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Non convulsive status epilepticus in the elderly

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Abstract

There is a higher incidence of status epilepticus in the older adult population that commonly presents as nonconvulsive status epilepticus (NCSE). NCSE most often corresponds to prolonged focal seizures with impaired consciousness with three main clinical presentations: *i*) an unexplained acute confusional state, *ii*) subtle eye, motor or behavioral signs or mood changes and *iii*) typical temporal or frontal seizures with impaired consciousness. Focal seizures without impaired consciousness or de novo absence status of late onset may also be met. The identified risk factors for NCSE onset are: a precession by a generalized tonic-clonic seizure, a known history of epilepsy, female gender, and an acute symptomatic cause or a known brain injury (especially a stroke sequelae). Diagnosis in this population may be difficult, as the clinical presentation is often not very suggestive (stupor, confusion, even coma), and requires an unrestricted use of EEG with an EEG diagnosis based on the EEG with now accepted criteria (so-called Salzburg EEG criteria).

The treatment is based first on the injection of benzodiazepines and in the second line on intravenous or oral or gastric tube administration of antiepileptic drugs. It is not recommended to resort to an intubation-ventilation (except necessary to treat respiratory distress, multi-organ failure ...). Prognosis is poor with about 30% mortality.

Key words: non convulsive status epilepticus, elderly, confusion, EEG, stroke

Abbreviations: NCSE = nonconvulsive status epilepticus, SE = status epilepticus, EEG= electroencephalogram, AED =antiepileptic drug, IV= intravenous, GPDs = Generalized periodic discharges, LPDs = lateralized periodic discharges, ICU = intensive care unit, SC = subcutaneous

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Epilepsy in the elderly offers the paradox of being both common and under-diagnosed. The potential atypical clinical presentation of seizures in elderly subjects partly account for the diagnostic difficulties. In the foreground of these atypical presentations, we will note the high prevalence of non-convulsive status epilepticus that often represents a diagnostic challenge.

1. Non-convulsive status epilepticus: epidemiology

Non-convulsive status epilepticus (NCSE) is particularly relevant for older patients [1] and thus should be systematically considered as a cause of unexplained coma or persistent confusional state even when there is no previous seizure history.

Taking into account both convulsive and non-convulsive status epilepticus (SE), the global incidence is 26.2 per 100,000 in the elderly population versus 5.2 per 100,000 in the younger population [2].

The specific incidence of NCSE in the global population is difficult to estimate because of its sometimes fuzzy diagnostic criteria. According to epidemiological studies, it would oscillate from 5.6 to 18.3 per 100,000, but could be greatly undervalued [3]. If we consider that NCSE could account for 25 to 50% of the whole status epilepticus cohort [4], the incidence of NCSE in the elderly could thus be estimated at a high range of 14 per 100,000.

Studies have shown that 32% of epilepsies beginning in the elderly presented as status epilepticus or as cluster seizures [5] and that 30% of acute seizures in elderly people manifested with status epilepticus [6,7].

When looking specifically at NCSE in the elderly hospitalized in an emergency department or in a gerontological intensive care unit, studies revealed that they represent 16% of the causes of confusion without a specific etiology [8] and 8% of unexplained coma causes [9].

2. NCSE: definitions and classifications

The International League against Epilepsy [10] recommend to classify SE according to the presence or absence of prominent motor symptoms and the degree (qualitative or quantitative) of impaired consciousness.

NCSE corresponds to status epilepticus without prominent motor symptoms and may be classified as:

- NCSE with coma (including so-called “subtle” SE)
- NCSE without coma:
 - Generalized
 - Typical absence status (non relevant in elderly)
 - Atypical absence status
 - Myoclonic absence status
 - Focal
 - Without impairment of consciousness (aura continua, with autonomic, sensory, visual, olfactory, gustatory, emotional/psychic/experiential, or auditory symptoms)
 - Aphasic status
 - With impaired consciousness
 - Unknown whether focal or generalized
 - Autonomic SE

NCSE in the elderly most often correspond to prolonged focal (temporal or frontal) seizures with impaired consciousness ("complex partial status epilepticus"). Coma may be the ultimate manifestation of undiagnosed status epilepticus. Focal NCSE without impaired consciousness are less frequent than in the younger population. A form of NCSE called “de novo absence status of late onset” much rarer, can also meet.

