Management of acute seizure and status epilepticus

พญ. ขวัญรัตน์ หวังผลพัฒนศิริ พบ.วว ประสาทวิทยา

หน่วยประสาทวิทยา สถาบันประสาทวิทยา

Outline

- Type of Status epilepticus
- Definition of status epilepticus, convulsive
- Pathophysiology of SE
- Management of SE
- Serious drug adverse events in SE

Types of Status epilepticus

- Convulsive SE*
- *Non-convulsive SE*

  NCSE with Coma → suble SE

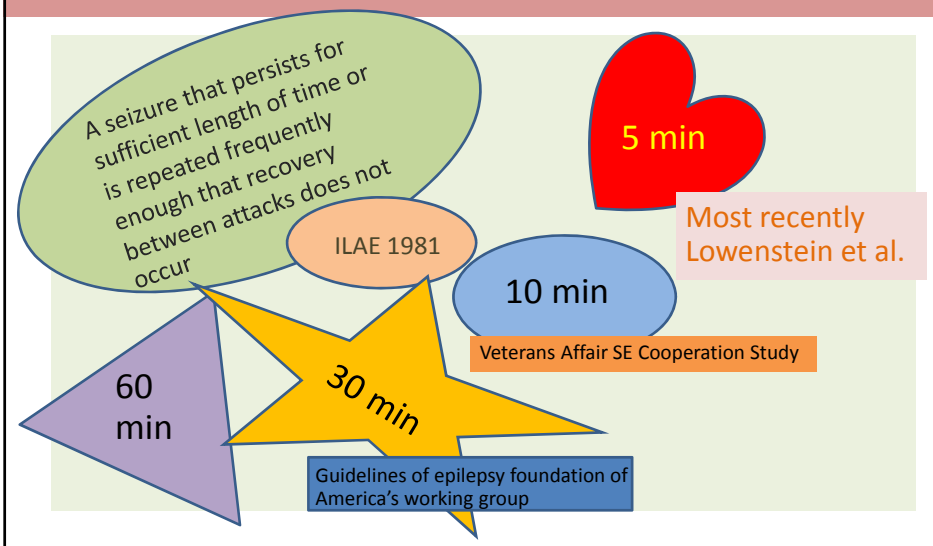
  NCSE with normal consciousness

  - Focal SE , EPC(epilepsia partialis continua)

  - Focal SE with dyscognitive feature

  - Generalized : Absence SE

Definition of Status epilepticus ?



SE Definition?

- Never truly fixed
- Not easily translated into clinical trials or into everyday practice
- " animal research'' shows

- repetitive seizures become self-sustaining and pharmaco-resistant within 15-30 min
- Neuronal injury

Epilepsia, 56(10):1515–1523, 2015

Conceptual definition of SE

- SE is 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 which can *have long-term consequences*(after time point t2) including neuronal death, neuronal injury and alteration of neuronal networks depending on the type and duration of seizures

Epilepsia, 56(10):1515–1523, 2015

Conceptual definition SE(cont.)

2 operational dimensions

- ✓ Length of seizure and the time point(t1) beyond which the seizure should be regarded as “continuous seizure activity”
- ✓ The second time point(t2) is the time of ongoing seizure activity after which there is a risk of long-term consequences
- ❖ Convulsive SE :t1 at 5 min, t2 at 30 min based on animal studies and clinical research

Epilepsia, 56(10):1515–1523, 2015

Conceptual definition SE(cont.)

- Time point t1 indicates when the patients should be treated as having SE,

  *even if not all patients are in established SE
- Time point t2 indicates when long term consequences** may appear

  **neuronal injury and time-dependent development of pharmaco-resistance

Epilepsia, 56(10):1515–1523, 2015

Operational dimentions time T1 T2 in Status epilepticus

Table 1. Operational dimensions with t_1 indicating the time that emergency treatment of SE should be started and t_2 indicating the time at which long-term consequences may be expected

Type of SE	Operational dimension 1 Time (t_1), when a seizure is likely to be prolonged leading to continuous seizure activity	Operational dimension 2 Time (t_2), when a seizure may cause long term consequences (including neuronal injury, neuronal death, alteration of neuronal networks and functional deficits)
Tonic–clonic SE	5 min	30 min
Focal SE with impaired consciousness	10 min	>60 min
Absence status epilepticus	10–15 min[a]	Unknown

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

Epilepsia, 56(10):1515-23,2015

Operational definition SE(cont.)

- Mean duration of generalized convulsion seizures in adults ranges from52.9-62.2 s
  and 59.9 s for electroencephalographic changes

  Epilepsia1992;33:68
- More than 40% of seizures lasting from 10-29 min stopped spontaneously without treatment, overall mortality was 2.6% versus 19% for SE lasting over 30 min($p<0.001$)

  Epilepsia 1999;40:164-69

Operational definition SE(cont.)

Generalized convulsive SE in adults and children older than 5 years was operationally defined as

"… ≥ 5min of (1) continuous seizure or (2) 2 or more discrete seizures between which there is incomplete recovery of consciousness"

Epilepsia ,56(10):1515-1523.2015

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

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

Epilepsia, 56(10):1515–1523, 2015

Classification of SE : 4 axes

1. Seizure semiology
2. Etiology
3. EEG correlates
4. Age

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

Terminology to describe EEG patterns in SE
1. Location
2. Name of the pattern
3. Morphology
4. Time-related features
5. Modulation
6. Effect of intervention (med) on EEG

Table 4. Etiology of status epilepticus

Known (i.e., symptomatic)
- Acute (e.g., stroke, intoxication, malaria, encephalitis, etc.)
- Remote (e.g., posttraumatic, postencephalitic, poststroke, etc.)
- Progressive (e.g., brain tumor, Lafora's disease and other PMEs, dementias)
- SE in defined electroclinical syndromes

