Status epilepticus

Surachai Likasitwattanakul, M.D.
Department of Pediatrics
Faculty of Medicine Siriraj Hospital
Mahidol University, Thailand

Disclosure

- This lecture is sponsored by Eisai Thailand

Scope

- Definition/Classification
- Pathophysiology
- Treatment strategies

Introduction

- SE is a common neurological emergency
- Incidence 10-41 (adult) and 17-23 (children) : 100000
- Thai: adult 5.1:100000 (Tiamkao S, et al. Inter j Neuroscience 2014;124:416-20)
- 45-74% of SE is generalized convulsive SE
- Mortality 20% in adult and 0.9-3.6% in children (FSE)
- Up to 50% occurred in patients without epilepsy

Betjemann JP, Lowenstein DH. Lancet Neurol 2015;14(6):615–24. Chin RF, et al. Lancet 2006;368:222-9

DeLorenzo RJ, et al. J Clin Neurophysiol 1995;12(4):316–25. Dham BS, Hunter K, Rincon F. Neurocrit Care 2014;20(3):476–83.

Hesdorffer DC, et al. Neurology 1998;50(3):735–41. Sindarth, et al. Seizure 2019;71:328-332

Introduction

- The longer a seizure lasts, the less likely it is to stop seizure
  - Convulsive seizure that lasted > 5 min has a strong tendency to last > 30 minutes (point of non-compensating physiologic changes
- Treatment protocols should be targeted to stop seizure rapidly

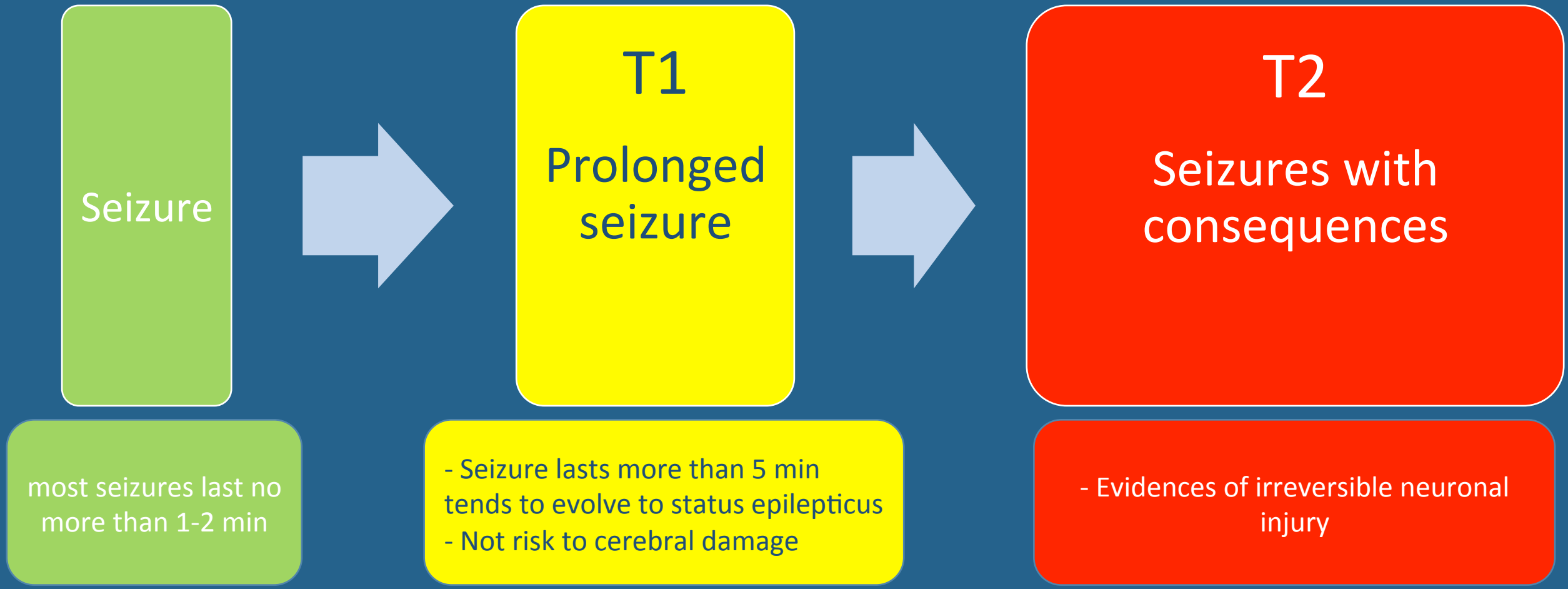
Goodkin HP, et al. J Neurosci 2005;25:5511-20
Sanchez Fernandez, Goodkin HP, Scott RC. Seizure 2018:
Eriksson K, et al. Neurology 2005;65:1316-1318

Definition of SE

- A failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to
- 1. Abnormally prolonged seizures (after time point t1).
- 2. Long-term consequences (after time point t2)
  - Neuronal death, neuronal injury, and alteration of neuronal networks

Trinka E, et al. Epilepsia 2015;56:1515-23

Progression of one seizure



Trinka E, et al. Epilepsia 2015;56:1515-23

Operation dimension with T1 and T2

Type of SE	T1	T2
Tonic-clonic SE	5 min	30 min
Focal SE with impaired consciousness	10 min	> 60 min
Absence SE	10-15 min*	Unknown

* Evidence for the time frame is currently limited

Trinka E, et al. Epilepsia 2015;56:1515-23

Classification

(A) with prominent motor symptoms

- Convulsive SE (GSE, Focal, unknown)
- Myoclonic SE (with or without coma)
- Focal motor SE (Jacksonian, EPC, Adversive, Oculoclonic, ictal paresis)
- Tonic SE
- Hyperkinetic SE

(B) without prominent motor symptoms (NCSE)

- NCSE with coma
- NCSE without coma
  - Generalized (absence, atypical absence, myoclonic absence)
  - Focal (without impairment of consciousness, aphasic status, with impaired consciousness)
  - Unknown (autonomic SE)

Trinka E, et al. Epilepsia 2015;56:1515-23

Nonconvulsive SE: Salzburg EEG consensus criteria

- Patients without known epileptic encephalopathy
  - ED > 2.5 Hz, or
  - ED ≤ 2.5 Hz or rhythmic delta/theta activity (>0.5 Hz) with 1 of the following
    - EEG and clinical improvement after IV AED or
    - Subtle clinical ictal phenomena or
    - Typical spatiotemporal evolution
- Patients with known epileptic encephalopathy
  - Increase inprominence of frequency when compared to baseline with observable change in clinical state
  - Improvement of clinical and EEG features with AEDs

