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CRITICAL CARE (SA MAYER, SECTION EDITOR)

Status Epilepticus: An Update

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Abstract Status epilepticus (SE) still results in significant mortality and morbidity. Whereas mortality depends mainly on the age of the patient as well as the cause, morbidity is often due to the myriad of complications that occur during prolonged admission to an intensive care environment. Although SE is a clinical diagnosis in most cases (convulsant), its treatment requires support by continuous electroencephalographic recording to ensure cessation of potential nonconvulsive elements of SE. Treatment has recently changed to incorporate four stages and must be initiated at the earliest possible time.

Keywords Status epilepticus · Definition · Treatment · Seizures · Antiepileptic drugs

Introduction

Status epilepticus (SE) remains a neurological emergency, which may lead to death or permanent neurological injury if not treated properly and timely. This update to an article published in 2009 [1] will include new guidelines on SE published in Europe [2] and the USA [3••].

Definition

The International Classification of Epileptic Seizures had previously defined SE as any seizure lasting 30 min or more or intermittent seizures lasting for more than 30 min without recovery of consciousness interictally [4, 5]. This definition, however, has evolved over the years, with a shorter period being adopted by many experts [3••]. A duration of 5 min or more of (1) continuous seizures or (2) two or more discrete seizures between which there is incomplete recovery of consciousness, proposed by Lowenstein et al. [6], offers the advantage of incorporating new knowledge, including the facts that most benign tonic–clonic seizures last for only 1–2 min (those lasting more than 5 min do not stop spontaneously) [7], that permanent neuronal injury occurs before 30 min, and that response to treatment is impeded with long seizure duration [8].

Refractory SE (RSE) has been defined as SE not controlled after the initial parenteral therapy with a minimum number of standard "front-line" antiepileptic drugs (AEDs; either two or three) [9] or after adequate doses of an initial benzodiazepine followed by a second acceptable AED [3••] or SE with a minimum duration of seizures that persist despite treatment (for either 1 or 2 h) [9].

More controversial is the definition of nonconvulsive SE (NCSE). Variable criteria have been proposed by a number of experts [10]. Most of them agree with the following: the presence of altered consciousness or behavior for 30 min or more, the absence of overt clinical signs of convulsive activity during that period, and the electroencephalographic (EEG) confirmation of seizures or activity that responds to treatment together with improvement of consciousness

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[11–13]. A compendium of 123 cases of NCSE with clinical descriptions and EEG patterns following a syndromic classification approach has been published recently [14].

Types of SE

Three major categories of SE have been described: generalized convulsive SE, focal motor SE (or epilepsia partialis continua) of Kojewnikov, and NCSE. The first two are easily recognized clinically owing to the overt tonic or clonic motor activity. NCSE, however, has a more obscure phenotype and can be subdivided into benign variants (typical absence SE and complex partial SE), electrical SE during sleep, atypical absence SE and tonic SE (usually in children with learning disabilities), or SE in coma (after significant brain injuries, such as hypoxia–ischemia, most commonly encountered in intensive care units, ICUs) [12]. A more recent taxonomy of SE along with the presence of motor symptoms and the level of consciousness distinguishes three types of SE: (1) SE with prominent motor symptoms (convulsive, myoclonic, tonic SE or epilepsia partialis continua), (2) SE without prominent motor symptoms (NCSE with coma, NCSE without coma), and (c) boundary syndromes (epileptic encephalopathy, acute coma with SE-like EEG patterns, epileptic behavioral disturbance and psychosis, and confusional states or delirium with epileptiform discharges) [15•].

Incidence

SE is a relatively common condition. It accounts for 3-5 % of all emergency department admissions for seizure disorders and occurs in 2-16 % of all epilepsy patients [16]. In a prospective population-based epidemiological study, the incidence of SE was estimated at 41–61 per 100,000 patients per year. For the USA, this translates to 125,000–195,000 episodes per year [17].