Unknown (i.e., cryptogenic)

Table 5. SE in selected electroclinical syndromes according to age

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

SE occurring mainly in childhood and adolescence
- Autonomic SE in early-onset benign childhood occipital epilepsy (Panayiotopoulos syndrome)
- NCSE in specific childhood epilepsy syndromes and etiologies (e.g., Ring chromosome 20 and other karyotype abnormalities, Angelman syndrome, epilepsy with myoclonic-atonic seizures, other childhood myoclonic encephalopathies; see Appendices 1–3)
- Tonic status in Lennox-Gastaut syndrome
- Myoclonic status in progressive myoclonus epilepsies
- Electrical status epilepticus in slow wave sleep (ESES)
- Aphasic status in Landau-Kleffner syndrome

SE occurring mainly in adolescence and adulthood
- Myoclonic status in juvenile myoclonic epilepsy
- Absence status in juvenile absence epilepsy
- Myoclonic status in Down syndrome

SE occurring mainly in the elderly
- Myoclonic status in Alzheimer's disease
- Nonconvulsive status epilepticus in Creutzfeldt-Jakob disease
- De novo (or relapsing) absence status of later life

These forms of SE may be encountered prevalently in some age groups, but not exclusively.

Epidemiology

- Annual incidence 10-41/100,000 (US)(all forms)
  - 27/100,000 per year for young adult
  - 86/100,000 per year for elderly **
- Overall mortality associated with SE is 20%
  - GCSE presenting about 45-74% of all cases
  - Mortality 14% for young adult(16-59 yrs) and 38% for elderly (>60 yrs)

Lancet neurol2015;14:615-24
Lancet neurol2006;5:246-56

Etiologies of SE in adults

	Frequency (%)	Mortality (%)
Acute		
Stroke	22%	33%
Metabolic abnormalities	15%	30%
Hypoxia	13%	53%
Systemic infection	7%	10%
Anoxia	5%	71%
Trauma	3%	25%
Drug overdose	3%	25%
CNS infection	3%	0%
CNS haemorrhage	1%	0%
Chronic		
Low concentration of anti-epileptic drugs	34%	4%
Remote symptomatic (eg, tumour, stroke, trauma)	25%	14%
Alcohol misuse	13%	20%
Tumour	7%	30%
Idiopathic	3%	25%

Some patients had more than one aetiology.

Table 1: **The frequency and mortality associated with acute and chronic causes of status epilepticus in adults[20]**

Acute symptomatic cause of convulsive SE

- *Common*

- Higher rate of morbidity and mortality

Lancet Neurol2015;14:14:615-24

Uncommon causes of SE

- *Immunologically mediated disorder*
- Mitochondrial diseases
- Uncommon infective disorders
- Genetic disorders
- Drugs or toxins

Uncommon causes of Status epilepticus

Table 5. Rare or Under-recognized Causes of Status Epilepticus

Structural	Occult cortical dysplasias and malformations of cortical development
Genetic	Mitochondrial disorders, porphyria
Systemic inflammatory disease	Neurosarcoidosis, systemic lupus erythematosus
CNS inflammatory disease	Rasmussen encephalitis, primary angiitis of the CNS, Hashimoto encephalopathy, ADEM, multiple sclerosis
Infections	Neurosyphilis, prion diseases, Bartonella, rabies, emerging forms of viral encephalitis
Illicit drugs	Cocaine, amphetamine derivatives, heroin, PCP, Ecstasy (MDMA)
Oncologic causes	Paraneoplastic limbic encephalitis
Toxic causes	Domoic acid and marine toxins, other causes of toxic leukoencephalopathy
Iatrogenic causes	Lithium toxicity, theophyllines, isoniazid (consider giving vitamin B_6), insulin, lidocaine, certain psychotropic agents, beta-lactam antibiotics, meperidine, cyclosporine, tiagabine, baclofen
Metabolic	Hypocalcemia, hypomagnesemia, hypoglycemia from insulinoma, nonketotic hyperglycemia
Vascular	Central venous sinus thrombosis, antiphospholipid syndrome

CNS = central nervous system; ADEM = acute disseminated encephalomyelitis; PCP = phencyclidine; MDMA = 3,4-methylenedioxy-N-methylamphetamine.

Journal of Intensive care medicine, Dec 2006

Prognostic factors

- Etiology: post-anoxia, low serum conc AEDs
- Age: elderly
- Seizure duration
- Response to treatment

Status Epilepticus Severity Score(STESS)

Table 1 | The Status Epilepticus Severity Score[14,24,49,99]

Clinical feature	Finding	Score
Level of consciousness at onset	Alert or somnolent; confused Stuporous or comatose	0 1
Seizure type at onset	Simple partial, complex or absent Generalized convulsive Nonconvulsive	0 1 2
Age at onset	≤65 years >65 years	0 2
History of seizures at onset	Prior seizures No prior seizures	0 1
Total possible score		0–6

nature REVIEWS NEUROLOGY

Status epilepticus severity score (STESS): A useful tool to predict outcome of status epilepticus

Manoj Kumar Goyal

Abstract

Objective

The treatment protocols for status epilepticus (SE) range from small doses of intravenous benzodiazepines to induction of coma. The pros and cons of more aggressive treatment regimen remain debatable. The importance of an index need not be overemphasized which can predict outcome of SE and guide the intensity of treatment. We tried to evaluate utility of one such index Status epilepticus severity score (STESS).

Methods

44 consecutive patients of SE were enrolled in the study. STESS results were compared with various outcome measures: (a) mortality, (b) final neurological outcome at discharge as defined by functional independence measure (FIM) (good outcome: FIM score 5–7; bad outcome: FIM score 1–4), (c) control of SE within 1 h of start of treatment and (d) need for coma induction.