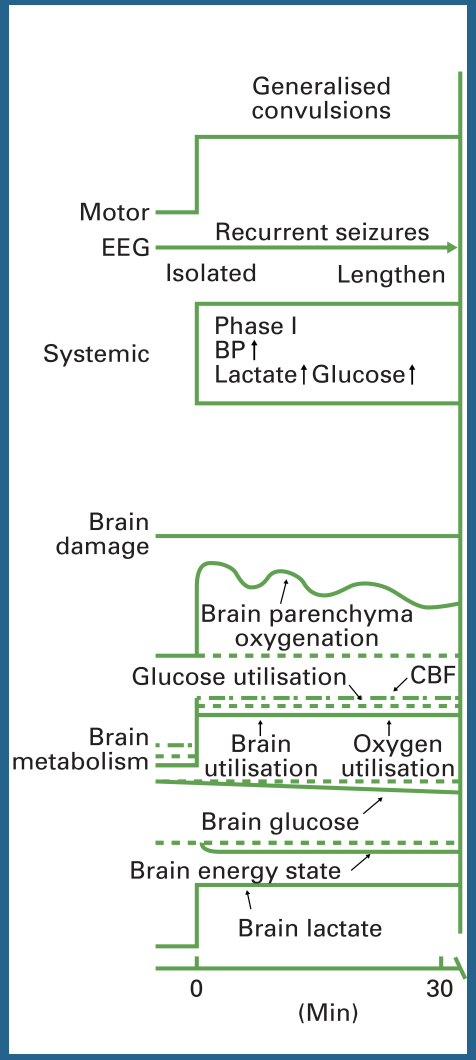
Trinka E, et al. Seizure 2017;44:65-73

Pathophysiology

- CSE is a dynamic process
- Clinical seizure:
  - overt CSE to subtle to NCSE
- EEG: changes of EEG
  - GSE to NCSE
- Body physiology:
  - compensatory to failure of compensatory mechanism
    - Hyperthermia, hypotension, hypoglycemia, acidosis

Sanchez Fernandez, Goodkin HP, Scott RC. Seizure 2018:

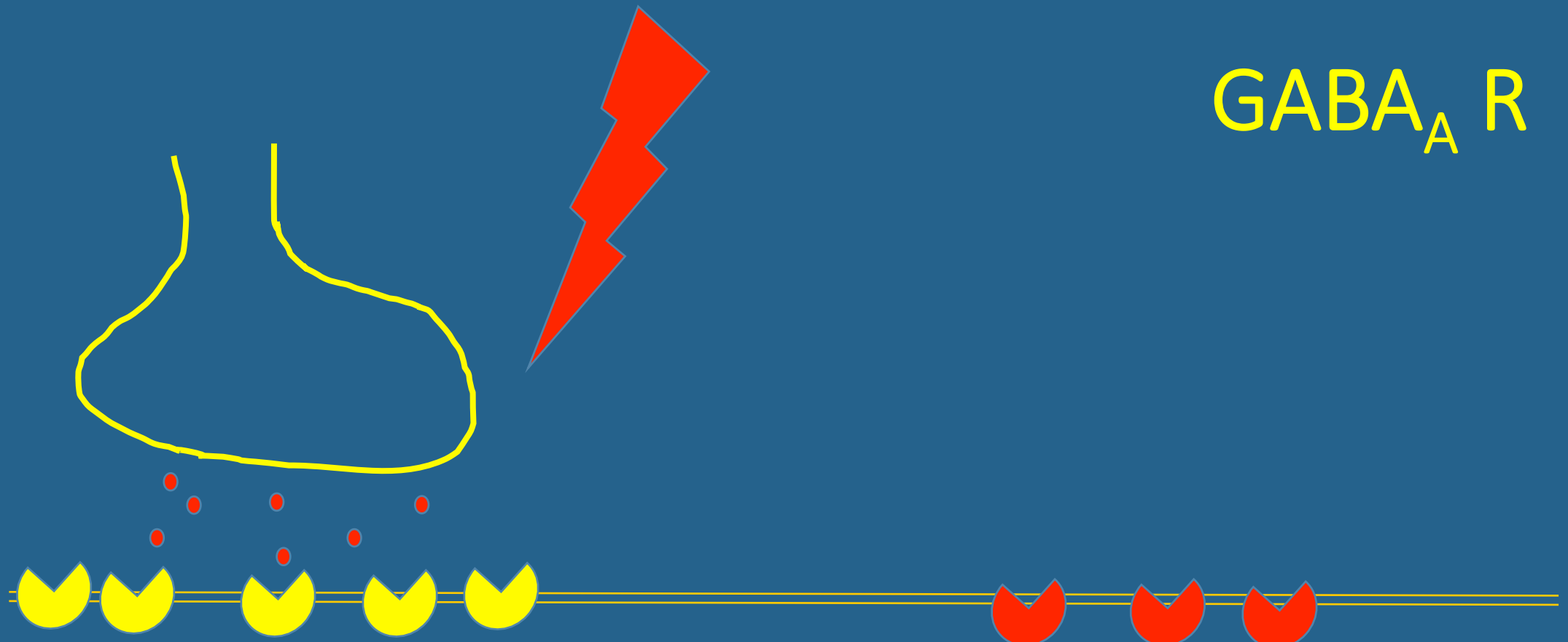
Physiology changes in status epilepticus



- Phase 1 Compensation
  - Physiologic changes to supply incrasing demand
- Phase 2 Decompensation
  - Failure of compensation result in altered cerebral and systemic metabolic pattern

