Management of status epilepticus in the prehospital setting, in the emergency department and in the intensive care unit (newborns excepted)

Hervé Outin, Papa Gueye, Vincent Alvarez, Stéphane Auvin, Bernard Clair, Philippe Convers, Arielle Crespel, Sophie Demeret, Sophie Dupont, Jean-Christophe Engels, Nicolas Engrand, Yonathan Freund, Philippe Gelisse, Marie Girot, Marie-Odile Marcoux, Vincent Navarro, Andrea Rossetti, Francesco Santoli, Romain Sonneville, William Szurhaj, Pierre Thomas, Luigi Titomanlio, Frédéric Villega, Hugues Lefort, Vincent Peigne

Author's affiliations and competing interests are described in the Declarations section, at the end of the manuscript.

Corresponding author : Vincent Peigne, Intensive care Unit, Centre Hospitalier Metropole-Savoie, Place Biset, 73000 Chambéry, France ; vincentpeigne@yahoo.fr

Abstract

Background: Management of status epilepticus (SE) is subject to many difficulties: diagnosis, etiological investigation, non-specific and specific treatment. The French Society of Intensive Care and the French Society of Emergency Medicine, with the Groupe Francophone de Réanimation et d'Urgences Pédiatriques, have developed guidelines to respond to the practical questions raised by SE management in the prehospital setting, in the emergency department and in the intensive care unit. Twenty-five experts analyzed the literature and formulated recommendations according to the Grade of Recommendation Assessment, Development and Evaluation methodology.
Results: The experts agreed on 96 recommendations. Recommendations with the strongest level of evidence concern only generalized tonic convulsive SE. In this setting, first-line use of benzodiazepines (direct intravenous clonazepam or intramuscular midazolam) is recommended, with a second injection in the case of clinical persistence of SE five minutes after the first injection. In the case of persistence of SE five minutes after this second injection, the recommendation is to administer second-line treatment: sodium valproate, (fos)phenytoin, phenobarbital or levetiracetam. The confirmed persistence of convulsions 30 minutes after the beginning of the administration of this second-line treatment defines refractory SE. At this stage, a coma should be rapidly induced by means of a third-line general anesthetic (midazolam and/or propofol). Additional specific recommendations focus on children (newborns excepted) and on other types of SE.

Keywords: status epilepticus, emergency, guidelines, benzodiazepines

Introduction

The incidence of status epilepticus (SE) is difficult to estimate, but is likely to be around 6 to 40 new patients per 100 000 individuals per year [1]. Generalized tonic-clonic SE (GTCSE) is its best known and most spectacular expression. SE can also have less disturbing (like partial motor SE) or less evocative (like aphasia or visual hallucinations) features and can remain unknown, for example if these features are not accompanied by convulsive clinical manifestations. SE can also be found on an electroencephalogram (EEG) recorded for coma after GTCSE, or incidentally on an EEG recorded in a patient with coma without convulsive manifestations.
Frequently embracing the course of a known epileptic illness, SE can also be inaugural, either and most often in the context of an acute structural or functional brain injury, or as the first manifestation of an epileptic illness, especially as a consequence of sequelae of prior lesions (traumatic, vascular, etc.).

The purpose of these recommendations is to improve the prognosis of SE patients by acting on the potentially controllable factors involved in SE. It is very important to emphasize that the vital and functional prognosis of SE is primarily determined by its etiology. Uncontrolled causal lesions may decrease the effectiveness of antiepileptic treatment. Identifying and treating whenever possible the cause(s) of SE is therefore urgent and paramount. For this reason, the part of the prognosis that is clearly attributable to the epileptic activity itself is very difficult to define. Many other factors can also affect the prognosis:
1) Clinical presentation of SE with or without altered consciousness

2) Duration: SE is all the more difficult to control as time goes by
3) Refractory nature or not of the SE
4) Age, comorbidities
5) Non-compliance with the current guidelines: precipitation, not taking into account the graduation of the introduction of antiepileptic drugs, their dosages and contraindications, inadequate use of therapeutic coma, imprecise control of the various brain injury factors, inappropriate and excessive treatment, EEG misinterpreted as SE, or, conversely, SE not taken into account, superficial etiological investigation, non-use of specialized expertise to help manage complex cases
6) Possible side effects of antiepileptic and anesthetic drugs
7) Intensive care-related adverse events, such as those resulting from the use of mechanical ventilation or the occurrence of sepsis [2,3].

Among the potentially controllable factors mentioned in the above list, some may have an even more negative impact if there is underlying structural acute brain injury.

These new recommendations should allow better management of each SE patient by emergency medicine practitioners and intensivists according to graduated and personalized protocols, modulated according to the type of SE and its etiology.

Methods

The organization committee identified four areas of interest (diagnosis of SE, etiology of SE, management of GTCSE and management of other types of SE) and defined the questions under consideration according to the PICO format (Patient Intervention Comparison Outcome). The GRADE® method was used to draw up the recommendations [4,5].

1. Diagnosis of status epilepticus

R1.1 Status epilepticus (SE) may be classified (see Table 1) according to two main clinical criteria: 1) predominant motor manifestations or not, 2) altered consciousness or not. (Expert advice) Strong agreement.