The highest incidence of SE occurs during the first year of life and during the decades after 60 years, and is also dependent on the SE subtype. Partial SE occurs in 25 % of cases of SE, and NCSE accounts for another 4–26 % [17, 18]. Because the incidence of NCSE requires timely or continuous EEG monitoring, the estimate for the latter is likely conservative [19] and may depend on the underlying neuropathological condition. For example, NCSE was discovered in 0 % of patients with acute stroke [20], 8 % of comatose ICU patients [21], 7 % of patients with intracerebral hemorrhage [22], 3-8 % of patients with subarachnoid hemorrhage [23], 6 % of patients with metastatic cancer [24], and 6 % of patients with head trauma [25]. RSE occurs in approximately 30-43 % of patients with SE. Risk factors that have been identified for RSE are encephalitis as a cause, severe consciousness impairment, de novo episodes of SE, NCSE, and focal motor seizures at onset [26, 27, 28•].

Etiology of SE

The three commonest causes of SE are low levels of AEDs (in 34 % of cases), remote symptomatic causes (history of neurological insults remote to the first unprovoked SE episode, 24 %), and cerebrovascular accidents (22 %). These are followed by hypoxia (13 %) and metabolic disturbances (15 %) . Because 82 % of patients in the remote group have a history of cerebrovascular disease, almost 50 % have either acute or remote cerebrovascular disease as the cause of SE [17]. In a prospective study of nonanoxic RSE, causes were divided into acute symptomatic (65.5 %), remote symptomatic (17.2 %), progressive symptomatic (13.8 %), and cryptogenic/idiopathic (3.4 %) and did not differ from those in the group with non-RSE [28•]. The cause of focal NCSE (or "complex focal or complex partial SE") in 45 % of patients is a focal frontal lesion, most often a tumor or a posttraumatic or postsurgical lesion, but also rarely drugs such as ciprofloxacin, lithium or theophylline intoxication, vigabatrin, tiagabine, and crack [15•].

The causes of SE in critically ill patients may be different from those in the general population and may mirror the causes of ICU seizures (Table 1). In general ICUs, metabolic abnormalities can account for 33 % of seizures, drug withdrawal for 33 %, drug toxicity for 14.5 %, and stroke for 9-39 % [29, 30]. In comatose patients admitted to general ICUs, the commonest cause of NCSE was anoxia–hypoxia (42 %), followed by stroke (22 %) [21]. In another study of ICU patients with RSE, SE was associated with anoxia (24 %) or ischemic stroke or infection (18 % in each case) [31]. The specific ICU patient population and the monitoring capabilities in that unit may play a role in which cause is detected. In NCSE patients in a coma, it may be difficult to assess if the coma is caused by the SE or by the brain injury itself and what the relative contribution of nonconvulsive seizures to the depth of the coma is. It may also be difficult to decide on the appropriate type of treatment (e.g., sedatives or general anesthetics in an already comatose patient) and prognosticate the effect of such a treatment. Using electroencephalography, one could detect the presence of generalized epileptiform discharges ("coma-GED") or lateralized epileptiform discharges ("coma-LED") [32]. In the former, diffuse brain injuries (anoxia, toxometabolic, infectious or degenerative disorders) are common and in the latter more focal causes, but rarely also diffuse conditions (diabetic or hypoglycemic coma, aminophylline intoxication) have to be excluded [15•]

Beyond these common causes of SE, rare causes may be challenging to the neurologist. In a systematic review of 513

Table 1 Common causes of status epilepticus (SE) or seizures in the intensive care unit (adapted from [88])

Neurological disease	Complications of critical illness
Neurovascular	Hypoxia/ischemia
Ischemic stroke	Drug/substance toxicity
Arteriovenous malformations	Antibiotics
Hemorrhage	Antidepressants
Cerebral sinus thrombosis	Antipsychotics
Tumor	Bronchodilators
Primary	Local anesthetics
Metastatic	Immunosuppressives
CNS infection	Cocaine
Abscess	Amphetamines
Meningitis	Phencyclidine
Encephalitis	Drug/substance withdrawal
Encephalitis (noninfectious)	Barbiturates
Paraneoplastic limbic	Benzodiazepines
NMDA-receptor antibodies	Opioids
Nonparaneoplastic limbic	Alcohol
Voltage-gated K^+ channel antibodies (leucine-rich, glioma inactivated 1)	Infection—fever (febrile seizures)
Inflammatory disease	Metabolic abnormalities
Vasculitis	Hypophosphatemia
Acute disseminated encephalomyelitis	Hyponatremia
Traumatic head injury	Hypoglycemia
Contusion	Renal/hepatic dysfunction
Hemorrhage	
Surgical injury (craniotomy)	
Primary epilepsy	
Primary CNS metabolic disturbance (inherited)	

