Status epilepticus

김 대 영
충남의대

Most seizures are self-limiting

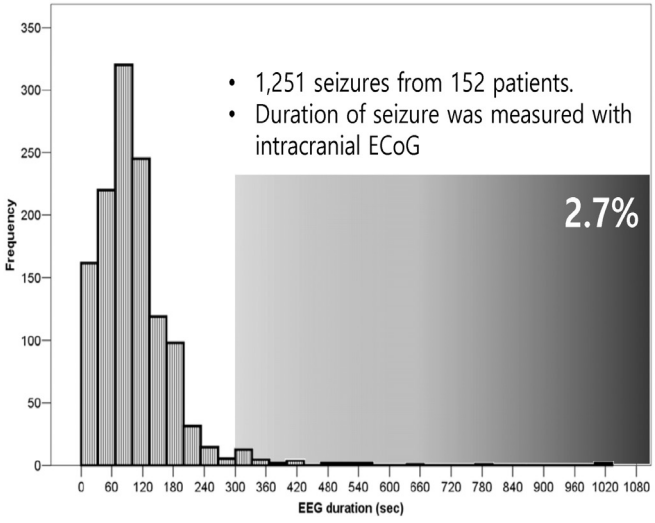

Figure 1. Distribution of the duration of all seizures. This histogram shows seizures lasting for > 5 minutes. **Kim D, et al. 2011**

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

The failure leads to ***abnormally prolonged seizures (after time point t_1)***.

Status epilepticus can have ***long-term consequences (after time point t_2)***, including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures.

SPECIAL REPORT

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

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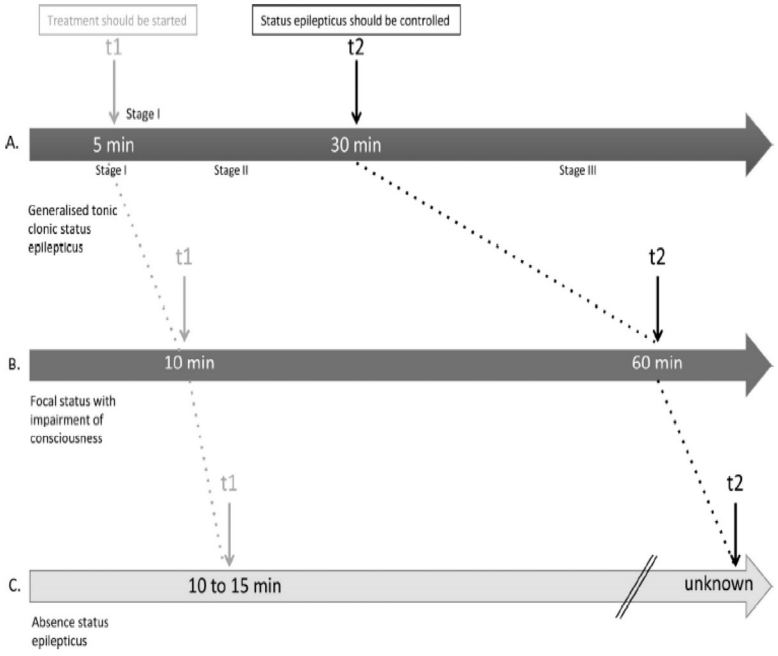
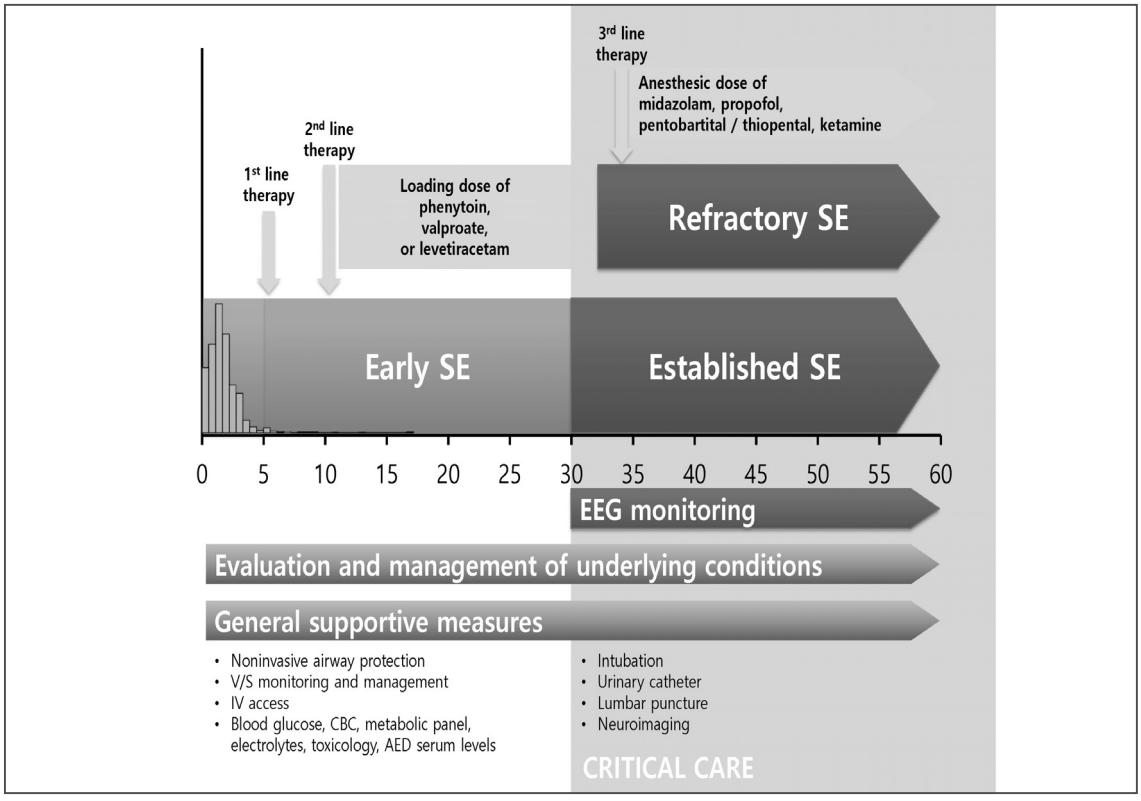
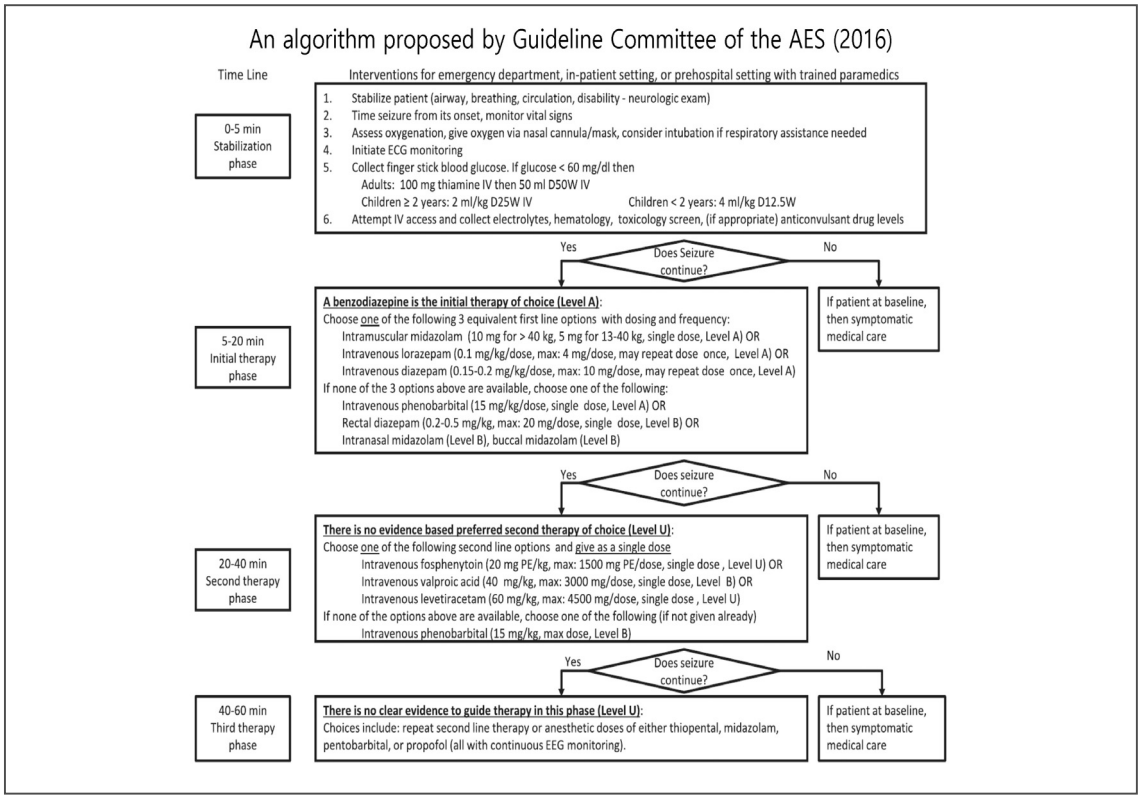
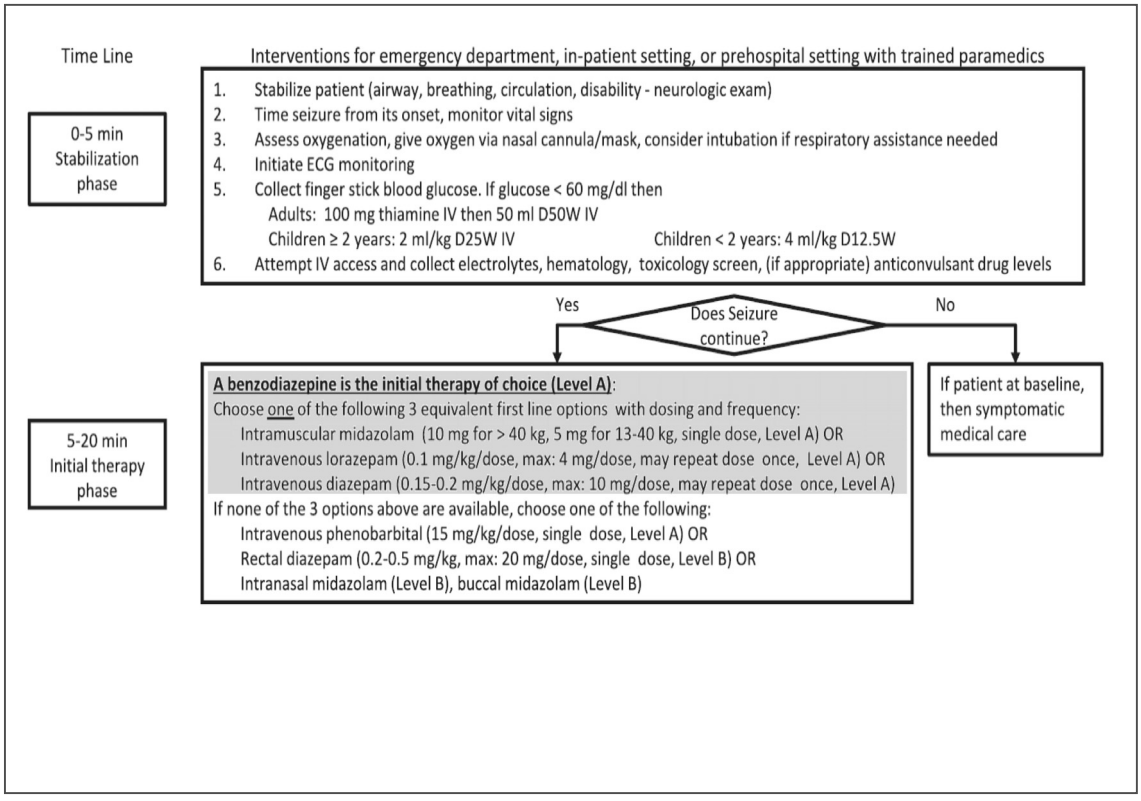
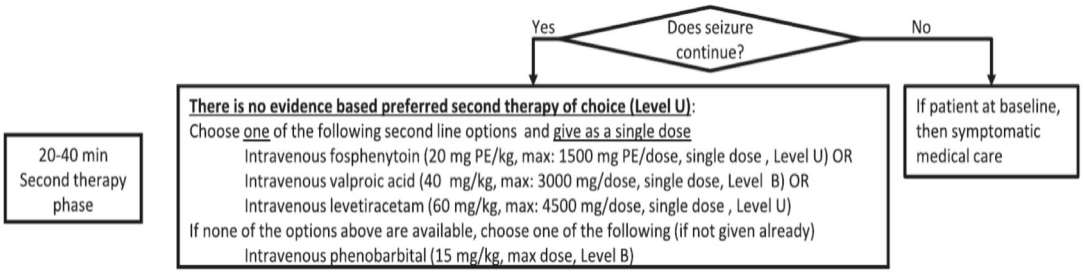



