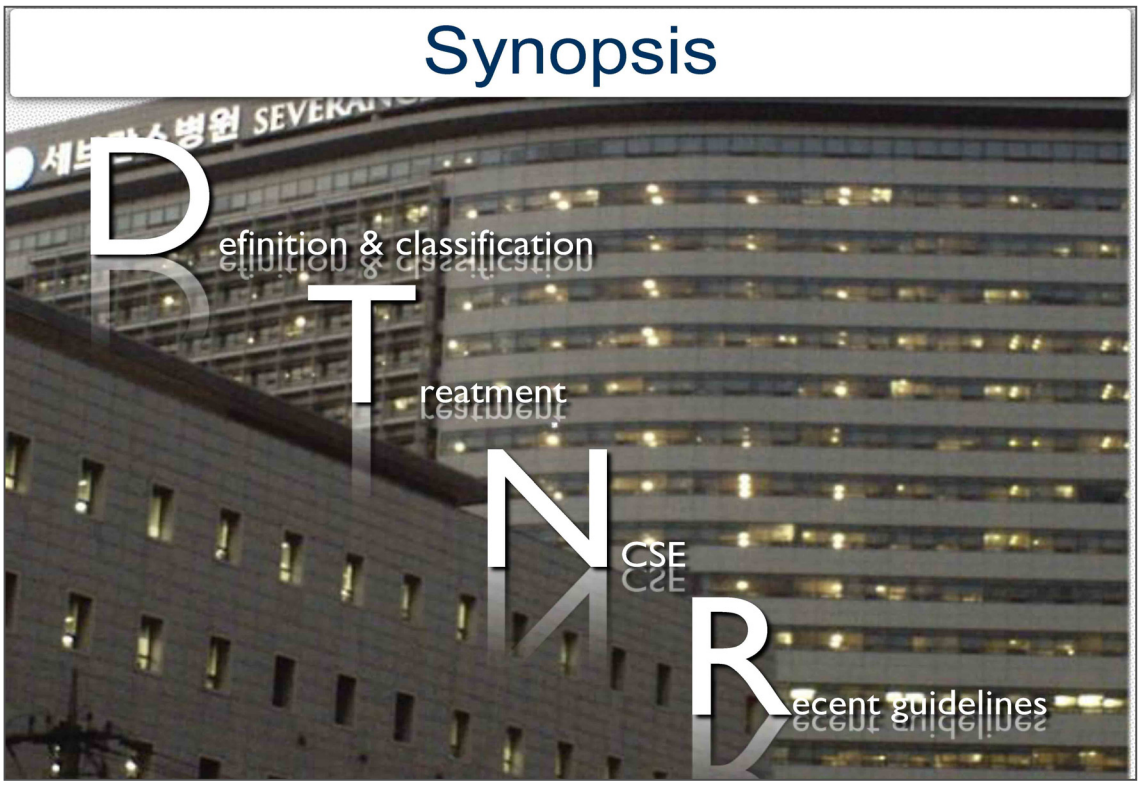
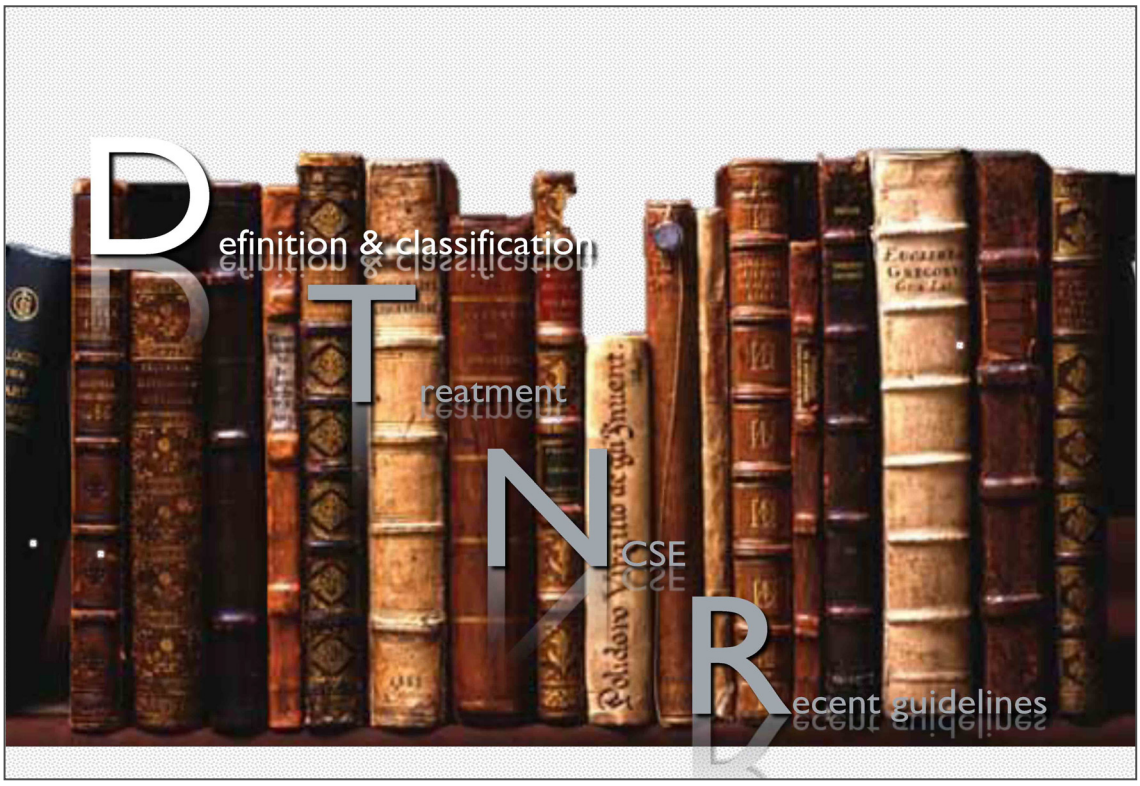
ICU Seizures and Status Epilepticus

조 양 제
연세의대 의과대학 신경과학교실





Definition

SE Definition, ILAE

: Dogma of 30 min

1970년과 1981년 국제뇌전증퇴치연맹(International League Against Epilepsy, ILAE)에 의해, "지속적인 뇌전증발작을 야기하기에 충분한 시간 동안 발작이 지속되거나, 발작 간에 완전히 회복이 이루어 지지 않을 만큼 짧은 시간 간격 동안 반복되는 경우"로 정의하였다. 하지만, 이 ILAE의 정의에는 "충분한 시간"에 대한 정확한 명시가 없었으며, 이후 바분 원숭이를 대상으로 한 실험을 근거로 30분 이상 발작을 하면 뇌 손상을 야기할 수 있다는 개념 하에, 30분 이상 발작을 할 경우 관습적으로 SE로 정의하여 왔다.

이러한 상태는 30년 이상 이어져 왔음에도 임상적으로는 여러 문제가 있었다. 예를 들어 SE로 진단하고 치료를 시작해야 하는데 30분 이상 발작이 지속되는 것을 지켜볼 수만 없다는 것이 실제적인 문제이며, 특히 내원 전 단계부터 치료를 시작할 때 더욱 문제가 된다. 또한 중요한 점은 여러 임상경험과 동물실험을 바탕으로 SE의 치료가 늦어질 수록 치료 성적 및 예후가 좋지 않다는 것이다. 이에 Lowenstein 등은 1999년에 전신성 경련SE는 5분 이상 발작이 지속되거나, 두 발작 사이에 완전히 의식을 회복 못하는 경우로 하자고 제안하였다.

Definition – NCS 2012

neurocritical care society Neurocrit Care (2012) 17:3–23
DOI 10.1007/s12028-012-9695-z

REVIEW

Guidelines for the Evaluation and Management of Status Epilepticus

2012 NCS Definition Guidelines : Recommendations

1. SE should be defined as **5 min** or more of continuous clinical and/or electrographic seizure activity or recurrent seizure activity without recovery between seizures (strong recommendations, moderate quality).

2. SE should be classified as either convulsive SE (convulsions that are associated with rhythmic jerking of the extremities) or non-convulsive SE (seizure activity seen on EEG without the clinical findings associated with convulsive SE) (strong recommendation,high quality).

3. Refractory SE should be defined as SE that does not respond to the standard treatment regimens, such as an initial benzodiazepine followed by another AED(strong recommendations, moderate quality).

4. The etiology of SE should be diagnosed and treated as soon as possible (strong recommendation, high quality).

Brophy et al *Neurocrit Care* 2012

Definition – ILAE 2015

SPECIAL REPORT

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

2015 ILAE Guidelines

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

		Operational dimension 2
	Time point t_1 = 5 min	
	time point t_2 = 30 min	
consciousness		
Absence status epilepticus	10–15 min[a]	Unknown

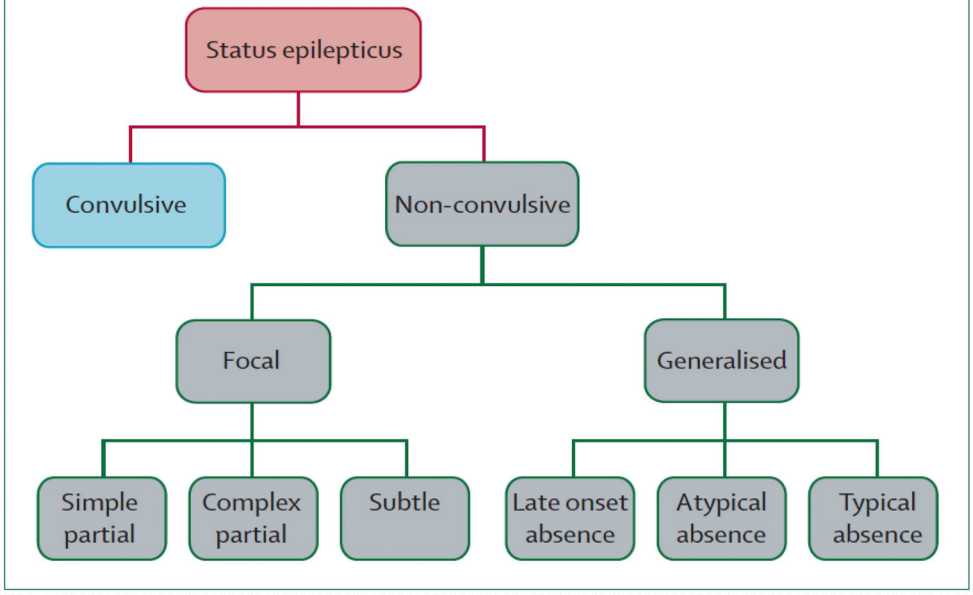
[a]Evidence for the time frame is currently limited and future data may lead to modifications.

Status epilepticus is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of

Time point t_1 indicates when treatment should be initiated, and time point t_2 indicates when long-term consequences may appear

Trinka et al *Epilepsia* 2015

Classification



Hartmut Meierkord & Martin Holtkamp *Lancer Neurol 2007*

2015 ILAE Definition

SPECIAL REPORT

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

Table 2. Axis 1: Classification of status epilepticus (SE)

(A) With prominent motor symptoms

(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

Trinka et al. *Epilepsia* 2015

Other Terminology

Terminology

Impending status epilepticus: continuous or intermittent seizures lasting more than 5 min, without full recovery of consciousness between seizures.

Established status epilepticus: clinical or electrographic seizures lasting more than 30 min without full recovery of consciousness between seizures.

Subtle status epilepticus: motor and electroencephalographic expression of seizures become less florid, yet the prognostic and therapeutic implications of that stage are still those of convulsive status epilepticus.

Other Terminology

Terminology

Successful therapy: SE is completely controlled by the therapy, without breakthrough or withdrawal seizures, or discontinuation due to side-effects, or death.

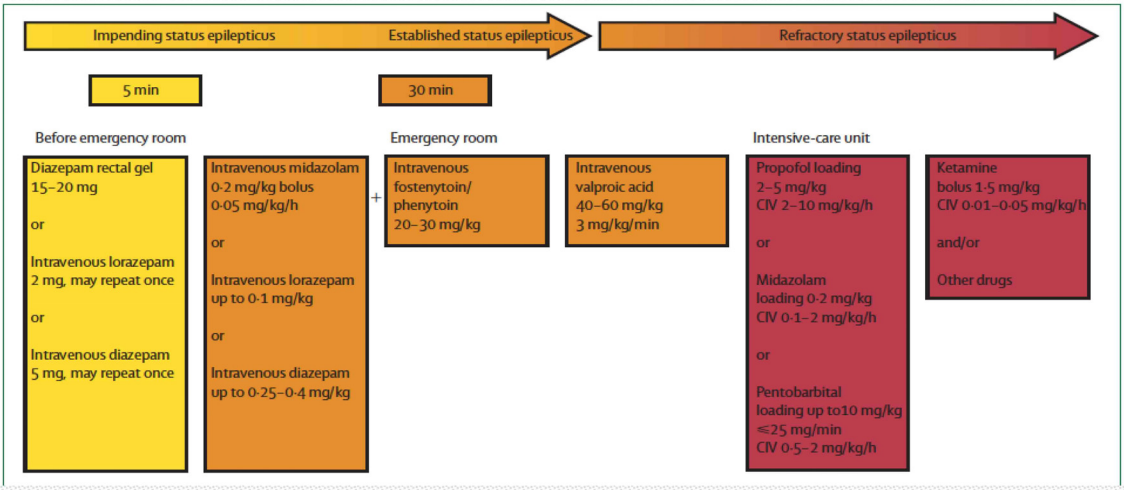
Initial failure: the therapy failed to control SE at all.

Breakthrough seizures: recurrence of status epilepticus during the treatment, despite initial control, resulting in the need for a change of therapy.

Withdrawal seizures: recurrence of status epilepticus during or immediately after the tapering or withdrawal of the therapy.