Results

A higher STESS score correlated significantly with poor neurological outcome at discharge ($p = 0.0001$), need for coma induction ($p = 0.0001$) and lack of response to treatment within 1 h ($p = 0.001$). A STESS of <3 was found to have a negative predictive value of 96.9% for mortality, 96.7% for poor neurological outcome at discharge and 96.7% for need of coma induction, while a STESS of <2 had negative predictive value of 100% for mortality, coma induction and poor neurological outcome at discharge.

Conclusion

STESS can reliably predict the outcome of status epilepticus. Further studies on STESS based treatment approach may help in designing better therapeutic regimens for SE.

Clineuro2015;139:96-99

Pathophysiology of *self-sustaining* SE

Seizures produce physiological and biological changes in brain

First msec-sec → Protein phosphorylation:
ionic channels open/close, NT and modulators released,receptor desensitisation

Secs-mins → receptor trafficking

Mins-hrs → maladaptive changes of neuropeptide modurators: ↑ proconvulsive neuropeptide
↓ inhibitory neuropeptide
→ Hyperexcitable state

Hrs,days or wks after seizure → changes in gene expression: neuronal death/reorganisation (?)

Based on Animal Studies

Mechanism in the transition of a single seizure to SE

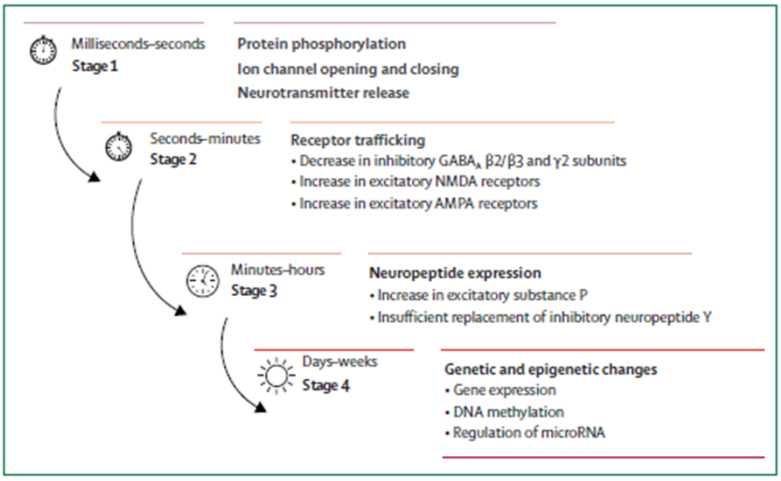


Figure 1: Cascade of selected mechanisms involved in the transition of a single seizure to status epilepticus

Pathophysiology of SE

Physiological and subcellular changes

1.Transition from single seizure to status epilepticus

2.Maladaptive changes in neuropeptide expression in self-sustaining SE

3.Seizure-induced neuronal injury and death

4.SE induced epileptogenesis

5. Development of time-dependent pharmacoresistance

1.Transition from isolated seizures to SE

1.1 Loss of GABA-mediated inhibition(α Time):

- Endocytosis of synaptic surface membrane GABA A β2,β3 and ϒ2 receptor

* *Extrasynaptic GABA A receptor not endocytosis*

1.2 AMPA and NMDA receptor subunits move to synaptic membrane(excitatory receptors)

->increased excitability in uncontrolled Sz

KETAMINE

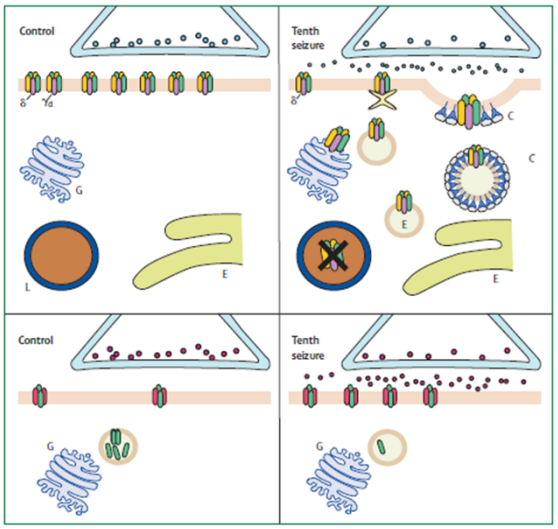


Figure 1: **Model of our hypothesis of receptor trafficking in transition of single seizures to status epilepticus**
Top: after repeated seizures, the synaptic membrane of $GABA_A$ receptors forms clathrin-coated pits, which internalise as clathrin-coated vesicles (C), inactivating the receptors because they are no longer within reach of the neurotransmitter. These vesicles develop into endosomes (E), which can deliver the receptors to lysosomes (L) where they are destroyed, or to the Golgi apparatus (G) from where they are recycled to the membrane. Bottom: by contrast, in NMDA synapses, subunits are mobilised to the synaptic membrane and assemble into additional receptors. As a result of this trafficking, the number of functional NMDA receptors per synapse increases whereas the number of functional $GABA_A$ receptors decreases.[39]

GABA A receptor moduration is contributed to pharmaco-resistance to BZP

Receptor trafficking

1.Transition from isolated seizures to SE(cont.)