NMDA *N*-methyl-D-aspartate

articles on SE, 181 uncommon causes of SE were identified and subdivided into immunologically mediated disorders, mitochondrial diseases, rare infectious disorders, genetic disorders, and drugs or toxins [15•, 33]

Pathophysiology of SE

Most seizures are self-terminating phenomena lasting from a few seconds to a few minutes. In specific circumstances, however, the inhibitory mechanisms fail and seizures progress to SE, which leads to tissue damage and further seizures. Neuronal injury during SE is the result of increased excitotoxicity [34–36], but also of a systemic derangement such as hypoxia, acidosis, hypotension, or multiorgan dysfunction [37].

Initially, the γ-aminobutyric acid (GABA) inhibitory circuits may be deficient, and this is why benzodiazepines or barbiturates, which work through GABAergic receptor agonism, are very effective AEDs during this early period. As time passes however, GABA receptors undergo a significant shift in their ability to respond to benzodiazepines [38]. Two other mechanisms then come into play: (1) excessive *N*-methyl-D-aspartate-type glutamate receptor neurotransmission, leading to glutamate excitotoxicity [36], and (2) increased brain expression of drug efflux transporters such as P-glycoprotein at the blood–brain barrier, which may reduce concentrations of AEDs at their brain targets [39].

Diagnosis of SE

The diagnosis of SE is primarily clinical and encompasses motor phenomena and alteration of mental status. Focal-onset convulsions can remain focal, follow a Jacksonian march, or immediately generalize to involve the whole body. Most of the time, this secondary generalization can be appreciated only during EEG recording. In addition, mental status alteration can differentiate simple partial SE (no change in mental status) from complex partial SE (disturbed sensorium). However, the presence or absence of motor phenomena and loss of consciousness do not necessarily correlate with the EEG activity during or after SE. For example, persistent electrographic seizures or NCSE after control of convulsive SE have been demonstrated with continuous EEG monitoring [40]. Conversely, altered mental status is also a poor clinical differentiator, since 87 % of patients successfully treated for convulsive SE and 100 % treated for NCSE remained comatose 12 h following the initiation of therapy [18]. Therefore, EEG monitoring is important for these patients. The EEG criteria for convulsive SE have been clearly delineated, but for NCSE a mix of clinical and EEG criteria should be met [13, 41–43]

A characteristic set of symptoms has recently been described in patients who have nonparaneoplastic limbic encephalitis associated with voltage-gated potassium channel antibodies, especially against leucine-rich, glioma-inactivated 1 protein. These patients can present with fasciobrachial seizures (brief, facial grimacing and ipsilateral arm posturing) often preceding the onset of amnesia, confusion, or temporal lobe seizures [44•, 45]. Because they may occur very frequently (in a series of 29 patients, the median occurrence was 50, with a range 6–360 per day [44•]), they may be considered as focal motor SE or epilepsia partialis continua, although they respond to immunosuppression rather than AEDs.

NCSE does not always imply absence of motor activity. Occasionally, very subtle motor activity (twitching or myoclonus in the face or limbs, nystagmus, blinking, chewing) with or without behavioral (confusion, agitation, lethargy,

speech arrest, verbal perseveration, blank starring, bizarre behavior) or vegetative (anorexia, nausea, vomiting) abnormalities is present.

Treatment of SE

The goals of the treatment include (1) emergent medical management, (2) termination of seizures, (3) prevention of recurrence of seizures, and (4) prevention or treatment of complications [46]. Significant practice variations, however, exist even among academic centers in the USA [47].

