Treatment of Status Epilepticus in Adults: Guidelines of the Italian League Against Epilepsy

*Fabio Minicucci, †Giancarlo Muscas, ‡Emilio Perucca, §Giuseppe Capovilla,
∥Federico Vigevano, and ¶Paolo Tinuper

*Clinical Neurophysiology, San Raffaele Hospital, Milan; †Epilepsy Center, Department of Neurology, Careggi Hospital, Florence;
‡Institute of Neurology, IRCCS C. Mondino Foundation and Clinical Pharmacology Unit, University of Pavia, Pavia; §Department of
Child Neuropsychiatry, C. Poma Hospital, Mantova; ∥Neurology Division, Bambino Gesu Children's Hospital, Rome; and
¶Department of Neurological Sciences, University of Bologna, Bologna, Italy*

Summary: Status epilepticus (SE) is a medical emergency which can lead to significant morbidity and mortality and requires prompt diagnosis and treatment. SE is differentiated into generalized or partial SE on the basis of its electro-clinical manifestations. The guidelines for the management of SE produced by the Italian League against Epilepsy also distinguish three different stages of SE (initial, established and refractory), based on time elapsed since the onset of the condition and responsiveness to previously administered drugs. Treatment should be started as soon as possible, particularly in generalized convulsive SE, and should include general support measures, drugs to suppress epileptic activity and, whenever possible, treatments aimed at relieving the underlying (causative) condition. Benzodiazepines are the first line antiepileptic agents, and i.v. lorazepam is generally preferred because it is associated with a lower risk of early relapses. If benzodiazepines fail to control seizures, i.v. phenytoin is usually indicated, though i.v. phenobarbital or i.v. valproate may also be considered. Refractory SE requires admission to an intensive care unit (ICU) to allow adequate monitoring and support of respiratory, metabolic and hemodynamic functions and cerebral electrical activity. In refractory SE, general anesthesia may be required. Propofol and thiopental represent first line agents in this setting, after careful assessment of potential risks and benefits. **Key Words:** Status epilepticus—Epilepsy—Treatment—Antiepileptic drugs—Guidelines—Italian league against epilepsy.

Status epilepticus (SE) is a major medical emergency associated with significant morbidity and mortality (Simon, 1985; Lothman, 1990). It often requires hospitalization for clinical-diagnostic definition and treatment. The present document was produced by the Commission on Guidelines, Subcommission on SE, of the Italian League against Epilepsy and is designed to provide guidance on the management of SE in adults.

DEFINITION AND GENERAL CONSIDERATIONS

Definition of SE

There is no universally accepted definition of SE. In particular there is no consensus on the duration of seizure manifestations (from 5 to 30 min) which is required to define SE. In 1993 the Epilepsy Foundation of America Working Group on SE established that anticonvulsant medication must be administered when seizures last for more than 10 min (Epilepsy Foundation of America's Working Group on Status Epilepticus, 1993). Based on clinical evidence that a single seizure seldom lasts for more than two min (Theodore et al., 1994; Shinnar et al., 2001), it has been suggested that generalized convulsive SE (GCSE) may be defined as either continuous seizures lasting for at least five min or two or more seizures without complete recovery of consciousness between them (Lowenstein and Alldredge, 1998; Lowenstein, 1999, Lowenstein et al., 1999). The clinical features of each SE episode (e.g., GCSE, generalized nonconvulsive SE, partial SE) are essential to guide specific treatment (DeLorenzo et al., 1999).

The Ad Hoc Working Group of the Italian League Against Epilepsy defined SE "either a clinical situation characterized by continuous seizure activity (generalized or partial, with or without motor manifestations) lasting for more than 20 min or seizures recurring at very short intervals (shorter than one min) establishing a persisting epileptic condition" (Baruzzi and Tinuper, 1989, unpublished).

Classification

SE is commonly classified, according to its electro-clinical features, as either generalized or partial. The occurrence of partial or generalized motor manifestations of epileptic activity constitute the major criteria in different classifications (Gastaut, 1983). Literature reports often use the term "non-convulsive status epilepticus" (NCSE) to indicate both absence SE and complex partial SE. The term NCSE is also commonly used to define some clinical conditions where a clear distinction between generalized and complex partial SE is difficult or impossible (for example, the condition that follows GCSE in comatose patients) (Kaplan, 1999).

Epidemiology (see synthesis and recommendations 1, 2, 3, 4)

The estimated annual incidence of SE varies in different surveys from 9.9 to 41 per 100,000 (DeLorenzo et al., 1996; Hesdorffer et al., 1998; Coeytaux et al., 2000; Knake et al., 2001; Vignatelli et al., 2003). A higher incidence above age 60 years (from 54 to 86 per 100,000) is commonly accepted, with more than one third of SE in this age group being represented by GCSE.