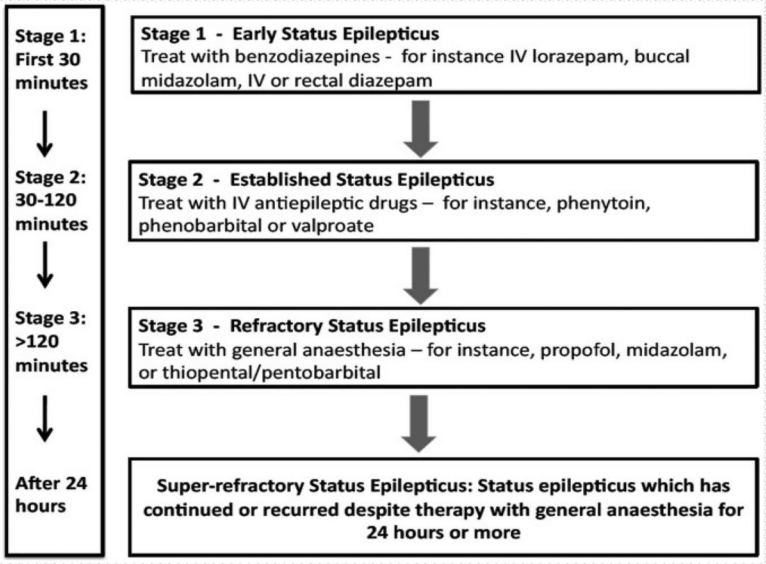
Treatment outline (1)

Treatment outline - Wasterlain, UCLA



Treatment outline (2)

Established, Refractory, Super-refractory SE



3rd London-Innsbruck Colloquium on status epilepticus (Shorvon & Trinka, 2011)

Treatment

1. Prehospital/ER Treatment

2. Intravenous IV AEDs

3. Treatment of RSE

Prehospital/ER Treatment

The New England Journal of Medicine

A COMPARISON OF FOUR TREATMENTS FOR GENERALIZED CONVULSIVE STATUS EPILEPTICUS

DAVID M. TREIMAN, M.D., PATTI D. MEYERS, M.P.A., NANCY Y. WALTON, PH.D., JOSEPH F. COLLINS, SC.D., CINDY COLLING, R.PH., M.S., A. JAMES ROWAN, M.D., ADRIAN HANDFORTH, M.D., EDWARD FAUGHT, M.D., VINCENT P. CALABRESE, M.D., BASIM M. UTHMAN, M.D., R. EUGENE RAMSAY, M.D., AND MEENAL B. MAMDANI, M.D., FOR THE VETERANS AFFAIRS STATUS EPILEPTICUS COOPERATIVE STUDY GROUP*

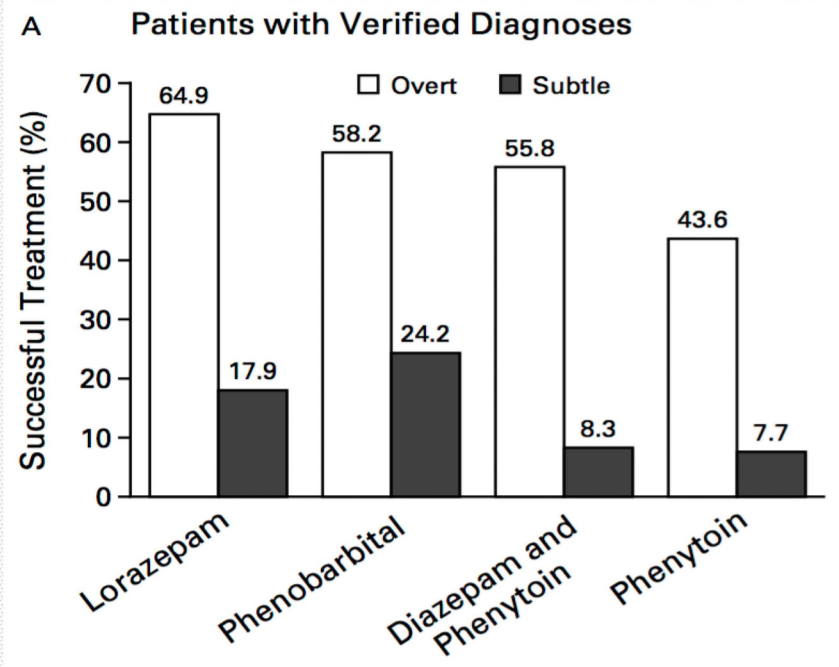
The First Study compared 4 IV AEDs for GCSE at ER (1998) – 384 pts, DB, MC, RCT

Lorazepam/Phenobarbital/Diazepam + Phenytoin/Phenytoin

LZP was significantly superior to Phenytoin

Treiman et al. *N Engl J Med 1998*

Prehospital/ER Treatment



Prehospital/ER Treatment

TABLE 3. DOSES, SERUM DRUG CONCENTRATIONS AFTER FIRST DRUG INFUSION, AND LENGTH OF DRUG INFUSION.*

REGIMEN	DOSE	SERUM CONCENTRATION	LENGTH OF INFUSION†
	mg/kg	μg/ml	min
Lorazepam	0.10±0.01	0.231±0.299	4.7±7.2
Phenobarbital	14.96±2.53	31.2±37.2	16.6±11.5
Diazepam and phenytoin	0.15±0.02 and 15.08±4.84	0.245±0.307 and 31.8±19.2	42.0±38.1
Phenytoin	16.02±3.21	30.0±13.6	33.0±20.1

*Values are means ±SD. To convert concentrations to micromoles per liter, multiply by the following: lorazepam, 3.11; phenobarbital, 4.31; diazepam, 3.51; and phenytoin, 3.96.

†P<0.001 for the differences among the drug regimens.

Prehospital/ER Treatment

VOLUME 345 AUGUST 30, 2001 NUMBER 9

A COMPARISON OF LORAZEPAM, DIAZEPAM, AND PLACEBO FOR THE TREATMENT OF OUT-OF-HOSPITAL STATUS EPILEPTICUS

BRIAN K. ALLDREDGE, PHARM.D., ALAN M. GELB, M.D., S. MARSHAL ISAACS, M.D., MEGAN D. CORRY, E.M.T.-P., M.A., FAITH ALLEN, M.D., SUEKAY ULRICH, R.N., M.S., MILDRED D. GOTTWALD, PHARM.D., NELDA O'NEIL, R.N., M.S.N., JOHN M. NEUHAUS, PH.D., MARK R. SEGAL, PH.D., AND DANIEL H. LOWENSTEIN, M.D.

The First Study of prehospital treatment (PHTSE trial)(2001)

Lorazepam (2mg)/Diazepam (5mg)/Placebo – 258 pts

LZP and DZP was significantly superior to Placebo.

The rates of respiratory or circulatory complications were 10.6 percent for LZP, 10.3 percent for DZP,

and 22.5 percent for placebo (P=0.08).

Alldredge et al. *N Engl J Med* 2001

Prehospital/ER Treatment

TABLE 2. STATUS EPILEPTICUS AT THE TIME OF ARRIVAL AT THE EMERGENCY DEPARTMENT.*

VARIABLE	LORAZEPAM GROUP (N=66)	DIAZEPAM GROUP (N=68)	PLACEBO GROUP (N=71)
		no. of patients (%)	
Status epilepticus terminated	39 (59.1)	29 (42.6)	15 (21.1)
Ongoing status epilepticus	27 (40.9)	39 (57.4)	56 (78.9)
	LORAZEPAM VS. PLACEBO	LORAZEPAM VS. DIAZEPAM	DIAZEPAM VS. PLACEBO
Odds ratio (simultaneous 95 percent CI) for termination of status epilepticus			
Unadjusted	5.4 (2.3–13.2)	1.9 (0.9–4.3)	2.8 (1.2–6.7)
Adjusted†	4.8 (1.9–13.0)	1.9 (0.8–4.4)	2.3 (1.0–5.9)

Prehospital/ER Treatment

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 16, 2012 VOL. 366 NO. 7

Intramuscular versus Intravenous Therapy for Prehospital Status Epilepticus

Robert Silbergleit, M.D., Valerie Durkalski, Ph.D., Daniel Lowenstein, M.D., Robin Conwit, M.D., Arthur Pancioli, M.D., Yuko Palesch, Ph.D., and William Barsan, M.D., for the NETT Investigators*

The Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART)(2012)

Silbergleit et al. *N Eng J Med* 2012

Prehospital/ER Treatment

Done by NETT(Neurological Emergencies Treatment Trials) group

Compared IM MDZ vs. IV LZP (5 mg vs. 2 mg)

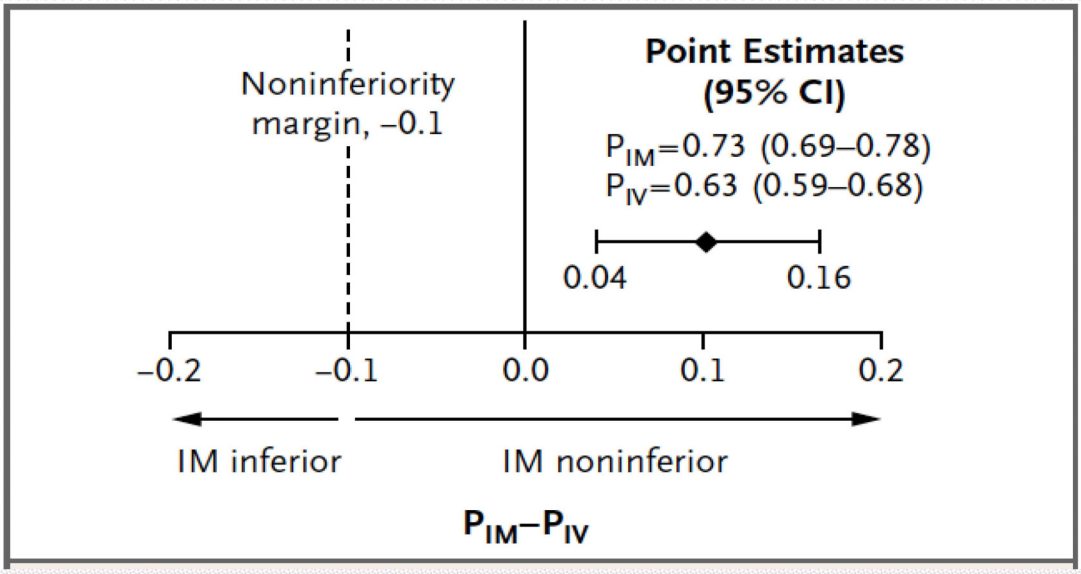
The primary outcome: absence of Szs at the arrival in ER.

5 minutes of SE, given test drugs by paramedics

893 assigned to trial (448 IM MDZ vs. 445 IV LZP)

SF 73.4% in the IM MDZ VS. 63.4% in the IV LZP ($P < 0.001$ for both non-inferiority and superiority)

Prehospital/ER Treatment

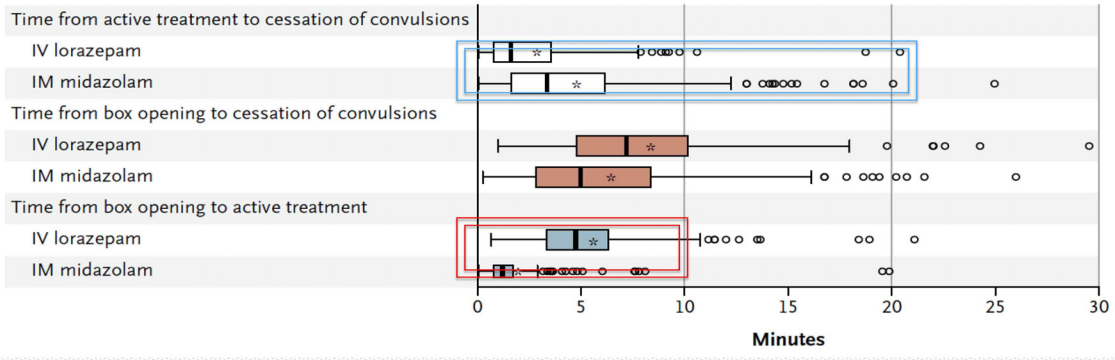


Prehospital/ER Treatment

Table 2. Primary and Secondary Outcomes.*

Outcome	Intention-to-Treat Analysis† (N=893)		Per-Protocol Analysis‡ (N=732)	
	IM Midazolam (N=448)	IV Lorazepam (N=445)	IM Midazolam (N=362)	IV Lorazepam (N=370)
Secondary outcomes				
Endotracheal intubation within 30 min after ED arrival				
No. of subjects — %	63 (14.1)	64 (14.4)	53 (14.6)	53 (14.3)
Relative risk (95% CI)	0.98 (0.70–1.34)		1.02 (0.71–1.45)	
Hospitalization				
No. of subjects — %	258 (57.6)	292 (65.6)	210 (58.0)	250 (67.6)
Relative risk (95% CI)	0.88 (0.79–0.98)		0.86 (0.77–0.96)	
ICU admission				
No. of subjects — %	128 (28.6)	161 (36.2)	102 (28.2)	138 (37.3)
Relative risk (95% CI)	0.79 (0.65–0.95)		0.76 (0.61–0.93)	
Recurrent seizure within 12 hr after ED arrival				
No. of subjects — %	51 (11.4)	47 (10.6)	37 (10.2)	39 (10.5)
Relative risk (95% CI)	1.08 (0.74–1.56)		0.97 (0.63–1.48)	
Hypotension				
No. of subjects — %	12 (2.7)	13 (2.9)	5 (1.4)	9 (2.4)
Relative risk (95% CI)	0.92 (0.42–1.98)		0.57 (0.19–1.67)	

Prehospital/ER Treatment



1.2 min vs. 4.8 min, median

3.3 min vs. 1.6 min, median

Prehospital/ER Treatment

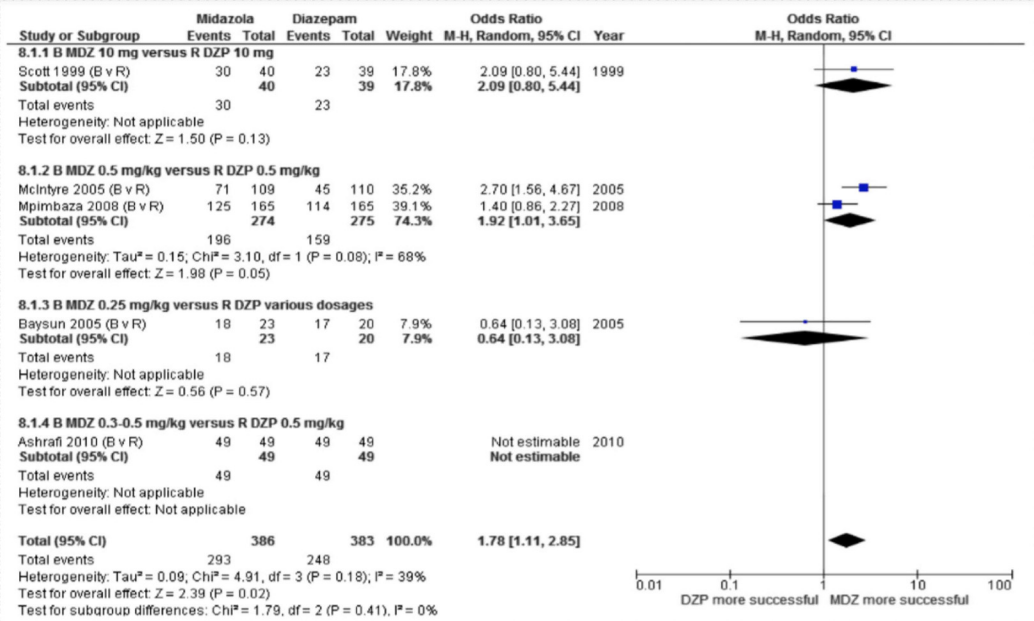
Other Route of BDZ

MDZ available for IM, Buccal, intranasal

MDZ is water/lipid-soluble, but changes in the body to un-ionized, highly lipid-soluble form (water soluble in acidic pH.)
IM peak serum concentrations at 17.5 to 25 min
(1hr for DZP, 1.2 hr for LZP)

