Status Epilepticus (SE)

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Status epilepticus (SE)

- A critical care emergency
  - Both convulsive and nonconvulsive status epilepticus (CSE >> NCSE)
- Current treatment approaches vary dramatically
- Goal
  - Rapid termination of the seizure activity
  - To reduce neurological injuries and deaths
- High mortality esp. refractory status epilepticus

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- **Trinka, et al. ILAE. Epilepsia 2015**

Table 1. Operational dimensions with t_1 indicating the time that emergency treatment of SE should be started and t_2 indicating the time at which long-term consequences may be expected

Type of SE	Operational dimension 1 Time (t_1), when a seizure is likely to be prolonged leading to continuous seizure activity	Operational dimension 2 Time (t_2), when a seizure may cause long term consequences (including neuronal injury, neuronal death, alteration of neuronal networks and functional deficits)
Tonic–clonic SE	5 min	30 min
Focal SE with impaired consciousness	10 min	>60 min
Absence status epilepticus	10–15 min[a]	Unknown

[a]Evidence for the time frame is currently limited and future data may lead to modifications.

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Etiologies: acute process

- Metabolic disturbances
  - Electrolyte abnormalities
  - Renal failure
  - Sepsis
- Central nervous system
  - Infection
  - Stroke
  - Head trauma
  - Drug toxicity
  - Hypoxia

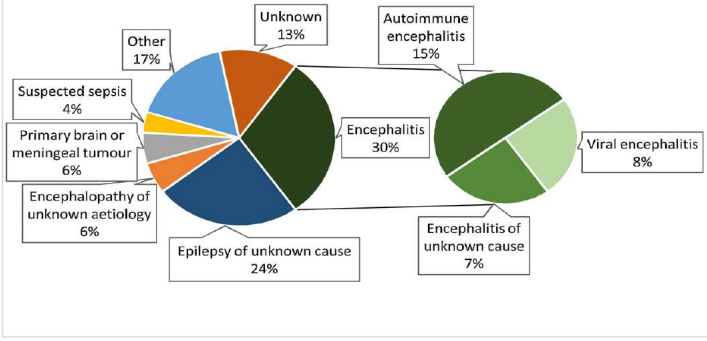

Fig. 1. A pie chart displaying the proportion of aetiologies recorded in the sample.

Kerin B, et al. Seizure 2021

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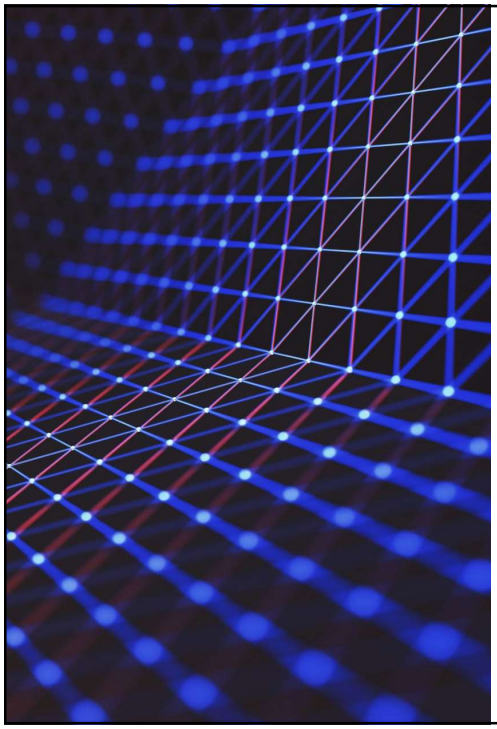

Cause: chronic process

- Breakthrough seizures
- Discontinuation of antiepileptic drugs
- Chronic ethanol abuse
- CNS tumors or strokes or head injury
- * Respond well to anticonvulsant Rx*

Chin RF, et al. Eur J Neurol. 2004

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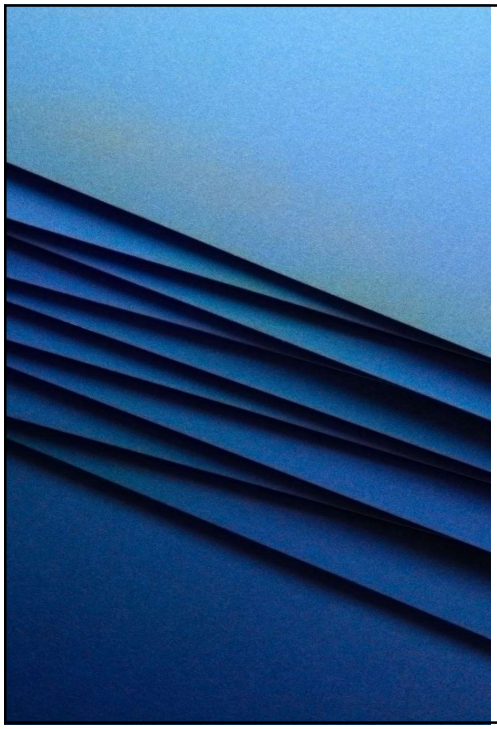

Status epilepticus

Convulsive status epilepticus

- Consisting of prolonged seizures or repeated generalized tonic–clonic (GTC) seizures with persistent postictal depression of neurologic function between seizures

Repeated partial seizures

- Manifested as focal motor signs, focal sensory symptoms, or focal impairment of function (e.g., aphasia) not associated with altered awareness (so called epilepsia partialis continua)

Nonconvulsive status epilepticus

- Where seizures produce a continuous or fluctuating "epileptic twilight" state

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Status epilepticus (SE) in ICU

- SE occur in up to 50% of critically ill patients with altered consciousness
- More than 80% of SE, they present without movements
- Focal status epilepticus (SE)

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Nonconvulsive seizures

We should know about….

Electrical abnormalities

Rhythmic or periodic EEG alterations **with evolution of field, amplitude and frequency**

Electrical (EEG) seizures:

Nonconvulsive seizures at least 10 seconds

Electrical status epilepticus:

Nonconvulsive status epilepticus at least 10 minutes

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EEG correlates

Terminology to describe EEG patterns in SE:
1 **Location:** generalized (including bilateral synchronous patterns), lateralized, bilateral independent, multifocal.
2 **Name of the pattern**: Periodic discharges, rhythmic delta activity or spike-and-wave/sharp-and-wave plus subtypes.
3 **Morphology:** sharpness, number of phases (e.g., triphasic morphology), absolute and relative amplitude, polarity.
4 **Time-related features:** prevalence, frequency, duration, daily pattern duration and index, onset (sudden vs. gradual), and dynamics (evolving, fluctuating, or static).
5 **Modulation:** stimulus-induced vs. spontaneous.
6 **Effect of intervention** (medication) on EEG.

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Review

Which EEG patterns in coma are nonconvulsive status epilepticus?