Table 1: Simplified classification of status epilepticus

	Diagnostic challenge	Severity
Status epilepticus (SE) with predominant motor symptoms		
Generalized tonic clonic SE	+/-	+++
Secondary generalized tonic clonic SE	+/-	+++
Focal motor SE: partial somatomotor or epilepsia partialis continua (conscious patient)	-	-
Myoclonic SE with or without coma	+/-	-
Tonic SE	+/-	+
SE without predominant motor symptoms		
SE with coma*	+++	+++
Absence SE	++	-
Focal SE without confusion	+++	-
Focal SE with confusion	+++	++

*after a generalized tonic-clonic SE or EEG recording of SE in a comatose patient

R2.2 Generalized convulsive SE is operationally defined as ≥5 min of continuous generalized seizure with motor manifestations or two or more discrete seizures between which there is incomplete recovery of consciousness (inability to answer or follow simple orders). (Expert advice) Strong agreement.

R1.3 Generalized convulsive SE must be distinguished from serial repeated tonic-clonic seizures, with mental status recovery between each, defined by the ability to respond to or follow simple orders. This case can be considered as a threat of SE. (Expert advice) Strong agreement.

R1.4 Focal SE (motor or not) with altered consciousness is pragmatically defined by a seizure that lasts more than 10 minutes, or by repeated seizures (≥ 2) with no mental status recovery between seizures (defined by the ability to answer simple questions). (Expert advice) Strong agreement.

R1.5 Focal SE (motor or not) with no alteration of mental status can be defined as a seizure that lasts more than 10 to 15 minutes. (Expert advice) Strong agreement.

R1.6 Absence SE is pragmatically defined as an absence that lasts more than 10 to 15 minutes. (Expert advice) Strong agreement.

R1.7 Myoclonic, clonic and tonic SE, often recurring, observed in the context of childhood epileptic encephalopathy, can be defined as a seizure that lasts more than 10 to 15 minutes. (Expert advice) Strong agreement.

R1.8 Refractory SE is defined by SE that persists (clinically or electrically) despite two lines of antiepileptic therapy with recommended class and dosage, and adequate time for onset of action. (Expert advice) Strong agreement.

R1.9 For generalized convulsive SE, the isolated presence of a persistent coma or seizures with consciousness recovery after two lines of treatment does not constitute the diagnosis of refractory SE. (Expert advice) Strong agreement.

R1.10 The refractory characteristic of SE is not defined by the use of any anesthetic agent when used in the following indications:

1. to intubate a patient with compromised respiratory status
2. to intubate a patient in coma
3. to help out-of-hospital transfer

(Expert advice) Strong agreement.

R1.11 Super refractory generalized convulsive SE is defined as SE that lasts or recurs after 24 hours of adequate therapeutic coma. (Expert advice) Strong agreement.

R1.12 Subtle SE is the very late clinical expression of untreated or inadequately treated SE. Its diagnosis is based on the EEG. (Expert advice) Strong agreement.

R1.13 An EEG consistent with SE may be observed in a patient in coma in various clinical settings*. The analysis requires particular attention because it may sometimes result in very different management, particularly with regard to the appropriateness and strength of treatment. (Expert advice) Strong agreement.

*1) Comatose patient without convulsion after adequately managed convulsive SE; 2) paucisymptomatic convulsive SE; 3) EEG requested for coma in a patient developing motor symptoms suggestive of seizures; 4) Comatose patient without any manifestation suggestive of seizure with EEG showing SE.

2. Etiology

R2.1 The SE etiology needs to be identified quickly. If available, a specific treatment tailored to the etiology has to be started as soon as possible. This may help to control SE and to improve patient outcome. (Expert advice) Strong agreement.

R2.2 The search for etiology is guided by history, the presence or not of previous seizures, the type of seizures (focal or generalized), a complete physical examination, lab tests, EEG, brain imaging and sometimes CSF analysis. Several etiologies may be responsible for the same SE event. (Expert advice) Strong agreement.

R2.3 In the case of SE in a patient living with epilepsy, the main etiologies to think about are (except when a new acute brain lesion is suspected) (Table 2):

1. Related to anti-epileptic therapy (nonadherence, low levels, treatment interruption…)
2. Acute metabolic abnormalities
3. Systemic infection outside the central nervous system
4. Alcohol/drug withdrawal/poisoning
5. Progression of underlying disease

(Expert advice) Strong agreement.

Table 2: Most frequent adult SE etiologies [1,15,19,23,24]

SE in patients living with epilepsy	%
Anti-seizure drug-related (nonadherence, recent change or low levels)	16-35%
Known epilepsy without provoking factors (breakthrough seizures)	15%
Alcohol or benzodiazepine withdrawal	5-20%
Brain tumor	14%
Cerebrovascular disease (acute or remote)	8-14%
Toxic or metabolic	4-15%
Infection (outside CNS)	5-7%
Remote traumatic brain injury	5%
CNS infection	3%

De novo SE	%
Cerebrovascular disease (acute or remote)	32%
Brain tumor (including acute changes within tumor like bleeding,)	3-18%
Drug poisoning	5-20%
Unknown	5-10%
Alcohol or benzodiazepine withdrawal	6-10%
Toxic or metabolic	6-10%
CNS infection	5-9%
Acute traumatic brain injury	7%
Inflammatory diseases (incl. auto-immune)	6%
Infection (outside CNS)	2%
Neurodegenerative disease	2%

R2.4 In children and teenagers, alcohol/drug poisoning/withdrawal is less frequent. A febrile illness can trigger longer seizures and sometimes SE in children living with epilepsy. (Expert advice) Strong agreement.

R2.5 In the case of *de novo* SE (first ever seizure episode), an acute structural lesion (vascular, infectious, proliferative or inflammatory) needs to be ruled out. Metabolic or toxic causes should be explored too (Table 2). (Expert advice) Strong agreement.