Intranasal MDZ has similar efficacy compared to IV DZP.
Intranasal or buccal MDZ has superior efficacy than rectal DZP (OR 1.78; 95% CI 1.11–2.85)

Prehospital/ER Treatment



F. Brigo et al. Epilepsy & Behav 2015

Intravenous AEDs

No definite superiority among AEDs

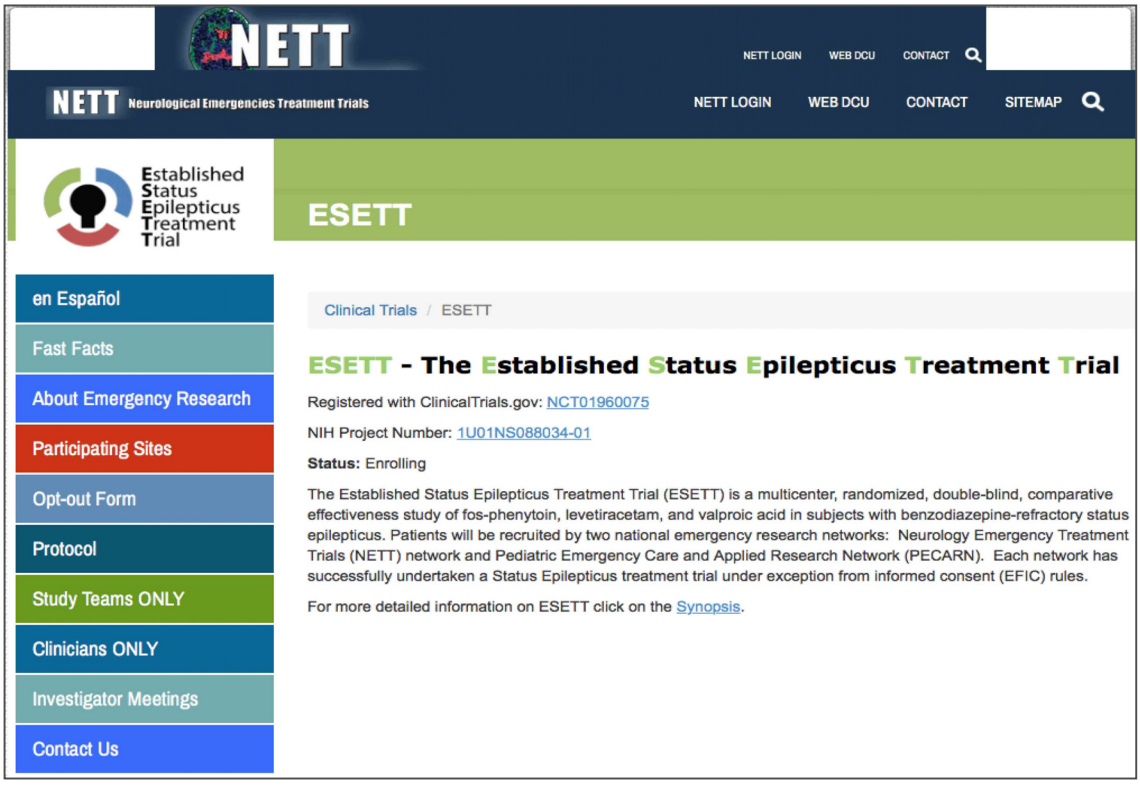
Results for other comparisons of anticonvulsant therapies were uncertain.
Prasad et al. Cochrane Database 2014

IV VPA has similar efficacy but better tolerability than IV phenobarbital (level B) as second therapy after BDZ failure

Insufficient data for the efficacy of PHT or LEV as second therapy after BDZ failure (level U).

Insufficient data for efficacy of phenytoin vs. fosphenytoin
(level U), but fosphenytoin is better tolerated compared with phenytoin (level B).

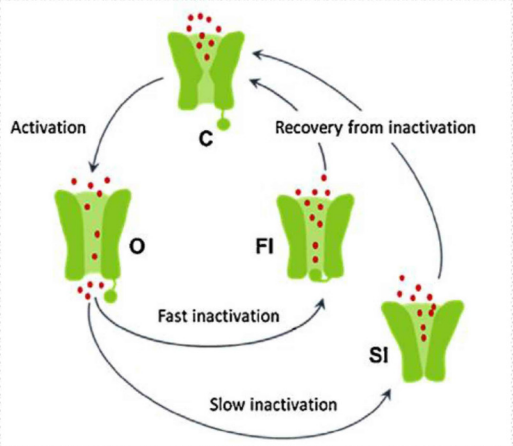
Glauser et al. AES Evidence-Based Guideline: 2016

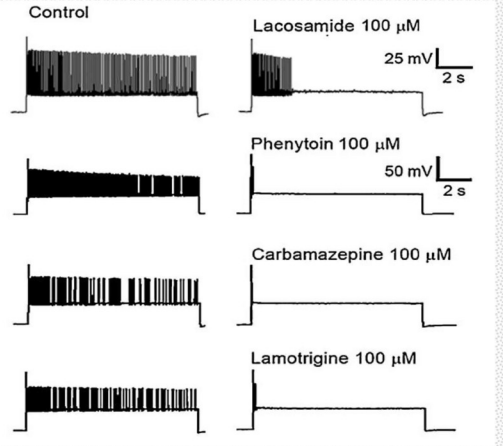


Intravenous AEDs

Lacosamide (LCS)

Act by slow inactivation of voltage-gated sodium channels
Usually 200–400 mg as fast infusion for 5–10 min.
(loading 10–12 mg/kg, maintenance 0.4 mg/kg/min)





Intravenous AEDs

Lacosamide in status epilepticus: Update on the TRENdS study

Aatif M. Husain *
Department of Neurology, Duke University Medical Center and Neurodiagnostic Center, Veterans Affairs Medical Center, Durham, NC, USA

Lacosamide (LCS)

Only one RCTs which terminated earlier due to poor recruitments & financial problem (74 out of 200 planned)

: TRENdS study (Treatment of Recurrent Electrographic Nonconvulsive Seizures) for comparison between IV LCS vs fPHT
; No results analyzed.

Intravenous AEDs

Lacosamide (LCS)

98 pts, retrospective case series by Spain multicenter

complete seizure cessation in 70.9% of episodes

48 pts, retrospective case series by E. Trinka

SF in 42 patients (88%). Success rate in patients with SE receiving LCM as first or second drug was 100% (8 of 8), as third drug 81% (11 of 15), and as fourth or later drug 75% (6 of 8).

Treatment of RSE

Table 1. Pharmcacological characteristics of anesthetics used in refractory SE

	Barbiturates	Propofol	Midazolam
Used since	Before 1960	End of 1980	Early1990
Mechanism of action			
$GABA_A$ agonistic	+++	+++	+++
NMDA antagonistic	+	(+)	
Ca channel modulation	(+)	(+)	
Na channel modulation		(+)	
Elimination half-life after prolonged administration	THP: 14–36 h PTB: 15–22 h	1–2 h	6–50 h
Accumulation	+++	(+)	++
Tachyphylaxis		(+)	+++
Hypotension	+++	+++	++
Other adverse effects	Immunological suppression	Infusion syndrome	
Administration (Lowenstein and Alldredge, 1998; Shorvon, 2001; Rossetti et al., 2004; Leppert et al., 2005; Chen and Wasterlain, 2006; Minicucci et al., 2006)			
Loading dose	THP: 2–7 mg/kg PTB: 5–15 mg/kg	2 mg/kg	0.1–0.3 mg/kg
Maintenance dose	THP: 3–5 mg/kg/h PTB: 1–5 mg/kg/h	2–10 mg/kg/h	0.05–0.6 mg/kg/h
Remarks	Long wash-out time	Limit to 48 h, Combine with BDZ	Increasing doses needed with time

THP, thiopental; PTB, pentobarbital; BDZ, benzodiazepines.

Treatment of RSE

Pentobarbital(US)/thiopental(EU)

: 3~5mg/kr/hr

Pros

- strong antiepileptic action: GABA (synap/extrasyn), NMDA
- extensive clinical experience
- tendency to lower core temperature/ICP
- theoretical neuroprotective effects

Cons

- Zero-order pharmacokinetics
- Body accumulation (long recovery time)
- Auto-induction, drug-drug interactions
- hypotension, cardio-respiratory depression, pancreatic & hepatic toxicity
- propylene glycol
- Immunological suppression

Treatment of RSE

Propofol

: 30~200 mcg/kr/min, Do not exceed > 65 mcg/kg/min

Pros

- excellent pharmacokinetic properties
- :very rapid onset & recovery
- no drug interactions
- less hypotension & cardio-respiratory depression

Cons

- propofol infusion syndrome, especially in children
- pain at the injection site
- drug-induced involuntary movements and seizures

Treatment of RSE

Propofol infusion syndrome in patients with refractory status epilepticus: An 11-year clinical experience*

Vivek N. Iyer, MD; Rebecca Hoel, PharmD; Alejandro A. Rabinstein, MD

Propofol infusion SD

: 1997~2008, records review, 31 RSE with pro

Sx: in 11 pts (35.4%) 3 C.A. (9.6%)

metabolic acidosis, rhabdomyolysis, cardiac arrest, lipid/hepatic problem, renal failure, death

Table 4. Propofol dosing and laboratory values in the propofol infusion syndrome (PRIS) versus non-PRIS group

Characteristics	PRIS Group (Other Than Cardiac Arrest)[a] (n = 11)	Non-PRIS Group (n = 17)	p
Peak creatine kinase levels, median (range)	619 (57–12017)	1513 (1241–1833)	.28
Lowest pH, median (range)	7.38 (7.19–7.41)	7.34 (6.92–7.42)	.89
Days of intravenous antiepileptics, median (range)	8.5 (2–55)	5 (2–29)	.13
No. of intravenous antiepileptics, median (range)	3 (2–4)	3 (1–5)	.89
Propofol dosing, median (range)			
Peak rate, μg/kg/min	102 (50–200)	43 (19–175)	.005
Total cumulative dose, mg	27,260 (9540–51,330)	3600 (336–43,870)	.001
Total infusion time, hours	92 (36–391)	36 (2–169)	.006
Infusion rate μg/kg/min,	57 (10–118)	30 (10–85)	.007

Treatment of RSE

Caution in Propofol use

: Do not exceed > 65 mcg/kg/min
: Do not exceed > 48 hrs (S. shorvon & Rossetti)
: Do not use or use in caution in children
: Use in caution in elderly

Refractory status epilepticus: third stage/intensive care unit

Time	Drug treatment	General measures	Emergency investigations
>60 min	General anaesthesia; Thiopental sodium 3–5 mg/kg bolus, then 3–5 mg/kg/h or Pentobarbital 10–15 mg/kg, then 0.5–1 mg/kg/h or Midazolam 0.2 mg/kg boluses, max. 2 mg/kg, then 0.05–2 mg/kg/h **or only in adults:** Propofol 1–2 mg/kg boluses, max. 10 mg/kg, then 2–4(–10) mg/kg/h	• Intensive care; ventilatory and haemodynamic treatment • Increased intracranial pressure; measure and treat if signs • Anaesthesia continued for 12–24 hours after last clinical or electrographic seizure • Optimise maintenance AED treatment	• Continuous EEG monitoring; electrographic seizures, depth of anaesthesia (burst-suppression) • Monitor Astrup, potassium, sodium, glucose, lactate, concentrations of AEDs

Kalviainen *et al. Finnish guidelines*

Treatment of RSE

Midazolam

: 0.05~2 mg/kr/hr

Pros

strong antiepileptic action
only BDZ with less accumulation (more water- soluble)
No propylene glycol

Cons

hypotension, cardio-respiratory depression
risk of hepatic and renal impairment
risk of tolerance & breakthrough seizures (tachyphylaxis, probably overestimated?)

Treatment of RSE

ketamine

: 1~7.5 mg/kr/hr

Pros

no cardiodepressant or hypotensive action
- so called sympathomimetic activity
anti-NMDA action: Neuroprotective potential

Cons

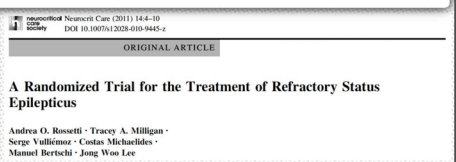
limited published experience
possible neurotoxicity
drug-induced involuntary movements and seizures

Comparison?

Only One RCT for RSE Treatment

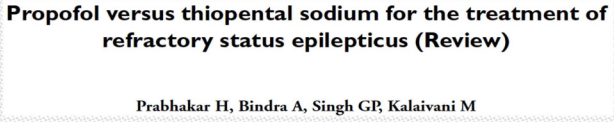
By Rossetti, In US & Swiss, 2011
Randomized, single blind, multi-center trial
Propofol vs. barbiturates
Target: 150 pts
Only 24 pts recruited after 3 yrs

RSE control:
43% in PRO vs. 22% barbiturates (P=0.40)
Mortality:
43 vs. 34%; (P=1.00)
Return to baseline at 3 months:
36 vs. 44%; (P=1.00)
Intubation days:
4 vs. 13.5; (P=0.030)



Comparison?

Cochrane DB Review



"There was no evidence of a difference between the drugs with respect to the outcome measures such as control of seizure activity and functional outcome at three months"

There is lack of robust and randomised controlled evidence that can clarify the efficacy of propofol and thiopental sodium over each other in the treatment of RSE.

Comparison?