3rd line therapy
Anesthesic dose of midazolam, propofol, pentobartital / thiopental, ketamine
2nd line therapy
1st line therapy
Loading dose of phenytoin, valproate, or levetiracetam
Refractory SE
Early SE
Established SE
0 5 10 15 20 25 30 35 40 45 50 55 60
EEG monitoring
Evaluation and management of underlying conditions
General supportive measures
• Noninvasive airway protection
• V/S monitoring and management
• IV access
• Blood glucose, CBC, metabolic panel, electrolytes, toxicology, AED serum levels
• Intubation
• Urinary catheter
• Lumbar puncture
• Neuroimaging
CRITICAL CARE


An algorithm proposed by Guideline Committee of the AES (2016)
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



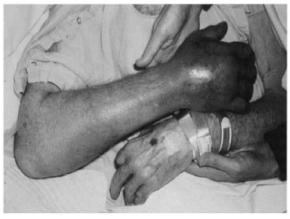
	Advantages	Disadvantages
Lorazepam	• Rapid onset of action • Longer duration of effect (>24 h) compared to diazepam • Efficacy and safety evaluated in RCT • Little risk of during accumulation	• Sedation, hypotension, respiratory depression • Risk of reaction at injection site
Diazepam	• Rapid onset of action • Rectal diazepam available • Efficacy and safety evaluated in RCT • Inexpensive, widely available	• Sedation, hypotension, respiratory depression • Rapid redistribution → short duration of action • Risk of drug accumulation after repeated doses and infusion
Midazolam	• Rapid onset of action by any route • IM, buccal, intranasal available • Efficacy and safety evaluated in RCT • Little risk of during accumulation	• Sedation, hypotension, respiratory depression • Risk of seizure recurrence due to short duration of action



- ~40% of patients with convulsive SE do not respond to benzodiazepines
- Loading of IV AEDs can be rapidly titrated to effective level
  - Phenytoin / fosphenytoin
  - Valproate
  - Levetiracetam
  - Phenobarbital
  - Lacosamide
  - Topiramate

Phenytoin

- MoA: Sodium channel modulation
- Loading dose: 18-20 mg/kg, up to 50 mg/min (up to 20 mg/min in elderly)
- Only compatible with saline
- Lipid soluble
- Contains propylene glycol
- AE: Hypotension, bradycardia, arrhythmia, respiratory depression, infusion site injury, metabolic acidosis, purple glove syndrome



Fosphenytoin

- Water-soluble prodrug of phenytoin ($t_{1/2}$: 8-15 min)
- 1.5 mg of FPH contains 1 mg of PHT (1 mg PE = 1.5 mg)
- Loading dose: 30 mg/kg = 20 mg PE/kg, up to 150 mg/min
- Compatible in saline, dextrose, lactated ringer's, etc
- Faster administration, fewer adverse events

