



Epilepsy in ICU

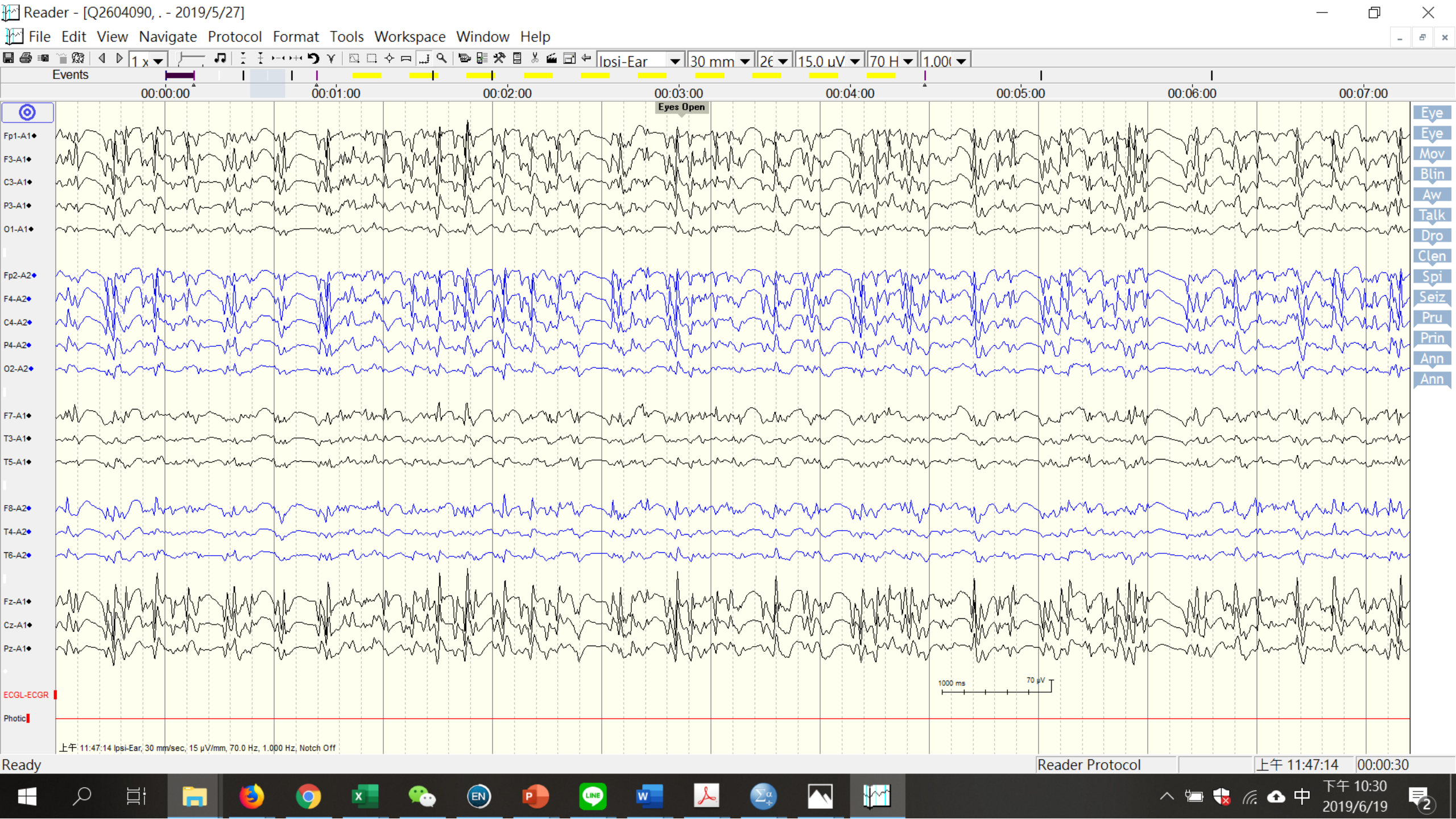
台中榮民總醫院 神經內科 章國政

2026.08.23













In ICU, seizure is often over-recognized and under-recognized

Epilepsia, 51(11):2338–2340, 2010
doi: 10.1111/j.1528-1167.2010.02683.x

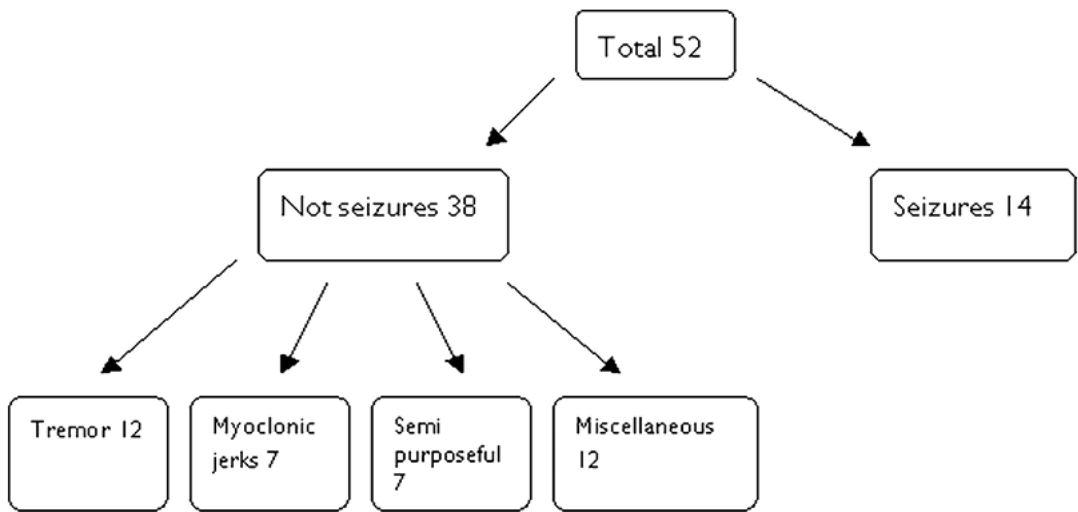
BRIEF COMMUNICATION

What’s shaking in the ICU? The differential diagnosis of seizures in the intensive care setting

Selim R. Benbadis, Shirley Chen, and Maria Melo

University of South Florida, Tampa General Hospital, Tampa, Florida, U.S.A.

Study on motor phenomena in critically ill patients show that only around **25%** abnormal movements or subtle motor phenomena in critically ill patients are epileptic seizures.



Detection of electrographic seizures with continuous EEG monitoring in critically ill patients

J. Claassen, MD; S.A. Mayer, MD; R.G. Kowalski, BS; R.G. Emerson, MD; and L.J. Hirsch, MD

570 patients with altered mental status (89% in ICU)

- **19%** (n=110) experienced seizures
- 92% of seizures were nonconvulsive seizure

Table 2 Primary admission diagnoses and frequency of seizures

Admission diagnoses	n	CEEG findings		
		Any seizure	NCS	NCSE
Epilepsy-related seizures	51	17 (33)	16 (31)	10 (20)
CNS infection	35	10 (29)	9 (26)	6 (17)
Brain tumor	43	10 (23)	10 (23)	5 (12)
Post neurosurgery	13	3 (23)	3 (23)	1 (8)
Hypoxic–ischemic encephalopathy	25	5 (20)	4 (16)	3 (12)
Subarachnoid hemorrhage	108	20 (19)	19 (18)	14 (13)
Traumatic brain injury	51	9 (18)	9 (18)	4 (8)
Toxic–metabolic encephalopathy	38	7 (18)	8 (21)	3 (8)
Unexplained decrease in LOC*	105	17 (17)	16 (15)	5 (5)
Intracerebral hemorrhage	45	6 (13)	6 (13)	4 (9)
Ischemic stroke	56	6 (11)	5 (9)	4 (7)
Overall	570	110 (19)	105 (18)	59 (10)

Table 1 Key epileptology definitions based on ILAE terminology	
Seizure	Transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain
Epilepsy	<i>Disease of the brain defined by any of the following conditions</i>
	1. At least two unprovoked (or reflex) seizures occurring > 24 h apart
	2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years
	3. Diagnosis of an epilepsy syndrome
Acute symptomatic seizure	Seizure that occurs in close temporal association with an acute CNS insult such as stroke, traumatic brain injury, infection, or metabolic disturbance. For definition of criteria, see [1]
Reflex seizure	Seizure consistently triggered by a specific stimulus or activity
Epilepsy syndrome	Characteristic cluster of clinical and EEG features, often supported by specific etiology (structural, genetic, metabolic, immune, infectious)
Status epilepticus	Seizure lasting ≥ 5 min for convulsive status epilepticus or ≥ 10 min for nonconvulsive status epilepticus or recurrent seizures without recovery of consciousness between them; condition resulting either from the failure of mechanisms responsible for seizure termination or from the initiation of mechanisms that lead to abnormally prolonged seizures
ILAE International League Against Epilepsy	

Acute Symptomatic Seizure (ASS)

- ASS occur in close temporal relationship with new-onset metabolic disturbances or structural brain damage.
- 10-year relapse risk for subsequent unprovoked seizures after an ASS is around 19%.
- Current guidelines discourage long-term treatment with ASM after ASS because of relatively low seizure-relapse risk.

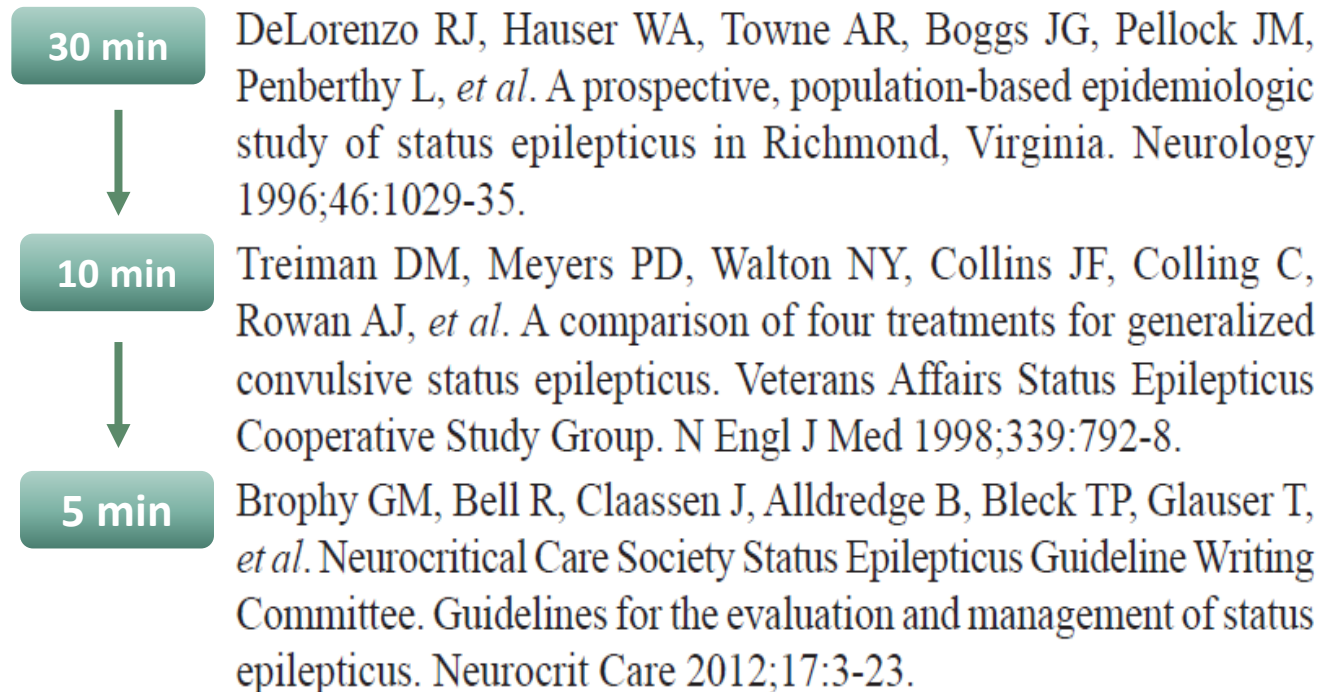
Cerebrovascular disease	Seizure occurring within 7 days of cerebrovascular attack
CNS infection	Seizure occurring in the acute phase of CNS infection
Immune-mediated encephalopathies	See CQ16-6 (page 161)
Head injury	Seizure occurring within 7 days of head trauma
Metabolic or systemic disorders	Seizure occurring in association with systemic diseases including electrolyte imbalance, hypoglycemia, non-ketotic hyperglycemia, uremia, hypoxic encephalopathy, hepatic encephalopathy, hypertensive encephalopathy, eclampsia, posterior reversible encephalopathy syndrome (PRES), systemic lupus erythematosus (SLE), and mitochondrial encephalopathy
Intoxication	Seizure occurring when taking narcotics (such as cocaine), prescribed drugs (such as aminophylline and imipramine), dangerous drugs, drug overdose, environmental pollution (such as carbon monoxide, lead, camphor, and organophosphorus), and alcohol (such as acute alcohol intoxication).
Withdrawal	Seizure occurring within 1–3 days after discontinuation of alcohol and drugs (such as barbiturate and benzodiazepines) in patients who are addicted to those agents
Post-neurosurgical operation	Seizure occurring immediately after intracranial surgery
Demyelinating disease	Seizure occurring in the acute phase of acute disseminated encephalomyelitis or multiple sclerosis
Post-radiotherapy	Seizures occurring within 24 hours after radiation exposure
Multiple etiologies	Seizure related to several concomitant conditions

Status epilepticus (SE)

Definition

- SE is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms
- (ILAE, 1970) “Seizure that persists for a sufficient length of time or is repeated frequently enough to produce a fixed and enduring condition.”
- (ILAE, 1981) “A seizure that persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur.”