The delay to speak of status and no longer of seizure is 10 minutes for focal SE with impaired consciousness, 30 minutes for focal SE without impaired consciousness. Recurrent seizures between which there is incomplete recovery of consciousness may also define SE with the same timescale.

3. NCSE: clinical presentation

3.1 Focal NCSE with impaired consciousness

Clinical manifestations of focal NCSE range from confusion to coma but may be more discreet: slight impairment of lucidity, unusual behavior, sometimes associated with minimal motor manifestations such as focal myoclonus or clonia. In all cases, the certainty diagnosis will be based on the EEG.

Three main clinical presentations may be met:

- Unexplained confusion
- Atypical subtle manifestations
- Typical manifestations

3.1.1 Unexplained confusion

Overall confusion is a very frequent reason for consultation in the elderly, with 14 to 56% of elderly patients presenting to the emergency department [11]. Acute confusional state (i.e. delirium) may be an ictal or postictal symptom in various epilepsy syndromes. Specifically, in elderly, ictal confusion is a frequent manifestation of NCSE [12].

A 1-year prospective study was conducted in patients aged 60 years or older, for whom EEG was requested because of confusion considered to be of unknown origin after initial complete standard investigations [13]. This study found that 16% of patients had in fact NCSE. In this study, lack of response to simple commands and a rapid onset of the symptoms, when

associated, had good sensitivity and specificity for NCSE. In another study [12], patterns compatible with NCSE were found in 28% of the elderly patients with delirium when continuous EEG monitoring was performed in the first 24 h after admission to the emergency room.

Even though NCSE is a recognized cause of acute confusional state, a large proportion of cases have either a diagnostic delay or go undiagnosed due to confounding factors:

- confusion due to the fact that NCSE may have a fluctuating pattern that is difficult to distinguish from other causes of delirium [14]: it can present as episodes of reduced cognitive ability with periods of near-normal functioning between [15].
- associated signs, if any, may be very subtle and unnoticed (see chapter below)

To help NCSE diagnosis, a suggested practical approach in confused older people was proposed by Woodford et al. [14] (figure 1).

3.1.2 Atypical subtle manifestations

Some clinical manifestations must alert and make suspect a diagnosis of NCSE [16]:

- subtle eye signs such as blinking, eye deviation, eyelid myoclonia or nystagmus in a stuporous patient
- subtle motor signs such as twitching, focused myoclonia (perioral or of the extremities)
- behavioral signs such as agitation, lethargy, speech problems, delusional disorders, inappropriate laughter, and crying [17]
- mood changes [12]
- “stroke plus” presentation: elderly patient with a proven stroke who is worsening or recovering less quickly than expected.

3.1.3 Typical manifestations

The NCSE diagnosis will of course be easier in the presence of:

- signs commonly encountered in focal seizures: gestural automatism, orolimentary automatisms, eye deflection, chewing
- secondarily generalized seizures
- identified risk factors of NCSE [14]:
 - precession by a generalized tonic-clonic seizure
 - known history of epilepsy: preexisting epilepsy is a risk factor for overall SE, including NCSE [18,19]
 - female sex: preponderance among female patients has been consistently reported in the literature. Studies reporting NCSE series observed 65% to 71% women [20,21].
 - An acute symptomatic cause (mainly stroke) or a known brain injury (mainly stroke sequelae): stroke is overall the most common etiology of new onset seizures in the elderly, followed by dementia, metabolic disorders, psychiatric disorders, and systemic infection [20]

3.2 Focal NCSE without impaired consciousness

Focal NCSE without impaired consciousness may manifest as a disturbance of language (without confusion or stupor) termed aphasic status epilepticus. This can appear quite similar to the new-onset aphasia from a stroke [11]. Epileptiform discharges are usually located in the Broca or the Wernicke regions. In a study that addressed clinical features associated with a diagnosis of NCSE in confused older people, aphasia was present in 26% of patients [14].

Mood disturbances with affective disinhibition or affective indifference with subtle impairment of cognitive functions without overt confusion were also described in NCSE of frontal origin [22].

Prolonged focal seizures from sensory or association areas of the brain may constitute other less frequent forms of NCSE [16].

