its administration [15]. It is metabolised in the liver into active metabolites: oxazepam, temazepam and desmethyldiazepam, which prolongs its effect [17]. Its half-life is approximately 48 hours [18].

In comparison with diazepam, lorazepam is slower in the penetration of the tissue vascular space, its therapeutic effect is longer and the risk of its accumulation in organs is lower (lower risk of cardiac depression) [1, 17]. Nevertheless, numerous studies confirm similar effectiveness of the two benzodiazepines [19–21].

Another drug from the benzodiazepine class, clonazepam, is administered intravenously or intramuscularly in a single dose of 1 mg in adults and 0.5 mg in children [7]. The speed of injection in adults should not exceed 0.25–0.5 mg

per minute. However, it should be stressed that this drug, despite evident efficiency and widespread availability in Poland is not included in the current international guidelines for treatment of SE.

In Poland, seizures are terminated using midazolam. Apart from the buccal dosage form (approved in Poland solely for children), it is also available in the intravenous and intramuscular dosage forms. Intravenous dosing differs depending on age: 2.5 mg in children <1 year of age, 5 mg in 1- to 5-year-old children, 7.5 mg in 5- to 10-year-old children, 10 mg in 10- to 18-year-old children ( $0.1\text{--}0.2\text{ mg kg}^{-1}$  i.v.) or  $0.2\text{ mg kg}^{-1}$  of body weight i.m. In the USA, it is also available in the intranasal form (which is currently in the clinical trials in several medical centres in Poland) [17]. Clinical studies revealed adequate safety and effectiveness of intramuscular administration of midazolam. Diazepam and lorazepam proved less effective and slower in intramuscular absorption because of low lipophilicity. Midazolam, due to its numerous advantages such as low cost, relative thermostability at room temperature, safety and effectiveness in different age groups, and the possibility of intramuscular and, in some countries, per rectum administration, was chosen in the USA as the optimum first-line drug to be used in the pre-hospital emergency treatment of SE. The recommended intravenous, intramuscular or per rectum dose in adults is  $0.2\text{ mg kg}^{-1}$  [1, 22].

The main side effects of benzodiazepines are sedation and respiratory depression including apnoea [7], observed chiefly after too fast intravenous administration or overdosing. Therefore, it is extremely important to determine whether our administration of the drug was preceded by emergency administration of benzodiazepines (e.g., by a guardian or during transportation, etc.) as well as whether the patient took benzodiazepines orally before the seizure. In the case of intravenous and intravascular administration of benzodiazepines, the drug should be injected or slowly infused intravenously. Because of the risk of life-threatening side effects, parenteral administration of benzodiazepines should be accompanied by close monitoring of the respiratory rate, heart rate and blood pressure. Resuscitation equipment should also be available [1, 6, 7].

The duration of SE prior to the initiation of treatment influences its effect, regardless of the type of drug used. The more time that elapses before the administration of medicine, the lower the chances of gaining control of the seizure through pharmacotherapy [12]. Moreover, the longer SE lasts, the poorer the effects of successive drugs are. In a study by Treiman [23], the effectiveness of termination of SE after administration of the first drug was 55% and less than 10% in the case of second and third drugs.

It has been demonstrated that approximately 10 min after the onset of SE, sudden changes develop in the structure of the GABA receptor subunits that bind benzodiazepines, which results in a weaker response to the drug or requires administration of larger doses to achieve the same therapeutic effect. Moreover, laboratory tests indicate that long-lasting seizures initiate kindling processes, increasing the probability of further seizures. Gookin [14] and Naylor [24] report that during SE, the GABA receptors internalise, which causes a weaker response to drugs acting through the GABAergic system. There is also evidence of a gradual increase in the number of AMPA and NMDA receptors. These changes increase the sensitivity of neurons to excitatory neurotransmitters [24].

