Staged treatment response in Status epilepticus - Lessons from the SENSE registry

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Abstract

Objectives: While in epilepsy patients the likelihood of becoming seizure-free decreases substantially with each unsuccessful treatment, to our knowledge this has been poorly investigated in status epilepticus (SE). We aimed to evaluate the proportion of SE cessation and functional outcome after successive treatment steps.

Methods: We conducted a post-hoc analysis of a prospective, observational, multicenter cohort (SENSE), in which 1049 incident adult SE episodes were prospectively recorded at 9 European centers. We analyzed 996 SE episodes without coma-induction before the third treatment step. Rates of SE cessation, mortality (in ongoing SE or after SE control), and favorable functional outcome (assessed with modified Rankin Scale) were evaluated after each step.

Results: SE was successfully treated in 838 (84.1%) patients, 147 (14.8%) had a fatal outcome (36% of them died while still in SE), and 11 patients were transferred to palliative care while still in SE. Patients were treated with a median of three treatment steps (range 1-13) with 540 (54.2%) receiving more than two steps (refractory SE, RSE) and 95 (9.5%) more than five. SE was controlled after the first two steps in 45%, with additional 21% treated after the 3rd, and 14% after the 4th step. Likelihood of SE cessation ($p<0.001$), survival ($p=0.003$), and reaching good functional outcome ($p<0.001$) significantly decreased between the first two treatment lines and the 3rd, especially in patients not experiencing convulsive generalized SE, but remained relatively stable afterwards.

Significance: The significant worsening of SE prognosis after the 2nd step clinically supports the concept of RSE. However, and differing from findings in human epilepsy, RSE remains treatable in around one third of patients even after several failed treatment steps. Clinical judgement remains essential to determine the aggressiveness and duration of SE treatment, and avoid premature treatment cessation in SE patients.

Key Points:

- SE cessation and good outcome likelihood decreases between the first two treatment steps and the third ,clinically reflecting the concept of refractory SE (RSE).
- In RSE the likelihood of treatment success and of reaching good outcome remains relatively stable (~30%) at each treatment attempt.
- RSE treatment should not be abandoned prematurely, especially in patients without known factors of poor prognosis.

Introduction

Status epilepticus (SE) is a common neurological emergency, which leads to significant morbidity and mortality (2, 3). Current guidelines for SE management recommend a three-steps therapeutic approach. In the initial stage, benzodiazepines should be administered, followed by intravenous (IV) anti-seizure medication (ASM) (4, 5). A patient not responding to 1st and 2nd line treatment is considered to have refractory SE (RSE), and therapeutic coma induction with general anesthesia (GA) should be considered, especially in generalized convulsive SE (GCSE) (6, 7). SE of longer duration is associated with increased mortality and neurological morbidity (7-11); additionally, experimental, and clinical observations suggest that it becomes progressively less responsive to therapy (12, 13).

Various studies in human epilepsy have shown that the chance of becoming seizure-free decreases substantially after each unsuccessful ASM attempt (14-17). To our knowledge, this has however not been studied in detail in SE patients, besides a preliminary analysis of rough response rates in our cohort (18), and the observation that early treatment has higher chances to control convulsive SE (13). Therefore, we aimed to evaluate the response rate to sequential treatment steps in SE, with the hypothesis that the likelihood of SE cessation would constantly decrease.

Methods

Study design

We performed a post hoc analysis of data collected in a large, multicenter, prospective observational cohort study, the Sustained Effort Network for treatment of Status Epilepticus (SENSE) cohort (19).

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the ethics committees of each participating center and registered with the German Clinical Trials Register (DRKS00000725). Informed consent was waived owing to the purely observational character and complete anonymization of the patients by all ethic committees except one (Innsbruck), which obtained consent for all patients.

Study population and clinical variables

The detailed SENSE study protocol and main results have been published (1, 19). Briefly, clinical, demographics, outcome and treatment data from adults presenting with SE between January 2011 and June 2015, defined by clinical seizures lasting ≥5 minutes or repetitive

seizures without return to neurological baseline within the same timeframe, were prospectively collected at nine participating centers in Austria, Germany and Switzerland. Non-convulsive SE (NCSE) was diagnosed according to recommendations at the time, implying EEG confirmation (20). Except patients with hypoxic-anoxic brain injury, excluded owing to markedly different prognosis, all adults patients with SE, diagnosed at admission or at any point during in-patient treatment, were included in the SENSE registry.

The SENSE cohort comprised 1049 patients experiencing 1179 SE episodes. For the present analysis, only incident SE episodes were considered, in order not to include the same patient twice. RSE was defined as ongoing SE despite treatment with 2 ASMs, and super-refractory SE as persistence >24hours after GA, or recurrence after its withdrawal (7, 21, 22). Patients intubated for SE management or airway protection before receiving two subsequent treatments with non-sedative ASM or benzodiazepines (violating current treatment guidelines) were excluded, as coma induction with GA would hinder a formal assessment of SE refractoriness (23).