Valproate

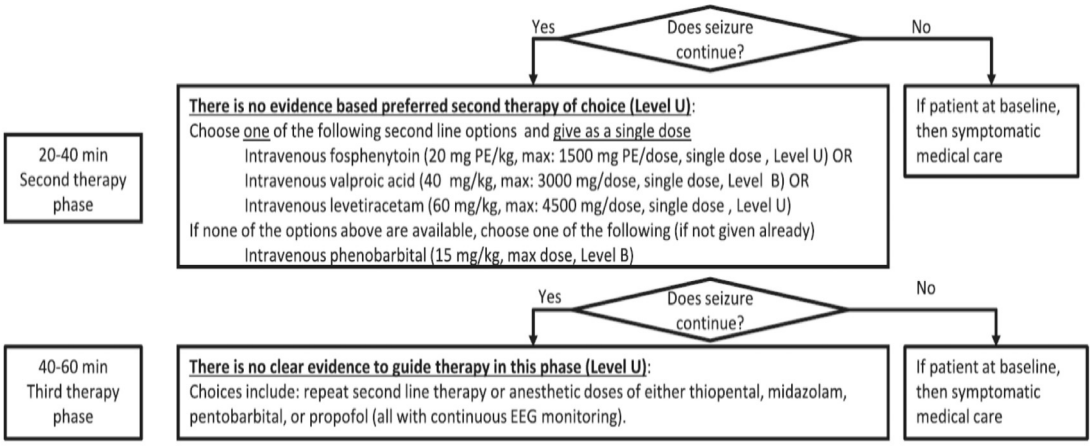
- MoA: Sodium channel modulation, GABA potentiation, NMDA inhibition
- Loading dose: 15-45 mg/kg, up to 6-10 mg/kg/min
- Adverse events: Thrombocytopenia, hyerammonemia, pancreatitis, hepatic toxicity

Levetiracetam

- MoA: Binds to synaptic vesicle protein 2A, acts as a neuromodulator
- Loading doses: 1,000-3,000 mg or 20-30 mg/kg
- Minimal drug interactions
- Adverse events: No major adverse events. Occasional behavioral issues

Phenobarbital

- MoA: GABA potentiation
- Loading doses: 10-20 mg/kg, up to 100 mg/min
- Adverse events: Sedation, respiratory depression, hypotension
- More adverse events when administered following benzodiazepines
- Prolonged sedation due to longer half-life



Midazolam

- Short half-life → significant prolongation of clearance with CI
- Tendency to develop tolerance with CI → increment of dosage requirement
- Respiratory and circulatory suppression
- Dosage
  - Loading dose: 0.2 mg/kg, up to 2 mg/kg
  - Continuous infusion: begins with 0.1 mg/kg/h → up to 2.0 mg/kg/h

Thiopental / Pentobarbital

- $GABA_A$ agonist
- Prolonged duration of action due to accumulation
- Autoinduction / drug interactions
- Hypotension, respiratory suppression, liver toxicity, pancreatic toxicity
- Dosage of thiopental
  - Loading dose: 100-250 mg
  - Continuous infusion: begins with 0.5 mg/kg/h → increasing to achieve BS pattern on EEG (up to 5 mg/kg/h)
- Dosage of Pentobarbital
  - Loading dose: 10-25 mg/kg
  - Continuous infusion: begins with 0.5-1.0 mg/kg/h → increasing to achieve BS pattern on EEG (up to 3 mg/kg)

Propofol

- A rapid onset and a short duration of action
- Less accumulation
- MoA: Enhance GABA, suppress NMDA and intracellular Ca influx
- Hypotension, respiratory suppression, bradycardia, hypertriglyceridemia
- Propofol infusion syndrome: lactic acidosis, hypertriglyceridemia, rhabdomyolysis, and myocardial failure
- Dosage
  - Loading dose: 2 mg/kg, up to 10 mg/kg
  - Continuous infusion: begins with 5-10 mg/kg/h → reducing to a minimal dose to maintain BS pattern on EEG

Risk factors of propofol infusion syndrome

- High doses for a prolonged period
  - administering propofol for more than 48 h or a dose of >4 mg/kg/h is not recommended
- Critical illness (sepsis, head trauma, etc.)
- Use of vasopressors
- Use of glucocorticosteroids
- Carbohydrate depletion (liver disease, starvation, or malnutrition)
- Carnitine deficiency
- Subclinical mitochondrial disease

Anesthetic treatment could be an independent risk factor of unfavorable outcome and death

Table 4 Crude and adjusted relative risks for primary outcomes according to antiepileptic treatment

	Crude			Adjusted for SE duration, STESS,[a] critical conditions, nonanesthetic third-line AEDs		
	RR	95% CI	*p* Value	RR	95% CI	*p* Value
Seizure control						
IVADs	0.93	0.85-1.01	0.103	0.94	0.85-1.04	0.226
Number of IVADs	0.96	0.91-1.01	0.151	0.97	0.91-1.04	0.456
No IVADs	Ref.			Ref.		
Midazolam only	0.96	0.86-1.06	0.416	0.94	0.85-1.05	0.299
Midazolam followed by propofol	0.94	0.82-1.07	0.334	0.95	0.83-1.10	0.483
Midazolam followed by barbiturates	0.86	0.66-1.11	0.238	0.89	0.64-1.22	0.465
GOS 1-3 (unfavorable outcome)						
IVAD	1.24	1.02-1.50	0.035[b]	1.25	1.01-1.54	0.041[b]
Number of IVADs	1.09	0.96-1.23	0.175	1.09	0.96-1.24	0.165
No IVADs	Ref.			Ref.		
Midazolam only	1.31	1.05-1.64	0.015[b]	1.30	1.05-1.63	0.019[b]
Midazolam followed by propofol	1.16	0.86-1.55	0.338	1.17	0.86-1.58	0.323
Midazolam followed by barbiturates	1.19	0.83-1.70	0.339	1.24	0.88-1.75	0.226
Death						
IVAD	2.96	1.51-5.82	0.002[b]	2.88	1.45-5.73	0.003[b]
Number of IVADs	1.55	1.15-2.09	0.004[b]	1.59	1.13-2.25	0.008[b]
No IVADs	Ref.			Ref.		
Midazolam only	2.71	1.20-6.12	0.017[b]	2.57	1.11-5.93	0.027[b]
Midazolam followed by propofol	3.12	1.36-7.18	0.007[b]	2.86	1.25-6.63	0.014[b]
Midazolam followed by barbiturates	3.27	1.23-8.72	0.018[b]	4.36	1.50-12.66	0.007[b]

Abbreviations: AED = antiepileptic drug; CI = confidence interval; GOS = Glasgow outcome Scale score; IVAD = IV anesthetic drug; Ref. = reference; RR = relative risk; SE = status epilepticus; STESS = Status Epilepticus Severity Score.
[a] STESS including the integral components age, level of consciousness, worst seizure type at SE onset, and history of seizures.
[b] Significant.

Sutter, et al. Neurology 2014

Anesthetic treatment could be an independent risk factor of unfavorable outcome and death

TABLE 2. Demographics and Clinical Characteristic of Patients With and Without Therapeutic Coma

Variable	All Patients (n = 467) (%)	Patients Without Therapeutic Coma (n = 417) (%)	Patients With Therapeutic Coma (n = 50) (%)
Age (yr; mean ± sd)	60.3 ± 18.6	60.7 ± 18.5	57.2 ± 19.2
Female gender	228 (48.2)	204 (48.9)	24 (48)
Potentially fatal etiology	237 (50.7)	210 (50.4)	27 (54)
Status epilepticus severity score (median, range)	3 (0–6)	3 (0–6)	3 (1–6)
Type of status epilepticus			
Simple partial	91 (19.5)	91 (21.8)	
Absence	7 (1.5)	7 (1.7)	
Myoclonic	1 (0.2)	1 (0.2)	
Complex partial	154 (33.0)	144 (34.5)	10 (20.0)
GCSE then partial	34 (7.3)	30 (7.2)	4 (8.0)
Proper GCSE	155 (33.2)	130 (31.2)	25 (50.0)
Nonconvulsive status epilepticus in coma	25 (5.4)	14 (3.4)	11 (22.0)

GCSE = generalized convulsive status epilepticus.

TABLE 4. Identified Variables Associated With Clinical Outcome in 467 Adults With Incident Status Epilepticus From the Fitted Multivariable Model

Variable	New Disability	Mortality
Age	**1.03 (1.01–1.05)**	**1.03 (1.01–1.05)**
Lack of previous seizures	**2.48 (1.49–4.15)**	1.35 (0.66–2.78)
Potentially fatal etiology	**2.72 (1.70–4.35)**	**7.2 (3.45–15.04)**
Status epilepticus severity score	1.12 (0.92–1.38)	**1.56 (1.17–2.10)**
Charlson Comorbidity Index	1.02 (0.92–1.13)	**1.18 (1.05–1.33)**
Therapeutic coma	**6.86 (2.84–16.56)**	**9.10 (3.17–26.16)**

Results are given as relative risk ratio and 95% CI, as compared to return to baseline clinical conditions. Variables with $p < 0.05$ in the univariable analysis were retained for the multivariable assessment. Significant values are given in bold.