Management of SE must begin with the emergency medical services in a prehospital setting. Several studies have attempted to assess the possibility of terminating SE even prior to arrival at the hospital. In a randomized, double-blinded study, lorazepam was 4.8 times and diazepam was 2.3 times more effective than placebo in terminating SE on arrival at the emergency department when given intravenously by paramedics [48]. In another prehospital study, midazolam at doses of 2 mg/kg for children and 10 mg/kg for adults intranasally or intramuscularly was comparable to or better than intravenously administered diazepam [35]. The RAMPART study was a double-blind, randomized, noninferiority trial comparing the efficacy of intramuscularly administered midazolam (10 mg) followed by intravenously administered placebo (n=448) with that of intramuscularly administered placebo followed by intravenously administered lorazepam (4 mg; n=445) for treatment of children and adults with SE treated by paramedics. At the time of arrival in the emergency department, seizures had ceased without rescue therapy in 73.4 % and 63.4 % of cases, respectively, favoring midazolam by an absolute 10 % (95 % confidence interval 4.0–16.1, p<0.001). Adverse events and endotracheal intubation were similar in the two groups. On these basis of these data it was concluded that intramuscularly administered midazolam is at least as safe and effective as intravenously administered lorazepam for prehospital seizure cessation [49].

Table 2 shows the proposed algorithm for treating SE in the hospital. A three-stage approach has been advocated, including the emergent initial stage, the urgent control stage, and the refractory stage [3••, 15•]. Recently, a fourth stage of "super-refractory SE" (10-15 % of all cases of convulsive SE) has been proposed [50••, 51].

In the emergent initial phase, the goals are protection of the airway, oxygenation, maintenance of blood pressure, exclusion of easily treatable causes (such as hypoglycemia and hyponatremia), and administration of first-line AEDs. Benzodiazepines are considered the best first-line AEDs, on the basis of the findings of large prospective randomized trials. Lorazepam administered intravenously [18], midazolam administered intramuscularly [49], and diazepam administered buccally or rectally [52] are considered the most effective agents. However, as newer AEDs enter our armamentarium, this may change. In a recent open-label randomized study of 79 patients with convulsive SE or subtle convulsive SE that compared levetiracetam (20 mg/kg) administered intravenously in 15 min with lorazepam (0.1 mg/kg) administered in 2–4 min, SE was controlled by levetiracetam in 76.3 % or patients and by lorazepam in 75.6 % of patients. In those patients resistant to the above-mentioned regimens, lorazepam offered slightly better control than levetiracetam (88.9 % vs 70 %), but also led more often to artificial ventilation and hypotension [53].

If seizures continue, stage 2 medications should be used. There is no significant difference between phenytoin and valproate for benzodiazepine-refractory SE as a second, urgent control treatment. There are some data suggesting a better response rate with valproate after failure to control seizures with phenytoin than with phenytoin after failure to control seizures with valproate [54]. Levetiracetam and phenobarbital administered intravenously are also acceptable choices. In a recent review of studies using levetiracetam after benzodiazepines in 334 patients with SE, its efficacy was reported as ranging from 44 % to 94 % [55] Overall, more than 700 patients with SE have been treated with an initial dosage of 2–3 g/day and with an estimated success rate around 70 % [56] In a retrospective study of 181 episodes of SE not responding to benzodiazepine first-line treatment, treatment with levetiracetam failed more often than treatment with valproic acid as a second-line AED for controlling SE [57]

If seizures continue for a prolonged period despite the use of benzodiazepines and second-stage AEDs, SE should be considered refractory (stage 3). Before more aggressive measures with anesthetic agents are taken, leading to intubation, mechanical ventilation, and hemodynamic support with pressors or inotropes, additional AEDs can be considered. Lacosamide can be administered intravenously, and in a recent review of 136 episodes of RSE had a success rate of 56 % (200–400 mg in 3–5 min was the most common bolus dose) [58]. Because of the urgency of controlling the seizures during SE and the questionable enteral absorption, especially while the patient is in a barbiturate coma, administration per os is not an option and only intravenous formulations should be used in the ICU. If, however, gastric residuals are not increased and ileus is not present, we and others have also used topiramate in dosages of 300–1,600 mg/day per orogastric tube [59]. In a recent study of 35 patients with RSE treated with topiramate as an adjunct AED, the response rate was 86 % (as the third AED), and remained stable at 67 % after administration of topiramate as the fourth, fifth, sixth, or seventh AED. Overall, RSE was terminated in 71 % of patients within 72 h after the first