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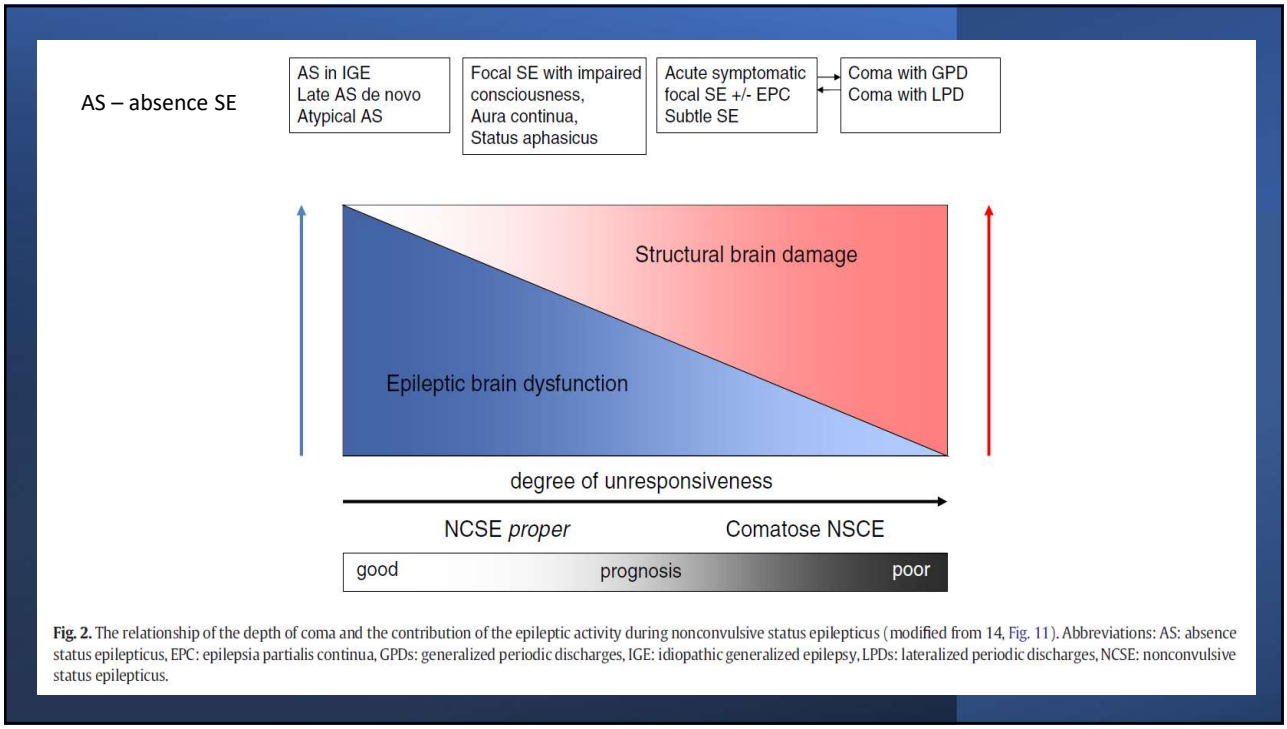

Fig. 2. The relationship of the depth of coma and the contribution of the epileptic activity during nonconvulsive status epilepticus (modified from 14, Fig. 11). Abbreviations: AS: absence status epilepticus, EPC: epilepsia partialis continua, GPDs: generalized periodic discharges, IGE: idiopathic generalized epilepsy, LPDs: lateralized periodic discharges, NCSE: nonconvulsive status epilepticus.

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Discharges

1) **Clear electrographic seizures and status epilepticus (SE),** i.e., generalized spike-wave discharges at 3/s or faster; and clearly evolving discharges of any type (rhythmic, periodic, fast activity), whether focal or generalized;

2. Clear interictal patterns, i.e., spike-wave discharges, periodic discharges, and rhythmic patterns at 1/s or slower with no evolution, unless accompanied by a clear clinical correlate, which would make them ictal regardless of the frequency

3. The ictal-interictal continuum, any EEG patterns that lie in between the above two categories

The term ictal-interictal continuum encompasses EEG patterns that are potentially harmful and can cause neuronal injury. There are no clear guidelines on how to treat EEG patterns that lie on this continuum.

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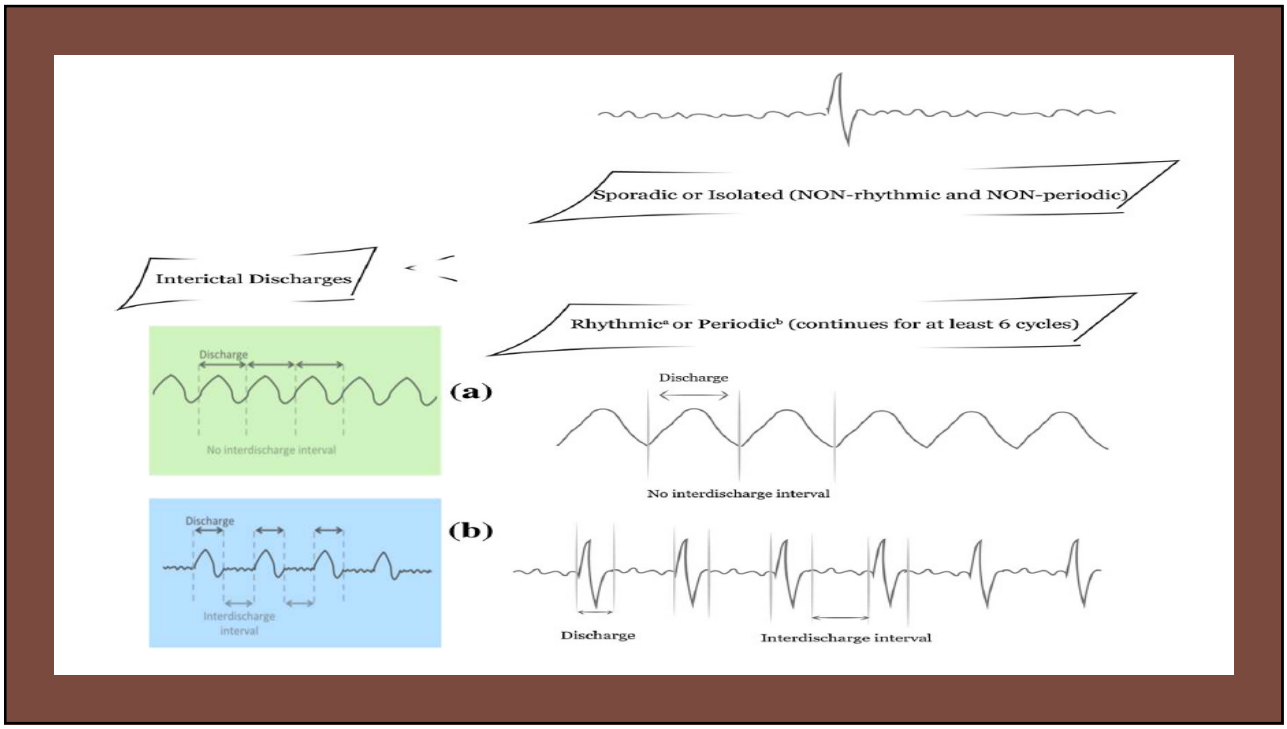
Sporadic or Isolated (NON-rhythmic and NON-periodic)
Interictal Discharges
Rhythmic[a] or Periodic[b] (continues for at least 6 cycles)
Discharge
No interdischarge interval
(a)
Discharge
No interdischarge interval
Discharge
Interdischarge interval
(b)
Discharge
Interdischarge interval