R2.6 In children, *de novo* SE may be observed in the case of a febrile seizure lasting long enough to progress to SE. (Expert advice) Strong agreement.

R2.7 The following laboratory data should be recorded as soon as possible (from an etiological point of view): blood sugar, blood sodium, blood calcium, blood magnesium, antiseizure drug level. Other assays or CSF analysis may be performed in some specific situations. (Expert advice) Strong agreement.

R2.8 In the case of de novo SE, brain imaging should be performed quickly (MRI preferred if available or CT scan with venous sequences) as soon as the patient is stable enough most of the time. Brain imaging is mandatory in the case of lumbar puncture in the setting of SE. (Expert advice) Strong agreement.

R2.9 In a patient living with epilepsy, brain imaging indications are broad: traumatic brain injury, first episode of generalized convulsive SE, known brain disease that may progress, persistent consciousness disorders or confusion, headache, meningism, neurological examination changes (recent deficit), unexplained fever, known neoplasia, immunosuppression, … (Expert advice) Strong agreement.

R2.10 Brain imaging may be waived in patients who return to baseline, if the etiology or provoking factors in a patient known to have epilepsy are obvious and if brain imaging would have no therapeutic consequence. (Expert advice) Strong agreement.

R2.11 In the case of strongly suspected infectious meningoencephalitis, a tailored treatment (antibiotic and antiviral drugs) should be started immediately. Lumbar puncture should be done after brain imaging (if no contraindication) in all patients with suspected CNS infection or immunosuppressed patients, but should not, in any case, delay proper tailored treatment. (Expert advice) Strong agreement.

R2.12 Lumbar puncture should be performed if no etiology has been clearly identified after a first evaluation including history, usual laboratory tests and brain imaging. CSF analysis should be repeated in the case of:

1. Suspected encephalitis – CSF may be normal in the very early phase
2. Moderate isolated pleocytosis (< 25 cells/µL)
3. Etiological work-up (auto-immune – specific antibodies, neoplastic,…)

(Expert advice) Strong agreement.

R2.13 In the case of *de novo* refractory and super-refractory SE without a clear etiology, a comprehensive work-up should be performed as soon as possible, looking for immune (paraneoplastic or not) or infectious processes especially (Table 3). (Expert advice) Strong agreement.

R2.14 Because of multiple SE etiologies, including some that need to be rapidly addressed and treated, a diagnostic algorithm/tool may be recommended. (Expert advice) Strong agreement.

Table 3: Recommended work-up in blood and CSF in the case of adult refractory SE without clear etiology (table as comprehensive as possible – may be adapted according to clinical setting)

Group	Blood analysis	CSF
General	• Complete blood count • Blood sugar • Hepatic and kidney function • Na+, K+, Ca++, Mg++ • Anti-epileptic drug levels, if applicable	• Cell count, protein, oligoclonal bands • Gram stain • Cytology
Auto-immunity	• *Anti-neuronal antibodies (intracellular):* anti-Hu, Yo, Ri, CV2 (CRMP5), Ma2, amphiphysin, GAD65, PCA-2, Tr, SOX1, titin, recoverin → Adapt according to up-to-date laboratory tests • *Surface/synaptic neuronal antibody panel*: Anti-NMDAR, AMPAR, GABAbR, LGI-1, CASPR2, DPPX → Adapt according to up-to-date laboratory tests • *Systemic disease:* anti-nuclear antibodies (ANA/cytoplasmic), ANCA, rheumatoid factor, anti-SSA, anti-SSB, anti-phospholipid, anti-thyroid peroxidase (TPO) and thyroglobulin, anti-transglutaminase angiotensin-converting enzyme	• *Surface/synaptic antibody panel*: Anti-NMDAR, AMPAR, GABAbR, LGI-1, CASPR2, DPPX

Infectious	• Serology:
	  • *Viruses: HSV 1 and 2, VZV, CMV, EBV, HHV6, enterovirus, measles, rubella, influenza A and B, HIV, JCV, flavivirus, HCV*
	  • *Bacteria:* Lyme disease, syphilis, *Mycoplasma pneumoniae* (± PCR), *Chlamydia* (± PCR)
	  • Parasitosis; toxoplasmosis (± PCR), thick blood smear (malaria)
	  • Fungus: *Cryptococcus neoformans* antigen
	→ Adapt serology according to the patient's travel history: West Nile virus (V), Japanese encephalitis V, Saint Louis encephalitis V, eastern equine encephalomyelitis V, western equine encephalomyelitis V, malaria, etc.
		• PCR: HSV 1 and 2, VZV, CMV, EBV, HHV6, enterovirus, measles, rubella, *influenza* A and B, HIV, JCV
		• PCR: BK, *Listeria monocytogenes*
		Mycoplasma pneumoniae
		• Lyme disease antibodies
		• *Cryptococcus neoformans* antigen

Other	• Porphyria • Lactate, pyruvate ± mitochondrial disease (genetic): MELAS, MERRF and POLG1 • Heavy metals	Lactate/pyruvate (in the case of mitochondriopathy)

3. Management of generalized tonic-clonic status epilepticus

The experts proposed an algorithm (Annex 1), to guide management of generalized tonic-clonic SE. (Expert advice) Strong agreement.

3.1 Differential diagnosis

R3.1.1 Serial generalized tonic-clonic seizures are not within the framework of SE even if they can progress to generalized tonic-clonic SE. The management of this threat of generalized tonic-clonic SE has the same level of urgency and requires benzodiazepines and if needed one or more second-line antiepileptic drugs. (Expert advice) Strong agreement.