Clinical, demographic, treatment, and outcome data were prospectively recorded from the SENSE cohort. Reasons for intubation were prospectively dichotomized as airway protection or SE treatment. Worst semiology during the index SE episode and etiology were reported according to the International League Against Epilepsy (ILAE) criteria (24). Level of consciousness was dichotomized as alert or somnolent versus coma or stupor. The Status Epilepticus Severity Score (STESS) was prospectively calculated on admission (25). SE semiology was dichotomized as generalized convulsive SE (GCSE) or non-GCSE (26). Treatment was categorized into benzodiazepines (clobazam, clonazepam, diazepam, lorazepam, midazolam); intravenous ASM (lacosamide, levetiracetam, phenobarbital, phenytoin, valproate); oral ASM ASMs (carbamazepine, eslicarbazepine, ethosuximide, felbamate, gabapentin, lamotrigine, oxcarbazepine, perampanel, piracetam, pregabalin, primidone, retigabine, rufinamide, stiripentol, topiramate, vigabatrin, zonisamide,); GA (etomidate, ketamine, midazolam as continuous infusion, propofol, sevoflurane, thiopental); and others (chloralhydrate, chlorazepate, corticosteroids, hypothermia, ketogenic diet, magnesium, resective surgery, vagal nerve stimulation) (23). Number of treatments and treatment sequence used to control SE was prospectively recorded for each patient. Each distinct treatment prescribed for controlling SE was considered a “treatment step”. A step could include benzodiazepines, iv ASM, loading of oral ASM (whether administered through nasogastric tube or not), GA, or other treatment types. Continuous infusions were considered as one step if they involved the same molecule (for example: repeated continuous MDZ infusion was considered as one step, but continuous infusions including first MDZ and then

PRO as two steps). For the present analysis, 1st and 2nd line treatments, consisting of benzodiazepines or ASMs (as patients intubated for any reasons before receiving two treatments lines with benzodiazepines and ASMs were excluded) were considered together, as the two first lines are often given almost simultaneously (1, 27).

Outcomes

SE resolution was clinically assessed, including EEG information when available (1). Mortality and functional outcome were prospectively assessed at discharge from acute hospitalization. The modified Rankin scale (mRS) before the index SE was prospectively estimated, similarly to a recent trial (28): mRS 0-2 or the lack of mRS worsening between admission and discharge were considered as good functional outcome.

Statistical Analysis

Statistical analyses were performed using IBM SPSS software (v. 27; SPSS, Inc., Chicago, IL) and R (v. 4.0.0, R Foundation for Statistical Computing, Vienna, Austria). Comparison of categorical data were performed through Chi-square or 2-sided Fisher's exact tests, and ordinal or continuous data were analyzed using Mann-Whitney or t-tests, as appropriated. The Benjamini-Hochberg procedure was applied to control the false discovery rate, using a q value of 0.05. Sankey diagrams were visualized using the free-ware web tool "SankeyMATIC" by Steve Bogart (https://sankeymatic.com/).

Results

Of the 1049 patients in the SENSE cohort, 53 were excluded due to intubation prior to first- or second-line treatment, and the remaining 996 were considered for analysis. Their clinical characteristics are presented in **Table 1**. A total of 838 (84.1%) survived with SE cessation, while 158 (15.9%) patients experienced SE persistence or death (among which 11 were transferred to palliative care while still in SE). Patients' outcomes are presented in **Figure 1**.

~~A total of 316 (31.7%) patients had predominantly generalized convulsive SE (GCSE), while the other 680 (68.3%) presented other forms (non-GCSE).~~ Patients were treated with a median of three treatment steps (range 1-13, interquartile range (IQR) 2-4). A total of 540 (54.2%) patients received more than two steps, 318 (31.9%) more than three, 176 (17.7%) more than four, and 95 (9.5%) were treated with more than five steps (**Table 2**).

Outcome after each treatment step is presented in **Table 2 and Figures 2-4**. Among the whole population, SE cessation was achieved after the first two steps in the largest proportion of patients (45%, 450/996), with additional 21% (206/996) responding after the 3rd step, and

<1.5% treated with more than 6 steps. Looking at stepwise cessation rates, we found 45.2% (450/996) after the first two steps, 38.1% (205/540) in patients treated with 3 steps, 41.2% (131/318) in those treated with 4 steps, and in around 30% thereafter (**Figures 3, 4**).

The population was then stratified between GCSE and non-GCSE, in analogy with the original SENSE analysis (1, 19). A total of 316 (31.7%) patients presented with GCSE and 680 (68.3%) had other SE forms. ~~(227 NCSE, 453 simple-partial/complex-partial/absence/myoclonic).~~ Among GCSE patients, 299 (94.6%) experienced SE resolution, 226 (71.5%) had a good functional outcome at discharge, and 24 (7.6%) had a fatal outcome (11 still in SE). Within non-GCSE patients, SE resolved in 632 (92.9%) patients, 404 (59.4%) had a good functional outcome and 123 (18.1%) died in hospital (43 still in SE). Patients suffering from GCSE were intubated, for any reason, more frequently (80/316, 25.3% vs 102/680 15.0%, P<0.001), however intubation for SE treatment was similar between the two groups (25/316, 7.9% vs 49/680, 7.2%, p=0.8).