Duration of seizure for defining SE



SPECIAL REPORT

A definition and classification of **status epilepticus** – Report of the ILAE Task Force on Classification of Status Epilepticus

*†‡Eugen Trinka, §Hannah Cock, ¶Dale Hesdorffer, #Andrea O. Rossetti, **Ingrid E. Scheffer, ††Shlomo Shinnar, ‡‡Simon Shorvon, and §§Daniel H. Lowenstein

Epilepsia, 56(10):1515–1523, 2015

doi: 10.1111/epi.13121

Cause **abnormally, prolonged** seizures after time point **t1**

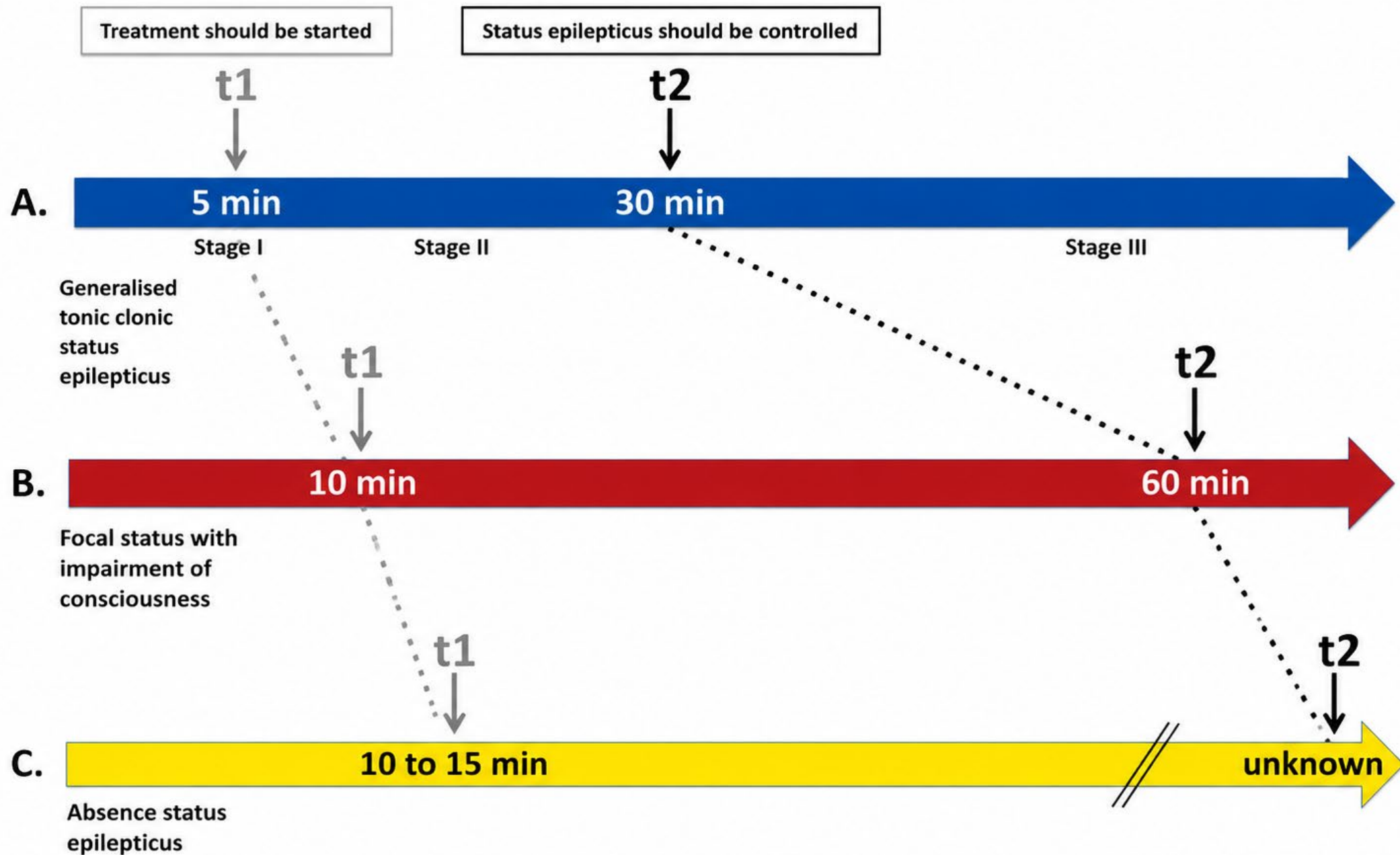
Result in **long-term consequences** after time point **t2**:
neuronal death, neuronal injury, and alteration of neuronal networks (depending on the type and duration of Seizures)

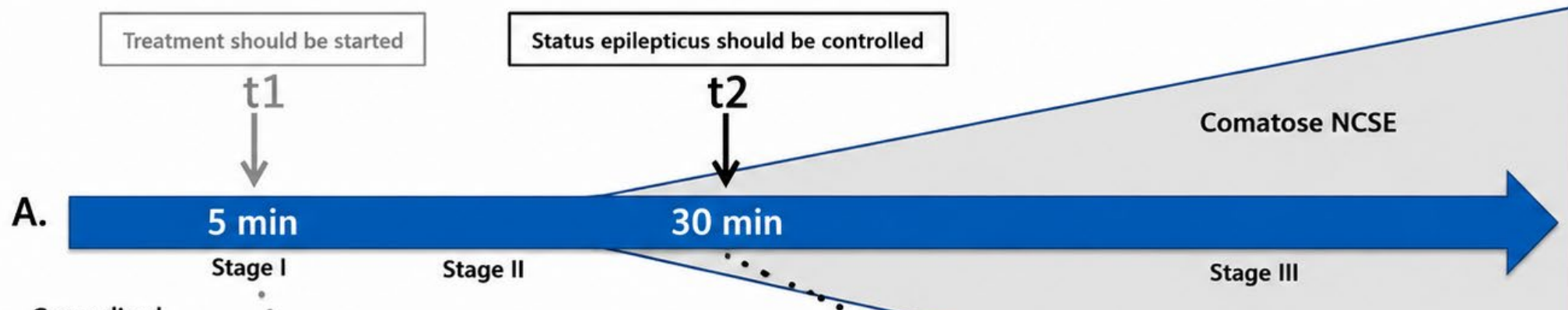
E. Trinka et al.

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

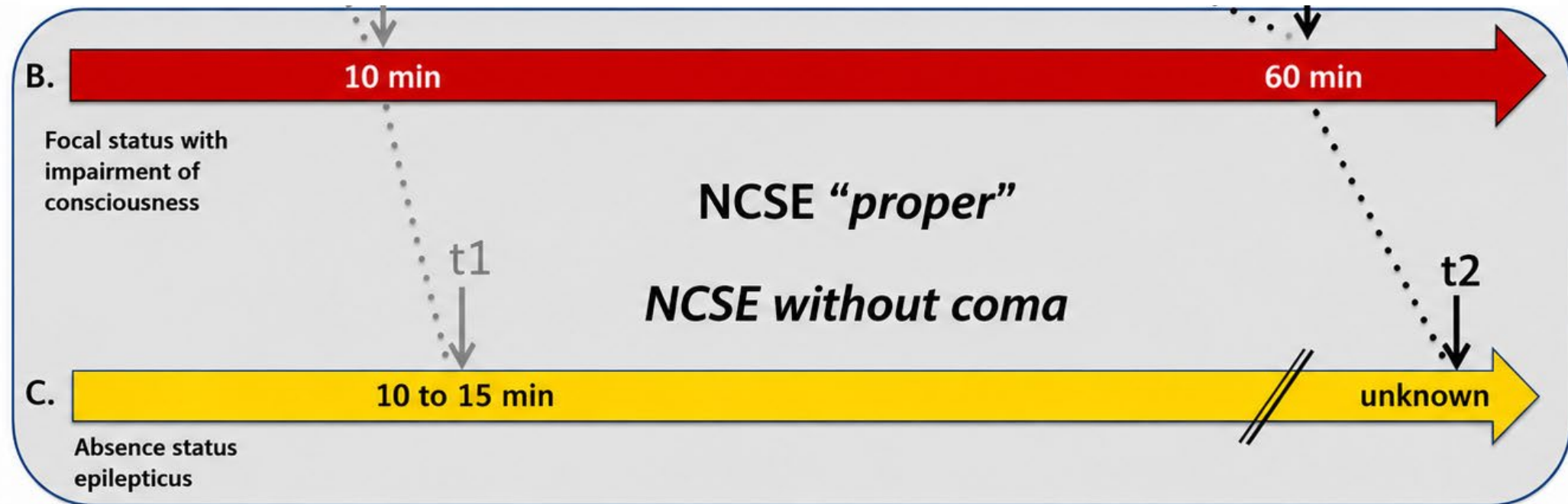
Type of SE	Operational dimension 1 Time (t_1) when a seizure is likely to be prolonged leading to continuous seizure activity	Operational dimension 2 Time (t_2), when a seizure may cause long term consequences (including neuronal injury, neuronal death, alteration of neuronal networks and functional 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

^aEvidence for the time frame is currently limited and future data may lead to modifications.





NCSE gradually emerges between t_1 and t_2





Refractory status epilepticus (RSE)

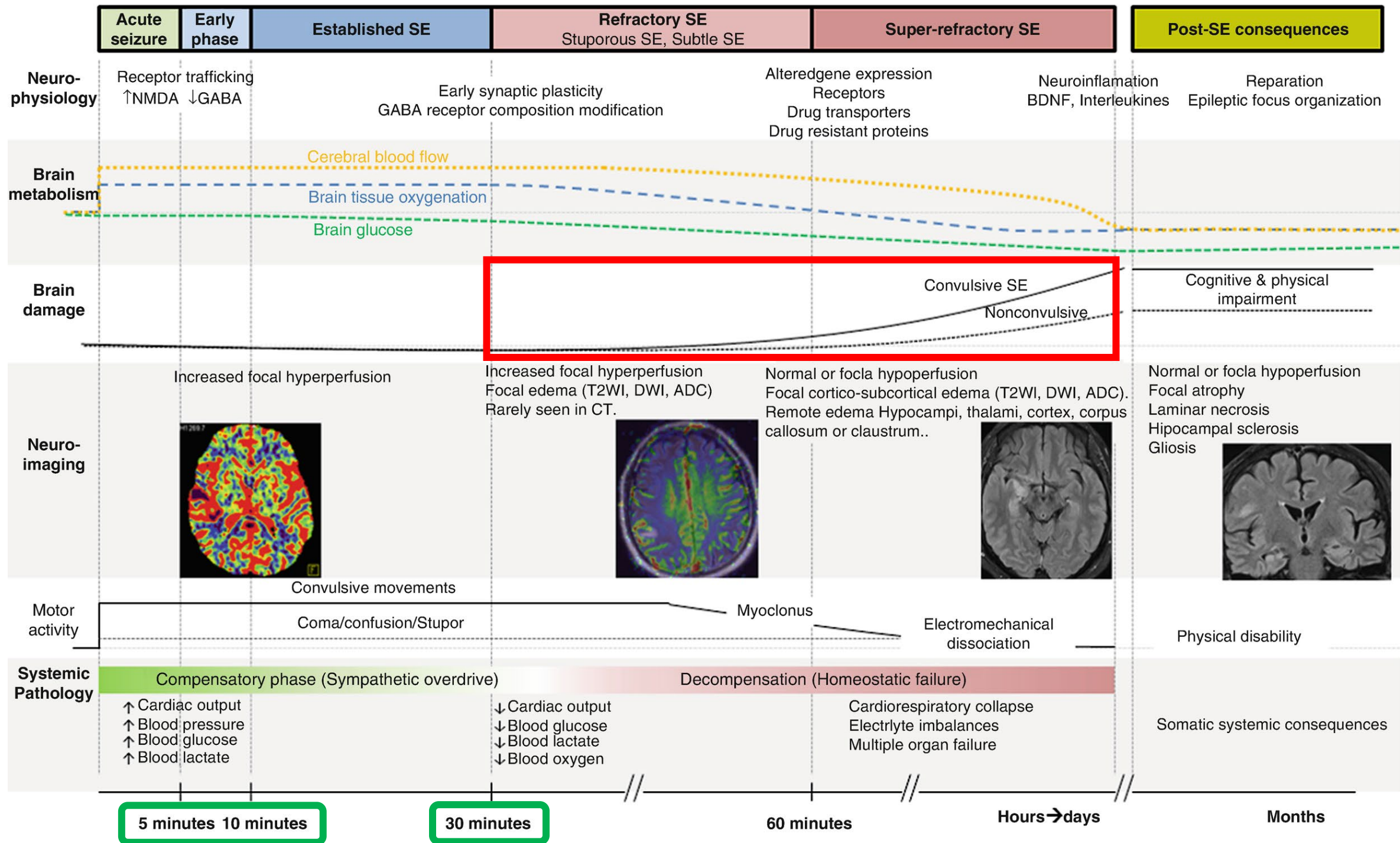
SE that does not respond to initial pharmacological therapy (one benzodiazepine and one non-benzodiazepine anticonvulsant medication) for **more than 30 minutes**.



Super-refractory status epilepticus (SRSE)

SE continues or recurs despite an adequate continuous infusion of intravenous anesthetic agents for **more than 24 hours**.

High mortality: **30% - 50%**.



Nonconvulsive Status Epilepticus

NCSE with coma

Comatose forms (Generalised, and focal)

(typically treat if >30
minutes duration)

NCSE in coma with
preceding
convulsive status.
(Subtle status
epilepticus)

Subtle status epilepticus

NCSE in coma
without preceding
convulsive status.

NCSE without coma

(NCSE propers)

Proper forms

Generalised (Absence)

(typically treat after 15
minutes activity)

1. Typical Absence
2. Atypical Absence
3. **de novo**
absence of late
onset

Focal

(typically treat after 10
minutes activity – if
altered consciousness)

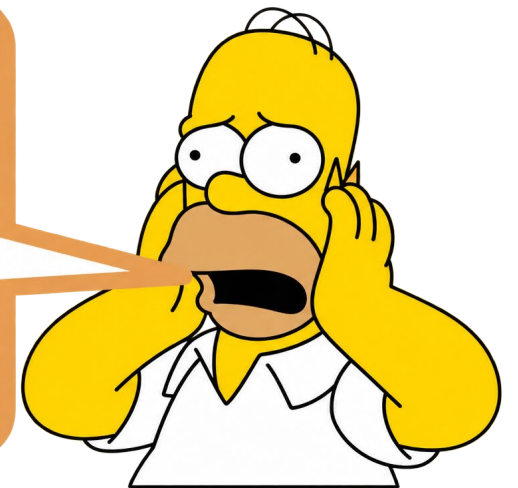
1. With
impairment of
consciousness
2. Without
impairment of
consciousness

*Time points taken from ILAE Task Force on Status Epilepticus-A
definition and classification of status epilepticus*

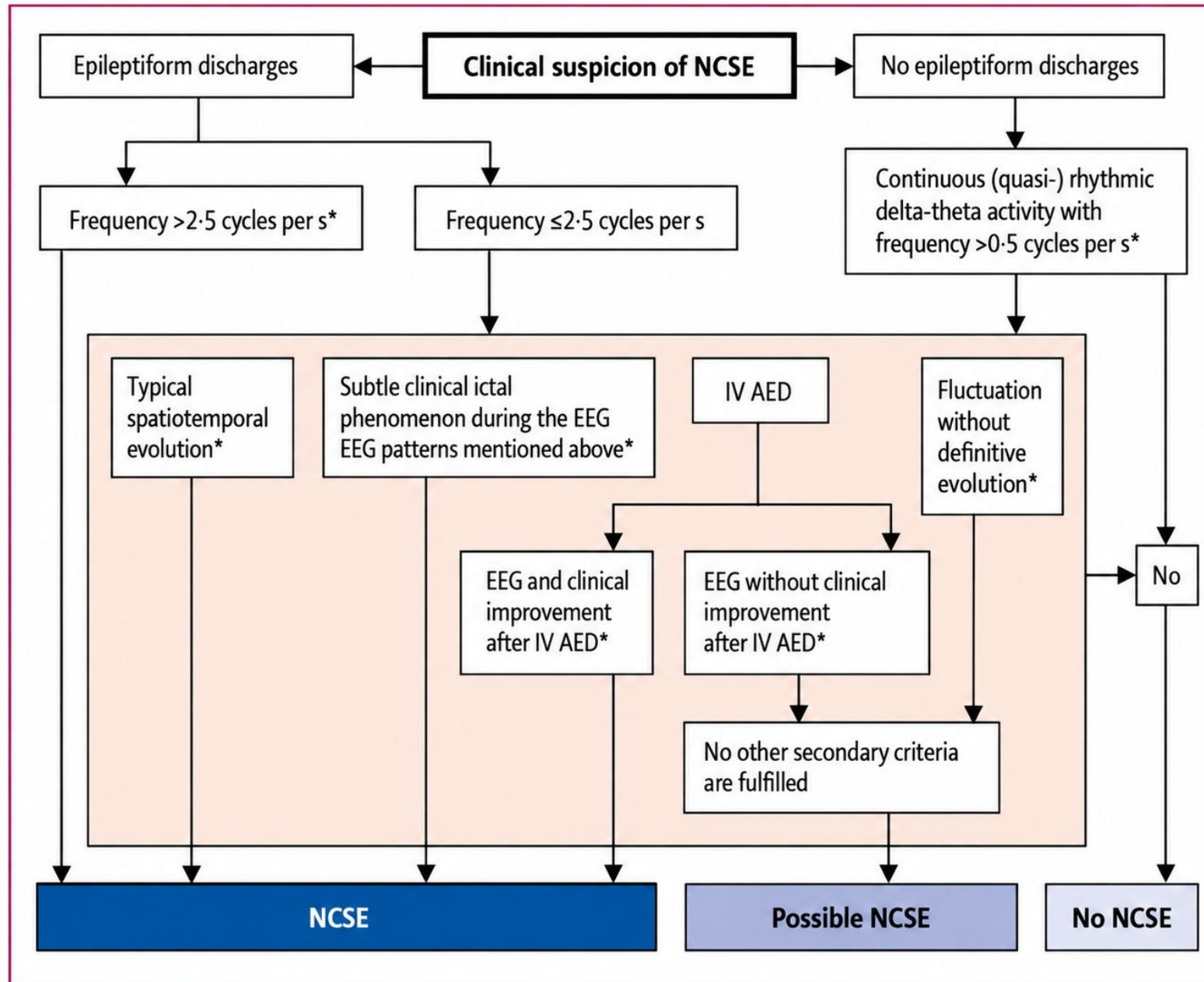
Clinical Suspicion of NCSE

1. Transition from premorbid to current ill state within minutes to hours
2. Patient did not improve significantly in last minutes to hours, apart from waxing and waning
3. No information from brain imaging sufficiently explaining EEG-pattern (e.g. brainstem hemorrhage)
4. No metabolic/toxicologic derangement sufficiently explaining EEG-pattern

