Status epilepticus: Update in Pediatrics

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Disclosure

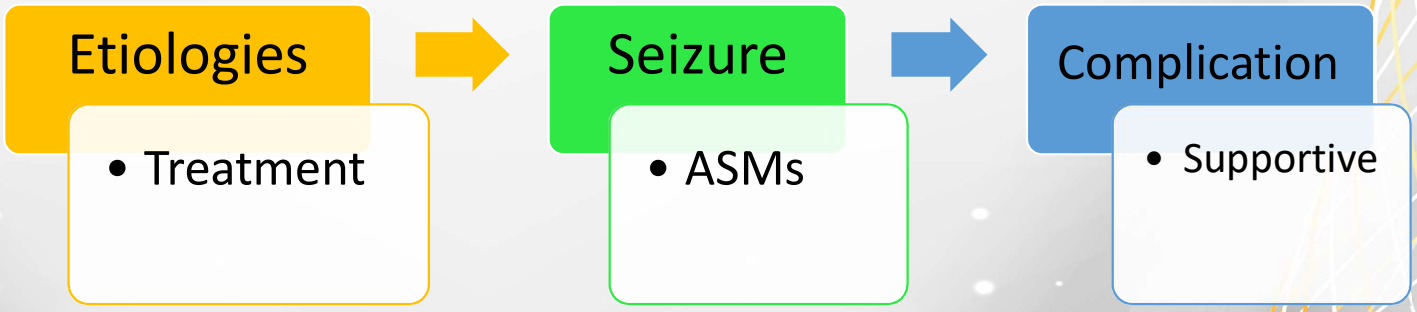
- No Conflict of interest

Outline

- Definition
- Management convulsive status epilepticus (CSE) in children
  - Medications in different stages, CSE/RSE/SRSE
  - Comparison of efficacy
  - New research of SE in children
  - Predicting score of SE
- NCSE in children
- Predicting outcome of SE during hospital stay and long term outcome of SE
- Future trends

Key points of management

1. Identification and mx of underlying precipitant etiologies
2. Administration of anticonvulsants to terminate the seizures
3. Identification and mx of systemic complications → secondary brain injury



Etiology of SE

Infection / febrile SE

Known

- Acute (e.g. stroke, intoxication, infection, etc)
- Remote (e.g. post-traumatic, post-encephalitis, post-stroke, etc)
- Progressive (e.g. brain tumor, Lafora's dis, PMEs, etc)
- SE in defined electroclinical syndromes

Unknown

- NORSE/FIRES (RSE/SRSE)

Definition

Length of the seizure T1

Status Epilepticus (SE) (T1)		
1. T-C SE > 5 min 2. Focal SE with impaired consciousness > 10 min 3. Absence SE > 10-15 min	1. Uncontrolled sz despite Rx > 30 min or 2. Persists after 1st line (BZP) and 2nd line	1. Uncontrolled sz despite anesthetic Rx > 24 hours

Epilepsia, 56(10):1515–1523, 2015

Definition

Length of the time before long term consequences T2

Status Epilepticus (SE) (T2)		
1. T-C SE : 30 min 2. Focal SE with impaired consciousness > 60 min 3. Absence SE: unknown	1. Uncontrolled sz despite Rx > 30 min or 2. Persists after 1st line (BZP) and 2nd line	1. Uncontrolled sz despite anesthetic Rx > 24 hours

Epilepsia, 56(10):1515–1523, 2015

Definition

Status Epilepticus (SE) (T2)	Refractory SE (RSE)	Super-refractory SE (SRSE)
1. T-C SE : 30 min 2. Focal SE with impaired consciousness > 60 min 3. Absence SE: unknown	1. Uncontrolled sz despite Rx > 30 min or 2. Persists after 1st line (BZP) and 2nd line	1. Uncontrolled sz despite anesthetic Rx > 24 hours

A Real-life Setting of Status Epilepticus

17-23

- Status epilepticus: Incidence 5-40 per 100,000

29-43%

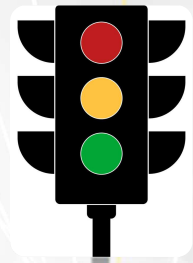
- Refractory status epilepticus

13-42%

- Super-refractory status epilepticus

4-12-26%

Facts of SE



- ILAE 2015: a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which leads to prolonged seizure

- Incidence: 17-23 (5-40) / 100,000
- Majority (up to 75%) of SE are children presenting with their 1st seizure
- Fatality: 3%
- Long term mortality in RSE: 5.1%

Curr Opin Pediatr 2018
Critical Care Research and Practice 2018

Risk Factors of Pediatric CSE

1. Young age at onset
2. Developmental retardation
3. Polypharmacy (ASMs)
4. Change ASMs in the past 3 months

1. Neonate
2. Developmental impairment
3. Intercurrent febrile illness
4. Men

Seizure 2014, 23; 692–698

Curr Opin Pediatr 2018, 30:359–363

Medications in SE

First line	Second line	Anesthetic

Benzodiazepine (BZP)
• **DZP**
  • IV
  • Rectal
  • *Intranasal*
• **MDZ**
  • IV
  • IM
  • Intranasal, Intrabuccal
• ***LZP***
  • *IV*
• ***CZP***
  • *IV*
	• **Phenobarbital**
	• **Phenytoin, Fos-Phenytoin**
	• **Sodium valproate**
	• **Levetiracetam**
	• **Lacosamide**
		• **Midazolam IV**
		• **Thiopental**
		• **Propofol**
		• **Ketamine**
		• **etc**

Europe: IV clonazepam

First-line medications

Route	Diazepam (max)	Midazolam (max)	Lorazepam (max)
IV	0.3 mg/kg (10 mg)	0.15 mg/kg (10 mg)	0.1 mg/kg (4 mg)
IM	-	**0.2** mg/kg (10 mg)	
Intranasal	*USA*	**0.2** mg/kg (10 mg)	0.1 mg/kg
Intrabuccal	-	0.2-0.5 mg/kg (10 mg)	
Rectal	0.3- **0.5** mg/kg		
Comparison	MDZ more effective than DZP in achieving seizure cessation No difference in efficacy between MDZ and LZP No difference in efficacy between IV DZP and IV MDZ and IV LZP		
	Higher rate AE in IV DZP than IV LZP *J Child Neurol 2016*		
	Insufficient to comment efficacy/safety for IM MDZ and IV LZP *Cochrane Database Syst Rev 2008*		
Study (adult+child)	No difference in time to sz cessation IV BZP vs non IV BZP *Epilepsia 2015*		
Study (adult)	IM MDZ faster sz cessation than IV LZP (pre-hos) *Epilepsia 2011*		
	Rectal route-slower time to achieve drug delivery than **IM**, buccal		
Non IV	IM, intranasal MDZ- best efficacy		