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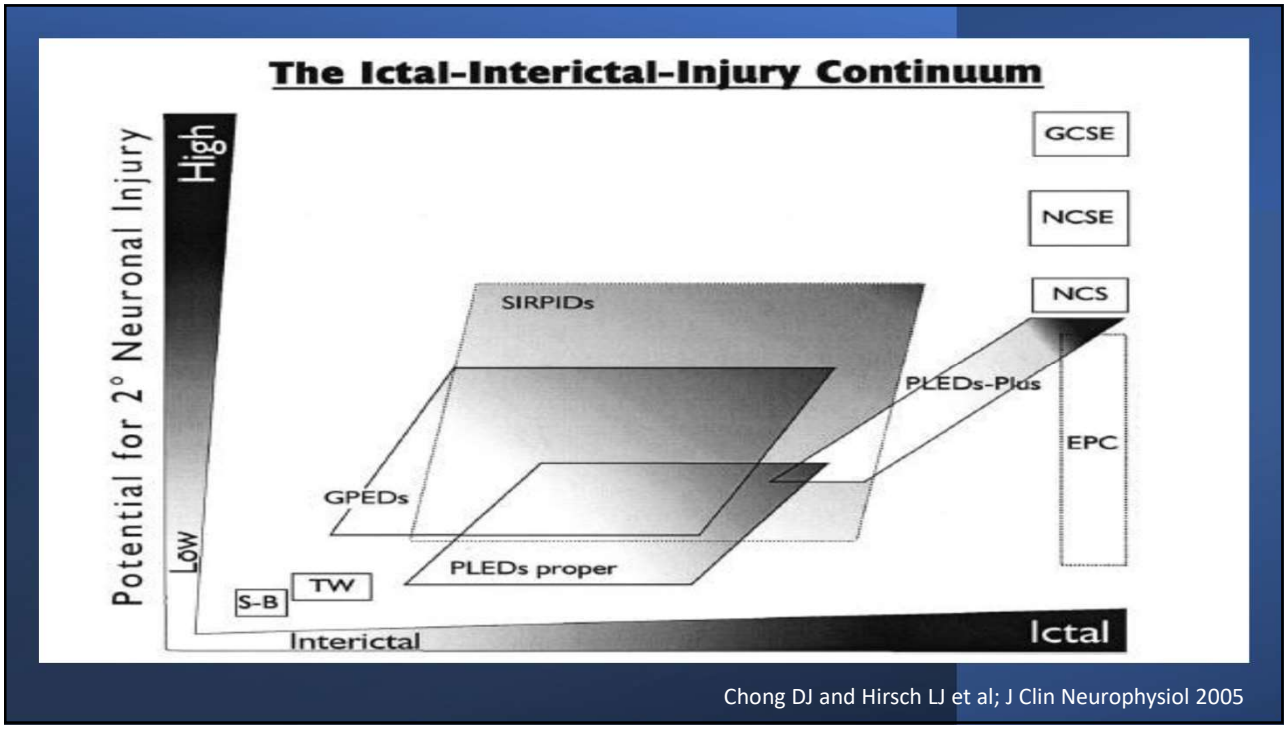
The Ictal-Interictal-Injury Continuum
Potential for 2° Neuronal Injury
High
Low
GCSE
NCSE
NCS
SIRPIDs
PLEDs-Plus
EPC
GPEDs
PLEDs proper
TW
S-B
Interictal
Ictal
Chong DJ and Hirsch LJ et al; J Clin Neurophysiol 2005

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TABLE 1. New Terms for Older Terms

OLD Term		NEW Term
Triphasic waves, most of record	=	continuous 2/s GPDs (with triphasic morphology)
PLEDs	=	LPDs
BIPLEDs	=	BIPDs
GPEDs/PEDs	=	GPDs
FIRDA	=	Occasional frontally predominant brief 2/s GRDA (if 1-10% of record)
PLEDS+	=	LPDs+
SIRPIDs* w/ focal evolving RDA	=	SI-Evolving LRDA
Lateralized seizure, delta frequency	=	Evolving LRDA
Semirhythmic delta	=	Quasi-RDA

*SIRPIDs = stimulus-induced rhythmic, periodic or ictal discharges.

Hirsch LJ et al; J Clin Neurophysiol 2013

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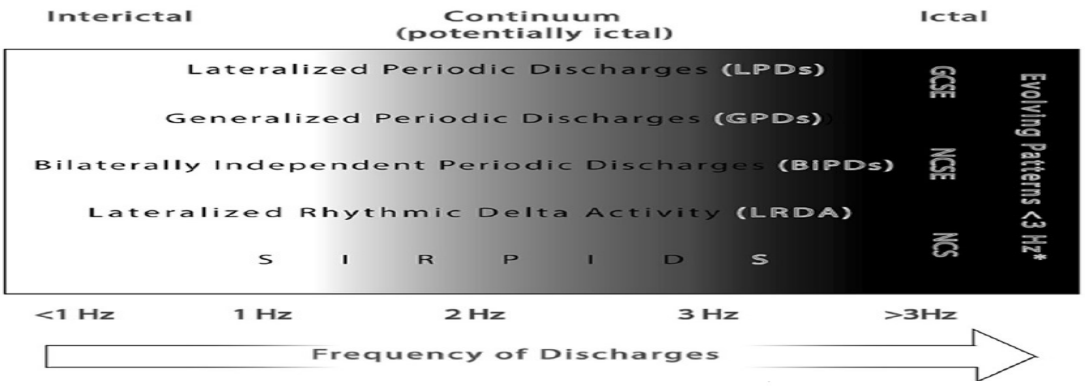

Fig. 3. This figure demonstrates various EEG patterns, primarily based on frequency depicted along the ictal-interictal continuum. The frequency of discharges is shown on the *x*-axis, which has traditionally been the benchmark guiding the aggressiveness of treatment. This frequency based division between intertical, continuum and ictal is arbitrary, conceptual, and does not take evolution of patterns into account. From our experience evolution of EEG patterns can be subtle, especially when observing long epochs in critically ill patients, and if often difficult to reach a consensus. However, the presence of even subtly evolving patterns increases the possibility of them being ictal. If clinical correlate is present with any of these patterns, it has to be considered ictal by definition, regardless of the frequency.*At least 1 Hz with clear (unequivocal) evolution in frequency, morphology, or location is considered to be ictal—see Table 1. *GCSE* generalized convulsive status epilepticus, *NCSE* nonconvulsive status epilepticus, *NCS* nonconvulsive seizure, *SIRPIDs* stimulus-induced rythmic periodic or ictal discharges

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EEG patterns	Do NOT reflect NCSE NOT TREATED	Reflect NCSE Should be TREATED	BORDERLINE Of NCSE in coma One additional criteria is needed to diagnose NCSE
❖ Classical coma patterm - Diffuse polymorphic delta activity - Spindle coma - Alpha/theta coma - Low votage - Burst suppression	× × × × ×		
❖ Ictal patterns with typical spatiotemporal evolution ❖ Epileptiform discharges > 2.5 Hz in comatose patients		× ×	
❖ GPDs or LPDs < 2.5 Hz ❖ Rhythmic discharges (RDs) > 0.5 Hz			× ×

Trinka U, et al. Epilepsy & Behav 2015

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LPDs

- DDx
- A variety of etiologies with cortical pathology
  - Encephalitis, stroke, subarachnoidal bleeding,
  - Trauma, tumors, cysticercosis, and intoxication
  - Subcortical pathology
- A long-lasting debate
  - Ictal, interictal, or semiictal pattern
- Comatose patients (coma-LPDs)
- LPDs
- LPD + F (with superimposed faster activity)
- BiPD, MfPD (bilateral, multifocal)

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Highly epileptiform patterns

- Represent as **high risk for seizures need to be vigilant**
- Periodic discharges (PDs) of any location
  - "Relatively uniform morphology and duration with a quantifiable
  - Inter-discharge interval between consecutive waveforms and recurrence, Nearly regular intervals
  - GPDs, LPDs, lateralized rhythmic delta activity [LRDA], GRDA, Brief potentially ictal rhythmic discharges [BIRDs])
- Recommend
  - Continuous EEG monitoring
  - Prophylaxis ASMs of cannot perform cEEG

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Epilepsia, 54(Suppl. 6):28–29, 2013
doi: 10.1111/epi.12270