Shorvon S. J Neuro Neurosurg Psychiatry 2001;70 (suppl I);ii22-ii27

$GABA_A$ R



Synaptic $GABA_A$ receptors

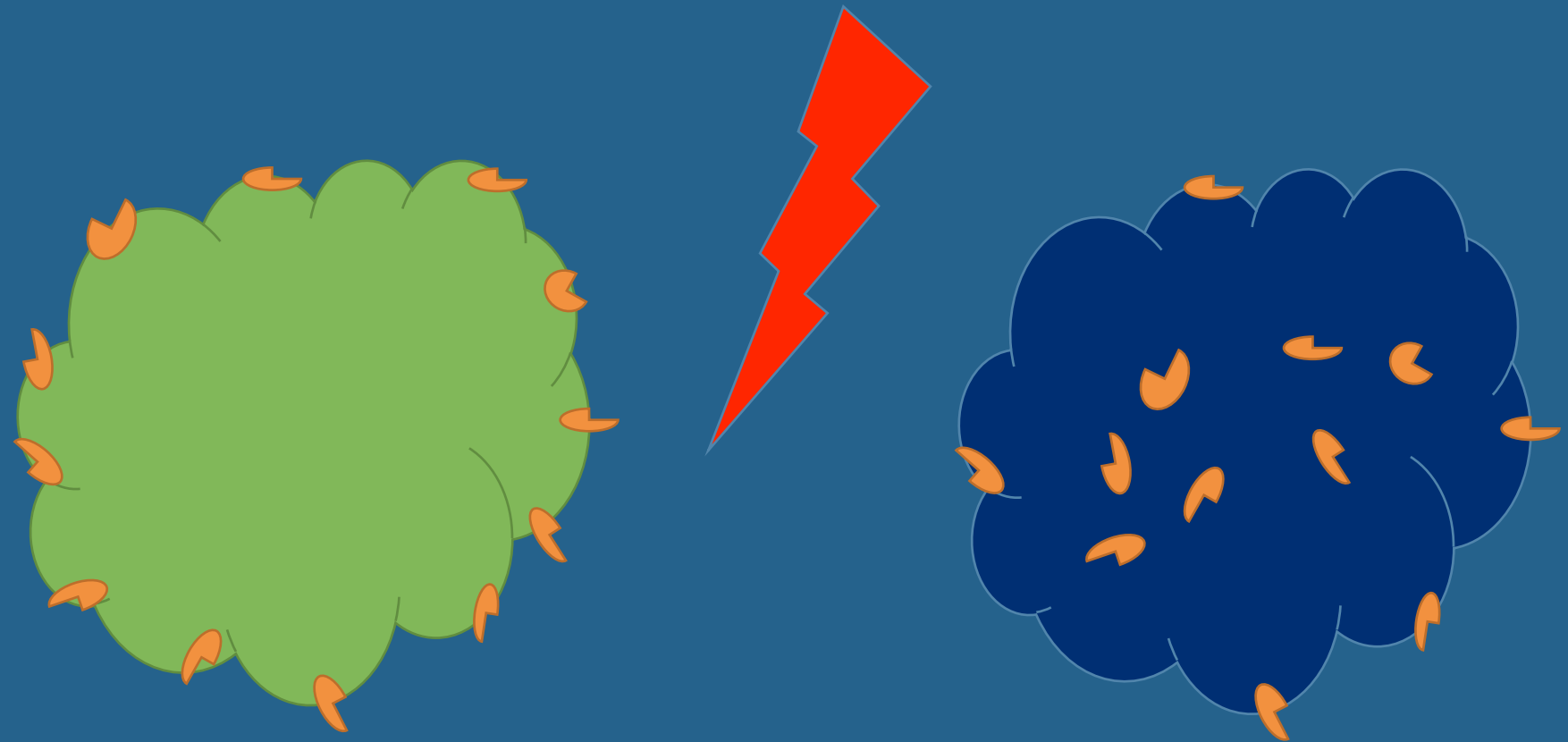
Extra-synaptic $GABA_A$ receptors

Augmentation of extra-synaptic $GABA_A$ R

Interanalization of $GABA_A$ R

Modified from Chuang SH, Reddy DS. J Pharmacol Exp Ther 2018;364:180-197

Redistribution of neurotransmitter in SE



$GABA_A$ R

NMDA R

AMPA R

Fernandez IS, et al. Seizure 2019;68:16-21

Receptor changes

- Internalization of synaptic $GABA_A$ receptor
  - Decrease by 50% of functional R/synapse in 1 hr. after SE
- NMDA R accumulate in the synapse
  - Increase in 38% of functional NMDA R/synapse in 1 hr. after SE
- Increase GluA2-lacking AMPA R in the membrane
- Tonic current augmentation of extra-synaptic $GABA_A$

Nalor DE, et al. J Neurosci 2005;25:7724
Leo A, et al. Epilepsia 2018;59:1098-1108
Chen JW, et al. Lancet Neuorol 2006:5:246-256
Sanchez Fernandez, Goodkin HP, Scott RC. Seizure 2018:

Brain pathology

- Cerebral hypoxia along with hyperthermia, hypotension, hypoglycemia, and acidosis contribute to CNS pathology
- Cortex, cerebellar and hippocampus
- HS is believed to be both cause and sequence of SE
- In NCSE, neuronal injury still occur but less severe

Scope

- Introduction
- Definition/Classification
- Pathophysiology
- **Treatment strategies**

Treatment strategies

1. Emergency medical management (ABC)
2. Terminate and prevent further seizure
   - Important predictor to other complications (ET, ICU, Deaths)
3. Find the cause
   - Important issues
   - In many cases, this is the key to control seizure
4. Prevent and treat complications

Emergency medical treatment

- ABC
- Initial labs (POCT, CBC, electrolyte, AED level, etc..)
- Rapid IV access
- AED

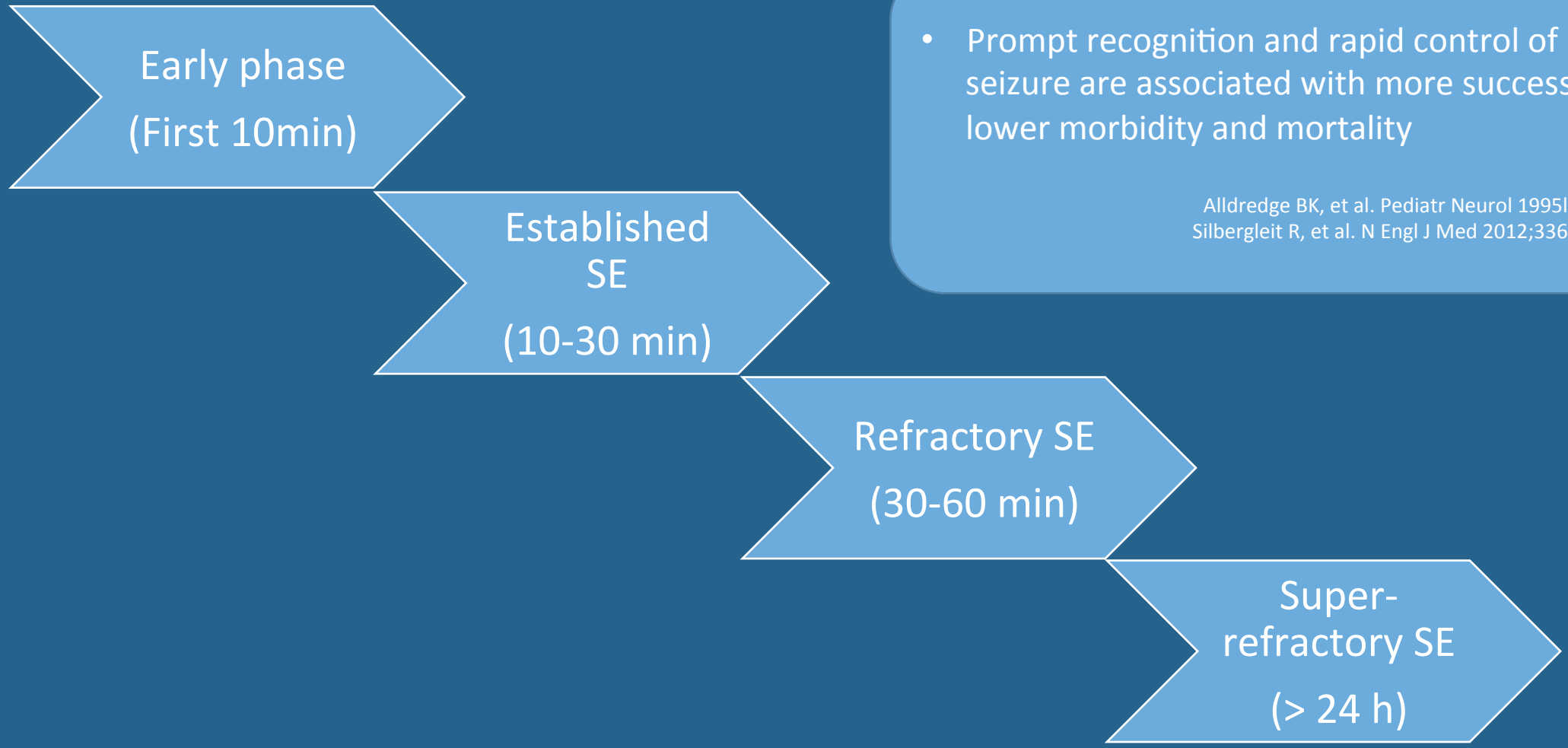
Treatment strategies

1. Emergency medical management (ABC)
2. **Terminate and prevent further seizure**
   - **Important predictor to other complications**
- 3. Find the cause
  - Important issues
  - In many cases, this is the key to control seizure
4. Prevent and treat complications

Ideal AEDs for SE

- Ease of administration
- Rapid onset of action
- Adequate but not prolonged duration of pharmacodynamic activity
- Broad spectrum
- Minimal side effects: CVS, CNS
- Useful as maintenance
- IV solution compatibility
- COST

Timeline-based treatment



- Prompt recognition and rapid control of seizure are associated with more success and lower morbidity and mortality

Alldredge BK, et al. Pediatr Neurol 1995l12:213-6
Silbergleit R, et al. N Engl J Med 2012;336:591-600

