

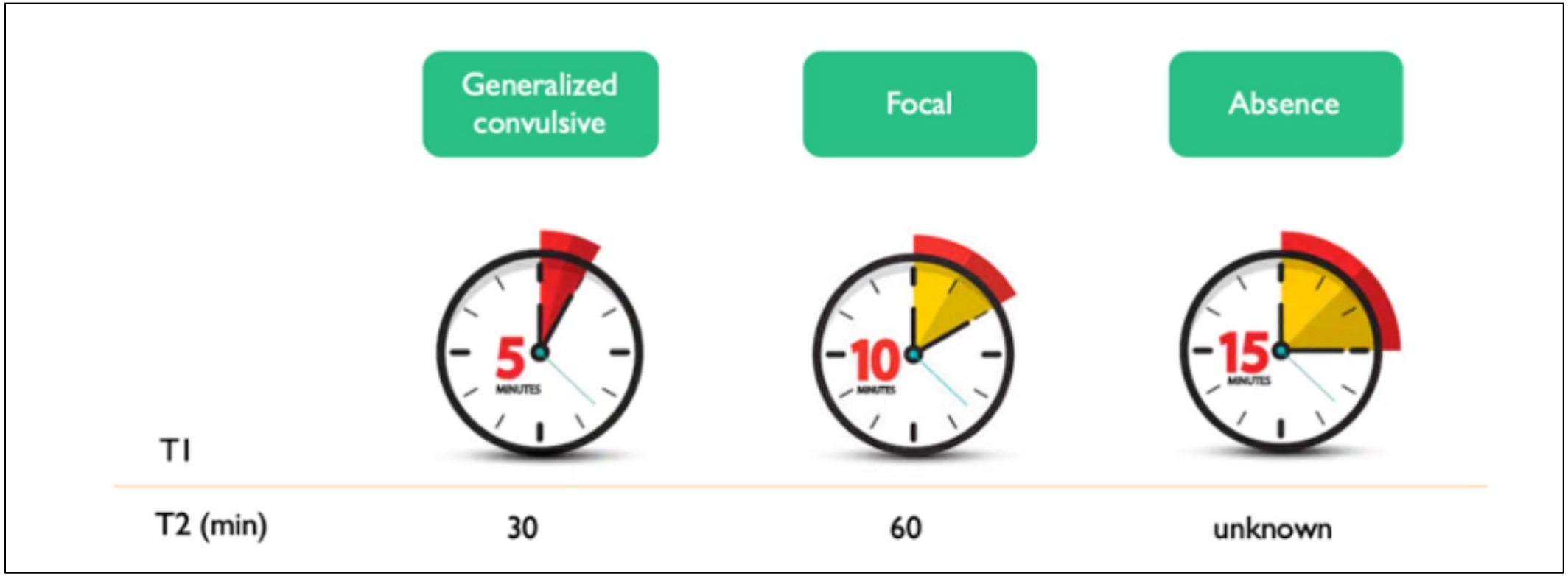

Status Epilepticus

Kullasate Sakpichaisakul, MD
Division of Neurology, Department of Pediatrics,
Queen Sirikit National Institute of Child Health

Outline

- Definition & classification of status epilepticus (SE)
- Pathophysiology
- Management of SE
- Outcomes of SE

Status Epilepticus (SE)



- ***Time T1*** is the time point at which the seizures becomes "**abnormally prolonged**"
- ***Time T2*** is the time point beyond which there is high risk for **long term sequelae**

Time is Brain!

It's all about time!

Trinka E, et al. *Epilepsia* 2015

How Long Do a Seizure Commonly Last?

- Children
  - Mean duration of partial seizure in children: 97 sec
  - 76% of new onset seizure lasts 3.6 min
  - 24% lasts 31 min
  - If seizure lasts more than 5-10 min, it is less likely to stop spontaneously
- Adult
  - Most seizures rarely last longer than 2 min

Holmes GL, 1984, Shinnar S, 2001

Physiological Changes

Compensatory phase (< 30 min)

- Increased CBF
- Sympathetic overactivity
- Increased cardiac output
- Tachycardia
- Hyperglycemia
- Lactic acidosis
- Salivation, incontinence
- Hyper/ normokalemia
- Intact BBB & neuron integrity

Refractory phase (> 30 min)

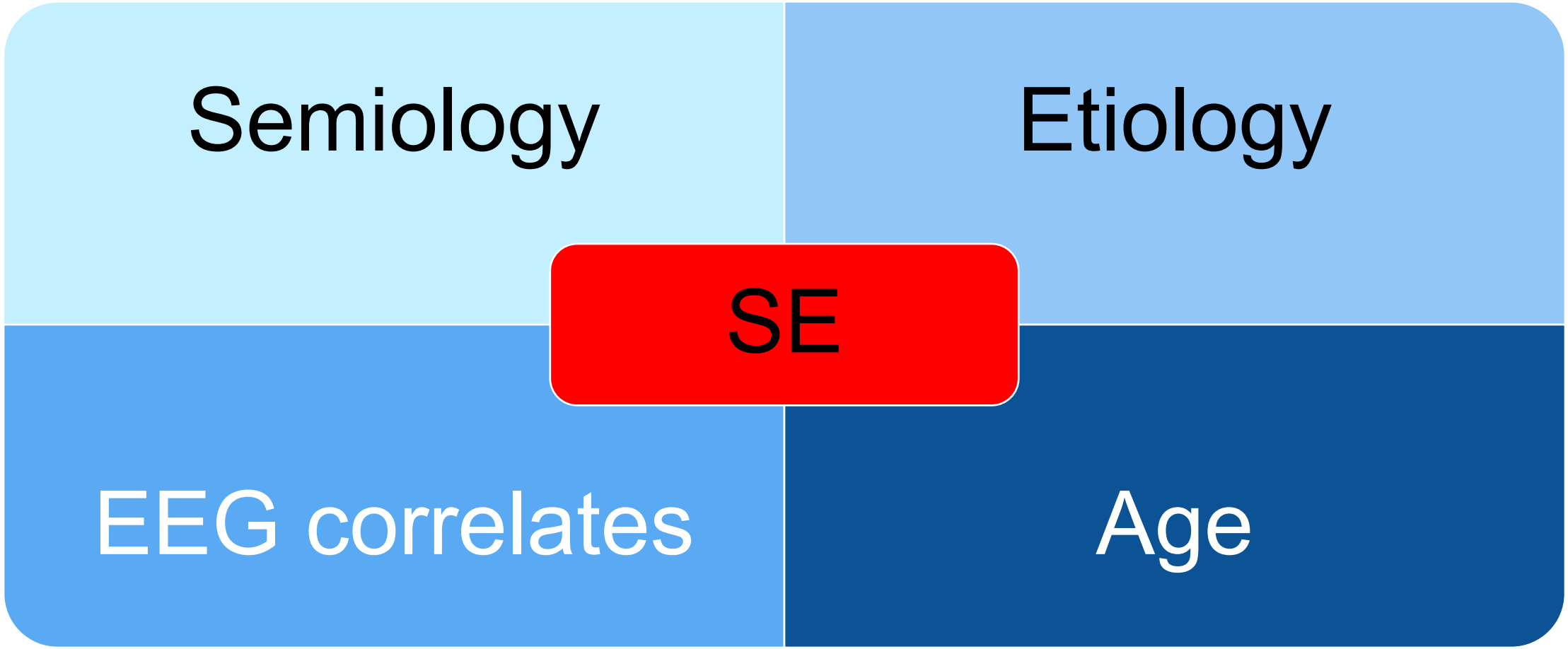
- Fall in cardiac output
- Hypoglycemia
- Cerebral autoregulation failure
- I-ICP & Cerebral edema
- Hyperpyrexia
- Rise in liver enzymes
- Rhabdomyolysis
- DIC
- Multi-organ failure

Status Epilepticus (SE)

- **Generalized convulsive status epilepticus (GCSE)** = seizures **lasting > 5 min**. Permanent neuronal damage expected at **30 min.**
- **Focal SE** = seizures lasting **>10 min.** Permanent neuronal damage expected at **60 min.**
- **Absence SE** = seizures lasting **>15 min.** There is no recommendation to when permanent neuronal damage is expected for this type of seizure.

