ANLS

The management of Status epilepticus

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2023/11/25

Definition of status epilepticus (SE)

- SE is a condition resulting either from

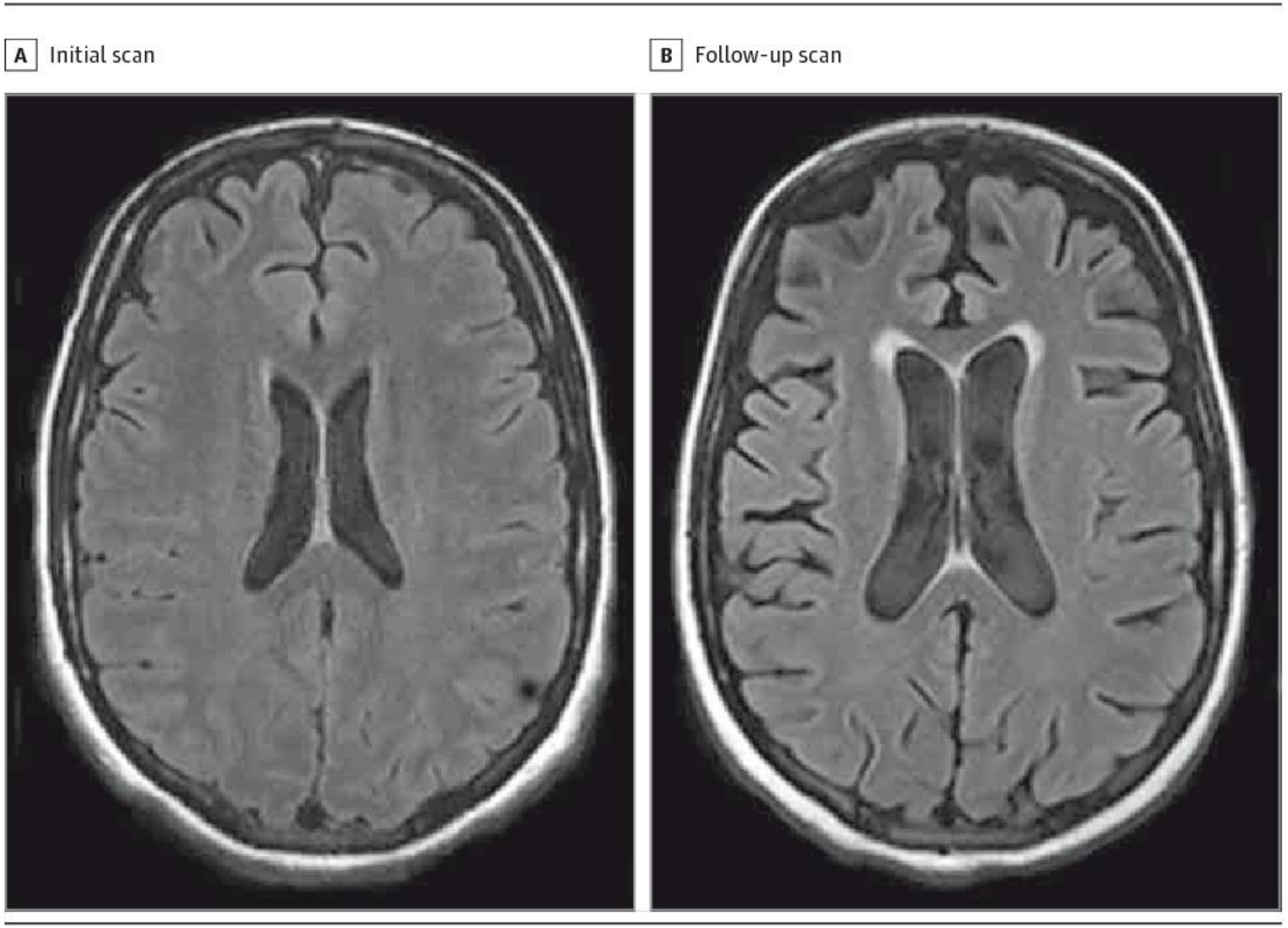
(1) The failure of the mechanisms responsible for seizure termination

(2) The initiation of mechanisms which lead to abnormally prolonged seizures

- It is a condition that can have long-term consequences.

Epilepsia, 56(10):1515–1523, 2015

Brain atrophy after SE



JAMA Neurology 1 October 2016

Operational definition of status epilepticus

abnormally prolonged seizures (after time point t_1).

have long-term consequences (after time point t_2)

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 SE	10-15 min	Unknown

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

Epilepsia, 56(10):1515–1523, 2015

Semiology of status epilepticus

With prominent motor symptoms

A.1 Convulsive SE (CSE, synonym: tonic–clonic SE)
- A.1.a. Generalized convulsive
- A.1.b. Focal onset evolving into bilateral convulsive SE
- A.1.c. Unknown whether focal or generalized

A.2 **Myoclonic** SE
- A.2.a. With coma
- A.2.b. Without coma

A.3 **Focal motor**
- A.3.a. Jacksonian
- A.3.b. Epilepsia partialis continua (EPC)
- A.3.c. Adversive status
- A.3.d. Oculoclonic status
- A.3.e. Ictal paresis (i.e., focal inhibitory SE)

A.4 **Tonic** status

A.5 **Hyperkinetic** SE

Without prominent motor symptoms
(i.e., nonconvulsive SE, NCSE)

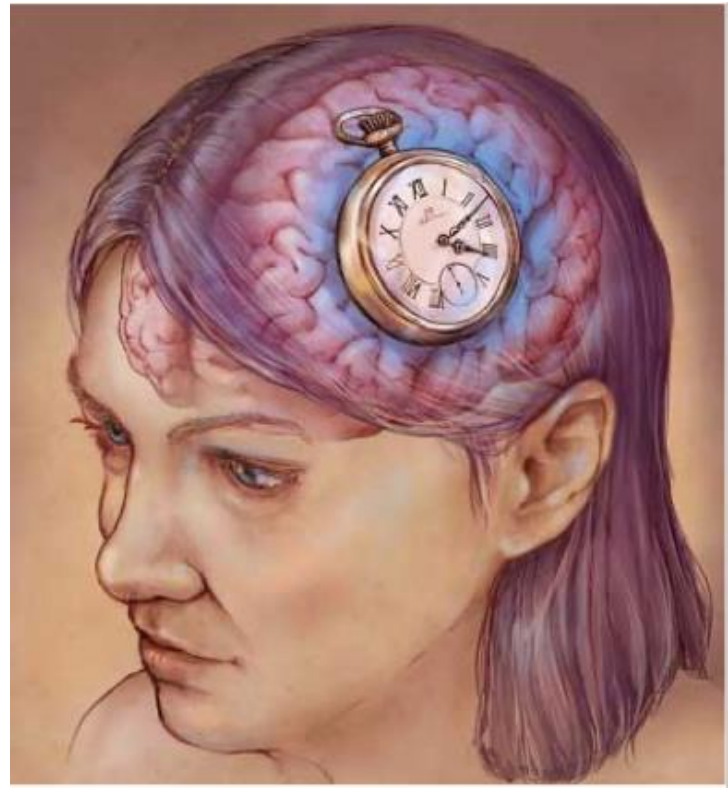
B.1 NCSE with coma (including so-called "subtle" SE)

B.2 NCSE **without coma**
- B.2.a. **Generalized**
  - B.2.a.a Typical absence status
  - B.2.a.b Atypical absence status
  - B.2.a.c Myoclonic absence status
- B.2.b. **Focal**
  - B.2.b.a Without impairment of consciousness (aura continua, with autonomic, sensory, visual, olfactory, gustatory, emotional/ psychic/experiential, or auditory symptoms)
  - B.2.b.b Aphasic status
  - B.2.b.c With impaired consciousness
- B.2.c Unknown whether focal or generalized
  - B.2.c.a Autonomic SE

Epilepsia, 56(10):1515–1523, 2015

Time is Brain!

- In a study of IV VPA (n=41), who failed IV lorazepam, to treat status epilepticus or serial seizure attacks



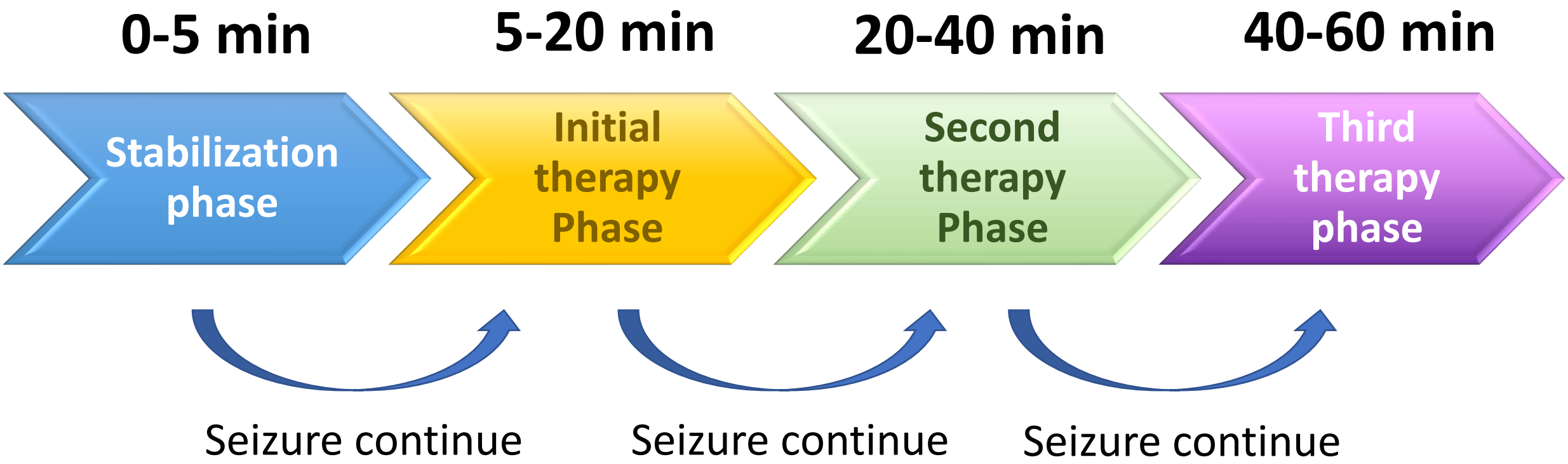
5% need anesthesia if treated < 3 hours

28% need anesthesia if treated 3-24 hours

60% need anesthesia if treated > 24 hours

Olsen KB et al. Acta Neurol Scand Suppl 2007;187:51-54

Timeline of management of status epilepticus



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

Stabilization Phase: 0-5 minutes

- **A**irway: 移除口腔內異物，擺復甦姿勢
- **B**reathing: 給氧氣, 必要時插管
- **C**irculation: 建立IV access
  - 如果血壓低，適度給hydration和升壓藥物
- **D**isability: 觀察神經學症狀
- **E**KG monitoring
- **F**inger sugar:
  - if < 60mg/dl, give D50W 50ml IV stat + (100mg thiamine IV)
- **G**et blood for further evaluation