Early SE
(10 min)

- No IV : MDZ (IM/IN 0.2 mg/kg, Buccal 0.2-0.5mg, max 10 mg)
  : Rectal DZP 0.2-0.5 mg/kg, max 20 mg)
- IV : DZP (0.15-0.2 mg/kg, max 10 mg)

60%

Established
(10-30 min)

- IV FosPHT 20 mgPE/kg (max 1500 mgPE, repeat 5-10 mg/kg if needed)
- PHT 20 mg/kg (max 1500 mg, repeat 5-10 mg/kg if needed)
- IV LEV 30-60 mg/kg (max 4500 mg, repeat 30 mg/kg if needed
- IV VPA 20 mg/kg (max 3000 mg, repeat 20 mg/kg if needed, avoid in mitochondrial disease
- IV PHB 20 mg/kg (may repeat 5-10 mg/kg if needed)

40%

Refractory SE
(> 30 min or refractory to BZD and 1st line AED)

- Admit ICU with EEG monitor with BS or seizure suppression EEG
- Midazolam 0.2 mg/kg bolus followed by 0.1-2 mg/kg/h
- Pentobarbital 5-15 mg/kg bolus followed by 0.5-5 mg/kg/h
- Thiopental 2-7 mg/kg bolus followed by 0.5-5 mg/kg/h
- Propofol 1-2 mg/kg bolus followed by 2-12 mg/kg/h
- Ketamine 1.54.5 mg/kg bolus followed by 2.75-5 mg/kg/h

30-40%
of Established SE

Singh A, Strendy CM, Loddenkepmper T. CNS Drugs 2020;34:47-63
Hocker S. Epilepsia 2018: 59(S2):188-192

Early SE (10 min)

- IV DZP (0.15-0.2 mg/kg, max 10 mg)
- No IV Rectal DZP 0.2-0.5 mg/kg, max 20 mg)
  MDZ (IM/IN 0.2 mg/kg, Buccal 0.2-0.5mg, max 10 mg)

Repeat **ONCE** after 5-10 min.

Singh A, Strendy CM, Loddenkepmper T. CNS Drugs 2020;34:47-63
Hocker S. Epilepsia 2018: 59(S2):188-192

Drug	Pharmacokinetic	Effects	Route	Side effects
DZP	- Highly lipid soluble	- Rapid onset - Fast redistribution - Anticonvulsant effect 15-30 min	- IV - Rectal	- 40% propylene glycol and 10% ethanol - thrombophlebitis
LZP	- Less lipid soluble than DZP	- Less rapid redistribution - Anticonvulsant effect 6-12 h	- IV - Rectal	** Need refrigerated
Midazolam	*water soluble	- Ultra-short half-life - Need continuous infusion	- IV - IM - IN, buccal	- No PPG

Route

- IV access available
  - IV diazepam ≈ IV lorazepam

Chamberlain JM, et al. JAMA 2014;311:1652-60

- Non-IV access
  - IM and IN midazolam are efficacious
  - Rectal diazepam is also effective but less socially acceptable

Arya R, et al. Neurology 2015;85:1859-68

Brigo F, et al. Epilepsy Behav 2015;49:325-36

Cautions & Pitfalls

Timing

- Given early is associated with good response
- Potency decrease 20-fold over 30 min of SE (GABA internalization)

Pitfalls

- Dosage
  - Suboptimal dose (20-70%) has less efficacy
  - Irrespective of initial BZD dose, respiratory failure increase after > 2 dose
- Accumulation dose
  - More than 2 doses (25-50%) was associated with
    - Respiratory compromised 43% VS 13%
    - Third dose of BZP resulted in seizure termination in 13%

Hill CE, et al. Ann Neurol 2017;82:155-65
Siefkes HM, et al. Pediatrics 2016;
Seinfeld S, et al. Epilepsia 2014;55:388-95
Tirupathi S, et al. Seizure 2015;75:1499

Established SE

Established SE
(10-30 min)

- IV FosPHT 20 mg/kg (max 1500 mgPE, repeat 5-10 mg/kg if needed
- PHT 20 mgPE/kg (max 1500 mg, repeat 5-10 mg/kg if needed)
- IV LEV 30-60 mg/kg (max 4500 mg, repeat 30 mg/kg if needed
- IV VPA 20 mg/kg (max 3000 mg, repeat 20 mg/kg if needed, avoid in mt. disease)
- IV PHB 20 mg/kg (may repeat 5-10 mg/kg if needed)

Singh A, Strendy CM, Loddenkepmper T. CNS Drugs 2020;34:47-63
Hocker S. Epilepsia 2018: 59(S2):188-192

2nd line Therapy

- 40% of patients with CSE reach this stage
- AES: 2nd line AED should be given when
  - Fail BZD has failed and
  - Duration > 20 min
- Other
  - If seizure > 10 min (preceded by BZD)

	Dose	Rate	Advantage
Phyenytoin (Fosphenytoin)	15-20 mg/kg	1 mg/kg/min	- Broad spectrum - Widely available
fosphenytoin	15-20 mgPE/kg	2 mgPE/kg/min	- Less side effects
Valproate	20-40 mg/kg	5-10 mg/kg/min	- Broad spectrum AED
Levetiracetam	40-60 mg/kg	6-8 mg/kg/min	- Minimum drug interaction
Phenobarbital	20 mg/kg	1-2 mg/kg/min	- High rate of success

Drug	Pharmacokinetic	Route	Effects
PHT	- High pH 12 - Insoluble in water - 40% propylene glycol and 10% ethanol	- IV (sugar free) - Slow infusion	- Risk of thrombophlebitis - Purple-glove syndrome - Hypotension and cardiac arrhythmia
Fos-PHT	- Aqueous form - pH 8.6-9 - Conversion rate not affected by age, hepatic or other drug	- IV - IM	- Level attained in 10-30 min after infusion (150 - <100 mg PE/min) - Peak 30 min IV or 3 hr IM - Fewer local adverse side effects - Hypotension and cardiac arrhythmia
VPA	- Liver metabolize - Hepatic failure	- IV	- Contraindicate in liver or patients with inborn error of metabolism - Broad spectrum AED
LEV	- Metabolized through hydrolysis - NOT cytochrome - Renal excretion	- IV	- No known drug interaction
PHB	- High alkaline - Less lipid soluble than DZP - Prolonged half-life	- IV	- Prolonged sedation, respiratory depression - Hypotension, immune dysregulation

Meta-analysis of 2nd AED in BZD-resistant SE

- VPA 75.7%
- PHB 73.6%
- LEV 68.5%
- PHT (fosPHT) 50.2%

Yasiry Z, Shorvon SD. Seizure 2014;23:167-75

Prospective clinical trials for 2nd AED in CSE

- EcLiPSE (LEV VS PHT for 2nd-line treatment of paediatric convulsive status epilepticus)
- ConSEPT (LEV VS PHT for 2nd –line treatment of convulsive status epilepticus in children)
- **ESETT** (Established Status Epilepticus Treatment Trial)
- **ESETT** with more children recruited

EcLiPSE (LEV VS PHT for second-line treatment of paediatric convulsive status epilepticus)

- Open-label, randomized clinical trial
- Child 6mo. – 18 yr. with CSE requiring 2nd treatment
- LEV: 40 mg/kg over 5 min
- PHT: 20 mg/kg over at least 20 min
- Primary endpoint
  - Time from randomization to cessation of CSE
- Of 1432 patients, 286 were included in the study (including patients taking PHT or LEV)