Trinka E, et al. *Epilepsia* 2015

Classfication of SE (4 Axes)



Trinka E, et al. *Epilepsia* 2015

Axis I: Semiology

(A) **With prominent motor symptoms**

1. Convulsive SE (CSE)
2. Myoclonic SE
3. Focal motor
4. Tonic status
5. Hyperkinetic SE

(B) **Without prominent motor symptoms** (nonconvulsive SE)

1. NCSE with coma (including subtle SE)
2. NCSE without coma

Trinka E, et al. *Epilepsia* 2015

Axis II: Etiology

Known (i.e. symptomatic)

I. Acute (e.g. stroke, intoxication, encephalitis, etc.)
II. Remote (e.g. poststroke, postencephalitis, etc.)
III. Progressive (e.g. brain tumor, PME diseases, dementias)

Unknown (i.e. cryptogenic)

Trinka E, et al. *Epilepsia* 2015

Etiology of Status Epilepticus in Adults

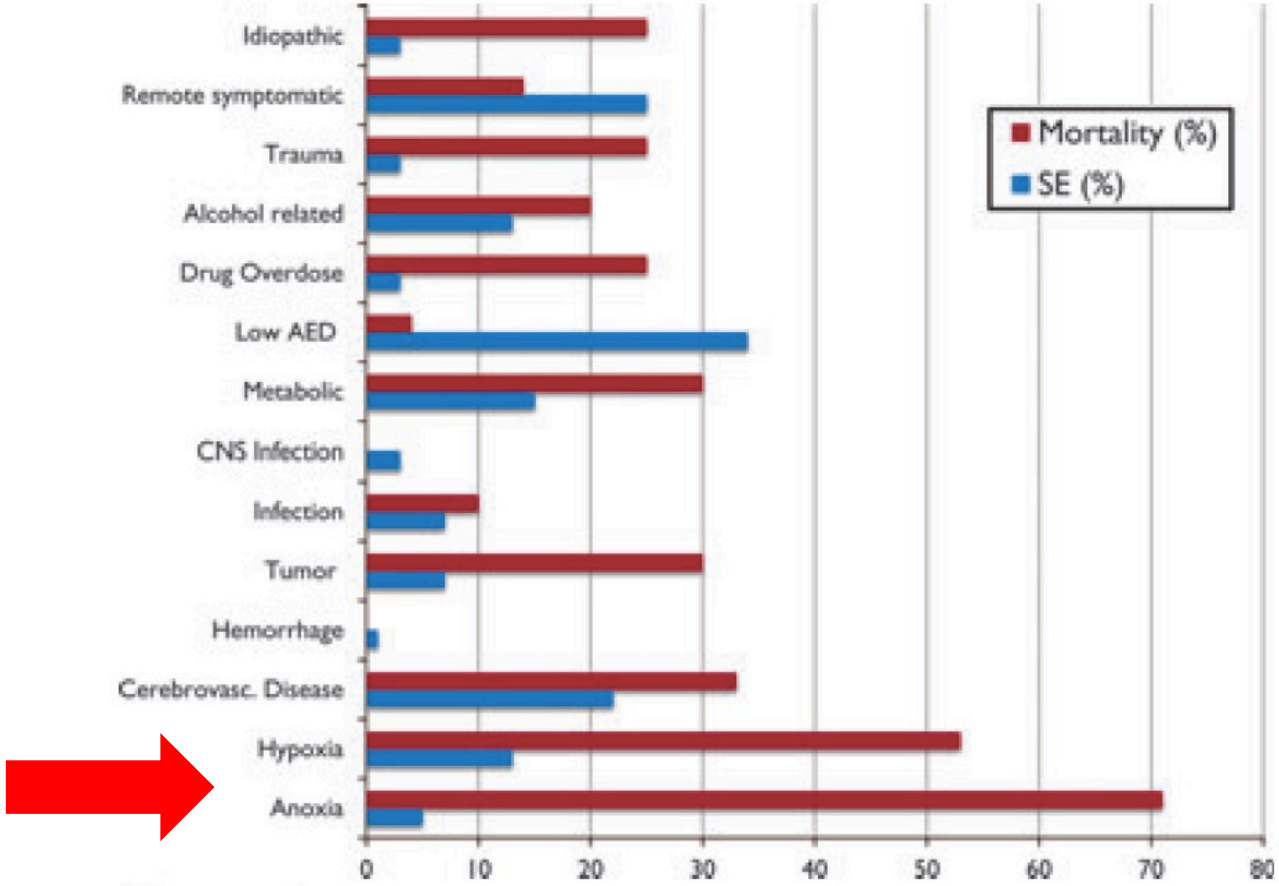


Figure 1.
Etiology of status epilepticus in adults, with associated mortality for each category. Based on data from DeLorenzo et al., 1995. AED, antiepileptic drugs; CNS, central nervous system.