STATUS EPILEPTICUS 2013

Unified EEG terminology and criteria for nonconvulsive status epilepticus

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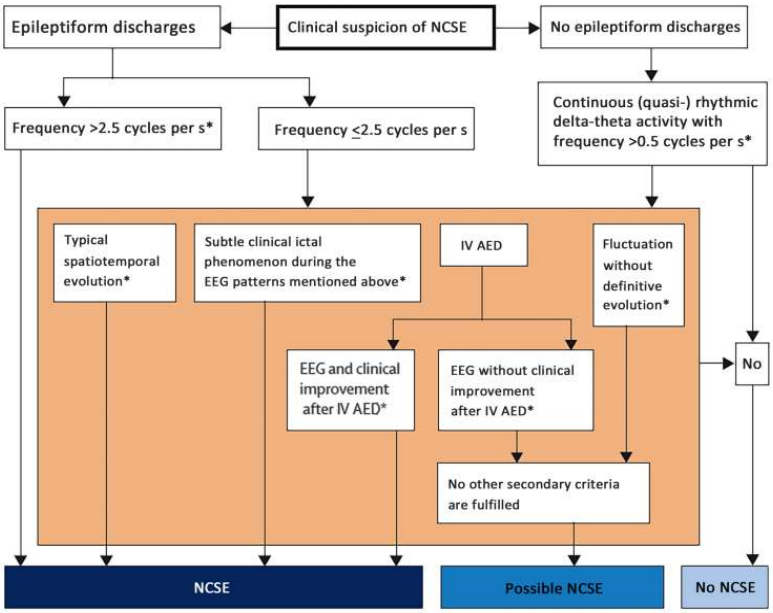
Salzburg Consensus Criteria for diagnosis of Non-Convulsive Status Epilepticus (SCNC) were proposed at the 4th London-Innsbruck Colloquium on status epilepticus in Salzburg (2013)



Validated in three different cohorts, with a sensitivity of 97.2%, a specificity of 95.9%, and a diagnostic accuracy of 96.3% in patients with clinical signs of NCSE

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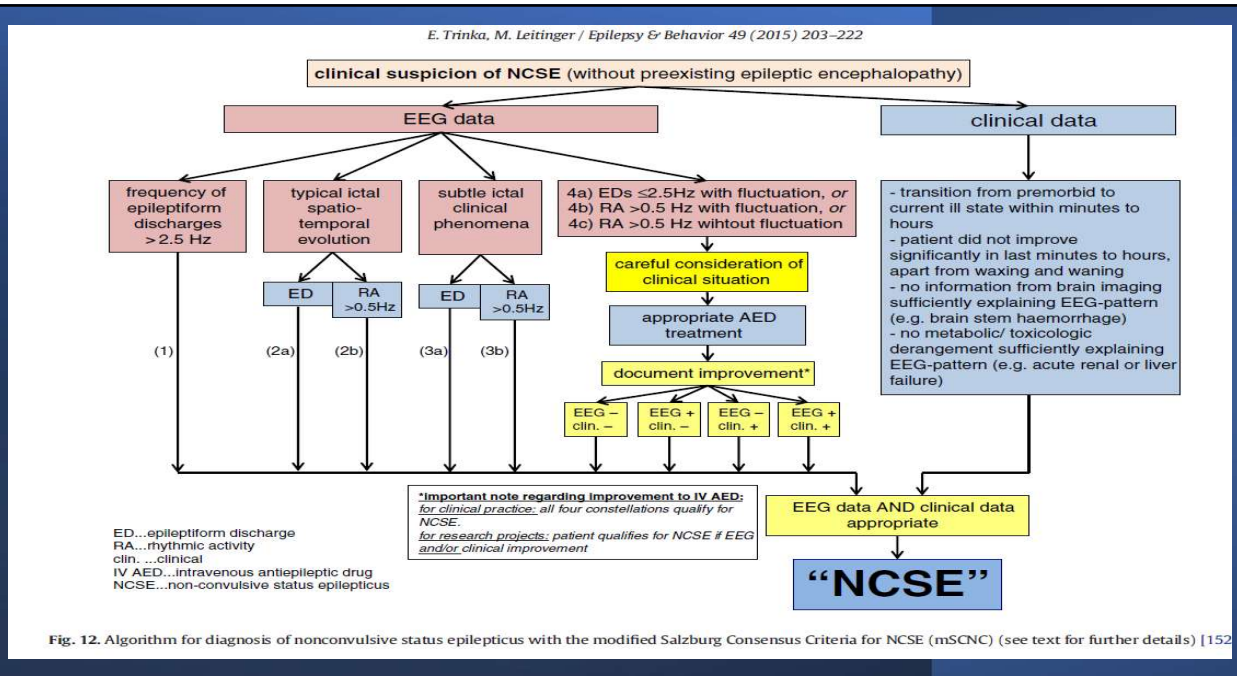

Fig. 12. Algorithm for diagnosis of nonconvulsive status epilepticus with the modified Salzburg Consensus Criteria for NCSE (mSCNC) (see text for further details) [152

Salzburg criteria for nonconvulsive status epilepticus: Details matter,Epilepsia. 2019;60:2334–2336.

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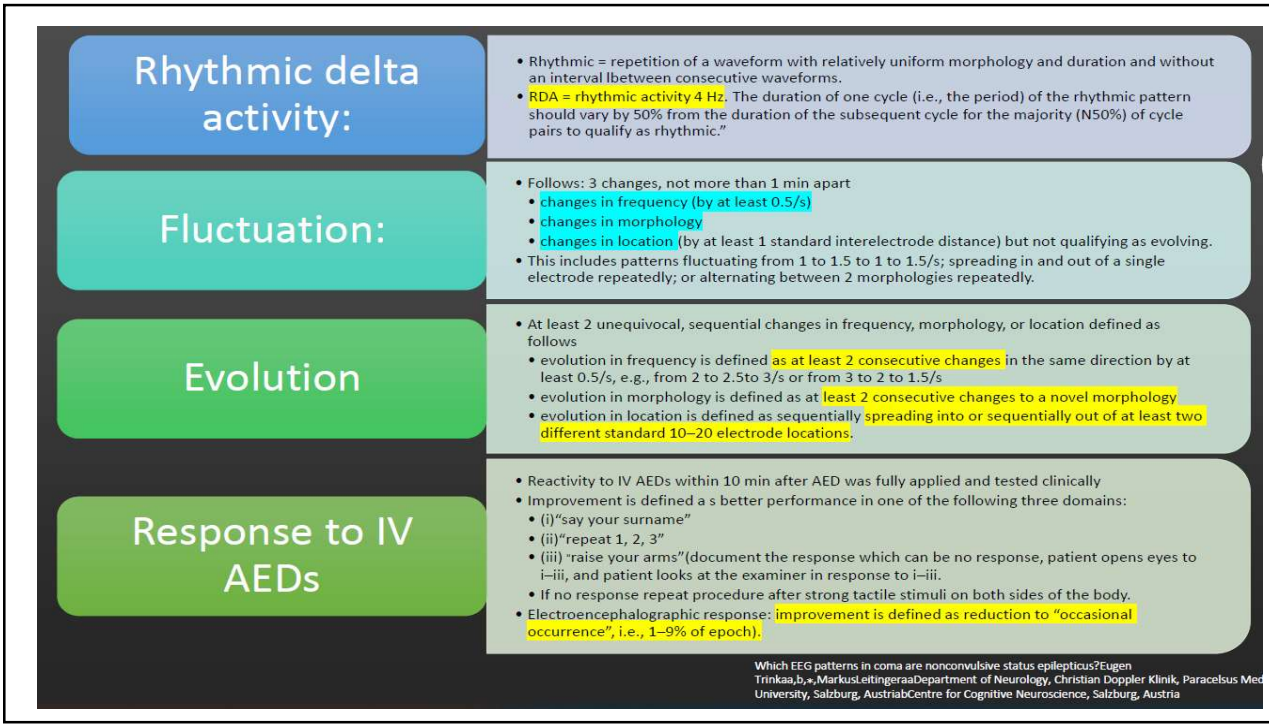