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

建議檢驗項目（初步檢查）

- CBC/DC
- Na、K、Ca、P、Mg、blood sugar、renal function、liver function、CRP
- Ammonia、CPK、myoglobulin、(prolactin)
- Drug level (valproic acid, phenytoin, phenobarbital, carbamazepine)
- U/A, urine drug or toxin screening
- (Brain imaging)
- (CSF study)

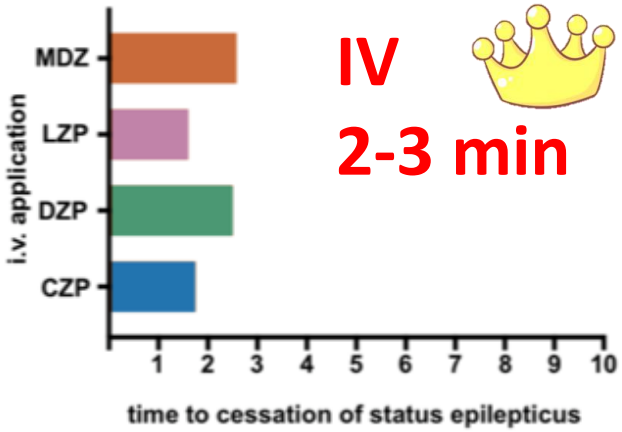
Initial Therapy Phase: 5-20 minutes

Early status epilepticus

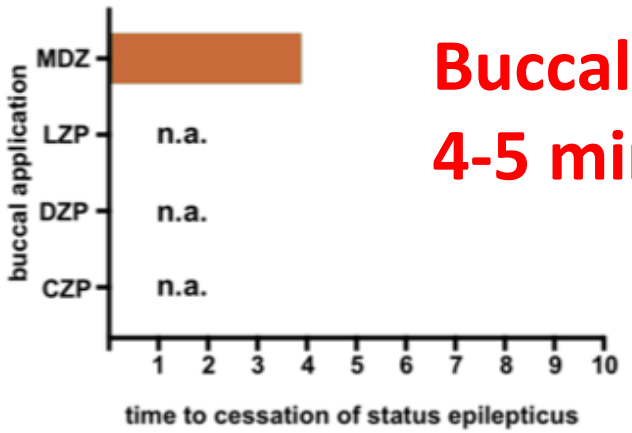
BZD	途徑	劑量建議	60kg 換算劑量	支(長庚)
Midazolam	IV/**IM**	10mg (> 40kg), 5mg (13-40kg)	10mg	2 amp
Lorazepam	**IV**/IM	0.1mg/kg, Max: 4mg/dose May repeat once after 5-10 minutes	4mg	2 amp
Diazepam	**IV**/IM	0.2mg/kg, Max: 10mg/dose May repeat once after 5-10 minutes	10mg	1 amp

Seizure control rate: around 70%

Routes of delivery

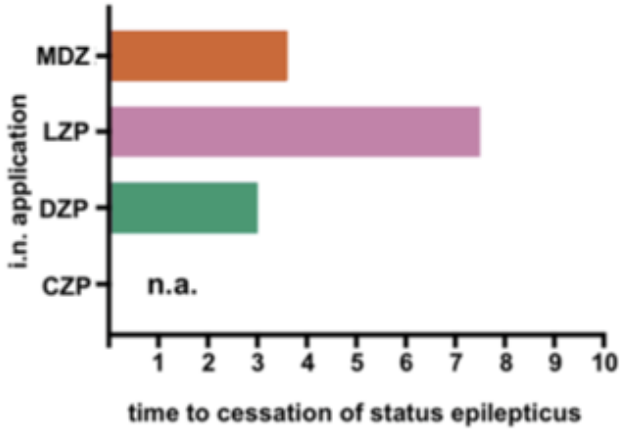


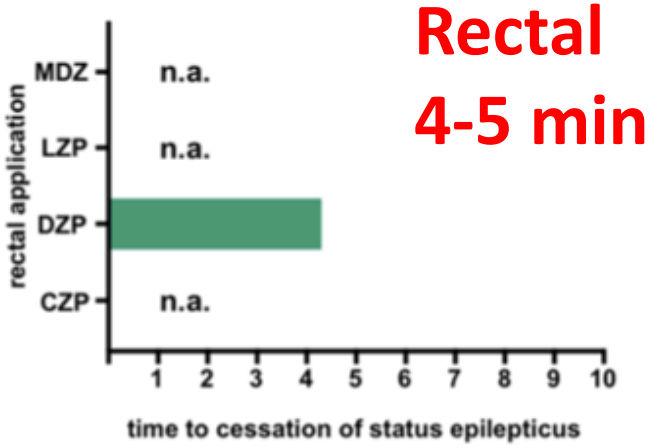
IV
2-3 min



Buccal
4-5 min

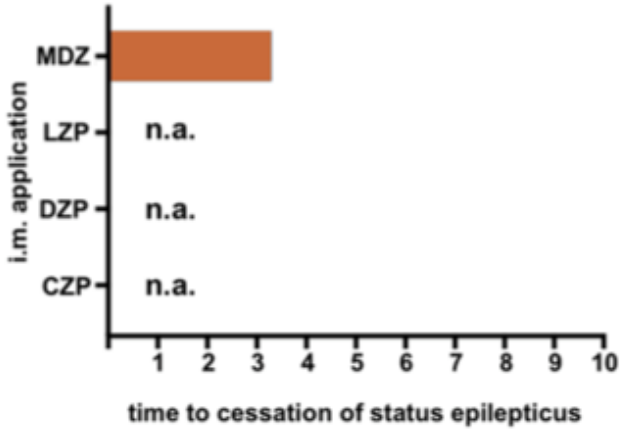
Intranasal
3-8 min





Rectal
4-5 min

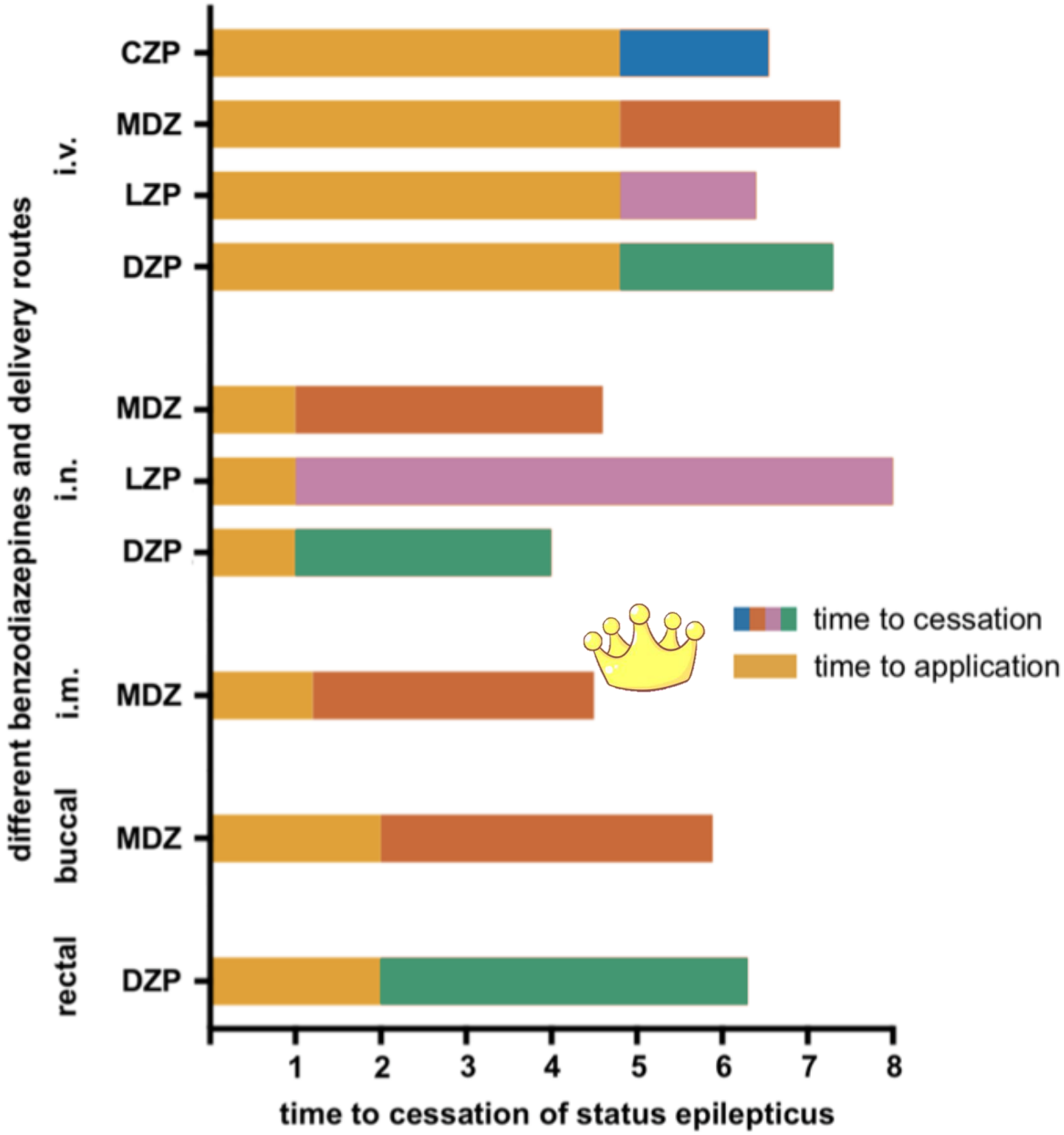
IM
3-4 min



Considering Time to application

RAMPART (n=329, 448 episodes)
– IM midazolam is better than IV lorazepam (73% versus 63%, P<-0.001)
– The reason for better seizure control is time of therapy
– Midazolam 1.2 min versus Lorazepam 4.8 min

- ✓ 在已有IV access的情況下，給予IV BZD
- ✓ 在沒有IV access的情況下，如果無法在1-2分鐘內打上IV line，可考慮先給IM BZD



Worry about BZD induced respiratory failure?

- Respiratory or circulatory complication rate
  - ~**10%** in both lorazepam and diazepam group
  - **22.5%** in placebo group (p=0.08)

✓ 癲癇沒控制好才是呼吸衰竭的主因

- Respiratory and cardiac symptoms are the most common encountered adverse events in SE. (Level A)
- Respiratory problems are lower in patients treated with BZD, therefore, consequence of untreated SE. (Level A)
- Respiratory depression are less frequently in children than adult. (Level B)

Leppik et al. JAMA 1983 249(11):1452-4
Alldredge et al. NEJM 2001 345(9):631-637

How about skip IV BZD and give IV ASM?