First-line medications

Benzodiazepine	DZP	MDZ	LZP	CZP
Intravenous				
Onset	Rapid	-	Rapid, slower than DZP	Rapid
Duration of action	☺ Short		Longer than DZP	Longer than DZP
Elimination	☺	Quickest be removed	Slower than DZP	
Accumulation	Risk if repeated	-	No	Little
Risk of injection site reaction	Yes	-	Yes	-
Non-intravenous				
Onset		Rapid		-
Duration of action	PR: short	Short		-
Accumulation	PR: yes			-
Efficacy	**PR**: less than non-IV MDZ and IV LZP	**IM/B**: better than IV LZP and IV/PR DZP	**N**: may effective as IV LZP	-

Seizure 2020

Medications in SE

First line	Second line	Anesthetic

Benzodiazepine (BZP)
• **DZP**
  • IV
  • Rectal
  • *Intranasal*
• **MDZ**
  • IV
  • IM
  • Intranasal, Intrabuccal
• ***LZP***
  • *IV*
• ***CZP***
  • *IV*
	• **Phenobarbital**
	• **Phenytoin, Fos-Phenytoin**
	• **Sodium valproate**
	• **Levetiracetam**
	• **Lacosamide**
		• **Midazolam IV**
		• **Thiopental**
		• **Propofol**
		• **Ketamine**
		• **etc**

First-line Plus Second-line (1)

- IV 0.1 mg/kg LZP vs.
- IV 18 mg/kg PB vs.
- IV 0.15 mg/kg DZP + IV 18 mg/kg PHT

} Similar efficacy

- IV LZP better than IV PHT alone
- PHT alone should not be recommended as <u>first line Rx</u>

- PB be therefore effective for initial Rx BUT potential respiratory depression

NEJ 1998

First-line Plus Second-line (2)

- No trial for VPA vs. DZP as first-line
- Trial: VPA vs. PHT
  : VPA vs. PHT + DZP

} Small n underpowered

- One study: IV 0.1 mg/kg LZP vs. IV 20 mg/kg LEV
  result: 75.6% vs 76.3% seizure freedom

- IV LEV + IV CZP vs. IV CZP + placebo
  result : no difference

First line study: should be compare with IV BZP

1/3 of patients do not response to BZP

Second-line Medications

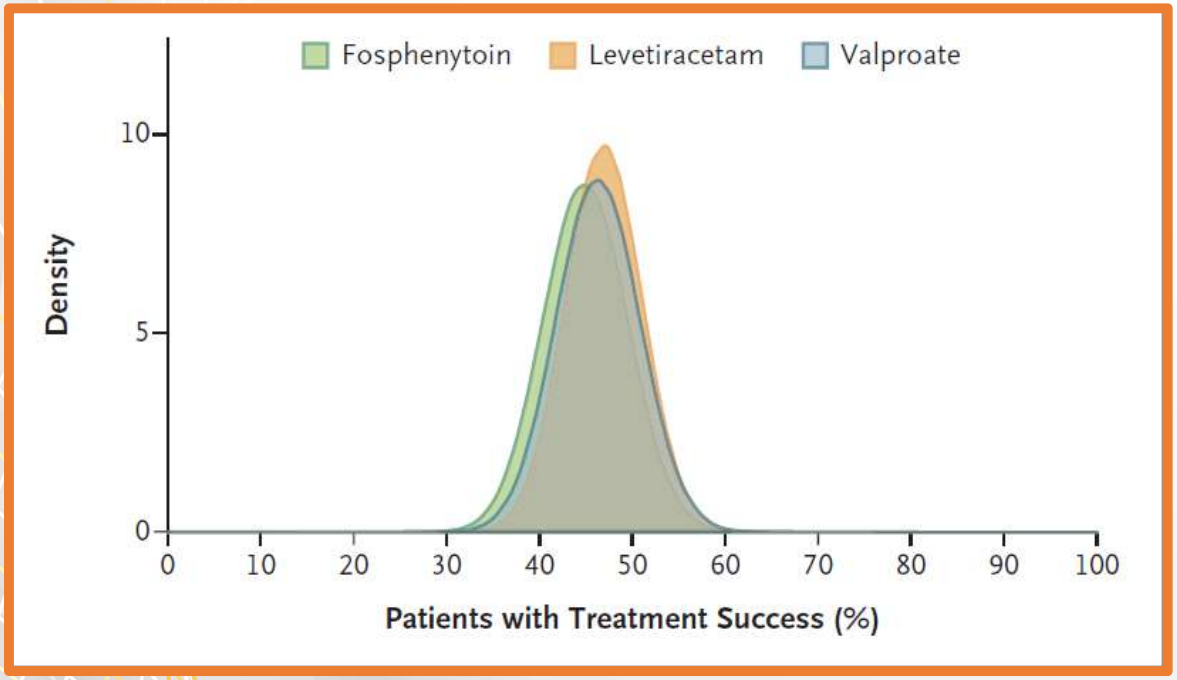
PB	PHT/FosPHT	VPA	LEV	LCM
1st and 2nd line Use in neonate	? Lower efficacy than alternatives	Alternative to PHT and PB	Similar efficacy to PHT, VPA Use in neonate	Variation of stage that introduced
20 mg/kg	18-20 mg/kg	25-40 mg/kg	20-**60** mg/kg	Loading: 400 mg or 2- 6 mg/kg (max 600 mg)
Stop CSE 76.3%	Stop CSE 60% (50-80%)	Stop CSE 65-75.7%	Stop CSE in adult 68% (80%)	Stop sz 57% overall Stop focal sz 92%
Sedation, respiratory depression, hypotension	Cardiac arrhythmia (rare) Hypotension Thrombophlebitis	In children: hepatotoxicity, mitochondrial dis, metabolic encephalopathy	Reduction of maintenance dose renal impairment. May exacerbate in known mood disorder	Precaution: bradycardia/hypotension