R3.1.2 Coma without motor signs after recognized GTCSE can be: secondary to the etiology of SE, the expression of SE that can be recognized only thanks to an EEG recording, or secondary to the administration of sedative drugs. An EEG recording is mandatory and urgent. (Expert advice) Strong agreement.

R3.1.3 Coma with moderate motor signs after recognized TCGSE suggestive of subtle SE calls for urgent electroencephalography. (Expert advice) Strong agreement.

R3.1.4 The eventuality of psychogenic non-epileptic seizures should systematically be considered throughout the management of GTCSE. (Expert advice) Strong agreement.

R3.1.5 In the case of anoxic-ischemic encephalopathy, myoclonia are sometimes of epileptic origin but rarely correspond to SE. (Expert advice) Strong agreement.

R3.1.6 Myoclonia with or without altered consciousness in the case of toxic or metabolic encephalopathies (renal failure, hepatic failure and so on) are most of the time not of epileptic origin. EEG recordings show encephalopathic features with typically triphasic waves.However, EEG recordings can sometimes be difficult to distinguish from SE in these cases. (Expert advice) Strong agreement.

R 3.1.7 Rigorous semiological analysis, context and sometimes EEG recordings will eliminate movement disorders associated with anti-NMDA receptor encephalitis, myoclonus in Creutzfeldt-Jakob disease, movements observed in some cases of brainstem stroke, dystonia, repetitive syncopes with myoclonus, thrills, tremor and so on. (Expert advice) Strong agreement.

R 3.1.8 Electroencephalography can show features that wrongly lead to a diagnosis of SE in comatose patients with brain lesions not preceded by convulsive manifestations. (Expert advice) Strong agreement.

3.2 Non-specific management

Apart from the etiology itself and differential diagnosis, several complementary clinically guided explorations should be carried out to evaluate the consequences of seizures (rhabdomyolysis, fractures, etc.), to control brain injuries, to assess the medical background, and to detect and treat intensive care-related complications. Only brain injury factors are detailed here. (Expert advice) Strong agreement.

R3.2.1 Starting from the prehospital management of a patient with GTCSE, it is necessary to prevent and control secondary brain injuries: hypotension, hypocapnia, hypoxemia, hypoglycemia, hyponatremia, hyperthermia, hypocalcemia, hyperoxia, substantial hypercapnia, some cases of arterial hypertension (for example, in the context of posterior reversible encephalopathy syndrome), rhythm or conduction disorder, hyperglycemia (Table 4). (Expert advice) Strong agreement.

R3.2.2 In this context, the recommended solution for adults is 0.9% saline, and for children an isotonic sugar solution supplemented with ions. (Expert advice) Strong agreement.

R3.2.3 Administration of thiamine 100 to 500 mg is necessary if vitamin B1 deficiency is suspected (chronic alcoholism, malnutrition, pregnancy, etc.) especially if a hypertonic glucose infusion is required to treat hypoglycemia. (Expert advice) Strong agreement.

Table 4: General parameters to monitor and correct during generalized tonic-clonic status epilepticus (GTCSE) in adults.

Parameters to monitor and correct	Target values	Means available
Blood oxygenation	SpO_2 95-99 % PaO_2 80-95 mmHg	- Patency of upper airways: Guedel cannula, tracheal suction, head positioning - Facial mask O_2 - Intubation with mechanical ventilation - Continuous SpO_2 monitoring
Hypo- or hypercapnia	$PaCO_2$ 35-45 mmHg if intracranial hypertension requiring intubation*	- Intubation with mechanical ventilation - Volume control mode - Continuous expired CO_2 monitoring
Mean blood pressure (MBP)	MBP 70-90 mmHg MBP $\geq$ 90 mmHg if intracranial hypertension*	- Moderate vascular filling - Catecholamines - Non-invasive or invasive blood pressure monitoring - Cardiac output monitoring if Tako-Tsubo (echocardiography)
Cardiac pulse	Risk of arrhythmias and conduction abnormalities	- Continuous electrocardiogram monitoring - Slow infusion of phenytoin (< 50 mg/min) or fosphenytoin (< 100 mg/min)
Blood glucose	1.4 – 1.8 g/L	- Measurement of blood glucose from initial care - Blood glucose monitoring during the whole care period - 30% glucose (50 mL) if hypoglycemia - Intravenous or subcutaneous insulin therapy if hyperglycemia according to a pre-established dose adjustment protocol
Blood sodium	135-145 mEq/L	- In the case of GTCSE caused by hyponatremia: correction of 1 to 2 mEq/L/h with 20% hypertonic saline until control of SE, without exceeding 8 mEq/L/day
Blood calcium	2.2-2.6 mEq/L	- In the case of GTCSE caused by hypocalcemia <1.6 mEq/L: correction with 10% calcium gluconate
pH	7.35 – 7.45	- Arterial blood gas analysis - Spontaneous correction of acidosis through seizure control in most cases - 1.4% Sodium bicarbonate in the case of very severe metabolic acidosis - Intubation with mechanical ventilation in the case of respiratory acidosis
Temperature	Normothermia (36.5 – 38 °C)	- Undress the patient - Paracetamol - If necessary (high fever): external cooling (cooling cover, ice packs on the vascular pathways) or internal cooling, with neuromuscular blockade (avoid shivering)

* context of acute severe brain injury, subarachnoid hemorrhage, stroke, and any cause of intracranial hypertension (ICH) or low cerebral blood flow.