- VASEC study (n=384, GCSE)
  - 65% controlled by IV lorazepam
  - 58% controlled by IV phenobarbital
  - 44% controlled by IV phenytoin
- In general, time to application and onset of IV BZD is faster than IV ASM

✓ 能快速取得，快速給予，快速產生藥效的藥物，就是好藥

Treiman DM et al. NEJM 1998;339:792-798

Second Therapy Phase: 20-40 minutes

Established status epilepticus (BZD-refractory SE)

ASM (IV)	loading劑量	Loading time	維持劑量（肝腎功能正常）
Fosphenytoin	20 mg PE/kg	100mg PE/min	
Phenytoin	15-20 mg/kg	50 mg/min	100 mg q8h
Valproic acid	30-40 mg/kg, Max: 3000mg	5-10 min	400-600 mg q8h
Levetiracetam	30-60 mg/kg, Max: 4500mg	10-15 min	500-1500 mg q12h
Phenobarbital	15 mg/kg; Max: 800mg	25-100 mg/min	1-3 mg/kg/day in 2 divided doses
Lacosamide	200-400mg	3-5 min	100-200mg q12h

The NEW ENGLAND JOURNAL of MEDICINE

Trial of Three Anticonvulsant Medications for Status Epilepticus

MULTICENTER, RANDOMIZED, DOUBLE-BLIND TRIAL

384
Children and adults with benzodiazepine-refractory status epilepticus

	Levetiracetam	Fosphenytoin	Valproate
	60 mg/kg	20 mg/kg (phenytoin equivalents)	40 mg/kg
Absence of clinically evident seizures and improved responsiveness at 60 min	47% (68/145)	45% (53/118)	46% (56/121)

No significant difference in rates of seizure cessation or in safety

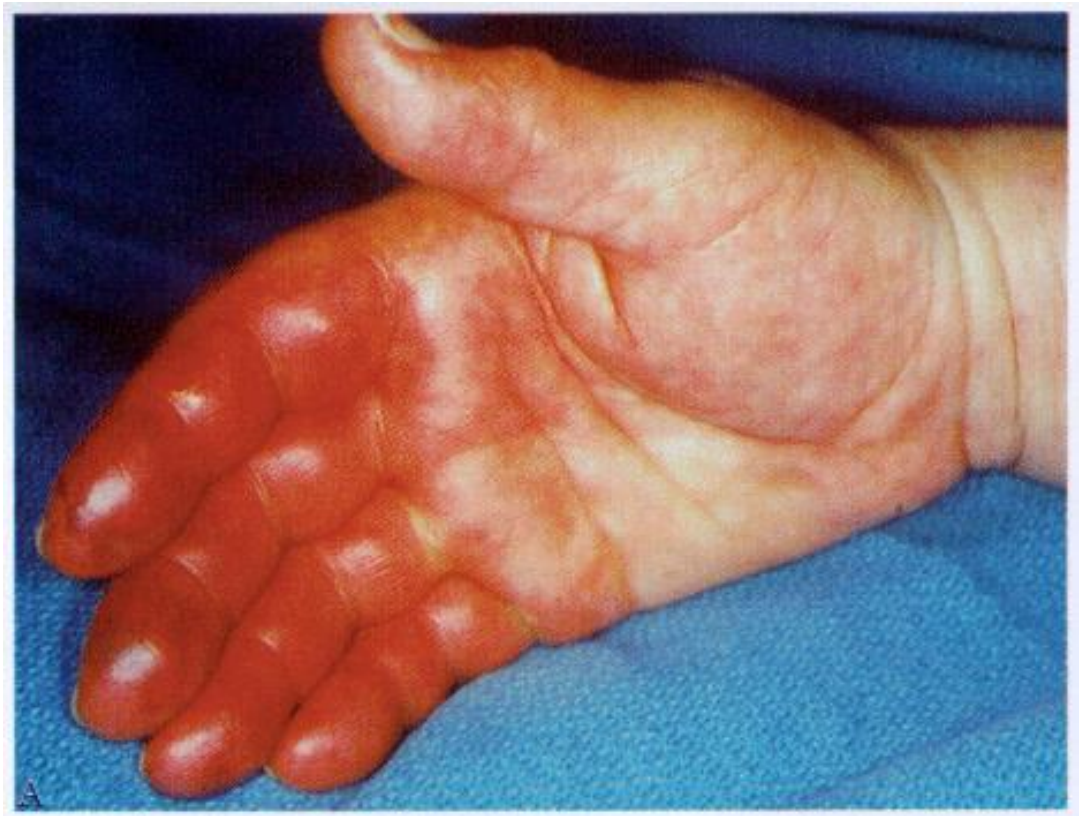
J. Kapur et al. 10.1056/NEJMoa1905795

Choose the first IV ASM

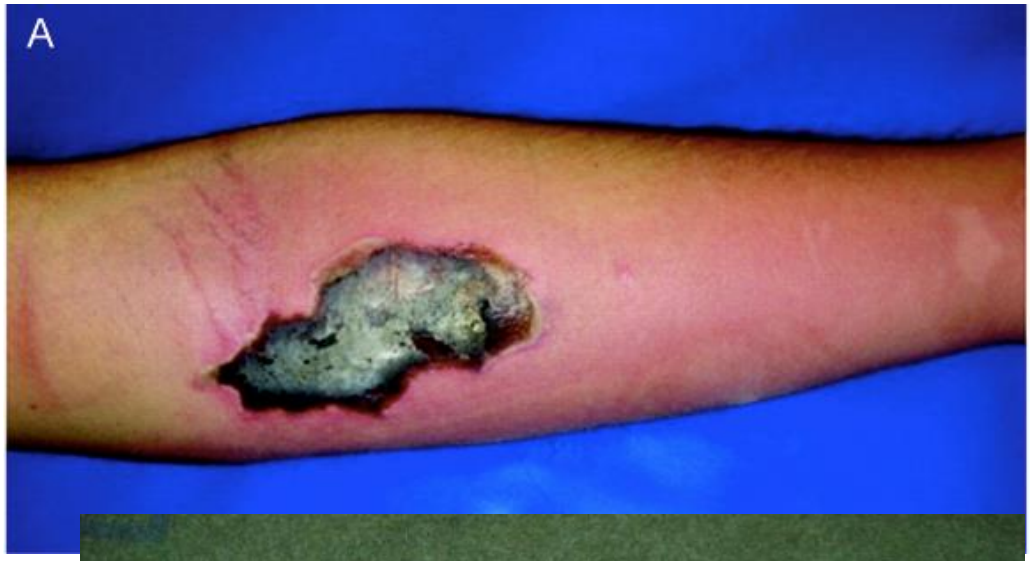
ASM	PHT	VPA	LEV	LCM	PHB
優點	● 對局部發作有效	●廣效 ●心肺影響小 ●作用快	●廣效 ●心肺影響小 ●作用快 ●藥物交互作用少 ●蛋白結合少	●對局部發作有效 ●作用快 ●藥物交互作用少 ●蛋白結合少	●對局部發作有效
缺點	●Infusion site reaction ●Hypotension ●Cardiac arrhythmia	●蛋白結合高 ●肝毒性 ●Ammonia高 ●血小板低下 ●腦病變 ●抗生素交互作用	●Psychosis	●Bradycardia ●AV block	●呼吸抑制 ●鎮定嗜睡

Phenytoin-related local cutaneous reaction

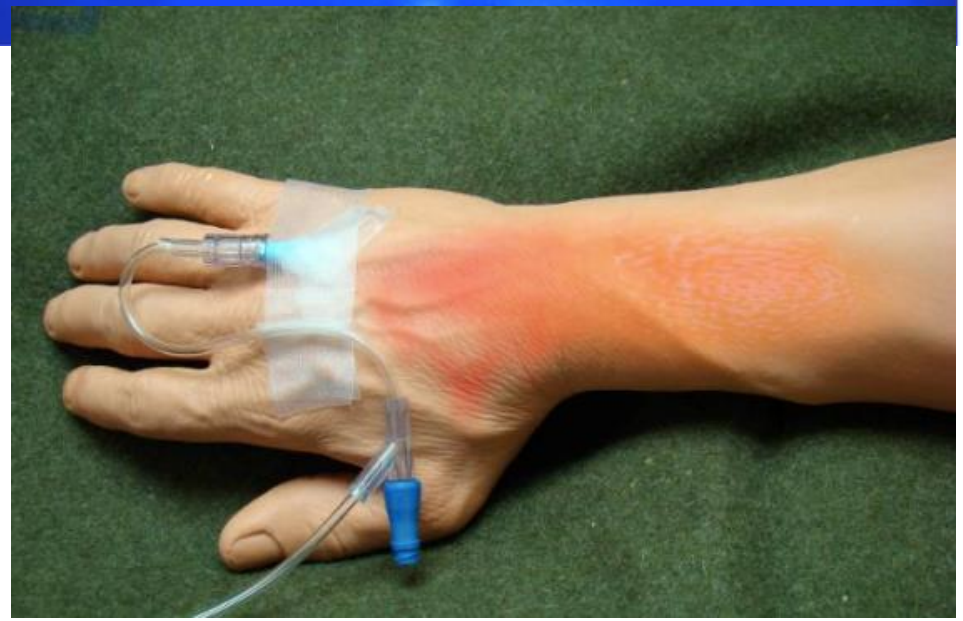
Purple glove syndrome



Soft tissue necrosis



Phlebitis



Third Therapy Phase: 40-60 minutes

Refractory status epilepticus (refractory to one BZD and one ASM)

Anesthesia	劑量建議
Propofol (500mg/50ml)	2 mg/kg loading, 持續滴注5-10 mg/kg/h (10cc stat, 20cc/h 上下調整至腦波BSP)
Midazolam (150mg/500ml N/S)	0.1-0.2 mg/kg loading,持續滴注0.1-0.4 mg/kg/h (10mg stat, 20cc/h 上下調整至腦波BSP, up to 80cc/hr)
Phenobarbital	5-15 mg/kg loading, then 1-3 mg/kg/day in 2-3 divided doses

Propofol related infusion syndrome (PRIS)

Symptoms:

1. Metabolic acidosis
2. Hepatomegaly → Hepatic failure
3. Rhabdomyolysis → renal failure
4. Bradycardia → cardiac arrest

Risk factors:

1. Long-term use
   Children > 48 h; Adult > 5 d
2. High dose (> 5 mg/kg/h)
3. Age (children)

Lab monitoring:

Lactate acid, CPK, myoglobulin, K,
ALT, Crea, GAS
EKG monitoring

避免長時間高劑量使用
給予足夠碳水化合物
監測並提早發現
—但發現要立即停藥
支持性療法/血液透析

Status Epilepticus (SE)

Convulsive SZ > 5 min

A condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures (after time point t1). It is a condition that can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks

Refractory Status Epilepticus (RSE)