Trinka E, et al. *Epilepsia* 2012

Etiology of Status Epilepticus in Children

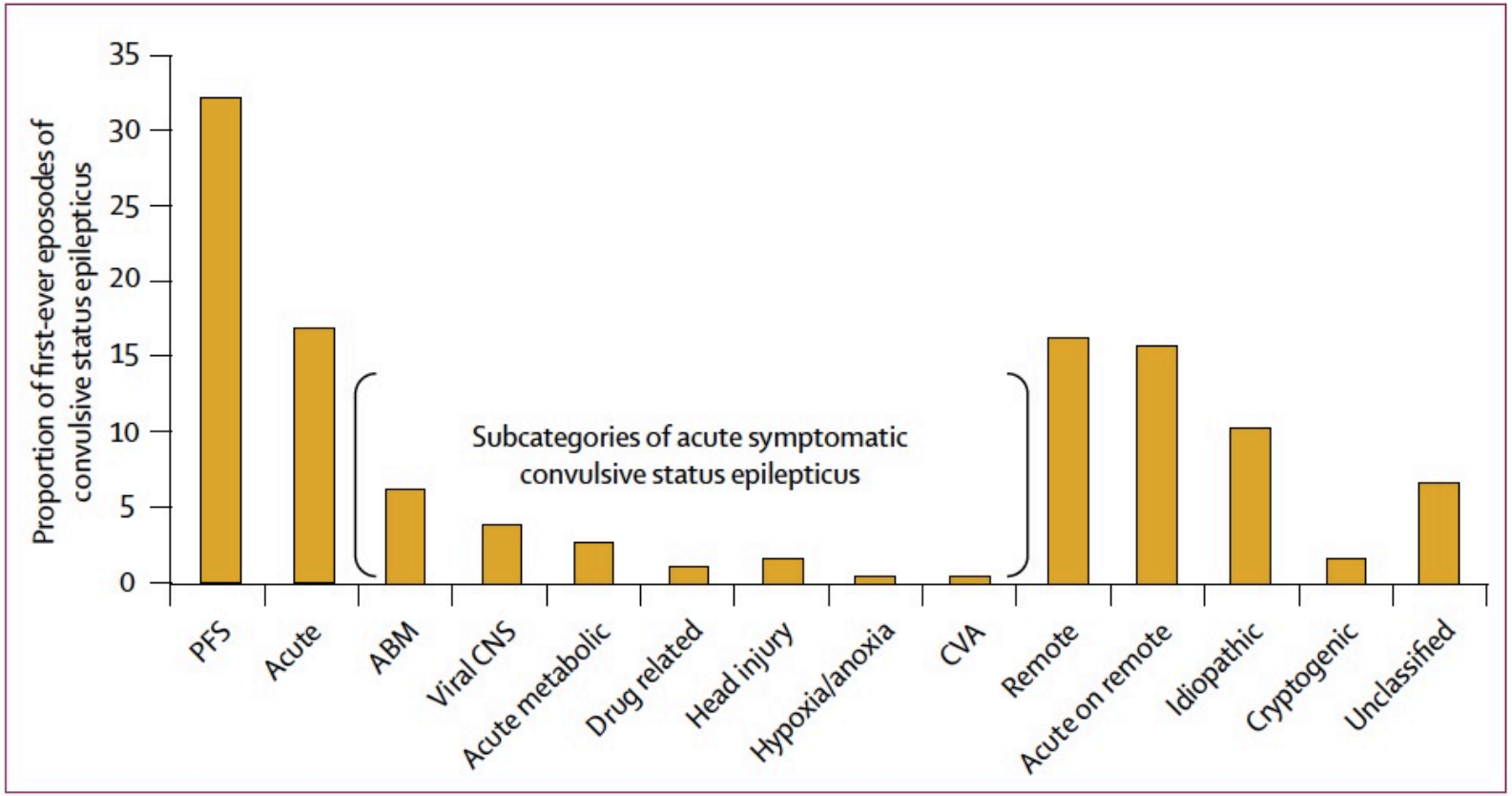


Figure 2: **Causes of first ever episodes of convulsive status epilepticus**
PFS=prolonged febrile seizure. Acute=acute symptomatic. ABM=acute bacterial meningitis. Viral CNS=acute viral CNS infection. Acute metabolic=acute metabolic disturbance. CVA=cerebrovascular accident. Remote=remote symptomatic. Acute on remote=acute on remote symptomatic. Idiopathic=ideopathic epilepsy related. Cryptogenic=cryptogenic epilepsy related.

Chin R, Lancet 2006

Axis III: EEG Correlates

EEG value is indispensable in diagnosis of NCSE

Describe EEG pattern in SE

1. Location: generalized, lateralized, bilateral independent, multifocal
2. Name of the pattern: periodic, rhythmic delta, etc.
3. Morphology
4. Time-related features: prevalence, frequency, onset, etc.
5. Modulation: stimulus induced vs spontaneous
6. Effect of intervention (medication) on EEG

Trinka E, et al. *Epilepsia* 2015

Modified Salzburg Criteria for NCSE

A. Patients without epileptic encephalopathy

1. EDs > 2.5 Hz
2. Typical ictal spatiotemporal evolution of

(2a) EDs OR (2b) Rhythmic activity (> 0.5 Hz)

3. Subtle ictal clinical phemomena with

(3a) EDs OR (3b) Rhythmic activity (> 0.5 Hz)

4. If 1-3 are not fulfilled, but one of the following pattern is present

(4a) EDs ≤ 2.5 Hz with fluctuation (4b) Rhythmic activity (> 0.5 Hz) with fluctuation OR (4c) Rhythmic activity (> 0.5 Hz) without fluctuation

B. Patients with known epileptic encephalopathy

In addition to the criteria A, these patients have to fulfill one of the following

- Increase in prominence or frequency when compared to baseline
- Improvement of clinical and EEG features with IV ASMs

Beniczky S, et al. *Epilepsia* 2013, Leitinger M, Epilepsy Behav 2015

Axis IV: Age

1. Neonatal
2. Infancy
3. Childhood (>2 - 12 y)
4. Adolescence and adulthood (>12 - 59 y)
5. Elderly (> 60 y)

Trinka E, et al. *Epilepsia* 2015

SE in selected Electroclinical Syndromes According to Age

SE occuring in neonatal and infantile onset epilepsy syndromes
- Tonic status (e.g. in Ohtahara syndrome or West syndrome)
- Myoclonic SE in Dravet syndrome
- Focal SE
- Febrile SE

SE occuring mainly in childhood and adolescence
- Autonomic SE in Payaniotopoulos syndrome
- NCSE in specific syndromes (Ring chromosome 20, Angelman syndrome)

SE occuring mainly in adolescence and adulthood
- Myoclonic SE in JME, Down syndrome
- Absence SE in JAE

SE occuring mainly in the elderly
- Myoclonic SE in Alzhemier's disease
- NCSE in Creutzfeldt-Jakob disease

Trinka E, et al. *Epilepsia* 2015

Management of SE

- Early seizure termination
- Prevention of seizure recurrence **(Quick escalation to 2nd line ASMs)**
- Identify and treatment of **underlying etiology (Specific Rx)**
- Management of secondary complications

Acute Seizure: Investigations

- Blood glucose
- ASMs level
- Simple metabolic derangement:
  - electrolytes, Ca^{++}, Mg^{++} (if clinically indicated)
- Lumbar puncture
- Electroencephalography (EEG)
- Toxicology
- Neuroimaging (CT scan or MRI)

CSE Treatment

Stabilization Phase (0-5 minute)	1. **Stabilize patient** **2. Time seizure from its onset** **3. Collect finger stick glucose** **4. Attempt IV access**
Early SE (within 10 min of seizure onset)	• **If no IV access: IM or IN Midazolam (0.2 mg/kg; max 10 mg) OR Rectal Diazepam (0.2-0.5 mg/kg; max 20 mg)** • **IV Diazepam 0.15-0.2 mg/kg (max 10 mg, can repeat <u>once</u>)**