**Status
Epilepticus
WITHOUT
The Shaking?
Whaaaat?**



Modified Salzburg Consensus Criteria for NCSE



Diagnosed by EEG



Continuous EEG (cEEG)

In critically ill patients, cEEG monitoring is recommended in several scenarios:

- Unexplained decreased consciousness, especially after status epilepticus
- Evaluation of paroxysmal motor phenomena
- Autonomic signs, such as sudden-onset tachycardia
- Abrupt increases in intracranial pressure

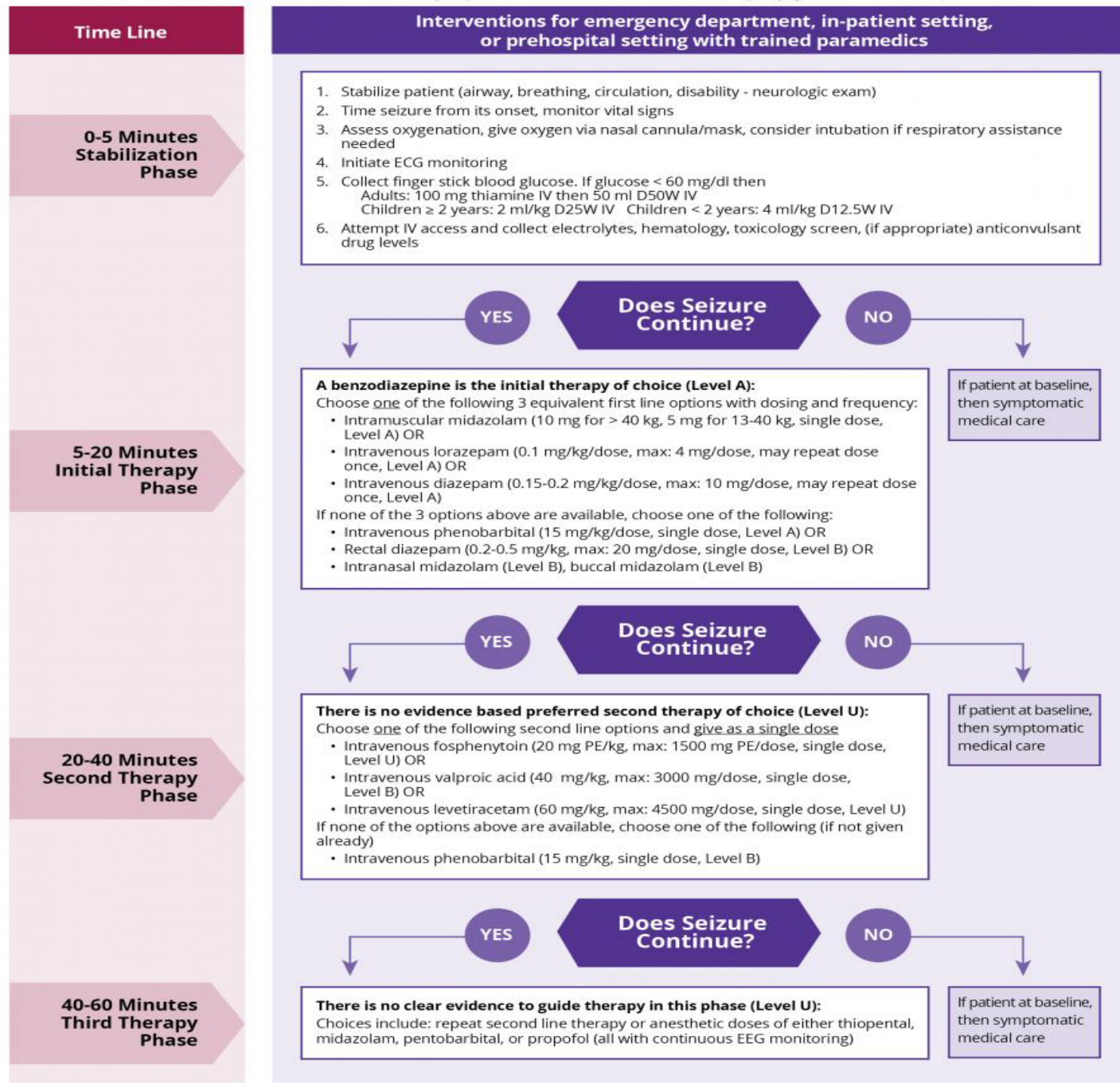


Treatment of CSE/NCSE



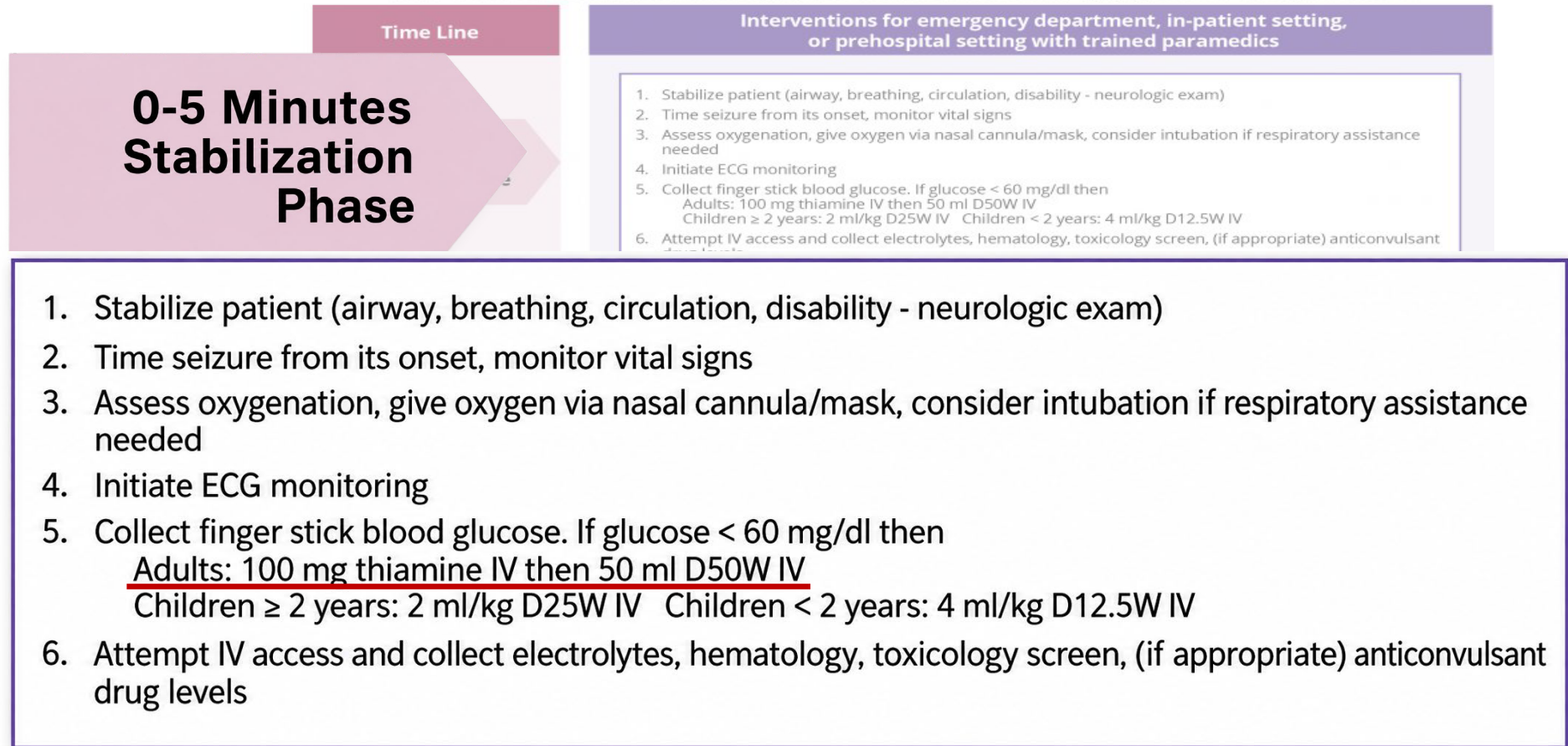
Proposed Algorithm for Convulsive Status Epilepticus

From "Treatment of Convulsive Status Epilepticus in Children and Adults," *Epilepsy Currents* 16.1 - Jan/Feb 2016

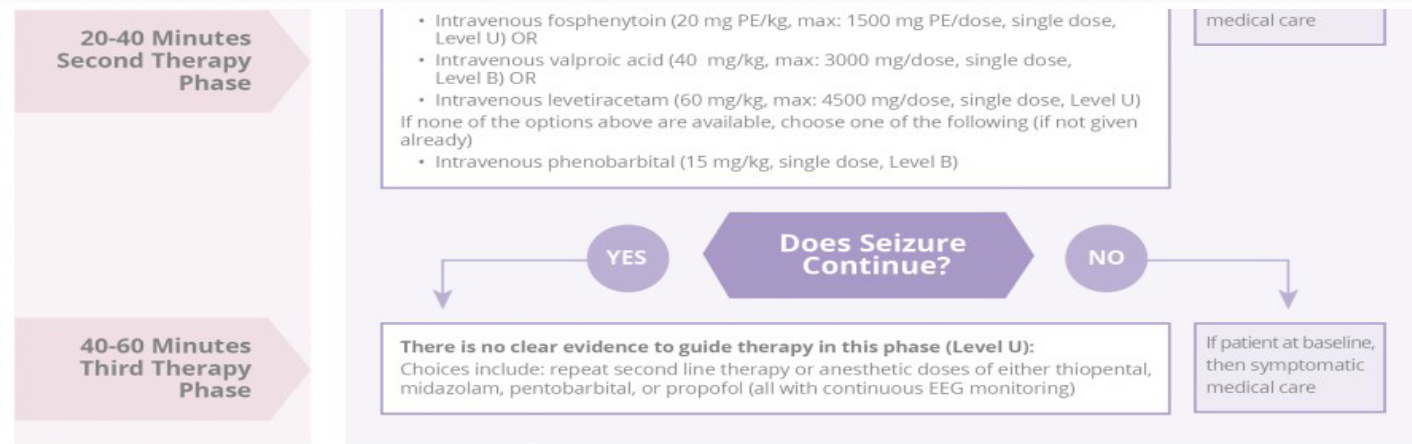


Proposed Algorithm for Convulsive Status Epilepticus

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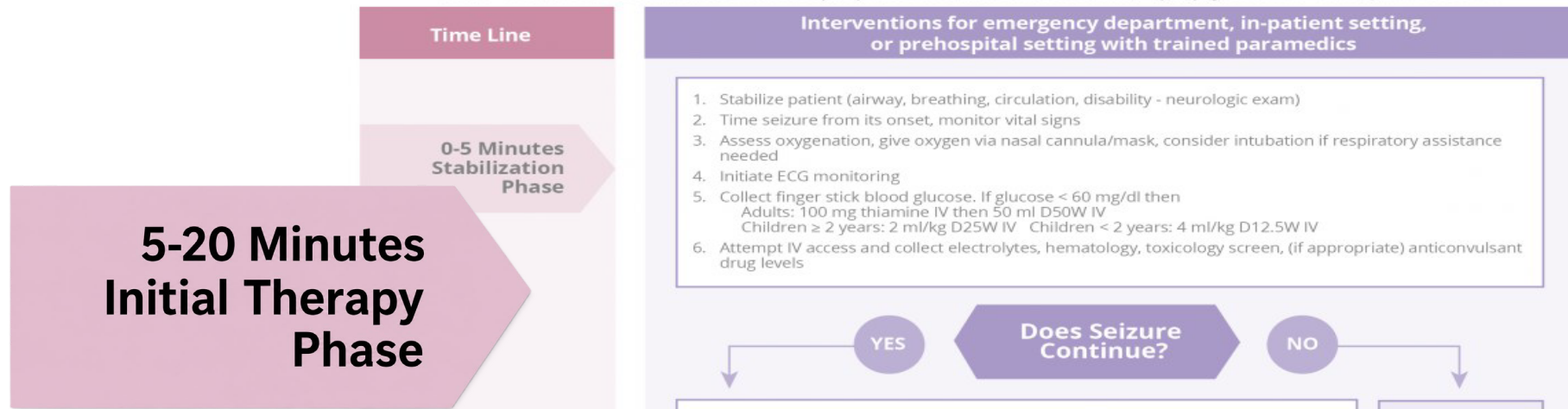


Thiamin substitution is indicated in **alcoholism** and/or **malnutrition** generally, especially in critically ill patients.



Proposed Algorithm for Convulsive Status Epilepticus

From "Treatment of Convulsive Status Epilepticus in Children and Adults," *Epilepsy Currents* 16.1 - Jan/Feb 2016



A benzodiazepine is the initial therapy of choice (Level A):

Choose one of the following 3 equivalent first line options with dosing and frequency:

- IV or IM** • Intramuscular midazolam (10 mg for > 40 kg, 5 mg for 13-40 kg, single dose, 0.1–0.2mg/kg, maximum 10mg/dose Level A) OR
- IV** • Intravenous lorazepam (0.1 mg/kg/dose, max: 4 mg/dose, may repeat dose once, Level A) OR
- IV** • Intravenous diazepam (0.15-0.2 mg/kg/dose, max: 10 mg/dose, may repeat dose once, Level A)

If none of the 3 options above are available, choose one of the following:

- Intravenous phenobarbital (15 mg/kg/dose, single dose, Level A) OR
- Rectal diazepam (0.2-0.5 mg/kg, max: 20 mg/dose, single dose, Level B) OR
- Intranasal midazolam (Level B), buccal midazolam (Level B)

- Rapid treatment appears to be more critical than the choice of BZD.
- Underdosing results in a lower probability of terminating epileptic activity.
- If necessary, BZD administration may be repeated once (5-10 minutes later).