Persistent SZ after giving 1 IV BZD and 1 IV ASM

SE persisting despite administration of at least 2 appropriately selected and dosed parenteral mediations

Super Refractory Status Epilepticus (SRSE)

Persistent SZ > 24 hours despite anesthetic treatment, or recurs when weaning anesthetic regimen

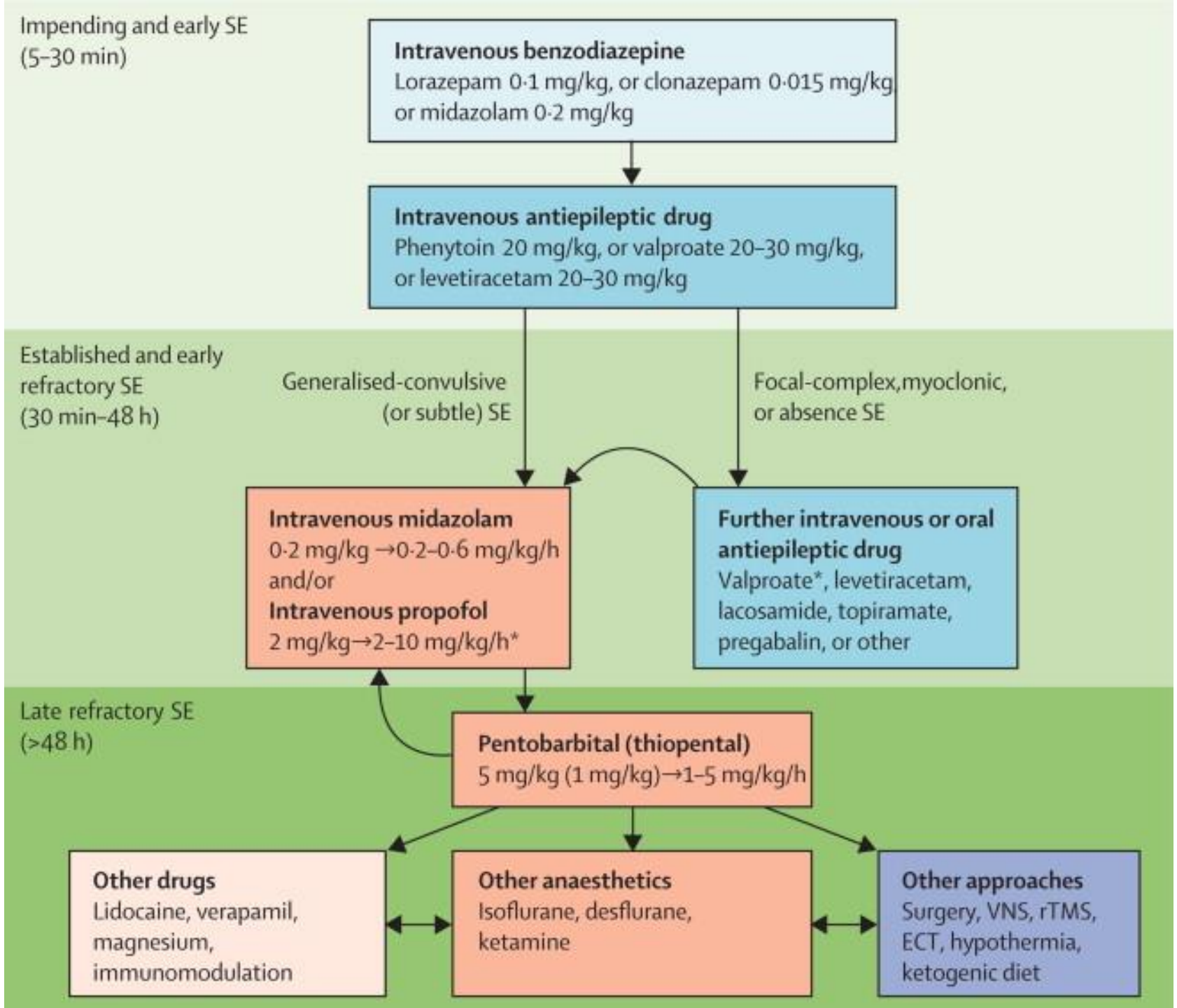
SE that continues for ≥ 24 hours despite anesthetic treatment, c
anesthetic regimen

Prolonged Super Refractory Status Epilepticus

Persistent SZ or need of ongoing anesthesia > 7 days

Super refractory status epilepticus that persists for at least 7 days, including ongoing need for anesthetics

1. Ketamine
2. Steroid
3. Ketogenic diet
4. Hypothermia
5. Surgery
6. Vagus nerve stimulation



Ketamine

Possible efficacy: 60-70%

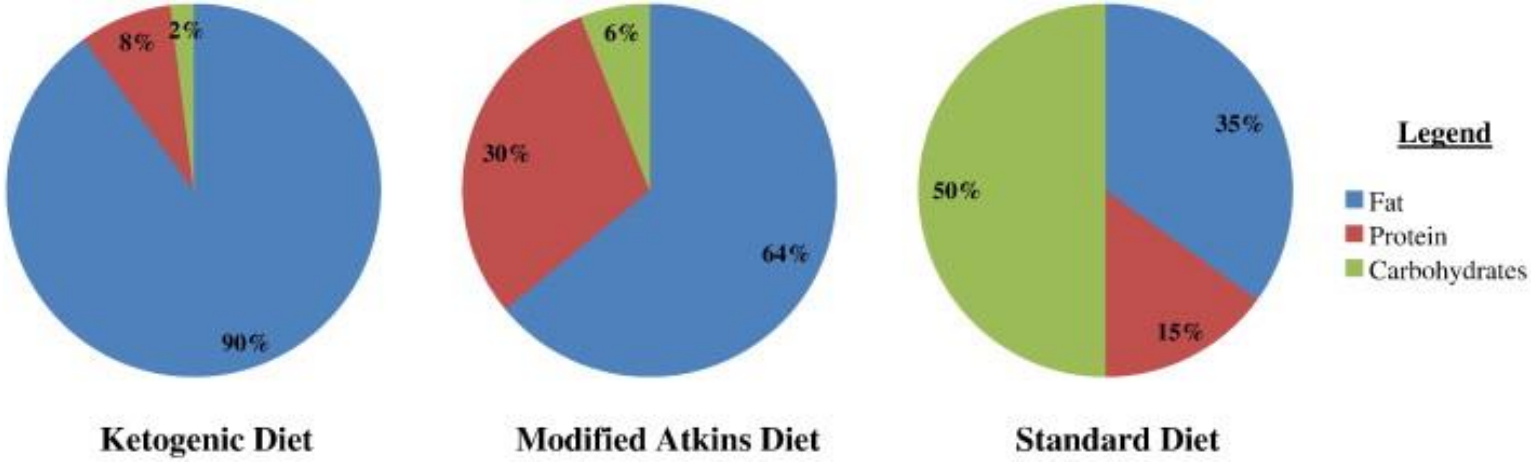
- Noncompetitive NMDA receptor antagonist
- Rapid onset (< 1minute)
- Dosage (500mg/10ml, 長庚)
  - Loading dose: 1-2.5 mg/kg (for 60kg person, 1-3 ml stat)
  - Infusion: 3 mg/kg/h, up to 10 mg/kg/h (for 60kg person, 3-10 ml/h)
- Contraindication:
  - severe hypertension, 3rd trimester of pregnancy, allergy
- Side effects: psychosis, metabolic acidosis
- Only case reports, results and methodology were heterogeneous.
- Ongoing clinical trials (NCT02431663 and for adults)
  - comparing KET, MDZ, and PRO in the treatment of RSE

Steroid or other immunomodulatory tx

- Do not forget to survey for autoimmune encephalitis.
- Check anti-TPO Ab, anti-NMDA-R Ab, Anti-LGI1 Ab, anti-GABA-R Ab
- New-onset refractory status epilepticus often starts as focal SE, evolves into CSE, usually results in SRSE, is mostly unresponsive to conventional ASMs, is temporarily responsive to IV anesthetic drugs, and is often treated empirically with steroids, IVIg, ketogenic diet, and other immunomodulatory or anti-inflammatory treatment.

不建議無差別性使用，
建議使用在確定或高度懷疑是自體免疫性腦炎之患者

Ketogenic diet



- After 6-7 days of KD, > 70-80% of patients showed resolution of SE.
- After SE control, may continue KD for at least 3 months
- Contraindication: porphyria, metabolic disorders, pregnancy
- Use in caution when concurrent use of propofol
- Side effects: dehydration, hypoglycemia, metabolic acidosis, GI symptoms

Hypothermia for Neuroprotection in Convulsive Status Epilepticus

Stephane Legriel, M.D., Virginie Lemiale, M.D., Maleka Schenck, M.D., Jonathan Chelly, M.D., Virginie Laurent, M.D., Fabrice Daviaud, M.D., Mohamed Srairi, M.D., Aicha Hamdi, M.D., Guillaume Geri, M.D., Ph.D., Thomas Rossignol, M.D., Julia Hilly-Ginoux, M.D., Julie Boisramé-Helms, M.D., et al., for the HYBERNATUS Study Group*

N Engl J Med 2016; 375:2457-2467

In this trial, induced hypothermia added to standard care **was not associated with significantly better 90-day outcomes** than standard care alone in patients with convulsive status epilepticus. **Adverse events were more frequent** in the hypothermia group than in the control group.

Endovascular hypothermic cortical irrigation as a novel technique to abort refractory seizures may be a quicker therapeutic option with minimal adverse effects.