Treatment of Refractory Status Epilepticus with Pentobarbital, Propofol, or Midazolam: A Systematic Review

*†Jan Claassen, †Lawrence J. Hirsch, †Ronald G. Emerson, and *Stephan A. Mayer

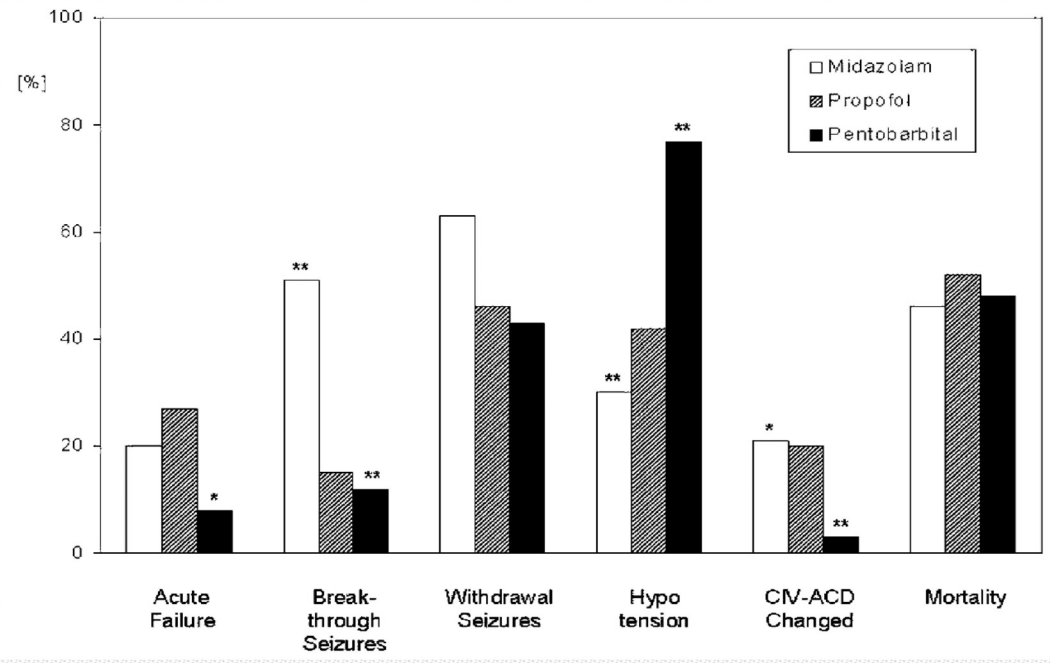
Review, Columbia (Claassen et al Epilepsia 2002)

193 pts, paper review, 48% mortality
PB vs. MDZ vs. PRO (PB - BS, PRO or MDZ – Sz T)
PB is superior in efficacy, but more hypotension
MDZ has more breakthourgh seizures

TABLE 3. *Treatment characteristics*

	Continuous i.v. medication		
	Midazolam	Propofol	Pentobarbital
Doses reported	53	32	62
Loading dose (mg/kg)	0.2	1.0	13.0
Minimal infusion rate (mg/kg/h)	0.08 ± 0.04	2.94 ± 2.00	1.84 ± 1.59
Maximal infusion rate (mg/kg/h)	0.23 ± 0.17	6.98 ± 5.34	3.17 ± 2.11
Duration of continuous infusion (h)	96.0 (53)	36.0 (31)	30.0 (61)
EEG monitoring			
Continuous EEG monitoring	80 (43/54)	76 (25/33)	27 (29/106)
Intermittent EEG monitoring	11 (6/54)	15 (5/33)	71 (75/106)
None or unknown	9 (5/54)	9 (3/33)	2 (2/106)
Titration goal			
Seizure control only	100 (43/43)	62 (13/21)	4 (3/82)
EEG background suppression	0 (0/43)	38 (8/21)	96 (79/82)

Comparison?



Comparison?

Experts' Opinions Survey

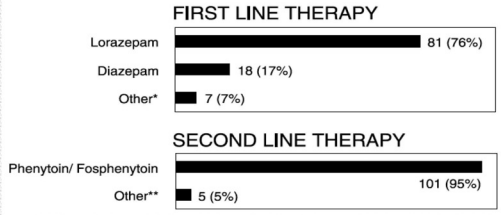
Journal of the Neurological Sciences 211 (2003) 37–41
www.elsevier.co

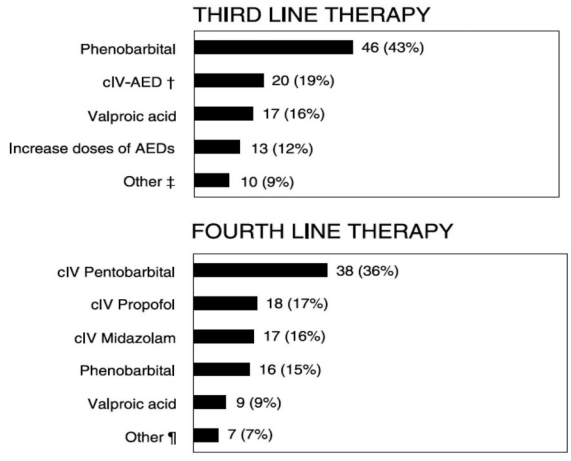
Treatment of status epilepticus: a survey of neurologists

Jan Claassen[a,b], Lawrence J. Hirsch[b], Stephan A. Mayer[a,*]

2003, by Columbia group

36% chose PB, 16% chose MDZ or PRO (17%) in RSE





Comparison?

Shorvon (2012)

BRAIN
A JOURNAL OF NEUROLOGY
REVIEW ARTICLE

The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy

Simon Shorvon and Monica Ferlisi

1168 pts, paper review

Less SE in midazolam (also less tachyphylaxis)

Sz control is least in PB, best in MDZ

Least mortality in MDZ

Table 2 Overall outcome of anaesthetic therapy

Outcome	Thiopental/pentobarbital (*n* = 192)	Midazolam (*n* = 585)	Propofol (*n* = 143)
Control	64% (123/192)	78% (458/585)	68% (97/143)
No control ever achieved[a]	5% (9/192)	16% (93/585)	11% (16/143)
Breakthrough seizures	0% (0/192)	3% (19/585)	1% (2/143)
Withdrawal seizures	9% (18/192)	<1% (2/585)	6% (8/143)
Therapy failure because of side-effects	3% (5/192)	<1% (1/585)	6% (8/143)
Death during therapy	19% (37/192)	2% (12/585)	8% (12/143)

Comparison?

Experts' Opinion Survey

Neurocrit Care (2013) 18:193–200
DOI 10.1007/s12028-012-9790-1

ORIGINAL ARTICLE

Treatment of Status Epilepticus: An International Survey of Experts

2013, NCS
Prefer cIV therapy, especially MDZ & PRO
In children, reluctant to choose PRO, pentobarbital was chosen later
71% selected 24 hr of maintenance after Tx success

Comparison?

Table 2 Case 1

First line: $N = 50$		
LZP	46	92 %
PHT	2	4 %
DZP	1	2 %
MDZ	1	2 %
Second line: $N = 50$		
PHT	40	80 %
Push 1	4	8 %
LEV	3	6 %
MDZ	1	2 %
VPA	1	2 %
Pb	1	2 %
Third line: $N = 50$		
MDZ	10	20 %
Propofol	10	20 %
Lev	10	20 %
Phenobarb	9	18 %
VPA	5	10 %
PHT	3	6 %
Pentobarb	1	2 %
Thio	1	2 %
Push 2	1	2 %
Fourth line: $N = 50$		
MDZ	12	24 %
Pentobarb	10	20 %
Propofol	8	16 %
VPA	6	12 %
Phenobarbital	5	10 %
Thiopental	4	8 %
Lev	3	6 %
Push 3	2	4 %
Fifth line: $N = 50$		
Pentobarb	14	28 %
Propofol	9	18 %
MDZ	9	18 %
Push 4	8	16 %
Lev	3	6 %
PB	3	6 %
Lacosamide	2	4 %
VPA	1	2 %
Thiopental	1	2 %

How deep sedation?

Intensity and Duration of RSE Treatment?

: No definite Randomized trial, based on Review and Opinions

2003 Survey by Claassen showed only 56% BS
: mostly by PB
: MDZ? – cessation of electrographic seizure

Drugs	EEG	Recommendations by	Comments
Thiopental	BS	Italian League Against Epilepsy	"No data to support a standardized regimen for the intensity and duration of treatment for RSE" NCS 2012 Guideline
Propofol	BS	EFNS	
Midazolam	Cessation of electrographic Sz	EFNS	
Isoflurane	BS	Italian League Against Epilepsy	

How deep sedation?

Epilepsia, 47(Suppl. 5):9–15, 2006
Blackwell Publishing, Inc.

Treatment of Status Epilepticus in Adults: Guidelines of the Italian League Against Epilepsy

MANAGEMENT OF REFRACTORY SE (AFTER 60–90 MIN)

Assistance of an anesthesiologist is required (see synthesis and recommendations 8,12,13)

Pharmacological treatment (see synthesis and recommendations 9,10,14)

Thiopental

5–7 mg/kg i.v. in 20 s. followed by 50 mg boluses at intervals of 2–3 min until complete seizure control and an EEG "suppression burst" pattern are obtained:

- subsequent continuous infusion (3–5 mg/kg/h) must be continued for 12–48 h, maintaining the EEG "suppression burst" pattern
- EEG monitoring is required

Propofol

2–5 mg/kg as i.v. bolus (a second bolus can be given), followed by continuous infusion (up to 5 mg/kg/h) for at least 1 h:

- EEG monitoring is required

Midazolam (see synthesis and recommendation 9):

- 5–10 mg i.m. or rectally. A second dose can be administered after 15 min
- 0.1–0.3 mg/kg as i.v. bolus, at a maximum infusion rate of 4 mg/min (a second dose can be administered after 15 min); as an alternative to the bolus, an i.v.

Isoflurane (see synthesis and recommendation 10):

- administered at 0.8–2 vol%, titrated to obtain the EEG "suppression burst" pattern
- use only for refractory SE

How deep sedation?

European Journal of Neurology 2010, **17:** 348–355 doi:10.1111/j.1468-1331.2009.02917.x

EFNS GUIDELINES/CME ARTICLE

EFNS guideline on the management of status epilepticus in adults

H. Meierkord[a], P. Boon[b], B. Engelsen[c,d], K. Göcke[e], S. Shorvon[f], P. Tinuper[g] and M. Holtkamp[h]

[a]*Institute of Neurophysiology, Charité – Universitätsmedizin Berlin, Berlin, Germany;* [b]*Department of Neurology, Ghent University Hospital, Ghent, Belgium;* [c]*Department of Neurology, Haukeland University Hospital, Bergen;* [d]*Department of Clinical Medicine, University of Bergen, Bergen, Norway;* [e]*Deutsche Epilepsievereinigung e.V., Berlin, Germany;* [f]*Institute of Neurology, University College London, London, UK;* [g]*Department of Neurological Sciences, University of Bologna, Bologna, Italy; and* [h]*Department of Neurology, Charité – Universitätsmedizin Berlin, Berlin, Germany*

Depending on the anaesthetic used in the individual in-house protocol, we recommend titration against an EEG burst suppression pattern with propofol and barbiturates. If midazolam is given, seizure suppression is recommended. This goal should be maintained for at least 24 h. Simultaneously, initiation of the chronic medication, the patient will be treated with in future should be initiated (GPP).

Treatment duration?

Duration of RSE Treatment?

: No definite Randomized trial, based on Review and Opinions

12-24 hr: Lowenstein and Alldredge, 1998
12 hr: S. Shorvon, 2001
24 hr: Chen and Wasterlain, 2006
12-24 hr: Holtkamp, 2007
48 hr: Swiss National Consensus, Leppert et al. 2007
12-48 hr: Italian Guidelines, Minicucci, 2006

.
.

Dosing of continuous infusion AEDs for RSE should be titrated to cessation of electrographic seizures or burst suppression (strong recommendation, very low quality).

A period of 24–48 h of electrographic control is recommended prior to slow withdrawal of continuous infusion AEDs for RSE (weak recommendation, very low quality).

Brophy et al. *Neurocrit Care* 2012

cEEG?

cEEG Guideline?

1. The use of cEEG is usually required for the treatment of SE (strong recommendation, very low quality).

2. Continuous EEG monitoring should be initiated within 1 h of SE onset if ongoing seizures are suspected (strong recommendation, low quality).

3. The duration of cEEG monitoring should be at least 48 h in comatose patients to evaluate for non-convulsive seizures (strong recommendation, low quality).

4. The person reading EEG in the ICU setting should have specialized training in cEEG interpretation, including the ability to analyze raw EEG as well as quantitative EEG tracings (strong recommendation, low quality).

Brophy et al *Neurocrit Care* 2012

cEEG?

Indications of EEG Monitoring in the ICU (Friedman D, et al. 2009)
1. Detection of nonconvulsive seizures and characterization of spells in patients with altered mental status with:
A history of epilepsy Fluctuating level of consciousness Acute brain injury Recent convulsive status epilepticus – subtle SE (SE in coma) Stereotyped activity such as paroxysmal movements, nystagmus, twitching, jerking, hippus, autonomic variability
2. Monitoring of ongoing therapy
Induced coma for elevated intracranial pressure or refractory status epilepticus Assessing level of sedation
3. Ischemia detection
Vasospasm in subarachnoid hemorrhage Cerebral ischemia in other patients at high risk for stroke
4. Prognosis
Following cardiac arrest Following acute brain injury

cEEG?