R3.2.4 Intubation of a patient with GTCSE is indicated only in the case of sustained respiratory distress (beyond a few minutes of postcritical stertorous breathing) or in the event of failure of well-

conducted first- and second-line treatments (persistence of seizures). The etiology of SE may mandate intubation: severe brain injury, subarachnoid hemorrhage, severe intracranial hypertension (Table 5). (Expert advice) Strong agreement.

R3.2.5 It does not seem legitimate to intubate a patient with persistent coma after seizure cessation, as long as respiratory status is good and there is no evidence for acute brain injury (severe brain trauma, etc.). (Expert advice) Strong agreement.

Table 5: Indication and non-indication for tracheal intubation in generalized tonic-clonic status epilepticus (GTCSE)

Indications for intubation with mechanical ventilation	When intubation and mechanical ventilation are not required
- Acute respiratory failure - Context of acute severe brain injury* - GTCSE refractory to well-conducted first- and second-line treatments - Altered consciousness despite cessation of seizures, with poor respiratory status - Transportation at high risk	- GTC epileptic seizure with stertorous breathing - Incomplete first- or second-line antiepileptic treatments with good respiratory status - Deep and prolonged alteration of consciousness despite cessation of convulsions, with good respiratory status

* context of acute severe brain injury, subarachnoid hemorrhage, stroke, and any cause of intracranial hypertension (ICH) or low cerebral blood flow.

3.3 Specific management

R3.3.1 Benzodiazepines have to be used as first-line treatment. (Grade 1+) Strong agreement.

R3.3.2 An intravenous (IV) injection of 0.015 mg/kg clonazepam (1 mg /70 kg; maximum 1.5 mg), or an intramuscular (IM) injection of 0.15 mg/kg midazolam (10 mg/70 kg) should probably be used. (Grade 2+) Strong agreement.

R3.3.3 In adults, in the absence of intravenous lines, IM midazolam should be used (0.15 mg/kg, 10 mg/70 kg). (Grade 1+) Strong agreement.

R3.3.4 In adults, in the absence of intravenous lines, intrarectal (IR) administration of 0.5 mg/kg diazepam (maximum 10 mg) or intrabuccal administration of 0.3 mg/kg midazolam (maximum 10 mg) is recommended. (Expert advice) Strong agreement.

R3.3.5 A benzodiazepine injection should be probably repeated if after 5 minutes following the first injection the GTCSE persists. If the patient shows respiratory impairment, it seems more reasonable to administer only a half dose at this step. (Grade 2+) Strong agreement.

R3.3.6 If after 5 minutes following the second injection the GTCSE persists, a second-line compound should be administered IV. (Grade 1+) Strong agreement.

R3.3.7 In adults (according to etiology, previous treatments, laboratory findings, familiarity of the prescribing physician) the following IV options exist:

1. Sodium valproate: 40 mg/kg in 10-15 minutes, maximum 3 g (another compound should be used in women of childbearing age);

2. Fosphenytoin (20 mg/kg phenytoin equivalent, maximally at 100-150 mg/min) or phenytoin (20 mg/kg, maximally at 50 mg/min or, if >65 years: 15 mg/kg and slow drip), with cardiac rhythm monitoring; contraindicated if arrhythmia or conduction disturbances are present, with caution if there is known previous cardiac disorder;
3. Phenobarbital: 15 mg/kg, at 50-100 mg/min, more sedative;
4. Levetiracetam: 30-60 mg/kg over 10 minutes, maximum 4 g

The full prescribed dose should be administered, even if convulsions stop. (Grade 2+) Strong agreement.

R3.3.8 Two particularities in children:

1. Sodium valproate is relatively infrequently used and should be avoided if the etiology is unknown, as it may worsen an underlying metabolic disorder;
2. As fosphenytoin kinetics are poorly understood in the under-5s, phenytoin should be preferred.

(Expert advice) Strong agreement.

R3.3.9 If the GTCSE is controlled, in an awake patient, and if the underlying etiology is not immediately reversible, a follow-up antiepileptic treatment, initially associated with clonazepam or clobazam, should be immediately considered. (Expert advice) Strong agreement.

R3.3.10 If convulsions persist 30 minutes after administration of the second-line treatment, refractory GTCSE is diagnosed. At this stage, a coma should be rapidly induced with a third-line general anesthetic. (Grade 2+) Strong agreement.

R3.3.11 In adults, it is possible to delay coma induction using a further second-line agent, if the patient has known epilepsy and lacks any signs/symptoms of a severe brain injury. This approach is recommended if there are limitations to the treatment strategy (e.g., no mechanical ventilation and only comfort care). (Expert advice) Strong agreement.

R3.3.12 In children with refractory GTCSE, an additional second-line agent is most often administered before coma induction. (Expert advice) Strong agreement.

R3.3.13 During anesthetic treatment of GTC SE, cessation of electrographic seizures or burst suppression over at least 24 hours should probably be targeted, before stepwise reduction of sedation over 6 hours with EEG monitoring. (Expert advice) Strong agreement.

R3.3.14 In the case of a super-refractory GTCSE, habitually used general anesthetics (midazolam or propofol) are resumed. If finally the SE is controlled (ideally with continuous electroencephalography monitoring), general anesthetics should be continued for an additional 24 hours, before stepwise reduction. If, on the contrary, GTCSE is still treatment-resistant, ketamine should probably be used (bolus of 1-3 mg/kg, then 0.5 -5 mg/kg/h) with a benzodiazepine. Thiopental is another possibility. If this also proves unsuccessful, general anesthesia should be resumed together with other options, such as further antiepileptic drugs, ketogenic diet, immunological treatment including steroids. (Expert advice) Strong agreement.