1.3 Maladaptive changes in synaptic enzyme function

1.4 Autophosphorylation of calmodulin kinase II ;Calcium independent enzyme->↑presynaptic glutamate release

2.Maladaptive changes in neuropeptide expression in self-sustaining SE

Immunocytochemical studies : HC shows(hrs)

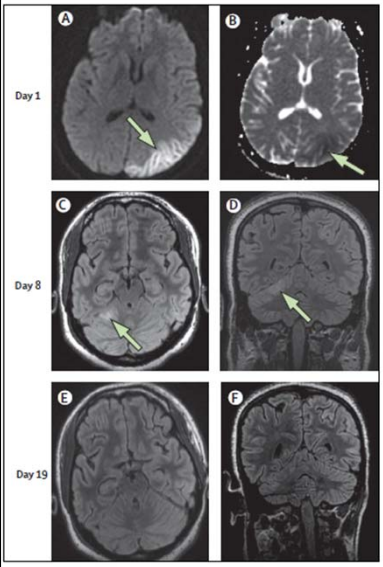
- Depletion of inhibitory peptides : dynorphin, galanin, somatostatin, neuropeptide Y
- Increased expression of proconvulsant : tachykinins substance P, neurokinin B

3.Seizure-induced neuronal injury and death

- Seizures, even no convulsive activity cause neuronal loss *Brain Res 1998:10;801:251-53*
- Non-convulsive electrographic seizures can result in neuronal damage and cell death *Arch neurol1973;29:82-87*
- Cell death is result of excessive neuronal firing through

  excitotoxic mechanism →necrosis/apoptosis and mitochondrial dysfunction
- Increased of neuron-specific enolase(marker neuronal injury)/acute brain edema and chronic atrophy from brain imaging after SE

Brain imaging in patient with SE



-MRI resemble stroke:T2hyper SI, restricted diffusion
-Abnormal seen at cortex,HC,BG, thalamus, pulvinar, leptomeninges (abn enhancement)
-reversible and resolve but focal atrophy and development of HS are common

Figure 2: **MRI of a single patient with focal left hemispheric status epilepticus during a single admission to hospital**
Diffusion-weighted imaging showing (A) cortically predominant restricted diffusion of the left parietal and occipital lobes with (B) low signal intensity on the corresponding apparent diffusion coefficient sequence. (C) Axial and (D) coronal T2 fluid-attenuated inversion recovery (FLAIR) sequences showing left hemispheric cortical hyperintense signal and an area of hyperintense signal in the right cerebellar hemisphere, consistent with crossed cerebellar diaschisis. (E) Axial and (F) coronal T2 FLAIR images at day 19 showing improvement from day 8 in the left hemispheric cortical hyperintense signal and resolution of the right cerebellar hyperintensity.

4. SE induced epileptogenesis

- From animal study
- Loss of GABAergic interneurons or sprouting of excitatory fibers- debated
- ? Human
- ? severe illness > SE induced epileptogenesis itself

risk of unprovoked seizures is 3.34 times higher after acute symptomatic SE(41%) than after single seizures(13%)

Ann Neurol 1998;44:908-12

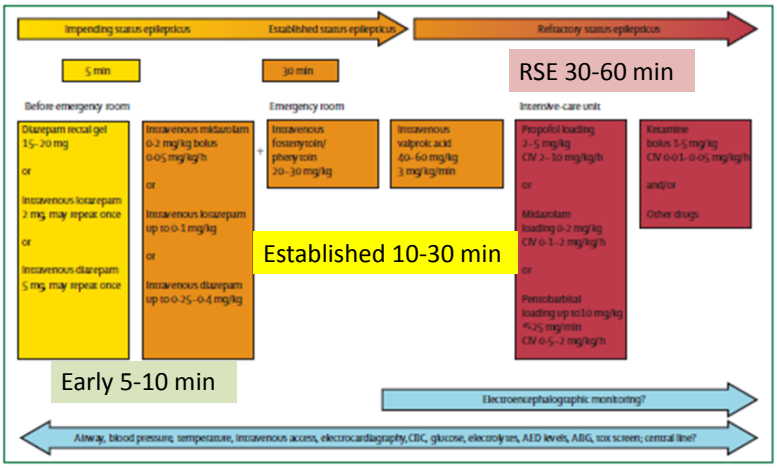
5.Time-dependent development of pharmaco-resistance

- Benzodiazepines and other anticonvulsants
- Well documented in animal studies
- ?Human, early treatment is much more effective than late treatment
  - several possible explanations

Stage of GCSE

Lancet Neurol 2006; 5: 246–56

"Time is brain "



Not to low, not to slow

Early or impending SE

- Continuous or intermittent seizures lasting more than 5 min without full recovery of consciousness between seizures*
- Not all patients are in SE but high risk of ongoing seizures to SE

* Definition can also be extended to other forms of SE, focal SE with dyscognitive features and absence SE

Established SE

- Clinical or electrographic seizures lasting >30 min without full recovery of consciousness
- Evidence from animal study:
  1. self –sustaining seizures
  2. neuronal damage
  3. pharmaco-resistant

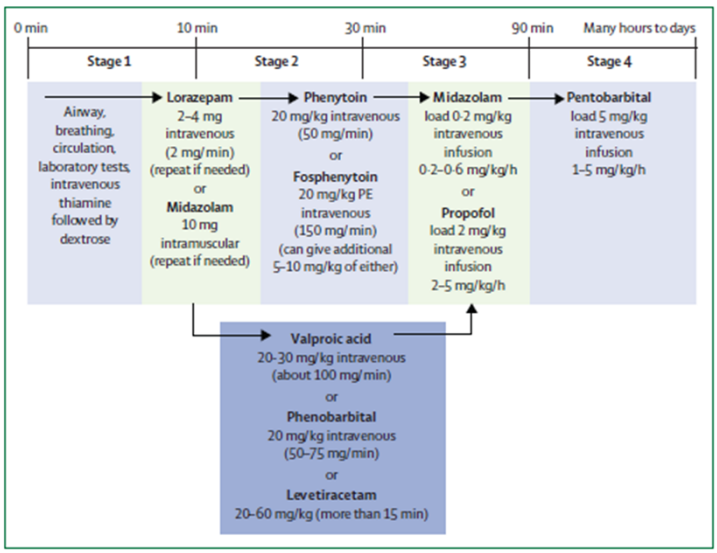


Figure 3: **Updated treatment algorithm for generalised convulsive status epilepticus in adults and older children**
PE=phenytoin equivalents.