Stepwise outcome after each treatment steps (grouping the first two) was analyzed in the whole population, and in the subgroups of GCSE and non-GCSE (**Figure 2**). Patients who received more than 7 steps were omitted for analysis due to their low number (n<50 per step). Outcome differed significantly (p<0.001) across subsequent treatment steps in the whole population, and considering separately GCSE, and non-GCSE (**Figure 2).** On stepwise analysis, outcomes were significantly different between the first two steps as compared to the 3rd (**Figure 2a**, p<0.001); but did not differ between subsequent steps. Looking more closely into mortality and functional outcome (**Table 2**); case fatality and likelihood of reaching good functional outcome significantly differed across treatment steps (respectively, p=0.030 and p<0.001 in the whole population). Here again, this was explained by the difference between the first two steps and the 3rd (p=0.009 for mortality and p=0.001 for good functional outcome) with no significant difference in mortality rate or functional outcome thereafter.

Comparing the 95 patients in the cohort receiving 6 and more steps with the rest of the population, the former had a more frequent history of previous seizures (60/95, 63% vs 423/901, 48.0%, p=0.005), and lower mRS on admission (median 3, IQR 1-4 vs median 3, IQR 2-4 p=0.03). They were intubated more often (56/95, 60% vs 126/901,14.0%, p<0.001), were less likely to achieve good functional outcome (37/95, 39% vs 593/901, 65.8%, p=.0.01), and had higher mortality (25/95, 24% vs 122/901, 13.5%, p=0.001). Other variables such as gender, STESS, level of consciousness at SE onset, seizure semiology, and proportion of acute etiologies did not significantly differ between the two groups.

Discussion

This study, analyzing prospectively collected data from a large, multicenter population of adults with SE, explores in detail the probability of SE cessation after each subsequent treatment step. Forty-five percent of SE episodes were controlled after the first two treatment steps. SE cessation rate, probability of reaching good functional outcome, and survival significantly decreased between the first two treatment steps and the 3rd. However, afterwards, the chance of SE resolution remained somewhat stable, with around 30% of the patients responding to each step, even following more than 10 unsuccessful attempts, challenging our initial hypothesis.

Unlike in epilepsy, the likelihood of treatment response in SE does not significantly decrease after the 3rd unsuccessful treatment attempt. In the treatment of epilepsy, the chance of response to treatment decreases with each additional unsuccessful ASM trial (14-16). In a hallmark study, following failure of the 1st ASM, only 11% additional patients were seizure-free after a 2nd ASM, and the probability of seizure-freedom, after more than three ASM, fell below 5% (16). Furthermore, after failure of 6 ASM, seizure freedom seems exceptionally rare (15).

During ongoing SE, changes in neurotransmission might potentially contribute to treatment resistance. In animal models, these alterations have been verified to favor the development of self-sustaining seizures and to render ASM with GABAergic mechanisms less effective and the glutamatergic receptor system upregulated over time, leading to marked disinhibition and hyperexcitability (12). These findings are only partially confirmed by our clinical findings: the proportion of SE cessation was significantly lower after the first two treatment steps, confirming the higher drug resistance of RSE (13); however, the proportion of SE cessation did not significantly decrease at further treatment steps, and no clear plateau was reached. It is tempting to speculate that the molecular mechanisms of disinhibition and hyperexcitability might be saturable and, therefore, may be overcome by a combination of several ASMs with different modes of action.

By definition, failure of the first two treatment steps is called RSE, which has been repetitively shown to be harder to treat than initial SE (1, 13, 23). However, response to each subsequent treatment step within RSE received limited attention (29). In our cohort, the observed difference in treatment response rate between RSE and non-RSE was mainly accounted by non-GCSE patients: while our proportion of GCSE is similar to other cohorts (30, 31), the lower number of GCSE patients (at a qualitatively similar treatment response trend as in non-GCSE) may explain this aspect. Importantly, the likelihood of reaching good functional outcome was similar

across all patients' groups between the first two and the 3rd step, illustrating the robustness of the RSE definition on a clinical counterpart.

Patients in whom more than five treatment steps had to be applied were probably somewhat selected, as clinicians deemed worthy using up to 13 attempts. They had lower baseline mRS and were more frequently known for prior epilepsy, factors associated with better SE outcome (10). These results emphasize that SE treatment should not be abandoned prematurely, especially in patients without known factors of poor prognosis such as severe underlying etiology. In prolonged SE, no single prognostic factor can predict outcome with certainty: RSE is not inherently invariably related to poor outcome and systematic therapeutic nihilism should not have place. Age and etiology have been described as the main independent predictors in SE (2, 10, 25, 32-34). Longer SE duration is associated with poorer outcome, but this probably essentially applies to the first hours after SE initiation (35), and following adjustment for other robust outcome predictors, the correlation seems weaker afterwards (23, 33, 35, 36). Furthermore, good recovery in patients treated for RSE for weeks to months has been reported in a substantial minority of patients (37-40). Clinical judgement remains therefore crucial to identify patients who can still respond to treatment, and to determine the aggressiveness and duration of it.