Lyttle MD, et al. Lancet 2019;393:2125-34

286 patients

EcLiPSE (LEV VS PHT for second-line treatment of paediatric convusive status epilepticus)

LEV (152)

- Cessation rate
  - 70%
- Median time from random to seizure cessation
  - 35 min
  - IQR 20
- Received additional drugs
  - 38%
- Any side effect
  - 12% (including hypotension)

PHT (134)

- Cessation rate
  - 64%
- Median time from random to seizure cessation
  - 45 min
  - IQR 24
- Received additional drugs
  - 37%
- Any side effect
  - 14% (including hypotension, 1/2 serious)

Lyttle MD, et al. Lancet 2019;393:2125-34

- LEV is not superior to PHT in term of
  - Cessation rate
  - Time taken to terminate convulsion
  - Adverse side effects
  - ****
  - Ease of administration

ConSEPT (LEV VS PHT for 2nd –line treatment of convulsive status epilepticus in children)

- Open-label clinical trial
- Child 3 mo. – 6 yr with CSE who failed 1st-line BZP
- LEV: 40 mg/kg over 5 min
- PHT: 20 mg/kg over 20 min
- LEV followed PHT or PHT followed LEV, if seizure continued
- Primary endpoint
  - Clinical cessation of seizure activity 5 min after the complete infusion
- Of 639 patients, 233 were enrolled (excluding patients taking PHT or LEV)

Dalziel SR, et al. Lancet 2019;393:2135-45

233 patients

ConSEPT (LEV VS PHT for 2nd –line treatment of convulsive status epilepticus in children)

PHT (114)

- Cessation rate after 5 min.
  - 60%
- Maintain seizure control at 2 h
  - 54%
- Received alternate study drug in first 2 h
  - 37%
- Cessation rate after one or both AED
  - 78%

LEV (119)

- Cessation rate after 5 min.
  - 50%
- Maintain seizure control at 2 hr.
  - 51%
- Received alternate study drug in first 2 h
  - 40%
- Cessation rate after one or both AED
  - 72%

Dalziel SR, et al. Lancet 2019;393:2135-45

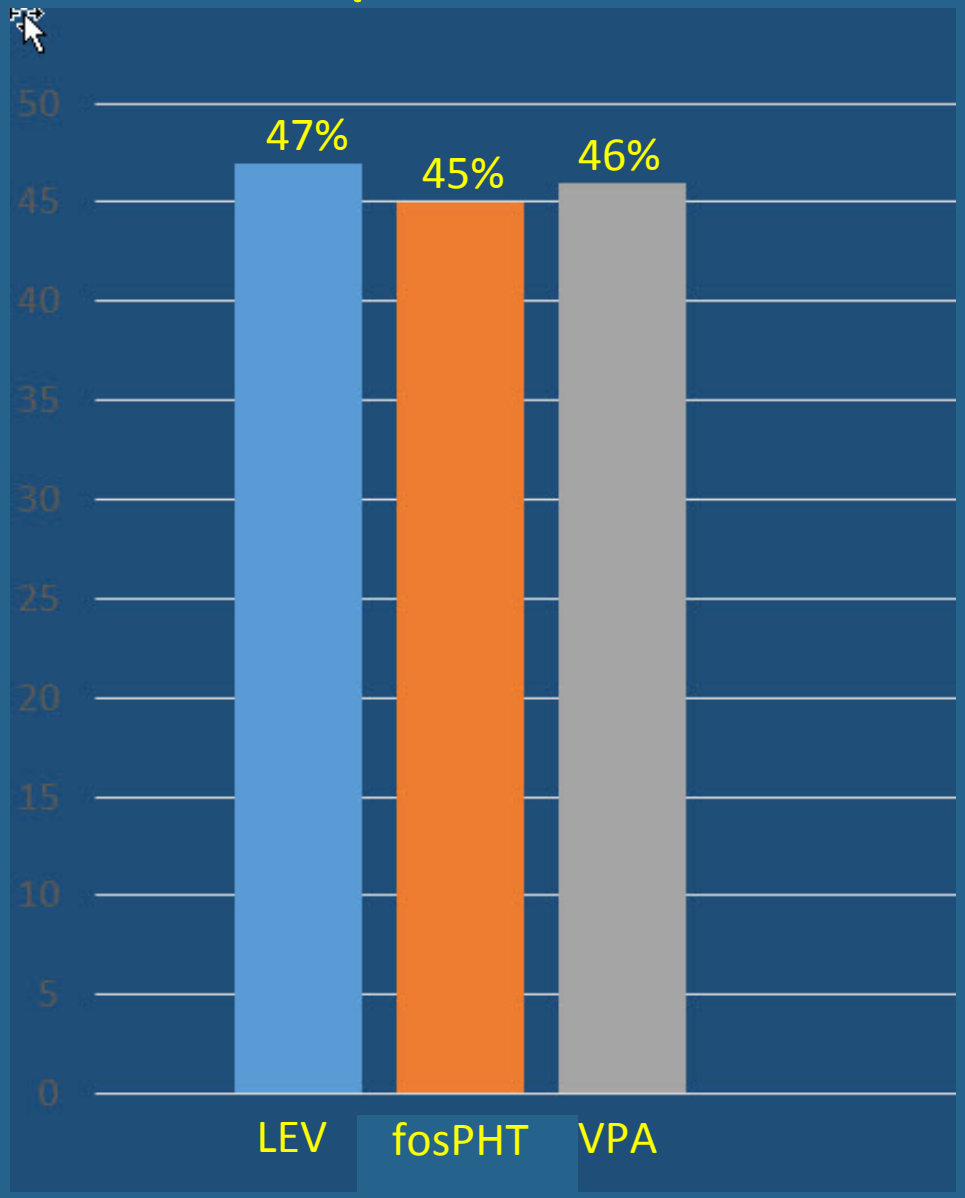
- LEV is not superior to PHT in term of
  - Cessation rate
  - Adverse side effects
  - Alternate AED reduce failure rate > 50%
  - ****
  - Sequential use of PHT and LEV should be considered before moving to anesthetic drug

ESETT (Established Status Epilepticus Treatment Trial)

- Randomized, blinded, adaptive trial
- Child > 2 yr with accepted BZP dose, with convulsion > 5 min and continue to have after BZP dose
- Assigned to infuse AED in 10 min
- LEV: 60 mg/kg (max 4500 mg)
- fPHT: 20 mgPE/kg (max 1500 mg)
- VPA: 40 mg./kg (max 3000 mg)
- Primary endpoint
  - Absence of clinically apparent seizure and improve in LOC at 60 min after the start of infusion
- 384 were enrolled (LEV, fosPHT, VPA in 145, 118, 121 respectively)

Kapur J, et al. N Engl J Med 2019;381:2103-13

ESETT (Established Status Epilepticus Treatment Trial)



- Three drugs are successful in ~ 50%
- Similar incidence of adverse events
- In numbers
  - fosPHT: hypotension, intubation
  - LEV: deaths

Kapur J, et al. N Engl J Med 2019;381:2103-13

ESETT-

- More children enrollment (76 children VS 2 adults)
- Compare effectiveness and safety among age groups
  - Child (<18 yr.) : 225
  - Adult (18-65 yr.) : 186
  - Older adult (>65 yr.) : 51
- 38% with LEV, 31% for fosPHT and VPA each