The mortality of SE varies from 1 to 22% in different series. Hauser et al. (1990) estimate at 2% the highest mortality rate secondary to SE alone. There are no studies demonstrating different mortality rates for the different clinical presentations of seizures (Towne et al., 1994), but a higher morbidity for GCSE is commonly accepted (Logroscino et al., 2001). Prognostic indicators of poor outcome include SE lasting for more than 1 h, anoxic etiology (DeLorenzo et al., 1999; Towne et al., 1994), and old age.

Etiology

The most common etiologies are stroke, traumatic brain injury, brain tumors, central nervous system (CNS) infections, metabolic or toxic encephalopathies, and electrolyte disorders. No clear etiology can be identified in 20% of cases, especially in patients with a previous diagnosis of epilepsy (Shorvon, 1994). In persons with epilepsy, more than 50% of cases of SE are related to deliberate or accidental withdrawal of chronic antiepileptic drug (AED) treatment. Etiology is the major prognostic factor in SE (Towne et al., 1994). Anoxia, stroke, CNS infections, and metabolic dysfunctions are associated with a worse prognosis. Low plasma levels of AEDs in patients with epilepsy, alcohol intoxication, and traumatic brain injury are associated with a better outcome.

METHODS

The Subcommission Chair (FM) searched published reports from 1966 to 2005 using the MEDLINE database (last search in December 2005). The search was limited to papers published in English. The subject term "status epilepticus" was combined with the terms "treatment" with and without the additional term "controlled clinical trial." In addition, the Cochrane Central Register of Controlled Trials (CENTRAL) was examined, as well as documents/guidelines published by the Tuscany and Lombardy regions. The Subcommission Chair produced a first draft of the document, which was then evaluated and revised by all members until consensus was reached. The document was then posted on the website of the Italian League against Epilepsy for comments from members. After final refinement, the document was approved by the Executive Council of the Italian League against Epilepsy on January 21st, 2006.

The following three ratings of recommendation were used, based on six levels of evidence:

Rating A

Level 1: evidence obtained from meta-analysis of randomized controlled trials (RCTs)

Level 1B: evidence obtained from at least one RCT

Rating B

Level 2: evidence obtained from at least one prospective controlled nonrandomized trial

Level 2B: evidence obtained from at least one "well designed," quasi-experimental study

Level 3: evidence obtained from descriptive, nonexperimental studies, such as comparative retrospective studies and case-control correlations

Rating C

Level 4: evidence obtained from expert committees or clinical experience of experts, in the absence of high quality studies

GENERAL MANAGEMENT CONSIDERATIONS

Given the risk of rapid occurrence of cerebral damage, diagnosis and treatment have to be provided at the same time. Diagnostic procedures are necessary to define the type of SE and to determine its etiology. Whenever possible, specific treatment(s) for the underlying disorder should be combined with symptomatic treatment. Anticonvulsant treatment must be associated with general life support measures.

In the section below, treatment options are provided separately for (i) initial SE (within 20–30 min); (ii) established SE (60–90 min); and (iii) refractory SE (after 60–90 min). This distinction, which is defined by temporal parameters and responsiveness to AED treatment, serves practical purposes, and is supported by pathophysiological data (Lothman, 1990). Existing guidelines are mainly directed to the treatment of GCSE. Although these guidelines are also commonly applied to the treatment of other types of SE, clinicians should assess in each specific situation the risks and benefits of pharmacological treatment and define accordingly an appropriate timing

for diagnostic and therapeutic procedures (D'Agostino et al.,1999; Panayiotopoulos, 2002). This document addresses the treatment of SE in adults. Although SE in children is generally treated according to recommendations derived from studies in adults (Martland et al., 1998; Igartua et al., 1999), this approach is suboptimal for many reasons, including the occurrence of differences in pharmacokinetics and pharmacodynamics between children and adults (Dieckmann, 1994).

MANAGEMENT OF INITIAL SE (WITHIN 20–30 MIN)

General support/monitoring measures (see synthesis and recommendation 2, 11, 15)

- Monitor and maintain ventilation (oxygen administration)
- Monitor and maintain blood pressure
- Establish venous line
- Obtain blood samples for: (i) complete blood cell count; (ii) ESR or C-reactive protein; (iii) coagulation tests; (iv) CPK; (v) LDH; (vi) hepatic and renal function; (vii) serum electrolytes (including calcium and magnesium, whenever possible); (viii) blood glucose; (ix) serum AED levels; and (x) toxicological assays
- Administer i.v. glucose, unless contraindicated (preceded by 100 mg i.m. thiamine in patients likely to have chronic alcohol abuse)
- Assess and treat metabolic acidosis

Pharmacological treatment (see synthesis and recommendations 5,6)
Lorazepam
0.05–0.1 mg/kg i.v. (maximum infusion rate 2 mg/min). A second bolus can be administered after 10 min.
   or
Diazepam
0.1 mg/kg i.v. (in 60 s). A second bolus can be administered after 10 min.