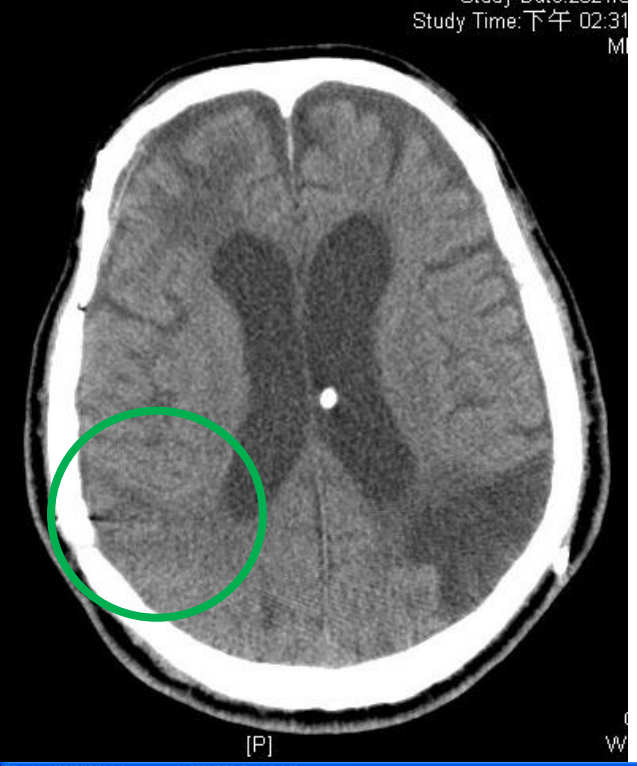
Surgical treatment

Table 1. Surgical procedures used in refractory status epilepticus

Focal resection
Lobar resection
Multilobar resection
Hemispherectomy—functional/anatomical/modified
Corpus callosotomy
Multiple subpial transaction ± focal resection
Vagal nerve stimulator implantation
Low-frequency repetitive cortical electrical stimulation

- 36 cases
  - 21 focal resection
  - 3 focal resection + multiple subpial resection
  - 2 focal resection + CC
  - 1 multiple subpial resection + CC
  - 8 hemispherectomy
- 27 good control of seizure **(>75%)**

Brain 2012: 135; 2314–2328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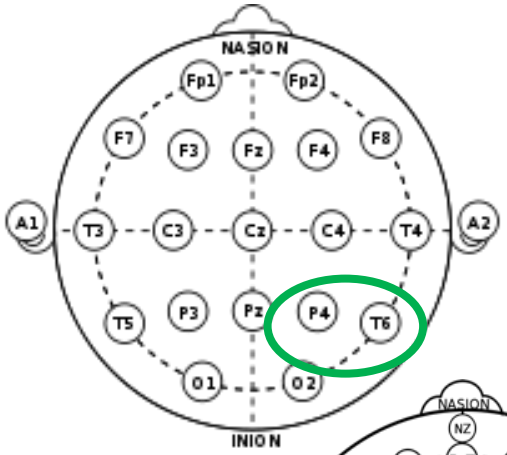
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O2
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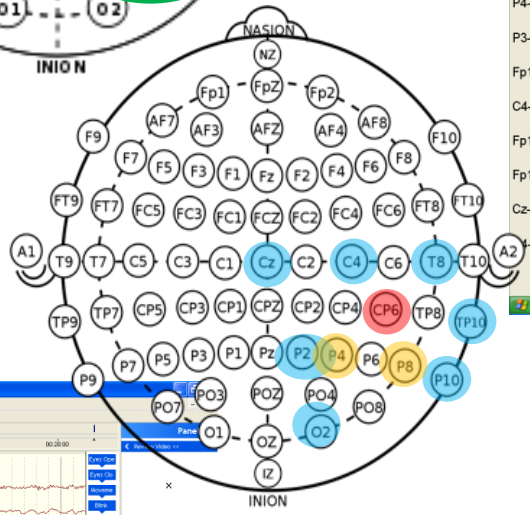
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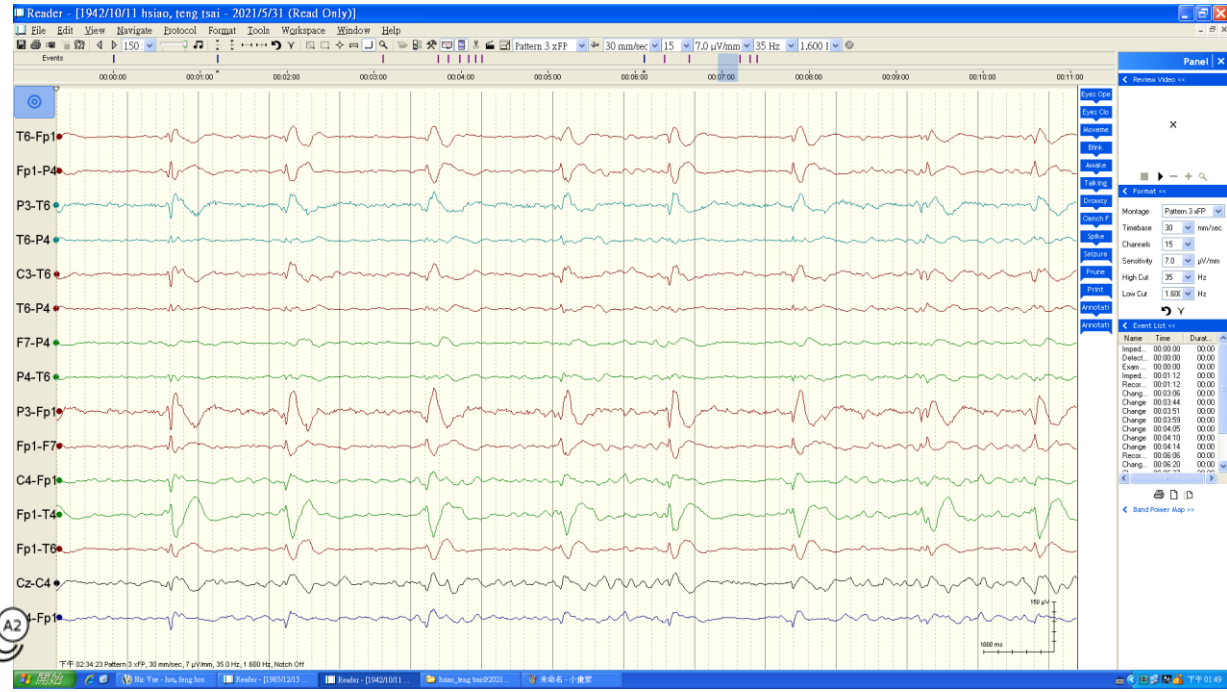
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P3-T6
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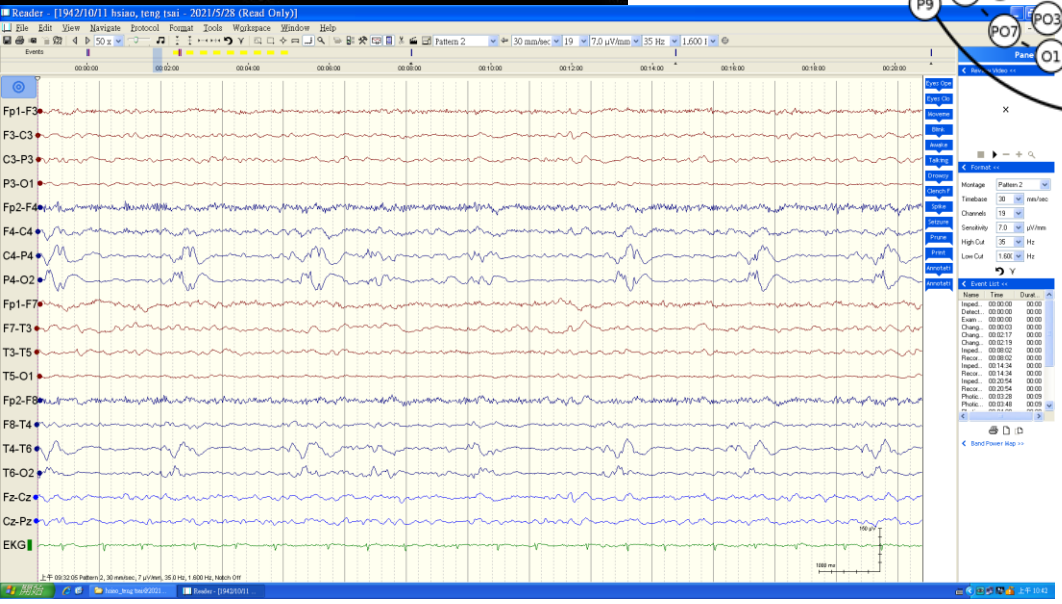
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F7-T3
T3-T5
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T6-O2
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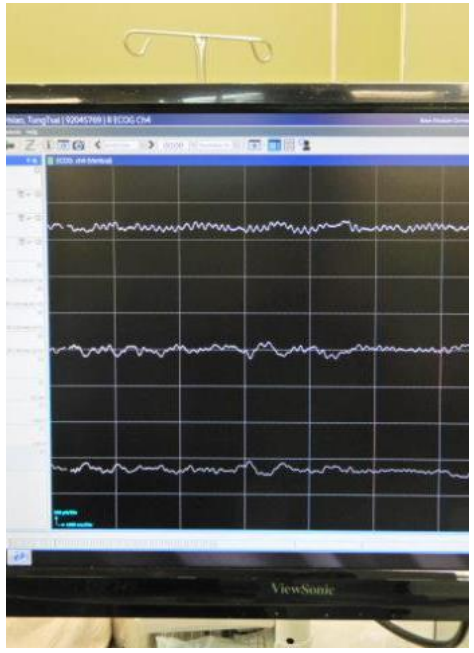
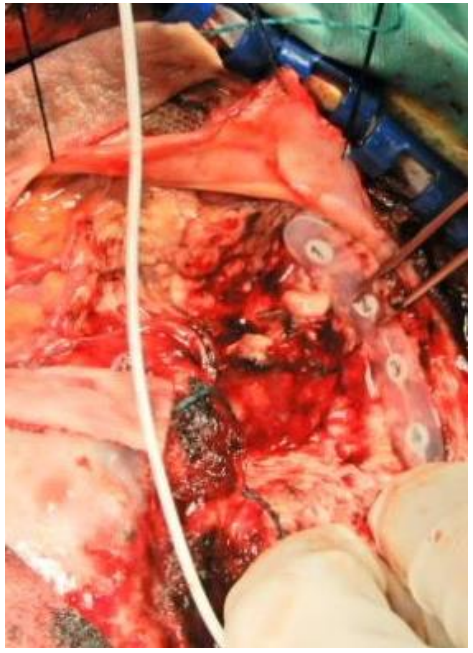
Cz-Pz
EKG





Vagus nerve stimulation in refractory and super-refractory status epilepticus – A systematic review

Maxine Dibué-Adjei [a, b, *], Francesco Brigo [c, d], Takamichi Yamamoto [e], Kristl Vonck [f], Eugen Trinka [g, h]