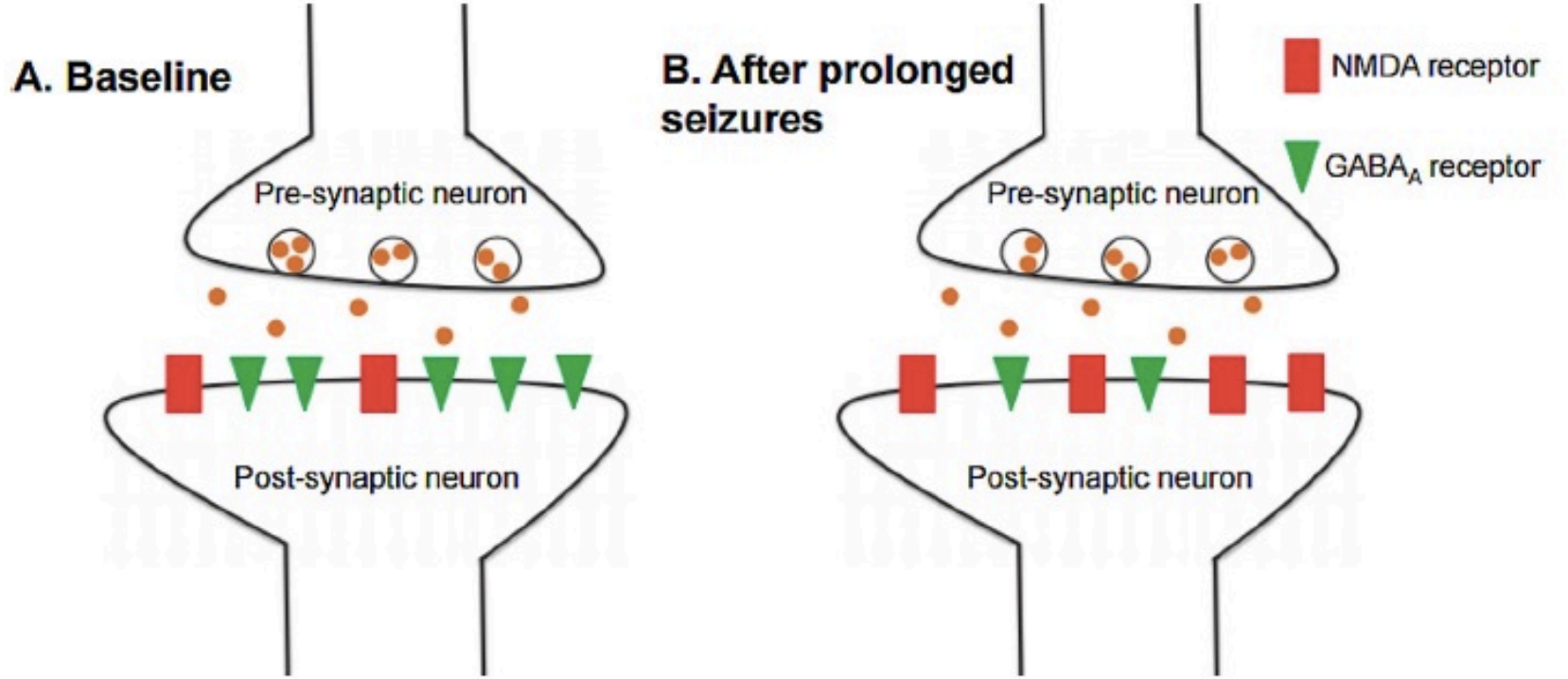
Glauser T, et al. AES 2016, Sing A, et al., CNS Drugs 2020

Early SE: Benzodiazepines First Line Therapy

	Diazepam	Midazolam	Lorazepam
Route	IV, PR	IV, IM, IN, buccal	IV
Max dose	10 mg for IV 20 mg for PR	10 mg	4 mg
Onset of action	1-3 min	3-5 min	6-10 min
Duration of action	15-30 min	15-30 min	12- 24 hr
Disadvantages	Prolonged sedation Respiratory depression	Short half-life Risk of seizure relapse	Rapid tolerance
Advantages	Rapid onset Widespread availability	Water soluble	Less lipid soluble

Sing A, et al. CNS Drugs 2020

Benzodiazepine Consideration



- Suboptimal dose = less efficacy
- > 2 doses is associated with side effects without a substantial increase in efficacy
- Potency of BDZ may decrease 20-fold over 30 min of SE

Gainza-Lein M, et al. Seizure 2019, Sing A, et al., CNS Drugs 2020

CSE Treatment

Stabilization Phase
(0-5 minute)

1. **Stabilize patient**
2. **Time seizure from its onset**
3. **Collect finger stick glucose**
4. **Attempt IV access**

Early SE
(within 10 min of seizure onset)

- **If no IV access: IM or IN Midazolam (0.2 mg/kg; max 10 mg) OR Rectal Diazepam (0.2-0.5 mg/kg; max 20 mg)**
- **IV Diazepam 0.15-0.2 mg/kg (max 10 mg, can repeat <u>once</u>)**

Established SE
(10-30 min of seizure)

- **IV PHT 20 mg/kg (max 1500 mg) or LEV 60 mg/kg (max 4500 mg) or VPA 40 mg/kg (max 3000 mg) or PB 15 mg/kg (max 1000 mg)**
- **Can repeat ASM above or give a different one if seizure persists**

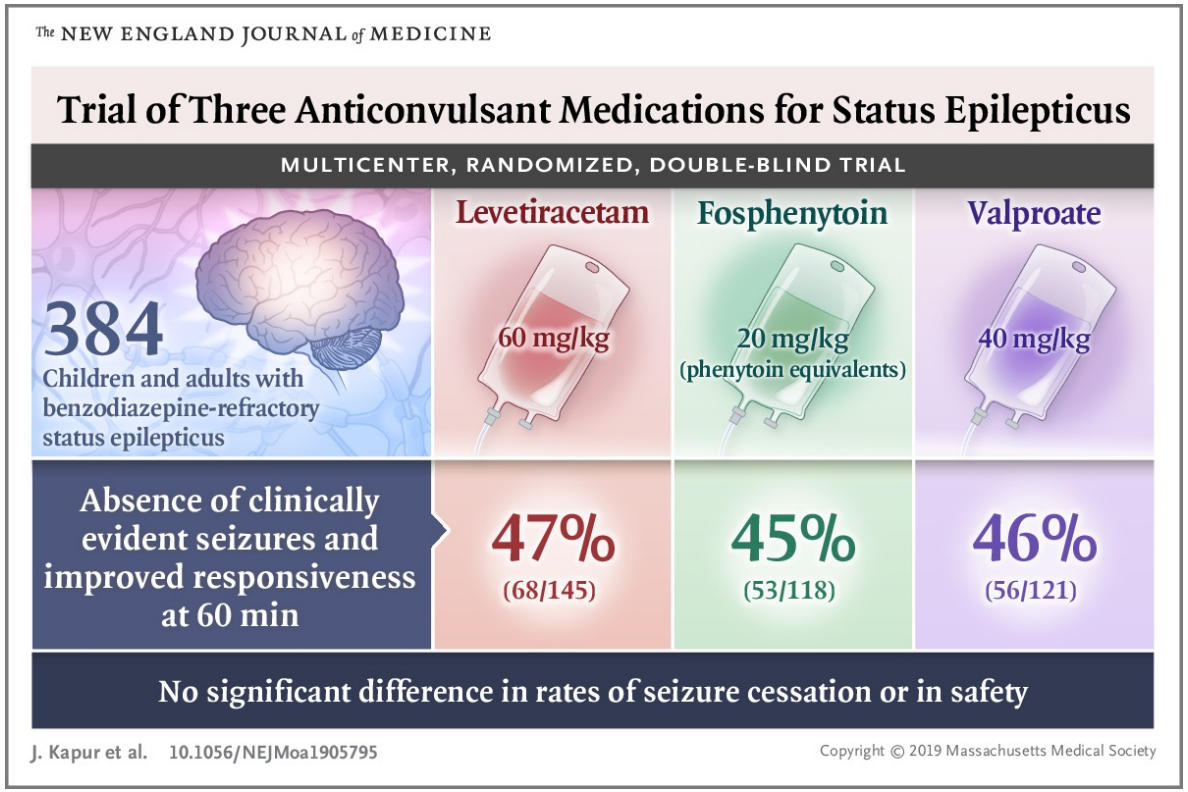
Glauser T, et al. AES 2016, Sing A, et al., CNS Drugs 2020

