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Evaluation of a clinical tool for early etiology identification in status epilepticus

Running title: *SEEIT: SE Etiology Identification Tool*

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Photo legend: Dr. Vincent Alvarez is a neurologist and epileptologist at the Hôpital du Valais and visiting scientist at the Brigham and Women's Hospital

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Summary:

Objectives: Since early etiologic identification is critical to select appropriate specific status epilepticus management, we aim to validate a clinical tool we developed that uses history and readily available investigations to guide prompt etiologic assessment.

Methods: This prospective multi-center study included all adult patients treated for SE of all but anoxic causes from four academic centers. The proposed tool is designed as a checklist covering frequent precipitating factors for SE. The study team completed the checklist at the time the patient was identified by EEG request. Only information available in the emergency department or at the time of in-hospital SE identification was used. Concordance between the etiology indicated by the tool and the determined etiology at hospital discharge was analyzed, together with inter-rater agreement.

Results: 212 patients were included. Concordance between the etiology hypothesis generated using the tool and the finally determined etiology was 88.7% (95% CI: 86.4 – 89.8) (kappa = 0.88). Inter-rater agreement was 83.3% (95% CI: 80.4 – 96) (kappa = 0.81).

Significance: This tool is valid and reliable to identify early the etiology of a SE. Physicians managing patients in SE may benefit from using it to identify promptly the underlying etiology, thus facilitating selection of the appropriate treatment.

Key words: Epilepsy; diagnostic test assessment; critical care; coma; neurologic emergency

Introduction:

With an annual incidence of 10–40 per 100,000 person years and a mortality between 7% - 33% [1, 2, 3] status epilepticus (SE) is one of the most frequent neurological emergencies. Several independent predictors of poor outcome have been identified, including advanced age, de novo presentation, impairment of consciousness before treatment, and seizure type, but the most critical factor by far is the underlying etiology [4, 5, 6, 7]. Although much attention has been paid to seizure cessation with administration of anti-seizure drugs (ASDs) [8, 9], it is far more critical to rapidly identify and target a treatable underlying etiology[9]. Indeed, some etiologies such as cerebrovascular events, severe metabolic disturbances, alcohol withdrawal or intoxication, brain tumor related events and infections need emergent and specific treatments beyond ASDs. Earlier identification of the SE etiology would enhance rapid and more focused treatment, and potentially improve outcome.

Due to the diversity of possible etiology[10], this is potentially a puzzling process in acute and emergent situation for a clinician unfamiliar with SE, particularly outside of a tertiary care facility. Clinical decision supporting tools may help clinicians to gather important data for the decision-making process, and guide medical management more effectively, thus reducing practice errors and costs [11]. These tools are widely available in many other clinical settings, and notably for other acute conditions for which rapid identification of the underlying etiology is fundamental, such as chest pain [12] or acute headache [13].

In order to assist a clinician to rapidly identify an underlying etiology, we developed a user-friendly tool labeled Status Epilepticus Etiology Identification Tool (SEEIT) utilizing elements of the clinical history and routinely available laboratory investigations that can be used at the bedside in the Emergency Department (ED) or

the intensive care unit (ICU) to streamline the evaluation into etiology. We performed a multi-center prospective observational study in order to determine the validity and reliability of this tool.

Methods:

- **Primary research question:**

  The primary research question was to evaluate the validity and reliability of the SEEIT by assessing its propensity to identify the correct etiology and its inter-rater agreement.

- **Standard Protocol Approvals, Registrations, and Patient Consents:**

  The Institutional Review Boards of each center approved this study. As this observational study involved no risk for patients and focused on acute phase of critically ill patients, consent was waived.

- **Cohort and SE definition:**

  In this observational study, we prospectively identified every consecutive adult patient (age >16 years) with SE admitted to four university hospitals, from February 1st 2013 at the Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland; from June 1st 2013 at the Brigham and Women's Hospital (BWH) and the Massachusetts General Hospital (MGH), Boston, USA; and from November 1st 2013 at the Beth Israel Deaconess Medical Center (BIDMC), Boston, USA. The inclusion period ended on February 28th 2014.. All patients with suspected SE at each institution have electroencephalograms (EEGs) within 24 hours, so subjects were screened through review of all EEGs ordered during that period. SE was defined as the occurrence of ongoing epileptic or repeated epileptic seizures without full recovery lasting more than 5 min [9]. EEG diagnosis was required for non-

convulsive SE, as recently described [14]. This cohort includes patients admitted for SE and also patients developing SE during the hospital stay, but patients with post-anoxic SE were excluded.