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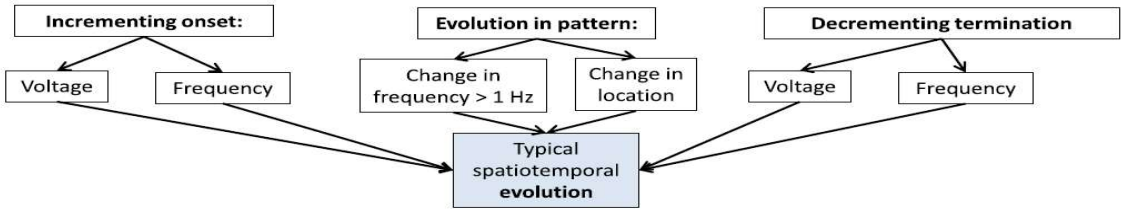

Evolution: *Incrementing onset (increase in voltage and change in frequency), or evolution in pattern (change in frequency >1 Hz and change in location), or decrementing termination (voltage and frequency).* ***AND ACNS criterion for "evolving" (ACNS-evolving)*** *"at least 2 unequivocal, sequential changes in frequency, morphology or location defined as follows: Evolution in frequency is defined as at least 2 consecutive changes in the same direction by at least 0.5/s, e.g. from 2 to 2.5 to 3/s, or from 3 to 2 to 1.5/s; Evolution in morphology is defined as at least 2 consecutive changes to a novel morphology; Evolution in location is defined as sequentially spreading into or sequentially out of at least two different standard 10-20 electrode locations. In order to qualify as present, a single frequency or location must persist at least 3 cycles (e.g. 1/s for 3 seconds, or 3/s for 1 second)"[2].*

ACNS-criterion for Rhythmic Delta Activity (ACNS-RDA) *"Rhythmic = repetition of a waveform with relatively uniform morphology and duration, and without an interval between consecutive waveforms. RDA = rhythmic activity < 4 Hz. The duration of one cycle (i.e., the period) of the rhythmic pattern should vary by <50% from the duration of the subsequent cycle for the majority (>50%) of cycle pairs to qualify as rhythmic." [2].*

Subtle ictal clinical phenomena: *minor twitching of mouth, periorbital region or extremities should appear in close temporal relation to EEG-pattern (be cautious concerning non-epileptic involuntary movements as mimicks, e.g. Parkinsonian tremor, drug induced myoclonus (e.g. opioids), serotonin syndrome,...),*

Reactivity to IV AEDs*: within 10 minutes after AED fully applied; clinical presentation tested: 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 tell, if no response demonstrate), (iv) patient opens eyes to i - iii, (v) patient looks at the examiner in response to i - iii. If no response repeat procedure after strong tactile stimuli on both sides of the body. EEG tested: improvement is defined as reduction to "occasional", i.e. 1-9% of epoch.*

ACNS criterion for fluctuation (ACNS-fluctuation) *" >3 changes, not more than one minute apart, in frequency (by at least 0.5/s), >3 changes in morphology, or >3 changes in location (by at least 1 standard inter-electrode distance), but not qualifying as evolving. This includes patterns fluctuating from 1 to 1.5 to 1 to 1.5/s; spreading in and out of a single electrode repeatedly; or alternating between 2 morphologies repeatedly." [2]).*

Fig. 13. Algorithm for EEG definition of typical spatiotemporal evolution (see text for further details) and definitions required for mSCNC.

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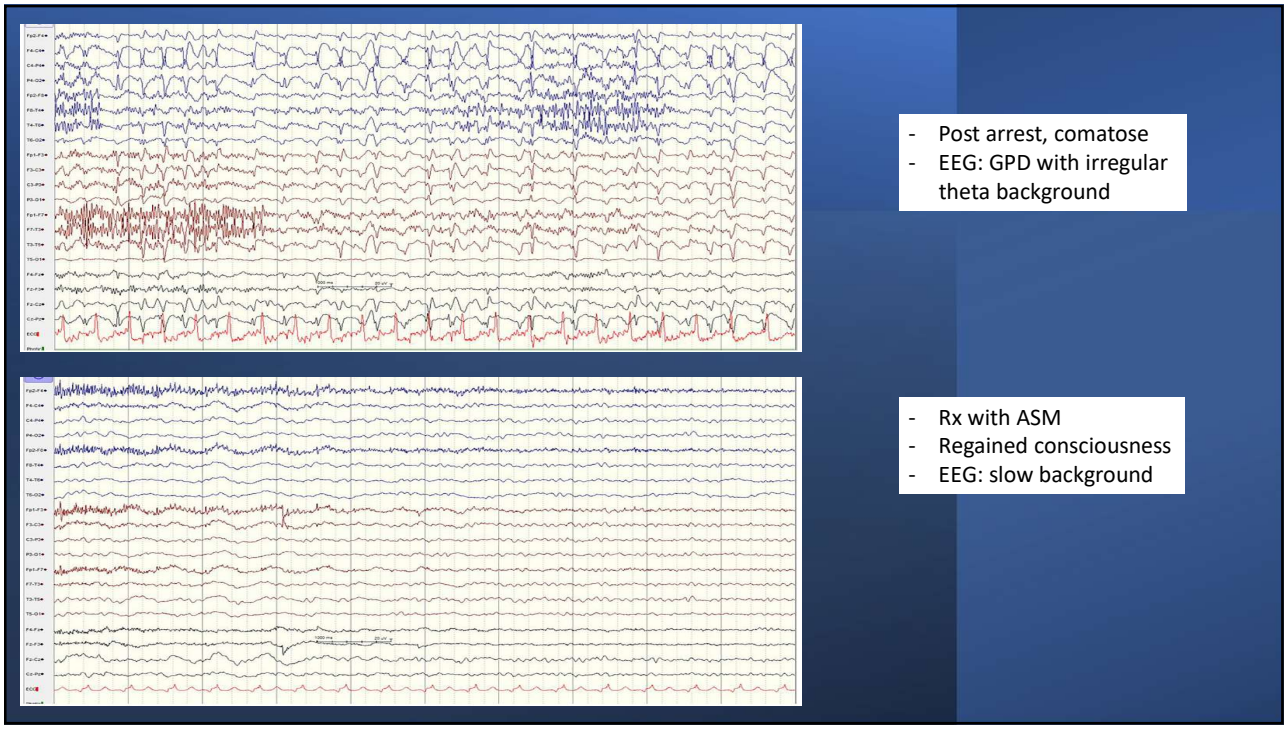
- Post arrest, comatose
- EEG: GPD with irregular theta background
- Rx with ASM
- Regained consciousness
- EEG: slow background