R3.3.15 In the case of refractory or super-refractory SE, it is mandatory to administer a second-line agent that will serve as underlying antiepileptic treatment. (Expert advice) Strong agreement.

R3.3.16 If motor manifestations cease spontaneously, it is not recommended to administer an antiepileptic treatment straight away, regardless of whether or not the patient is in a coma. (Expert advice) Strong agreement.

R3.3.17 After treatment of GTCSE, a persistent coma should not prompt an increase in treatment, unless the EEG shows ongoing SE. (Expert advice) Strong agreement.

R3.3.18 In a comatose patient presenting signs suggestive of subtle SE (R1.12.), benzodiazepines or even a second-line treatment may be justified, at least pending electroencephalography. (Expert advice) Strong agreement.

R3.3.19 If a patient is admitted to an intensive care unit and is mechanically ventilated and sedated for reasons other than GTCSE, with no convulsions under certain conditions* it seems reasonable to consider weaning of sedation. (Expert advice) Strong agreement.

*1 intubation for respiratory insufficiency, coma, poorly characterized motor symptoms;
2 intubation for transportation;
3 known etiology compatible with sedation weaning;
4 lack of severe complications (such as respiratory impairment).

R3.3.20 The ideal treatment strategy in patients with non-convulsive SE during coma (diagnosed only on EEG) is not evidence-based. It seems reasonable to consider a first- or second-line agent with continuous electroencephalography. Institution of general anesthetics should follow only after a specialist's advice. Looking for the underlying cause is mandatory. (Expert advice) Strong agreement.

3.4 Role of electroencephalography

R3.4.1 Electroencephalography should be rapidly available in any hospital managing patients with SE. (Expert advice) Strong agreement.

R3.4.2 Electroencephalography should be performed as soon as possible in the case of (i) no improvement in consciousness after cessation of convulsions, (ii) suspected psychogenic non-epileptic seizures, metabolic/toxic encephalopathy, subtle or refractory status. (Expert advice) Strong agreement.

R3.4.3 In SE in comatose patients, epileptic activity is defined by rhythmical activity unresponsive to stimulation, often showing spatial and temporal dynamics. This activity is continuous or repetitive without background activity. Recently, the Salzburg criteria have been proposed to assist in the diagnosis of SE in comatose patients. (Expert advice) Strong agreement.

R3.4.4 Electroencephalography may help to diagnose certain causes of SE (herpes simplex encephalitis, anti-NMDA receptor encephalitis, etc.) and to define sedation management. (Expert advice) Strong agreement.

R3.4.5 Video-electroencephalography with recording of muscular activity helps to diagnose psychogenic non-epileptic seizures. Interpretation of EEG is difficult during motor manifestations because of the artifacts, but the EEG is normal between motor manifestations. (Expert advice) Strong agreement.

R3.4.6 Collaboration between emergency physicians and neurophysiologists should be strongly encouraged, ideally 24 hours a day, given the difficulty of correctly interpreting the EEG in intensive care. In particular, encephalopathy should not be misdiagnosed as SE. (Expert advice) Strong agreement.

R3.4.7 After recovery of consciousness following GTCSE, a standard EEG (at least 20 minutes) should be rapidly recorded. (Expert advice) Strong agreement.

R3.4.8 Continuous electroencephalography monitoring (at least 24 hours) should be performed as far as possible: for the management of refractory GTCSE; if there is no recovery of consciousness one hour after the cessation of convulsions; if standard electroencephalography indicates a subtle status; in the case of new seizures. (Expert advice) Strong agreement.

R3.4.9. In GTCSE, if continuous electroencephalography monitoring is not available, a monitor including fewer electrodes (at least four, at best nine electrodes, four on each side and one middle center electrode) can be used. However, a standard EEG should be recorded as soon as possible. (Expert advice) Strong agreement.

R3.4.10 Bispectral index must not be used for the management of SE. (Expert advice) Strong agreement.

3.5 Orientation – pathway

R3.5.1 Admission to intensive care unit is required in the following cases: persistence of generalized convulsive SE; prolonged coma after seizure cessation; respiratory or other vital distress. (Expert advice) Strong agreement.

R3.5.2 In the case of rapid recovery of consciousness, in the absence of other organ failure, the patient can be referred to the emergency department. (Expert advice) Strong agreement.

R3.5.3 In the case of serial repeated tonic-clonic seizures, admission to intensive care unit is required in the following cases: persistence of seizures after administration of benzodiazepines and at least one second-line antiepileptic drug; alteration of consciousness between seizures; respiratory or other vital distress. (Expert advice) Strong agreement.

R3.5.4 If brain imaging is indicated in the etiological work-up of SE (cf. 2.8 and 2.9 recommendations), it should be done as soon as possible, ideally before admission to intensive care or to a step down unit. Imaging does not justify the use of mechanical ventilation in the pre-hospital setting. (Expert advice) Strong agreement.

R3.5.5 Management of SE and interpretation of the EEG requires specialized expertise in the following cases: super-refractory SE; nonconvulsive SE diagnosed from the EEG (without any convulsion before or during management). In the absence of an electrophysiology team in the hospital, the EEG should at least be addressed to a specialized team. In the absence of video-electroencephalography monitoring, the transfer of the patient to a specialized intensive care unit should be discussed. (Expert advice) Strong agreement.