- **Definition of variables**

  Demographic data recorded included: 1) age, 2) gender; 3) worst seizure type categorized as focal seizures without impairment of consciousness, focal seizures with impairment of consciousness, generalized convulsions, absence seizures, myoclonic seizures [15] and non-convulsive SE in coma (NCSEC); 4) level of consciousness before treatment was categorized as follows: alert, confused, somnolent (arousable with clear contact), stuporous (arousable without contact) and comatose. The STatus Epilepticus Severity Score (STESS) was calculated for every patient using age, seizure type, level of consciousness and history of previous seizures [16]. The timing of onset of the SE was determined as precisely as possible using pre-hospital chart and emergency department summaries. For SE episodes without clear onsets (unwitnessed, subtle non-convulsive SE), we considered the last observed time of good health as the beginning of the SE. Each ASD treatment was recorded prospectively, but treatments modified or initiated after control of seizures were not evaluated. Refractory SE was defined as failure to respond to an adequate dose of an initial benzodiazepine followed by a second-line of a non-sedating ASD [9]. The end of the SE episode was defined by the last clinical or electrical seizure without recurrence for at least 48 hours, off sedation.

  The etiology of each SE episode was described in free text based on medical charts and then assigned to the nineteen categories listed in **Table 1**.

Outcome at discharge was categorized as return to pre-morbid baseline, new morbidity or death.

- **Status Epilepticus Etiology Identification Tool (SEEIT) description and evaluation**

  The proposed tool, shown in **Figure 1**, was developed by two of the authors (VA and AOR) based on the list of the potential underlying etiology included in the current SE guidelines [9] and adapted based on their clinical experience. After its completion, it was reviewed by two others authors, experts in the field (JWL and FWD). Hypertensive encephalopathy was not included in the tool: since hypertension is frequently seen secondary to the acute brain injury, too much emphasis on hypertension in the acute setting could be misleading. Moreover hypertensive encephalopathy is not a frequent cause of SE [10,17].
  The tool is designed as a checklist including 4 main parts and several subsequent questions. The first part aims to confirm the diagnosis of SE (fulfilling the operational definition) [18] and also raises the question of psychogenic non-epileptic status epilepticus (PNESE), which can be mistaken for refractory SE [19]. The tool then discriminates between SE in the setting of known epilepsy or a structural brain disorder vs. occurring without any known brain pathology. For each of these parts, the tool includes questions about common treatable etiologies. Finally, the fourth part emphasizes signs suggestive of a CNS infection and includes cerebrospinal fluid (CSF) findings if a lumbar puncture is performed. At the end of the assessment, the rater is invited to record the suspected etiology as free text based on the assessment directed by the SEEIT. The tool also includes the list of investigations required by current guidelines for SE evaluation [9]. The etiology is eventually placed into

one of the 19 categories (see **Table 1)** to enable evaluating concordance with the definitive etiology determined at the end of the hospital stay. Of note, for the concordance evaluation, when an acute precipitating factor occurred in the context of a remote brain injury, the "acute" condition was considered predominant, as the tool aims to identify acute treatable conditions.

The SEEIT was completed for every patient at the time of identification by the study team -- based only on the information available in the ED or at the time of in-hospital SE identification and before discharge summary diagnosis was available. The first author (VA) completed the SEEIT for the three centers involved in Boston, USA (BWH, MGH, BIDMC) and the EEG attending filled the assessment under the same conditions for the patients in the CHUV, Lausanne, Switzerland.

Because the SEEIT was designed to be used by non-specialist physicians and was also completed by neurologists with specialty training in epilepsy, an inter-rater evaluation between one of the investigators (VA) and an emergency physician (fourth year Emergency resident at BWH) (DC) was performed for the first 30 cases of SE treated at BWH. To reflect the "real-life" use of the tool, the ED physician did not receive any training in use of the SEEIT.

- **Statistical analysis**

  Inter-rater evaluation between VA and DC, and concordance between the etiologies generated by the SEEIT and the etiology finally determined during the hospitalization, were evaluated with Cohen's kappa coefficient. In order to identify any misleading factors for correct early etiology identification, patients with correct and incorrect etiologies generated using the SEEIT were compared using χ^2, ANOVA and Wilcoxon rank-sum test, as required.

Significance was assumed with $p < 0.05$. Data were analyzed using Stata 11.1 (StataCorp, College Station, Texas, USA).

Results:

The **Figure 2** outlines the study profile. A total of 212 consecutive patients were included in the study. Demographics and SE characteristics are summarized in **Table 2**. Gender was evenly distributed; the median age was 60 years old (range: 18-93). Premorbid seizures occurred in 49.1% patients. About half of the subjects had generalized convulsive seizures, followed by 28.9% with focal seizures with consciousness impairment, 15% with focal seizures without impairment of consciousness, and 8% with NCSEC. Absence and myoclonic status were infrequent, 1.42% and 0.5% respectively. Consciousness was impaired in most, with 17% of patients presenting as “comatose” and 41.5% “stuporous”. The mean STESS was 2.64 (SD: 1.63) and around half of patients suffered from refractory SE. A median of 3 ASDs (range: 0-13) was used and 11.3% underwent intubation as part of a SE treatment protocol. The mortality rate was 12.8%, while 45.3% of patients returned to their premorbid clinical baseline at discharge.