Third Therapy Phase

Choices include: repeat second line therapy or anesthetic doses of either thiopental, midazolam, pentobarbital, or propofol (all with continuous EEG monitoring)

Return to baseline, then symptomatic medical care

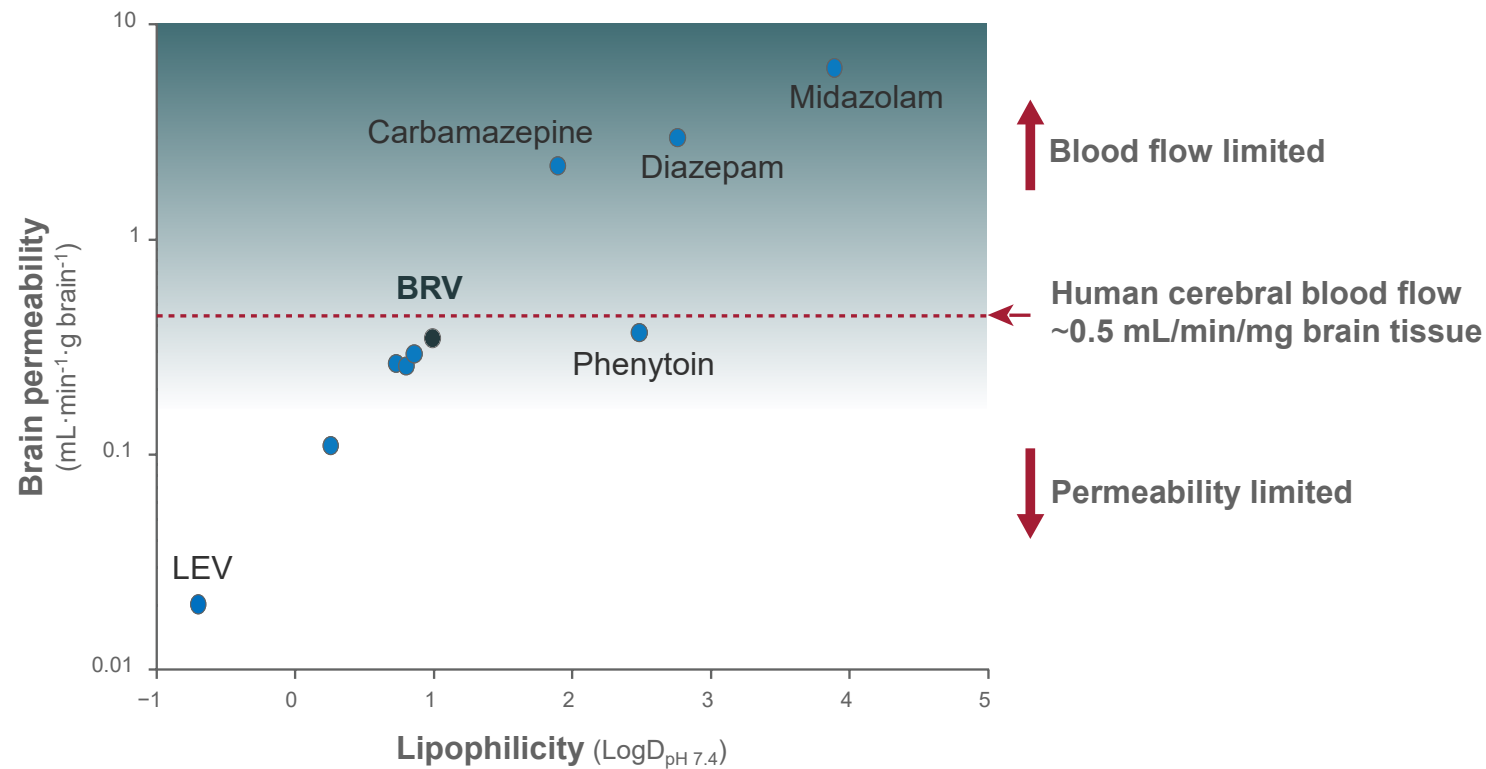
Benzodiazepines versus non-benzodiazepine antiseizure medications as first-line agents for status epilepticus: analysis of real word data from a 9-years prospective cohort



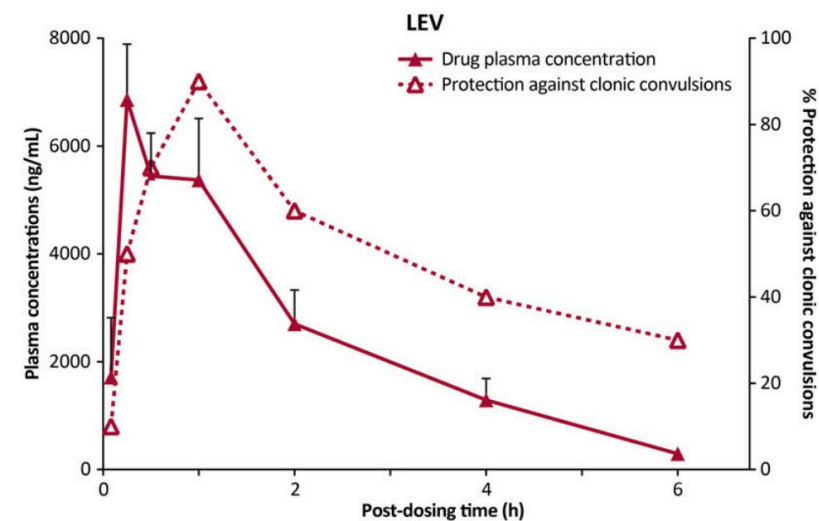
Italian 9-year cohort: 630 patients > 14-year-old
BZD or non-BZD ASM as first line for SE treatment

First-line non-BDZ therapy	Numbers of patients (%)
Carbamazepine	1 (0.6)
Phenobarbital	1 (0.6)
Zonisamide	1 (0.6)
Brivaracetam	2 (1.2)
Phenytoin	9 (5.4)
Lacosamide	28 (16.8)
Levetiracetam	62 (37.1)
Valproic acid	63 (37.7)

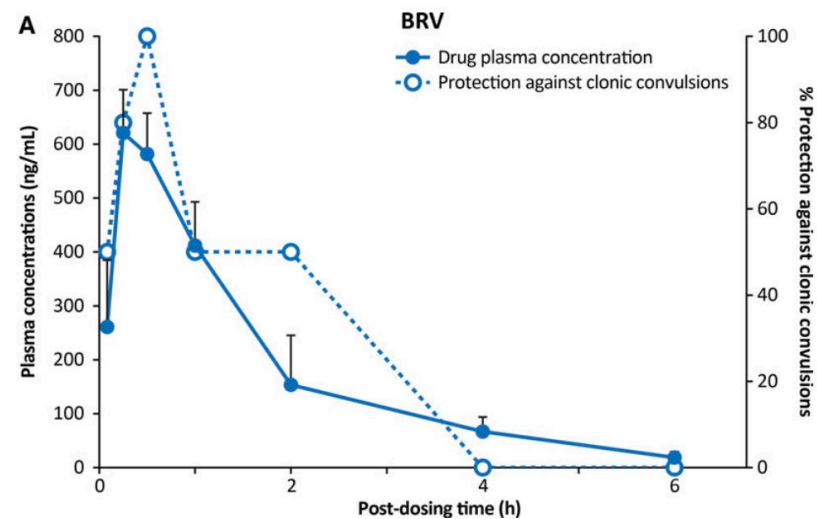
Outcomes ^a	Total	BDZ first-line therapy, 463 patients (73.5%)	Non-BDZ first-line, 167 patients (26.5%)	<i>p</i> -value
Need for anaesthetics within 24 h of SE onset, <i>n</i> (%)	134 (21.3)	76 (16.4)	58 (34.7)	<0.001
Progression to refractory SE, <i>n</i> (%)	171 (27.1)	101 (21.8)	70 (41.9)	<0.001
Progression to super-refractory SE, <i>n</i> (%)	80 (12.7)	48 (10.4)	32 (19.2)	0.006
Need for orotracheal intubation, <i>n</i> (%)	166 (26.4)	90 (19.4)	76 (45.8)	<0.001
Admission to intensive care unit, <i>n</i> (%)	210 (33.3)	124 (26.8)	86 (51.5)	<0.001
Length of stay in intensive care unit, days, median (IQR)	14 (8–28)	13 (7–24)	19 (10–36)	<0.001
CE cessation according to SENSE criteria, <i>n</i> (%)	220 (35.6)	409 (88.3)	139 (83.2)	0.107
Time to SE cessation, days, median (IQR)	2 (1–5)	2 (0–5)	3 (1–7)	<0.001
Worsening of functional status (mRS at discharge > pre-SE mRS), <i>n</i> (%)	374 (59.4)	253 (54.6)	121 (72.5)	<0.001



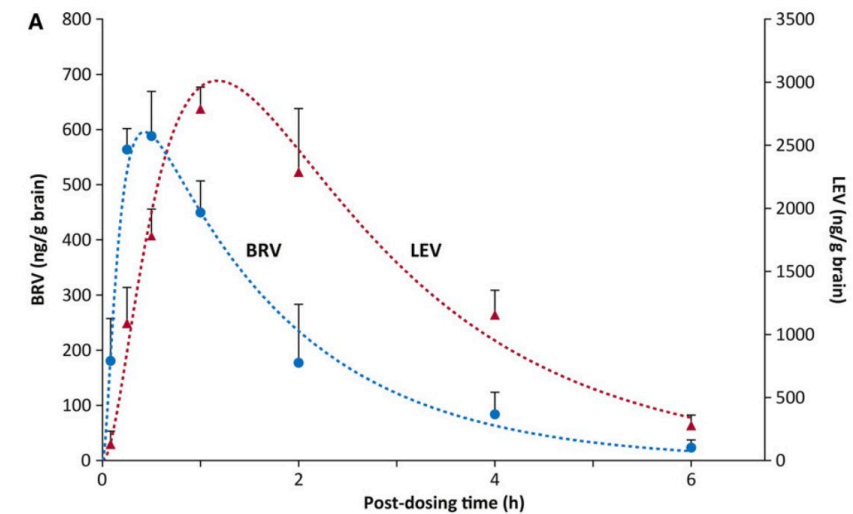
Nicolas JM, et al. Epilepsia. 2016;57:201-9.



Plasma level of LEV



Plasma level of BRV



Brain (CSF) level of LEV

In NCSE dominant subgroup:

- 30-day mortality was 30.7% (43/140), with no difference between BDZ-treated patients (30%; 21/70) and those who received non-BDZ (31.4%; 22/70) ($p = 1.000$).
- No difference in secondary outcomes, except for a shorter time to SE cessation among BDZ-treated patients.

Outcomes ^a	Total	BDZ first-line therapy, 70 patients (50%)	Non-BDZ first-line, 70 patients (50%)	<i>p</i> -value
Need for anesthetics within 24 h of SE onset, <i>n</i> (%)	42 (30)	18 (25.7)	24 (34.3)	0.357
Progression to refractory SE, <i>n</i> (%)	53 (37.8)	23 (32.9)	30 (42.9)	0.296
Progression to super-refractory SE, <i>n</i> (%)	29 (20.7)	14 (20)	15 (21.4)	1.000
Need for orotracheal intubation, <i>n</i> (%)	57 (40.7)	25 (35.7)	32 (46.4)	0.230
Admission to intensive care unit, <i>n</i> (%)	66 (47.1)	28 (40)	38 (54.3)	0.127
Length of stay in intensive care unit, days, median (IQR)	16 (8–36)	12 (6–26)	20 (9–41)	0.049
Return to pre-SE condition at discharge, <i>n</i> (%)	44 (31.4)	20 (28.6)	24 (34.3)	0.585
CE cessation according to SENSE criteria, <i>n</i> (%)	93 (66.4)	45 (64.3)	48 (68.6)	0.721
Time to SE cessation, days, median (IQR)	3 (1–7)	1 (0–4)	4 (2–8)	<0.001
Worsening of functional status (mRS at discharge > pre-SE mRS), <i>n</i> (%)	91 (65)	43 (61.4)	48 (68.6)	0.479

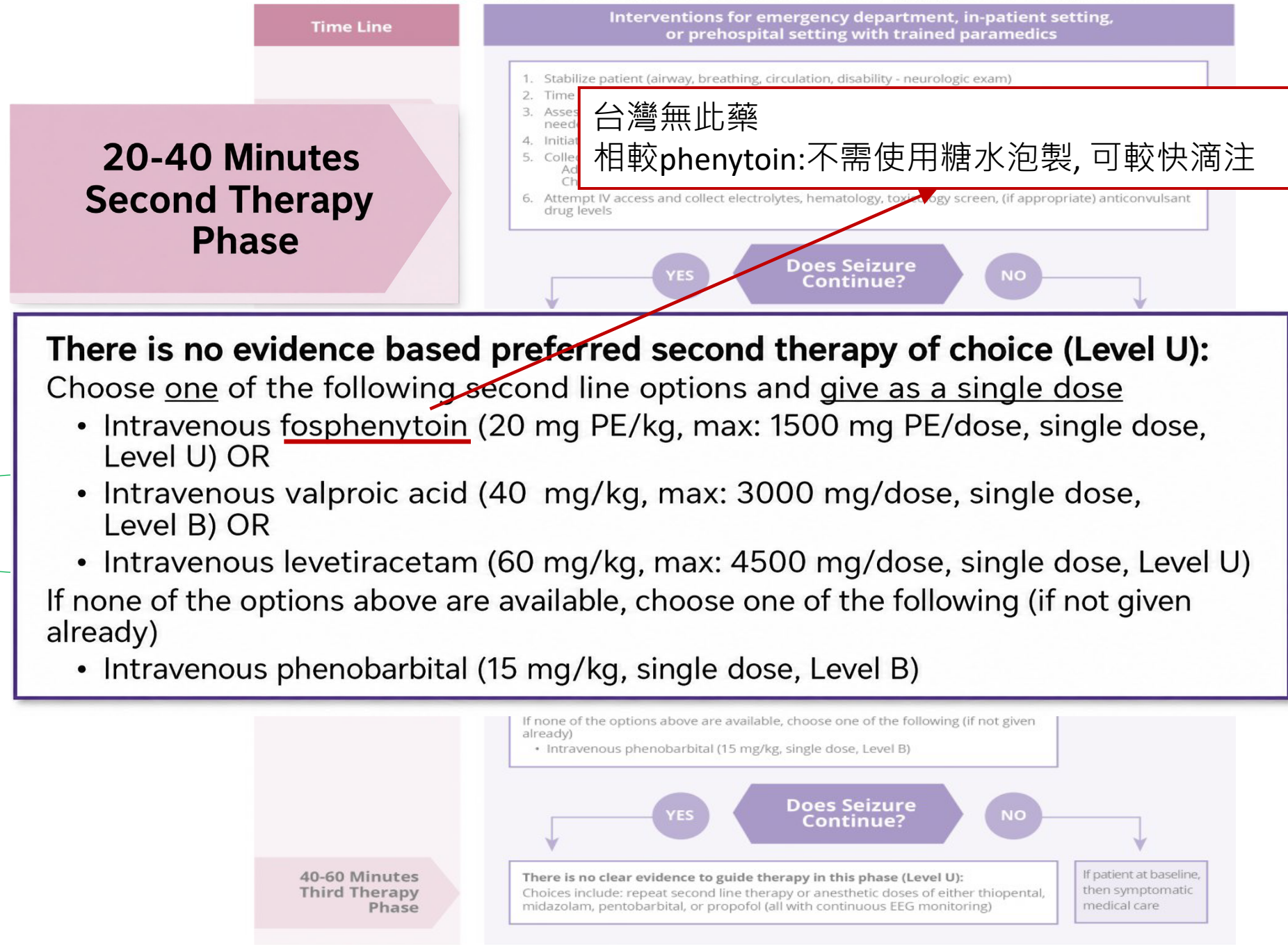
BZD Used in Treatment of SE

	Diazepam	Lorazepam	Midazolam	Clonazepam
Advantage	Rapid onset (IV) Rectal formulation available Long standing clinical experience in adults and children Widespread availability	Rapid onset (IV) Long lasting effect (>24h) after a single injection Less lipid redistribution Proven efficacy in randomized controlled trials in GCSE	Rapid onset with all routes Water solubility (IB, IN, IM)	Rapid onset (IV) Long lasting effect (>24h) after a single injection
Disadvantage	Short action duration due to rapid redistribution Accumulation with the risk of prolonged sedation and respiratory depression	Rapid development of tolerance	Short duration of action with risk of seizure relapse	Lack of RCTs