Marchi, et al. Critic Care Med 2015

AED polytherapy for SE

In animal models

	Post-treatment seizure	Toxicity score
Control (sham injection)	100 ± 7	
DZP 20 mg/kg	100 ± 8	11.2 ± 0.9
DZP 1 mg/kg + KET + VPA	8 ± 2	1 ± 0.4
DZP 1 mg/kg + KET + BRV	8 ± 4	0.8 ± 0.2

Monotherapy with KET 10 mg/kg, VPA 30 mg/kg, BRV 10 mg/kg, DZP 1, 5, or 10 mg/kg, and other AEDs also failed to stop SE.

Wasterlain CG, et al. 2012

Translational gap

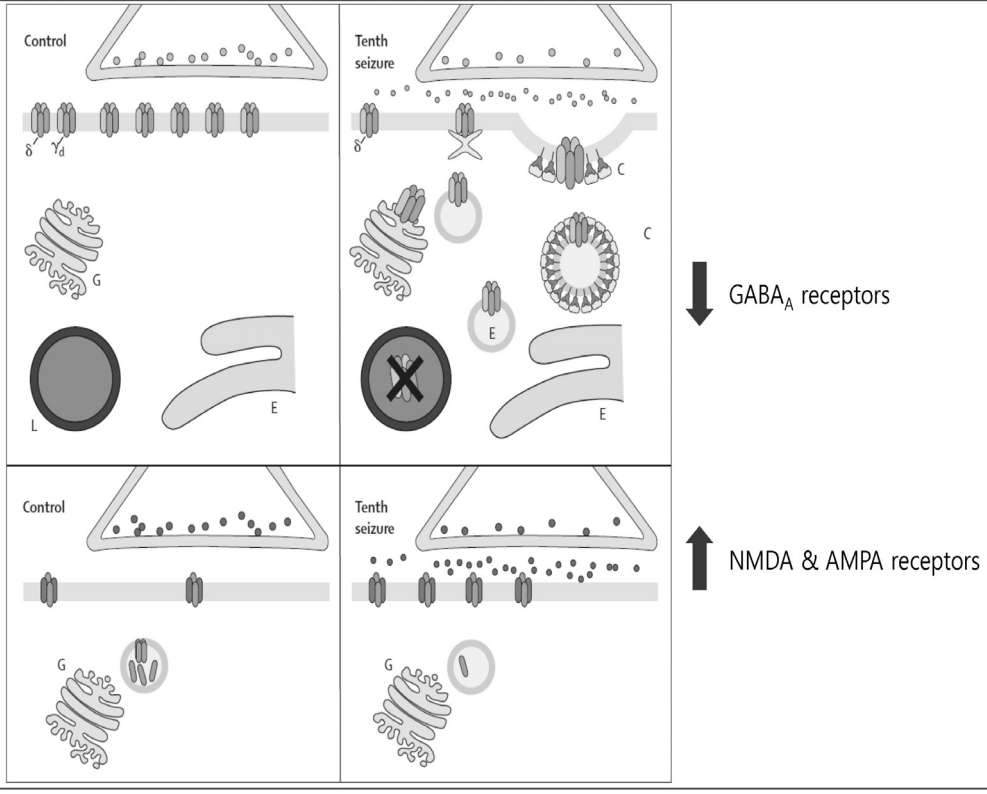
AED polytherapy for SE

Table 6 Suggested approach to antiepileptic drug therapy in refractory status epilepticus

Choice of drug regimen depends on clinical context
Polytherapy with two antiepileptic drugs
High-dose regimens
Avoid frequent switching
Favour antiepileptic drugs with low interaction potential
Favour antiepileptic drugs with predictable kinetic properties
Favour antiepileptic drugs without renal or hepatic toxicity
Avoid GABAergic antiepileptic drugs

Shorvon S, Ferlisi M. 2012

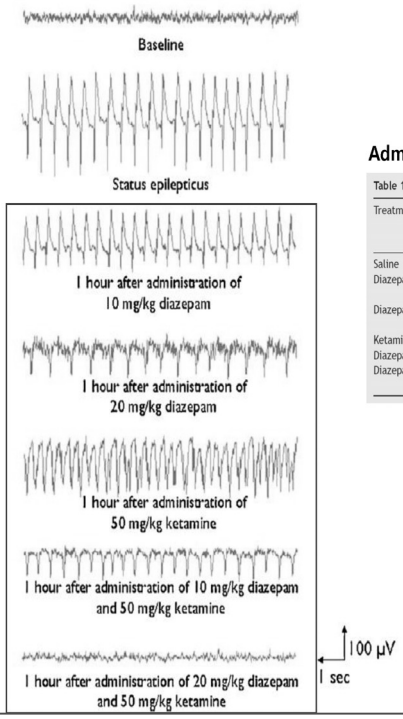
Possible choices: LEV, LCM, PER, TPM, ...



NMDA antagonists are usually recognized as **not being able to arrest seizures when given too early**. However, even in these conditions, **ketamine may still offer some functional benefits**.