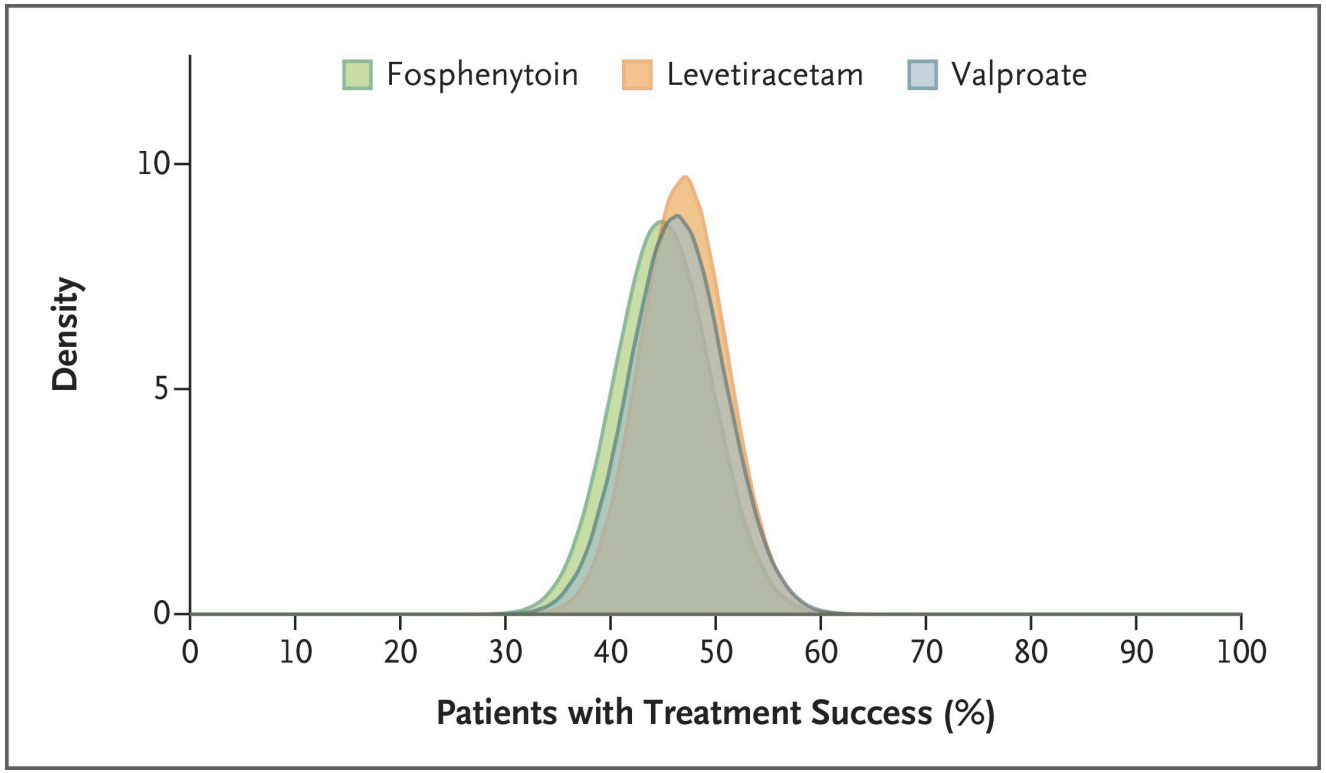
Evidence Based of 2nd Line Therapy for Established SE

- ESETT (Established Status Epilepticus Treatment Trial)
  - Children > 2 yo, GTC > 5 min and continue Sz after adequate doses of BDZ
  - LEV 60 mg/kg (max 4500 mg)
  - fPHT 20 mg/kg (max 1500 mg)
  - VPA 40 mg/kg (max 3000 mg)
- EcLiPSE (Emergency treatment with Levetiracetam or Phenytoin in Status Epilepticus in Children)
  - Children aged 6 mo – 18 years requiring 2nd line Rx
  - PHT 20 mg/kg over 20 min vs LEV 40 mg/kg over 5 min
- ConSEPT (Convulsive Status Epilepticus Paediatric Trial)
  - Children aged 3 mo – 16 years who failed 1st line BDZ
  - PHT 20 mg/kg over 20 min vs LEV 40 mg/kg over 5 min

Kapur J, NEJM 2019, Chamrberlain JM, Lancet 2020, Lyttle MD, Lancet 2019, Dalziel SR, Lancet 2019

ESETT





Kapur J, NEJM 2019

ESETT

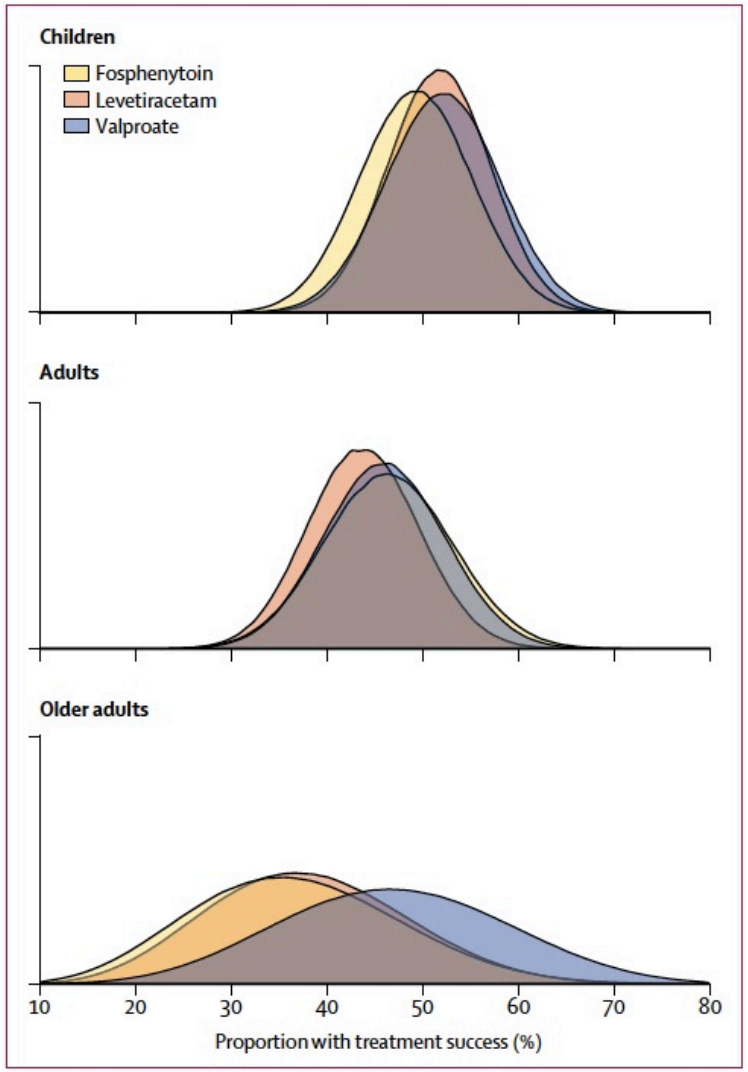


Figure 2: Posterior probabilities of success by age and treatment groups for the primary outcome