Table 2 Treatment algorithm for SE (modified from [1, 3••, 15•, 51])

Stage 1: emergent initial measures	Preserve airway and oxygenation by oxygen face mask or intubation, as needed.
	Establish intravenous access.
	Order EEG to be available during therapy.
	Measure finger-stick blood glucose level. Administer 1 ampoule of 50 % dextrose in water intravenously if less than 60 mg/100 dL and 100 mg thiamine intravenously.
	Send to the laboratory: antiepileptic blood levels, electrolytes, complete blood count, liver function tests, arterial blood gases, toxicology screen (urine and blood).
	At the same time as the above: immediate administration of benzodiazepines—lorazepam (0.07-0.1 mg/kg) intravenously or diazepam (0.15-0.25 mg/kg) intravenously. If no intravenous access, diazepam (20 mg) per rectum or midazolam (10 mg) intramuscularly, buccally, or intranasally
Stage 2: urgent control	Phenytoin loading dose of 20 mg/kg intravenously at 50 mg/min or fosphenytoin at 20 mg/kg PE intravenously at 150 mg/min.
	If allergic to phenytoin, valproate (25–40 mg/kg) intravenously, load at 1.5-3 mg/kg/min, or levetiracetam (30–70 mg/kg) intravenously (500 mg/min) or phenobarbital (20 mg/kg) intravenously (rate 100 mg/min).
	If seizures continue, phenytoin or fosphenytoin (additional 5–10 mg/kg or 5–10 mg/kg PE). Goal serum level 20–25 mg/dL. If phenytoin allergy, additional valproate load of 20 mg/kg intravenously.
	EEG connected and running
Stage 3: refractory SE	If nonconvulsive SE and patient not intubated yet, one or more of phenytoin, valproic acid, levetiracetam, phenobarbital (not been administered in stage 2), or lacosamide can be tried.
	Intubation and mechanical ventilation.
	Hemodynamic support by pressors and intravenous fluid boluses.
	Propofol 2 mg/kg intravenous bolus and 150–200 μg/kg/min infusion, or thiopental 2–3 mg/kg intravenous bolus and 0.3–0.4 mg/kg/min infusion, or midazolam 0.2 mg/kg intravenous bolus, which can be repeated every 5 min up to a total of 2 mg/kg, followed by infusion at 0.1-0.2 mg/kg/h.
	If seizures continue: pentobarbital, 10 mg/kg intravenous load, at up to 50 mg/min, can be repeated several times until an electroencephalographic burst-suppression pattern with 20-30-s suppression goal is achieved. Start at the same time continuous infusion at 1 mg/kg/h and titrate up to 10 mg/kg/h for the same goal
Stage 4: alternative therapies for super-refractory SE (in order from the first to the last resort)	Ketamine, 0.5-4.5 mg/kg intravenous bolus and up to 5 mg/kg/h infusion.
	Isoflurane or desflurane or gabapentin or levetiracetam (in acute intermittent porphyria).
	Topiramate, 2–25 mg/kg/day (children) or up to 300–1,600 mg/day (adults) per orogastric tube.
	Magnesium infusion, 4 g intravenous bolus, 2–6 g/h infusion.
	Pyridoxine, 180–600 mg/day intravenously or per orogastric tube.
	Steroids, 1 g/day intravenously for 3 days, followed by 1 mg/kg/day for 1 week or immunoglobulin, 0.4 g/kg/day intravenously for 5 days or plasmapheresis.
	Hypothermia of 32–35 °C for less than 48 h.
	Ketogenic diet 4:1.
	Neurosurgical resection of epileptic focus.
	Electroconvulsive therapy.
	Vagal nerve or deep brain stimulation or transcranial magnetic stimulation