Benzodiazepines may induce respiratory depression and sedation.

MANAGEMENT OF ESTABLISHED SE (60–90 min)

General support/monitoring measures
- Determine etiology of SE
- Start EEG monitoring to confirm diagnosis and to monitor response to treatment
- Monitor and treat blood pressure changes
- Plan patient's admission to intensive care unit (ICU) for subsequent treatment
- Monitor and treat metabolic disturbances

Pharmacological treatment (see synthesis and recommendation 7)

For patients already treated with full doses of benzodiazepines:

Phenytoin
15–18 mg/kg i.v., at a maximum infusion rate of 50 mg/min

- a further 5 mg/kg i.v. dose may be administered if seizures are not controlled
- avoid dilution in glucose solution, because precipitation may occur
- infuse through a large independent venous line to avoid phlebitis
- monitor heart rate and blood pressure
- possible side effects: sedation, hypotension, cardiac dysrhythmias, "purple glove syndrome" and skin reactions, including Stevens–Johnson syndrome; respiratory depression is theoretically possible but extremely rare
- contraindicated in patients with second-degree heart block or severe hypotension

Phenytoin may be substituted by fosphenytoin, a phenytoin prodrug, administered by the i.v. or i.m. route. Although fosphenytoin has fewer adverse effects than phenytoin, particularly a reduced risk of local irritation, it is not currently available in Italy.

Other pharmacological options are reported in the section "Alternative therapeutic options."

MANAGEMENT OF REFRACTORY SE (AFTER 60–90 MIN)

Assistance of an anesthesiologist is required (see synthesis and recommendations 8,12,13)

Pharmacological treatment (see synthesis and recommendations 9,10,14)
Thiopental
5–7 mg/kg i.v. in 20 s. followed by 50 mg boluses at intervals of 2–3 min until complete seizure control and an EEG "suppression burst" pattern are obtained:

- subsequent continuous infusion (3–5 mg/kg/h) must be continued for 12–48 h, maintaining the EEG "suppression burst" pattern
- EEG monitoring is required
- pharmacological support of blood pressure is often required
- risk of respiratory depression and hypotension
- risk of cardiac arrest when administered to patients with massive bleeding, hypovolemia, sepsis, or toxemia

   or

Propofol

2–5 mg/kg as i.v. bolus (a second bolus can be given), followed by continuous infusion (up to 5 mg/kg/h) for at least 1 h:

- EEG monitoring is required
- hypotension, bradyarrhythmias, hypertriglyceridemia may occur
- risk of "propofol syndrome in ICU" characterized by: hypotension, bradyarhythmias, heart failure, hyperkalemia, hepatomegaly, lipemia, metabolic acidosis, and rhabdomyolysis

ALTERNATIVE THERAPEUTIC OPTIONS

The drugs listed below may not be included in some literature guidelines, but they can be efficacious. They may be valuable in specific conditions, when classical drugs are ineffective or contraindicated.

Sodium valproate (see synthesis and recommendation 7):

- 15 mg/kg i.v. in five min or more (some authors suggest 30 mg/kg) followed by 1–2 mg/kg/h as continuous infusion depending on clinical response
- Valproate does not induce hypotension, respiratory depression, or severe sedation (see synthesis and recommendation 7)

Midazolam (see synthesis and recommendation 9):

- 5–10 mg i.m. or rectally. A second dose can be administered after 15 min
- 0.1–0.3 mg/kg as i.v. bolus, at a maximum infusion rate of 4 mg/min (a second dose can be administered after 15 min); as an alternative to the bolus, an i.v. infusion may be administered at a rate of 0.05–0.4 mg/kg/h
- 10 mg by buccal instillation, using a syringe or catheter
- side effects are similar to other benzodiazepines; it is not licensed for epilepsy in Italy

Phenobarbital (see synthesis and recommendations 5,7,9):

- 10–20 mg/kg i.v., infused over 10 min or more (50–75 mg/min)
- phenobarbital may induce sedation, hypotension, and respiratory depression, and may require ventilation support

Isoflurane (see synthesis and recommendation 10):