Detection of electrographic seizures with continuous EEG monitoring in critically ill patients

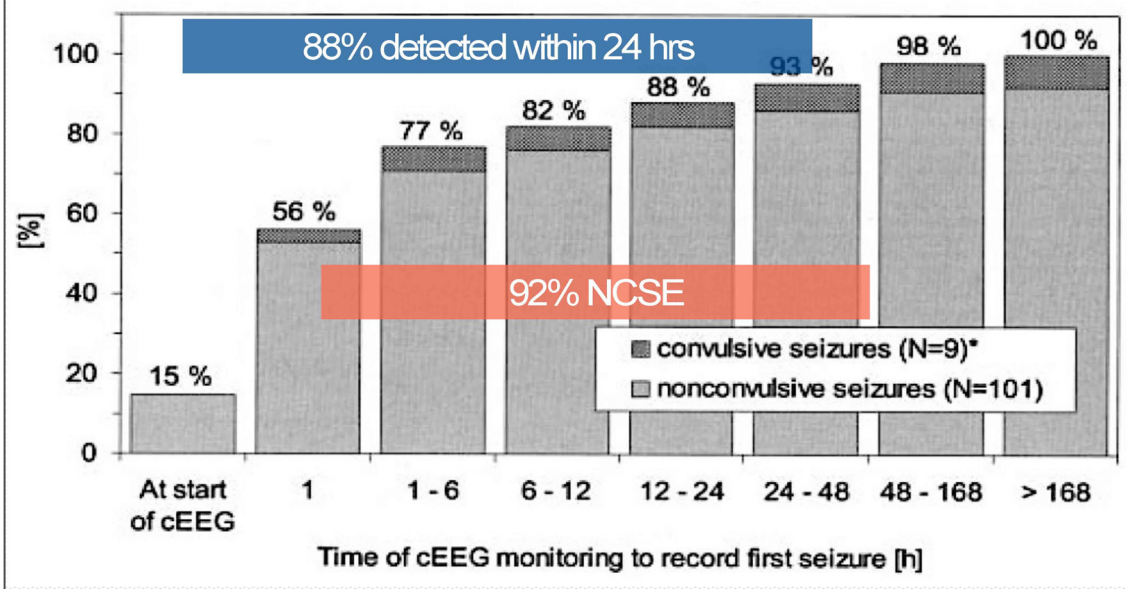
J. Claassen, MD; S.A. Mayer, MD; R.G. Kowalski, BS; R.G. Emerson, MD; and L.J. Hirsch, MD

Abstract—*Objective:* To identify patients most likely to have seizures documented on continuous EEG (cEEG) monitoring and patients who require more prolonged cEEG to record the first seizure. *Methods:* Five hundred seventy consecutive patients who underwent cEEG monitoring over a 6.5-year period were reviewed for the detection of subclinical seizures or evaluation of unexplained decrease in level of consciousness. Baseline demographic, clinical, and EEG findings were recorded and a multivariate logistic regression analysis performed to identify factors associated with 1) any EEG seizure activity and 2) first seizure detected after >24 hours of monitoring. *Results:* Seizures were detected in 19% (n = 110) of patients who underwent cEEG monitoring; the seizures were exclusively nonconvulsive in 92% (n = 101) of these patients. Among patients with seizures, 89% (n = 98) were in intensive care units at the time of monitoring. Electrographic seizures were associated with coma (odds ratio [OR] 7.7, 95% CI 4.2 to 14.2), age <18 years (OR 6.7, 95% CI 2.8 to 16.2), a history of epilepsy (OR 2.7, 95% CI 1.3 to 5.5), and convulsive seizures during the current illness prior to monitoring (OR 2.4, 95% CI 1.4 to 4.3). Seizures were detected within the first 24 hours of cEEG monitoring in 88% of all patients who would eventually have seizures detected by cEEG. In another 5% (n = 6), the first seizure was recorded on monitoring day 2, and in 7% (n = 8), the first seizure was detected after 48 hours of monitoring. Comatose patients were more likely to have their first seizure recorded after >24 hours of monitoring (20% vs 5% of noncomatose patients; OR 4.5, $p = 0.018$). *Conclusions:* CEEG monitoring detected seizure activity in 19% of patients, and the seizures were almost always nonconvulsive. Coma, age <18 years, a history of epilepsy, and convulsive seizures prior to monitoring were risk factors for electrographic seizures. Comatose patients frequently required >24 hours of monitoring to detect the first electrographic seizure.

NEUROLOGY 2004;62:1743–1748

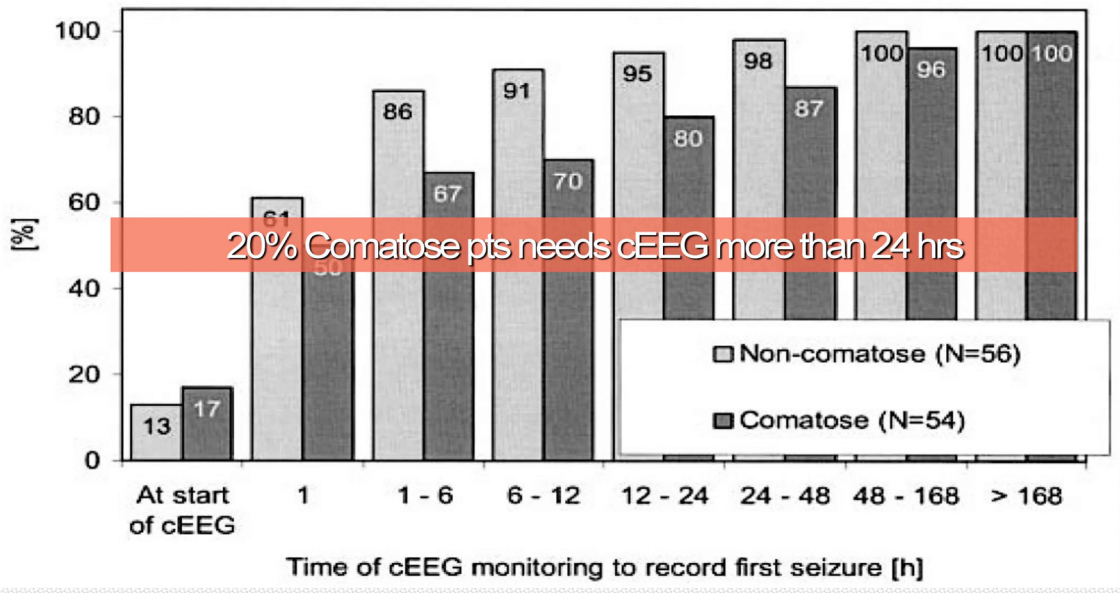
Claassen, et al. 2004

cEEG?



Claassen, et al. 2004

cEEG?



Claassen, et al. 2004

Other Treatments

Table 3 Non-anaesthetic therapies

Treatment	Dose recommended[a]/ physical parameter	Range of doses used (from the literature review)	Major adverse effects	Contrain
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 f
Pyridoxine	30 mg/kg (children) 100–200 mg/day (adults)	2–300 mg/day	Bradycardia, hypothermia, apnoea, sensory neuropathy	Hyperse
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 hyperten- sion o
Immunoglobulins	Intravenous immunoglobulins 0.4 g/kg/day for 5 days (see text)	Various	Coagulation disorders, hypertension	Coagulopathy, selective deficiency of IgA

Results were controversy!
NMDA blocking effect
TARGET: 35~142 mEq/L

Usually in borderline of metabolism!
Anecdotal reports in non pyridoxine dependent

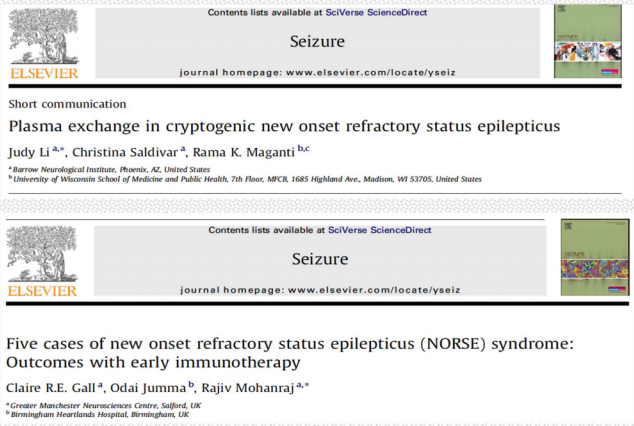
9 patients in 4 series
All SF, 7/9 recovered

Recent Hot issues related with immune related RSE

Other Treatments

Increased Use of immune modulations

Increased identification of NORSE, anti-NMDA R encephalitis, FIRES



Contents lists available at SciVerse ScienceDirect

Seizure

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

Short communication

Plasma exchange in cryptogenic new onset refractory status epilepticus

Judy Li [a,*], Christina Saldivar [a], Rama K. Maganti [b,c]

[a] Barrow Neurological Institute, Phoenix, AZ, United States
[b] University of Wisconsin School of Medicine and Public Health, 7th Floor, MFCB, 1685 Highland Ave., Madison, WI 53705, United States

Contents lists available at SciVerse ScienceDirect

Seizure

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

Five cases of new onset refractory status epilepticus (NORSE) syndrome: Outcomes with early immunotherapy

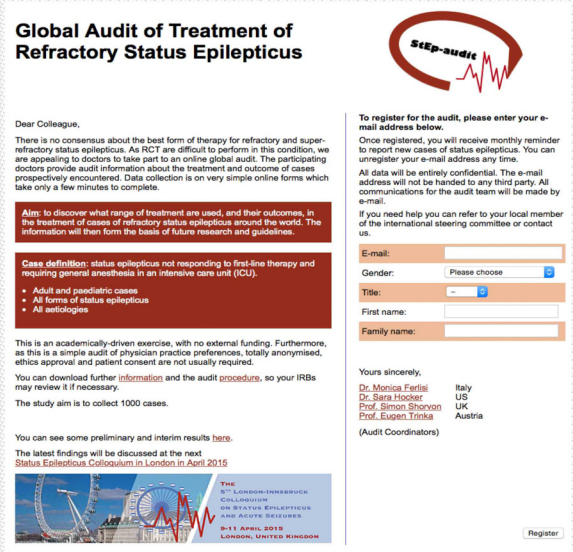
Claire R.E. Gall [a], Odai Jumma [b], Rajiv Mohanraj [a,*]

[a] Greater Manchester Neurosciences Centre, Salford, UK
[b] Birmingham Heartlands Hospital, Birmingham, UK

new onset refractory status epilepticus (NORSE)

Global Audit of RSE

Needs for collaborative studies
: Global Audit of Treatment of RSE



Global Audit of Treatment of Refractory Status Epilepticus

StEP-audit

Dear Colleague,

There is no consensus about the best form of therapy for refractory and super-refractory status epilepticus. As RCT are difficult to perform in this condition, we are appealing to doctors to take part to an online global audit. The participating doctors provide audit information about the treatment and outcome of cases prospectively encountered. Data collection is on very simple online forms which take only a few minutes to complete.

Aim: to discover what range of treatment are used, and their outcomes, in the treatment of cases of refractory status epilepticus around the world. The information will then form the basis of future research and guidelines.

Case definition: status epilepticus not responding to first-line therapy and requiring general anesthesia in an intensive care unit (ICU).

- Adult and paediatric cases
- All forms of status epilepticus
- All aetiologies

This is an academically-driven exercise, with no external funding. Furthermore, as this is a simple audit of physician practice preferences, totally anonymised, ethics approval and patient consent are not usually required.

You can download further information and the audit procedure, so your IRBs may review it if necessary.

The study aim is to collect 1000 cases.

You can see some preliminary and interim results here.

The latest findings will be discussed at the next Status Epilepticus Colloquium in London in April 2015

THE 5TH LONDON-INNSBRUCK COLLOQUIUM ON STATUS EPILEPTICUS AND ACUTE SEIZURES
9-11 APRIL 2015
LONDON, UNITED KINGDOM

To register for the audit, please enter your e-mail address below.

Once registered, you will receive monthly reminder to report new cases of status epilepticus. You can unregister your e-mail address any time.

All data will be entirely confidential. The e-mail address will not be handed to any third party. All communications for the audit team will be made by e-mail.

If you need help you can refer to your local member of the international steering committee or contact us.

E-mail:
Gender: Please choose
Title:
First name:
Family name:

Yours sincerely,

Dr. Monica Ferlisi — Italy
Dr. Sara Hocker — US
Prof. Simon Shorvon — UK
Prof. Eugen Trinka — Austria

(Audit Coordinators)

Register

London-Innsbruck Colloquium on status epilepticus (Shorvon & Trinka)