New Trial in Rx Status Epilepticus in Children

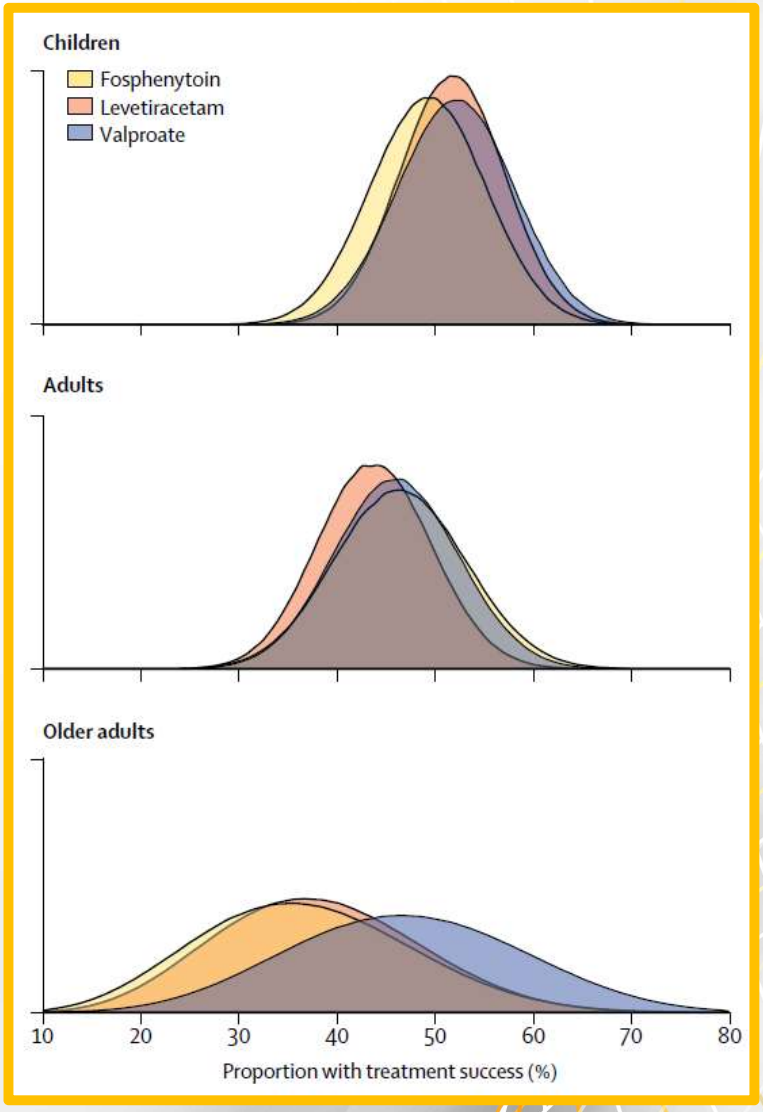
- ConSEPT, EcLiPSE, ESETT in 2019

Comparison of the new studies of SE in children

Study	Number, age	Study	Findings
ConSEPT (Aus + Nz) Open-label randomized	233, 3 mo-16 yrs	PHT vs. LEV 20 mg/kg vs. 40 mg/kg 20 min vs. 5 min	**LEV is not superior to PHT** for 2nd line Mx of ped CSE **Both** effective 50-60% (LEV/PHT) *Lancet 2019*
EcLiPSE (UK) Open-label randomized	286, 6 mo- 18 yrs	PHT vs. LEV Same dose of ConSEPT	**LEV is not superior to PHT** Appropriate alternative to PHT Sz cessation 70 % vs 64% (LEV/PHT) *Lancet 2019*
ESETT (USA) Blinded, randomized	384, 1-94 yrs (**adults** + > 1 yr **peds**)	20 mg/kg FosPHT vs. 40 mg/kg VPA vs. 60 mg/kg LEV in 10 min	**FosPHT-VPA-PHT** Sz cessation approx 50% No difference in safety outcomes *NEJ 2019* *Lancet 2020*



NEJ 2019



Lancet 2020

Definition

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1. T-C SE > 5 min 2. Focal SE with impaired consciousness > 10 min 3. Absence sz > 10-15 min	1. Uncontrolled sz despite Rx > 30 min or 2. Persists after 1st line (BZP) and 2nd line	1. Uncontrolled sz despite anesthetic Rx > 24 hours

29-43%

Anesthetic med

	MDZ	Thiopental	Propofol	Ketamine
Loading	0.2 mg/kg (2 mg/min) (max 2 mg/kg)	2-7 mg/kg (<50 mg/min)	1-2 mg/kg q 3-5 min (max 10 mg/kg)	1-3 mg/kg q 3-5 min until seizures stop (max 4.5 mg/kg)
Maintenance	0.05-2 mg/kg/hr or **1-20 ug/kg/min**	**0.5-5 mg/kg/hr**	1-10 mg/kg/hr (**5**) 20-200 ug/kg/min	**1-10 mg/kg/hr** 10-100 ug/kg/min
Breakthrough SE	**Bolus:** 0.1-0.2 mg/kg **Titrate:** 0.05-0.1 mg/kg/hr in time interval	**Bolus:** 1-2 mg/kg **Titrate:** 0.5-1 mg/kg/hr	Increase maintenance by 5-10 ug/kg/min	**Bolus:** 1-2 mg/kg **Titrate:** 5-10 ug/kg/min max of 100 ug/kg/min
Precaution	Hypotension, respiratory depression Tachyphylaxis	Hypotension, respiratory depression, cardiac depression Auto-induction	Same as thiopental **PRIS** ↓ ICP	HT ↑ ICP
Mechanism	GABA agonist	GABA agonist, barbiturates	GABA agonist, NMDA antagonist property	NMDA antagonist

Propofol-related infusion syndrome (PRIS)

Syndrome: acute refractory bradycardia→ asystole plus one of the following

- Metabolic acidosis
- Rhabdomyolysis
- Hyperlipidemia
- Enlarged liver/ fatty liver

Association: dose> 4 mg/kg/hr
: duration > 48 hrs

Predisposing factor:

- Young age
- Severe CNS/respiratory illness
- Exogenous catecholamine or glucocorticoid given
- Inadequate CHO intake
- Subclinical mitochondrial disease

Super-refractory status epilepticus

- Repeat anesthetic infusion at higher doses for a longer period
- Immunosuppressive medications:
  - IVIG
  - IVMP
  - PLEX
  - Rituximab, Anakinra, Tocilizumab, Cyclophosphamide
  - Hypothermia
  - KD, VNS, DBS

Predicting the outcome in SE

J Neurol 2008

STESS score

Status epilepticus severity score

1. Age
2. Type of seizure
3. Hx of previous seizures
4. Level of consciousness

Before treatment

Score = 0-6 (STESS-4 = bad outcome)

Adults > 16 yrs

Features Score	Status Epilepticus Severity Score (STESS)	
Consciousness	Alert or somnolent/confused	0
	Stuporous or comatose	1
Worst seizure type	Simple-partial,Complex partial, absence, myoclonic	0
	Generalised-convulsive	1
	Non-convulsive,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

Later with meta-analysis: specific 80%, sensitivity 53%

Predicting the outcome in SE

J Neurol 2008

STESS score

Status epilepticus severity score

1. Age
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Before treatment

Score = 0-6 (STESS-4 = bad outcome)