In view of the above, it can be assumed that a trained guardian and/or emergency team have a high chance of administering benzodiazepines during the time when the probability of seizure termination with drugs is the highest. This fact has been confirmed by numerous reports, including the randomised clinical trial Prehospital Treatment of Status Epilepticus (PHSTE), in which the patients were divided into 3 groups and treated intravenously with diazepam, lorazepam or a placebo. The study revealed that successful seizure control before reaching the hospital was significantly higher in patients treated with diazepam and lorazepam than in those given a placebo. Patients who were given one of the drugs were admitted to the hospital considerably less frequently than those given a placebo. Moreover, it was found that 30 individuals from the placebo group suffered from unfavourable consequences of prolonged seizure such as acquired neurological deficits or death, despite the lack of statistical significance of that variable. The trial also revealed higher effectiveness of lorazepam than of diazepam in controlling seizures. Therefore, the authors recommend lorazepam as the most effective first-line drug used intravenously in the treatment of SE. However, intravenous administration of the drug can prove ineffective in some patients, and so in ambulatory practice, the patients with a history of prolonged seizures are often treated with diazepam in the form of rectal gel. It is currently the only drug from the benzodiazepine class administered per rectum, absorbed through the large intestine mucosa, allowing termination of epileptic seizure or SE and omitting oral and intravenous administration. Here, it should again be noted that the effectiveness of diazepam and midazolam in controlling seizures is lower than that of lorazepam. Therefore, it seems appropriate to postulate the increase in the availability of the lorazepam, which, according to preliminary reports, can be administered in any of the abovementioned forms and ways (excluding rectal administration, which was found ineffective) [25–27].

## EARLY AND ESTABLISHED STATUS EPILEPTICUS SECOND-LINE THERAPY (20–60 MINUTES)

If the first-line therapy proves ineffective and the seizure persists for at least 20 min, SE enters the established phase, which requires the introduction of second-line therapy. Second-line therapy usually takes place in hospital conditions. Drugs used in the second-line therapy include fosphenytoin (not approved in Poland) and phenytoin, which stabilises the central neuronal membranes. Phenytoin is administered in the doses of 15–20 mg kg<sup>-1</sup>, very slowly (50 mg min<sup>-1</sup>) and using a cardiac monitor [12, 16, 17, 28]. Phenytoin is perfect for gaining quick control over a seizure as well as for prolonged therapy [15]. It reaches the peak concentration in the cerebrospinal fluid after 20 min [16]. Its half-life is 24 hours, but it can last longer with high concentrations of phenytoin in the blood [7]. Monitoring of the cardio-vascular system is necessary because of the possibility of hypotension (27%) and bradyarrhythmia (7%). Other phenytoin-related side effects include the purple glove syndrome – swelling, discoloration and pain distal to the place of injection [29]. The advantages of phenytoin include a long-lasting effect, quick achievement of peak concentration in the CSF, availability and long-term experience in its administration. Drawbacks include a lack of confirmation of safe administration to elderly patients (related to possible negative effects of phenytoin on the cardio-vascular system and not always desired neuroprotective action of the drug) [12].

An alternative second-line drug is phenobarbital. It is administered with a dose of 20 mg kg<sup>-1</sup>, with a maximum speed of 50 mg min<sup>-1</sup> [1]. In the past, the drug was used in benzodiazepine-resistant seizures. As other drugs from the barbiturate class, it causes increased sedation and can induce hypotension, particularly when administered together with benzodiazepines. Therefore, it is currently less used. Some studies also report that in 20% of patients whose symptoms of SE were terminated clinically using phenobarbital, electrographic features of SE persist (NSCE, non-convulsive status epilepticus) [30].

Second-line therapy also allows the intravenous administration of valproic acid, 20–40 mg kg<sup>-1</sup> at a speed of 6 mg kg<sup>-1</sup> min<sup>-1</sup>, or levetiracetam, 20–60 mg kg<sup>-1</sup> (1000–3000 mg), administered over 15 minutes, or lacosamide, 200–400 mg [1, 31–33].

## REFRACTORY STATUS EPILEPTICUS THIRD-LINE THERAPY

Status epilepticus that cannot be terminated with benzodiazepines and phenytoin or other second-line antiepileptic drugs in appropriate doses is known as refractory SE (> 60-minute duration) [1, 31]. It requires treatment in the intensive care unit [1].