Chamberlain JM, et al. Lancet 2020;395:1217-1224

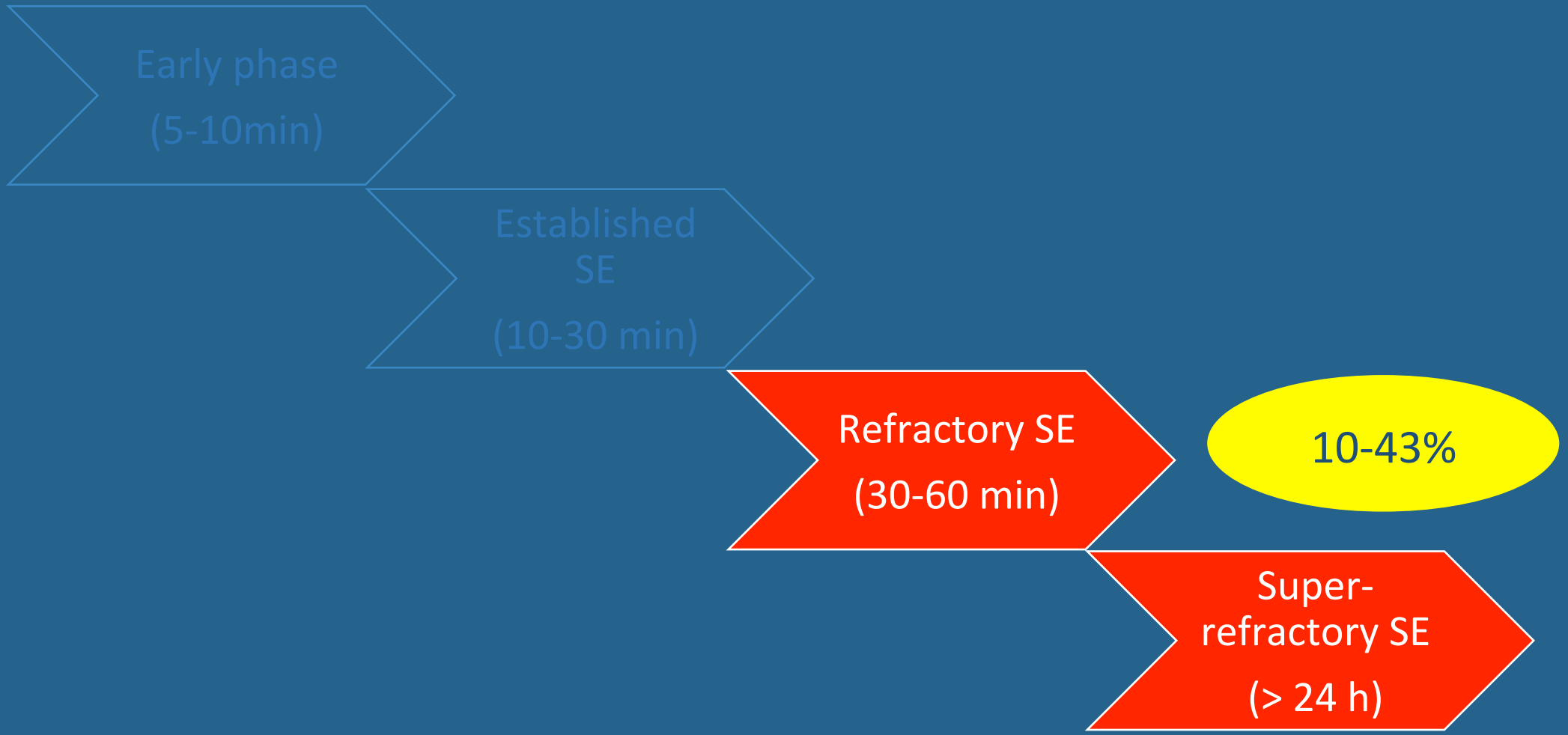
Response rate

	LEV (%, 95% CI)	fosPHT (%, 95% CI)	VPA (%, 95% CI)
Child	52% (41–62)	49% (38–61)	52% (41–63)
Adult	44% (33–55)	46% (34–59)	46% (34–58)
Older adult	37% (19–59)	35% (17–59)	47% (25–70)

- ≈ half of the patients respond to LEV, fosPHT, VPA
- No different in effectiveness and safety among age groups
- Hypotension and ET tube was higher in fosPHT group

Chamberlain JM, et al. Lancet 2020;395:1217-1224

Timeline-based treatment



RSE and SRSE

- RSE occur in 10-43% of all cases of SE
- Risks:
  - Lower level of consciousness
  - New diagnosis of epilepsy
  - Focal seizure
  - NCSE

Nelson SE, Varelas PN. Continuum 2018;24:1683-1707

Definition

- RSE
  - No consensus in terms of
    - Number of drugs (BZD+1/2/3 AEDS)
    - Duration of seizure (none, 1/2/3 hr.)

Hocker S, et al. Curr neurol Neurosci Rep 2014;14:452

RSE

- Ongoing seizures despite two appropriately selected and dosed antiepileptic drugs (AEDs) including a benzodiazepine.

Hocker S, et al. Curr neurol Neurosci Rep 2014;14:452

SRSE

- continuous or recurrent seizures lasting 24 h or more following initiation of anesthetic medications, including cases in which seizure control is attained after induction of anesthetic drugs but recurs on weaning the patient off the anesthetic agent

Shorvon S, Ferlisi M. Brain 2011;134:2802-18

When should IV anesthesia be used?

- Mortality rate of 16-43.5%
- Choices
  - Additional bolus of 2nd-line AED
  - Continuous infusions of anesthetic agents
  - **NO CLEAR guidelines for how to choose between 2 options
- Best practice: when seizures fail to response to BZP and 2nd AED
- In practice, however, IV anesthesia if often administered after the 3rd AED

Holtkamp M, et al. J Neurol neurosurg Psychiatry 2003;263:799-806

Others AEDs

- Topiramate
- Lacosamide
- Perampanel
- Brivaracetam
- Clobazam

Allen B, Vespa PM. Curr Opin Crit Care 2019;25:117-125

Topiramate

- Cohort study of 106 patients
- TPM after failing other AED, median 5 AED
- Loading 25-500 mg (median 100 mg)
- Overall success 29/106 (27.4%)
  - RSE 31.8% VS 20% in SRSE
- Other studies success rate 0-100%

Fechner A, et al. Epilepsia 2019;60:2448-2458

- Pediatric dose 2-25 mg/kg/d (most 5-10)

Shelton SM, et al. J Pediatr Pharmacol Ther 2014;19:317-324

- 10 mg/kg/day for 2 days then 5 mg/kg/day

Perry MS, et al. Epilepsia 2006;47:1070-1071

Lacosamide: systematic review

- 552 (486 adults and 36 children)
- Adult: 200-400 mg IV
- Child: 4-10 mg/kg (mean 8 mg/kg)
- Overall success 57% (both CSE and NCSE)
- Better success in focal motor SE (92%)
- SE: dizziness, abnormal vision, diplopia, ataxia

Strzelczyk A, et al. Epilepsia 2017;58:933-950

Perampanel

- 52/1319 patients with SE received PER
- Used post BZD, and median of 5 AED … SRSE
- Median dose 6 mg to 10 mg/day (max)
- Via Oral or NG tube
- Response in 19/52 (36.5%)

Strzelczyk A, et al. Acta Neurol Scan 2019;139:369-376

PER in RSE and SRSE

- Retrospective study 30 patients
- Success in 5/30 (17%)
- High dose (16-32, median 24) 14, 2/5 success
- Standard dose 16 (2-12)
- Time to response 6-72 hr.
- High dose does not have significant CVS or lab changes