One should however note that there is a tendency that outcome in terms of mortality and functional outcome becomes less favorable the more treatment steps failed. While 75% of patients with treatment responsive SE after the first two steps had a good functional outcome and only 8% died in hospital, only 38% had good functional outcome, and mortality raised up to 26%, in those treated with more than five ASMs. These proportions are comparable to those in the literature (7, 8, 41).

SE cessation after the first two treatment steps in our cohort was lower than in randomized clinical trials (RCT) (42-44). This was especially true regarding the 1st treatment: while only 15.5% of our population achieved SE cessation after the 1st line, in RCTs response rates ranged around 60-80% (42-44). In clinical practice, 1st and 2nd treatment steps are often given virtually at the same time (29, 45), this might contribute to the seemingly low success rate of 1st line. Indeed, pooled together the success rate after the first two steps raised to 45.2%, lower but more similar to RCTs, where success rate after 2nd treatment step lies between 45-60% (44, 46). Our lower initial success rate might be explained by the "real life" observational setting of the SENSE registry, which includes patients with non-convulsive SE, as opposed to the aforementioned trials targeting convulsive SE. Furthermore, contrary to randomized trials in which medications are controlled both regarding doses and timing, in our cohort almost 90%

of patients were not treated according to guidelines (no benzodiazepines as 1st line, underdosed treatment). This tendency not to follow guidelines in real-life settings has been previously reported in other cohorts and could have influenced outcome (1, 23, 45, 47, 48). Indeed, as outlined in the previous SENSE analysis and other cohorts, including large pediatric registries, the initial administration of benzodiazepines and the total dose of medications given during the initial 30 to 60 minutes exert a notable impact on SE cessation (1, 23, 45, 47, 48). The call for a more rigorous application of existing guidelines to close the gap between them and real practice appears obvious. Additionally, our population was relatively old (median age 70 years vs 33, 53 and 58 years in the aforementioned RCTs (42, 44, 46)), and was mostly treated outside intensive care units. In fragile, older patients, with focal SE and preserved consciousness clinicians may choose a less aggressive treatment strategy to minimize side effects (49).

Some study limitations must be acknowledged. The information was gathered from centers specialized in treating SE without a capillary coverage of the relative communities; however, our data were sourced from a reliable SE registry that has strong internal validity, and generalizability seems reasonable given the broadly similar semiological distribution and mortality rate to other cohorts (27, 31). The contribution of various centers in terms of patients' number varied, leading to a potential limitation in terms of homogeneity. Additionally, there was no independent validation between hospital coding of SE data and the database entries. This could have introduced some level of reporting bias, particularly underascertainment. As this was a post hoc analysis, only associations, but not causative assumptions can be inferred. This study provides a depiction of how SE is managed in real-life situations, but several variables that could potentially impact the outcomes were not accessible, such as EEG findings. Our analyses were mainly descriptive without correction for several potential confounders, such as treatment timing, incomplete treatment dose, etiology, witnessed onset, location of onset, used of rescue medication, semiology, which could influence outcome. We therefore cannot formally state whether the treatment response evolution we report would hold true in every SE case or if it was also influenced by other variables. Similarly, as we did not analyze treatment dosages, we cannot infer on this aspect regarding treatment response. Furthermore, potential treatment restrictions, such as advanced directives limiting intubation or transfer to ICUs, were not available. These limitations could have further influenced outcomes, and additional studies addressing this topic are required. Caregivers estimated the onset and termination of SE without systematic possibility of EEG verification. Finally, because cEEG was not routinely employed, in accordance with common European practice (28), the proportion of non-convulsive-SE (NCSE) or recurrence after SE resolution may have been underestimated. Nevertheless, we believe this risk to be low, since patients were closely

monitored using repetitive or extended EEGs, especially those who were intubated for SE treatment, as detailed previously (23).

In conclusion, the likelihood of SE cessation significantly differed between the first two treatment steps and the 3rd, clinically confirming the concept of RSE. However, unlike in epilepsy, the likelihood of treatment success remains relatively stable at around 30% thereafter for each treatment attempt. Our results emphasize that SE cessation could be achieved even after prolonged RSE, and despite failure of multiple treatments. This should warn clinicians against premature treatment cessation in selected RSE cases. Further studies investigating the impact of treatment restrictions on mortality and clinical outcomes in SE are required.