3.3 NCSE with coma

From a clinical standpoint, comatose NCSE represents deep coma of various etiologies without any clinical motor signs of status epilepticus but with characteristic epileptiform EEG pattern [23]. Coma is defined here as unarousable psychologic unresponsiveness in which the subject lies with eyes closed [24].

Comatose NCSE may be divided into:

- subtle SE: ultimate evolution of a convulsive generalized status epilepticus insufficiently treated with an electroclinical dissociation between decreasing motor phenomena and ongoing ictal EEG activity [25]
- deeply comatose patients with epileptiform EEG discharges where the coma may be linked to the NCSE underlying etiology, and/or the functional impairment caused (or reflected) by the ictal discharges [23]

Severe metabolic or anoxic encephalopathies with continuous epileptiform EEG abnormalities and encephalopathies with triphasic waves are excluded from the definition of NCSE with coma [26,27].

In all cases, EEG is required to the diagnosis of comatose NCSE [23]

3.4 De novo absence status of late onset

De novo absence status of late onset was first described by Thomas et al. [28]. It occurs in elderly patients who have abruptly stopped their anxiolytic or sedative treatment. Associated precipitating factors such as the excessive use of psychotropic drugs, a history of chronic alcoholism or a metabolic disorder (hypocalcemia, hyponatremia) are often found.

Typically, de novo absence status of late onset occurs in patients over 50 years old with no history of epilepsy. The clinical and electroencephalographic presentation resembles that of absence status of subjects with idiopathic epilepsy: confusion, impaired lucidity and generalized spike-wave discharges on the EEG. All episodes are resolutive, without recurrence, after intravenous benzodiazepine injection and resumption of interrupted treatment. Long-term antiepileptic therapy is not necessary.

4. NCSE: medical check up

Once the diagnosis of NCSE is made, the etiological assessment should be conducted. It will differ according to whether there is a known antecedent of epilepsy (one will then suspect priority of a lack of observance) or not. In any case, it will be guided by the clinical examination and the context [14].

We will seek in priority:

- By patient and / or family history: benzodiazepine or alcohol withdrawal, the recent introduction of a drug known to promote seizures (tramadol, quinolones, theophylline, baclofen, ...), a predisposing disease for epilepsy (Alzheimer's disease, history of stroke)
- By blood tests: an ionic or metabolic disorder (e.g., hypoglycemia, hypoxia, hyponatremia, hypocalcemia and hypomagnesemia), a drug overdose, an

inflammatory syndrome revealing an underlying infection, an infection (serology, blood cultures ...)

- By neuroimaging: an acute or remote lesion (stroke, subdural hematoma, tumor,)

More specific examinations (lumbar puncture in particular) will depend on the clinical context: fever, meningeal syndrome, cancer and hematological diseases.

In patients with a history of seizures, NCSE is often precipitated by antiepileptic drug (AED) change or non-adherence.

5. NCSE: differential diagnosis

The main differential diagnoses to consider are:

- The other causes of acute delirium
- Toxic or metabolic encephalopathies: epidemiological data suggest that encephalopathy correlates with age, the number of patients with encephalopathy increasing after the age of 65 years. People older than 75 years, who reside in nursing homes have a 60% chance of developing encephalopathy, whereas encephalopathy occurs in 10–40% of hospitalized patients older than 65 years [29].
- Psychiatric disorders
- Pseudo status epilepticus: older patients over 55 years represent about 10% of all cases of psychogenic non-epileptic seizures (PNES). Elderly patients do not demonstrate significant differences in clinical semiology as compared to younger patients. As in young patients, ictal eye closure is a reliable clinical feature for differentiating pseudo-SE from SE [30]. Conversely, when compared with younger patients exhibiting PNES, older patients are less likely associated with antecedent sexual abuse, and more likely to have multiple comorbidities and to health-related traumatic experiences [31].

- Misinterpretation of the electroencephalogram including periodic lateralized epileptiform discharges, bilateral periodic epileptiform and triphasic waves [32,33]

6. NCSE : EEG

NCSE is a challenging neurological emergency and its diagnosis cannot be established without EEG confirmation. The EEG shows paroxysmal rhythmic activities that are not reactive to different stimuli. In generalized NCSE, these activities are bilateral and often predominate in the anterior region. In focal NCSE, these activities are focal, or asymmetric, or more or less diffuse. Figures 2 and 3 show EEG samples of NCSE. Salzburg criteria assist in EEG diagnosis.