Rohracher A, et al. Epilepsia 2018;59(S2):234-242

IV anesthesia

- Propofol
- Midazolam
- Barbiturates: thiopental, pentobarbital
- Ketamine

RSE & SRSE

Refractory SE

(> 30 min or refractory to BZD and 1st line AED)

- Admit ICU with EEG monitor with BS or seizure suppression EEG
- Midazolam 0.2 mg/kg bolus followed by 0.1-2 mg/kg/h
- Pentobarbital 5-15 mg/kg bolus followed by 0.5-5 mg/kg/h
- Thiopental 2-7 mg/kg bolus followed by 0.5-5 mg/kg/h
- Propofol 1-2 mg/kg bolus followed by 2-12 mg/kg/h
- Ketamine 1.5-4.5 mg/kg bolus followed by 2.75-5 mg/kg/h

Singh A, Strendy CM, Loddenkepmper T. CNS Drugs 2020;34:47-63
Hocker S. Epilepsia 2018: 59(S2):188-192

Anesthetic agents: site of action

- $GABA_A$:
  - Propofol (extrasynaptic $GABA_A$ R)
  - Midazolam
  - Barbiturates
- NMDA R
  - Ketamine (may increase potency of BZP)
  - Nitrous oxide
  - Xenon

Prisco L, Ganau M, Aurangzeb S, et al. Seizure 2020;75:153-164

Indication

SE type	Indication of IV anesthesia
GCSE	Failure of a BZP + 1 additional AED
NCSE in coma	Failure of a BZP + 2 additional AED
Focal motor or focal NCSE (with consciousness impairment)	Failure of a BZP + ≥2 additional AED
Epilepsia partialis continua	Consider in patients with a good prognosis if functionally limiting or painful and refractory to BZP + ≥2 additional AED
Absence status epilepticus	Not indicated

Hocker S. Epilepsia 2018: 59(S2):188-192

Drug	Bolus	Maintenance
Midazolam	0.2 mg/kg	0.1-2 mg/kg/h
Propofol	1-2 mg/kg	2-12 mg/kg/h
Pentobarbital	5-15 mg/kg	0.5-5 mg/kg/h
Thiopental	2-7 mg/kg	0.5-5 mg/kg/h
Ketamine	1.5-4.5 mg/kg	2.75-5 mg/kg/h

Hocker S. Epilepsia 2018: 59(S2):188-192

Drug (diluents)	Mechanism	Metabolism	Advantage	Adverse reaction
Midazolam	$GABA_A$ agonist	Hepatic	- Fast onset (1-5 min) - Short T1/2 (1-6 hr.) - (increase with prolonged use)	- Hypotension - Respiratory depression - Tachyphylaxis with prolonged use
Propofol (lipid emulsion)	$GABA_A$ agonist	Hepatic	- Ultrafast - Rapid clearance (increase with prolonged use)	- Hypotension - Hypertriglyceridemia - PRIS - Contraindicate in mitochondrial disease/ relative in children
Pentobarbital (propylene glycol)	$GABA_A$ agonist	Hepatic	- Higher success rate - Decrease break through seizure	- Hypotension - CVS and Res. depression - Immune suppression - Decrease core body temp. - Hepatic dysfunction
Ketamine	- NMDA R antagonist - *extrasynaptic $GABA_A$ R agonist	Hepatic	- Alternating mechanism - Rapid onset	- Hypertension - Hallucination

Rezink ME, Berger K, Claassen J. J Clin Med 2016;54
Cook AM. CCSAP, Book 3. 2017: p 7-26
Singh A, Stredny CM, Loddenkemper T. CNS Drugs 2020;34:47-63
Wang SD, et al. Anesthesiology 2017;126:666-677

Monitor

- EEG monitoring is very useful in RSE/SRSE patients
- Impact clinical care
- Change in treatment strategies
  - Start-change-discontinuation of drugs

Kilbride RD. Arch Neurol 2009;66:723-28

How deep and how long of barbiturate coma

- All should have EEG
- Level of EEG:
  - burst-suppression VS complete suppression?
  - Deeper suppression was associated with fewer relapse
  - Not necessarily to control all epileptiform discharges as isolated epileptiform d/c did not correlate with recurrence
- How long:
  - Most recommend 24-48 hr.
  - But more prolonged (>96 hr.) was with less likely to relapse

Endpoint of treatment

- **Burst-suppression**
  - reduction in cerebral metabolic activity,
  - often with sustained termination of seizure activity
  - With propofol, thiopental
  - Not differ in mortality and functional outcomes
- **Seizure suppression**
  - With midazolam

Meierkord H. et al. Eur J Neurol 2010;17:1671-97
Claassen J, et al. Epilepsia 2002;43:146-53

Causes of SE

Acute causes

- Stroke
- Trauma
- HIE
- Infection (CNS, sepsis)
- CNS inflammation
- Toxic/metabolic
- Drug/substance withdrawal
- Idiopathic