Lancet Neurol 2015; 14: 615–24

FIGURE 1. Proposed treatment algorithm for status epilepticus.

Time Line	Interventions for emergency department, in-patient setting, or prehospital setting with trained paramedics
0-5 min Stabilization phase	1. Stabilize patient (airway, breathing, circulation, disability - neurologic exam) 2. Time seizure from its onset, monitor vital signs 3. Assess oxygenation, give oxygen via nasal cannula/mask, consider intubation if respiratory assistance needed 4. Initiate ECG monitoring 5. Collect finger stick blood glucose. If glucose < 60 mg/dl then Adults: 100 mg thiamine IV then 50 ml D50W IV Children ≥ 2 years: 2 ml/kg D25W IV Children < 2 years: 4 ml/kg D12.5W 6. Attempt IV access and collect electrolytes, hematology, toxicology screen, (if appropriate) anticonvulsant drug levels
	Yes — Does Seizure continue? — No
5-20 min Initial therapy phase	**A benzodiazepine is the initial therapy of choice (Level A)**: Choose one of the following 3 equivalent first line options with dosing and frequency: Intramuscular midazolam (10 mg for > 40 kg, 5 mg for 13-40 kg, single dose, Level A) OR Intravenous lorazepam (0.1 mg/kg/dose, max: 4 mg/dose, may repeat dose once, Level A) OR Intravenous diazepam (0.15-0.2 mg/kg/dose, max: 10 mg/dose, may repeat dose once, Level A) If none of the 3 options above are available, choose one of the following: Intravenous phenobarbital (15 mg/kg/dose, single dose, Level A) OR Rectal diazepam (0.2-0.5 mg/kg, max: 20 mg/dose, single dose, Level B) OR Intranasal midazolam (Level B), buccal midazolam (Level B)
	If patient at baseline, then symptomatic medical care
	Yes — Does seizure continue? — No
20-40 min Second therapy phase	**There is no evidence based preferred second therapy of choice (Level U)**: Choose one of the following second line options and give as a single dose Intravenous fosphenytoin (20 mg PE/kg, max: 1500 mg PE/dose, single dose , Level U) OR Intravenous valproic acid (40 mg/kg, max: 3000 mg/dose, single dose, Level B) OR Intravenous levetiracetam (60 mg/kg, max: 4500 mg/dose, single dose , Level U) If none of the options above are available, choose one of the following (if not given already) Intravenous phenobarbital (15 mg/kg, max dose, Level B)
	If patient at baseline, then symptomatic medical care
	Yes — Does seizure continue? — No
40-60 min Third therapy phase	**There is no clear evidence to guide therapy in this phase (Level U)**: Choices include: repeat second line therapy or anesthetic doses of either thiopental, midazolam, pentobarbital, or propofol (all with continuous EEG monitoring).
	If patient at baseline, then symptomatic medical care

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

American Epilepsy Society Guideline

Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society

- BZP(im midazolam,iv lorazepam,iv diazepam) is recommended as initial therapy of choice(Level A)
- Pre-hospital setting, rectal diazepam, intranasal midazolam,buccal midazolam-alternatives(Level B)
- Initial therapy should be administered as adequate single dose, not multiple smaller doses (Iv lorazepam,diazepam can be repeated at full dose once) (Level A)

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

Initial tx should begin at 5 min and conclude of response by 20 min

The 2nd line therapy

- Second-therapy: fos-PHT(Level U), VPA(LevelB), LEV(LevelU)

  No evidence that any one of these options is better than the others

ESETT (The established Status Epilepticus Treatment Trial)
- *RCT comparing Fos PHT, VPA, LEV for treatment BZP-refractory SE*
- *initiate enrolment in 2015*

- iv PB as second therapy alternative because of AE (LevelB)

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

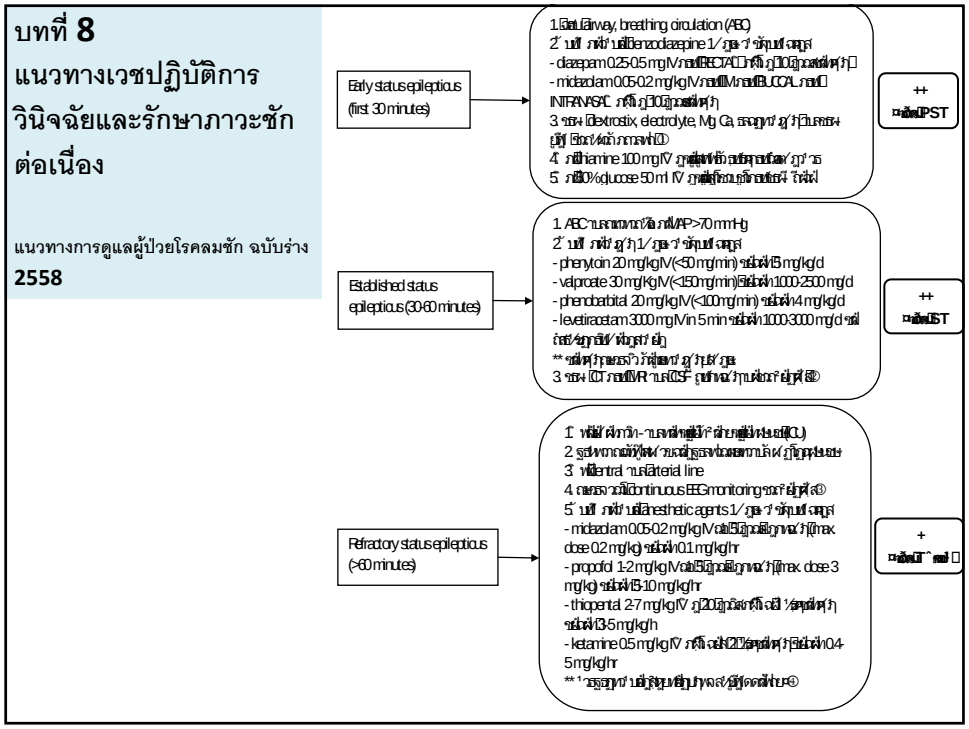
Second-therapy begin at 20 min and should conclude by 40 min