6.1 Salzburg criteria

In 2013, an expert panel provided unified EEG terminology and criteria for the diagnosis of NCSE (the so-called Salzburg criteria). It was refined by implementing the American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology and modified Salzburg criteria were proposed as follow [32-35]. Epileptiform discharges include spikes, polyspikes, sharp-waves, and sharp-and-slow-wave complexes.

6.1.1 Patients without known epileptic encephalopathy

EEG criteria for the diagnosis of NCSE are:

1. Repetitive epileptiform discharges at >2.5 Hz, or
2. Epileptiform discharges ≤ 2.5 Hz or rhythmic delta/theta activity (>0.5 Hz) including one of the additional criteria:
 - a. Clinical improvement after intravenous (IV) anti-epileptic drugs (AEDs), with improvement in EEG reactivity, and appearance of EEG background.
 - b. Focal ictal symptoms during the patterns (e.g. facial twitching, nystagmus,

myoclonus)

c. Spatiotemporal evolution.

Reactivity to IV AED occurs within 10 min after the AED is fully applied. The normalization of the EEG within seconds or minutes after the intravenous injection of AED only asserts the diagnosis if there is a significant clinical improvement in the confusional state. Clinical improvement is defined as better performance in one of five domains: *i*) “say your surname”, *ii*) “repeat 1,2,3”, *iii*) “raise your arms” (first say, if no response demonstrate), *iv*) patient opens eyes to *i-iii*, and *v*) patient looks at the examiner in response to *i-iii*. If no response, the procedure must be repeated after strong tactile stimuli on both sides of the body. EEG improvement is defined as reduction of epileptiform discharges, i.e., 1–9% of epoch. If EEG improvement occurs without clinical improvement, then it is considered as “possible” NCSE. The negativity of this AED test does not eliminate the diagnosis [36]. Spatiotemporal evolution means incrementing onset (increase in voltage, with increase or decrease in frequency), pattern evolution (increase or decrease in frequency >1 Hz or location), decrementing termination (voltage or frequency) or post-periodic epileptiform discharges with background slowing or attenuation.

6.1.2 Patients with known epileptic encephalopathy

EEG criteria for the diagnosis of NCSE are:

1. Frequent or continuous generalized spike-wave discharges, which show an increase in profusion or frequency when compared to baseline EEG with observed change in clinical state.
2. Improvement in clinical or EEG features with IV AEDs. If only EEG improvement without clinical improvement again this is best considered possible NCSE.

6.2 Coma patterns

In comatose patients, classical coma patterns such as diffuse polymorphic delta activity, spindle coma, alpha/theta coma, low output voltage, or burst suppression do not reflect NCSE. On the opposite, any ictal patterns with a typical spatiotemporal evolution or epileptiform discharges faster than 2.5 Hz in a comatose patient reflect nonconvulsive seizures or NCSE and should be treated. Generalized periodic discharges or lateralized periodic discharges (GPDs/LPDs) with a frequency of less than 2.5 Hz or rhythmic discharges faster than 0.5 Hz are the borderland of NCSE in coma. In these cases, at least one of the additional criteria is needed to diagnose NCSE: *a)* subtle clinical ictal phenomena, *b)* typical spatiotemporal evolution, or *c)* response to AED treatment [25].

There is currently no consensus about how long these patterns must be present to qualify for NCSE.

6.3 Continuous EEG monitoring

Continuous EEG monitoring (ideally coupled with the video) appears more relevant to diagnose NCSE than standard 20-minute EEG. This is particularly true in elderly patients with acute stroke in whom NCSE was found in 3-4%, most often within the first week [36]. A prolonged EEG-video (>6 h), compared to a standard EEG, allowed to diagnose NCSE based on long-term monitoring in the absence of suggestive clinical manifestations in 40.6% of cases. Moreover, the French Intensive Care Society and French Society of Emergency Medicine recommended that the use of continuous video-EEG monitoring should be considered in two situations: *i)* in refractory SE, particularly those with confusional state and *ii)* in the monitoring encephalopathies and encephalitis, in order to look for authentic seizures or even SE [36].