EEG electroencephalograph, *PE* phenytoin equivalents

administration of topiramate [60]. When primary or metastatic brain tumor was the presumed cause of SE, a combination of phenytoin intravenously, levetiracetam intravenously (median dose of 3 g per day), and pregabalin per os (median dose of 375 mg per day) led to 70 % control of SE on average 24 h after addition of the third AED [61] However, the major treatment options, which should not be delayed in unresponsive RSE, are propofol or midazolam infusions at high rates and under continuous EEG monitoring. The advantage of using either of these sedatives is that the pharmacological clearances are brief, and they provide the ability to induce a burst-suppression coma (especially with propofol) for several hours.They also allow the intensivist to assess whether a brief period of

EEG suppression is even sufficient to terminate SE. Should seizures continue or recur, the current approach favors proceeding to a deep barbiturate coma. Pentobarbital is an intermediate-duration barbiturate (half-life approximately 24 h), offering the advantage of faster emergence from coma compared with phenobarbital. In a meta-analysis, it also appears to be superior to midazolam or propofol in controlling RSE (but with more side effects, such as hypotension) [62].

The depth of the EEG suppression that must be achieved by barbiturates is unknown, but despite some experts recommending a shorter burst-suppression pattern of 5–10 s, complete suppression or a "flat record" led to better seizure control, with fewer relapses and a trend for better outcome in a retrospective study [63]. There is also disagreement regarding the duration of barbiturate coma. Although a duration of 12–24 h is advocated by some experts [34], others recommend up to 96 h burst suppression [64]. We also prefer longer periods of deep coma, on the basis of a study of 44 RSE cases which showed that patients with more prolonged barbiturate treatment (more than 96 h) and those receiving phenobarbital at the time of pentobarbital taper were less likely to relapse [65]. European guidelines recommend titration of propofol and barbiturate to EEG burst suppression, and midazolam to seizure suppression, maintained for at least 24 h [2].

Barbiturate coma, however, is a challenge for any intensivist. The neurological examination of the patient is essentially completely compromised, the myocardial function is suppressed, leading to hypotension, cough is absent, with increased risk of the development of atelectasis or pneumonia, the bowel peristalsis is slowed or ceases entirely, and the immune responses are diminished, increasing the risk of infection or sepsis. In addition, skin ulceration at compression points or under the EEG leads and thromboembolism due to immobility are common. Therefore, all efforts should aim at discontinuation of this treatment as soon as possible. We wean patients from pentobarbital infusion at 0.5 mg/kg/h every 6 h and follow the EEG pattern as background rhythm returns. If breakthrough seizures recur, we administer pentobarbital at 10 mg/kg intravenously until the same or longer burst suppression is achieved and continue infusion for 3–7 days before attempting to wean the patient again. This cycling has been advocated by other experts [51], although not all agree with this intense and prolonged electrical activity suppression treatment because of the lack of data showing a benefit in mortality [66]

If SE continues for 24 h or more after the onset of administration of anesthetic agents or recurs after reduction or withdrawal of them, stage 4 therapies for super-refractory SE can also be initiated [50••, 51]. Ketamine offers the advantage of *N*-methyl-D-aspartate receptor antagonism, which may be important in the late phase of SE, and also the absence of cardiac depressant or hypertensive properties. Early [67] or late [68] use of ketamine has been reported in small case series with various success rates. Neurotoxic effects of this drug after prolonged infusions are of concern.

Pyridoxine hydrochloride in an intravenous or enteral form at a dosage of 100–300 mg/day can be used in stage 4 or earlier stages, as it is a cofactor in the synthesis of the inhibitory neurotransmitter GABA, which may play a role in the initial phase of SE [69]. There are no strong data for its effectiveness, except in infants with inborn error of metabolism [70], pregnant patients [69], or malnourished patients or after isoniazide intoxication [71], but it can be used as a cheap and safe alternative [51]. The same paucity of strong data is also true for magnesium, which has been successfully used in two girls with juvenile Alper's syndrome [72]. Verapamil can also be used (intravenous initial dose of 0.075-0.15 mg/kg in 2–3 min, followed by infusion at 0.125 mg/min or administration enterally at 120–240 mg/day) because of the theoretical direct anticonvulsant properties though inhibition of P-glycoprotein in the epileptic focus endothelium (this protein may inhibit the penetration of anticonvulsant drugs to the seizure site) [73] Clinical effectiveness is limited to two children with Dravet's syndrome, where addition of verapamil contributed to seizure control [74]. Use of steroids, plasmapheresis, or intravenously administered immunoglobulin has also been advocated, together with resection of the epileptic focus after mapping with intracranial EEG electrodes as the next treatment step [50••, 51]. If all these measures fail, hypothermia [75, 76], vagus nerve stimulation [77], low-frequency cortical stimulation via intracranial electrodes [78], and electroconvulsive therapy [79] could be considered.