	LEV (%, 95 CI)	fPHT (%, 95 CI)	VPA (%, 95 CI)
Children	52% (41-62)	49% (38-61)	52% (41-63)
Adults	44% (33-55)	46% (34-59)	46% (34-58)
Older adults	37% (19-59)	35% 17-59)	47% (25-70)

Chamrberlain JM, Lancet 2020

EcLiPSE and ConSEPT Trial

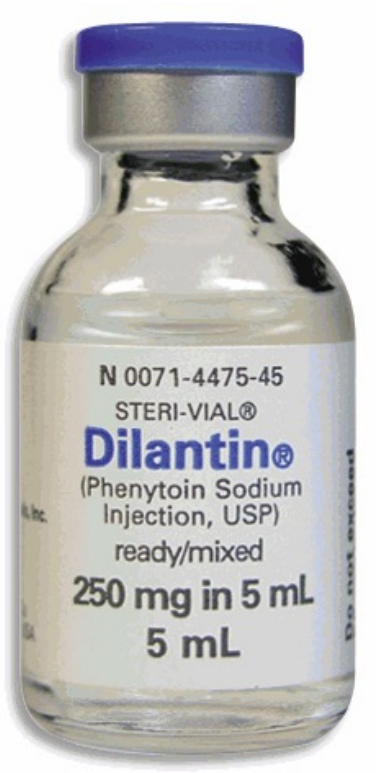
	EcLiPSE (n = 296)	ConSEPT (n = 233)
Patients	Age 6 mo – 18 years	Age 3 mo – 16 years
Study	Multicenter, RCT, UK	Multicenter, RCT, AUS + NZ
Intervention	PHT 20 mg/kg over 20 min vs LEV 40 mg/kg over 5 min	
Outcome	Time to randomization to cessation of CSE	Clinical cessation of seizure activity 5 min after infusion end
Resutls	Median time to stop: PHT 45 min vs LEV 35 min	PHT (60%) vs LEV (50%)
Conclusion	LEV is not superior	No significant difference

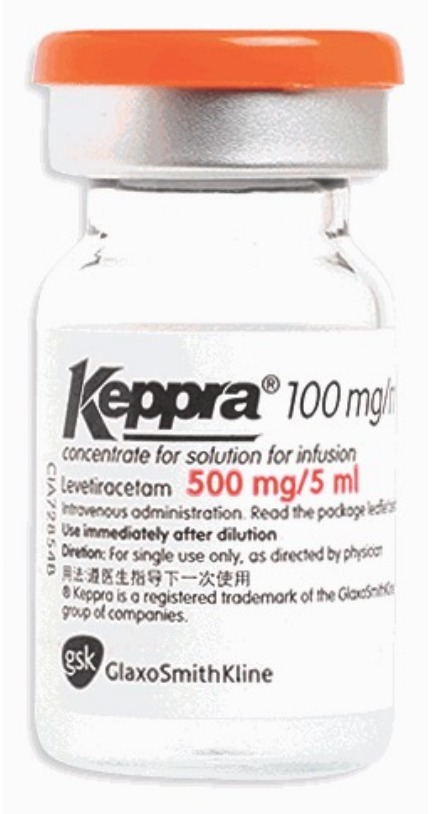
Lyttle MD, Lancet 2019, Dalziel SR, Lancet 2019

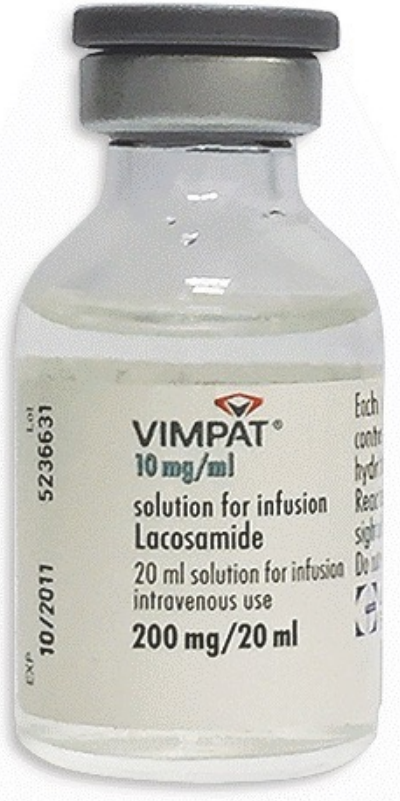
Established SE

- IV PHT 20 mg/kg (max 1000 mg) OR
- IV VPA 40 mg/kg (max 3000 mg) OR
- IV LEV 60 mg/kg (max 4500 mg) OR
- IV PB 20 mg/kg (max 1000 mg)

Intravenous ASMs in Thailand







Intravenous ASMs in Thailand

	PB	PHT	VPA	LEV	LCM
Dose (mg/kg/dose)	20	20	40	40-60	8-10
Vd	0.8	0.8	0.2	0.6-0.9	0.6
Infusion rate (mg/kg/min)	2	1	3	6-12	0.4
Side effect	Sedation	Arrhythmia Hypotension	LFT elevate	Dizziness Somnolence	PR prolonged Mild sedation

CSE Treatment

Stabilization Phase
(0-5 minute)

1. **Stabilize patient**
2. **Time seizure from its onset**
3. **Collect finger stick glucose**
4. **Attempt IV access**

Early SE
(within 10 min of seizure onset)

- **If no IV access: IM or IN Midazolam (0.2 mg/kg; max 10 mg) OR Rectal Diazepam (0.2-0.5 mg/kg; max 20 mg)**
- **IV Diazepam 0.15-0.2 mg/kg (max 10 mg, can repeat <u>once</u>)**

Established SE
(10-30 min of seizure)