7. NCSE: treatment

Therapeutic management of NCSE is less standardized than that of convulsive status epilepticus, but includes treatment of the NCSE's etiology, management of the comorbid medical illnesses, and balancing out the side effects and drug interactions of introduced AEDs. The treatment is based first on the injection of benzodiazepines and in the second line on intravenous or oral or gastric tube administration of AEDs. The last French conference of consensus on the management of status epilepticus recommend the following treatment lines [36].

7.1 Benzodiazepine as the first-line treatment

- 1) *Clonazepam* IV injection: it seems reasonable to recommend a first dose of 0.5 mg for the elderly, in contrast to adults, for whom 0.015 mg/kg (1 mg per 70 kg) is recommended;
- 2) *Midazolam* either by intramuscular injection (there again half-dose is recommended for the elderly, i.e.: 0.075mg/kg or 5 mg IM) or subjugal injection (Buccolam®: 10 mg), if the intravenous approach is not quickly available.

7.2 Second line therapeutic options

Second-line drug management is different from convulsive SE and therapeutic attitudes must clearly be adapted to several factors:

- The severity of the NCSE: a confusional SE should clearly be treated more energetically than a non-confusional SE,
- Patient's age: dosages and rates should be reduced in elderly patients because of decreased tolerability of AEDs due to age-related changes in pharmacokinetics and pharmacodynamics, the presence of polypharmacy with increased probability of drug interactions or idiosyncratic reactions,
- Comorbidities.

There is a wide range of therapeutic options:

- 1) *Intravenously*: (fos)phenytoin, valproate of sodium, levetiracetam, lacosamide, phenobarbital. Lower doses (adjusted according to the comorbidities and the semiology), and slower infusion rate will be recommended in the elderly, compared to recommendations for adults in NCSE. In the elderly subject, priority is for the least sedative molecules (avoid phenobarbital and sodium valproate) and without cardiological side effects (avoid (fos)phenytoin), leading to prefer levetiracetam or lacosamide. If these two drugs fail, the other therapeutic options should be considered ((fos)phenytoin, phenobarbital and valproate of sodium). As an indication, AED dosages are proposed in table 1, adapted from Cheng [8].
- 2) *Orally or by gastric tube* (if the patient has alertness or swallowing disorders), in case of contraindication of previous AEDs, no available intravenous approach, or the impossibility of monitoring in a intensive care unit (ICU), a loading dose of carbamazepine (unless the patient is of Asian origin due to an increased risk of skin allergy), or phenytoin, perampanel, zonisamide, topiramate, pregabalin, phenobarbital are recommended.

In all cases, it is strongly recommended to monitor in the ICU with continuous EEG monitoring and to have an expert neurological advice for the choice of second-line treatments. Intubation-ventilation is not recommended as in generalized convulsive status epilepticus (except necessity to treat respiratory distress, multi-visceral failure...). The use of anesthetic agents, which requires intubation and mechanical ventilation, is rarely considered because the risks of such an approach are usually higher than the expected benefit.

Treating the underlying cause and medical complications are the most important aspects of treatment in NSCE, but it should be clear that attention to semiology and EEG as a method of classifying NCSE is important to guide treatment. Treatment of non-convulsive status must be individually tailored to the specific subtype of status involved. For example, absence status epilepticus responds rapidly and efficiently to intravenous or oral benzodiazepines alone.

8 Management of NCSE in palliative care patients

Prolonged seizures and SE are relevant problems in palliative care. Timely recognition and effective early treatment with first- and second-line AEDs may prevent unnecessary hospitalizations. Seizures should be recognized and addressed like any other symptom that causes discomfort or reduces quality of life. Diagnosing NCSE in the palliative care setting can be challenging. If there is no possibility for EEG-based diagnosis, probatory therapy with benzodiazepines is a reasonable approach. While continuous EEG monitoring is a vital tool for SE in the ICU, ongoing EEG monitoring in dying patients who transition to end-of-life care may engender medical interventions that are not symptom-based, and therefore unnecessary EEG-monitoring should be avoided [37]. Use of alternative AED administration routes (buccal, intranasal, or subcutaneous) may offer possibilities for effective and individualized AED therapy (table 2) [38]. Although these are off-label recommendations, they are valuable options and better than leaving the patient without any treatment. However, in hospice or home care, vascular access devices for long-term use allow the intravenous approach.