Adults > 16 yrs

STESS/EMSE: more useful in CSE than NCSE in predicting hospital mortality

Neurocrit Care 2015

ESME score

Epidemiology-based mortality score in SE

1. Age
2. Etiology
3. Comorbidity
4. EEG
5. Duration
6. Level of consciousness

Adults > 21 yrs

ESME: more advantage over STESS

Status Epilepticus in Pediatric patients Severity Score (STEPSS)

Status Epilepticus in Pediatric patients Severity Score (STEPSS): A clinical score to predict the outcome of status epilepticus in children- a prospective cohort study

Sidharth[a], Suvasini Sharma[b,*], Puneet Jain[c,d], Surendra Bahadur Mathur[a], Rajeev Kumar Malhotra[e], Virendra Kumar[f]

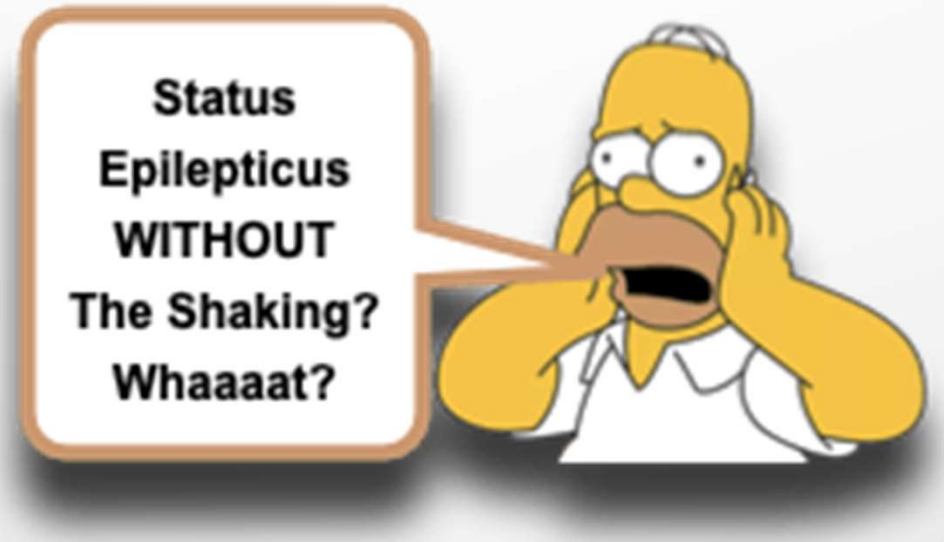
Seizure 2019: 71;328–332

Status Epilepticus Severity Score (STESS) and its modification Status Epilepticus in Pediatric patients Severity Score (STEPSS).

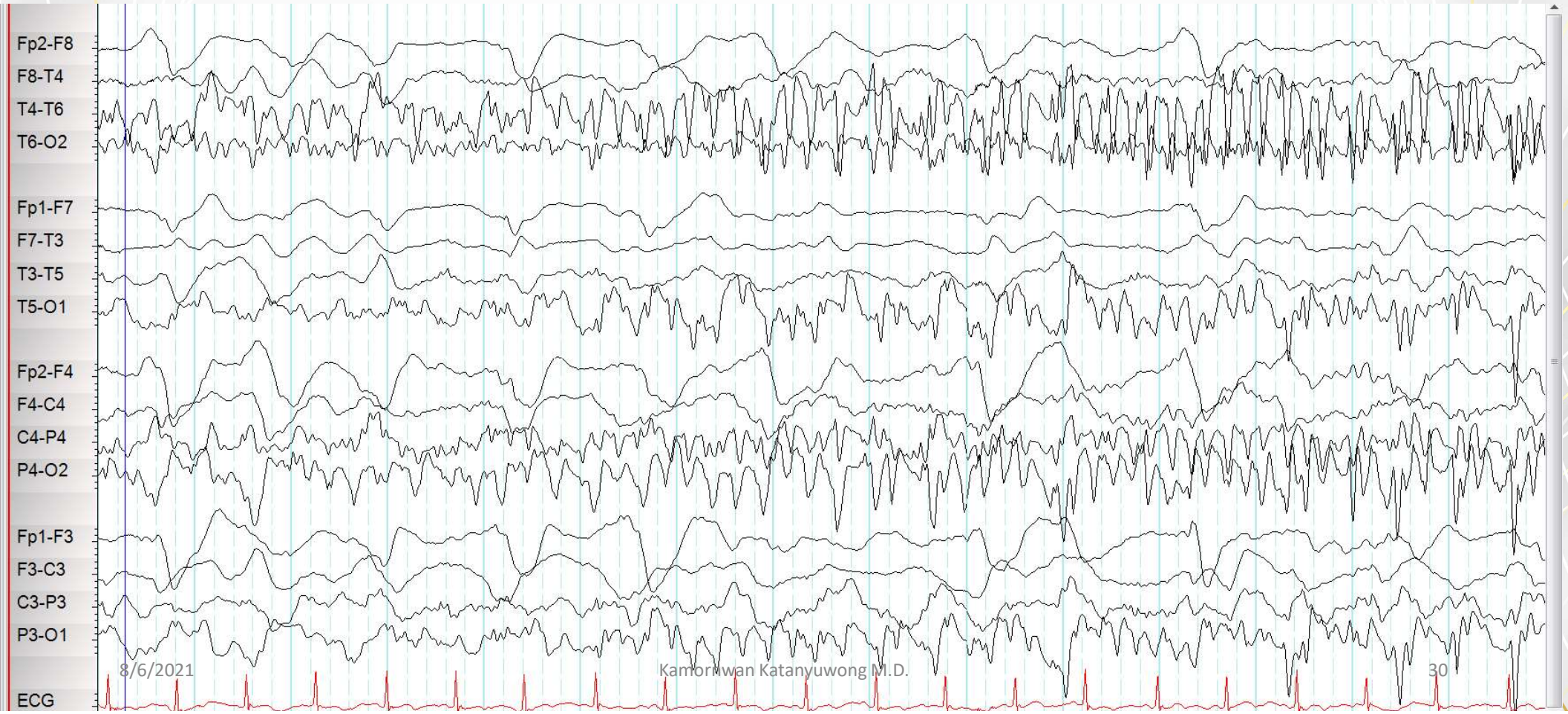
Features Score	Status Epilepticus Severity Score (STESS)		Status Epilepticus in Pediatric patients Severity Score (STEPSS)	
Consciousness	Alert or somnolent/confused	0	Alert or somnolent/confused	0
	Stuporous or comatose	1	Stuporous or comatose	1
Worst seizure type	Simple-partial,Complex partial, absence, myoclonic	0	Simple-partial,Complex partial, absence, myoclonic	0
	Generalised-convulsive	1	Generalised-convulsive	1
	Non-convulsive,status epilepticus in coma	2	Non-convulsive,status epilepticus in coma	2
Age	< 65 years	0	**≥ 2 years**	0
	≥65 years	2	**< 2 years**	2
History of previous seizures	Yes	0	Yes	0
	No or unknown	1	No or unknown	1
TOTAL		0-6		0-6