- administered at 0.8–2 vol%, titrated to obtain the EEG "suppression burst" pattern
- use only for refractory SE
- isoflurane may induce hypotension, atelectasia, paralytic ileus and deep venous thrombosis

Lidocaine (see synthesis and recommendation 10):

- 1.5–2 mg/kg as i.v. bolus (commonly 100 mg in adults), at a maximum rate of 50 mg/min. A second bolus can be administered if needed
- lidocaine may induce hypotonia, hallucinations, and bradyarrhythmias, and should only be administered by physicians experienced in its use

SYNTHESIS AND RECOMMENDATIONS

Synthesis 1: GCSE is a major medical emergency requiring prompt and adequate treatment to reduce morbidity and mortality (Alldredge et al., 2001).

Recommendation 1: Treatment of GCSE must be started as soon as possible from the pre-hospitalization phase (Level 1B, Rating A).

Synthesis 2: Complex partial SE (CPSE) may also be associated with a high morbidity. There is no consensus on what is the optimal therapeutic approach to CPSE (Engel et al., 1978; Treiman and Delgado-Escueta, 1983; Drislane and Schomer, 1994; Shorvon, 1994; Krumholz et al., 1995; Young and Jordan, 1998; Drislane, 1999; Kaplan, 1999).

Recommendation 2: Acute CPSE should be treated according to the same strategies described for initial and established GCSE (Level 3, Rating B).

Synthesis 3: Absence SE, myoclonic SE in patients with myoclonic epilepsy, partial SE without impairment of consciousness, and CPSE in patients with epilepsy should not be considered major emergencies, but they do require adequate treatment (Drislane and Schomer, 1994; Shorvon, 1994; Drislane, 1999; Kaplan, 1999; Dziewas et al., 2002).

Recommendation 3: Absence SE, myoclonic SE in patients with myoclonic epilepsy, partial SE without impairment of consciousness, and CPSE in patients with epilepsy should be treated according to the same strategies described for initial and established GCSE. Timing and choice of specific treatments should take into consideration the clinical presentation (e.g. in absence SE some AEDs, as phenytoin and phenobarbital, do not represent acceptable choices) (Level 3, Rating B).

Synthesis 4: Myoclonic SE in anoxic-ischaemic encephalopathy is associated with poor outcome. In this condition, treatment of SE does not generally influence prognosis (Krumholz et al., 1988; Young et al., 1990; Jumao-as and Brenner, 1990; Towne et al., 1994; Hui et al., 2005).

Recommendation 4: Myoclonic SE in anoxic-ischaemic encephalopathy does not require aggressive pharmacological treatment, such as high doses of AEDs or general anesthetics (Level 4, Rating C).

Synthesis 5: Phenytoin, phenobarbital, diazepam, lorazepam, and midazolam are efficacious in treating initial and established GCSE. Benzodiazepines are the first line drugs (Leppik et al., 1983; Shaner et al., 1988; Appleton et al., 1995; Treiman et al., 1998).

Recommendation 5: i.v. lorazepam or diazepam are indicated for the treatment of initial GCSE. i.v. lorazepam is the benzodiazepine of choice because it is associated with a lower risk of early relapses (Level 1B, Rating A).

Synthesis 6: Outside the hospital setting, if a venous line is not available, lorazepam and diazepam may be administered by rectal route. They should not be administered i.m. Only midazolam may be administered i.m., but it is approved in Italy only for sedation and anesthesia and not for the treatment of epilepsy or SE (Milligan et al., 1984; Appleton et al., 1995; Cereghino et al., 1998; Scott et al., 1999; Alldredge et al., 2001).

Recommendation 6: GCSE may be treated with rectal diazepam or lorazepam if a venous line is not available. In children, rectal diazepam is probably preferable (Level 1, Rating B).

Synthesis 7: Whenever benzodiazepines fail to control seizures, i.v. phenytoin (preferable choice) or phenobarbital are indicated (Delgado-Escueta et al., 1982; Shaner et al., 1988; Epilepsy foundation of America's Working Group on status epilepticus, 1993; Shorvon, 1994; Lowenstein and Alldredge, 1998; Lowenstein, 1999; Holtkamp et al., 2003). Some studies suggest that sodium valproate may also be a valuable option for established SE (Sinha and Naritoku, 2000; Uberall et al., 2000; Limdi et al., 2005). Phenytoin may be substituted by fosphenytoin, which has less undesirable effects and may be administered i.m.. Fosphenytoin, however, is not licensed in Italy (Fisher et al., 2003; ACEP Clinical Policies Committee and Clinical Policies Subcommittee on Seizures, 2004).