In addition to the 212 patients in SE, two had EEGs for SE but were eventually found to have PNESE. Both were treated acutely as refractory SE. One was intubated for “convulsion control.” Of note, in the patients’ charts, there were descriptions of the events including features such as “waxing-and-waning” symptoms “stopped by suggestion” for the first patient; and “waxing and waning” and “pelvic thrusting movements” for the second. The SEEIT-generated etiology was correct for these two events.

The definitive etiologies at hospital discharge are listed in **Table 1**. ASD related causes (non-adherence, iatrogenic withdrawal, sub therapeutic level) were the most frequent, occurring in 16.3%, followed by brain tumor (without acute change in the tumor) in 13.2%. The “unclassified” category included 3 cases of multiple sclerosis, 2 confirmed and 1 possible posterior reversible encephalopathy syndrome (PRES), 2 neoplastic meningitis, and single cases of NMDA encephalitis, neurosarcoidosis, eclampsia, arterio-venous malformation without bleeding, and microangiopathic hemolytic anemia. A need for specific etiologic treatment in addition to ASDs was considered necessary in 90 of 212 patients (42.45%).

The etiology identified early using the SEEIT was correct in 188 patients (88.7%) (95% CI: 86.4 – 89.8) with a kappa coefficient of 0.88. There was inter-rater agreement in 83.3% (95% CI: 80.4 – 96) of cases between VA and the DC, with a kappa coefficient of 0.81.

A further analysis comparing features of patients with a correct SEEIT-generated etiology versus an incorrect one did not show any significant differences regarding age (p=0.95), gender (p=0.08), participating center (p=0.81), type of seizure (p=0.81), level of consciousness (p=0.94), time to treatment (p=0.36), or refractory SE (p=0.50). Only the absence of previously known seizures was associated with a higher risk of incorrect early etiology identification. A total of 103 of the 188 patients with an etiology correctly determined by the SEEIT had a history of earlier seizures (54.8%), whereas this was the case in only 5 of 24 patients with an incorrectly SEEIT-determined etiology (20.8%) (p=0.002, χ^2).

Table 3 provides a detailed description of the 24 cases in which the etiology generated using the tool was incorrect. Seven (29.2%) were misdiagnosed due to

information missed on early imaging, five (20.8%) due to CSF misinterpretation, three (12.5%) to incomplete history, and three (12.5%) presentations were probably too complex to be diagnosed accurately in the ED setting (1 NMDA-encephalitis, one with microangiopathic hemolytic anemia, and one with toxoplasmosis). In two patients (8.4%), known remote conditions were incorrectly assumed to be the etiology when others factors were actually responsible. One misdiagnosis (4.2%) was due to misinterpretation of a systemic inflammatory response syndrome (SIRS). Finally, three (12.5 %) were misdiagnosed due to disagreement on causality judgment of minor precipitants between the tool rater and the hospital discharge summary.

Discussion:

The principal finding of this study is that early identification of the underlying etiology for SE is possible using a tool designed to guide differential diagnosis assessment. The SEEIT appears valid, with concordance in 88.7% of cases between the etiology hypothesis generated using SEEIT and the definitive etiology determined at hospital discharge. It is also reliable, with a high inter-rater agreement between physicians of different subspecialties and levels (ED resident and trained neurologist). Consequently, the SEEIT may be of assistance to non-specialist physicians in guiding their identification of the etiology of SE promptly and expeditiously.

This early identification of SE etiology is important, as in this cohort nearly half of patients warranted a specific treatment of the illness causing their SE, along with ASD treatment. Further, because etiology is one the most important determinants of SE outcome [4, 5, 10, 20], an etiology-tailored treatment should be initiated as early as possible, particularly in conditions such as CNS infection, sepsis, metabolic

disturbances, or acute cerebrovascular illnesses. This tool may be valuable in prompting clinicians to think earlier about etiology-guided treatment. Trying to improve ASD protocols and refining them may have a limited impact on SE outcome. Indeed, protocol adherence [21] and newer ASDs do not appear to affect prognosis [22] while intramuscular treatment [23] and prehospital protocols [24] already allow very rapid ASD administrations. Therefore, alternatives to ASD trials should be explored to improve outcome of patients suffering from SE. Efforts aimed at identifying and targeting the underlying biological background could be one option [10], [25].

A further relevant finding is that two patients presenting with PNESE signs noted in the first part of the SEEIT were treated as having refractory SE, possibly because of lack of awareness of PNESE symptoms in the ED; one was even intubated. Indeed, these episodes are frequently misdiagnosed as “refractory SE” [19] and poor outcome due to overtreatment has been reported [26]. By highlighting some clinical features of PNESE, the SEEIT may help avoid unnecessary, and potentially harmful, treatment in these occasions. Of note, the rate of PNESE mistaken for SE is low in this cohort. This is likely explained by the tertiary care setting and the 24/7 availability of neurology consultants in the four centers involved in this study.