The 3rd line therapy

- No evidence to guide therapy in this place
- Compared with initial therapy, second therapy is often less effective(LevelA) and third therapy is substantially less effective (LevelA)than initial therapy
- *If second therapy fails* ,treatment considerations should include <u>repeating second line therapy</u> or <u>anaesthetic agents</u>

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

Third therapy should begin when seizure duration reaches 40 min



Refractory SE

- Defined by failure of adequate amounts of 2 intravenous drugs (1st line agent-BZP, 2nd line AED(PHT,VPA,LEV or PB)) to stop seizures
- 23-43% of pateints with SE
- VPA,*PB and LEV/LCS* have emerged as alternative/ adjacent second-line AEDs for treatment SE before proceeding to general anaesthesia*

* other centres do not use in RSE because of the risk of delaying general anaesthesia

Chest 2004;126:582-91

- *Time of general anaesthesia* ****(uncontrolled SE >1-2 hr)

Refractory SE(cont.)

- √ Previous convention for GCSE refractory to initial treatment with lorazepam and a 2nd line AED

  - additional trials of 2nd AEDs before giving an anaesthetic agent

- Now advocate ?

  - early escalation to anaesthetics (within 30-60 min of seizure onset) rather than give another 2nd line AED drugs for GCSE

Lancet neurol2015;14:615-24

Additional 2nd non-anaesthetic AEDs used in SE

Efficacy of intravenous levetiracetam as an add-on treatment in status epilepticus: A multicentric observational study☆

Maria Aiguabella [a,*], Mercè Falip [a], Vicente Villanueva [b], Pilar de la Peña [c], Albert Molins [d], Irene Garcia-Morales [e], Rosa Ana Saiz [c], Julio Pardo [f], Diego Tortosa [g], Gemma Sansa [h], Júlia Miró [a]

Seizure 20 (2011) 60–64

frontiers in NEUROLOGY

MINI REVIEW ARTICLE
published: 05 August 2013
doi: 10.3389/fneur.2013.00111

Review of levetiracetam as a first line treatment in status epilepticus in the adult patients – what do we know so far?

Hae Won Shin and Robin Davis*

Department of Neurology, University of North Carolina Health Care, Chapel Hill, NC, USA

The use of levetiracetam in refractory status epilepticus

Seizure (2006) 15, 137–141

Nitin C. Patel [a,*], Ivan R. Landan [b,1], Jeffrey Levin [c,2], Jerzy Szaflarski [d,3], Andrew N. Wilner [e,4]

Additional 2nd non-anaesthetic AEDs used in SE

Neurology Asia 2012; 17(4) : 297 – 302

The efficacy of topiramate in status epilepticus, experience from Thailand

Tanita Suttichaimongkol, Somsak Tiamkao, Kittisak Sawanyawisuth, Intregrated Epilepsy Research Group

Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

Epilepsia, 54(3):393–404, 2013
doi: 10.1111/epi.12058

CRITICAL REVIEW AND INVITED COMMENTARY

Lacosamide as a new treatment option in status epilepticus

Julia Höfler and Eugen Trinka

Department of Neurology, Christian Doppler Klinik, Paracelsus Medical University of Salzburg, Salzburg, Austria

Perampanel in patients with refractory and super-refractory status epilepticus in a neurological intensive care unit

A. Rohracher, J. Höfler, G. Kalss, M. Leitinger, G. Kuchukhidze, I. Deak, J. Dobesberger, H. Novak, G. Pilz, A. Zerbs, E. Trinka *

Department of Neurology, Christian Doppler Klinik, Paracelsus Medical University Salzburg, Ignaz Harrer Straße 79, A-5020 Salzburg, Austria
Centre for Cognitive Neuroscience Salzburg, Ignaz Harrer Straße 79, A-5020 Salzburg, Austria

Epilepsy & Behavior 49 (2015) 354–358

Pharmacological treatment for refractory GCSE and subtle SE

Type	Dosage
Phenobarbital	Initial bolus of 20 mg/kg iv (50 mg/min),administration of additional boluses requires intensive care conditions
Valproic acid	Intravenous bolus of 25-45 mg/kg infused at rates of 6 mg/kg/min
Levetiracetam	Intravenous bolus of 1,000-3,000(2000) mg administered over a period of 15 min
Barbiurates: Thiopental	A bolus of 3-5mg/kg, then further boluses of 1-2 mg/kg every 2-3 min until seizures are controlled, then continuous infusion 3-7 mg/kg/h
Midazolam	0.2 mg/kg bolus followed by continuous infusion 0.05-0.4 mg/kg/h
Propofol	A bolus of 2-3 mg/kg,then further boluses 1-2 mg/kg until seizures are controlled,then continuous infusion 4-10mg/kg/h
Ketamine***	Bolus of 0.5-3 mg/kg then infusion 0.3-7.5mg/kg/hr