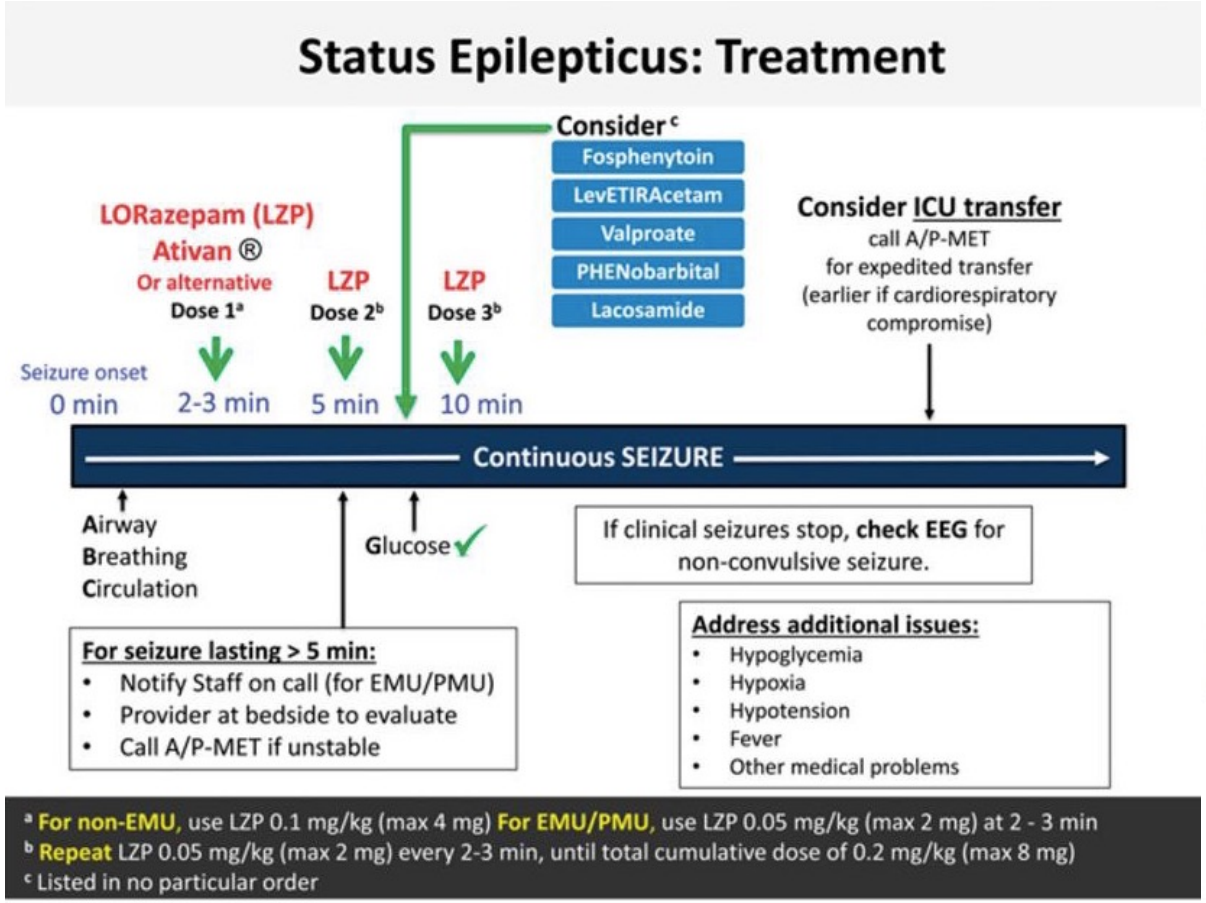
- **IV PHT 20 mg/kg (max 1500 mg) or LEV 60 mg/kg (max 4500 mg) or VPA 40 mg/kg (max 3000 mg) or PB 15 mg/kg (max 1000 mg)**
- **Can repeat ASM above or give a different one if seizure persists**

Refractory SE
(seizure persist > 30 min)

- **Repeat 2nd line therapy or anesthetic agents (thiopental, midazolam, propofol)**

Glauser T, et al. AES 2016, Sing A, et al., CNS Drugs 2020

Status Epilepticus Pocket Card



227320203255

Status Epilepticus Medications

Rescue Benzodiazepines

Medication	Dose (Max)	Comments
I.V. LORazepam LZP (Ativan®)	0.05 - 0.1 mg/kg/dose (2 - 4 mg)	For non EMU, use Ativan 0.1 mg/kg or 4 mg whichever is lower, can repeat x1. For EMU/PMU, use 0.05 mg/kg or 2 mg whichever is lower; can redose every 3 min for continued seizure to a cumulative dose of 0.2 mg/kg or 8 mg, whichever is lower
Rectal DiazePAM DZP (Diastat ®)	Weight **AND** age based	6 month to 5 yrs: 0.5 mg/kg 6 - 12 yrs: 0.3 mg/kg 12 + yrs: 0.2 mg/kg (max 20 mg) (round to nearest 2.5 mg)
Nasal Midazolam MDL (Versed¤)	0.2 - 0.3 mg/kg (5 -10 mg)	< 40 Kg 0.2-0.3 mg/kg ≥ 40 Kg, give 10 mg (max dose) (half the dose in each nostril)
I.M. Midazolam MDL (Versed¤)	0.2 - 0.3 mg/kg (5 - 10 mg)	< 13 Kg 0.2-0.3 mg/kg 13-40 Kg, give 5 mg > 40 Kg, give 10 mg (max dose)
I.V. DiazePAM DZP (Valium®)	0.15 - 0.3 mg/kg, max 10 mg	Shorter duration compared to Ativan. Higher risk for respiratory depression.

Tier 2 Drugs

Medication	Dose Range (max dose)	Comments
Fosphenytoin FOS (Cerebyx®)	20 mg PE/kg (max 1500 mg)	Drug levels quickly available for titration. Avoid if known generalized epilepsy, Dravet syndrome. Watch for hypotension, bradycardia. Tissue extravasation is potentially dangerous.
LevETIRAcetam LEV (Keppra®)	60 mg/kg (max 4500 mg)	Also effective for myoclonic seizures.
Valproate VPA (Depacon®)	40 mg/kg (max 3000 mg)	Effective in JME, myoclonic status and absence status. Caution needed in patients with liver dysfunction and select metabolic diseases. (e.g., POLG1)
PHENobarbital PB (Luminal®)	10-20 mg/kg (max 1000 mg)	Drug of 1st choice in newborns. Watch for hypotension. Closely monitor for respiratory depression. May use in adults if previously on this med with status due to missed (or held) doses.
Lacosamide LCM (Vimpat®)	5-10 mg/kg (max 400 mg)	Caution if cardiac issues - can prolong PR interval. Use if previously on med and status due to missed (held) doses

1. IV Ativan is the preferred drug.
2. Use alternatives when IV access is not available.
3. Establish IV access ASAP, even if alternate route used.

1. Do not exceed max dose, use ideal body weight as appropriate
2. In actively convulsing patient, tier-2 drugs above can be given over 10 min; exceptions are levetiracetam which can be given over 5 min, and phenytoin (not listed above), if used, should be infused over 20 min. Otherwise, infuse over 30-60 min.

Pocket Card adapted Glauser T, et al. Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Guideline of the American Epilepsy Society. *Epilepsy Currents*. 2016 Jan: 16 (1) 48-61.