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Authors contribution

IB	Design of the work, analysis and interpretation of data. Drafting the work. Final approval of the version to be published. Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved
JN, FR, CK, SR, CT, ET, IU, ZU	Acquisition of data. Revising the manuscript critically for important intellectual content. Final approval of the version to be published. Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved
AS and AR	Acquisition of data. Design of the work. Revising the manuscript critically for important intellectual content. Final approval of the version to be published. Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Table 1: Description of the studied population		
		Whole population n=996
Sex	Female, n (%)	517 (51.9)
Age	Median (IQR)	70 (54–80)
Previous seizure	Yes, n (%)	492 (49.4)
Treated with ASM before SE	Yes, n (%)	462 (46.4)
Worst Semiology	Other, n (%)	453 (45.5)
	GCSE, n (%)	316 (31.7)
	NCSE in coma, n (%)	227 (22.8)
Consciousness	Alert/somnolent, n (%)	594 (59.6)
	Stuporous/comatose, n (%)	402 (40.4)
STESS score	Median (IQR)	3 (2–4)
mRS before SE	Median (IQR)	3 (1–4) *
Etiology	Acute, n (%)	311 (31.2)
	Acute on remote, n (%)	94 (9.4)
	Remote only, n (%)	318 (31.9)
	Progressive, n (%)	159 (16.0)
	Unknown/other, n (%)	114 (11.4)
Intubation and GA for any reason	Yes, n (%)	182 (18.4) *
Intubation and GA for SE	Yes, n (%)	74 (7.5)
Received at any step	Benzodiazepines, n (%)	913 (91.7)
	IV ASMs, n (%)	825 (82.8)
	Oral ASMs, n (%)	142 (14.3)
	Other treatments, n (%)	17 (1.7)
RSE	Yes, n (%)	545 (54.7)
SRSE	Yes, n (%)	52 (5.2)
SE duration (Hours)	Median (IQR) **	8 (2–48)
Duration of hospital admission (Days)	Median (IQR) ***	10 (4–18)
Death at discharge	Yes, n (%)	147 (14.8)
	Death in SE, n (%)	53/147 (36.1)
mRS at discharge	Median (IQR)	4 (2–5)
	Good (0–2, or same as at onset)	630 (63.3)

ASM: anti-seizure medication; GA; general anesthetics, GCSE: generalized convulsive status epilepticus; IQR, interquartile range; IV, intravenous; mRS, modified Rankin Scale; NCSE: nonconvulsive status epilepticus; RSE: refractory status epilepticus; SE, status epilepticus; SRSE: super refractory status epilepticus.
Patients with missing data: * 1–5 patients, ** 181 patients; *** 12 patients

Table 2: Outcome according to each treatment step

	Patients receiving this step *	Last step **	Outcome after each treatment step in patients not treated with subsequent ASM				
			SE end (including death not in SE) ** N=931 (93.5%)	Mortality overall *** N= 147 (14.8%)	Mortality in SE *** N=54 (5.4%)	Poor outcome (SE persistence or death) ** N=158 (15.9%)	Good functional outcome (mRS≤2 or unchanged) *** N=630 (63.3%)
Step 1	996 (100)	154 (15.5)	154 (15.5)	9 (5.8)	0 (0.0)	851 (85.4)	130 (84.4)
Step 2	842 (84.5)	302 (35.9)	296 (35.2)	26 (8.6)	6 (2.0)	566 (67.2)	213 (70.5)
Step 1-2⁺	996 (100)	456 (45.8)	450 (45.2)	35 (7.7)	6 (1.3)	578 (58.0)	343 (75.2)
Step 3	540 (54.2)	222 (41.1)	206 (38.1)	36 (16.2)	14 (6.3)	356 (65.9)	140 (63.1)
Step 4	318 (31.9)	142 (44.7)	131 (41.2)	28 (19.7)	9 (6.3)	206 (64.8)	77 (54.2)
Step 5	176 (17.7)	81 (46.0)	67 (38.1)	23 (28.3)	12 (14.8)	120 (68.2)	33 (40.7)
Step 6	95 (9.5)	45 (47.4)	42 (44.2)	8 (17.8)	2 (4.4)	59 (62.1)	23 (51.1)
Step 7	50 (5.0)	21 (42.0)	14 (28.0)	8 (38.1)	6 (28.6)	38 (76.0)	7 (33.3)
Step 8	29 (2.9)	14 (48.3)	9 (31.0)	6 (42.9)	4 (28.6)	22 (75.9)	5 (35.7)
Step 9	15 (1.5)	7 (46.7)	5 (33.3)	2 (28.6)	1 (14.3)	11 (73.3)	1 (14.3)
Step 10	8 (0.8)	3 (37.5)	3 (37.5)	1 (33.3)	0 (0.0)	6 (75.0)	0 (0.0)
Step 11	5 (0.5)	3 (60.0)	2 (40.0)	0 (0.0)	0 (0.0)	3 (60.0)	0 (0.0)
Step 12	2 (0.2)	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)	1 (50.0)	1 (100)
Step 13	1 (0.1)	1 (100)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

SE: status epilepticus. mRS: modified Rankin scale.