European journal of Neurology2010,17:348-355

Anaesthetic therapy

European journal of Neurology2010,17:348-355

Type	Main advantages	Main disadvantages
Barbiurates: Thiopental/ pentobarbital	Strong anti-epileptic action, potential neuroprotective action, reduces intracranial pressure	prolonged recovery phase, acute tolerance, cardiorespiratory depression, hypotension***
Midazolam	Strong anti-epileptic action, less tendency to accumulate than barbiturate or other BZP Midazolam-Tachyphylaxis	Tendency for *acute tolerance* to develop resulting in breakthrough seizures, hypotension,cardiorespiratory depression,hepatic metabolism
Propofol	Ease to use,excellent PK	PRIS, pain at injection side, involuntory movements(myoclonus), no intrinsic anti-epileptic action,hypotension,cardiac depression
Ketamine***	Lack of cardiorespiratory depression, hypotension, neuroprotective action	Potential for neurotoxicity, hypertension, increased intracranial pressure

subtle/partly treated SE

- Prolong SE, both motor and electrographic seizure become less florid , prognostic and therapeutic implication are same as GCSE
- >10% of patients treated for GCSE, clinical seizures stop or only subtle symptoms but electrographic seizures continue(NCSE)
- ?continuing seizure activity is harmful

  -> experimental evidence : uncontrolled firing alone can kill neurons

Science 1987;235:73-76

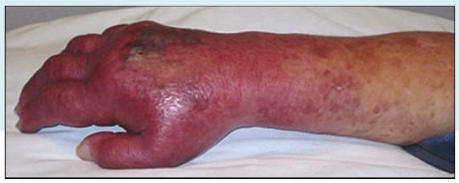
Propofol infusion syndrome(PRIS)

- Rhabdomyolysis
- Hypertriglyceridaemia
- Cardiac dysfunction, bradycardia
- Renal failure
- Hyperkalemia
- Metabolic acidosis,lactic acidosis

Risk - children
- continue infusion more than 48 hrs
- corticosteroids or catecholamines treatment

Purple glove syndrome

- Only reported for phenytoin extravasation
- Fos-PHT causes few side effects: pain, phlebitis
- *10-15 min needed for dephosphorylation of fosPHT is compensated by faster infusion rate 150mg/min vs 50 mg/min(PHT)*



Super-refractory SE

- Defined as *status epilepticus that continues or recurs 24 hrs or more after the onset of anaesthetic therapy*, including cases where SE recurs on the reduction or withdrawal of anaesthesia
- 15% of all cases with SE
- No RCT trial , therapy is based on clinical reports and expert opinion
- Identify cause is still important!

Causes of super-refractory SE

- Severe brain insult (e.g severe head injury, infection, stroke)

Less common causes

- Immunological disorders
- Mitochondrial disorders
- Uncommon infectious disease
- Drugs or toxins
- Uncommon genetic diseases
- No obvious cause is found- syndrome?

  NORSE(new-onset refractory SE)

  DESC(devastating epileptic encephalopathy in school-aged children)

  FIRES(Febrile infection-related epilepsy syndrome)

Recommended treatment of super-refractory SE

- Identify and treat cause
- Intensive treatment unit care and EEG monitoring
- Antiepileptic drugs
- General anaesthetic drugs: 3 conventional agents, *Ketamine*
- Magnesium sulphate infusion*
- Hypothermia*
- Pyridoxine infusion: young children, adult?

In all cases

Recommended treatment of super-refractory SE:In Specific conditions

- In cases where the cause is not identified
  ➡ steroids and immunotherapy*
- In cases where a lesional cause is identified
  ➡ resective neurosurgery –last resort
- In cases where SE continues despite previous tx
  ➡ Ketogenic diet, hypothermia
  other measures: electroconvulsive therapy or CSF drainage???
  Lidocaine,verapamil ??

Table 3 Non-anaesthetic therapies

Treatment	Dose recommended[a]/ physical parameter	Range of doses used (from the literature review)	Major adverse effects	Contraindications
Magnesium	Infusion to increase serum level to 3.5 mmol/l[b]	Bolus: 4 g Infusion: 2–6 g/h	High dose: hypotension, arrhythmia, neuromuscular block	Kidney failure
Pyridoxine	30 mg/kg (children) 100–200 mg/day (adults)	2–300 mg/day	Bradycardia, hypothermia, apnoea, sensory neuropathy	Hypersensitivity
Hypothermia	32–35°C (for <48 h) by endovascular cooling	30–36°C	Coagulation disorders, venous thrombosis, hypotension, shivering, acid–base and electrolyte disturbances, infections, cardiac arrhythmia, ileus, bowel ischaemia	Coagulopathy. Caution in immunodepression.
VNS	Up to 1.25 mA	0.25–1.75 mA	Bradycardia, asystole, coughing, hoarseness, Horner's syndrome	History of previous neck surgery or prior cervical vagotomy
Ketogenic diet	4:1 ketogenic ratio (see text)	1:1 to 4:1 ketogenic ratio	Constipation, acidosis, hypoglycaemia, hypercholesterolaemia.	Pyruvate carboxylase and β-oxidation deficiencies, propofol anaesthesia, porphyria.
Electroconvulsive therapy	Daily sessions for 3–8 days	3 daily sessions—6 sessions over 2 weeks	Intracranial pressure increases, cardiac arrhythmias, hypo/ hypertension	Brain space-occupying lesions, recent history of myocardial infarction, cerebral vascular disease.
Steroids	Prednisolone 1 g/day intravenous for 3 days followed by 1 mg/kg/day (see text)	Various	Gastrointestinal ulceration, Cushingoid syndrome, fluid and sodium retention, psychiatric disturbance	Infection, severe hypertension or diabetes mellitus
Immunoglobulins	Intravenous immunoglobulins 0.4 g/kg/day for 5 days (see text)	Various	Coagulation disorders, hypertension	Coagulopathy, selective deficiency of IgA

a Recommended on the basis of experience and/or the literature review.
b The regimen recommended by Visser *et al.*, 2011.
VNS = vagal nerve stimulation; IgA = immunoglobulin A.