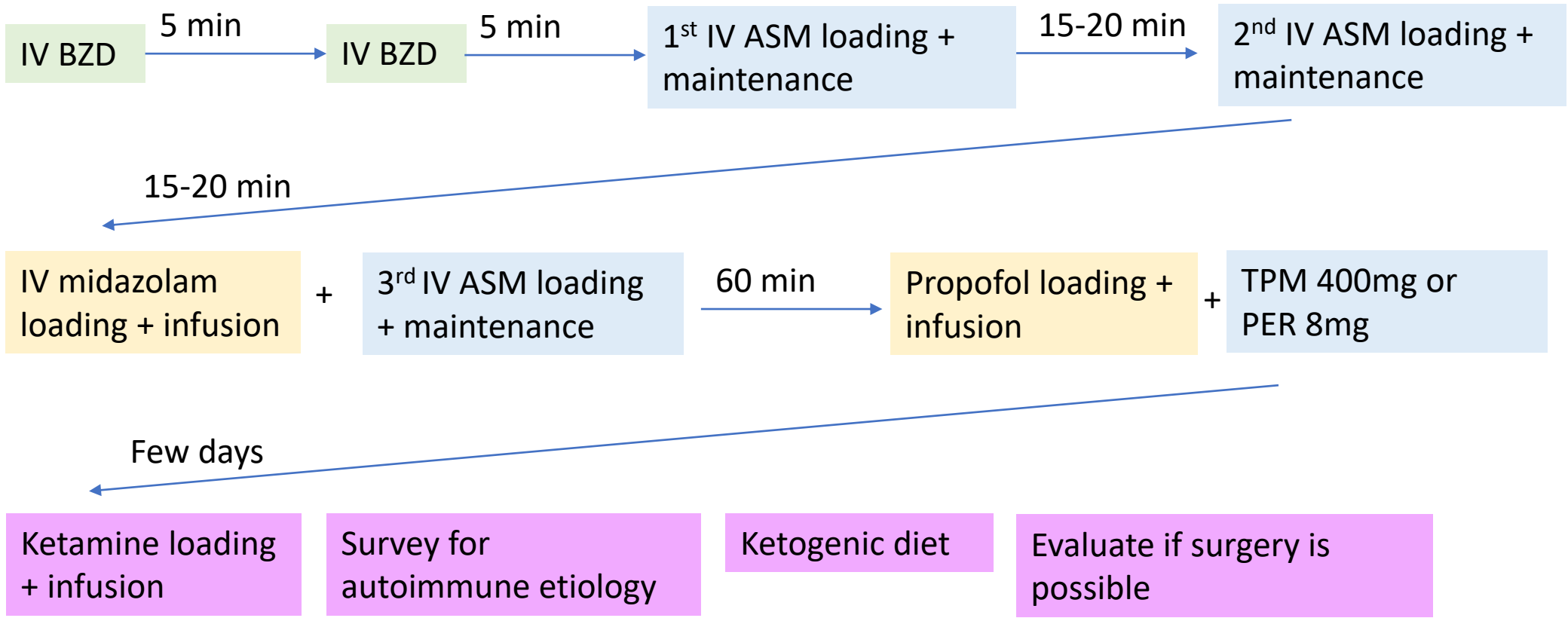
Brain Stimulation 12 (2019) 1101-1110

- 28/38 (**74%**) cessation after acute implantation
- Median duration:
  - pre-op: **18** days (3-1680 days)
  - post op: **8** days (3-84 days) until seizure cessation
- Positive outcome: 31/38 (**82%**), 4 (11%) death
- 大約藥物治療2-3週後考慮VNS

Key points of management of SE

- 及**早**治療，**積極**治療！

- 能越早給的藥物就是好藥
- 劑量給好給滿



Semiology of status epilepticus

With prominent motor symptoms

A.1 Convulsive SE (CSE, synonym: tonic–clonic SE)
- A.1.a. Generalized convulsive
- A.1.b. Focal onset evolving into bilateral convulsive SE
- A.1.c. Unknown whether focal or generalized

A.2 **Myoclonic** SE
- A.2.a. With coma
- A.2.b. Without coma

A.3 **Focal motor**
- A.3.a. Jacksonian
- A.3.b. Epilepsia partialis continua (EPC)
- A.3.c. Adversive status
- A.3.d. Oculoclonic status
- A.3.e. Ictal paresis (i.e., focal inhibitory SE)

A.4 **Tonic** status

A.5 **Hyperkinetic** SE

Without prominent motor symptoms
(i.e., nonconvulsive SE, NCSE)

B.1 NCSE with coma (including so-called "subtle" SE)

B.2 NCSE **without coma**
- B.2.a. **Generalized**
  - B.2.a.a Typical absence status
  - B.2.a.b Atypical absence status
  - B.2.a.c Myoclonic absence status
- B.2.b. **Focal**
  - B.2.b.a Without impairment of consciousness (aura continua, with autonomic, sensory, visual, olfactory, gustatory, emotional/ psychic/experiential, or auditory symptoms)
  - B.2.b.b Aphasic status
  - B.2.b.c With impaired consciousness
- B.2.c Unknown whether focal or generalized
  - B.2.c.a Autonomic SE

Epilepsia, 56(10):1515–1523, 2015

Continuous EEG: 19%有seizure

Table 2 *Primary admission diagnoses and frequency of seizures*

		CEEG findings		
Admission diagnoses	n	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)

Data are given as n (% of patients with this admission diagnosis).

Neurology 2004;62;1743-1748

Time to Detection of the First Seizure in Patients with NCSE in the Neurological ICU

Seizure rate: 30/200: 15%

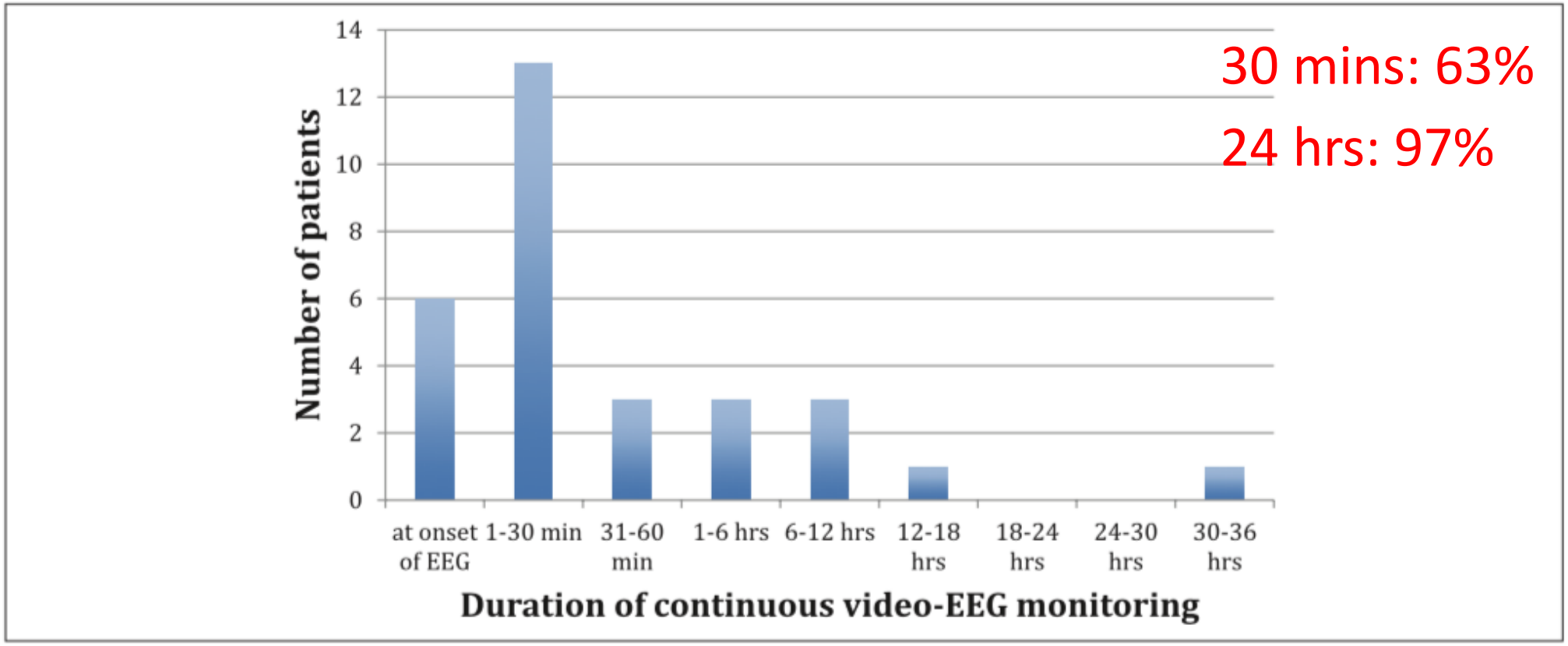
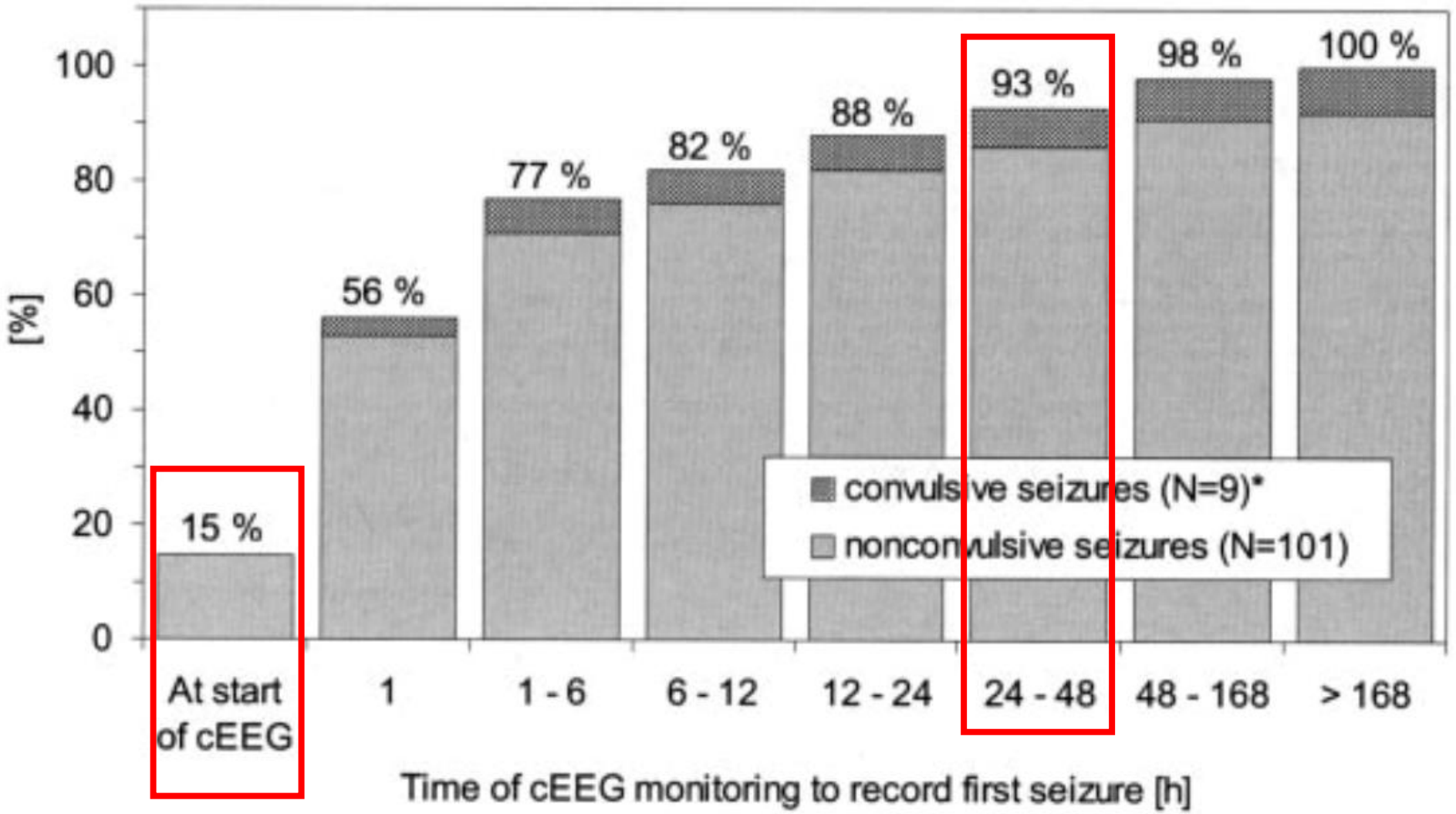


Figure 1. Duration of continuous video-EEG monitoring required to detect the first nonconvulsive seizure.