Aggressive unlimited ICU treatment of refractory SE in palliative care patients is mostly not indicated. At worst, intensive care can be futile and possibly harmful. High severity of acute illness, overall frailty, poor functional status before hospital admission, and the presence of severe comorbidities all increase the probability of poor outcome of intensive care. When

several of these factors are present, consideration of withholding intensive care may be in the patient's best interests. Anticipated outcomes influence patients' preferences also in this palliative setting.

9 NCSE: prognosis

Mortality is much higher in the elderly subject than in the younger subject (31% vs. 7%) despite over-representation of NCSE in the elderly population [39]. Previous case-series of NCSE in the elderly report high mortality ranging from 15% [13] to 52% [40], 22.5% in a recent study [41].

The prognosis of SE largely depends on the degree of impairment of consciousness and the underlying etiology. The identified factors of poor prognosis for SE in the elderly are: patient's age, SE duration (>12hours), level of consciousness and acute symptomatic etiology [42].

Patients with epilepsy who have an episode of NCSE with preserved consciousness have a good prognosis and rarely require aggressive treatment. In the case of de novo absence status of late onset, all episodes are resolute, without recurrence, after intravenous benzodiazepine injection and resumption of interrupted treatment. Long-term antiepileptic therapy is not necessary.

10 Conclusion

NCSE must be considered in all elderly patients with unexplained confusion/delirium or an atypical neurological picture. The diagnosis of NCSE is a challenging neurological emergency in the elderly since possible etiologies of confusion may present with the same clinical picture, and its diagnosis cannot be established without EEG confirmation, based on so-called Salzburg EEG criteria. NCSE in the elderly carries major morbidity and mortality,

attributable primarily to etiology, and treatment is complex, involving treatment of the etiology and concomitant medical illnesses, whilst balancing the side effects and drug interactions of AEDs.

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Figures legends

Figure 1: A suggested practical approach to the diagnosis of non-convulsive status epilepticus in confused older people (adapted from Woodford [14])

Figure 2: EEG sample of a woman aged 86 years old, addressed for confusional state. Spikes and polyspikes in left fronto-temporal area.

Figure 3: EEG sample of a woman aged 87 years old with dementia, addressed for subtle repetitive twitching of right leg, associated with spikes in left frontal area, diffusing in the contralateral region.

Tables

Table 1: Second-line Antiepileptic drugs dosing for NCSE (adapted from Cheng [8])

Phenytoin		
Loading		15-18mg/kg body weight at 12.5-25mg/min
Maintenance		<70kg : 150mg i/v every 12 hours ; start 6 hours after loading 70-90kg : 175mg i/v every 12 hours ; start 6 hours after loading >90kg : 200mg i/v every 12 hours ; start 6 hours after loading
Valproic acid		
Loading	<60y	30-45mg/kg i/v in 30 minutes
	60-80y	20-30mg/kg i/v in 30 minutes
	>80y	15-25mg/kg i/v in 30 minutes
Maintenance		Start the same dose as the loading dose concomitantly over 24 hrs
Levetiracetam		
Loading	<60y	25-30mg/kg i/v in 15 minutes
	60-80y	15-25mg/kg i/v in 15 minutes
	>80y	10-20mg/kg i/v in 15 minutes
Maintenance	<60y	1000-1500mg every 12 hours
	60-80y	750-1000mg every 12 hours
	>80y	500-750mg every 12 hours

Table 2: Protocol for treatment of status epilepticus in palliative care (adapted from Kälviäinen and Reinikainen [38] ; Intravenous Lorazépam is not available in France). IV= intravenous, SC = subcutaneous

		Hospital	Hospice/Home care
Stage 1 5-10min	Premonitory SE	Clonazepam IV 0.5 mg Repeat if necessary	Midazolam buccal or intranasal 0.2 mg/kg Repeat if necessary
Stage 2 10-60min	Established SE	Levetiracetam IV Lacosamide IV (Fos)Phenytoin IV Valproate IV	Levetiracetam SC/IV Lacosamide SC/IV Valproate IV
Stage 3	Refractory SE	In selected cases one trial of propofol or midazolam - based 12-hour anesthesia in the ICU	Consider palliative sedation
Stage 4	Super refractory SE	Consider palliative sedation	Consider palliative sedation