R3.5.6 After cessation of SE, the patient should be transferred if possible to the neurology department, if not to the medicine department. After discharge, follow-up with a neurologist should be systematically organized. (Expert advice) Strong agreement.

4. Management of other types of status epilepticus

4.1 Differential diagnosis

R 4.1.1 In the case of focal motor, myoclonic or tonic SE, it is right to eliminate:

- Tremor, myoclonia, chorea, dystonia, dyskinesia, muscular or pyramidal spasms, limb shaking. Movement disorders may be associated with anti-NMDA receptor encephalitis, Creutzfeldt-Jakob disease, some cases of brainstem stroke, dystonia, repetitive syncopes.
- Psychogenic movement disorders and even sometimes common thrills.

(Expert advice) Strong agreement.

R 4.1.2 Numerous non-epileptic movements can be removed or attenuated by benzodiazepine or antiepileptic drug injection. (Expert advice) Strong agreement.

R 4.1.3 In the case of SE without predominant motor manifestations, with or without a confusional state, various symptoms (auditory, visual, paresthesic, aphasic, olfactory, gustatory, psychic, autonomic, behavioral, with or without automatisms and so on) can point to consideration of numerous diagnoses, especially a migraine attack, transient ischemic attack, and psychiatric disorders. (Expert advice) Strong agreement.

R 4.1.4: Semiological analysis, video-electroencephalography and brain MRI will provide evidence in favor of an epileptic origin. (Expert advice) Strong agreement.

4.2 Role of electroencephalography

R4.2.1 Electroencephalography should be performed as soon as possible in the case of a confusional state of unclear origin or which continues after an epileptic seizure, in order to exclude generalized or focal non-convulsive SE. (Expert advice) Strong agreement.

R4.2.2 Electroencephalography is needed in the case of various central nervous system manifestations of sudden onset if the origin is not identified or if the etiology indicates a potential to develop SE. (Expert advice) Strong agreement.

R4.2.3 Electroencephalography is mandatory for the diagnosis and classification of non-convulsive SE. It shows rhythmic continuous or recurrent paroxysmal activities that are unresponsive to different stimuli. In generalized SE, these activities are bilateral and often predominate over the anterior regions. In focal SE, these activities are focal or asymmetrical. Recently published criteria (from Salzburg) are available for the diagnosis of non-convulsive SE. (Expert advice) Strong agreement.

R4.2.4 For absence SE and non-convulsive focal SE, the rapid normalization (few seconds or minutes) of the EEG after IV benzodiazepines confirms the diagnosis of non-convulsive SE if there is a marked clinical improvement. A negative result of this test does not discount the diagnosis. (Expert advice) Strong agreement.

R4.2.5 Continuous video-electroencephalography monitoring should be considered in refractory SE, especially in non-convulsive SE. (Expert advice) Strong agreement.

R4.2.6 Continuous video-electroencephalography monitoring should be considered in the assessment of some encephalopathies or encephalitis to detect epileptic seizures or discrete SE. (Expert advice) Strong agreement.

4.3 Specific management

R4.3.1 A benzodiazepine should probably be used as first-line treatment. The following can be used:

1. Clonazepam, with a protocol similar to that for convulsive SE.
2. Intrabuccal midazolam (10 mg for adults).
3. Diazepam (intrarectal administration at 0.3 to 0.5 mg/kg, but not more than 10 mg) is also an option in children.

(Expert advice) Strong agreement.

R4.3.2 Second-line drug treatment is different from GTCSE. Various antiepileptic treatments may be used, as soon as possible, based on the advice of a neurologist, without the same level of emergency as in the treatment of the GTCSE. (Expert advice) Strong agreement.

R4.3.3 The interval between each new line of treatment will depend on the type of SE, its clinical consequences, its progression, underlying etiology, the patient's history, previous treatments, pharmacokinetics of the drugs and the associated prognosis. (Expert advice) Strong agreement.

R4.3.4 Second-line antiepileptic drugs are numerous for adults, with respect to precautions for use (3.3.7):

1. Intravenous drugs are: (fos)phenytoin, sodium valproate, levetiracetam, lacosamide, phenobarbital. Unlike GTCSE, which requires fast infusion, the infusion rate of the drugs can be slowed and the dose reduced, to be adapted to the patient's history and clinical semiology.
2. Available drugs given orally or administered by a gastric tube (in the case of disorders of consciousness or swallowing difficulties) can be used if the previous available intravenous drugs are contraindicated, or if no intravenous route is available, or if no monitoring is available in the ongoing care unit: carbamazepine (except in Asian patients because of a high risk of cutaneous allergy), phenytoin, perampanel, zonisamide, topiramate, pregabalin, phenobarbital. (Expert advice) Strong agreement.

R4.3.5 In children, intravenous phenytoin, phenobarbital and levitacetam can be used; fosphenytoin is used after the age of 5 years. Valproate should be avoided if the etiology of SE is not identified, because of possible worsening in the case of metabolic diseases. Phenytoin, zonisamide, perampanel, topiramate and phenobarbital are available orally and might also be administered by gastric tube. (Expert advice) Strong agreement.

R4.3.6 Anesthetic drugs requiring intubation and mechanical ventilation should be very rarely used because the risks of such therapy are usually greater than their benefits. (Expert advice) Strong agreement.