Model	Animal species	Ketamine dose (mg/kg)/route/mode of administration	Ketamine effects; ED_{50} mg/kg (confidence interval 95%)	Note	References
Kainic acid	Rat	1–20/SC/PTr	Neuroprotective despite persistence of epileptic discharges	Reinjections every 30 min.	[23]
Kainic acid	Rat	50/IP/Tr	Antiepileptic	Not effective alone, effective with diazepam	[133]
Intrahippocampal pilocarpine	Rat	50/IP/Tr	Moderate neuroprotection	SE stopped by thiopental. Repeated injection of ketamine afterwards	[134]
Lithium-pilocarpine	Rat	100/IP/Tr	Antiepileptic (partial effect) and neuroprotective		[135]
Lithium-pilocarpine	Rat	100/IP/Tr	Neuroprotective/does not prevent epileptogenesis	15 min after SE onsetior with clonazepam at 120 min	[136]
Lithium-pilocarpine	Rat	100/SC/Tr	Neuroprotective (behavior and other long term consequences)	5 min after convulsion onset	[128,132, 137–139]
Lithium-pilocarpine	Rat	100/SC/Tr	Robust cognitive/memory sparing despite neuronal damage	Idem	[129,131,140]
Lithium-pilocarpine	Rat	50–100/IP/Tr	Antiepileptic (partial effect)	Doses below 100 mg/kg ineffective. Synergistic effects with diazepam	[141]
Lithium-pilocarpine	Rat	22.5/IP/Tr	Anticonvulsant and neuroprotective (histology and behavior)	Young rats. Ketamine given either 15 or 60 min after injection of pilocarpine	[127]
Pilocarpine	Rat	1.5–2/IP/PTr	Antiepileptic	Ketamine given 30 min prior to pilocarpine	[142]
Pilocarpine	Rat	0.5–1/IP/PTr	Antiepileptic	Ketamine given 30 min prior to pilocarpine	[143]
Pilocarpine	Rat	50/IP/Tr	Anticonvulsant and protection against memory deterioration	Ketamine given 2 min after onset of seizures	[144]
Soman	Guinea pig	10–60/IM/Tr	Antiepileptic and neuroprotective	Repeated injections starting 30 min or 60 min post-soman. Combined with atropine	[81]
Soman	Guinea pig	15–20/IM/Tr	Anticonvulsant and neuroprotective	Repeated injections of S(+) ketamine starting 1 or 2 h post-soman. Combined with atropine	[145]
Soman	Rat	15/IP/Tr	No effect		[106]
Soman	Mouse	25–100/IP/PTr	Anticonvulsant and neuroprotective. Reduction of neuroinflammation	Repeated injections starting 30 min or 60 min post-soman. Combined with atropine	[146]
Soman	Mouse	100 then 50 twice/IP/Tr	Anticonvulsant and neuroprotective. Protection against some metabolic changes	Repeated injections starting 1 or 2 h post-soman. Combined with atropine	[147]
NMDA	Rat pup	50/IP/Tr	Anticonvulsant		[148]
NMDA	Mouse	Variable/IP/PTr	Anticonvulsant. ED_{50} 45.9 (16.1–60.2)		[149]
NMDA	Mouse	10–55/IV/IP/Tr	Anticonvulsant ED_{50} 46.4 (33.0–67.5)		[37]
NMDA	Ratmouse	10–50/IP/PTr or Tr	Antiepileptic		[150]
NMDA	Mouse	Variable/IP/PTr	Anticonvulsant ED_{50} 16 (11–22)		[151]
NMDA	Mouse	Variable/IP/PTr	Anticonvulsant ED_{50} 53.2 (23.3–121.5)		[152]
NMDA (intrahippocampal)	Rat	15, 60 or 180 /IP/PTr or Tr	Partial neuroprotection as a delayed treatment		[153]
Bicuculline	Rat	10/SC/PTr followed by Tr	Neuroprotectant without any antiepileptic effect	Reinjections every 30 min.	[154]
Bicuculline	Rat	≥ 30/IV/PTr	Anticonvulsant		[155]
Bicuculline	Rat	5–40/IP/Tr	Antiepileptic	Rats of different ages Better efficacy against generalized tonic-clonic seizures	[156]
Bicuculline	Mouse	Variable/IP/PTr	Anticonvulsant (tonic phase) ED_{50} 15 (10–22)		[157]
Focal seizures (penicillin injection)	Cat	5–20/IV/Tr	Antiepileptic (transiently)	3–4 injections at 1–1.5 h interval	[158]
Focal seizures (penicillin injection)	Rabbit	20–40/IV/Tr	Antiepileptic (for 20–30 min.)		[159]
Pentylenetetrazol (PTZ, metrazol)	Rat	5–100/IP/PTr	Antiepileptic		[160]
Pentylenetetrazol (PTZ, metrazol)	Mouse	0.1–5/IP/PTr	Antiepileptic	Increase seizure threshold	[161]
Pentylenetetrazol (PTZ, metrazol)	Rat	1–40/IP/Tr	Antiepileptic	Rats of different ages Better efficacy against generalized tonic-clonic seizures	[162]
Mercaptopropionate and PTZ	Mouse	90/IP/PTr	Anticonvulsant		[163]
Mercaptopropionate	Rat	30 (followed by infusion 9.12 mg/kg/h for 2 h/IV/Tr	Antiepileptic	Experiments in paralyzed rats	[164]
Picrotoxin	Rat	20–100/IP/Tr	Antiepileptic (partial effect)	Treatment before the onset of seizures	[160]
Picrotoxin	Rat	5–40/IP/Tr	Antiepileptic	Rats of different ages Better efficacy against generalized tonic-clonic seizures	[156]
Lidocaine	Mouse				[165]
4-aminopyridine	Rat	3/IP/PTr	Delay 4-AP-induced convulsions and % of animals with convulsions. Partial reduction of cFOS immunoreactivity	Ketamine injected 10 min before 4-AP	[166]
Tetramethylenedisul-fotetramine	Mouse	35–70/IP/Tr 35/IP/PTr	Anticonvulsant at 70 mg/kg Not anticonvulsant – increases survival	Early administration at first clonic convulsions	[167]
Guanidinosuccinic acid	Rat	60/IP/PTr – Tr	Antiepileptic and neuroprotective	1 dose prior and 1 dose at 60 min	[168]

Control of kainic acid-induced SE in rats



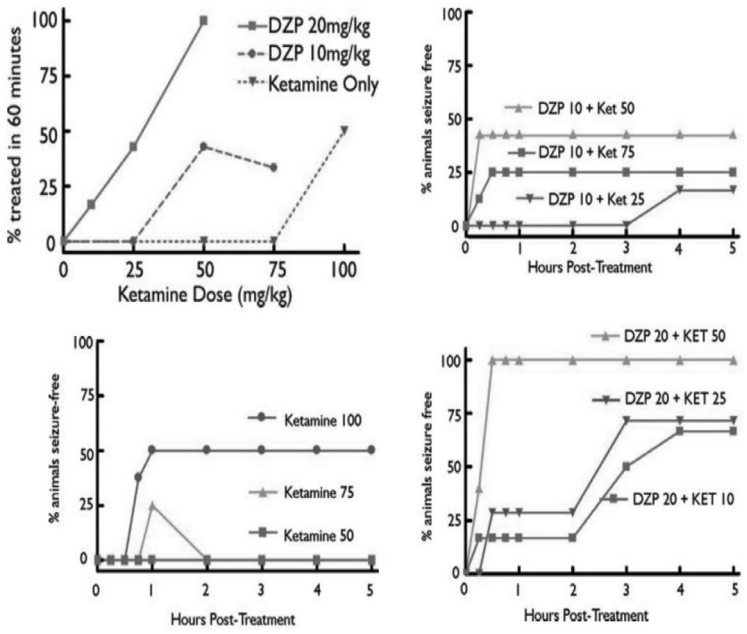
Administered 90 min after SE

Table 1 Data overview.

Treatment (mg/kg)	Number of animals with electrographical SE control 1 h post-treatment	Time to control SE (min ± SD)	Time until first reoccurring seizure (min ± SD)
Saline	0/6	n/a	n/a
Diazepam (10)	2/7	12.50 ± 3.54 (*n* = 2)	279 ± 37.22 (*n* = 2)
Diazepam (20)	3/6	21.67 ± 14.43 (*n* = 3)	263.84 ± 46.28 (*n* = 3)
Ketamine (50)	0/6	n/a	n/a
Diazepam (10) + ketamine (50)	2/6	15 ± 7.07(*n* = 2)	322.5 ± 17.68 (*n* = 2)
Diazepam (20) + ketamine (50)	8/8	22.25 ± 23.76 (*n* = 8)	467.5 ± 148.97 (*n* = 8)

Vermoesen K, et al. *Epilepsy Res* 2010

Ketamine-DZP combination in lithium-pilocarpine-induced SE



Martin BS & Kapur J. *Epilepsia* 2008

Ketamine use in the treatment of refractory status epilepticus

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Seizures;
Status epilepticus;
Refractory status epilepticus;
NMDA receptor

Summary Refractory status epilepticus (RSE) occurs when status epilepticus (SE) fails to respond to appropriate therapy with typical antiepileptic drugs (AEDs). Animal studies have shown ketamine to be a highly efficacious agent in this setting, but very few case reports describe use of ketamine in human SE or RSE. We report a retrospective review of 11 patients who were treated for RSE with ketamine infusion in addition to other standard AEDs over a nine-year period. Data collection included age, gender, history of epilepsy, etiology of RSE, daily dose of ketamine, co-therapeutic agents, duration of seizures, treatment response, and disposition. RSE was successfully terminated in all 11 patients treated with ketamine. Dosing ranged from 0.45 mg/kg/h to 2.1 mg/kg/h based upon the preference of the treating clinician and response to therapy, with maximal daily doses ranging from 1392 mg to 4200 mg. Ketamine was the last AED used prior to resolution of RSE in 7/11 (64%) cases. In the remaining four cases, one other AED was added after ketamine infusion had begun. Time from ketamine initiation to seizure cessation ranged from 4 to 28 days (mean = 9.8, SD = 8.9). In 7/11 patients, RSE was resolved within one week of starting therapy. Administration of ketamine was uniformly associated with improvement in hemodynamic stability. Six of the seven patients (85%) who required vasopressors during early treatment for RSE were able to be weaned from vasopressors during ketamine infusion. No acute adverse effects were noted. These findings suggest that ketamine may be a safe and efficacious adjunctive agent in the treatment of RSE.

Epilepsy Research (2013) 105, 183–188

Table 1 The published literature on treatment outcomes

Therapy	Number of published papers reporting outcome data	Number of published cases in which outcome data are provided
Pentobarbital/thiopental	23	192
Propofol	24	143
Midazolam	20	585
Ketamine	7	17
Inhalational anaesthetics	7	27
Hypothermia	4	9
Magnesium	2	3
Pyridoxine	2	2
Immunotherapy	8	21
Ketogenic diet	4	14
Vagal nerve stimulation	4	4
Deep brain stimulation	1	1
ECT	6	8
Emergency neurosurgery	15	36
CSF drainage	1	2
Topiramate	10	60
Levetiracetam	8	35
Pregabalin	1	2
Lacosamide	2	10

All patients had received more than one therapy, but we have included in this table only the therapies highlighted in individual papers. The anaesthetic reports include patients with refractory and super-refractory status epilepticus.