We were unable to demonstrate any significant factors that interfered with correct etiology identification using our tool, other than presence of prior seizures. This may reflect the fact that medication non-adherence or recent treatment adjustments are common SE causes and are easy to recognize. This reinforces the principle that all patients with SE should be evaluated carefully to identify the underlying etiology, independently of age, seizure type, or SE severity.

The detailed description of misdiagnosed cases (**Table 3**) shows that brain MRI is crucial if history and CT scan fail to identify the etiology; in another smaller study, MRI improved the diagnosis by 32% in a cohort of 34 patients [27]. CSF data may be misleading. Some cases of SE were incorrectly labeled as due to infectious processes because of the CSF pleocytosis -- which turned out to be non-infectious (due to neoplasic or auto-immune conditions) or due to the SE itself in one case of mild pleocytosis, which can be seen in 10% of SE occurring in the setting of a known epilepsy [28]. Nevertheless, because the exact cause of CSF pleocytosis may take several days to be clarified, and in view of the potential poor outcome associated with CNS infections, it is still reasonable to consider all SE with pleocytosis as infectious until proven otherwise. This study also included a 75-year-old man with new onset refractory SE associated with fever and a normal CSF study (4 white cells) performed 36 hours after symptom onset his and CSF PCR showed HSV 1 encephalitis. CSF is abnormal in 95% of HSV1 encephalitis [29], but can be normal early in the illness [30], as illustrated by this case. This particular pitfall is pointed out in the SEEIT tool.

As reported earlier [31, 32], subtherapeutic ASD levels due to non-adherence or treatment adjustment are among the most frequent causes of SE. This should be addressed carefully by a thorough history, and ASD levels should be obtained when appropriate. Because some newer ASD levels cannot be measured quickly, detecting non-adherence based on this feature alone can be difficult. A careful history with relatives is thus very important in such cases. The relatively high incidence of SE due to brain tumors in this cohort, as opposed to previous studies [31, 33] is likely due to a referral bias, as the four institutions in this study have, or are closely associated with, large neuro-oncology clinics. Similarly, while alcohol withdrawal was a frequent

precipitant in other series, ranging from 13% [32] to 17% [31] it was infrequent in ours (2.8%), also probably explained by a referral bias.

The strength of this study is the large number of patients from four international sites and the prospective evaluation implying a good potential for generalization and good data quality. The main limitation is that the SEEIT was completed by the study investigator familiar with it (a neurologist) and not by the treating physician. This could help to explain the high concordance coefficient between the SEEIT and the etiology determined after a comprehensive evaluation. Still, the inter-rater agreement evaluation between the study investigator and an emergency physician was high, and there was no difference in the agreement rate among the four centers involved. Another limitation is that the SEEIT relies on history for some items and sometimes there are neither relatives nor witnesses. A comprehensive history is a key component in the management of many conditions, including SE, and unfortunately, our tool cannot fill the lack of information in these situations. Moreover, as patients were screened by using the EEG request (and not in the ED), we could not exclude the possibility that some information available in the EEG laboratory influenced the investigator completing the tool, but only information available during the ED stay was used for the early etiology assessment. Also, we cannot exclude that due to the EEG screening process, some brief or unrecognized SE episodes were missed. Indeed, in these situations, treating physician might not have requested an EEG. Also, the yield of each item in the SEEIT was not evaluated, but in clinical practice, a diagnosis is made after a global assessment and not based on one particular feature alone. Another shortcoming is that the SEEIT failed to identify definite etiology correctly because sometimes history, imaging or some data were not available. The results would perhaps have been different if all information were available in each

case. However, in that case, this would probably have increased the performance of SEEIT. The tertiary hospital setting may also confer a selection bias. Indeed, this may have resulted in the inclusion of more patients with severe SE. We do not believe that this should influence the validity of the SEEIT. Moreover, fewer patients were enrolled at the MGH than at the BWH. We cannot exclude the possibility of under sampling at the MGH and do not expect this to have influenced our findings. Finally, we used broad inclusion criteria: all types of SE, and an operational definition [9], as opposed to more rigorous inclusion criteria focusing on generalized convulsive SE lasting more than 30 minutes. As the SEEIT is designed to be used in daily practice, these inclusion criteria may better reflect “actual clinical practice".

This study shows that the SEEIT correctly identify the cause of a SE in 88.7%. It also demonstrates that it is possible to identify the etiology of an episode of SE early with a valid and reliable clinical tool to guide differential diagnosis, used by physicians from different subspecialties. Further studies are needed to evaluate whether the SEEIT will improve decision-making process in SE management, avoiding unnecessary investigations or treatments, influencing the length of stay, or impacting on clinical outcome.