**Table 1.** Dosing of drugs used for general anaesthesia in status epilepticus treatment [1, 22]

	Dosing
Thiopental	3–5 mg kg <sup>-1</sup> i.v. bolus, subsequent doses of 1–2 mg kg <sup>-1</sup> repeated every 2–3 min until the seizure is terminated subsequently 3–7 mg kg <sup>-1</sup> min <sup>-1</sup>
Pentobarbitone	10–15 mg kg <sup>-1</sup> i.v. bolus subsequently 0.5–1 mg kg <sup>-1</sup> h <sup>-1</sup>
Midazolam	0.2 mg kg <sup>-1</sup> i.v. bolus subsequently 0.05–0.4 mg kg <sup>-1</sup> h <sup>-1</sup>
Propofol	2–3 mg kg <sup>-1</sup> i.v. bolus, subsequent doses of 1–2 mg kg <sup>-1</sup> repeated until the seizure is terminated subsequently 2–10 mg kg <sup>-1</sup> h <sup>-1</sup>

There are no studies confirming the effectiveness of lorazepam in refractory SE (that is, in patients whose pre-hospital first-line therapy proved ineffective). To date, it has not been decided which drug is optimal for inducing a pharmacological coma. The most frequently used drugs include pentobarbitone, thiopental, propofol and midazolam. Reports show that the effectiveness of these drugs is similar [1, 18, 22].

Refractory SE requires the administration of barbiturates, thiopental, midazolam or propofol in doses inducing general anaesthesia (Table 1).

There are no data that clearly indicate the drug of choice. It is recommended to increase the dose until the EEG shows burst suppression in the case of propofol and barbiturates or until the seizure is terminated with the use of midazolam and to maintain this effect for at least 24 hours. Moreover, long-term antiepileptic treatment should be introduced [1]. Some authors suggest that particular care should be taken when using propofol because its administration has been reported to increase mortality rates [34, 35].

In third-line therapy of SE, other drugs, such as valproic acid or levetiracetam, can also be considered [1].

The mechanism of action of valproic acid salt is complex. It decreases the state of excitement by acting on sodium channels in neuronal membranes and affecting the GABA concentration [34]. When administered intravenously, valproic acid is relatively fast in terminating the seizure (6–30 minutes) [22]. Its chief advantage is the lack of cardiodepressive action [7]. High doses of this drug may lead to hyperammonaemia. There is also a risk of its toxic influence on the liver and pancreas as well as encephalopathy. Moreover, the drug influences the platelet function and can increase the susceptibility for bleeding, which may be dangerous, e.g., in an acute stroke [12]. Sodium valporate can be used as the first-line drug in absence and myoclonic status epilepticus [7].

**Table 2.** Division of status epilepticus depending on the response to treatment [31, 47–52]

	Duration	Characteristics
Early SE	6–20 min/6–30 min	First-line therapy: BDZ 1–2 × (if necessary – introduction of second-line therapy: PHT/FPHT/ PHB/VPA/LEV)
Established SE	30–60 min	Clinical or electroencephalographic seizure activity Introduction or continuation of second-line therapy
Refractory SE	> 60 min	Persisting seizures despite double-drug therapy (BDZ + additional drug) Necessity to introduce general intravenous anaesthesia (thiopental, pentobarbitone, propofol or midazolam) (alternative to general anaesthesia: VPA, LEV, TPM, LCM, ketamine, hypothermia or ketogenic diet)
Super-refractory SE		Persisting seizures despite 1 cycle of general anaesthesia Presence of burst suppression changes in EEG or > 24 h from introduction of anaesthesia Administration of inhalational anaesthetics: desflurane/isoflurane or neurosurgical intervention

BDZ — benzodiazepine, PHT — phenytoin, FPHT — fosphenytoin, PHB — phenobarbitone, VPA — valproic acid, LEV — levetiracetam

Levetiracetam is used intravenously in the following doses: 1000 to 3000 mg or 20 mg kg<sup>-1</sup> [1, 12, 13, 36]. It is well tolerated by children and adults as well as by the elderly. The most frequent side effect is moderate sedation. Unfavourable effects on the cardiovascular or respiratory systems have not been reported [7, 12]. Moreover, levetiracetam does not interact with other drugs [12]. Platelet count monitoring is recommended [37].