Shorvon S & Ferlisi M. *Brain* 2012

A retrospective study to examine patterns of use, efficacy, and safety of IV ketamine for RSE

- 10 academic medical centers in North America and Europe
- 1999-2012, 58 subjects, 60 episodes of RSE
- Ketamine appears to be a relatively effective and safe drug for the treatment of RSE.

Table 2. Determinants of ketamine efficacy (N = 60 episodes)

	Likely response (N = 7)	Possible response (N = 12)	Likely or possible response (N = 19)	No response (N = 41)	p-Value (univ.)[$]	p-Value (multiv.)
Latency to ketamine; median (range)	12 h (6 h–7 d)	5 d (18 h–30 d)	4.5 d (6 h–30 d)	10 d (12 h–122 d)	0.0053	NS
Number of previously failed drugs; median (range)	4 (3–7)	6 (3–11)	6 (3–11)	8 (3–16)	0.0012	<0.01
Etiology						
Unknown (N = 34)	1	7	8	26	<0.001	NS
Anoxic (N = 7)	4	0	4	3		
Acute nonanoxic (N = 13)	2	2	4	9		
Remote (N = 6)	0	3	3	3		
SE classification						
Generalized convulsive (N = 14)	2	4	6	8	NS	–
Generalized nonconvulsive (N = 3)	0	1	1	2		
Focal convulsive (N = 4)	0	2	2	2		
Focal nonconvulsive (N = 38)	5	5	10	28		
Infantile spasms (N = 1)	0	0	0	1		
Maximum infusion rate (mg/kg/h); median (range)[a]	7 (0.9–10)	1.8 (0.6–7)	2 (0.6–10)	3 (0.05–10)	NS	–
Loading dose administered[b]	6/6 (100%)	5/8 (63%)	11/14 (79%)	23/32 (72%)	NS	–
Duration of administration	1 (0–2)	3 (0–10)	2 (0–10)	5 (0–27)	<0.001	NS
Number of concurrent drugs	3 (1–5)	5 (1–11)	4 (1–11)	6 (1–10)	<0.001	NS
Number of concurrent anesthetic drugs[c]	1 (0–1)	1 (1–3)	1 (0–3)	2 (1–3)	<0.001	NS

h, hours; d, days; m, months; univ., univariate analysis; multiv., multivariate analysis.
[$]p-value refers to analysis using likely, possible, and no response as three separate categories.
[a]Information available in 54 of 60 cases.
[b]Information available in 46 of 60 cases.
[c]Anesthetic drugs included pentobarbital, thiopental, midazolam, and propofol.

Gaspard N, et al. *Epilepsia* 2013

CNS Drugs
https://doi.org/10.1007/s40263-018-0569-6

SYSTEMATIC REVIEW

Ketamine for Refractory Status Epilepticus: A Systematic Review

Anna Rosati[1] · Salvatore De Masi[2] · Renzo Guerrini[1]

Published online: 19 September 2018

Table 1 Selected case series

Population	Study design		
	Retrospective No. of studies (no. of patients)	Prospective No. of studies (no. of patients)	Total
Adult	8 (219)	0 (0)	8 (219)
Paediatric	2 (11)	4 (18)	6 (29)

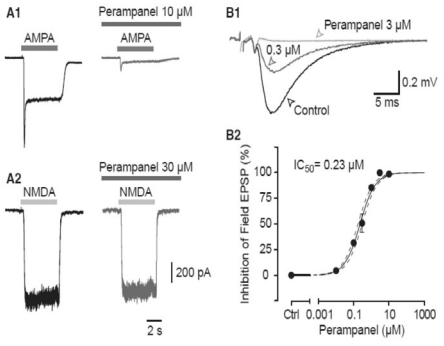
- Overall, 248 individuals (29 children) with a median age of 43.5 years (range 2 months to 67 years)
- Regardless of the SE type, KET was twice as effective if administered early
  - 64% in RSE lasting 3 days
  - 32% in RSE with mean duration of 26.5 days
- Doses were extremely heterogeneous and did not appear to be an independent prognostic factor

Ketamine

- NMDA receptor antagonist: preferred mechanism in RSE
- Short half-life
- No hypotension
- Hypertension, arrhythmia, increased ICP, hallucination, possible neurotoxicity
- Dosage (based on limited reports)
  - Loading dose: 1-2 mg/kg
  - Continuous infusion: 0.6-10 mg/kg/h

Perampanel

A potent, non-competitive, selective AMPA receptor antagonist



Accepted: 24 November 2017
DOI: 10.1111/epi.14492

SUPPLEMENT ARTICLE

Epilepsia®

Efficacy and safety of perampanel oral loading in postanoxic super-refractory status epilepticus: A pilot study

Simone Beretta[1] | Giada Padovano[1] | Andrea Stabile[1] | Anna Coppo[2] | Graziella Bogliun[1] | Leonello Avalli[2] | Carlo Ferrarese[1]

- 8 postanoxic patients with super-refractory NCSE were treated with PER (dose range = 6-12 mg).
  - CEEG monitoring showing definite generalized NCSE
  - Favorable multimodal prognostic indicators (presence of brainstem reflexes, presence of bilateral N20 responses, absence of PDs/GPDs)
- In 6 (75%), SE resolved within 72 hours after adm. of PER
- In 4 (50%), neurological outcomes at 3 months were return to normal or minimal disability
- A mild cholestatic liver injury, which required no specific treatment, was observed in five patients (62.5%).
- Perampanel 6-12 mg oral loading appeared to be an effective option in selected patients with postanoxic super-refractory NCSE with good prognostic indicators.
- Safety data indicate a risk of cholestasis.

SUPPLEMENT ARTICLE

Epilepsia®

Perampanel in patients with refractory and super-refractory status epilepticus in a neurological intensive care unit: A single-center audit of 30 patients

Alexandra Rohracher[1,2] | Gudrun Kalss[1,2] | Caroline Neuray[1,2] | Julia Höfler[1,2] | Judith Dobesberger[1,2] | Giorgi Kuchukhidze[1,2,3] | Rudolf Kreidenhuber[1,2] | Cristina Florea[1,2] | Aljoscha Thomschewski[2] | Helmut F. Novak[1,2] | Georg Pilz[1,2] | Markus Leitinger[1,2] | Eugen Trinka[1,2]

Epilepsia. 2018;59(S2):234–242.

- All 30 patients with refractory SE in NICU who received add-on PER between Sep 2012 and Feb 2018.
  - High-dose group [a median initial dose: 24 (16-32) mg]: 14 patients (47%)
  - Standard dose group [a median initial dose: 4 (2-12) mg]: 16 patients (53%)
- Outcome

	All (30)	High dose (14)	Standard dose (16)
SE termination	5 (17%)	2 (14%)	3 (19%)
Good recovery	9 (30%)	8 (56%)	7 (44%)
Unfavorable oucome (PSV, death)	13 (43%)	5 (36%)	8 (50%)

- Adverse events:
  - no changes in cardiorespiratory function after "standard" and "high-dose" treatment.
  - Elevated liver enzymes without clinical symptoms 23% (57% high dose vs 43% standard dose)
- Oral PER in loading doses up to 32 mg were well tolerated but could terminate SE only in a few patients.

Received: 30 October 2018 | Revised: 10 December 2018 | Accepted: 30 December 2018
DOI: 10.1111/ane.13061

ORIGINAL ARTICLE

WILEY Acta Neurologica Scandinavica

Perampanel for treatment of status epilepticus in Austria, Finland, Germany, and Spain

Adam Strzelczyk[1,2,3] | Susanne Knake[2,3] | Reetta Kälviäinen[4,5] | Estevo Santamarina[6] | Manuel Toledo[6] | Sophia Willig[1,3] | Alexandra Rohracher[7,8] | Eugen Trinka[7,8,9] | Felix Rosenow[1,3]

- 5 European hospitals between 2011 and 2015
- Of 1319 patients identified as experiencing SE, 52 (3.9%) received perampanel
- Median initial dose was 6 mg/d, up-titrated to a median max dose of 10 mg/d.