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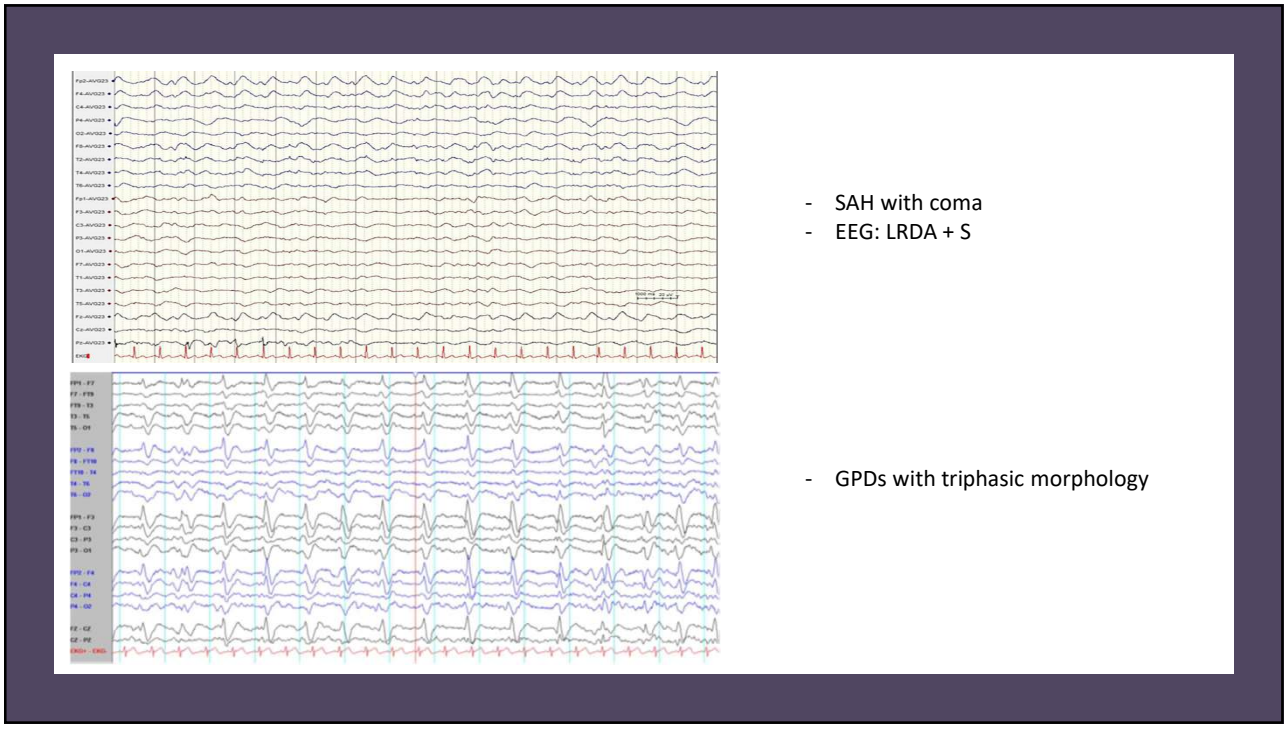
- SAH with coma
- EEG: LRDA + S
- GPDs with triphasic morphology

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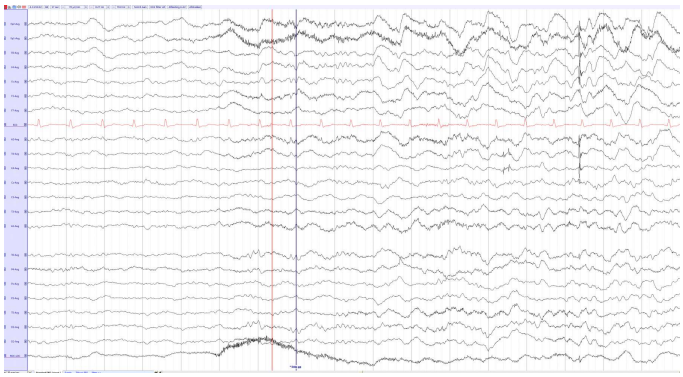
Modulation: (SIRPIDs)
Stimulus-induced rhythmic, periodic, or ictal discharges



- Induced by alerting stimuli such as auditory stimuli, sternal rub, examination, suctioning, turning, and other patient-care activities
- Commonly elicited by stimulation in critically ill (stuporous or comatose), encephalopathic patients
- Pathophysiology of SIRPIDs is unknown
- The relationship between clinical seizures and SIRPIDs is unclear, although some association is found between SIRPIDs and clinical status epilepticus

Epilepsia . 2004

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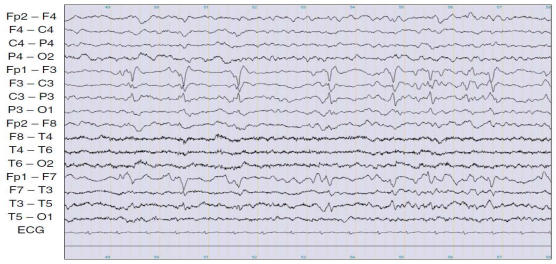
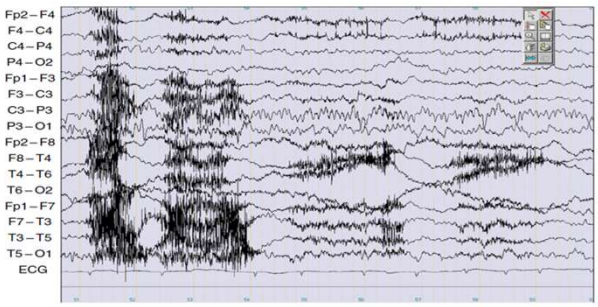


- Acute left MCA stroke
- Left LPDs with fluctuation of interburst intervals

- Shorter interval
- Decrease amplitude
- LPDs +, merging to ictal activity

- Electrographic seizure



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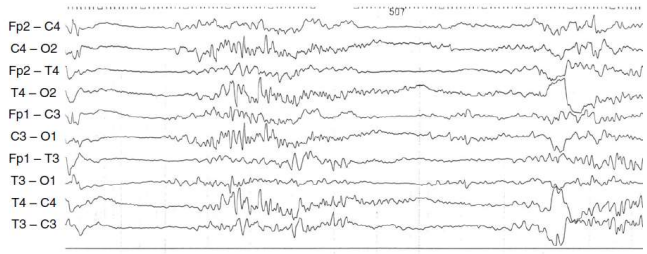
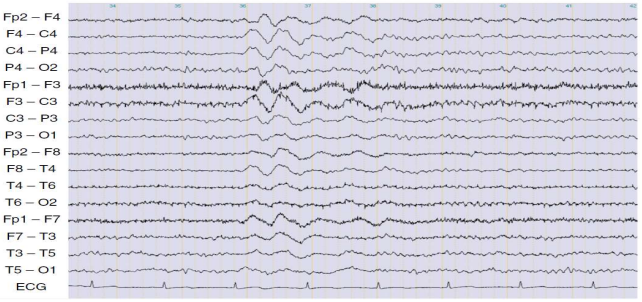


- Burst-suppression:
- Non epileptiform, as no evolution
- Poor prognosis



- มาด้วยชัก Dx PRES
- ยังซึม
- EEG: FIRDA (non-epileptiform)

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- Acute aphasia
- Rhythmic sharp waves – triphasic-like, with spatiotemporal evolution
- Clinical and abnormal EEG disappeared after IV ASM

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Duration for EEG monitor

Critically ill patients at least 48 h of continuous EEG are needed in order to capture more than 90% of epileptic events (Classen et al, 2004)

A useful seizure-risk predicting tool (using the eponym of ‘‘2HELPS2B”)

Claassen et al., 2004, Struck et al., 2017b

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‘‘2HELPS2B”

- The score was created in 2017, and validated in 2020
- To stratify seizure risk in hospital inpatients
- It does not apply to patients admitted for elective epilepsy monitoring and post-cardiac arrest patients
- To improve cost-effectiveness of continuous EEG (cEEG)
- By doing an initial 1 hour-long EEG and applying the score, patients can be stratified to stop EEG monitoring at that point, or continue to 12 hour or 24-hour cEEG monitoring