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Required statement:

Our work described here is consistent with the Journal's guidelines for ethical publication

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Tables and Figures:

Table 1: List of diagnostic categories and their frequencies as definitive SE etiology

Total, n=212	n	%
ASD related (non-adherence, recent change or low levels)	34	16.04
Brain tumor without acute change (no change or increase in tumor load)	28	13.21
Acute hemorrhagic cerebrovascular event	21	9.91
Known epilepsy (non-structural) without provocative factors (breakthrough seizures)	16	7.55
Remote ischemic cerebrovascular event	14	6.6
Unclassified*	13	6.13
CNS infection (meningitis or encephalitis)	12	5.66
Unknown origin	11	5.19
Toxic-metabolic	10	4.72
Systemic infection / sepsis	10	4.72
Remote hemorrhagic cerebrovascular event	8	3.77
Acute TBI	7	3.3
Acute ischemic cerebrovascular event	5	2.36
Remote TBI	6	2.83
Alcohol related (withdrawal or intoxication)	6	2.83
Brain tumor with acute change (bleeding, recent biopsy/surgery or rapid increase in edema)	5	2.36
Benzodiazepine withdrawal	4	1.89
Neurodegenerative disease	2	0.94
Other drugs known to reduce seizure threshold	0	0

Abbreviations: ASD = anti-seizure drug, CNS = central nervous system, TBI = traumatic brain injury

*: Unclassified includes: 3 multiple sclerosis, 2 confirmed and 1 possible posterior reversible encephalopathy syndrome (PRES), 2 tumoral meningitis, 1 NMDA encephalitis, 1 neurosacroidosis, 1 eclampsia, 1 arteriovenous malformation without bleeding and 1 cases of microangiopathic hemolytic anemia

Table 2: Cohort description

Patients (n=212):		
Demographics:		
Age (median, range)	60	18-93
Male (n,%)	106	50
History of previous seizures (n,%)	104	49.1
Center (n,%)		
CHUV	104	49.1
BWH	65	30.7
MGH	30	14.2
BIDMC	13	6.1
SE characteristics		
Worst seizure type (n,%)		
Focal without consciousness impairment	32	15.1
Focal with consciousness impairment	57	28.9
Absence	3	1.42
Myoclonic	1	0.5
Generalized convulsive	102	48.1
Non-convulsive SE in coma	17	8
Level of consciousness before treatment (n,%)		
Alert	24	11.3
Confused	51	24.1
Somnolent	13	6.1
Stuporous	88	41.5
Comatose	36	17
STESS (mean, SD)	2.64	1.63
Refractory SE (n,%)	119	56.12
Number of different ASD used (median, range)	3	0 - 13
Coma induction for SE control (n,%)	24	11.3
Outcome at discharge (n,%)		
Return to clinical premorbid baseline	96	45.3
New morbidity	89	42
Death	27	12.8

Abbreviations: ASD = anti-seizure drug; BWH= Brigham and Women's Hospital; BIDMC = Beth Israel Deaconess Medical Center; CHUV = Centre Hospitalier Universitaire Vaudois; MGH= Massachusetts General Hospital; STESS = Status Epilepticus Severity Score.

Table 3: Details of patient for which the early suspected etiology using the SEEIT was incorrect**.**