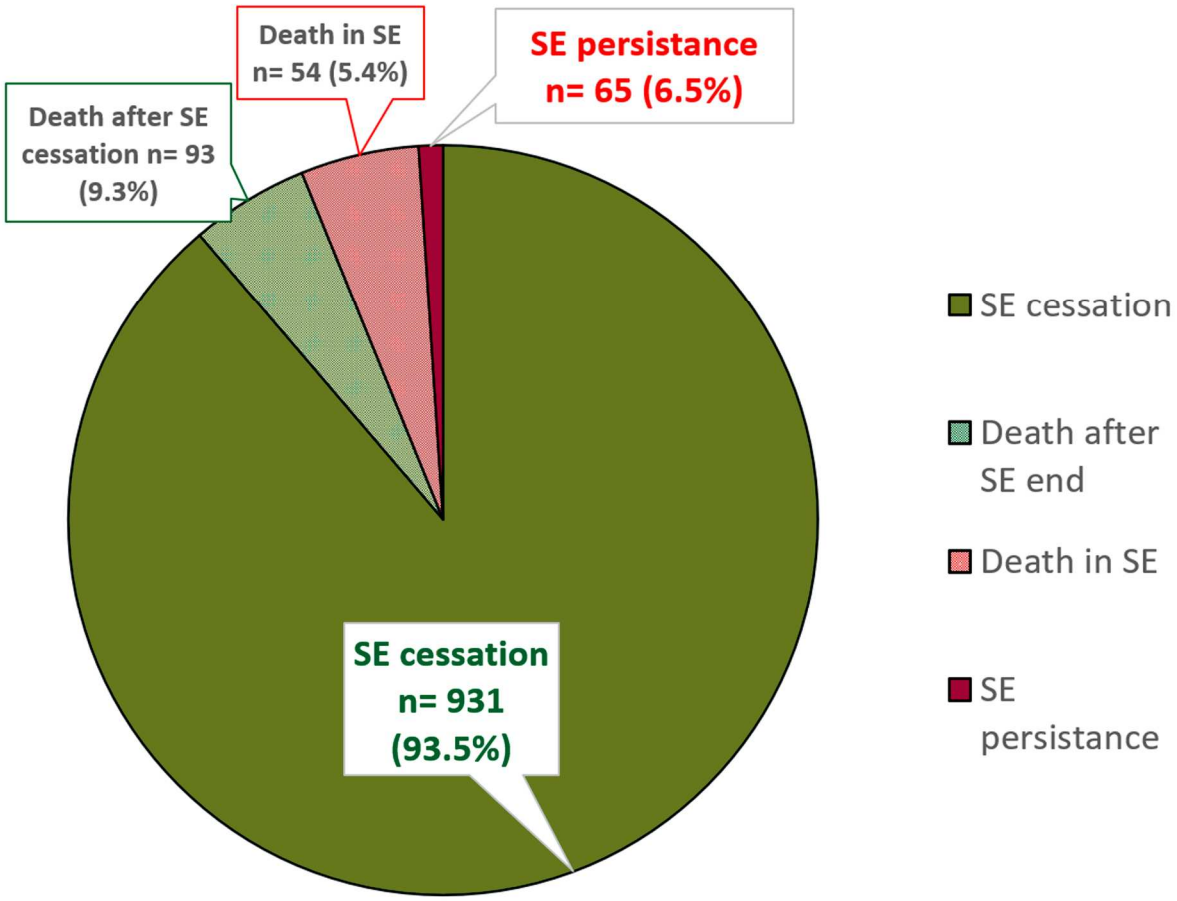
⁺**Step 1-2**: first two lines of treatment (step 1 and step 2) considered together, as the two first lines are often given almost simultaneously

Overview of patients' outcome after successive treatment step. Percentage denominators vary through the table according to their clinical relevance (* whole cohort percentage, **** percentage of patients receiving the treatment step, ***** percentage of patients receiving the treatment step and no subsequent ASM (last step))

- The 1st column presents the total number of patients receiving the treatment step; percentages are expressed according to the whole population.
- The 2nd column presents the number of patients receiving the treatment step and no further treatment; percentages are therefore expressed according to the total number of patients receiving this treatment step.
- The 3rd and 6th column reports the proportion of patients experiencing SE cessation after the treatment step; percentages are expressed according to the number of patients receiving the step.
- The 4th, 5th and 7th columns represent outcome according to the number of received treatment steps. Percentages are therefore expressed according to the number of patients receiving the step without further SE treatment (last step).