Another drug sometimes used in refractory SE treatment is lacosamide [12]. However, reports of its use in SE are scarce [13].

Some patients in SE do not react to any of the above-mentioned drugs. There are reports of using other treatment methods in such cases. They are usually descriptions of isolated cases or studies conducted on very small groups [7]. There are reports of refractory SE treated with ketamine (non-competitive NMDA receptor antagonist) [13, 38], isoflurane [39] or verapamil [40]. In the case of ketamine, it is essential to administer it in a bolus form increasing the dose from 0.06 mg kg<sup>-1</sup> h<sup>-1</sup> to 7.5 mg kg<sup>-1</sup> h<sup>-1</sup> to avoid an excessive increase in blood pressure. Shorvon and colleagues [22] suggest the average therapy duration at approximately 120 hours. Scarce research on ketamine increases the need for further practical verification.

Moreover, there are reports of the administration of antiepileptic drugs that do not have intravenous forms and are administered through a nasogastric tube, such as topiramate [41] or oxcarbazepine [42]. Immunomodulation with adrenal cortical glucocorticoids, intravenous immunoglobulins or plasma exchange are also sometimes used for the treatment of patients with refractory SE [43], including the cases where there is no clear evidence of inflammatory aetiology [7]. With respect to steroid therapy, some trials were conducted with intravenously administered methylprednisolone at a 1 g dose for 3 days and subsequently 1 mg kg<sup>-1</sup> for approximately 6 weeks. Immunoglobulins are

administered in the 0.4 mg kg<sup>-1</sup> dose for 5 days; treatment is repeated twice in 2-week intervals. To date, only immunotherapy has not been thoroughly tested and therefore, there are no standardised guidelines regarding this treatment [22].

For decades, patients with epilepsy, especially children, have been on a ketogenic diet. Sporadically, a ketogenic diet is also introduced in the treatment of refractory SE. The effects of the therapy should be expected after several days or even weeks [18, 19]. According to study findings, positive treatment outcomes have been achieved using hypothermia; in adults, by intravascular cooling and in children by external cooling to 32–35°C [22, 31].