Fesler J. et al. Neurology Clinical Practice 2020

Definition of Prolonged SE

- Refractory SE (RSE): SE persisting despite adminstration of at least 2 appropriately selected and dosed parenteral medication includings a BZD. There is no specific seizure duration required

- Super-Refractory SE (SRSE): SE persisting at least 24 h after onset of anesthesia, either without interruption despite appropriate Rx with anesthesia; recurring while on appropriate anesthetic Rx; or recurring after withdrawal of anesthesia and requiring anesthetic reintroduction

- Prolonged RSE (PRSE): RSE persists for ≥ 7 days despite appropriate Rx, but without use of anesthetic

- Prolonged SRSE (PSRSE): SRSE persists for ≥ 7 days, including ongoing need for anesthetics

Hirsch L, Epilepsia 2018

Refractory GCSE

Medication	Initial Dose	Maintenance Dose	Serious Adverse Effects
Midazolam	0.2 mg/kg	0.05-0.2 mg/kg/h	Respiratory depression, hypotension, tachyphylaxis
Propofol	1-2 mg/kg	30-200 mcg/kg/min	Respiratory depression, hypotension, propofol infusion syndrome
Pentobarbital	5-15 mg/kg	0.5-5 mg/kg/h	Cardiac and respiratory depression, hypotension, ileus, loss of neurologic exam
Thiopental	2-7 mg/kg	0.5-5 mg/kg/h	Cardiac and respiratory depression, hypotension
Ketamine	0.5-4.5 mg/kg	1-10 mg/kg/h	Hypertension, arrhythmia, anaphylaxis, pulmonary edema

Nelson S, Continuum 2018

New Onset Refractory SE (NORSE) and Febrile Infection-Related Epilepsy Syndrome (FIRES)

- **NORSE:** a clinical presentation, not a specific diagnosis, in a patient without active epilepsy or other preexisting relevant neurological disorder, with new onset of RSE without a clear acute or active structural, toxic, or metabolic cause.

- **FIRES:** a subcategory of NORSE that requires a prior febrile infection, with fever starting between 2 weeks and 24 hours prior to onset of refractory SE, with or without fever at onset of SE. This applies to all ages.

Hirsch L, Epilepsia 2018

Etiologies of NORSE

- Unknown: 50%
- Inflammatory and autoimmune encephalitis: 40%
- Infectious encephalitis: 10%
- Genetic disorders: Rare

Sculier C, Seizure 2019

Immune Therapies in NORSE and FIRES

TABLE 1 Summary of patients who receive immune therapies or therapies that might have an antiinflammatory effect

Therapies	Suggested dosage	Cryptogenic FIRES (N = 225)		Cryptogenic NORSE (N = 101)	
		Number of treatments	Positive effects (some cases only transient) (%)	Number of treatments	Positive effects (some cases only transient) (%)
Steroids	IV methyldprednisolone 1000 mg per day for 3-5 d (adults) IV methyldprednisolone 10 to 30 mg/kg (up to 1000 mg) per day for 3-5 d (children) Sometimes followed by oral prednisone 1 mg/kg per day	63	11 (17)	40	15 (38)
Intravenous immunoglobulins	1.2 to 2 g/kg over 3-5 d	94	5 (5)	17	5 (30)
Ketogenic diet	N/A	35	19 (54)	12	8 (67)
Plasmapheresis	3 to 5 exchanges, one every other day	18	2 (11)	15	6 (40)
Hypothermia	N/A	5	3 (60)	4	2 (40)
Rituximab	N/A	3	1 (33)	0	NA
Azathioprine	N/A	1	0 (0)	0	NA
Tacrolimus	N/A	1	0 (0)	0	NA
Cyclophosphamide	N/A	1	0 (0)	0	NA

Gaspan N, Epilepsia 2018

Mortality

- Associated with delays in initiating treatment and prolonged seizure duration
- Children: 0-3% in developed countries, 6-11% in Thailand
- Older adults: 20-30% (15-25% in Thailand)

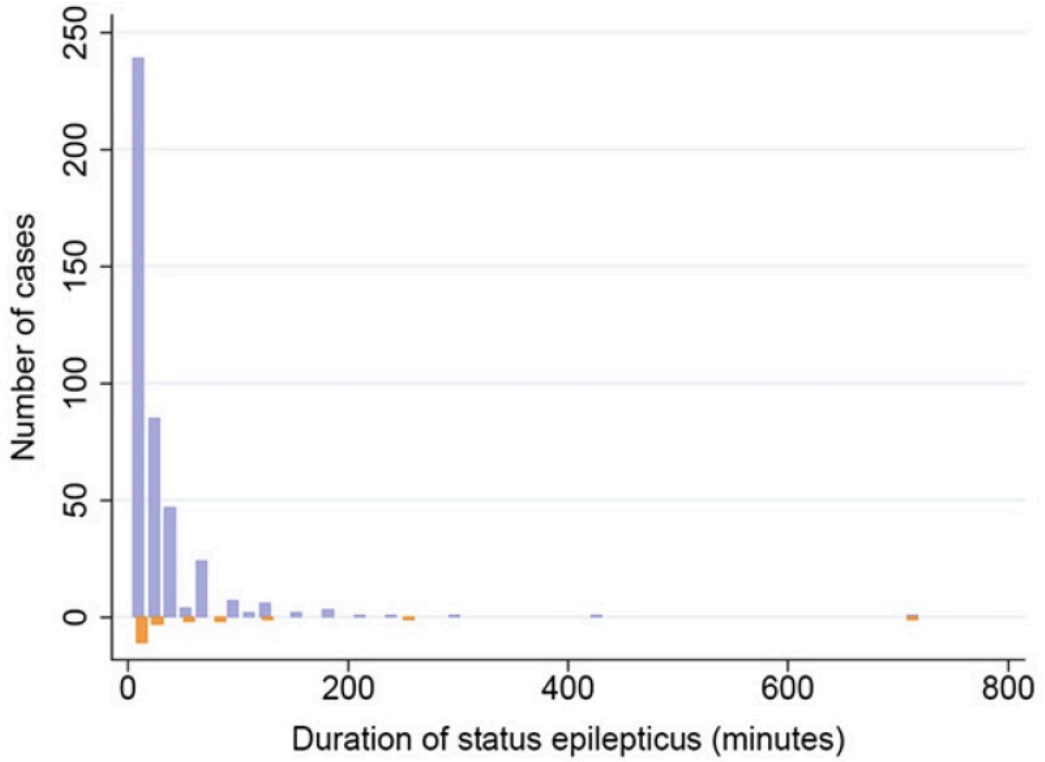


Fig. 2. Histogram of the seizure duration comparing patients who survived (lavender, positive values in the y axis) and those who died (orange, negative values in the y axis).

Visudtibhan A, J Med Assoc Thai 2006, Sanchez Fernandez I, Epilepsy Behav 2014, Sakpichaisakul K, J Pediatr Epilepsy 2017, Kulamtrakorm K, Neurology Asia 2014, Tiamkao S, J Neurol Sci 2017

Morbidity

- Etiology is a primary predictor of long-term outcome
- Low morbidity in
  - Children without previous neurologic disorder
  - Early aggressive treatment
  - Febrile SE and idiopathic SE
- Subsequent unprovoked seizure 30%
- Long-term mortality & morbidity was mostly related to
  - Acute insult to CNS
  - Complication
  - Underlying disease

Pitfall in Management of SE

- Delayed in diagnosis & initiation of treatment
- Frequently use multiple doses of BZDs (>2 doses)
- Delayed escalation to non-BZDs medications
- Delayed & inadequate maintenance dose of ASMs
- Do not treat underlying condition & cause

Take Home Message

- CSE is a time-sensitive emergency condition
- Underdosing of ASMs and delays initiation of Rx are associated with mortality
- Early transition from BZD to other ASMs help reduce treatment resistance in CSE
- Etiology is a primary predictor of long-term outcome


Thank You For Your Attention