Received: 30 October 2018 | Revised: 10 December 2018 | Accepted: 30 December 2018
DOI: 10.1111/ane.13061
ORIGINAL ARTICLE
WILEY Acta Neurologica Scandinavica
Perampanel for treatment of status epilepticus in Austria, Finland, Germany, and Spain
Adam Strzelczyk[1,2,3] | Susanne Knake[2,3] | Reetta Kälviäinen[4,5] | Estevo Santamarina[6] | Manuel Toledo[6] | Sophia Willig[1,3] | Alexandra Rohracher[7,8] | Eugen Trinka[7,8,9] | Felix Rosenow[1,3]

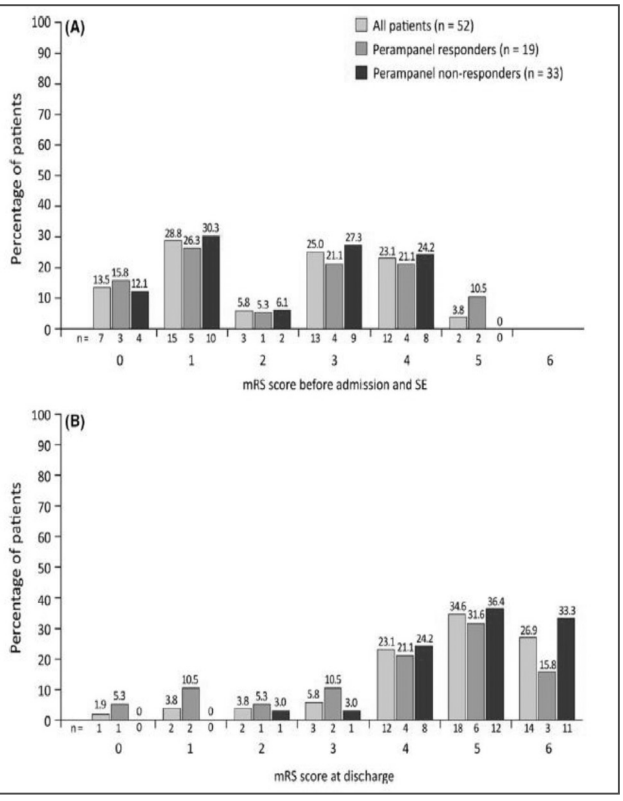
Level	Description
0	No symptoms
1	No significant disability, despite symptoms; able to perform all usual duties and activities
2	Slight disability; unable to perform all previous activities but able to look after own affairs without assistance
3	Moderate disability; requires some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requires nursing care and attention

Adapted from Rankin, 1957[9] and van Swieten et al., 1988[10]

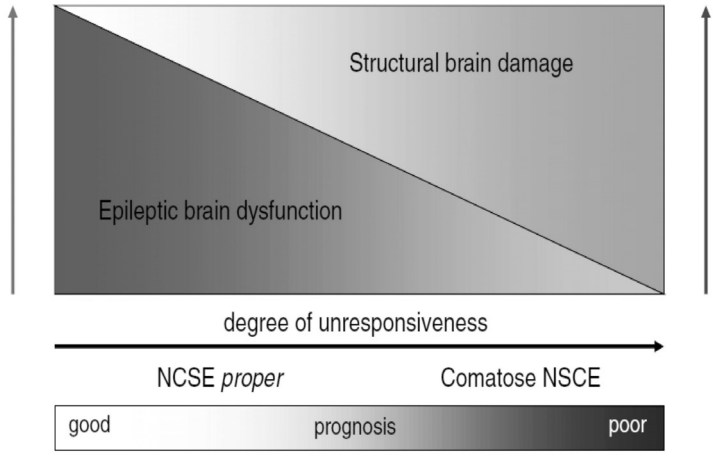
PER was the last drug added in 32/52 (61.5%), with response attributed to PER in 19/52 (36.5%).

PER non-responders:
- more SRSE (51.5% vs 31.6%)
- a higher mean # of AEDs before initiating PER (5.9 vs 5.1)

Most commonly reported adverse effects: dizziness (1.9%) and somnolence (1.9%)



Etiology is a most powerful prognostic factor



RSE is more likely to have an acute etiology

Table 2: Etiology of RSE in selected studies.

Study	*N*	Known (%)			Unknown (%)
		Acute	Remote	Progressive	
Delaj et al. (RSE versus NRSE)ˆ [21]	RSE = 301	58.5	12.6#	20.9	8.6
Delaj et al. (RSE versus SRSE)ˆ [21]	RSE = 268 SRSE = 33	51.6	15.2	18.2	9
Holtkamp et al. [3]	36	50*	22.2	16.7	0
Giovannini et al. [10]	26	77*	12	4	0
Kantanen et al. [16]	75	41	51	5	3

#NRSE was significantly more likely to have a remote etiology as compared to RSE; *RSE was significantly more likely to have an acute etiology as compared to NRSE; ˆDelaj et al. differentiated RSE and SRSE cases in their cohort (RSE = refractory status epilepticus and NRSE = nonrefractory status epilepticus).

Marawar R, et al. 2018

CRITICAL REVIEW AND INVITED COMMENTARY

Epilepsia®

Proposed consensus definitions for new-onset refractory status epilepticus (NORSE), febrile infection-related epilepsy syndrome (FIRES), and related conditions

Lawrence J. Hirsch[1] | Nicolas Gaspard[2] | Andreas van Baalen[3] | Rima Nabbout[4] | Sophie Demeret[5] | Tobias Loddenkemper[6] | Vincent Navarro[7] | Nicola Specchio[8] | Lieven Lagae[9] | Andrea O. Rossetti[10] | Sara Hocker[11] | Teneille E. Gofton[12] | Nicholas S. Abend[13] | Emily J. Gilmore[1] | Cecil Hahn[14] | Houman Khosravani[15,16] | Felix Rosenow[17] | Eugen Trinka[18,19]

NORSE is 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

New-onset refractory status epilepticus

Etiology, clinical features, and outcome

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Benjamin Legros, MD
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Brandon M. Westover, MD, PhD

ABSTRACT

Objectives: The aims of this study were to determine the etiology, clinical features, and predictors of outcome of new-onset refractory status epilepticus.

Methods: Retrospective review of patients with refractory status epilepticus without etiology identified within 48 hours of admission between January 1, 2008, and December 31, 2013, in 13 academic medical centers. The primary outcome measure was poor functional outcome at discharge (defined as a score >3 on the modified Rankin Scale).

Results: Of 130 cases, 67 (52%) remained cryptogenic. The most common identified etiologies were autoimmune (19%) and paraneoplastic (18%) encephalitis. Full data were available in 125 cases (62 cryptogenic). Poor outcome occurred in 77 of 125 cases (62%), and 28 (22%) died. Predictors of poor outcome included duration of status epilepticus, use of anesthetics, and medical complications. Among the 63 patients with available follow-up data (median 9 months), functional status improved in 36 (57%); 79% had good or fair outcome at last follow-up, but epilepsy developed in 37% with most survivors (92%) remaining on antiseizure medications. Immune therapies were used less frequently in cryptogenic cases, despite a comparable prevalence of inflammatory CSF changes.

Conclusions: Autoimmune encephalitis is the most commonly identified cause of new-onset refractory status epilepticus, but half remain cryptogenic. Outcome at discharge is poor but improves during follow-up. Epilepsy develops in most cases. The role of anesthetics and immune therapies warrants further investigation. ***Neurology*® 2015;85:1604-1613**

New-onset refractory status epilepticus

Etiology, clinical features, and outcome

Table 1 **Eventual etiology of new-onset refractory status epilepticus after extensive evaluation**

Etiology	No. (%)
Cryptogenic	67 (52)
Nonparaneoplastic autoimmune	25 (19)
Anti-NMDA receptor	7 (5)
Anti-VGKC complex	5 (4)
SREAT	5 (4)
Cerebral lupus	4 (3)
Anti-GAD65	3 (2)
Anti-striational	1 (1)
Paraneoplastic	23 (18)
Anti-NMDA receptor	9 (7)
Anti-VGKC complex	3 (2)
Anti-Hu	3 (2)
Anti-VGCC	2 (2)
Anti-CRMP5	1 (1)
Anti-Ro	1 (1)
Seronegative	4 (3)
Infection-related	10 (8)
EBV	2 (2)
VZV	2 (2)
CMV	1 (1)
WNV	1 (1)
Mycoplasma pneumoniae	2 (2)
Syphilis	1 (1)
Toxoplasma gondii	1 (1)
Others	5 (4)
SESA	2 (2)
Leptomeningeal carcinomatosis	2 (2)
Creutzfeldt-Jakob disease	1 (1)