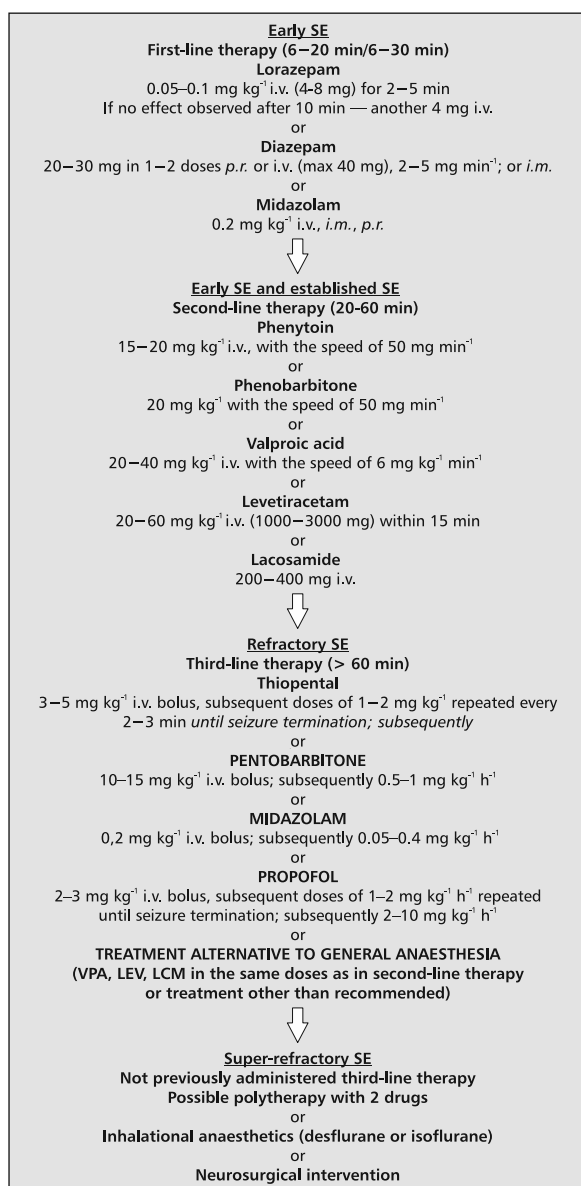
### SUPER-REFRACTORY STATUS EPILEPTICUS

Super-refractory SE is diagnosed when the third-line therapy with one cycle of intravenous anaesthetics proves ineffective. Further treatment includes alternative third-line therapy and thus is similar to the procedure in refractory SE. It differs from the latter as it allows polytherapy with two antiepileptic drugs simultaneously. Some authors stress the importance of choosing low interaction risk drugs, administering them in large doses and avoiding frequent replacements. It is also important to choose drugs of low hepato- and nephrotoxicity risk. Moreover, better results are achieved avoiding the GABAergic drugs [22].

Other non-pharmacological treatment methods, especially of super-refractory SE, include implantation of a vagus nerve stimulator [44] and surgical treatment (removal of epileptic focus, hemispherectomy, callosotomy, multiple incisions of cerebral cortex) [45, 46] (tab. 2).

Once the SE is terminated, it is crucial to immediately introduce longterm antiepileptic treatment [1] (Fig. 2).

In practice, treatment of SE is based on the guidelines set by a group of experts. In most countries, including Poland, therapeutic protocols are based on the consecutive administration of benzodiazepines, phenytoin and phenobarbitone.



**Figure 2.** Treatment of status epilepticus (SE) in adults [1, 7, 12, 13, 17, 18, 22, 28, 53]

At each stage, the treatment can be stopped when the therapeutic effect is reached. In cases of ineffective treatment, the final stage is intubation, mechanical ventilation and general anaesthesia.

Over the last several years, these procedures underwent certain modifications. Some authors report that the second drug therapy is effective in only 5% of patients with SE and that administration of the third drug is effective in only 2.3% of the affected. Moreover, following the procedure of using 2–3 drugs consecutively, considerably prolongs the duration of treatment, which in the case of refractory SE, ends with general anaesthesia and EEG monitoring until the

burst suppression pattern appears. This last element of the procedure has positive effects in 23% of patients. The above observations demonstrate that prolongation of therapy often does not induce the intended effect. Therefore, American scientists propose the introduction of a new, shortened protocol for the treatment of SE, with simultaneous administration of lorazepam and phenytoin, eliminating the stage of phenobarbitone. The suggested strategy enables intensive treatment and faster induction of pharmacological general anaesthesia, which according to the authors, considerably improves the final therapeutic outcome in patients with refractory SE [6].

Notwithstanding the above, a crucial factor in therapy is close and early initiated cooperation between neurologists and anaesthesiologists aimed at minimising the risk of development of refractory SE.

It should also be noted that the aim of treatment is not only the termination of clinical and electrographic features of SE but also the prevention of epileptic seizure recurrence, as well as the treatment of SE-related complications and those resulting from the applied therapy [22].

Looking at the guidelines for SE treatment used several years or decades ago, we can see that they describe the rules of how NOT to treat this disease. Retrospective evaluation of the methods used in the past, it seems that lack of effectiveness could have resulted from a number of factors, including too small doses of drugs, irregular dosing too early ceasing of aggressive treatment [30]. However, without these 100 years of work of many generations of neurologists and physicians specialising in emergency treatment and intensive care, we would not have been able to reach the current conclusions. Therefore, the guidelines that we put forward, at the current level of theoretical knowledge and experience, seem the most optimal for the fastest termination of GCSE; however, their significance would be verified in the future.

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