Sensitivity 93%,
Specificity 81%

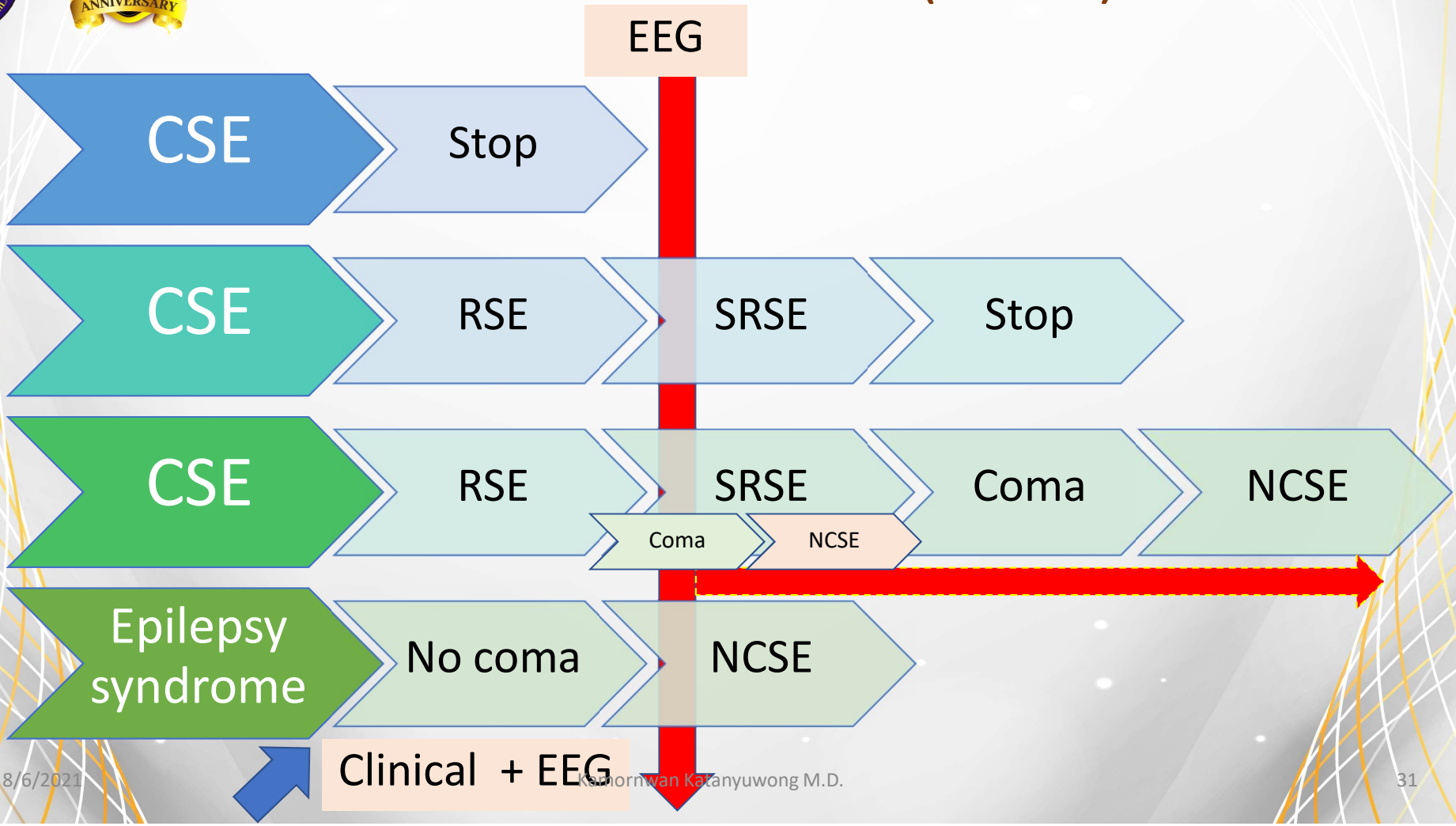
Score > 3 = unfavorable outcome


Status
Epilepticus
WITHOUT
The Shaking?
Whaaaat?

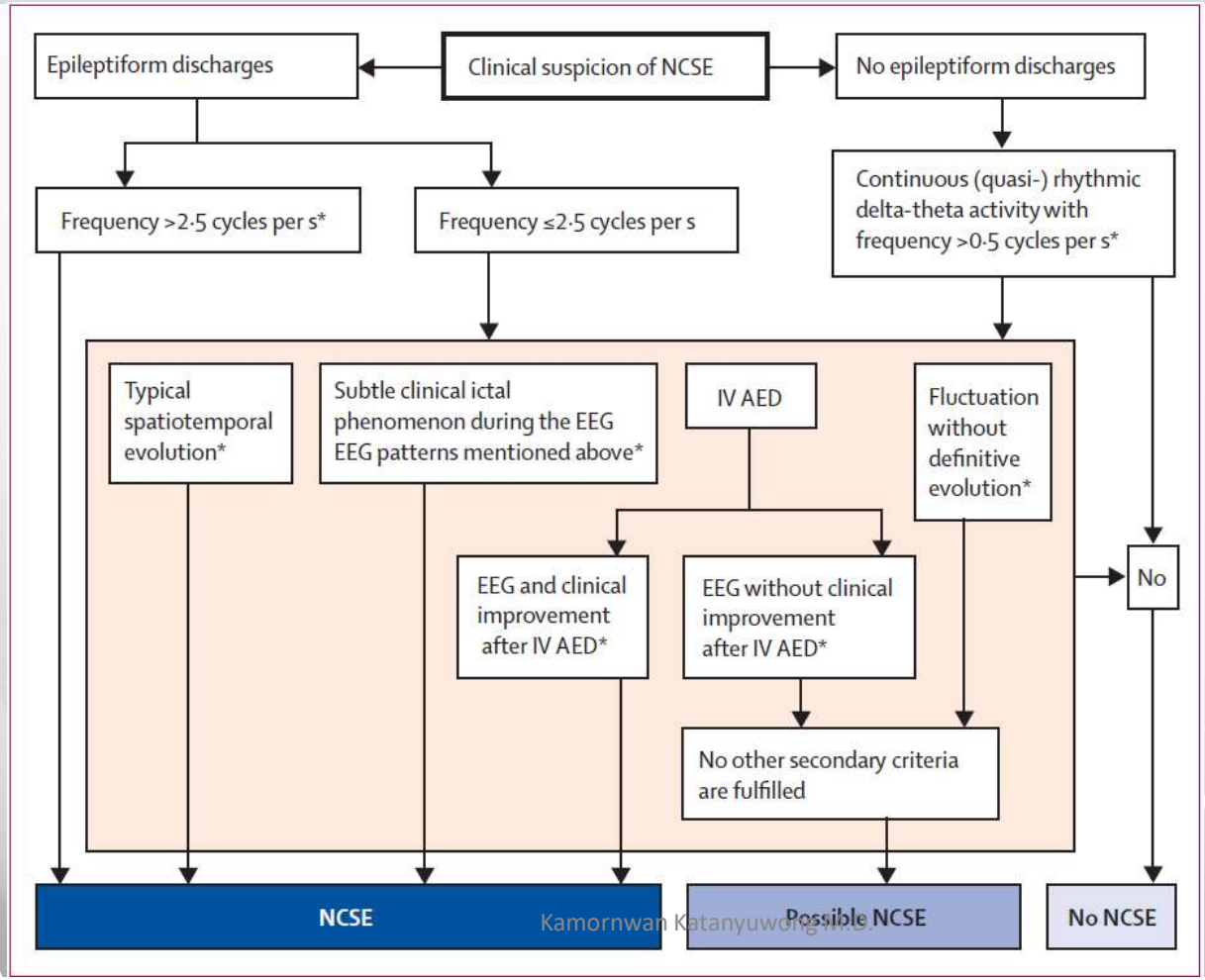
Non-convulsive SE (NCSE)