Proposed Algorithm for Convulsive Status Epilepticus

From "Treatment of Convulsive Status Epilepticus in Children and Adults," *Epilepsy Currents* 16.1 - Jan/Feb 2016



台灣無此藥

相較phenytoin:不需使用糖水泡製,可較快滴注

ESETT trial (2019)

ORIGINAL ARTICLE

Randomized Trial of Three Anticonvulsant Medications for Status Epilepticus

Jaideep Kapur, M.B., B.S., Ph.D., Jordan Elm, Ph.D., James M. Chamberlain, M.D., William Barsan, M.D., James Cloyd, Pharm.D., Daniel Lowenstein, M.D., Shlomo Shinnar, M.D., Ph.D., Robin Conwit, M.D., Caitlyn Meinzer, Ph.D., Hannah Cock, M.D., Nathan Fountain, M.D., Jason T. Connor, Ph.D., and Robert Silbergleit, M.D., for the NETT and PECARN Investigators*

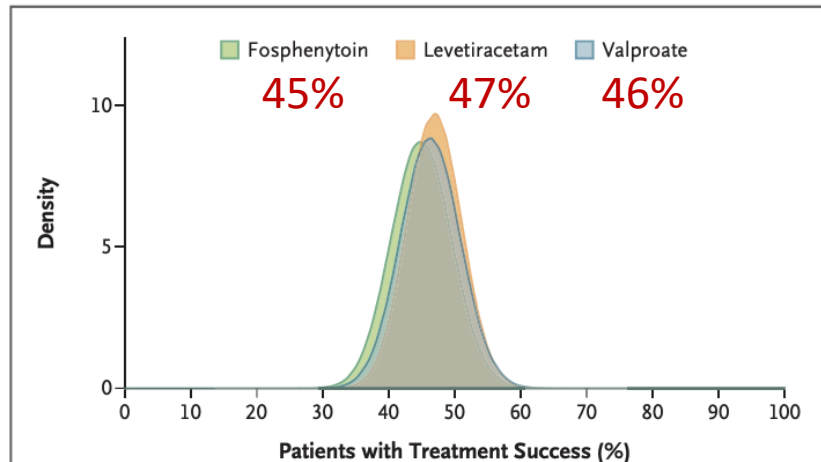


Figure 2. Posterior Probabilities of Success According to Treatment Group for the Primary Outcome of Cessation of Status Epilepticus at 60 Minutes.

The relative posterior probabilities of treatment success with regard to the primary outcome for each drug are shown. The percentage of patients with treatment success was 47% (95% credible interval, 39 to 55) in the levetiracetam group, 45% (95% credible interval, 36 to 54) in the fosphenytoin group, and 46% (95% credible interval, 38 to 55) in the valproate group.

- **384 children and adults** with BZD-refractory CSE
- **Primary outcome:** absence of clinically evident seizures and consciousness improvement by 60 minutes after the start of drug infusion, without additional anticonvulsant medication.

Table 2. Efficacy Analyses.*

Outcome and Population	Levetiracetam (N=145)	Fosphenytoin (N=118)	Valproate (N=121)
Primary efficacy outcome: cessation of seizures and improvement in consciousness at 60 min without other anticonvulsant medications			
Intention-to-treat population			
No. with outcome	68	53	56
Percent of patients with outcome (95% credible interval)	47 (39–55)	45 (36–54)	46 (38–55)
Probability that treatment is the most effective	0.41	0.24	0.35
Probability that treatment is the least effective	0.24	0.45	0.31
Per-protocol population			
No. with outcome/total no.	51/109	37/79	43/91
Percent of patients with outcome (95% credible interval)	47 (38–56)	47 (36–58)	47 (37–57)
Probability that treatment is the most effective	0.31	0.34	0.36
Probability that treatment is the least effective	0.34	0.35	0.31
Secondary efficacy outcomes			
Admission to ICU — no. (%)	87 (60.0)	70 (59.3)	71 (58.7)
Median length of ICU stay (IQR) — days	1 (0–3)	1 (0–3)	1 (0–3)
Median length of hospital stay (IQR) — days	3 (1–7)	3 (1–6)	3 (2–6)
Median time from start of trial-drug infusion to termination of seizures for patients with treatment success (IQR) — min†	10.5 (5.7–15.5)	11.7 (7.5–20.9)	7.0 (4.6–14.9)

2023 台灣癲癇診療指引建議

醫院內處理抽搐型時序癲癇發作狀態的藥物劑量參考

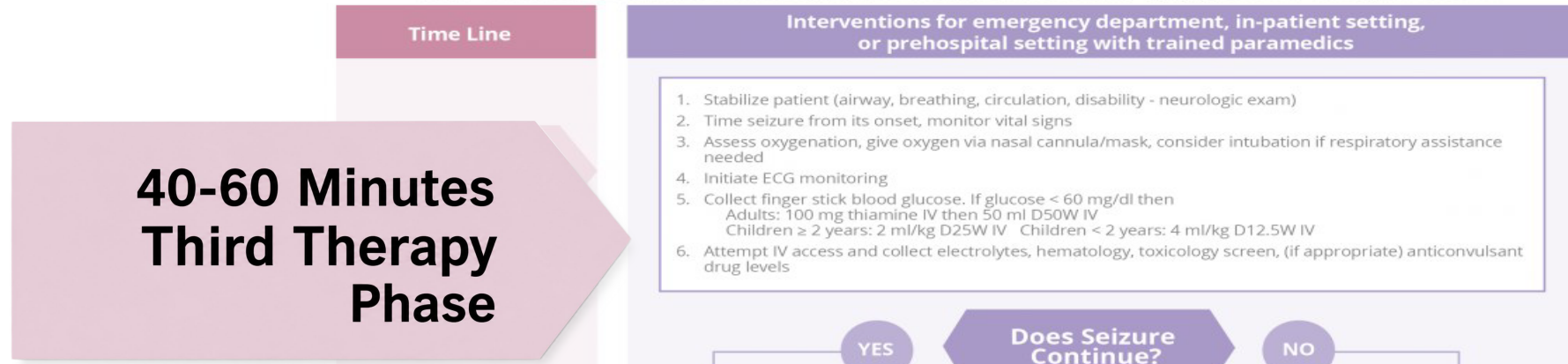
Stage 1: stage of early status (0-10/30 min)	Stage 2: stage of established status (10/30-60/90 min)	Stage 3: stage of refractory status (> 60/90 min)
Lorazepam (initial 4 mg slow IV push, may repeat once)	Phenytoin (initial 15-20 mg/kg IV infusion at 50 mg/min, additional Phenytoin 5-10 mg/kg/day IV infusion at 50-75 mg/min)	Midazolam (0.1-0.3 mg/kg at 4 mg/min IV bolus, followed by a continuous IV infusion of 0.05-0.4 mg/kg/hr)
Midazolam (initial 10 mg IM, may repeat once)	Valproic acid (initial 15-30 mg/kg IV infusion at 3-6 mg/kg/min, maintain dose 20-30 mg/kg/day IV infusion)	Phenobarbital (10-20 mg/kg IV infusion at 100 mg/min, maintain dose 1-3 mg/kg/day)
Diazepam (10 mg slow IV push, may repeat once)	Levetiracetam (initial 30-60 mg/kg IV infusion, maintain dose 2000-4000 mg/day IV infusion)	Propofol (1-2 mg/kg IV bolus, followed by a continuous IV infusion of 5-10 mg/kg/hr)
Severe renal or hepatic insufficiency : 劑量各減25%	Lacosamide (200-400 mg IV rapid loading dose over 3-5 min, followed by a daily dose of 200-400 mg)	Pentobarbital (10-20 mg/kg at 25 mg/min IV bolus, followed by a continuous IV infusion of 0.5-3 mg/kg/hr)
CKD只要沒洗腎都是單一劑量，HD病人目前沒FDA approval尚不建議使用	Brivaracetam (200 mg IV rapid loading dose over 3-5 min, followed by 100 mg Q12H IV infusion)	Thiopental (100-250 mg IV bolus over 20 s, followed by a continuous IV infusion of 3-5 mg/kg/hr)

較後期 (如 stage 2 或 stage 3 之處置應包含較前期 (stage 1 或 stage 1 與 2) 之處置。

粗體字型為一般較為建議或方便換算的劑型、劑量。

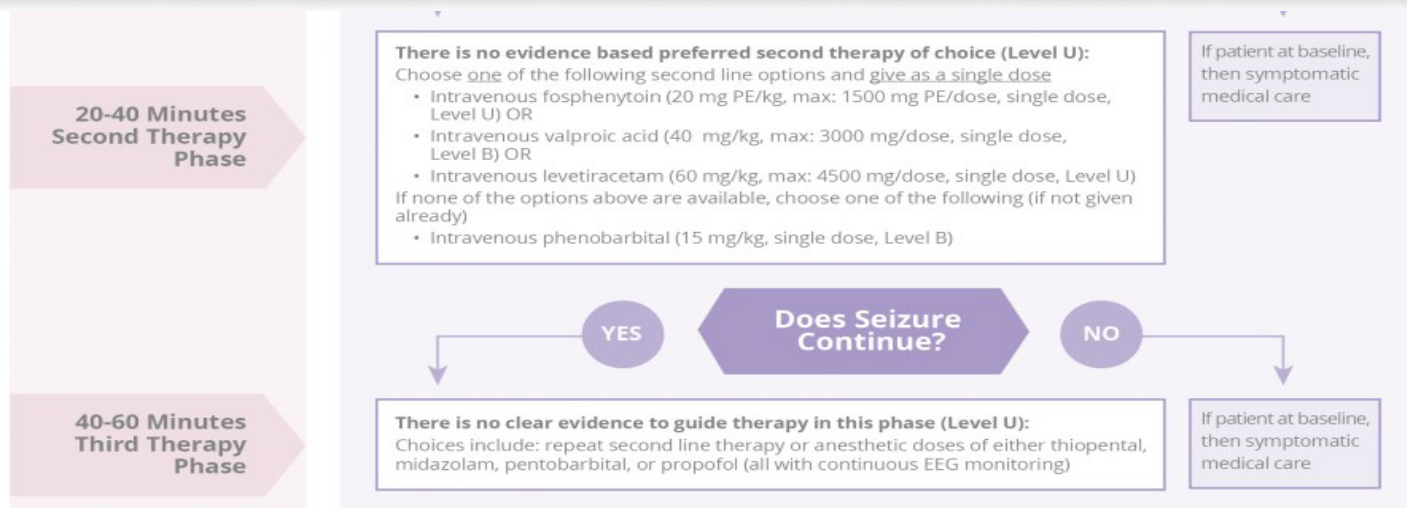
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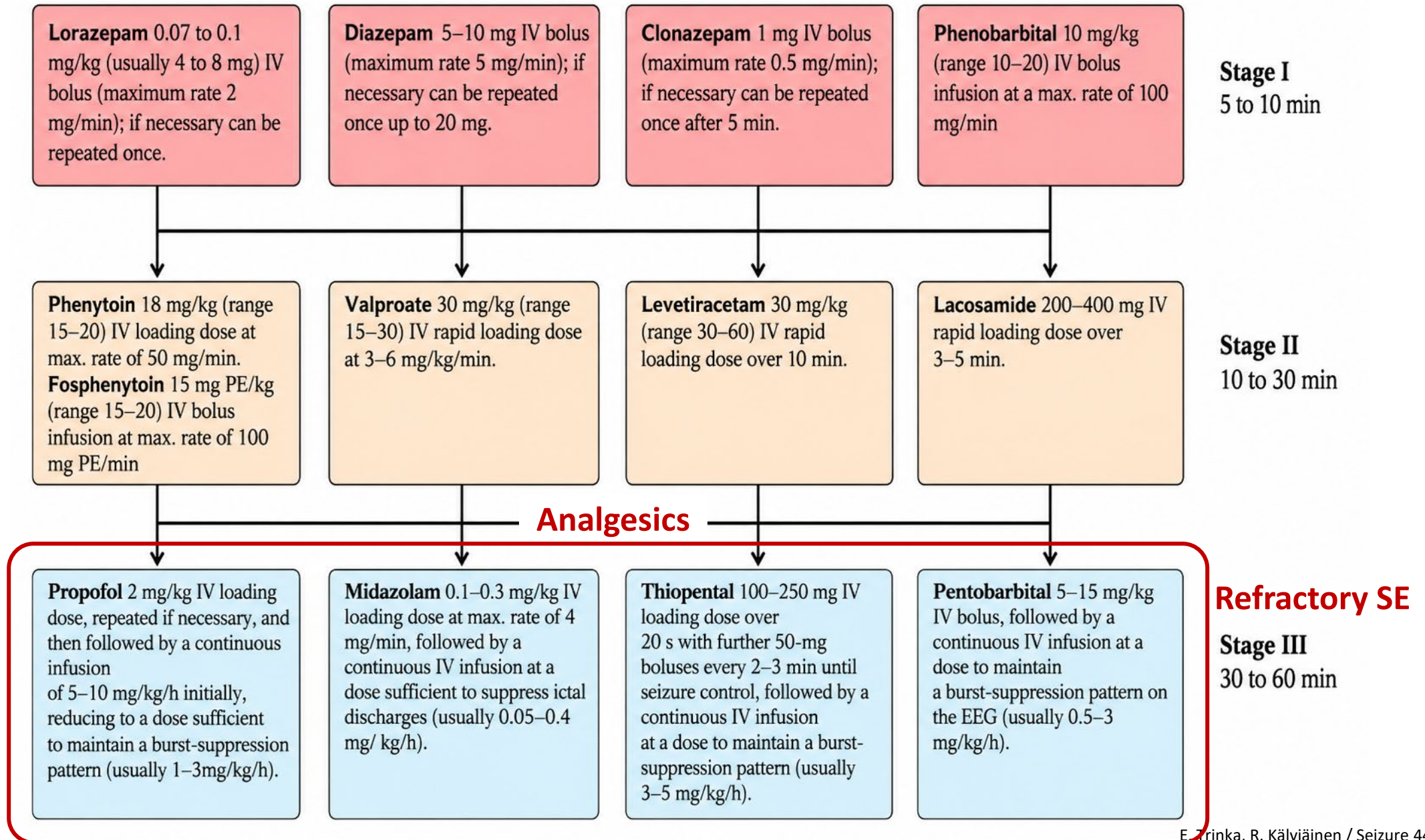