Target:1,000 RSE

https://www.status-epilepticus.net

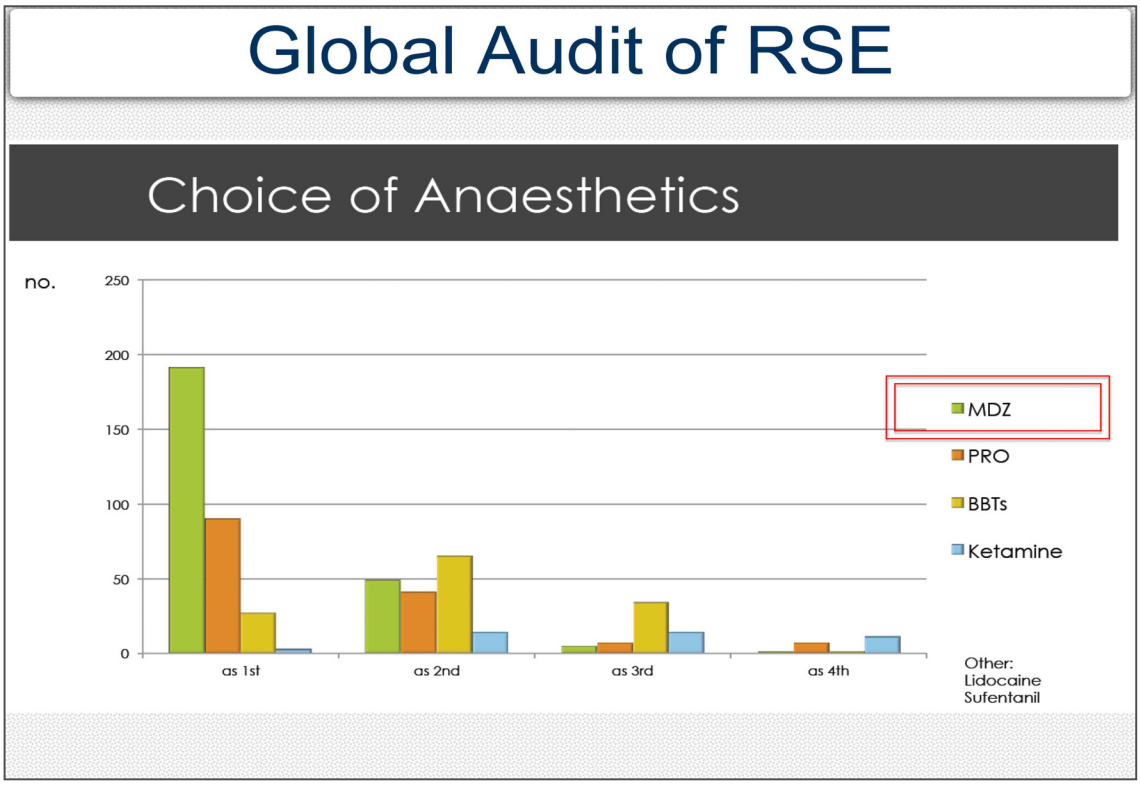
Global Audit of RSE

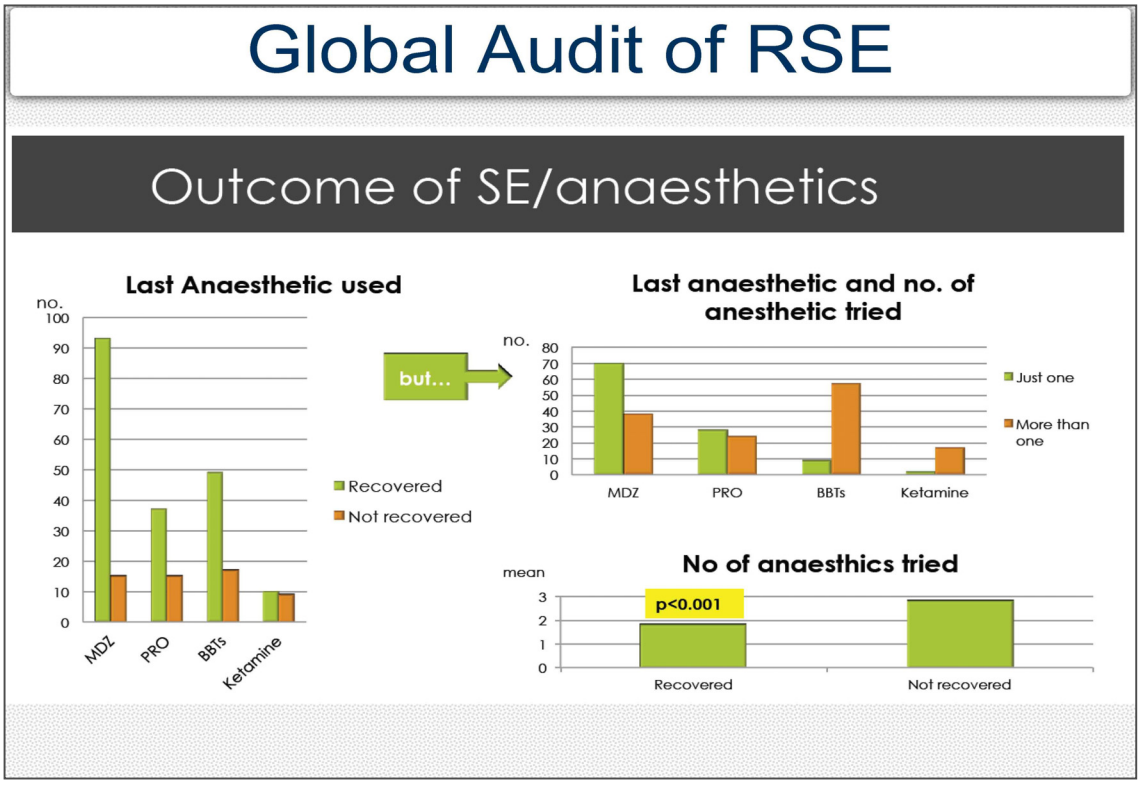
Countries involved:	Asia:8	25.81%
	Africa:3	5.36%
	Europe:18	37.5%
	Middle East:4	19.05%
	North America:2	50%
	Pacific:1	5%
	South America:3	23.08%
	Total :39	**18.06%**

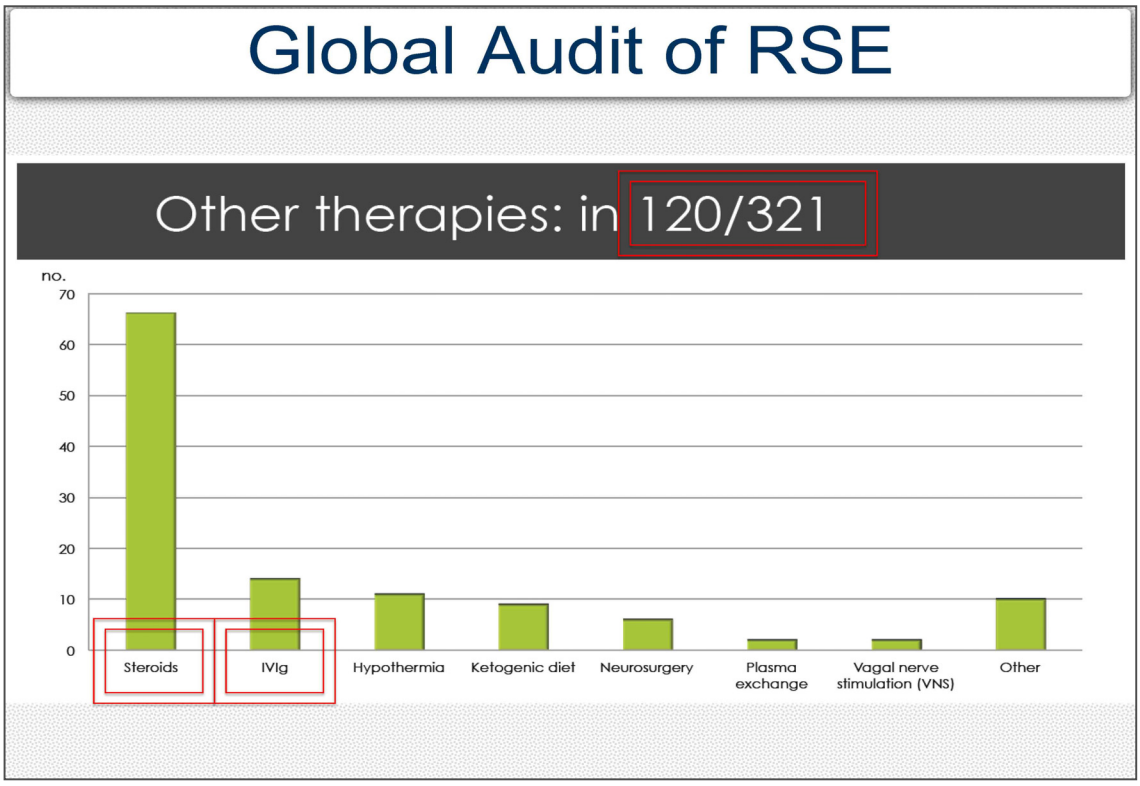
321 cases
260 case with known outcome
57 cases with 6 months of follow up

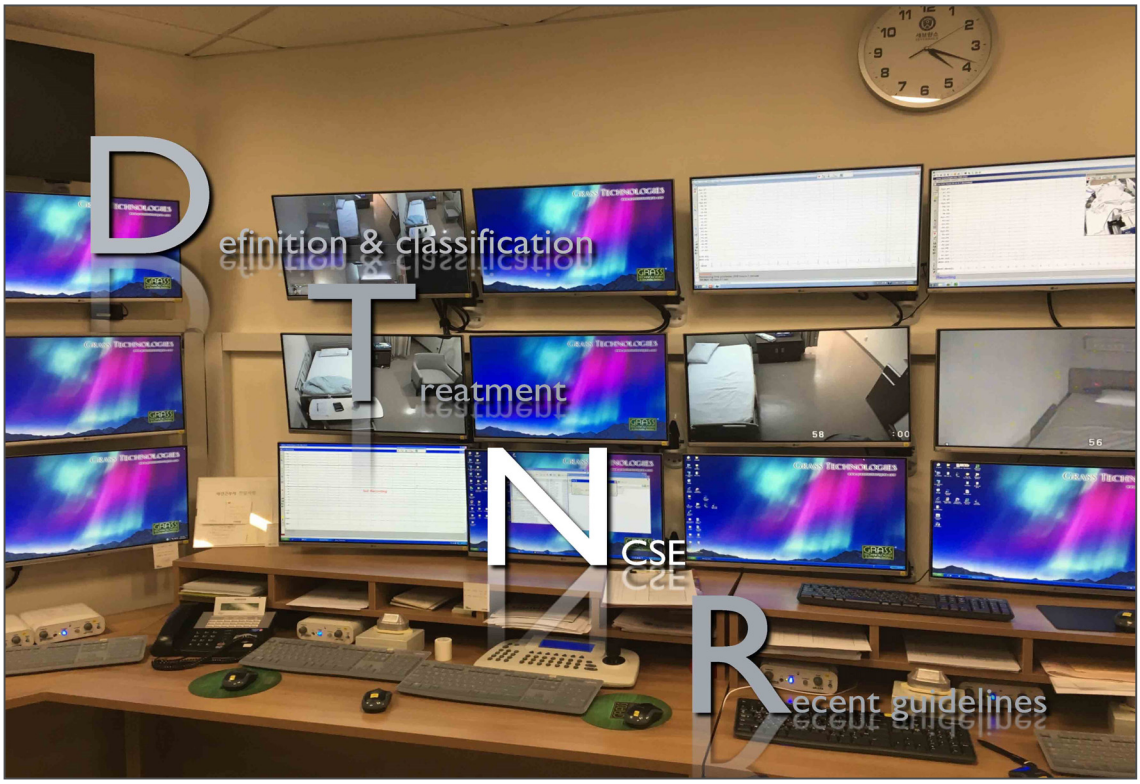
Global Audit of RSE

Age	35 y (mean)	0-91y (range)
Gender	M 58%	F 42%
Prior history of epilepsy	Yes 40%	No 60%
Etiologies	Cryptogenic	22%
	Acute encephalitis	12%
	Vascular	12%
	Anoxic	12%
	Other infection	8%
	AEDs withdrawal	7%
	Cerebral tumor	6%
	Immunological	6%
	Metabolic	5%
	Trauma	4%
	Alcohol	4%


Global Audit of RSE
Choice of Anaesthetics
no.
250
200
150
100
50
0
as 1st
as 2nd
as 3rd
as 4th
MDZ
PRO
BBTs
Ketamine
Other:
Lidocaine
Sufentanil


Global Audit of RSE
Outcome of SE/anaesthetics
Last Anaesthetic used
no.
100
90
80
70
60
50
40
30
20
10
0
MDZ
PRO
BBTs
Ketamine
Recovered
Not recovered
but...
Last anaesthetic and no. of anesthetic tried
no.
80
70
60
50
40
30
20
10
0
MDZ
PRO
BBTs
Ketamine
Just one
More than one
No of anaesthics tried
mean
3
2
1
0
p<0.001
Recovered
Not recovered


Global Audit of RSE
Other therapies: in 120/321
no.
70
60
50
40
30
20
10
0
Steroids
IVIg
Hypothermia
Ketogenic diet
Neurosurgery
Plasma exchange
Vagal nerve stimulation (VNS)
Other


D
efinition & classification
T
reatment
N
CSE
R
ecent guidelines

NCSE

Status epilepticus: a seizure that persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur" ILAE 1981

: Majority of GTCS <2-3 min, Operational definition: 5 min (Lowenstein)

Non-convulsive Status epilepticus: enduring epileptic condition with reduced/altered consciousness, behavioral and vegetative abnormalities or merely subjective symptoms, without major convulsive movements ILAE 1981

: Operational definition: 30 min (Lowenstein)

Prevalence of NCSE in ICU

Study	Study population	EEG type	Design	*N*	Percentage of patients with any seizures (%)	Percentage of seizure patients who had NCSz only (%)
Privitera et al.[5]	Patients with altered level of consciousness or suspected subclinical seizures anywhere in medical center.	37% routine EEG[a]	Prospective	198	37	100 (32% had no subtle clinical signs)
Jordan[6]	Patients admitted to neuro ICU undergoing Ceeg.	cEEG	Retrospective	124	35	74
DeLorenzo et al.[11]	All patients with prior convulsive SE and altered level of consciousness without clinical seizure activity.	cEEG	Prospective	164	48	100 (29% NCSE)
Vespa et al.[9]	All patients with moderate to severe traumatic brain injury admitted to the neuro ICU.	cEEG	Retrospective	94	22	52
Towne et al.[4]	ICU patients in coma without clinical seizure activity.	Routine EEG	Retrospective	236	8	100 NCSE
Vespa et al.[10]	Patients admitted to neuro ICU with stroke or intracerebral hemorrhage.	cEEG	Prospective	109	19	79
Claassen et al.[2]	Patients of all ages with unexplained decreased level of consciousness or suspected subclinical seizures.	cEEG	Retrospective	570	19	92
Pandian et al.[3]	Neuro ICU patients undergoing cEEG for diagnostic purposes or for titration of intravenous therapy for SE.	cEEG	Retrospective	105	68	? (27% NCSE)
Jette et al.[7]	Patients <18 yr old admitted to ICU with unexplained decreased level of consciousness or suspected subclinical seizures.	cEEG	Retrospective	117	44	75
Claassen et al.[8]	Patients with intracerebral hemorrhage with unexplained decreased level of consciousness or suspected subclinical seizures.	cEEG	Retrospective	102	31	58
Oddo et al.[68]	Medical ICU patients without known brain injury undergoing cEEG with unexplained decreased level of consciousness or suspected subclinical seizures.	cEEG	Retrospective	201	10 (additional 7% with PEDs)	67

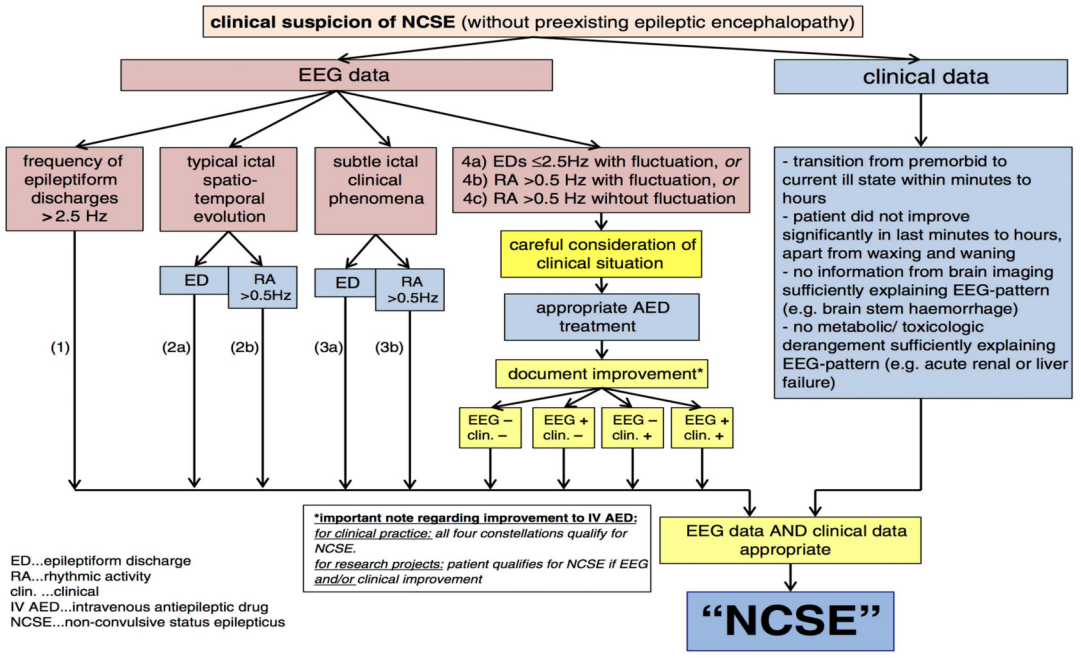
SE = status epilepticus; ICU = intensive care unit; cEEG = continuous EEG; NCSE = nonconvulsive status epilepticus; NCSz = nonconvulsive seizure; PED = periodic epileptiform discharge.
[a] Routine EEG is 30–45 min of recording with or without video.