Non-convulsive SE (NCSE)



Salzburg EEG criteria for the diagnosis of NCSE



Lancet Neurol 2016; 15: 1054–62

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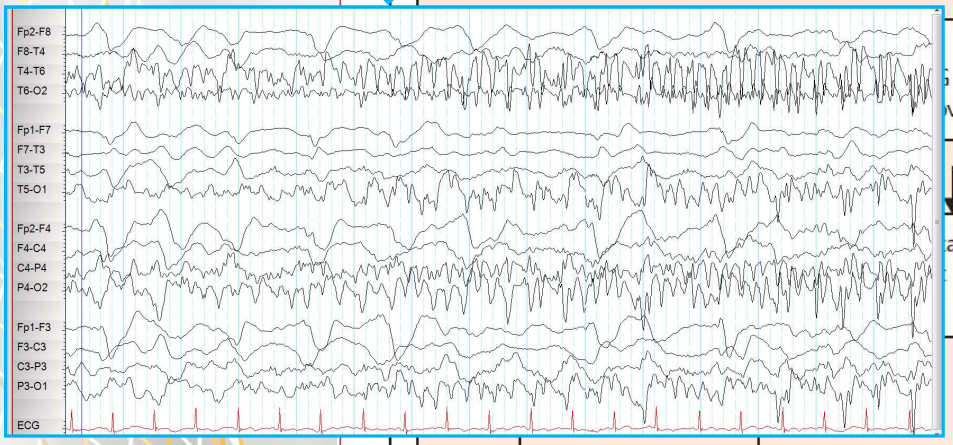

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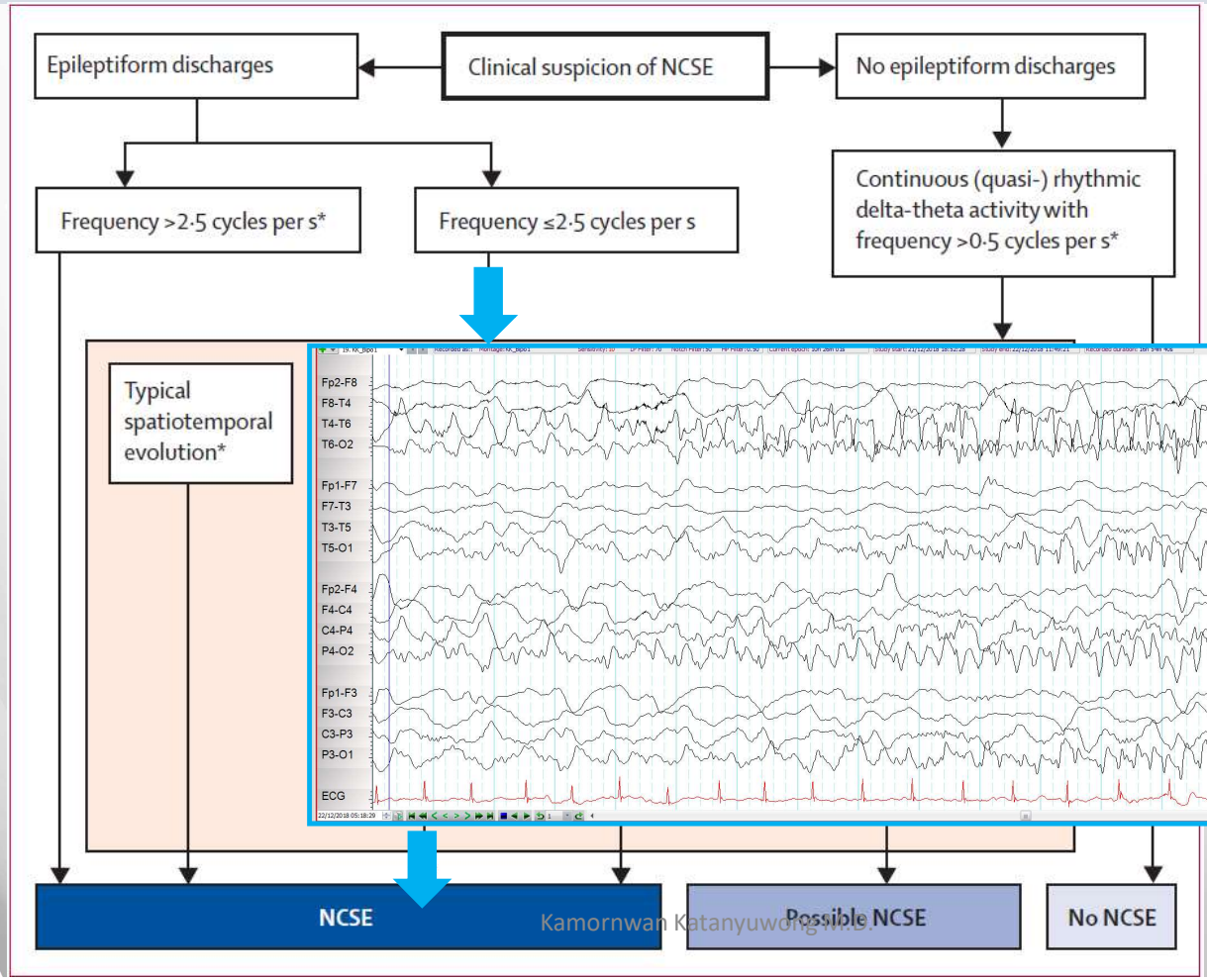
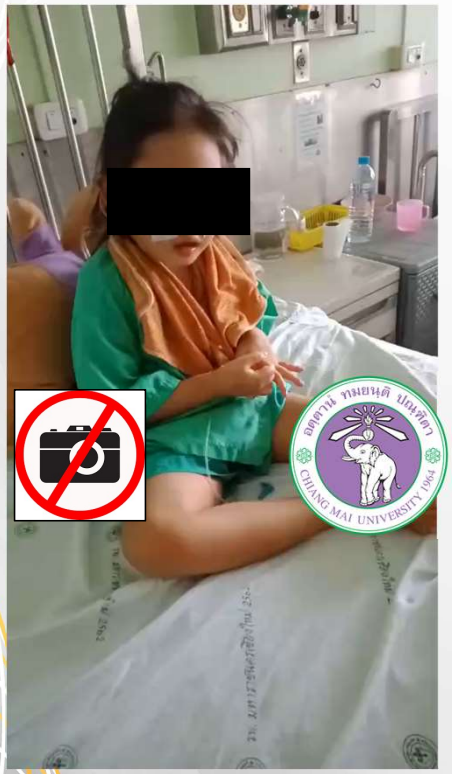
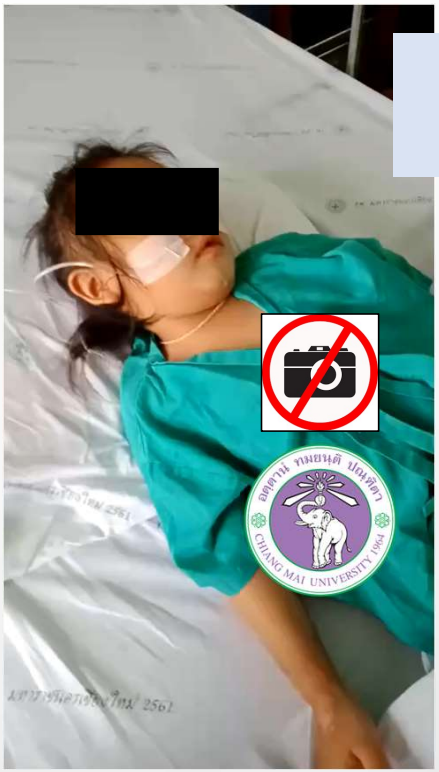