Recommendation 7: If benzodiazepines failed to control seizures, phenytoin is the preferred next choice, followed by phenobarbital. If phenytoin or phenobarbital are contraindicated, sodium valproate may be used (Level 3, Rating B).

Synthesis 8: Refractory SE is associated with a high mortality rate, which is mainly related to the underlying etiology (De Lorenzo et al., 1992, 1999 Towne et al., 1994; Mayer et al., 2002; Holtkamp et al., 2005).

Recommendation 8: General anesthetics are indicated only in selected patients. Clinicians should assess risks and benefits of treatment in each individual case (Level 3, Rating B).

Synthesis 9: In a study conducted in a small group of patients with refractory SE (Krishnamurthy and Drislan, 1999), the "EEG suppression" pattern obtained with continuous infusion of AEDs and/or general anesthetics appeared to be preferable to the "suppression burst" pattern. Nevertheless, complete suppression of EEG activity is associated with a higher risk of hypotension and there are no data demonstrating that it is associated with a lower mortality. There are no studies comparing these options and no expert consensus on which is preferable (Delgado-Escueta et al., 1982; Kumar and Bleck, 1992; Epilepsy Foundation of America's Working Group on Status Epilepticus,

1993; Shorvon, 1994; Walker et al., 1995; Lowenstein and Alldredge, 1998; Lowenstein, 1999; Igartua et al., 1999; Prasad et al., 2001; Claassen et al., 2002; Ulvi et al., 2002; Holtkamp et al., 2003; Rossetti et al., 2004). Important adverse effects of most drugs used to treat refractory SE include respiratory depression and haemodynamic changes (Kang, 2002; Van Gestel et al., 2005; Walker, 2005).

Recommendation 9: Barbiturates, propofol, and midazolam are indicated for the treatment of refractory GCSE only in ICU after evaluation of potential risks and benefits in the individual patient. EEG monitoring is required when these agents are used to treat refractory SE (Level 3, Rating B).

Synthesis 10: Lidocaine and inhaled anesthetics (isoflurane) can be efficacious in some cases of refractory SE. Nevertheless, there are no well-defined criteria to determine when they should be used and their optimal dosing schedule (Kofke et al., 1989; Hilz et al., 1992; Aggarwal and Wali, 1993; Teng and Wilkins, 1994; Walker and Slovis, 1997; Mirsattari et al., 2004).

Recommendation 10: Potential risks and benefits of treating GCSE with lidocaine and inhaled anesthetics should be carefully evaluated in the individual patient. These drugs should only be administered by physicians experienced in their use and they are only indicated when other drugs have failed, after assessment of prognostic factors (Level 4, Rating C).

Synthesis 11: Sudden withdrawal of AEDs may lead to SE and increased seizure frequency (Barry and Hauser, 1994; Shorvon, 1994; Maytal et al., 1996).

Recommendation 11: Chronic AED treatment should be continued during SE in patients with epilepsy (Level 4, Rating C).

Synthesis 12: SE may induce cerebral edema, but there are no data demonstrating the benefit of specific antiedema treatments during SE (Calistri et al., 2003; Hong et al., 2004).

Recommendation 12: Specific treatments for edema (e.g. mannitol or steroids) are indicated in selected cases only, depending on the patient's clinical conditions. Use of these treatments requires careful assessment of potential contraindications (Level 4, Rating c).

Synthesis 13: SE is associated with a high risk of relapse and/or further seizures (DeLorenzo et al., 1995, 1996; Hesdorffer et al., 1998; Knake e t al., 2001).

Recommendation 13: AED treatment is generally required after resolution of SE to prevent relapses. The choice of different AEDs and the duration of treatment depends on etiology, clinical status, and individual patient's characteristics (Level 2B, Rating B).

Synthesis 14: Continuous muscular activity during GCSE may cause systemic adverse complications, which may worsen the patient's conditions and prognosis. Neuromuscular blocking agents have been used to prevent these

complications (Browne, 1978; Jordan, 1994; Walls and Segarin, 1998; Gordon et al., 2000).

Recommendation 14 : Neuromuscular blocking agents are indicated in the treatment of convulsive SE in ICU. They should be used only in association with EEG monitoring to allow assessment of cerebral seizure activity (Munn and Farrell, 1993) (Level 3, Rating B).

Synthesis 15: Measuring serum AED levels may be useful in optimizing further treatment in patients with epilepsy (Barry and Hauser, 1994; Maytal et al., 1996).

Recommendation 15: Serum AED levels should be measured, but therapeutic decisions should take primarily into account the patient's clinical conditions (Level 4, Rating C).

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