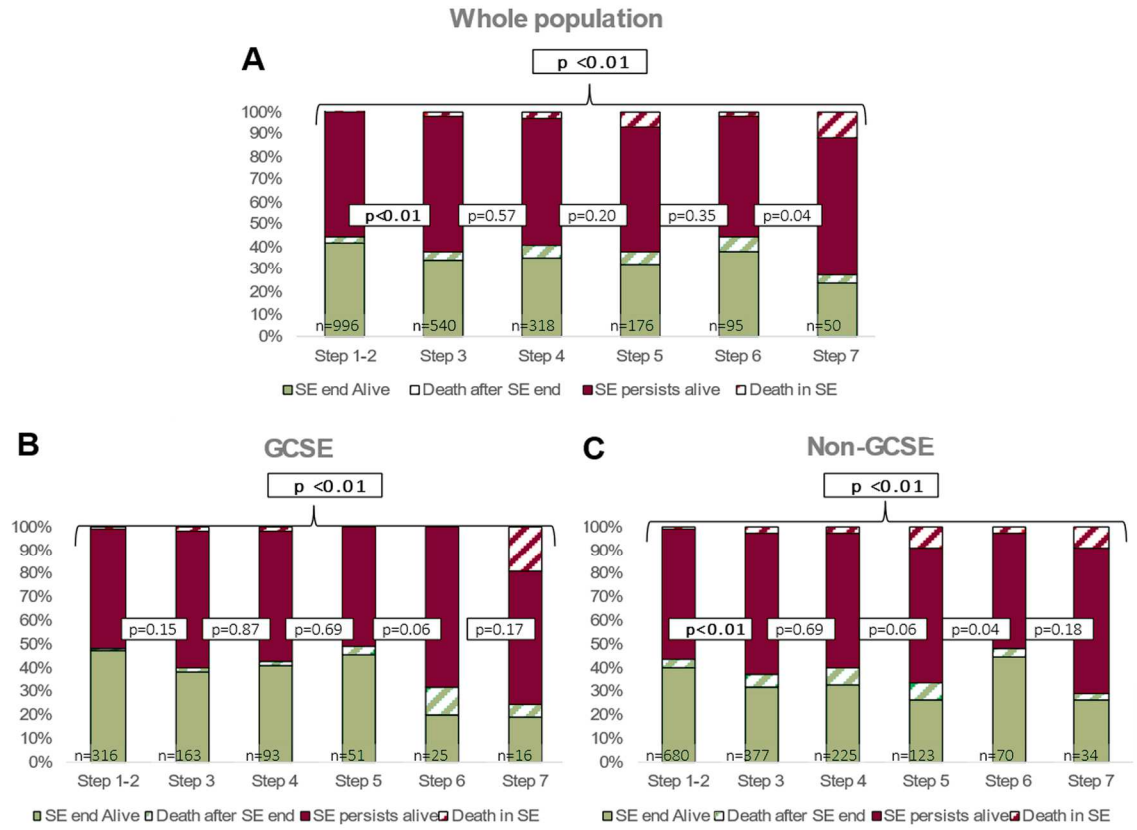
Figures

Figure 1: Patients' outcome



Patients' outcome represented according to the proportion of patients experiencing SE cessastion, SE persistance and mortality (both in and after SE cessation). A total of 54 patients died while still in SE, representing 5.4% (54/996) of the whole population, 36.7% (54/147) of all the fatal cases and 83.1% (54/65) of the patients with SE persistance at discharge. A total of 93 patients died after SE cessation, representing 9.3% (93/996) of the whole population, 63.3% (93/147) of the fatal cases and 10% (93/931) of the patients with SE cessation at discharge.

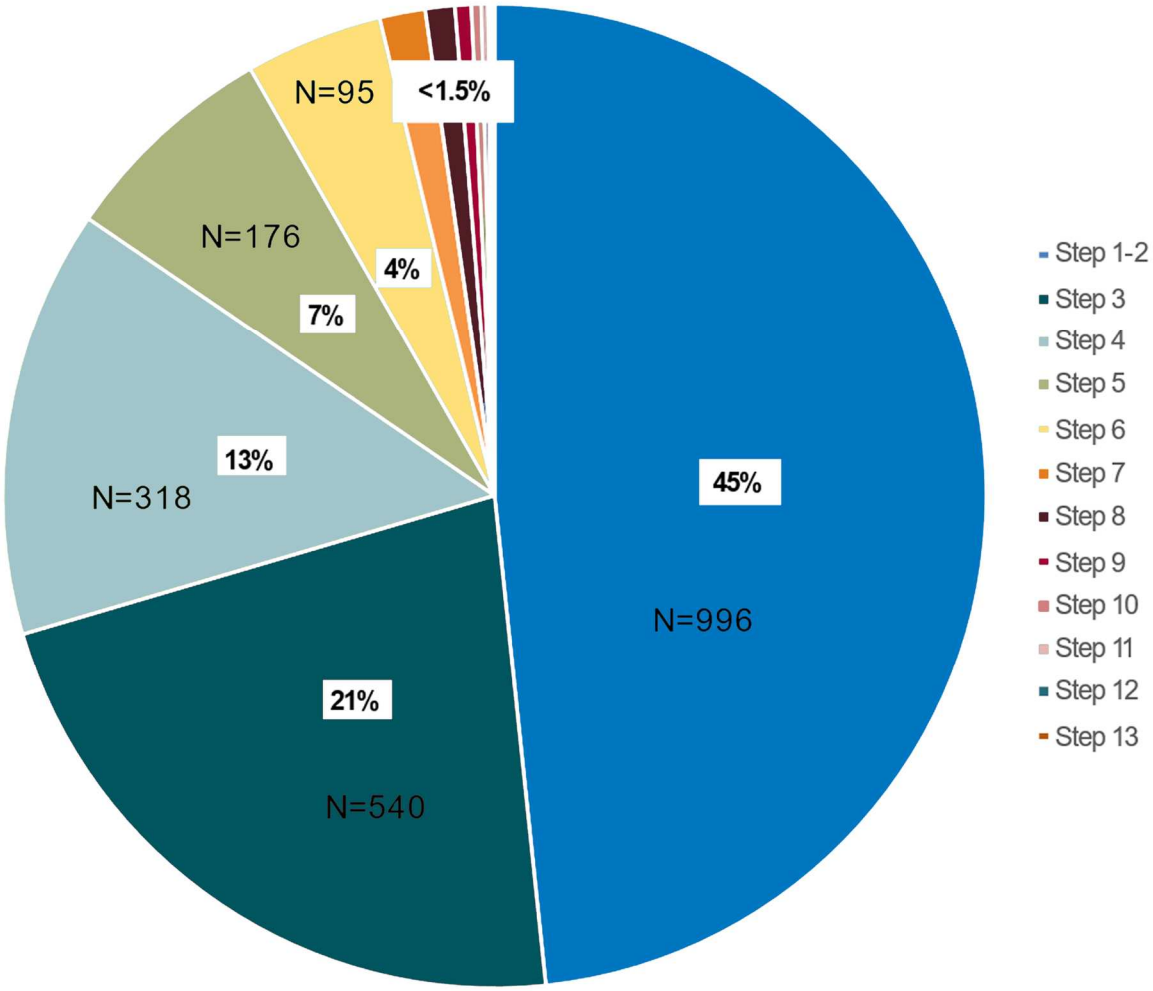
Figure 2: Outcome after each treatment step