Claassen et al., 2004, Struck et al., 2017, Mofet EW, et al. Neurocrit Care 2020

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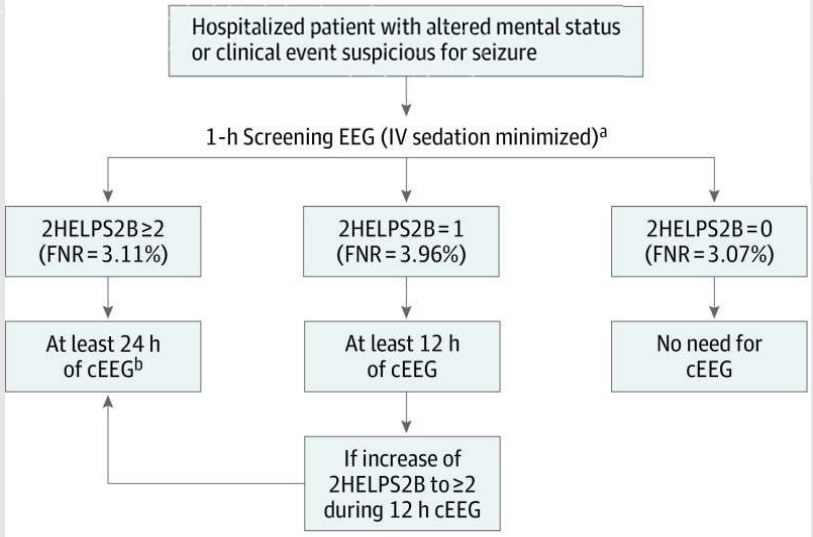
2HELPS2B Score



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2HELPS2B: Estimate duration of EEG monitoring needed to detect 95% of seizures

Risk Factor	Points
Frequency > **2Hz** [a]	1
Sporadic **E**pileptiform Discharges	1
LPD/BIPD/LRDA	1
Plus Features [b]	1
Prior **S**eizure	1
Brief Ictal Rhythmic Discharge	2
	Total Score

Total Score:	0	1	2	3	4	5	>6
Seizure Risk:	<5%	12%	27%	50%	73%	88%	>95%

Fig. 1 Illustration of factors used to calculate the 2HELPS2B score. The total score represents the sum of points, which is associated with a particular seizure risk. *BIPD* brief independent periodic discharge, *cEEG* continuous EEG, *GPD* generalized periodic discharge, *LPD* lateralized periodic discharge, *LRDA* lateralized rhythmic delta activity. [a]Frequency > 2 Hz applies to GRDA, LRDA, BIPDs, LPDs, or GPDs. [b]Plus features are defined as superimposed rhythmic, fast, or sharp activity for GRDA, LRDA, BIPDs, LPDs, or GPDs

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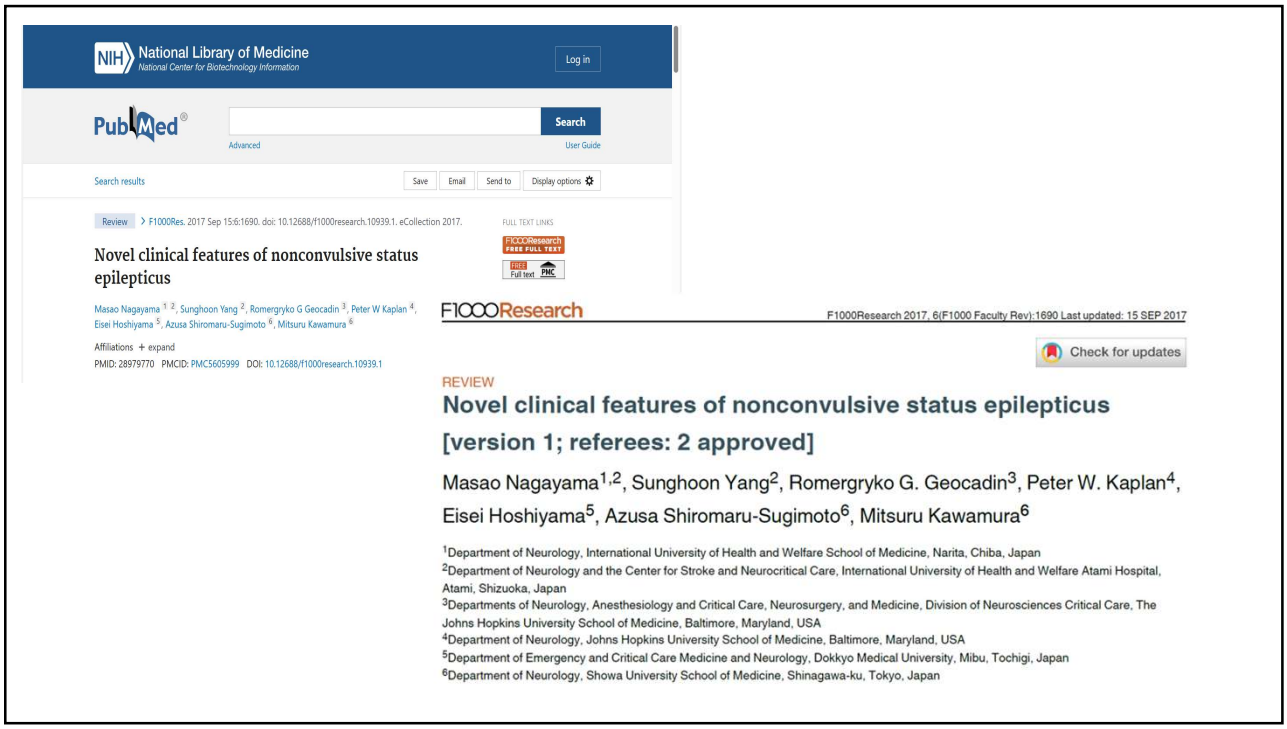

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Table 2. Expanded spectrum of manifestations of nonconvulsive status epilepticus (NCSE).

- Classical clinical features
  - Complex partial seizures type
    - Staring, repetitive blinking, chewing, swallowing, or automatism
    - Clouding of consciousness generally characterized by
      - alteration of mental function
      - consciousness with concurrent language disturbances
  - Simple partial seizures type
    - Symptoms linked to the anatomical and functional locations of the CNS foci
    - Temporal lobe epilepsy, amygdalar and hippocampal lesions
      - epigastric discomfort and uncinate fits
        - such as autonomic seizures, psychic seizures, and parosmia
    - Lateral temporal lesions
      - auditory hallucinations and language disturbance
    - Frontal lobe epilepsy
      - motor seizures
        - not only tonic seizures and seizures with fencing postures
        - but also those with complex gesticulation
    - Parietal lobe epilepsy
      - somatosensory abnormalities such as numbness
    - Occipital lobe epilepsy
      - visual seizures

Nagayama M, et al. F1000Research 2017.

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- Consciousness disturbance
  - Acute consciousness disturbance
    - Comatose state
    - Mental alteration
    - Fluctuation of consciousness level
  - Prolonged consciousness disturbance
    - Protracted coma
    - Fluctuation of consciousness level
  - Recurrent loss of consciousness attack
- Transient neurological attack (TNA)
  - including isolated vertigo, dizziness, and headache
- Higher brain dysfunction
  - Wernicke's aphasia, Broca's aphasia, Klüver–Bucy syndrome
  - Amnesia, indifference
  - Confabulation, hallucinatory delusion, delirium
  - Body schema disturbances (e.g. abnormal proprioception and supernumerary phantom limbs)
  - Neglect, auditory and visual hallucinations, cortical blindness
- Cognitive impairment and psychiatric manifestations
  - Dementia, including acute dementia
  - Abnormal behavior and/or speech
    - Persistent laughing (status gelasticus)

Nagayama M, et al. F1000Research 2017.