Patients with NORSE had better outcome with immunotherapy

Contents lists available at ScienceDirect

Epilepsy & Behavior

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

New-onset refractory status epilepticus (NORSE) — The potential role for immunotherapy

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ABSTRACT

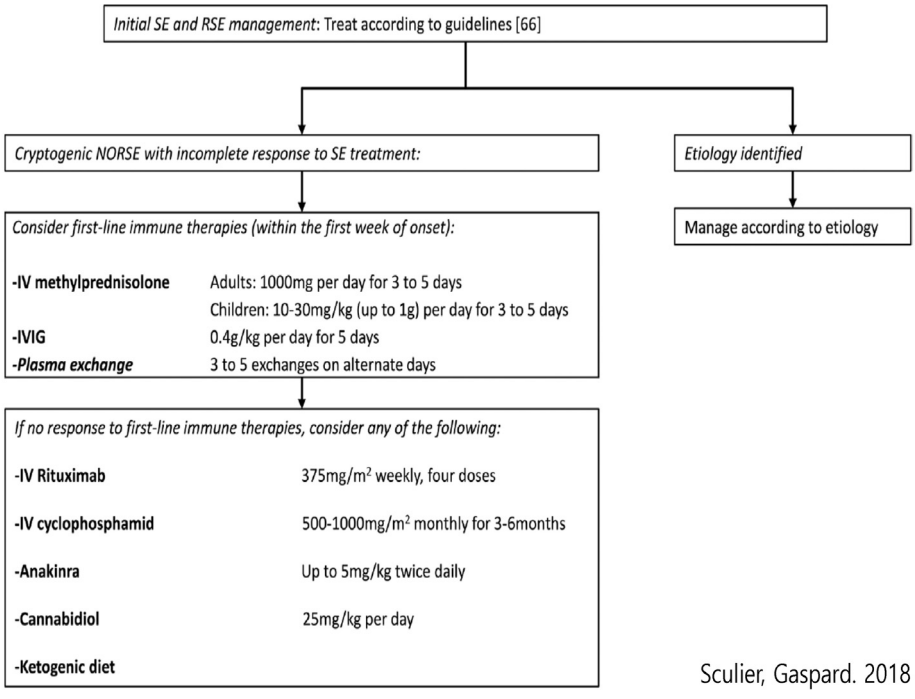
New-onset refractory status epilepticus (NORSE) is defined as a state of persistent seizures with no identifiable etiology in patients without preexisting epilepsy that lasts longer than 24 h despite optimal therapy. Management of NORSE is challenging, and the role of immunotherapy (IT) is unclear. We identified patients fulfilling the criteria for NORSE at a single institution. These patients were described, analyzed, and compared with NORSE cases available from the literature. Finally, a pooled analysis of available case series was conducted to compare the outcomes in patients who received IT with those not treated with IT during the course of NORSE in order to generate hypotheses for further research. In our case series, NORSE was diagnosed in 11 patients (9 females) with a mean age of 48 years and a mean duration of 54.4 days. Autoantibodies were identified in 7 patients, of which anti-GAD (glutamic acid decarboxylase) and anti-NMDAR (N-methyl-D-aspartate receptor) were most frequent. Of the 11 patients, 8 were treated with IT (intravenous steroids, immunoglobulins, plasmapheresis, or a combination), and 4 received chemotherapy. Of the 8 patients treated with IT, 6 had favorable outcomes (defined as any outcome other than death, vegetative state, or inability to take care of oneself) compared with 0 out of 3 patients who did not receive IT. Difference in outcomes was significant ($p = 0.026$). Pooled analysis of all identified case series, including ours, showed a statistically significant effect ($p = 0.022$), with favorable outcomes in 42% of the patients who received any IT compared with 20% in those who did not. In all patients with refractory SE and negative comprehensive investigations, a diagnosis of NORSE should be considered. This would aid planning for early immunotherapy. Currently, only Class IV evidence for the use of immunotherapy in NORSE is available. Prospective multicenter studies are necessary to assess the true efficacy of IT in NORSE.

Consider autoimmune etiology in patients with status epilepticus

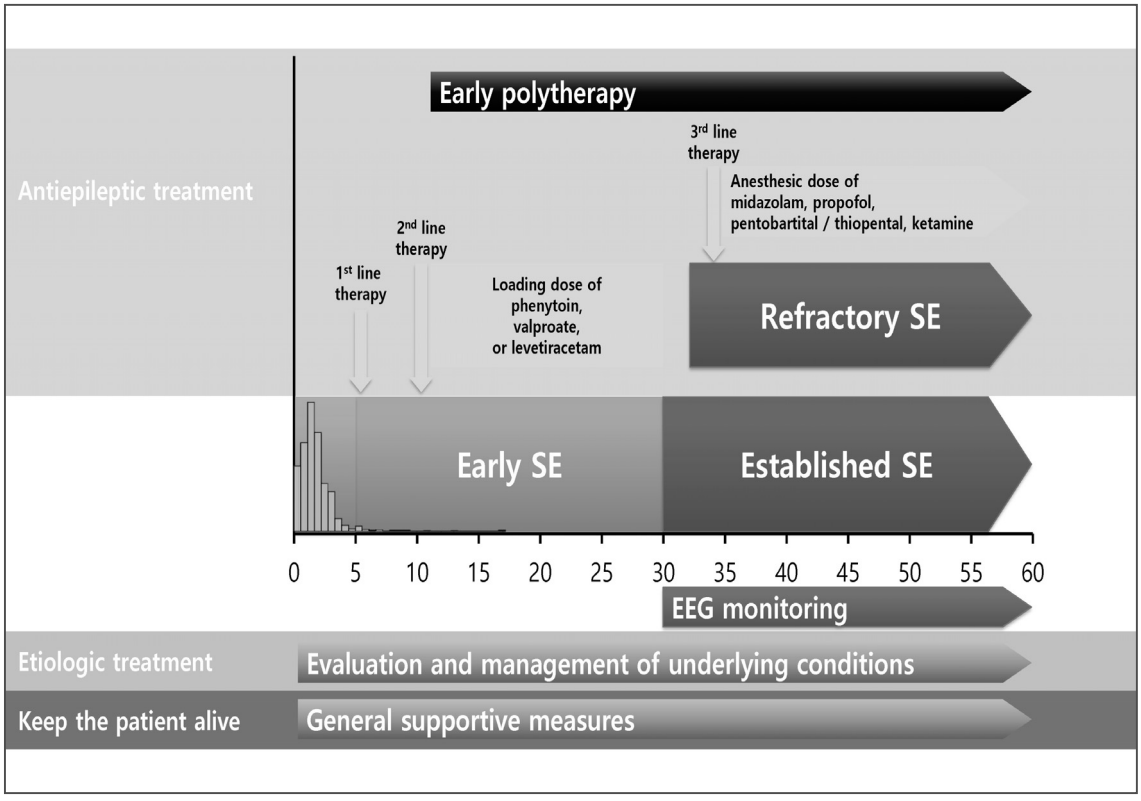
- SE as presentation of new-onset seizures
- progression to RSE or SRSE
- Relatively recent but explosive onset of seizures
- the absence of established epilepsy history
- the presence of other neurological problems such as memory loss, autonomic or hypothalamic dysfunction, and ataxia or movement disorder
- new psychiatric symptoms or behavioral changes
- known history of cancer
- lymphocytic pleocytosis on CSF examination

LoPinto-Khoury C, Sperling MR. 2013

NORSE treatment algorithm: Commonly used drugs in NORSE and FIRES with most frequently reported doses (expert opinion)



Sculier, Gaspard. 2018


Antiepileptic treatment
Early polytherapy
3rd line therapy
Anesthesic dose of midazolam, propofol, pentobartital / thiopental, ketamine
2nd line therapy
1st line therapy
Loading dose of phenytoin, valproate, or levetiracetam
Refractory SE
Early SE
Established SE
0 5 10 15 20 25 30 35 40 45 50 55 60
EEG monitoring
Etiologic treatment
Evaluation and management of underlying conditions
Keep the patient alive
General supportive measures