Outcome

SE still carries a significant mortality and morbidity. Distinct variants of SE have different mortalities, and the range is quite broad: from zero mortality for absence or complex partial SE in ambulatory patients [11] to 19-27 % 30-day mortality for generalized tonic–clonic SE [18, 80] and 64.7 % 30-day mortality for subtle SE [18]. Variables playing an important role in the outcome are the underlying cause (regarded by most authorities as the most important variable), the duration of SE (mortality of 32 % if persistent for more than 1 h vs 2.7 % if persistent for less than 1 h), the type of SE, the treatment administered, and the age of the patient (children have better outcome than adults) [80–82]. The cause of SE remains the most important prognostic factor, with alcohol withdrawal and AED withdrawal having the best outcomes; structural brain injuries, such as anoxia–ischemia, vascular lesions, and brain tumors, have the worst prognosis. Novel treatment approaches, however, may affect

the outcome even in the worst scenarios. For example, application of hypothermia may change the fatal outcome in postanoxic SE [83].

The most resistant cases pose significant dilemmas with regard especially to the length of treatment using barbiturate coma and the potential for acceptable prognosis. For RSE, for example, in-hospital mortality is 31.7 % and the poor functional outcome rate at discharge is 76.2 % [84]. The duration of drug-induced coma, arrhythmias requiring intervention, and pneumonia are associated with poor functional outcome, and prolonged mechanical ventilation was associated with mortality, and seizure control without a burst-suppression or isoelectric electroencephalogram was associated with good functional outcome [84].

A prognostic score, the SE severity score (STESS), has been developed to predict survival before initiation of SE treatment (range 0–6) [85]. This score relies on the assessment of age (no points for under 65 years or two points for 65 years or older), previous history of seizures (no points if there is a history, one point if there is no history or if the history is unknown), seizure type (no points for simple partial, complex partial, absence of, or myoclonic seizure, one point for generalized tonic–clonic seizure, or two points for NCSE in a coma), and extent of consciousness impairment (no points for alert or somnolent/confused, one point if stuporous or comatose). A favorable score of 0–2 is highly related to survival (negative predictive value of 0.97) and likelihood to return to the baseline clinical condition in survivors, although the positive predictive value for death was low (0.39) for those with an unfavorable score (3–6) [86].

The risk of recurrence of afebrile SE has also been assessed in a population-based study in Minnesota. Among the 183 episodes of first afebrile SE, the risk of recurrent SE was reported to be 31.7 % over a 10-year follow-up period. The risk of recurrence was about 25 %, regardless of the underlying cause, except in those patients with SE occurring in the setting of a progressive brain disorder (who had 100 % risk). Female gender, generalized (vs partial) SE, and lack of response to the first AED after the initial episode of SE identified those individuals at greatest risk of recurrence [87].

Conclusion

SE remains a common admission diagnosis, carrying significant mortality and morbidity, which depend mainly on the age of the patient and the cause. Electroencephalography is still an important diagnostic tool, since a number of patients may present with or evolve to NCSE. The treatment, which is based on supportive measures and benzodiazepine administration, followed by staged AEDs and anesthetics for resistant cases, should be initiated without delay at the scene and continued in the emergency department, and, if SE becomes refractory, in the ICU.

Compliance with Ethics Guidelines

Conflict of Interest Panayiotis N. Varelas declares no conflict of interest.

Marianna V. Spanaki declares no conflict of interest.

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- • Of importance
- •• Of major importance

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