R4.3.7 Specific therapeutic strategies should be followed for a large number of types of SE:

1.In focal motor SE, the reinforcement of therapies should be gradual: antiepileptic drugs can be administered intravenously or orally, as second-line treatment. In the case of secondary

generalized SE, the management should be that of GTCSE. Epilepsia partialis continua is a particular form of focal SE that is not associated with generalization and is pharmacoresistant: in this case, the interval between the therapy lines can be prolonged and anesthetic drugs and transfer to intensive care are not necessary.

2. Absence SE, occurring during the course of idiopathic generalized epilepsy, often showing few myoclonia, can be related to the interruption of a treatment or the introduction of an inappropriate antiepileptic drug (for example, carbamazepine, gabapentine, etc). Benzodiazepine should be used first, then the previous antiepileptic drug should be reintroduced. If the SE continues, intravenous sodium valproate can be used, according to the precautions for use, and after expert advice in children.

3. In the *de novo* absence SE after sudden withdrawal of a benzodiazepine in elderly patients, the reintroduction of a benzodiazepine is usually sufficient.

4. In nonconvulsive SE with confusion, from the frontal or temporal lobe, therapy adapted to the etiology should be considered first. Intravenous second-line treatment can be (fos)phenytoin, lacosamide, levetiracetam, and potentially phenobarbital. If a mitochondrial disease is suspected, sodium valproate should be avoided.

5. In myoclonic SE without alteration of consciousness during the course of generalized idiopathic epilepsy, benzodiazepines are effective.

6. In tonic SE, during the course of Lennox-Gastaut syndrome, benzodiazepines should be avoided, because their sedative effect can increase the tonic seizures. Infection should be carefully sought. (Expert advice) Strong agreement.

4.4 Orientation- Pathway

R4.4.1 Admission to intensive care unit for patients with motor focal SE (simple motor partial, myoclonic or tonic SE) is required in the case of impaired consciousness (secondary generalization, altered consciousness linked to the etiology or therapeutics) or any other vital distress. (Expert advice) Strong agreement.

R4.4.2

The decision to transfer to intensive care unit a patient with SE without predominant motor manifestations, with or without confusional state, can be based on the underlying situation:

- If the chosen antiepileptic drug requires medical monitoring (use of fosphenytoin with cardiac rhythm monitoring)
- In the case of altered consciousness
- If the underlying etiology suggests possible worsening
- If generalized convulsion occurs
- If other organ dysfunction occurs

(Expert advice) Strong agreement.

R4.4.3 The patient should preferentially be transferred to the neurology department, if not to the medicine department. The decision to discharge the patient or to transfer the patient to another department should be taken after neurological assessment. The decision is based on the etiology of the epilepsy, the notion of controlled epilepsy, the underlying situation and comorbidities, but also on the own organization of the care establishment. After discharge, follow-up by a neurologist should be systematically organized. (Expert advice) Strong agreement.

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and material: Not applicable.

Competing interests: The authors declare the following competing interests: SA : EISAI, Nutricia, Shire, UCB Pharma ; AC: EISAI, UCB Pharma ; SDu : EISAI, UCB Pharma, Advicenne, Novartis ; PG:EISAI; VN: EISAI, UCB Pharma, LivaNova ; WS: EISAI, UCB Pharma. The remaining authors declare no competing interests.

Funding: This work was financially supported by the French Intensive Care Society (SRLF) and the French Society of Emergency Medicine (SFMU).

Acknowledgements: Guidelines reviewed and endorsed by the SRLF and SFMU boards

Authors' information :

Hervé Outin, Service de réanimation médico-chirurgicale, Centre hospitalier (CH) intercommunal de Poissy - Saint-Germain en Laye

Papa Gueye, SAMU, CHU de la Martinique, Fort-de-France

Bernard Clair, CHU Poincaré, Paris

Sophie Demeret, CHU de la Pitié-Salpétrière, Paris

Nicolas Engrand, Fondation Rothschild, Paris

Francesco Santoli, CH Aulnay-sous-Bois

Romain Sonneville, CHU Bichat, Paris

Jean-Christophe Engels, Service départemental d'incendie et de secours, Haute-Savoie

Yonathan Freund, CHU de la Pitié-Salpétrière, Paris

Marie Girot, CH régional universitaire de Lille

Luigi Titomanlio, CHU Robert Debré, Paris

Stéphane Auvin, CHU Debré, Paris

Marie-Odile Marcoux, CHU de Toulouse

Frédéric Villega, CHU de Bordeaux

Vincent Alvarez, Hôpital du Valais, Sion et CH vaudois, Lausanne

Andrea Rossetti, Hôpital du Valais, Sion et CH vaudois, Lausanne

Philippe Convers, CHU de Saint-Etienne

Arielle Crespel, CHU de Montpellier

Philippe Gelisse, CHU de Montpellier

Sophie Dupont, CHU de la Pitié-Salpétrière, Paris
Vincent Navarro, CHU de la Pitié-Salpétrière, Paris
William Szurhaj, CHU de Lille
Pierre Thomas, CHU de Nice
Hugues Lefort, Structure des Urgences, Hôpital d'instruction des armées Legouest, Metz
Vincent Peigne, service de réanimation, CH Métropole-Savoie, Chambéry

Annex 1: See attached file

References

1. Betjemann JP, Lowenstein DH. Status epilepticus in adults. Lancet Neurol. Elsevier Ltd; 2015;14:615.624.

2. Hocker S. Systemic complications of status epilepticus--An update. Epilepsy Behav EB. 2015;49:83–7.

3. Rossetti AO, Logroscino G, Bromfield EB. A clinical score for prognosis of status epilepticus in adults. Neurology. 2006;66:1736–8.

4. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924–6

5. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004;328(7454):1490.