Pt	Age	Gender	Previous seizures	Etiology generated using the SEEIT	Final etiology	Case description	Explanation
1	54	F	No	Cryptogenic	Brain Glioma	Small temporal glioma was missed in the CT performed in ED, but seen on MRI later. Of note, because seizures were focal, the tool advised an MRI.	Etiology missed on CT
2	76	M	No	Cryptogenic / encephalitis?	Brain Glioma	Because of new onset refractory epilepsy with normal CT and normal CSF analysis, SEEIT evoked a cryptogenic SE or encephalitis in early phase / autoimmune process. The later MRI revealed a glioma.	Etiology missed on CT
3	40	F	Yes	Drugs related (ciprofloxacine)	Known epilepsy without provocative factors	Patient with known epilepsy experienced SE in the context of ciprofloxacine prescribed for UTI without systemic involvement. The discharge summary did not retain ciprofloxacine as provocative factor.	Disagreement on causality judgment of minor precipitants
4	57	F	No	Meningo-encephalitis (infectious)	Carcinomatous leptomeningitis	SE after lumbar surgery for vertebral metastasis (breast cancer). CSF showed a pleocytosis (115 white cells/mm3). Infectious meningitis was proposed by the SEEIT. Further CSF analysis revealed metastatic cells.	CSF data misinterpreted
5	21	F	No	Meningo-encephalitis (infectious)	NMDA encephalitis	Presented with refractory SE and mild CSF pleocytosis. Possible CNS infectious was retained using the SEEIT. Further analysis didn't find any infectious agent and revealed NMDA anti-bodies.	Failure to identify a complex disease in the emergency setting
6	72	M	No	Remote ischemic stroke	Lymphomatous meningitis	Known for Waldenstrom disease. Initial imaging showed an old previously asymptomatic stroke retained as responsible using the SEEIT. LP done because of unexpected evolution revealed lymphomatous meningitis.	Remote brain pathology incorrectly retained
7	19	F	Yes	Known epilepsy without provocative factors	Cryptogenic	History revealed a couple febrile seizures during childhood and no other explanation. Because of the very long time before recurrence of seizure, she was not considered as having epilepsy before the SE episode and thus considered as cryptogenic.	Disagreement on causality judgment of minor precipitants
8	71	F	No	Drug related (clozapine)	Posterior reversible encephalopathy syndrome (PRES)	In the context of severe anxiety for 3 days, clozapine was prescribed and increased. Then the patient presented with altered mental status and visual hallucinations. Focal SE was diagnosed after EEG. Initial imaging was non conclusive. The etiology retained using the SEEIT was related to the clozapine. Later MRI revealed a PRES.	Etiology missed on CT
9	67	F	No	Meningo-encephalitis (infectious)	Cryptogenic	Refractory SE and fever at the presentation. Despite a mild pleocytosis, the CSF remained sterile. The pleocytosis was attributed to seizures.	CSF data misinterpreted
10	75	M	No	Cryptogenic	HSV 1 encephalitis	Because of fever and new onset SE, the SEEIT suggested a CSF analysis, which was normal (4 WBC). Later, PCR came back positive for HSV1. LP was performed early (ca. 36 hours after onset), so the SEEIT warned against "false" normal CSF in early phase of an encephalitis.	CSF data misinterpreted
11	46	F	Yes	Sepsis	Possible posterior reversible encephalopathy syndrome (PRES)	SE in the context of sepsis (pulmonary origin) and known epilepsy. So, using the SEEIT, sepsis was considered as a provocative factor. Later MRI was consistent with a PRES. However it was not excluded for certain that the MRI changes were due to seizures.	Etiology missed on CT
12	40	F	Yes	Sepsis	Known epilepsy without provocative factors	SE in the context of fever, systemic inflammatory response syndrome (SIRS) and known epilepsy. So, using the SEEIT, sepsis was considered as a provocative factor. The complete evaluation did not find any infectious source. The SIRS was attributed to the SE itself.	SIRS incorrectly suspected

13	54	F	No	Acute ischemic stroke	Brain abscess due to Bacillus Cereus endocarditis	Patient known for acute myeloid leukemia. Initial CT showed a probable new ischemic stroke. Subsequent MRI revealed an abscess. Endocarditis was subsequently found.	Etiology missed on CT
14	60	M	No	Cryptogenic	Alcohol withdrawal	Alcohol withdrawal was denied during initial assessment.	Incomplete history information
15	79	M	No	Dementia	Chronic lymphocytic leukemia with CNS infiltration	Known for advanced dementia and chronic lymphocytic leukemia. Initial imaging was non conclusive. MRI was performed 4 days later and showed focal lesions likely due to infiltrative lymphoma.	Remote brain pathology incorrectly retained
16	69	F	No	Toxicometabolic (in the context of a known CNS B lymphoma)	Microangiopathic hemolytic anemia	Initial laboratory testing showed renal and liver impairments of unknown origin. The extensive evaluation revealed a microangiopathic hemolytic anemia.	Failure to identify a complex disease in the emergency setting
17	71	M	No	Meningo-encephalitis (infectious)	Diffuse large B-cell lymphoma with CNS infiltration	Presented with SE preceded by rapid cognitive decline. CSF showed pleocytosis (728 white cells/mm3). CNS infection was suspected. Extensive evaluation did not find any etiology. A malignant edema leaded to herniation. Autopsy showed a diffuse CNS infiltration by large B-cell lymphoma.	CSF data misinterpreted
18	36	M	No	Brain lesion of unclear origin	Cerebral toxoplasmosis	Known for HIV. The evaluation in the emergency department identified a newly diagnosed mass without clear precision. The complete evaluation revealed a cerebral toxoplasmosis.	Failure to identify a complex disease in the emergency setting
19	76	M	No	Cryptogenic	Remote subarachnoid hemorrhage	The previous history of subarachnoid hemorrhage was unknown at initial presentation.	Incomplete history information
20	68	F	No	Toxic-metabolic	Acute ischemic stroke	Presented with several mild metabolic disturbances and the initial CT was considered as normal. Subsequent MRI, advised by the SEEIT because of focality in the clinical manifestation, revealed an acute stroke.	Etiology missed on CT
21	83	F	No	Cryptogenic	Acute ischemic stroke	Initial imaging was considered as normal. Subsequent MRI, advised by the SEEIT because of focality in the clinical manifestation, revealed an acute ischemic stroke.	Etiology missed on CT
22	79	F	No	Drugs intoxication	Dementia	Patient had mild increase in anti-psychotic treatment in setting of dementia and very mild hypernatremia. However, the features identified by the SEEIT were not considered as sufficient to provoke SE.	Disagreement on causality judgment of minor precipitants
23	49	F	Yes	Known epilepsy without provocative factors	ASD related	Patient known for epilepsy treated with LEV, VPA and LCM. There was no evidence of non-adherence in initial evaluation. Later, low level of VPA level became available and pointed out non-adherence.	Incomplete history information
24	27	F	No	CNS infection	Cryptogenic (NORSE)	Presented with flu-like symptoms a week before entering a prolonged refractory non-convulsive SE in coma. The CSF in early phase showed a mild lymphocytosis (15 white blood cells / mm3). Despite a very broad evaluation including wide infectious and autoimmune panels, no etiology was found. She left the hospital 74 days later with significant cognitive problems.	CSF data misinterpreted