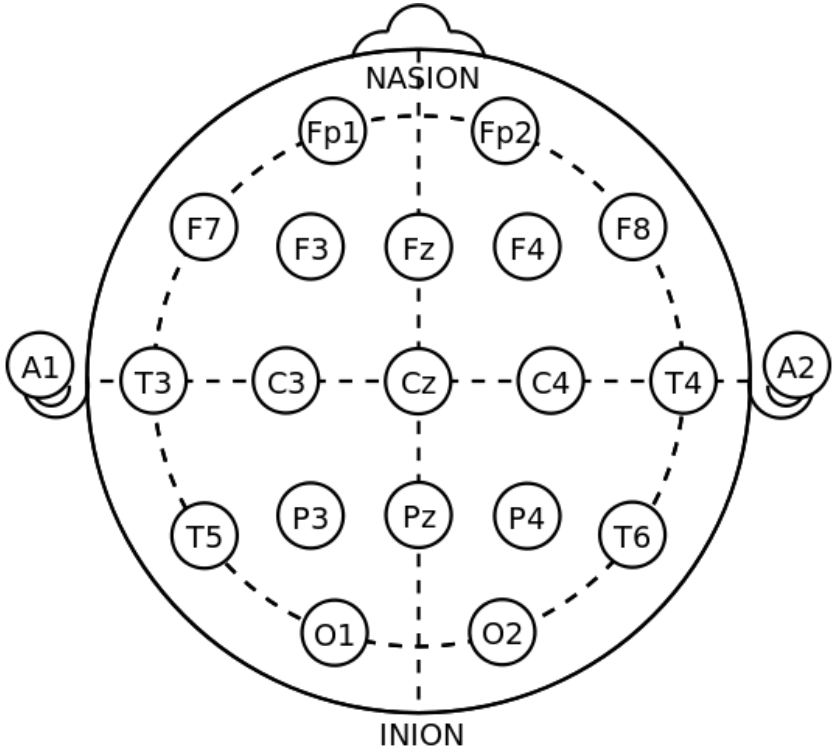
Clinical EEG and Neuroscience 2019, aug

Time to record first seizure



Neurology 2004;62;1743-1748

Full montage



Seizure detection:

Sensitivity 0.758

Specificity 0.958

Reduced montage

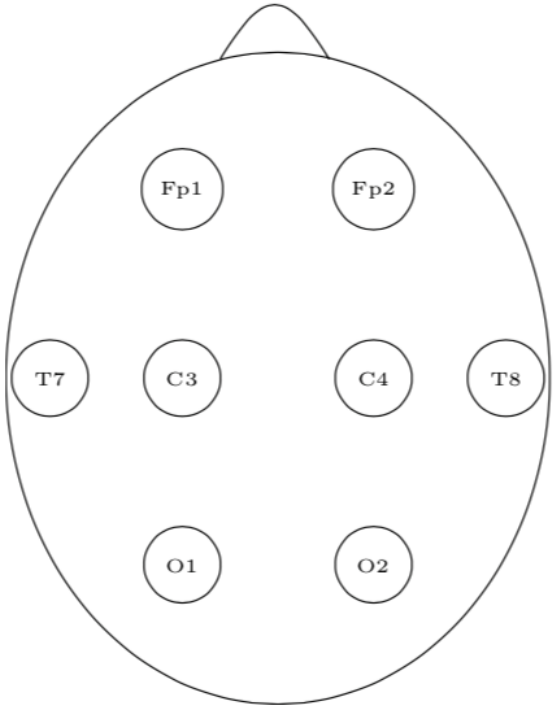


Figure 1. The electrodes used in the reduced montage.

Seizure detection:

Sensitivity 0.653 (-10%)

Specificity 0.968

March 2022 Scientific Reports 12(1):4621

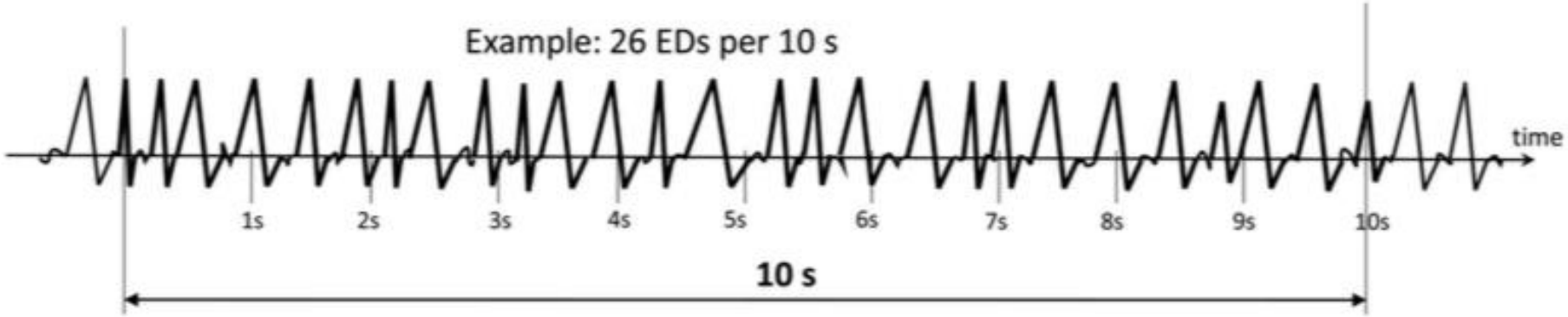
Diagnosis of NCSE

- NCSE may be diagnosed on the basis of either electrographic or electroclinical seizures
- **Electrographic seizures** (or electrographic status epilepticus) refers to patients who are having *unequivocal electrographic seizures* on their EEG
- **Electroclinical seizures** (or electroclinical status epilepticus) refers to patients who show a combination of EEG abnormalities *plus* clinical manifestations

Salzburg Consensus Criteria

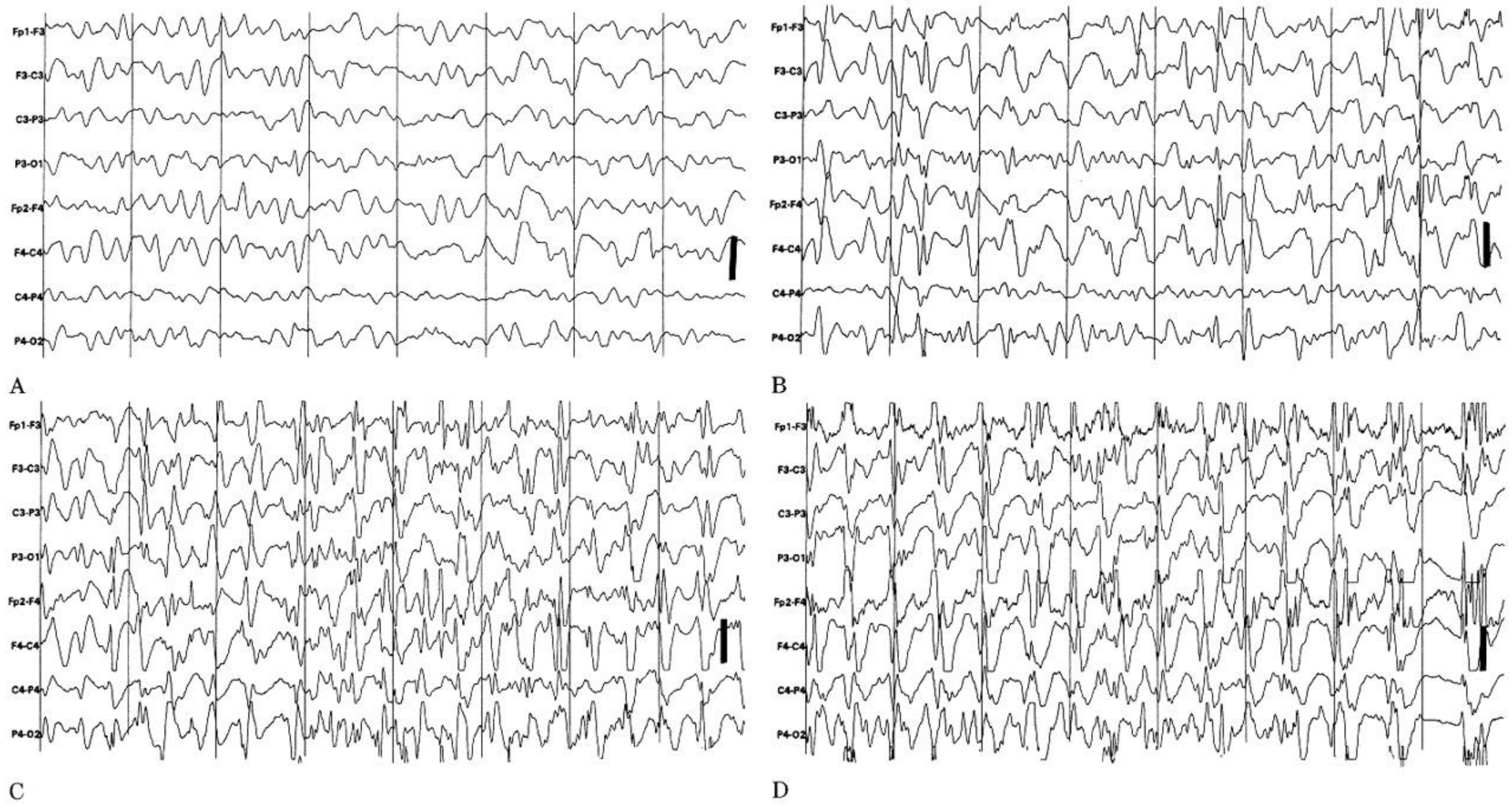
Electrographic seizure (Esz)

Epileptiform discharges averaging **>2.5 Hz** for **≥10 s** (>25 discharges in 10 s)