Brain 2011: 134; 2802–2818

How do these therapies work ?

1. Magnesium infusion

- blocking NMDA receptor
- safe ,no significant toxicity
- iv bolus and infusion at dose that increases serum level to **3.5** mmol/l

2. Hypothermia

- reduce brain metabolic rate, O2 utilization, ATP consumption, glutaminergic drive, mitochondrial dysfunction,Ca2+overload, free radicle production and oxidative stress
- endovascular cooling , mild hypothermia(32-35 'c) for 24-48 hrs
- SE: acid-base, E'lyte disturbance, DIC, coagulation disorders, cardiac arrthymia, infection , bowel ischemia and paralytic ileus

Why these therapies help ?(cont.)

3. *Steroids and immunotherapy (*even in absence of evident immunological cause or cause is not identified*)

- recognition that super-refractory SE may be due to Ab directed against neural tissues

eg.Ab against VGKC, NMDA receptor

- evidence of inflammation plays role in epileptogenesis esp. activation of interleukin-1 receptor/toll-like receptor(IL-1R/TLR)

- IVIG or PE can be added if no response within 2 days after steroids

Brain2011;134:2802-18

Treatment of Super-refractory SE

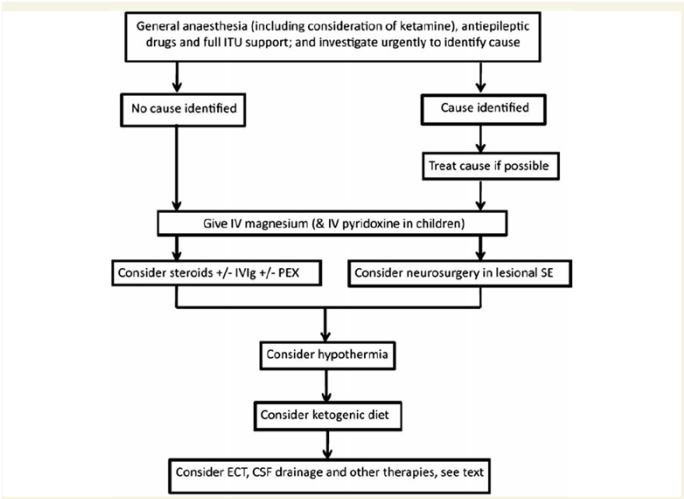
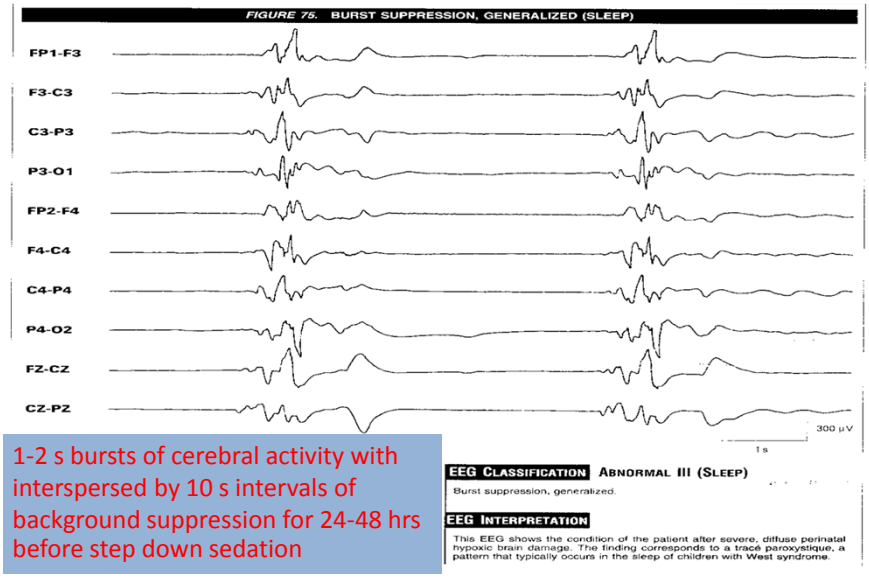


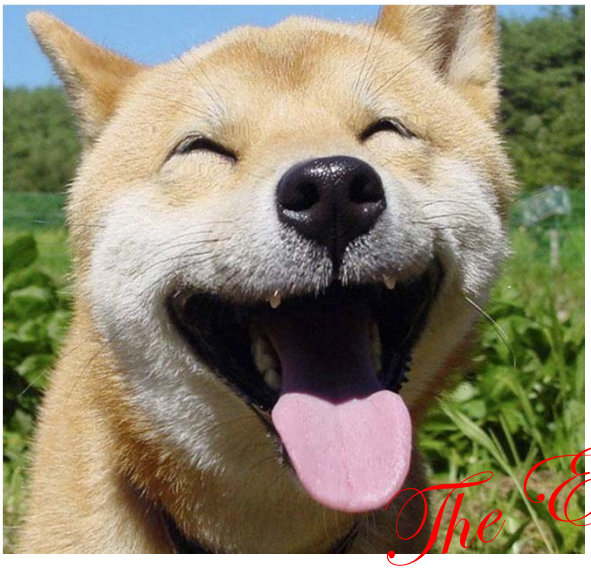
Figure 2 Flowchart for the treatment of super-refractory status epilepticus. The flowchart is proposed as the basis of a protocol for the treatment of super-refractory status epilepticus (SE). The order and choice of therapy proposed will depend on the clinical context and the local facilities. ECT = electroconvulsive therapy; ITU = intensive treatment unit; IV = intravenous; PEX = plasma exchange.

Brain 2011: 134; 2802–2818

Burst-suppression



1-2 s bursts of cerebral activity with interspersed by 10 s intervals of background suppression for 24-48 hrs before step down sedation



The End