Figure 1: The Status Epilepticus Etiology Identification Tool (SEEIT)

Legend: The SEEIT tool as been designed to guide SE etiology assessment. It has to be used along with anti-seizure-drug protocol. Each point has to be assessed.

Figure 2: Study profile

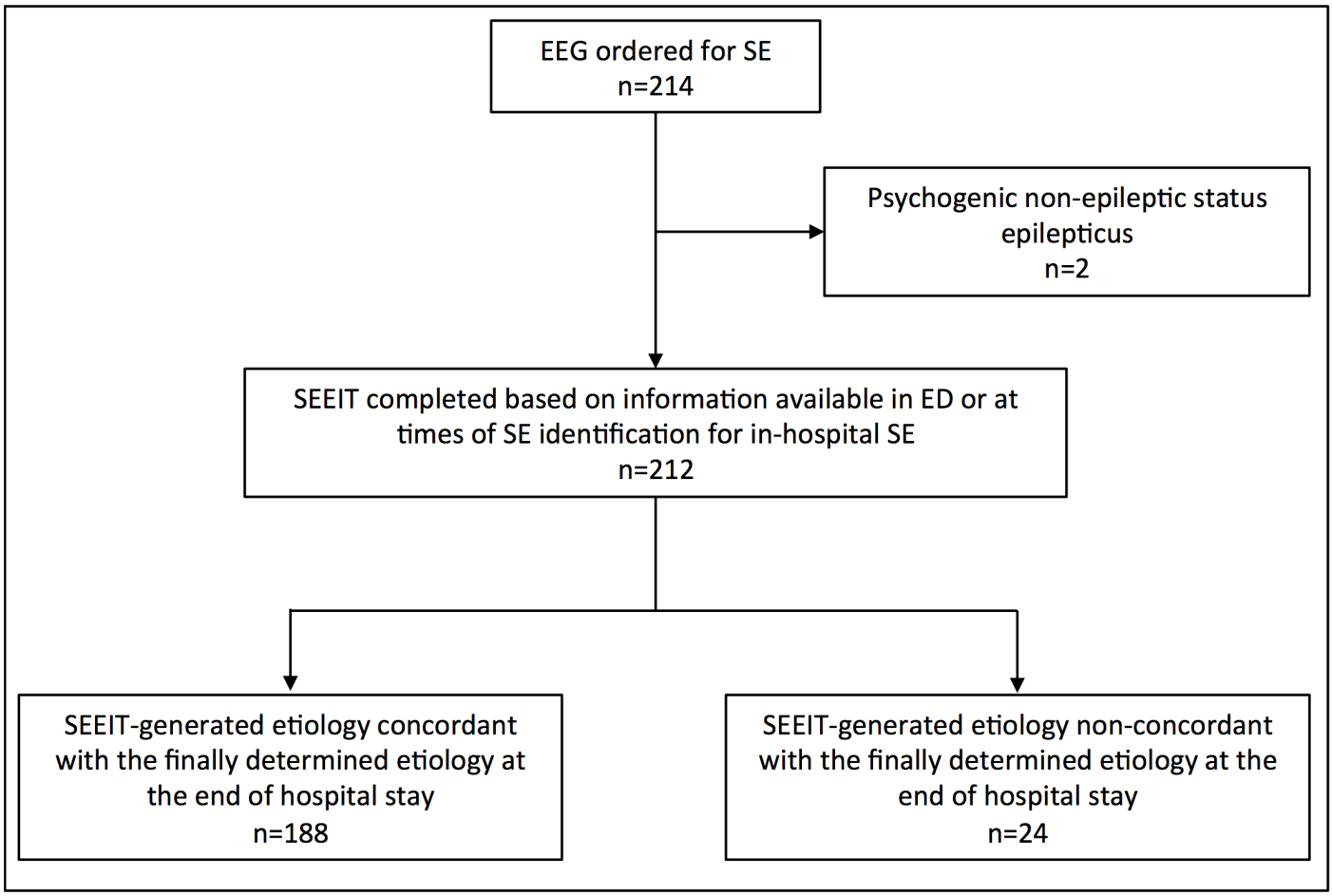
Abbreviations: EEG: electroencephalogram; SE: status epilepticus; SEEIT: Status Epilepticus Etiology Identification Tool.