Lancet Neurol 2016; 15: 1054–62

VDO NCSE-syndrome





Clinical suspicious seizures
No EEG at the time

Table 2. Axis I: Classification of status epilepticus (SE)

(A) 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 (prominent epileptic myoclonic jerks)
A.2.a. With coma
A.2.b. Without coma
A.3 Focal motor
A.3.a. Repeated focal motor seizures (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
(B) 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

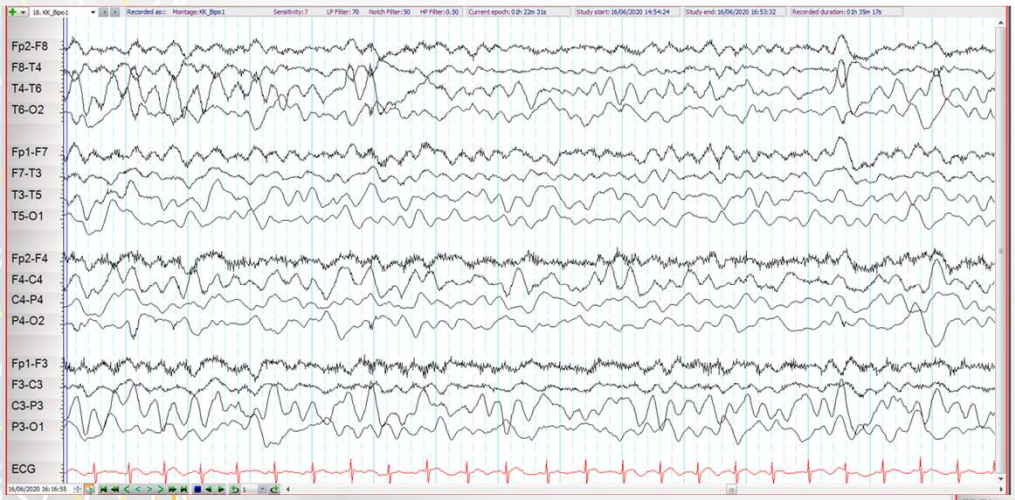
Chromosomal aberrations and genetic anomalies

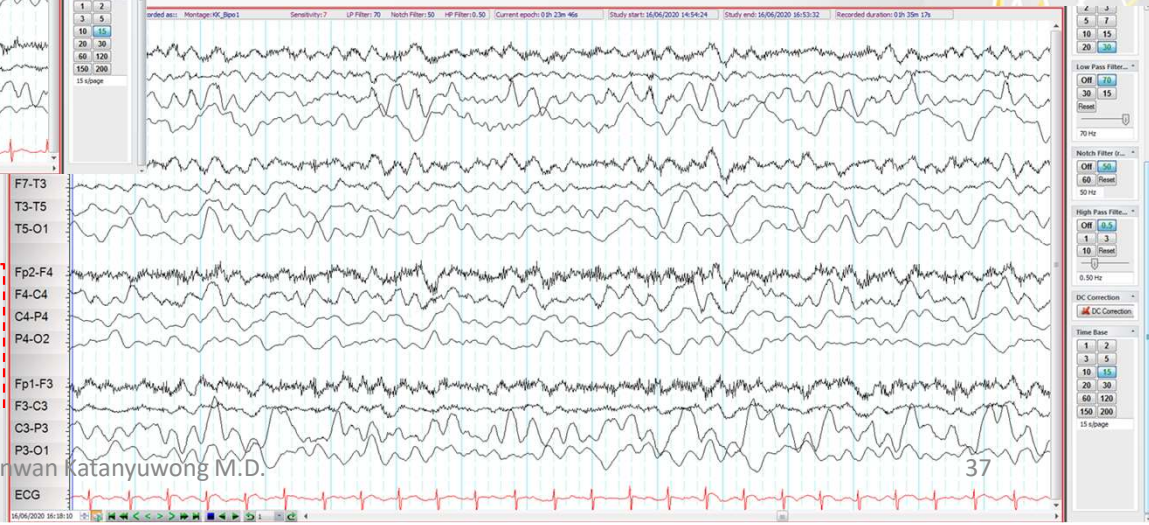
- Ring chromosome 20
- Angelman syndrome
- Wolf-Hirshhorn syndrome
- Fragile X syndrome
- X-linked mental retardation syndrome
- Ring chromosome 17
- Rett syndrome
- Down syndrome