There is no clear evidence to guide therapy in this phase (Level U):

Choices include: repeat second line therapy or anesthetic doses of either thiopental, midazolam, pentobarbital, or propofol (all with continuous EEG monitoring)



Staged Treatment of SE



Aggressive Treatment for SRSE

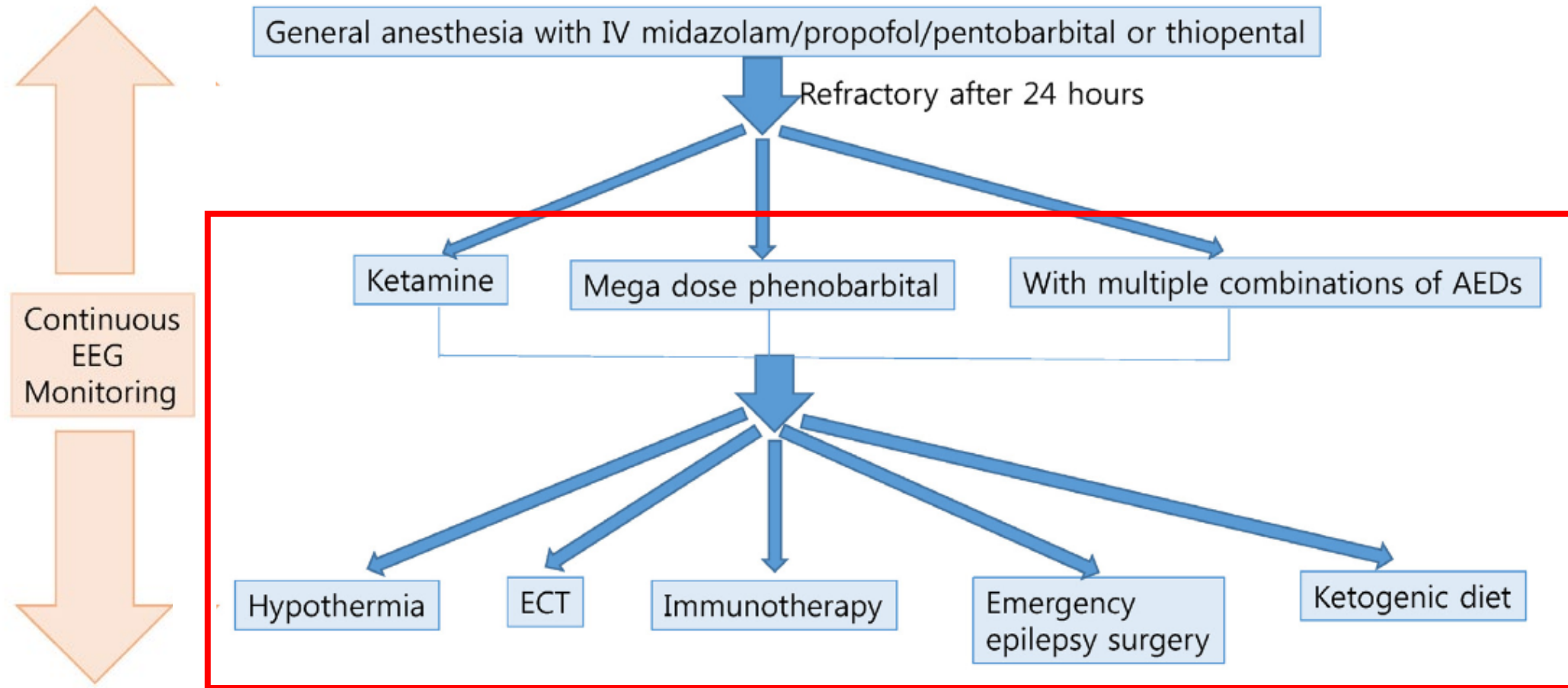


Figure 6. Suggested treatment algorithm for refractory status epilepticus and super-refractory status epilepticus. IV, intravenous; EEG, electroencephalogram; AED, antiepileptic drugs; ECT, electroconvulsive therapy.

Ketamine (S-Ketamine)



Ketamine is being increasingly used for the treatment of RSE

- A strong NMDA receptor antagonist
- Short half-life time: 1-2 hours

2 retrospective case series^{1,2} and 9 single case reports, reporting 80 episodes of RSE treated with ketamine:

- Overall success rate was **56%**
- Most often used bolus dose: ranging from 0.5 mg/kg to 2 mg/kg, followed by infusion ranging from 0.6 mg/kg/h to maximal 10 mg/kg/h
- Duration 2h to 140 days

1: Synowiec et al, Epilepsy Res 2013

2: Gaspard et al, Epilepsia 2013

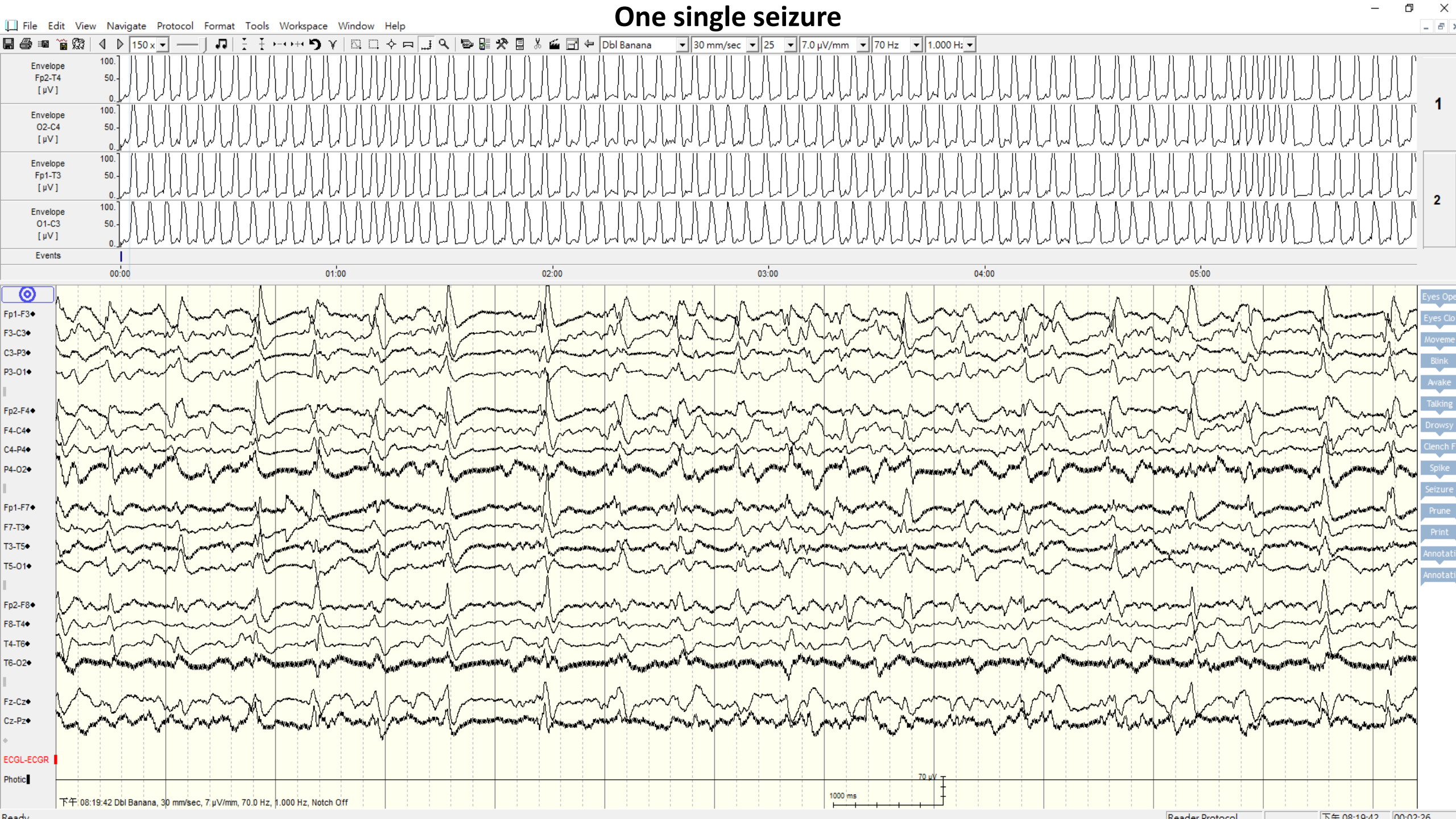
IVIg

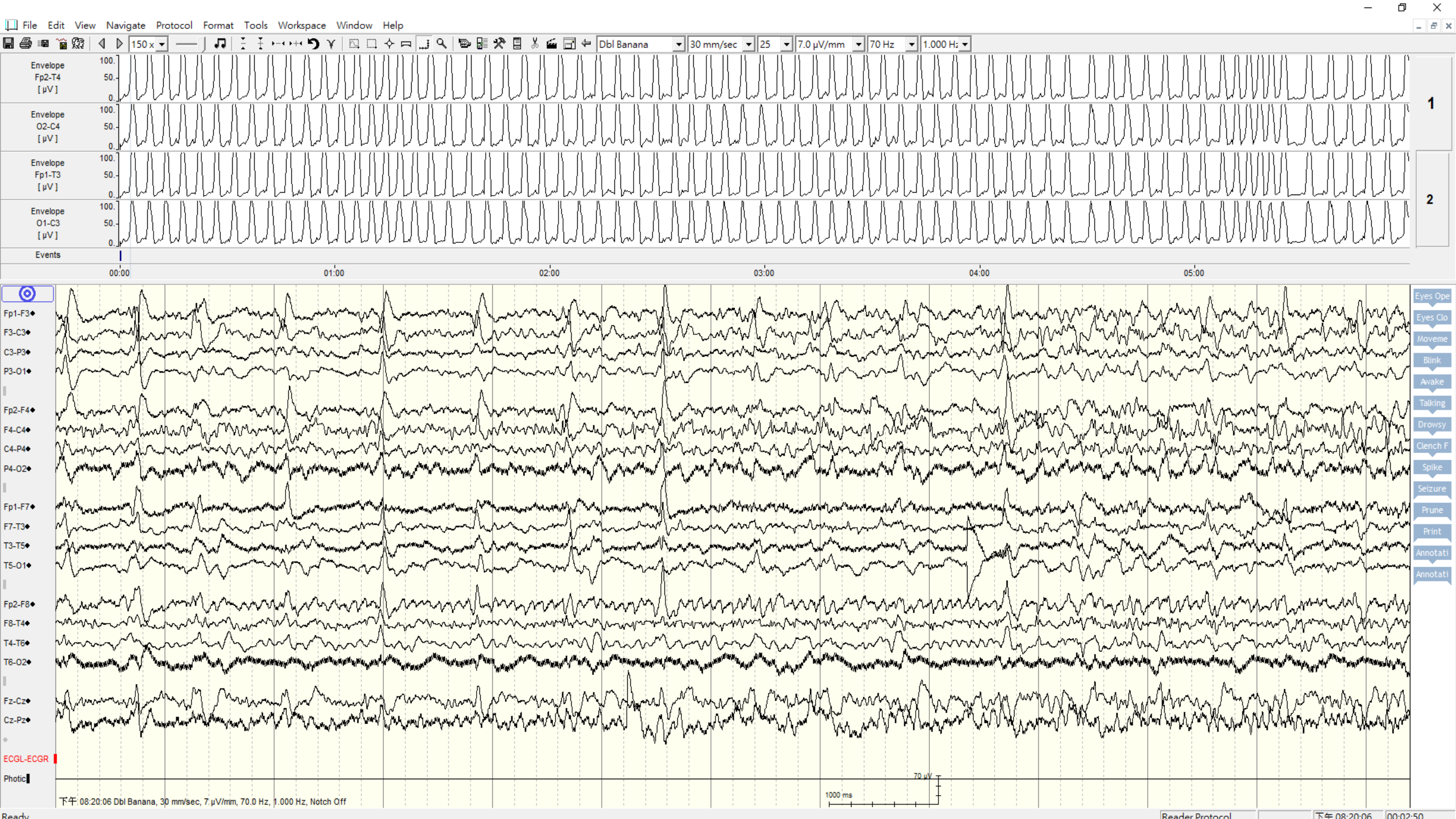
A 24 years-old man, diagnosed as NORSE, admitted into our ICU for persistent **convulsive SE** for days.