Any pattern with definite evolution lasting ≥10 s

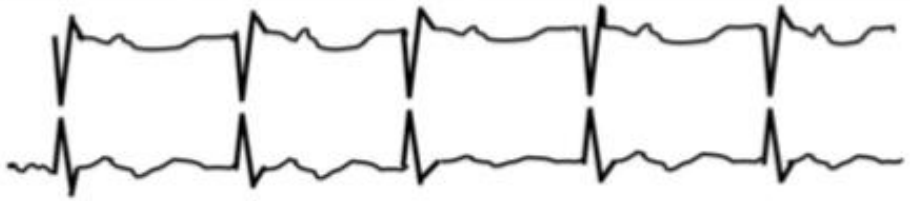
Evolution



Electroclinical seizure (ECsz)

Any EEG pattern with either:

Definite clinical correlate time-locked to the pattern (of any duration)



time-locked clinical correlate, e.g., jerk

time-locked clinical correlate, e.g., jerk

time-locked clinical correlate, e.g., jerk

time-locked clinical correlate, e.g., jerk

time-locked clinical correlate, e.g., jerk

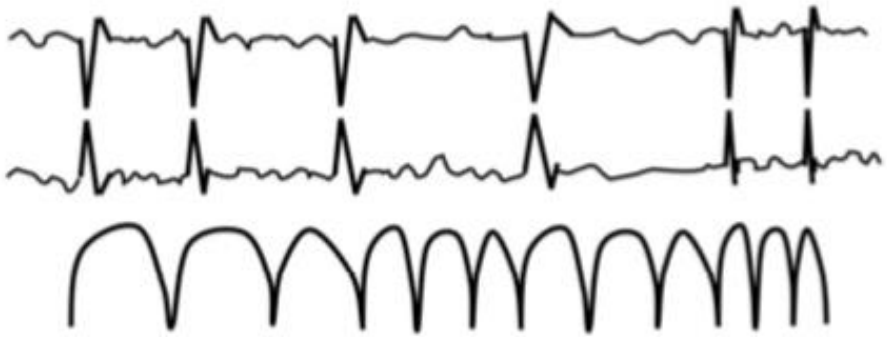
time-locked clinical correlate, e.g., jerk

time-locked clinical correlate, e.g., jerk

time-locked clinical correlate, e.g., jerk

OR

EEG ***AND*** clinical improvement with a parenteral (typically IV) anti-seizure medication



anti-seizure medication

clinical improvement

+

EEG-improvement

Electrographic and electroclinical status epilepticus

- Status epilepticus is defined as one of the following abnormalities.
  - (1) >10 minutes of electrographic or electroclinical seizure
  - (2) electrographic or electroclinical seizure occurring >20% of the time over the space of an hour.
- In the absence of a prominent motor correlate, these EEG abnormalities would be classified as electrographic or electroclinical nonconvulsive status epilepticus.

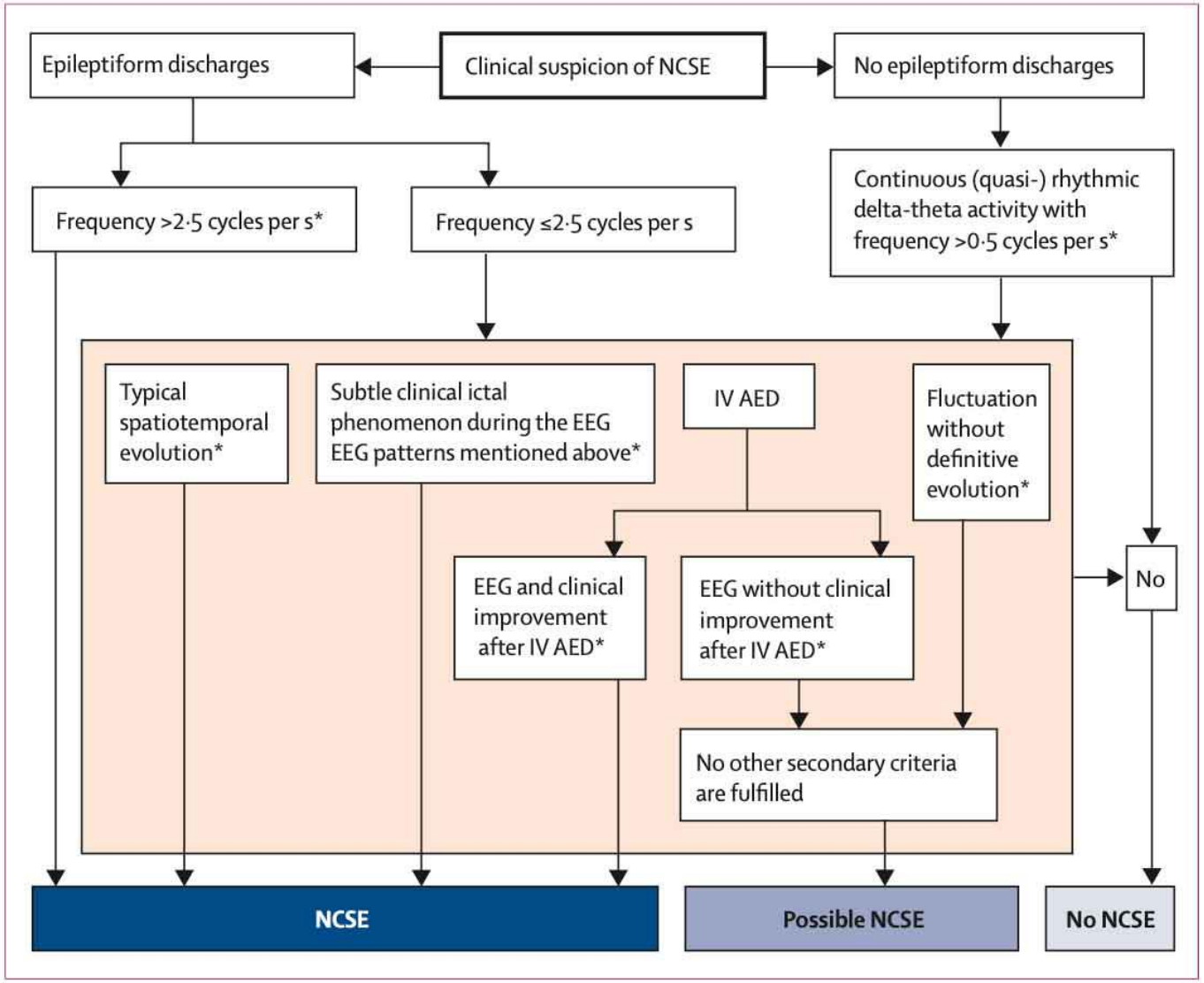


***Figure* 1: Salzburg EEG criteria for the diagnosis of NCSE**

To qualify for a diagnosis of NCSE, the whole EEG recording should be abnormal, and EEG criteria have to be continuously present for at least 10 s. If criteria are not fulfilled at any stage, EEG recording will not qualify for a diagnosis of NCSE or possible NCSE. NCSE=non-convulsive status epilepticus. IV AED=intravenous antiepileptic drug. *Patients with known epileptic encephalopathy should fulfil one of the additional secondary criteria: increase in prominence or frequency of the features above when compared to baseline, and observable change in clinical state; or improvement of clinical and EEG features with IV AEDs (panel).

Leitinger M et al. PMID 27571157

JAMA Neurology | Original Investigation

Association of an Electroencephalography-Based Risk Score With Seizure Probability in Hospitalized Patients

Aaron F. Struck, MD; Berk Ustun, PhD; Andres Rodriguez Ruiz, MD; Jong Woo Lee, MD, PhD; Suzette M. LaRoche, MD; Lawrence J. Hirsch, MD; Emily J. Gilmore, MD; Jan Vlachy, MS; Hiba Arif Haider, MD; Cynthia Rudin, PhD; M. Brandon Westover, MD, PhD

December 2017 Volume 74, Number 12

1 point each:

2H: Frequency exceeding **2 Hz**

E: Independent sporadic **e**pileptiform discharges

L: **L**ateralized rhythmic or periodic patterns, including lateralized periodic discharges, bilateral independent discharges, or lateralized rhythmic delta activity

P: **P**lus features, including superimposed rhythmic, fast, or sharp activity

S: Prior **s**eizure history, epilepsy, or suspicion for acute clinical seizure

2 points:

2B: **B**rief ictal rhythmic discharges (not reaching the 10-second threshold for definitive electrographic seizure)

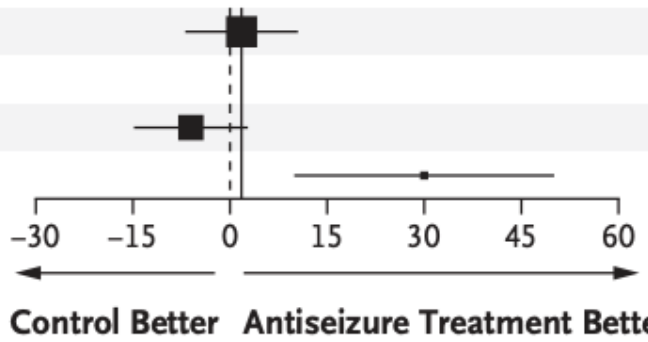
2HELPS2B Screening EEG Risk Score	Predicted Seizure Risk	Actual Seizure Risk[a]
0	<5%	3-4%
1	12%	12-15%
2	27%	34%
3	50%	52-55%
4	73%	71-75%
5+	88%	84-93%

Treating Rhythmic and Periodic EEG Patterns in Comatose Survivors of Cardiac Arrest

Barry J. Ruijter, M.D., Ph.D., Hanneke M. Keijzer, M.Sc., Marleen C. Tjepkema-Cloostermans, Ph.D., Michiel J. Blans, M.D., Albertus Beishuizen, M.D., Ph.D., Selma C. Tromp, M.D., Ph.D., Erik Scholten, M.D., Janneke Horn, M.D., Ph.D., Anne-Fleur van Rootselaar, M.D., Ph.D., Marjolein M. Admiraal, Ph.D., Walter M. van den Bergh, M.D., Ph.D., Jan-Willem J. Elting, M.D., Ph.D., et al., for the TELSTAR Investigators*

B Post Hoc Analysis: GPDs vs. Non-GPD Patterns

Subgroup	Control	Antiseizure Treatment	Difference (95% CI)
	no. of patients with good outcome/total no. (%)		*percentage points*
Overall	7/83 (8)	9/88 (10)	2 (–7 to 10)
Type of rhythmic and periodic activity			
GPDs, 0.5–2.5 Hz	7/67 (10)	3/68 (4)	–6 (–15 to 3)
Non-GPD patterns	0/16	6/20 (30)	30 (10 to 50)



Type of rhythmic and periodic activity			
GPDs, 0.5–2.5 Hz	7/67 (10)	3/68 (4)	–6 (–15 to 3)
Electrographic seizures, ≥2.5 Hz	0/8	2/9 (22)	22 (–5 to 49)
Evolving patterns, 0.5–2.5 Hz	0/3	1/2 (50)	50 (–19 to 119)
Other, 0.5–2.5 Hz	0/5	3/9 (33)	33 (2 to 64)

The end