Seizure
: 8~68%

NCSE
: 27~100%

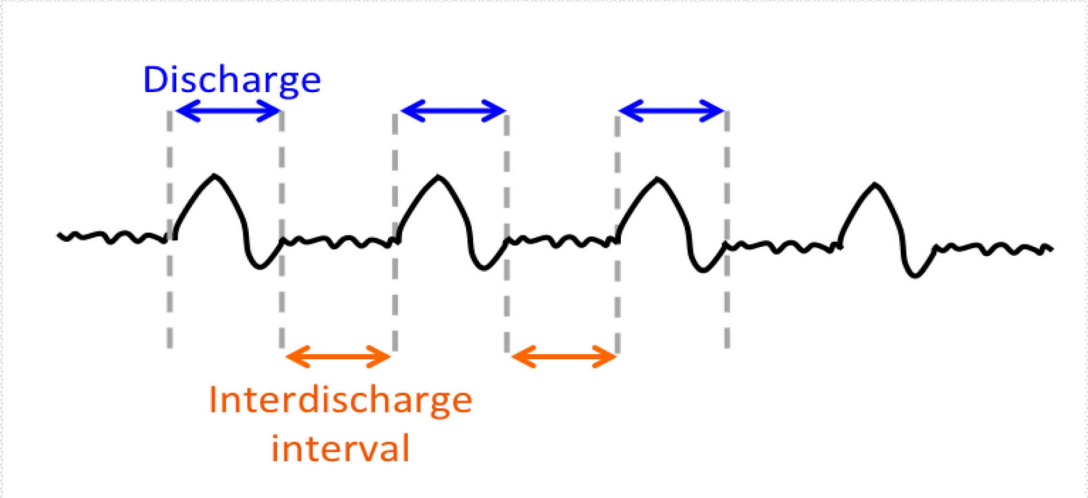
Friedman D, et al. 2009

Salzburg & ACNS Guidelines



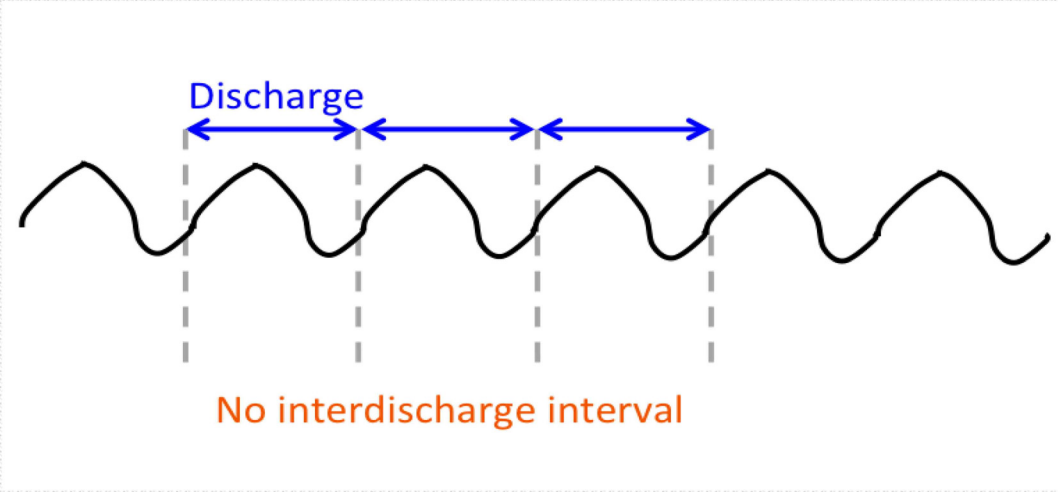
ACNS Standardized ICU-EEG Nomenclature 2012

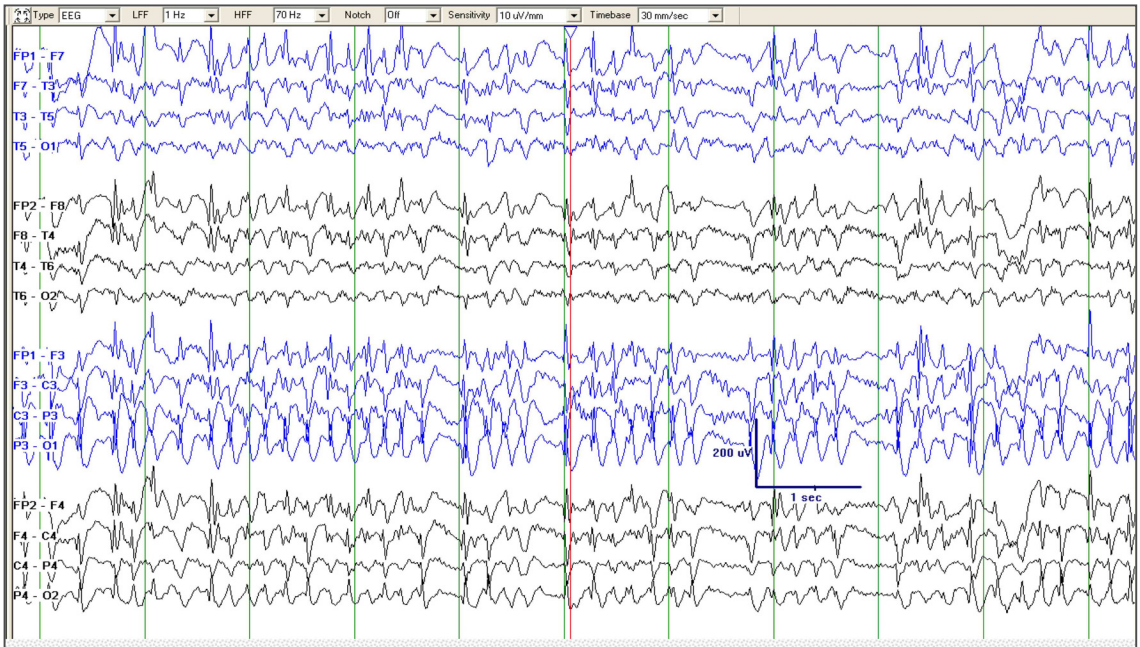
Periodic: Periodic Discharges (PDs)



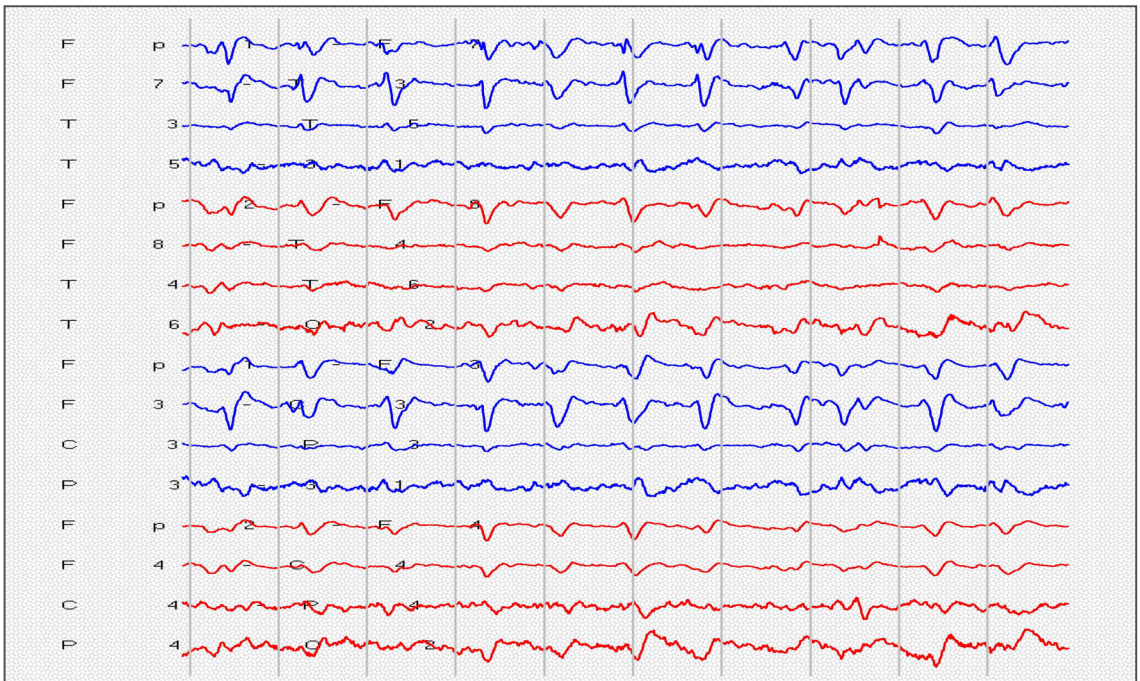
ACNS Standardized ICU-EEG Nomenclature 2012

Rhythmic: Rhythmic Delta Activity (RDA)

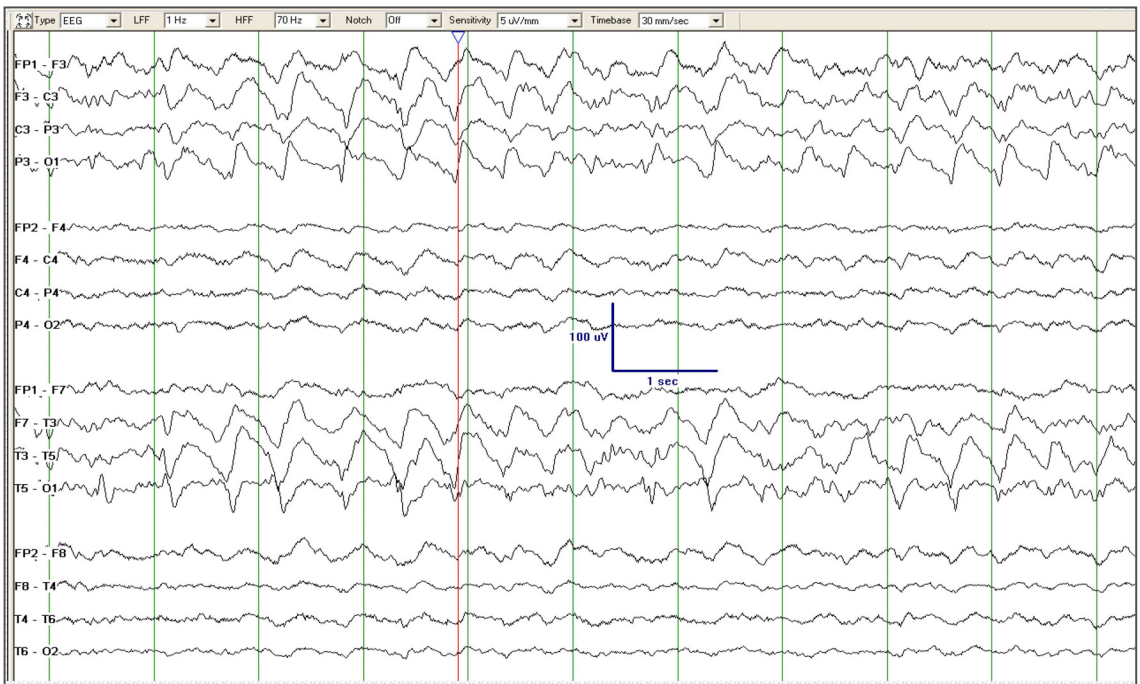




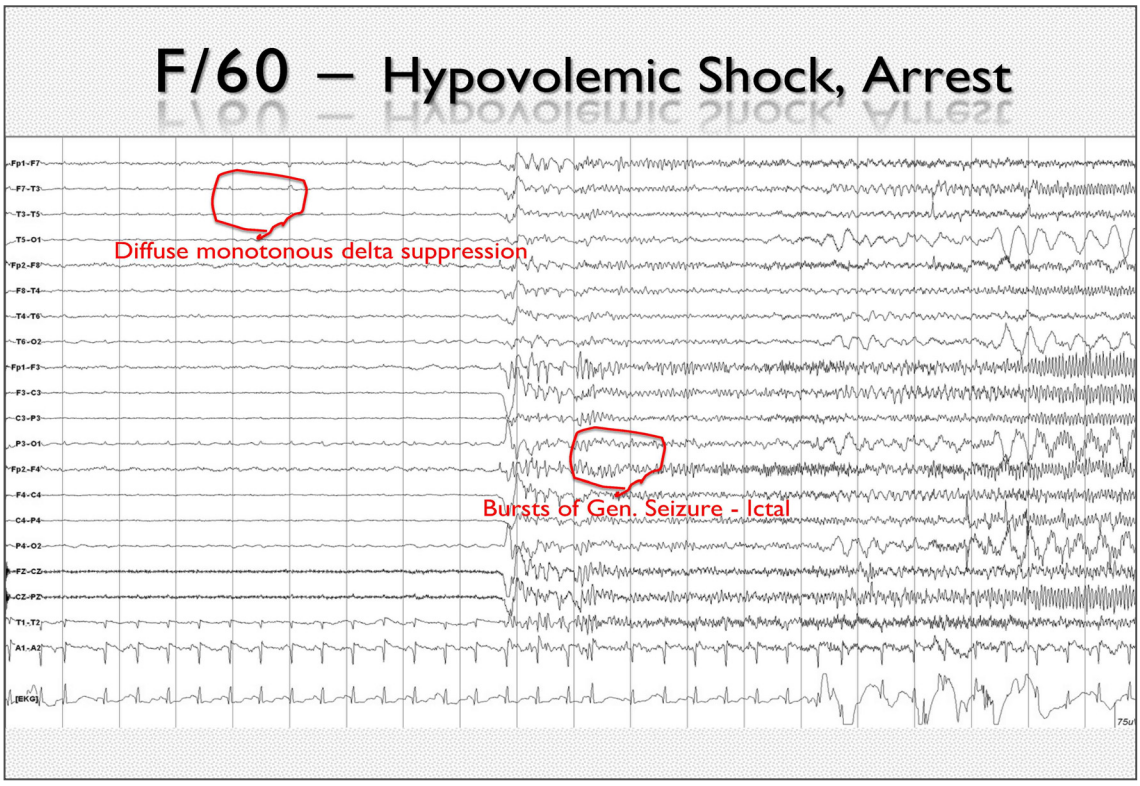
Seizure (NCSE; Since its frequency is more than 4/s, this pattern would not be included in this nomenclature)