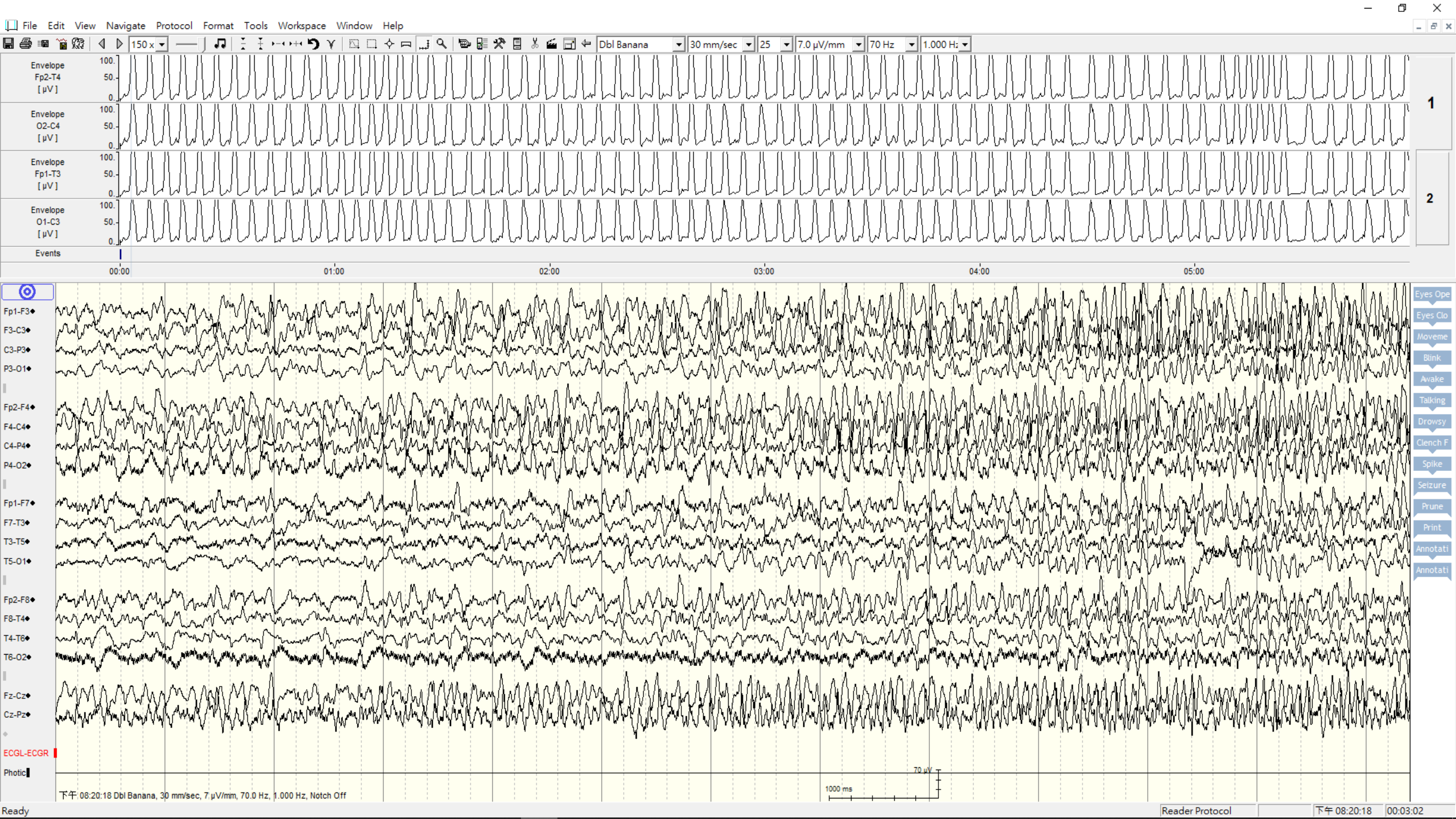


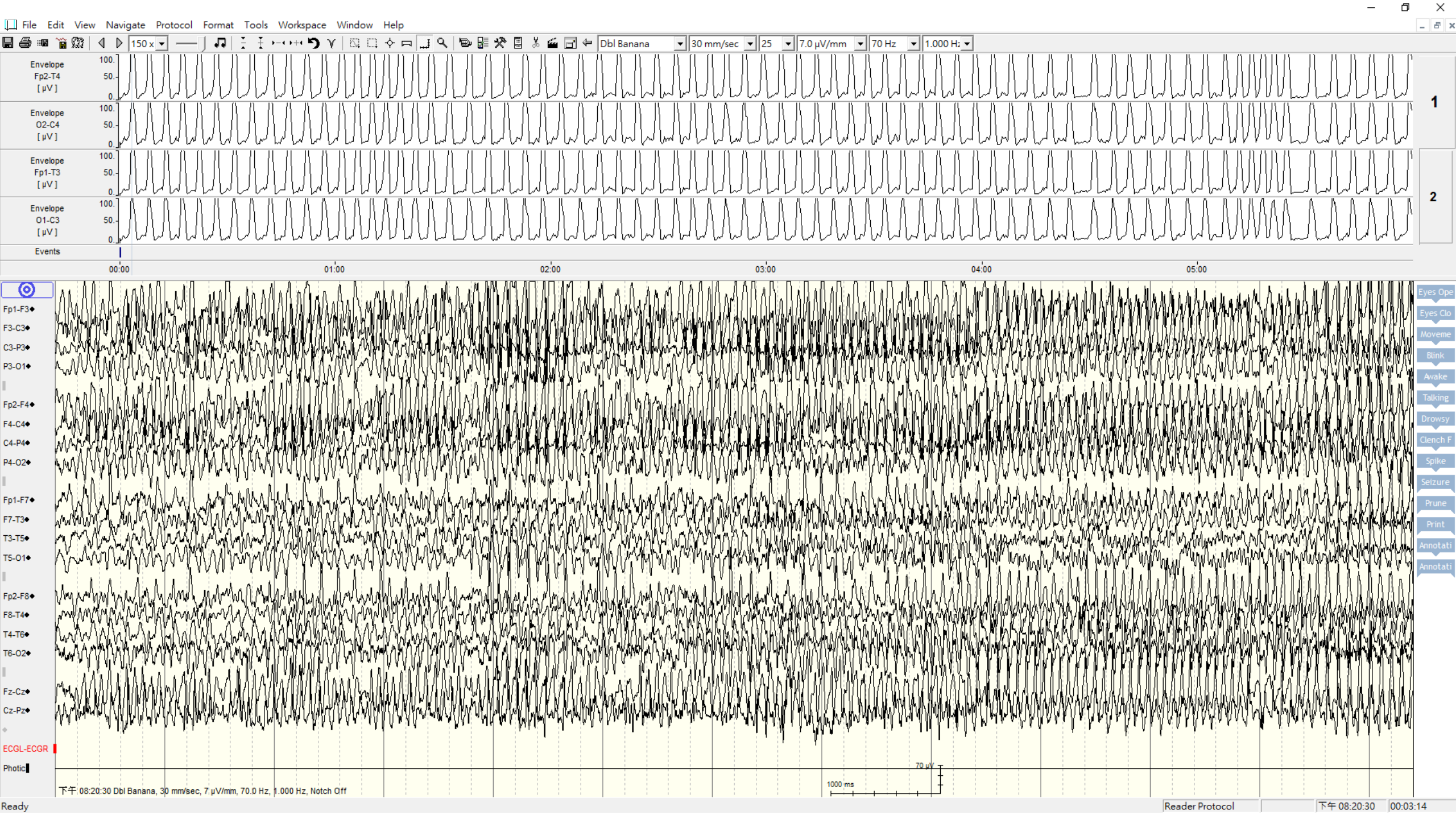
EEG before PP and IVIG

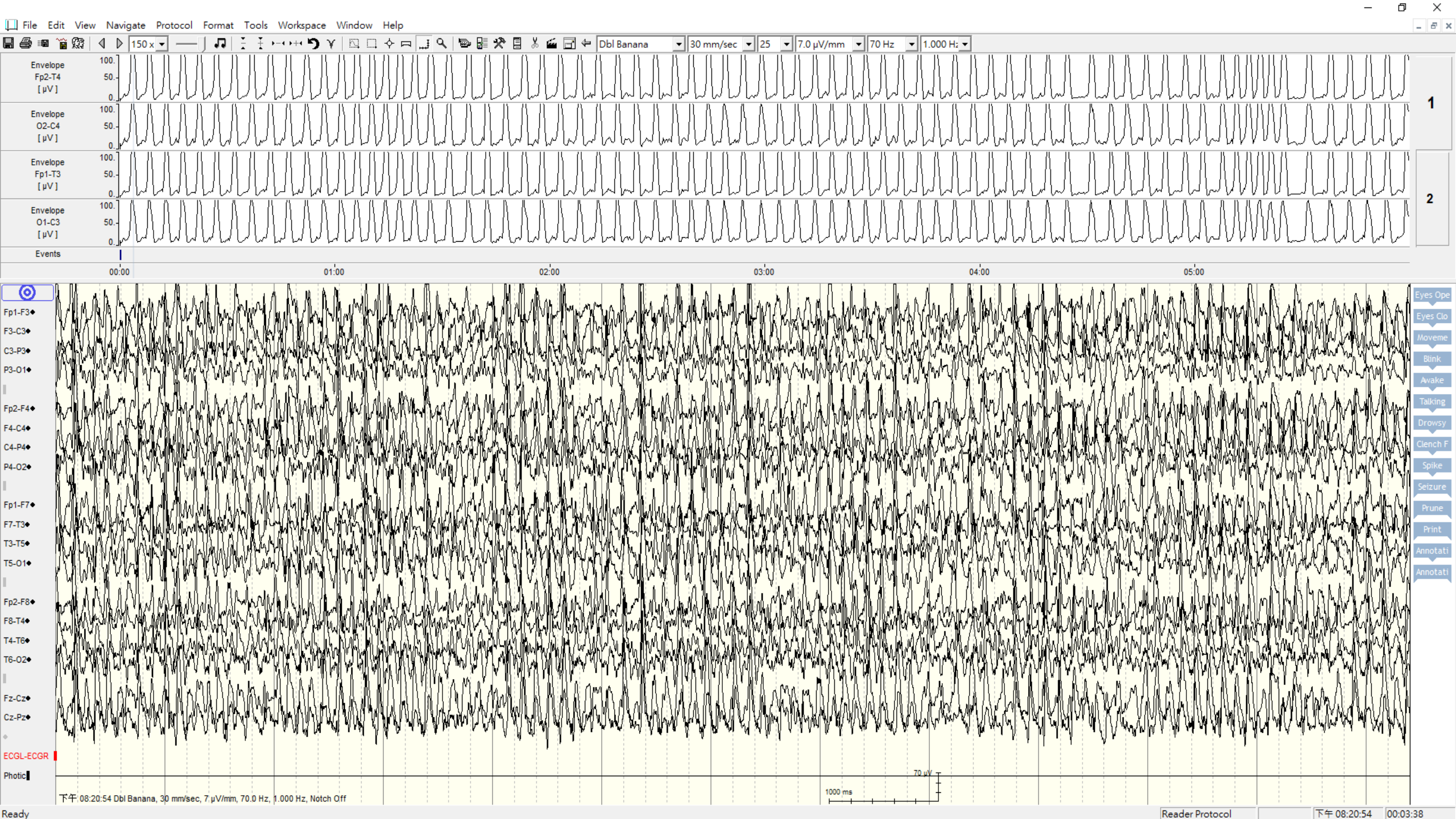


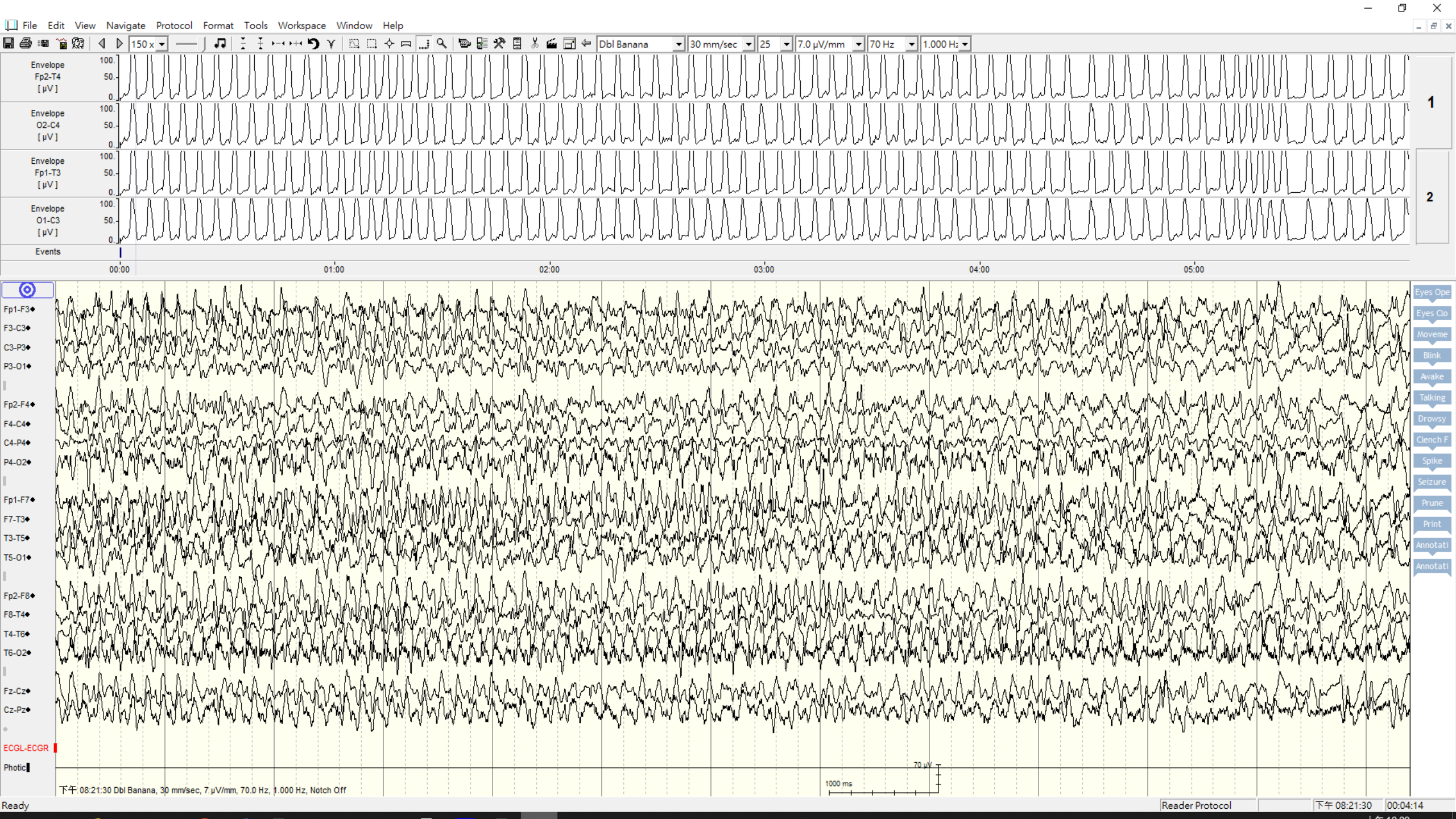










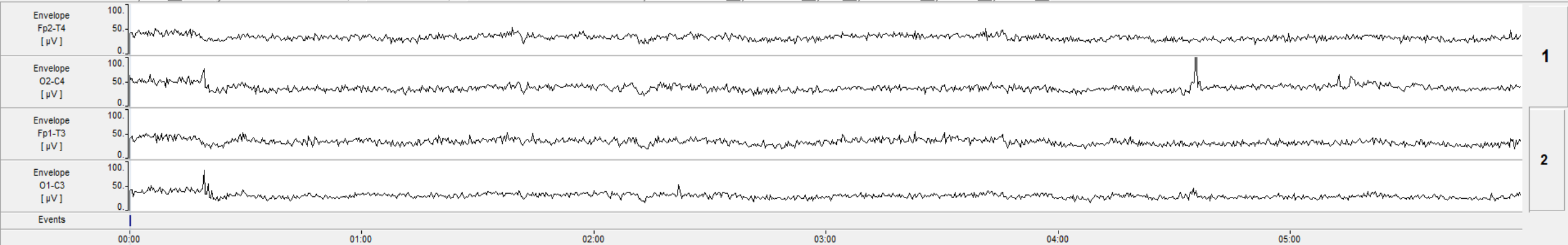




Completing IVIg treatment

File Edit View Navigate Protocol Format Tools Workspace Window Help

150x 30 mm/sec 25 7.0 μ V/mm 70 Hz 1.000 Hz



1

2

Eyes Ope

Eyes Clo

Moveme

Blink

Awake

Talking

Drowsy

Clench F

Spike

Seizure

Prune

Print

Annotati

Annotati



Ketogenic diet for status epilepticus in adult intensive care unit patients: a standard operating procedure

- KD is a high-fat, low-carbohydrate, and adequate-protein diet that induces ketosis, exerting anticonvulsant effects.
- Classical KD: high fat-to-carbohydrate/protein ratios (4:1).

KD should be considered in adult ICU patients meeting following criteria:

- RSE lasting > 72 h, despite treatment with at least 3 different ASM or diagnosis of SRSE.
- Persistent seizure activity, reflected clinically and/or by cEEG.
- Early initiation after ICU admission, preferably within 24 h in cases where SRSE is anticipated, to maximize potential benefits and minimize treatment delays.