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- Automatism
  - Licking chops, nose wiping, facial pantomime
- Abnormal eye position and movement
  - Conjugate deviation of eyes, spontaneous nystagmus
- Myoclonus of the face and extremities
  - Especially interictal small myoclonus of the face and extremities
- Autonomic dysfunction
  - Gastrointestinal or cardiovascular autonomic events
  - Panayiotopoulos syndrome
- Acute organ dysfunction (epilepsy-related organ dysfunction [Epi-ROD])
  - Acute apnea, including prolonged post-hyperventilation apnea
  - Acute cardiac arrest, acute dysfunction of other organs
  - May cause sudden unexpected death in epilepsy (SUDEP)

In general, neurological deficits of an unexplained, episodic, fluctuating, or recurrent nature should arouse suspicion of NCSE. We need to consider convulsive SE and especially NCSE in the differential diagnosis of various acute organ dysfunctions, even in the absence of overt seizures.

Nagayama M, et al. F1000Research 2017.

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Table 3. Epilepsy-related organ dysfunction (Epi-ROD).

Features	Frequent in both convulsive status epilepticus (SE) and nonconvulsive status epilepticus (NCSE) Convulsive SE 60%, NCSE 40%, both 60% Life-threatening/high mortality (33.3%) with acute encephalopathy, stroke, and central nervous system infection, and so on Heterogeneous in nature
Implication	Differentiate SE in acute OD, even without overt seizure

OD: organ dysfunction

- 60% of NCSE: multiple organ failure, arrhythmia, and liver dysfunction
- 40.0%: acute respiratory failure, alveolar hypoventilation, acute cardiopulmonary arrest, acute takotsubo cardiomyopathy, renal dysfunction, and QT interval prolongation
- 60%: renal dysfunction, multiple organ failure, and disseminated intravascular coagulation with neurogenic diabetes insipidus

Nagayama M, et al. F1000Research 2017.

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Convulsive SE

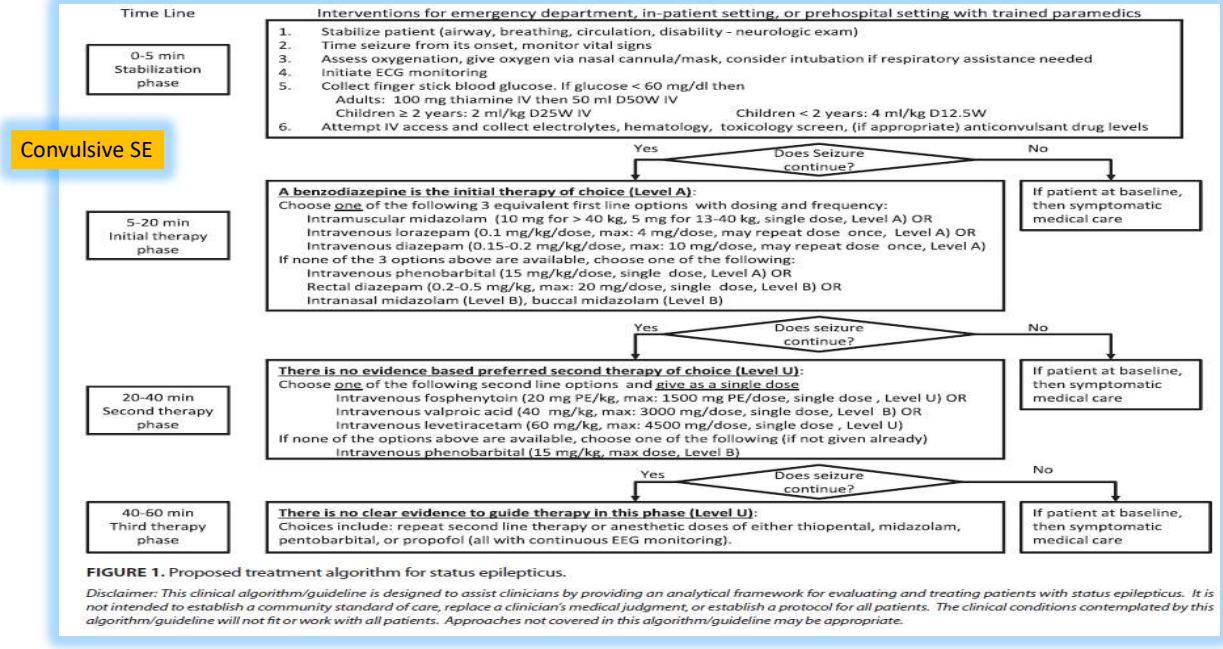

FIGURE 1. Proposed treatment algorithm for status epilepticus.

Disclaimer: This clinical algorithm/guideline is designed to assist clinicians by providing an analytical framework for evaluating and treating patients with status epilepticus. It is not intended to establish a community standard of care, replace a clinician's medical judgment, or establish a protocol for all patients. The clinical conditions contemplated by this algorithm/guideline will not fit or work with all patients. Approaches not covered in this algorithm/guideline may be appropriate.

AES. Epilepsy Currents, Vol. 16, No. 1 (January/February) 2016 pp. 48–61

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Prognosis of refractory status epilepticus

- Refractory status epilepticus
  - A risk of physiological compromise
  - Neuronal damage
  - Progressive drug resistance
- Rx
  - ICU for early anesthesia
- Prognosis
  - Poor
  - Mortality 17-48%
    - Approximately 3 times > non-refractory SE
  - No morbidity only 29%

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Prognosis of NCSE

NCSE -- Harmful to neurons, especially in the setting of acute brain injury

- Early treatment leading to shorter hospital stays and better outcome

Some studies disagree…….

- Isolated seizures are not harmful
- Neither seizures nor NCSE were significant predictors of outcome
- The use of IV benzodiazepines was associated with an increased risk of death (p = 0.03).
- IV anesthetic drips used for treatment of refractory SE (RSE) are associated with worse outcomes
- The use of continuous IV anesthetic-dose anti-seizure medications was associated with higher mortality, intubation, hypotension and poor function with long-term outcome
- therapeutic coma was associated with worse outcome at hospital discharge, new disability (with a relative risk, RR of 4.6), mortality (RR 5.5), more infections, and longer hospital stays

Claassen et al., 2007, Sutter et al., 2014, Marchi et al., 2015

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Predictive value of the Status Epilepticus Severity Score (STESS)

	Features	STESS
Consciousness	Alert or somnolent/confused	0
	Stuporous or comatose	1
Worst seizure type	Simple-partial, complex-partial, absence, myoclonic*	0
	Generalized-convulsive	1
	Nonconvulsive status epilepticus in coma	2
Age	< 65 years	0
	≥ 65 years	2
History of previous seizures	Yes	0
	No or unknown	1
Total		0–6

* complicating idiopathic generalized epilepsy

- **In-hospital mortality correlated highly significantly with STESS, the optimal cut-off was 4**

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Long-term anticonvulsant therapy

- Must be given
- The choice of drug depends on
  - Previous Rx
  - The type of epilepsy
  - The clinical setting
- Other maintenance can be started also by giving oral loading doses

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Conclusion:

Status epilepticus

Persistent seizure, causing neuronal damage

Type

- Convulsive, Nonconvulsive, Focal status
- SE, refractory SE, super-refractory SE, NORSE, FIRES

High morbidity & mortality

- Overall mortality ~ 20% (SE) → up to 80%
  (super-refractory SE with unproper Rx or most severe etiologies)

EEG for diagnosis and guide for Rx

Requiring prompt treatment

- ABC, initial anticonvulsant, anesthetic agent, supportive care in ICU
- Consider: autoimmune encephalitis and Rx without delays

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Thank you

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