Outcomes in term of SE cessation and alive, SE cessation but death in-hospital, SE persistence and alive, or death in SE, are presented A) in the whole population (n=996), B) in patients presenting with generalized convulsive SE (n=316) and C) in patients presenting with other form of SE (n=680). Percentages are reported according to the number of patients receiving the treatment steps. For the whole population, detailed numbers are presented in table 2.

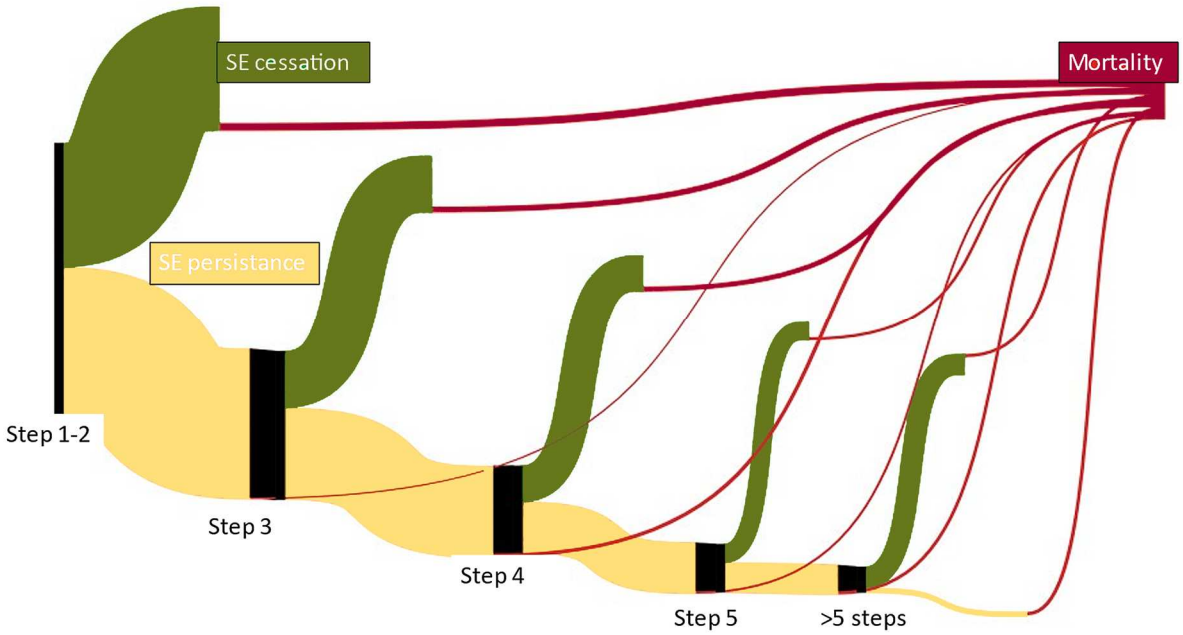
GSE: Generalized Convulsive status epilepticus. In bold: p values significant after Benjamini-Hochberg correction.

Figure 3: Proportion of SE cessation after each treatment step according to the whole population



Percentages of number of treatment steps necessary to obtain SE cessation in the whole population. Percentages are expressed according to the whole population (n=996) and numbers represent the patient count receiving the step (while 540 patients received 3 or more steps, SE cessation was achieved in 21% (206/996) after 3 steps. SE cessation was achieved after the first two treatment steps in 45%, with <1.5% of the patients requiring more than 6 steps achieving SE cessation after subsequent steps.

Figure 4: Evolution in patients' outcome after successive treatment steps



Sankey diagram illustrating patients' outcomes in term of SE termination, SE persistence, and mortality according to successive treatment steps.

Patients who received 6 or more treatment steps are pooled together. Patients who never experienced SE cessation ultimately died (see table 2 for detail).

SE=Status Epilepticus