醫師部份

1. NPO

2. Q4H 驗 尿酮(chemical) 及 血糖 +/- 血酮，

若：A. 尿酮>2+

B. sugar<52

C. 有低血糖症狀

開始供應生酮飲食

3. 第一天只給 1/2 量（本病人 _____ 卡），觀察是否有不適症狀。

如無問題，次日（經一整天）再加至全量（_____ 卡）。

4. 每日早上測尿酮，請維持在尿酮 2-3 價。

5. 如穩定維持尿酮，可觀察 1 週，症狀是否改善。

如尿酮價數降低，症狀改善不明顯，請通知營養師，調整油的比例。

6. 另外要添加綜合維他命（自備：如_善存 2#day），追蹤電解質。

- 一定不能打有含葡萄糖等含糖類的 IV，否則酮體立刻消失。

護理師部分

- 每天送 3 次，每次 2 杯

■ 一杯灌食

■ 另一杯請冰起來，要灌的時候再復熱-隔水加熱，油要混勻

- 請直接用 灌食空針 (X pump 灌食)

- 油請儘量倒乾淨，油量不足會影響生酮。

- 切勿灌入任何其他家屬自備食物，否則酮體立刻消失。

Emergency Discontinuation Criteria of KD

If any of the following conditions persist despite appropriate corrective measures for >48 h, KD must be discontinued to prevent severe metabolic complications:

- Severe **metabolic acidosis** (pH < 7.1 despite bicarbonate correction)
- Uncontrolled **hypertriglyceridemia** > 1000 mg/dL.
- **Hepatic failure** or severe **hyperammonemia**.
- Refractory **hypoglycemia** despite glucose administration.



In patients under KD, propofol is relatively contraindicated:

- Propofol can impair mitochondrial fatty-acid β oxidation
- In combination with KD (high lipid load), the risk of mitochondrial energy failure (and consequent propofol infusion syndrome) may increase

→ **Shift propofol to midazolam pump for seizure control**



Identification of Valproic Acid Glucuronide Hydrolase As a Key Enzyme for the Interaction of Valproic Acid with Carbapenem Antibiotics

Eiko Suzuki, Naotoshi Yamamura, Yuji Ogura, Daisuke Nakai, Kazuishi Kubota, Nobuhiro Kobayashi, Shin-ichi Miura, and Osamu Okazaki

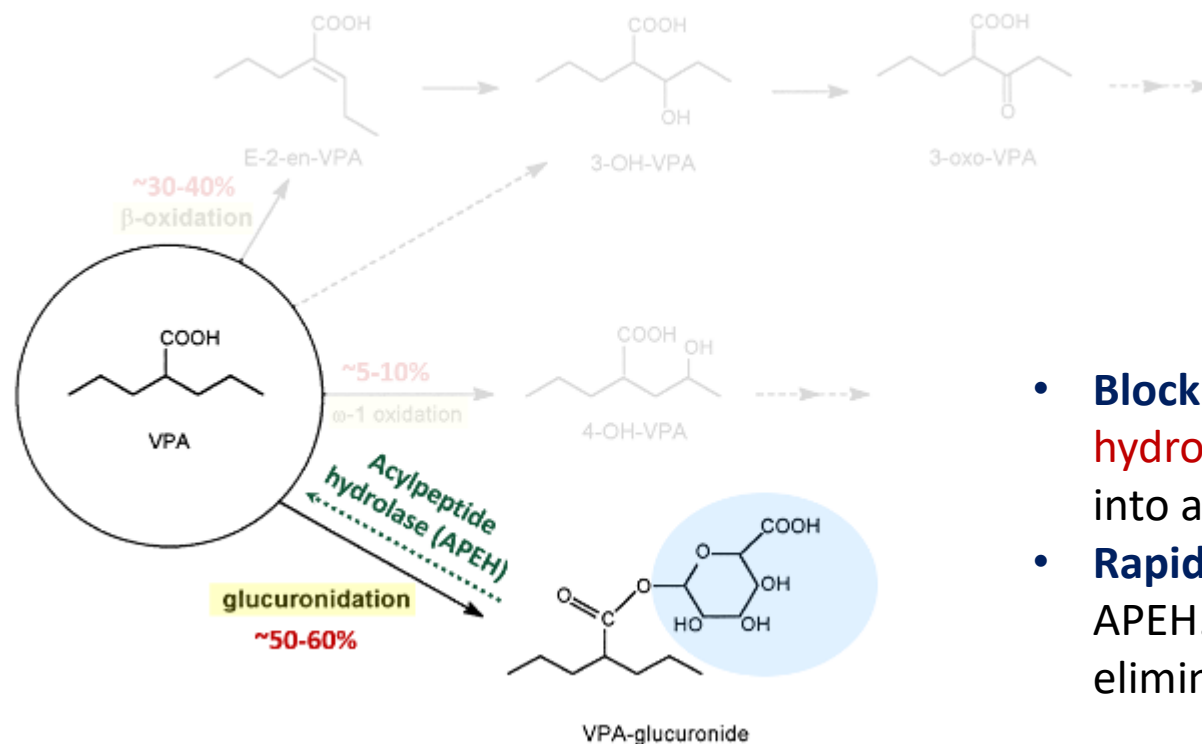
Drug Metabolism and Pharmacokinetics Research Laboratories (E.S., N.Y., D.N., N.K., O.O.) and Translational Medicine and Clinical Pharmacology Department (Y.O., K.K., S.M.), Daiichi Sankyo Co., Ltd., Tokyo, Japan

Received February 23, 2010, accepted June 15, 2010

ABSTRACT:

Plasma levels of valproic acid (VPA) are decreased by concomitant use with carbapenem antibiotics, such as panipenem (PAPM). One of the plausible mechanisms of this interaction is the inhibition of VPA glucuronide (VPA-G) hydrolysis by carbapenems in the liver. To elucidate this interaction mechanism, we purified VPA-G hydrolase from human liver cytosol, in which the hydrolytic activity was mainly located. After chromatographic purification, the VPA-G hydrolase was identified as acylpeptide hydrolase (APEH). APEH-depleted cytosol, prepared by an immunoadsorption method, completely lacked the hydrolytic activity. These results demonstrate that APEH is a single enzyme involved in PAPM-sensitive VPA-G hydrolysis in cytosol. In addition, the hydrolytic activity of recom-

profile by typical esterase inhibitors (diisopropyl fluorophosphate, 5,5'-dithiobis-(2-nitrobenzoic acid), *p*-chloromercuribenzoic acid, and *o*-saccharic acid 1,4-lactone) was similar to that of human liver cytosol. Cytosolic VPA-G hydrolase activity was slightly inhibited by cholinesterase and carboxylesterase inhibitors, β -Glucuronidase activity remained in APEH-depleted cytosol, whereas VPA-G hydrolase activity was completely abolished. Thus, other cholinesterase, carboxylesterase, or β -glucuronidase in cytosol would not be involved in VPA-G hydrolysis. Taken together, APEH plays a major role in the PAPM-sensitive VPA-G hydrolysis in the liver. These findings suggest that APEH could be a key enzyme for the drug interaction of VPA with carbapenems via VPA-G hydrolysis.



- **Blocking Recycling Pathway:** Under normal conditions, **acylpeptide hydrolase (APEH)** breaks down valproate-glucuronide (VPA-G) back into active valproate, extending its half-life.
- **Rapid Elimination:** Carbapenem strongly and irreversibly inhibits APEH. VPA-G cannot recycle back into active VPA and is quickly eliminated through urine and bile.

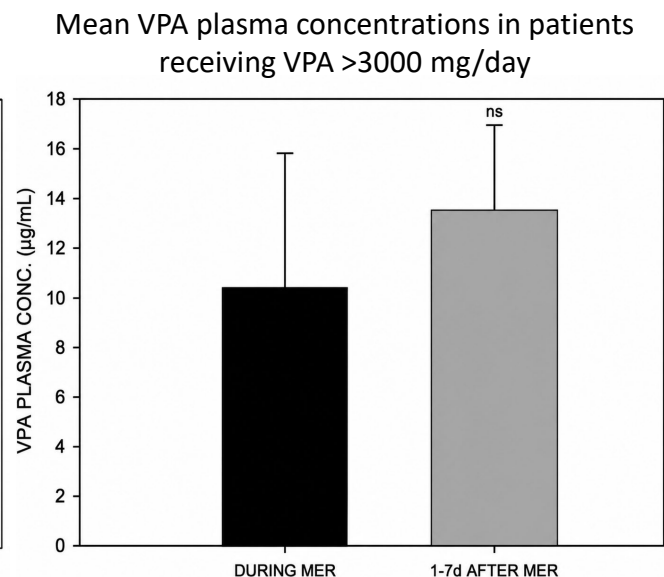
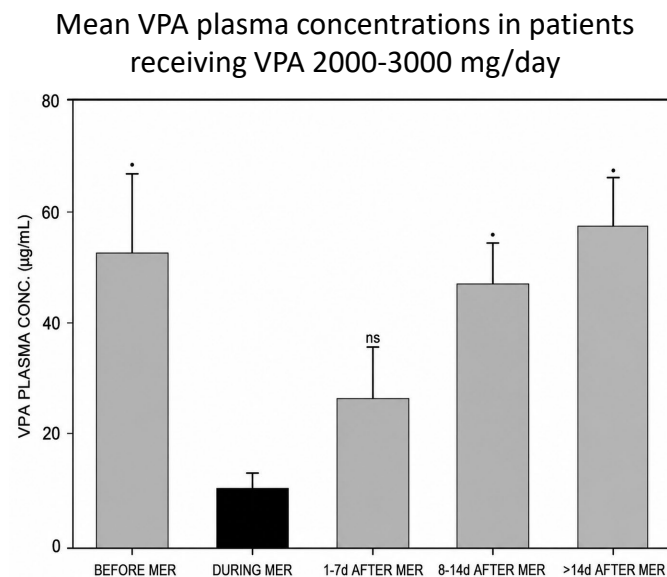
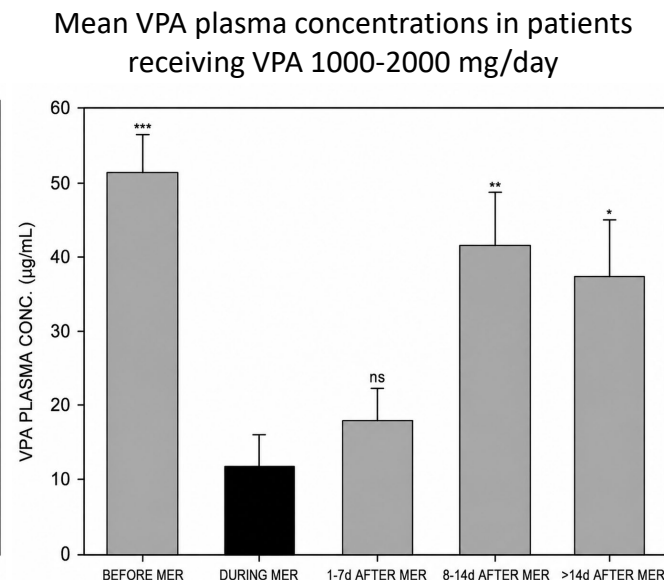
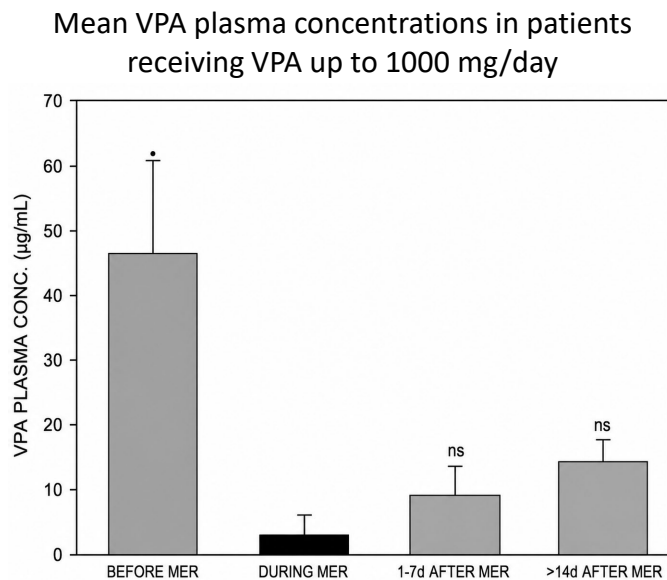
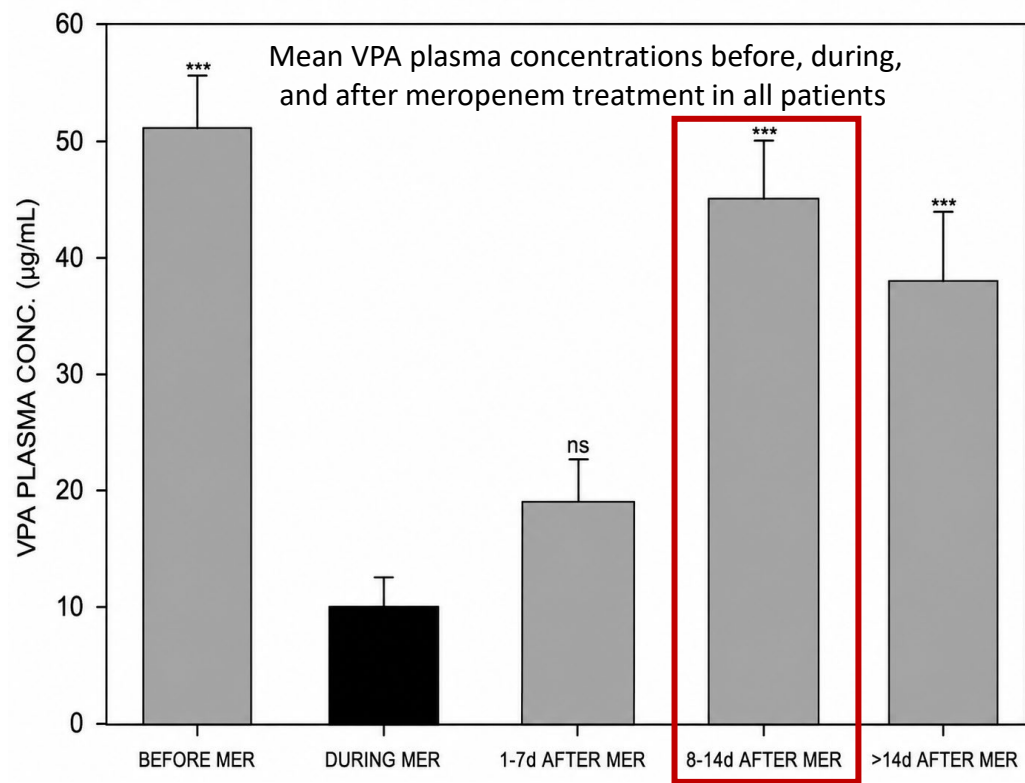
Plasma VPA levels decrease within 24h; remain low at 7 days after stopping carbapenem; gradually increase after 8-14 days

Full Access

Valproic Acid Plasma Concentration Decreases in a Dose-Independent Manner Following Administration of Meropenem A Retrospective Study

Mr Simon Haroutiunian MSc, Ms Yael Ratz BSc, Ms Bella Rabinovich MSc, Ms Miriam Adam MSc, Dr Amnon Hoffman PhD

First published: 07 March 2013 | <https://doi.org/10.1177/0091270009334377> | [VIEW METRICS](#)



Take Home Messages

01

Seizure mimics and chameleons

Not every abnormal movement in the ICU is a seizure, and many ICU seizures are nonconvulsive.

02

Consider EEG when consciousness does not recover

Continuous EEG should be considered when consciousness does not recover as expected or when subtle seizure activity is suspected.

03

Treat status epilepticus early and adequately

Rapid administration of an adequate dose of benzodiazepine is more important than the choice of benzodiazepine, followed promptly by a second-line antiseizure medication when needed.

04

Escalate early in refractory status epilepticus

Treatment may require continuous anesthetic therapy, EEG-guided management, and selected additional therapies such as immunotherapy, ketamine or ketogenic diet.