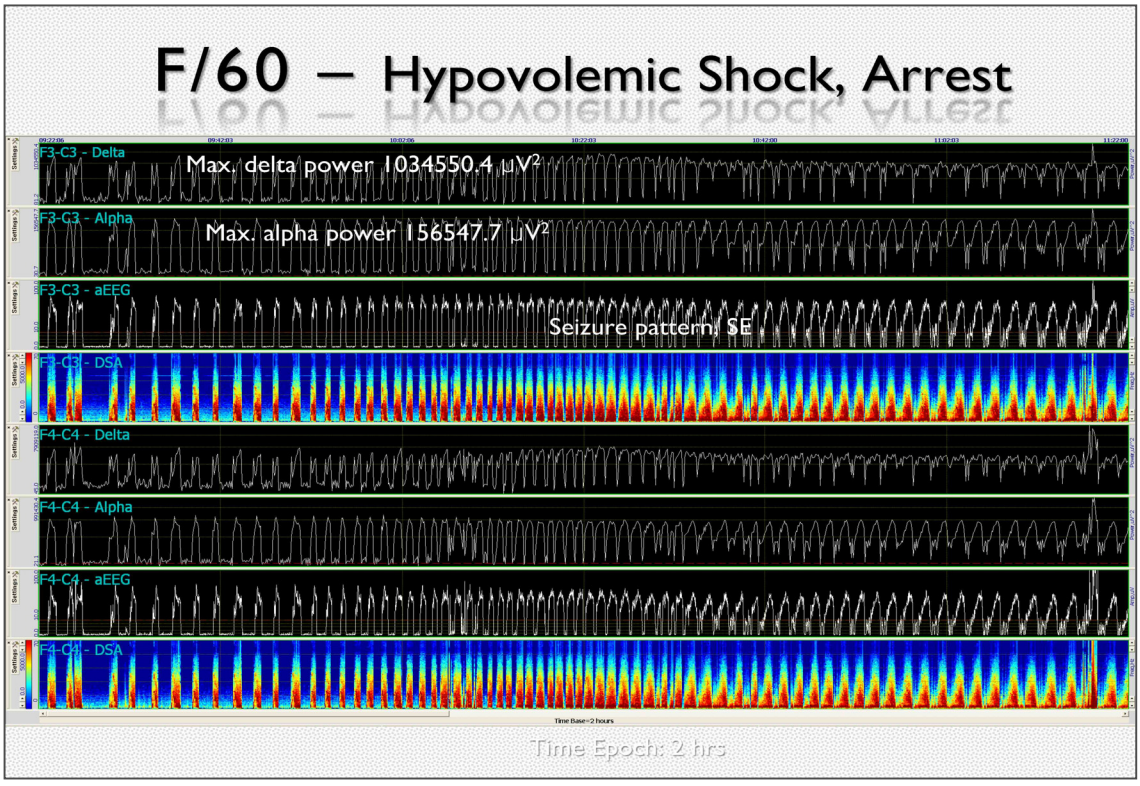


Lateralized Periodic Discharges (LPDs), bilateral asymmetric

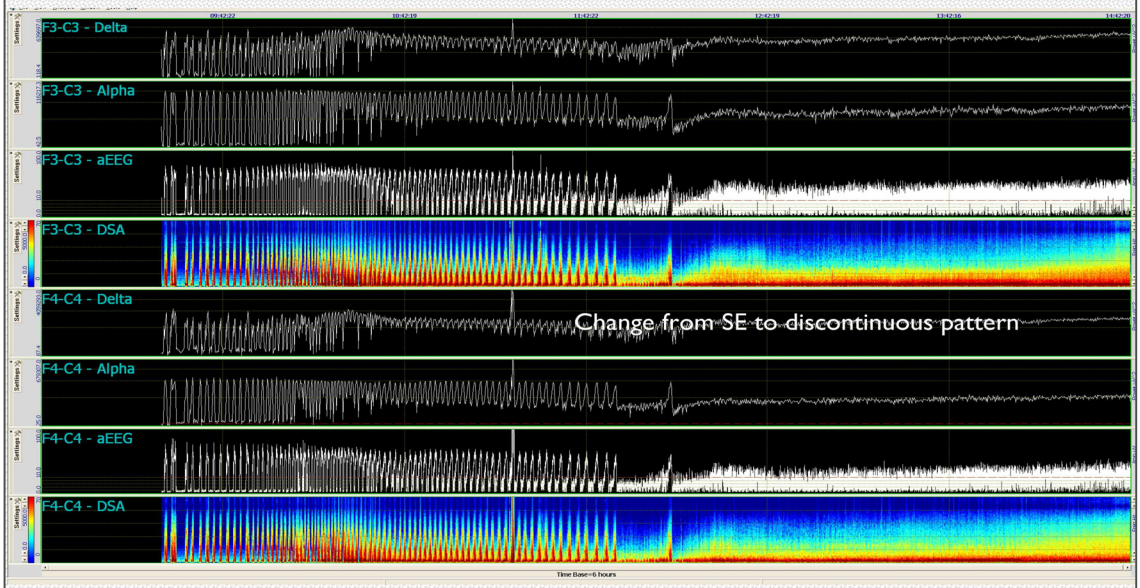


Fluctuating LRDA+S. Superimposed fast activity could qualify for +F if it were present only with RDA (i.e. absent from background), which is not possible to determine


F/60 – Hypovolemic Shock, Arrest
Diffuse monotonous delta suppression
Bursts of Gen. Seizure - Ictal


F/60 – Hypovolemic Shock, Arrest
F3-C3 - Delta
Max. delta power 1034550.4 µV²
F3-C3 - Alpha
Max. alpha power 156547.7 µV²
F3-C3 - aEEG
Seizure pattern, SE
F3-C3 - DSA
F4-C4 - Delta
F4-C4 - Alpha
F4-C4 - aEEG
F4-C4 - DSA
Time Epoch: 2 hrs

F/60 – Hypovolemic Shock, Arrest



Always Good Prognosis?

Table 2. Axis 1: Classification of status epilepticus (SE)

(A) With prominent motor symptoms

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

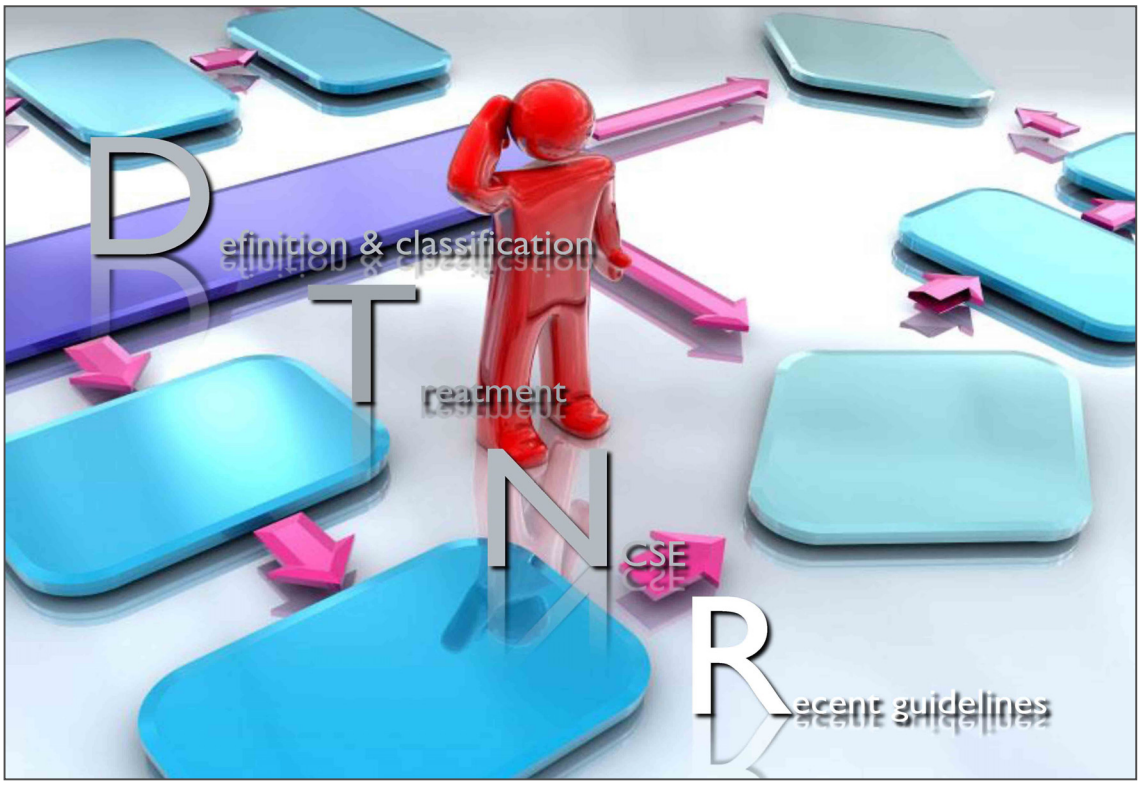
B.1 NCSE with coma (including so-called "subtle" SE)

~~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

NCSE with coma: one of SE with the worst prognosis.

"subtle" SE: treat SE like CSE.



2016 AES Guidelines

EPILEPSY CURRENTS

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

38 RCTs of anticonvulsant treatment for seizures lasting longer than 5 minutes.

4 class I RCTs
: Veterans Affair SE cooperative study group, PHTSE trial, RAMPAT trial, PECARN trial for children
2 class II RCTs

2016 AES Guidelines

Q1. Which Anticonvulsants Are Efficacious as Initial and Subsequent Therapy?

In adults with CSE, IM midazolam, IV lorazepam, IV diazepam and IV phenobarbital are established as efficacious as initial therapy (Level A).

In children, IV lorazepam and IV diazepam are established as efficacious at stopping seizures lasting at least 5 minutes (Level A) while rectal diazepam, IM midazolam, intranasal midazolam, and buccal midazolam are probably effective (Level B).

2016 AES Guidelines

Q2. What adverse events are associated with anticonvulsant administration?

Respiratory and cardiac symptoms are the most commonly encountered treatment-emergent adverse events associated with intravenous anticonvulsant drug administration in adults with convulsive status epilepticus (Level A).

The rate of respiratory depression in patients with convulsive status epilepticus treated with benzodiazepines is lower than in patients with convulsive status epilepticus treated with placebo indicating that respiratory problems are an important consequence of untreated convulsive status epilepticus (Level A).

2016 AES Guidelines

Q3. Which is the most effective benzodiazepine?

IM midazolam has superior effectiveness compared to IV lorazepam in adults with convulsive status epilepticus without established intravenous access (Level A).

No significant difference in effectiveness has been demonstrated between IV lorazepam and IV diazepam in adults or children with convulsive status epilepticus (Level A).

In children with status epilepticus, non-IV midazolam (IM/intranasal/buccal) is probably more effective than diazepam
(IV/rectal)(level B).

2016 AES Guidelines

Q4. Is IV fosphenytoin more effective than IV phenytoin?

When both are available, fosphenytoin is preferred over phenytoin based on tolerability but phenytoin is an acceptable alternative (Level A).

2016 AES Guidelines

Q5. When does anticonvulsant efficacy drop significantly (i.e. after how many different anticonvulsants does status epilepticus become refractory)?

"~ the overall success rate of the first administered therapy was 55.5%. If the first study drug did not succeed, the second study drug was able to stop the status epilepticus for an additional 7.0% of the total population; the third drug helped only an additional 2.3% of patients."

In children, the second anticonvulsant anticonvulsant appears less effective, and there are no data about third anticonvulsant efficacy (level C).

2016 AES Guidelines

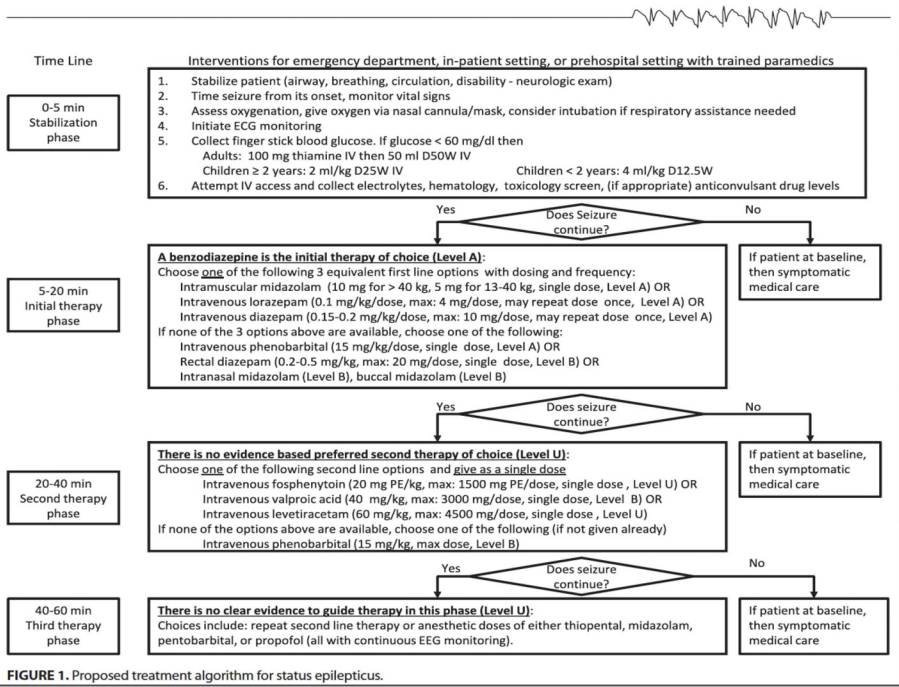


FIGURE 1. Proposed treatment algorithm for status epilepticus.