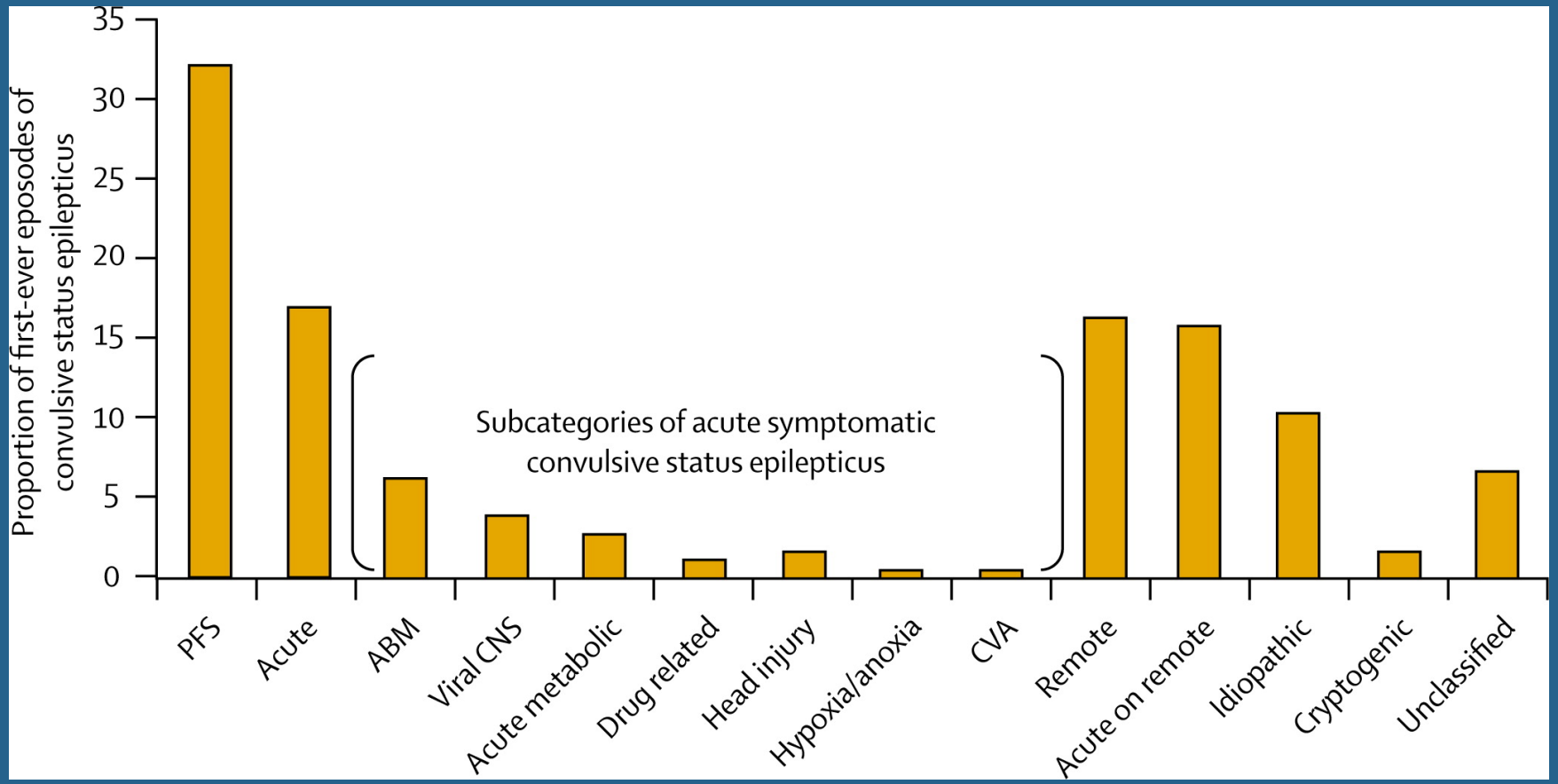
Chronic causes

- Epilepsy
- Brain tumor
- Previous brain insult

- Febrile seizure status
- IEM

Nelson SE, Varelas PN. Continuum 2018;24:1683-1707

Cause of SE



Chin RF, et al. Lancet 368:222–229

Treatment strategies

1. Emergency medical management (ABC)
2. Terminate and prevent further seizure
   - Important predictor to other complications
- **3. Find the cause**
  - **Important issues**
  - **In many cases, this is the key to control seizure**
4. Prevent and treat complications

Causes of SE

Acute causes

- Stroke
- Trauma
- HIE
- Infection (CNS, sepsis)
- **CNS inflammation**
- Toxic/metabolic
- Drug/substance withdrawal
- Idiopathic

Chronic causes

- Epilepsy
- Brain tumor
- Previous brain insult

Nelson SE, Varelas PN. Continuum 2018;24:1683-1707

Inflammatory process

- Inflammatory process (infectious and autoimmune) are the cause of SE in 6-12%

Lin CH, et al. Front Neuro 2019;10

Shin JW, et al. J Neuroimmunol. 2018 315:1–8.

Spatola M, et al. Neurology 2015 85:464–70

- Patient with psychosis, NCSE, and SRSE were more common in autoimmune than infectious cause

Lin CH, et al. Front Neuro 2019;10

Definition

NORSE (new onset refractory SE)

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

FIRES (febrile infection-related epilepsy syndrome)

- a subcategory of NORSE that requires a prior febrile infection, with fever starting between 2 weeks and 24 hours prior to onset of refractory status epilepticus, with or without fever at onset of status epilepticus

Hirsch LJ, et al. Epilepsia 2018;59:739-744

NORSE and FIRES

- NORSE and FIRES are clinical presentations rather than a specific diagnosis
  - Viral infection
  - Autoimmune encephalitis
  - Others
- FIRES is a subtype of NORSE

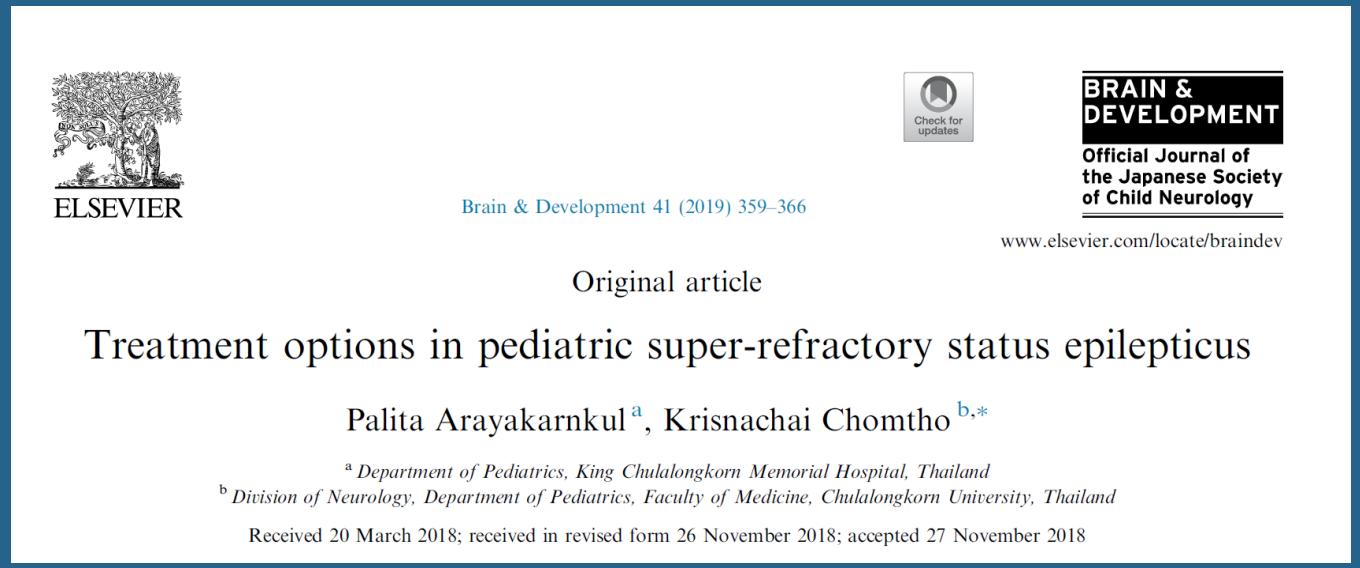
Hirsch LJ, et al. Epilepsia 2018;59:739-744
Gaspard N, et al. Epilepsia 2018;59:745-752

Treatment options

	Cryptogenic FIRES	Cryptogenic NORSE
Steroid (methylprednisolone)	11/63 (17%)	15/40 (38%)
IVIG	5/94 (5%)	5/17 (30%)
KD	19/35 (54%)	8/12 (67%)
PE	2/11 (11%)	6/15 (40)

- Other treatment; hypothermia, Rituximab, Cannabis,

Gaspard N, et el. Epilepsia 2018;59:745-52



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Original article

Treatment options in pediatric super-refractory status epilepticus

Palita Arayakarnkul [a], Krisnachai Chomtho [b,*]

[a] *Department of Pediatrics, King Chulalongkorn Memorial Hospital, Thailand*
[b] *Division of Neurology, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Thailand*

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- 17 patients: 30% each with autoimmune encephalitis, epilepsy
- Anesthetic: midazolam (94%), propofol (53%)
- Immunological (77%)
- Ketogenic diet (77%)
- B6/PLP (70%)
- Mortality rate 17.6%

Arayakarnkul P, Chomtho K. Brain & Devel 2019;41:359-366

Summary

- Status epilepticus is a true neurologic emergency
- Time is brain, a stepwise and clear plan should be made in order to stop seizure ASAP
- Dose and frequency of AED should be strictly followed
- Prompt recognition and early seizure termination are the key success
- Beware of some treatable cause such as CNS infection/inflammation, IEM

Thank You