Date:……
Patient ID:……..
……..

STATUS EPILEPTICUS ETIOLOGY IDENTIFICATION TOOL (SEEIT)

- It is designed to guide clinical assessment in acute phase of status epilepticus and it is not supposed to be exhaustive.
- It has to be performed in parallel with the usual anti-epileptic drugs (AED) treatment (ttt) protocol.
- Each item from point 1, 2, 3 or 4 **has to be assessed**.
- For every patient this work-up should be done: (cf. Guidelines for the Evaluation and Management of Status Epilepticus, Brophy 2012):
  - Finger stick glucose & Monitor vital signs
  - Head computed tomography (CT) scan (required for most cases)
  - Laboratory test including: blood glucose, complete blood count, basic metabolic panel, calcium, magnesium, anti-epileptic drug levels if appropriate.
  - Electroencephalograph (EEG)

1. Is it really a Status Epilepticus (SE) episode?	⇩	
A. Any signs for Psychogenic Non-Epileptic Seizure (opposition to eyes opening, « waxing and waning » movements, pelvic thrusting, stopped or induced by suggestion)	Yes → avoid AED escalation	No
B. Seizures lasting more than 5 min or repeated seizures without regain of consciousness	Yes ⇨ Point 2	No →Review dx
2. A) Previous seizures, known epilepsy, or B) De novo seizures but known structural brain damage (stroke, trauma, old meningo-encephalitis…) or C) De novo seizure but known brain progressive condition (dementia, tumor…)? • *Specify*: ……	**Yes** ⇩	**No ⇨ Point 3**
A. AED non-compliance / recent decrease dosage / low level: *Specify*:……..	Yes	No
B. Systemic infection: *Specify*:……..	Yes	No
C. Alcohol or drug (incl. benzodiazepine and illicit drugs) withdrawal or acute intoxication • Consider toxicology screen: *Specify*:……	Yes	No
D. Significant metabolic disturbances (i.e. blood glucose and natremia). *Specify*:……..	Yes	No
E. Progression or change in previous neurological condition clinically or radiology (e.g., new symptoms, tumor progression, bleeding, biopsy, recent surgery…): *Specify:* ……	Yes	No
F. Refractory SE without clear explanation, new neurological abnormality, neck stiffness or fever without systemic explanation. *Specify:*……	Yes ⇨ point 4	No
G. None of these.	Yes → no acute etiology→ adapt AED ttt	
3. De novo SE (first ever seizure) without known brain disease?	**Yes** ⇩	**No ⇨ Point 2**
A. Newly diagnosed, previously asymptomatic structural brain damage or EEG suggesting Idiopathic Generalized Epilepsy (IGE) / Genetic Generalized Epilepsy (GGE): *Specify*:……	Yes	No
B. Acute brain lesion (ischemic or hemorrhagic stroke, cerebral venous thrombosis, SAH, SDH, traumatic brain injury, encephalitis…): *Specify*:……	Yes	No
C. Alcohol or drug (incl. benzodiazepine and illicit drugs) withdrawal or acute intoxication • Consider toxicology screening: *Specify*:……	Yes	No
D. Significant metabolic disturbance (i.e. blood glucose and natremia). *Specify*:……	Yes	No
E. Severe systemic infection (sepsis): *Specify*:……	Yes	No
F. Refractory SE without clear explanation, neck stiffness or fever without systemic explanation. *Specify:*……	Yes ⇨ point 4	No
G. None of these with favorable evolution under AED	Yes →SE possibly cryptogenic, but consider MRI if clinical/EEG focal sign and normal CT	
4. Fever or systemic inflammatory response without extra-neurological infectious process, meningeal sign, unusual headache, recent behavior change, or refractory SE without clear etiology • *Specify*:…… • Think about IV empirical antimicrobial therapy for meningo-encephalitis and blood culture, then lumbar puncture if no contraindication	**Yes** ⇩	**No** ⇨ Stop
A. Normal CSF (pay attention to normal CSF in early phase of encephalitis)? • CSF details:…… …… ……	Normal CSF→ May be cryptogenic. Consider autoimmune disease	Abnormal CSF→ Empirical antimicrobial therapy. Consider autoimmune causes
➢ **Suspected etiology after the first evaluation:**		


EEG ordered for SE
n=214
Psychogenic non-epileptic status epilepticus
n=2
SEEIT completed based on information available in ED or at times of SE identification for in-hospital SE
n=212
SEEIT-generated etiology concordant with the finally determined etiology at the end of hospital stay
n=188
SEEIT-generated etiology non-concordant with the finally determined etiology at the end of hospital stay
n=24