Epilepsia, 56(10):1515–1523, 2015

EEG during non-ictal period

Baseline EEG of atypical absence @ underlying epilepsy syndrome/clinical syndrome





Atypical absence sz in Rett syndrome

Predicting the Outcome in Ped NCSE

Epilepsy & Behavior 82 (2018) 68–73

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Nonconvulsive status epilepticus after cessation of convulsive status epilepticus in pediatric intensive care unit patients

Jin Chen, Lingling Xie, Yue Hu, Xinghui Lan, Li Jiang *

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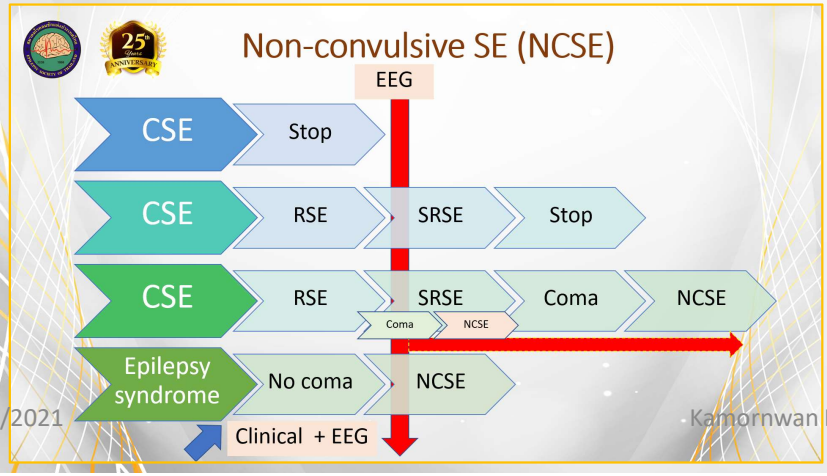
[b] Ministry of Education Key Laboratory of Child Development and Disorders, China International Science and Technology Cooperation Base of Child Development and Critical Disorders, Chongqing Key Laboratory of Pediatrics, Chongqing 400014, China

Age > 12 yrs



Predictor factor: the recurrence of EEG seizures within 2 hrs of initiat^{n} of CIVAD at the dose of greater than half the proposed maximal dose predicts unfavorable outcome in NCSE after CSE

(OR, 9.63; 95%CI, 1.08–86.18; p=0.043)

Status Epilepticus in Neonates

- Management guidelines for **neonatal status epilepticus** derived from the recommendations for neonatal and infantile seizures.
- Neonatal status epilepticus has not been clearly defined, but 5 minutes seems appropriate
- Challenges: seizure semiology, average duration, difficult to evaluate mental status after seizure
- Medication: 1st line- lorazepam iv

  2nd line – PB

  Then alternative PHT/LEV/MDZ

Outcome of Ped SE

- New neurological deficits: 9% of survivor
  (almost occurred in children with acute or progressive neurological insults)
- New neurological deficit : 29% vs 6% (young children vs. older children)
- Children without prior epilepsy → 30% subsequent seizures
- Pts with no prior epilepsy → 50% recurrent unprovoked seizures
  → 16.9% repeated RSE episodes during F/U
- 40% of pts with RSE → new neurological deficits at F/U
  → correlated with a longer electroclinical RSE duration

Curr Opin Pediatr 2014, Epilepsia 2021

Conclusion in Management update CSE

Challenging

- Early stage: **Time**, IM midazolam may be preferable
- Established SE: **ESETT**: FosPHT vs. VPA vs. LEV
- RSE and SRSE: Thiopental has good response but DDI
  : Ketamine + Midazolam or Propofol
- SRSE: may need immunosuppressive agents

New Trial in the Future

Epilepsy & Behavior Reports 15 (2021) 100409

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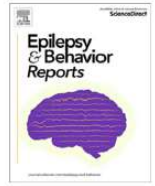
journal homepage: www.elsevier.com/locate/ebcr



The unmet need for rapid epileptic seizure termination (REST)

Aviva Asnis-Alibozek [a,*], Kamil Detyniecki [b]

[a] University of Lynchburg, School of PA Medicine, Doctor of Medical Science Program (DMSc Candidate), Lynchburg, VA 24501, United States
[b] University of Miami Miller School of Medicine, Department of Neurology, Miami, FL 33136, United States

Table 2
Investigational potential REST treatments [32,36,38].

Drug-delivery system description (Sponsor)	Method of administration	Time to REST effect	REST Evidence	Phase of development
Stacatto® alprazolam (Engage Therapeutics, a wholly owned subsidiary of UCB)	Oral inhalation of heated drug vapor	30 seconds* T_{max} = 2 minutes	• Abrogation of PPR • Seizure termination response > placebo	Phase 3 REST planned
Zeneo® midazolam (Crossject)	Needle-free transdermal injection of drug solution to muscle	3.3 minutes† T_{max} = NR	• Zeneo injection bioequivalence to IM product delivery	FDA orphan drug designation for status epilepticus
Midazolam autoinjector (Seizalam® Meridian Medical)	Intramuscular autoinjection of drug solution	3.3 minutes† T_{max} = 30 minutes	• Status epilepticus termination = IV lorazepam	Phase 3 status epilepticus completed

NR, not reported; PPR, photoparoxysmal response
*30 second mean time to seizure cessation in phase 2b across all responding seizure types
† Intramuscular (IM) midazolam median time from active treatment to cessation of convulsions [23,36]

New Future (1)

- Rational **polytherapy** between 1st and 2nd line ASMs with synergistic action for **SE**
  - Animal studies: DZP + KTM + VPA
    : MDZ + KTM
    : DZP + PER, DZP + LEV, DZP + BRV
    : PB + PHT + PGB
    : DZP + =B + scopolamine
  - Human studies: BZP + fosPHT
    : *VPA + LTG*

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New Future (2)

- Rational **polytherapy** between ASMs with synergistic action for **RSE**
  - Animal studies: MDZ + KTM
    : DZP + KTM + VPA
    : KTM + BRV
    : MDZ + KTM + VPA *better* than MDZ + FosPHT+VPA
  - Human studies: Propofol + KTM
  - On going human studies: MDZ + KTM

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Thank you for your attention