Outcome and Pragmatic Approaches for Refractory & Super-Refractory Status Epilepticus

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Status epilepticus (SE)

- A neurological emergency that has significant disability, high morbidity, and mortality rates up to 20%
- Refractory status epilepticus (RSE): in 23–50% of cases, SE does not respond to the first- and second-line medications, systemic anesthetics are the treatment of choice for RSE
- Super-refractory SE (SRSE): defined as status epilepticus (SE) that continues or recurs 24hours or more after the onset of anesthetic therapy or recurs on the reduction/withdrawal of anesthesia

Trinka and Leitinger, 2022, Continuum;
Cornwall et al., 2023, JAMA Neurol

Comparison of Refractory and Super-Refractory Status Epilepticus (1)

Criteria	RSE	SRSE
Definition	Seizures persist despite administration of first and second-line anti-seizure medications.	Seizures continue for 24 hours or more despite the use of anesthetic agents or recur upon their withdrawal.
Morbidity and Mortality	Associated with high morbidity and mortality; rates vary based on underlying etiology and patient demographics.	Even higher morbidity and mortality rates compared to RSE due to prolonged seizure activity and treatment resistance.
Long-term Cognitive Effects	Significant long-term cognitive impairments, including memory deficits and decreased executive function.	Often results in worse neurological outcomes, including severe disability, even if seizures are controlled.
Neurological Outcomes	Prolonged seizures can lead to permanent neurological damage, including encephalopathy and chronic epilepsy.	Similar to RSE, with additional challenges due to longer duration and more resistant nature of seizures.

Trinka and Leitinger, 2022, Continuum

Betjemann and Lowenstein, Lancet Neurol. 2015; Chen and Wasterlain, Lancet Neurol. 2006

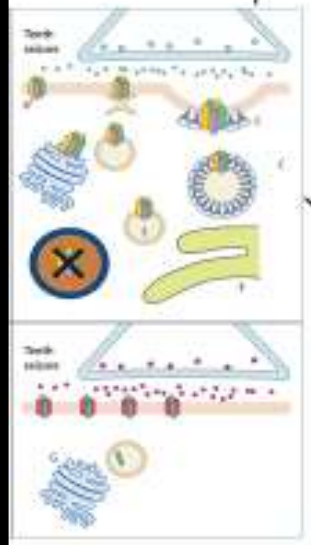
mechanisms involved in the transition of status epilepticus

Milliseconds–seconds
Stage 1

Protein phosphorylation
Ion channel opening and closing
Neurotransmitter release

Seconds–minutes
Stage 2

Receptor trafficking
- Decrease in inhibitory $GABA_A$ β2/β3 and γ2 subunits
- Increase in excitatory NMDA receptors
- Increase in excitatory AMPA receptors



Minutes–hours
Stage 3

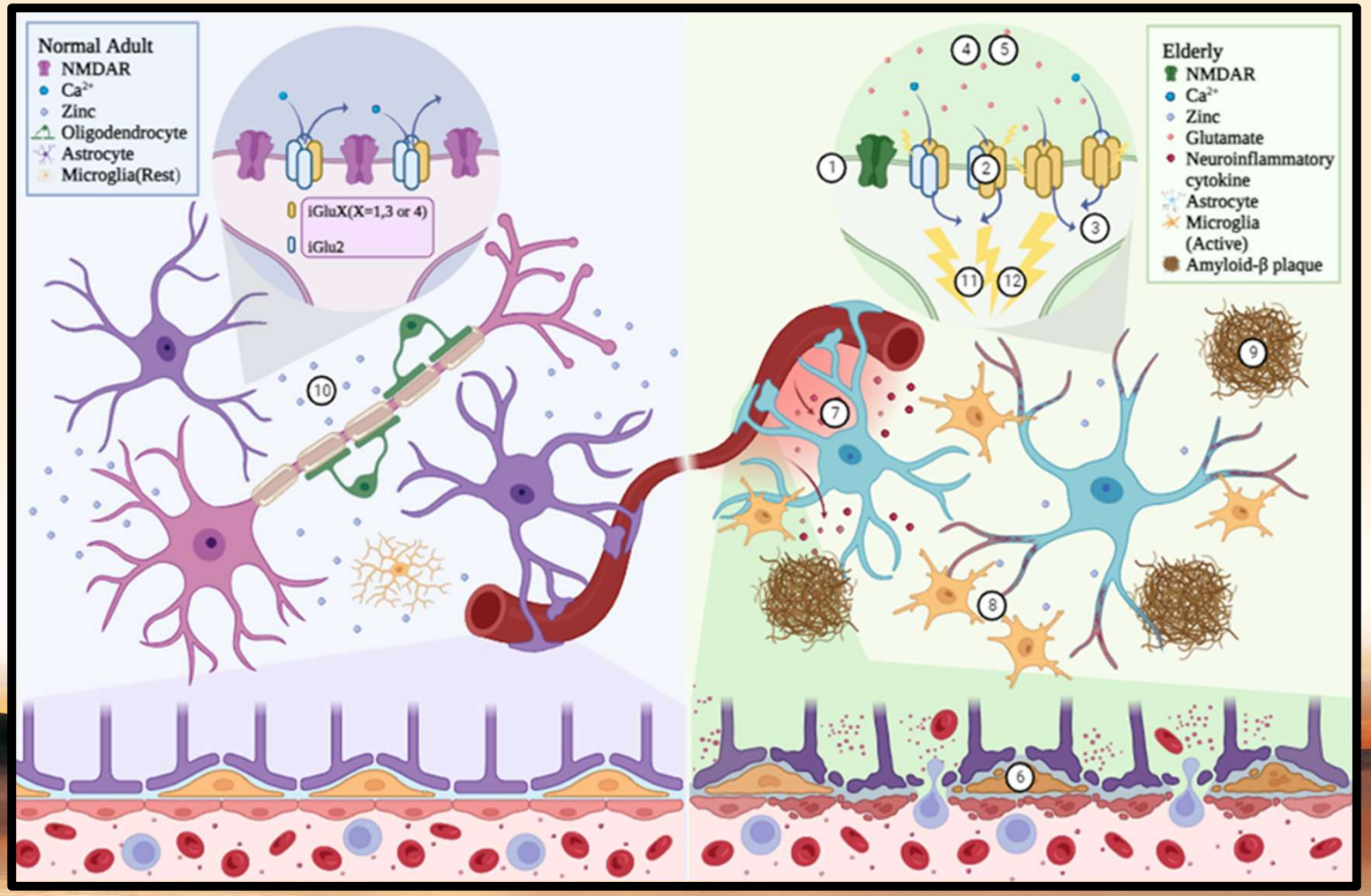
Neuropeptide expression
- Increase in excitatory substance P
- Insufficient replacement of inhibitory neuropeptide Y

Days–weeks
Stage 4

Genetic and epigenetic changes
- Gene expression
- DNA methylation
- Regulation of microRNA

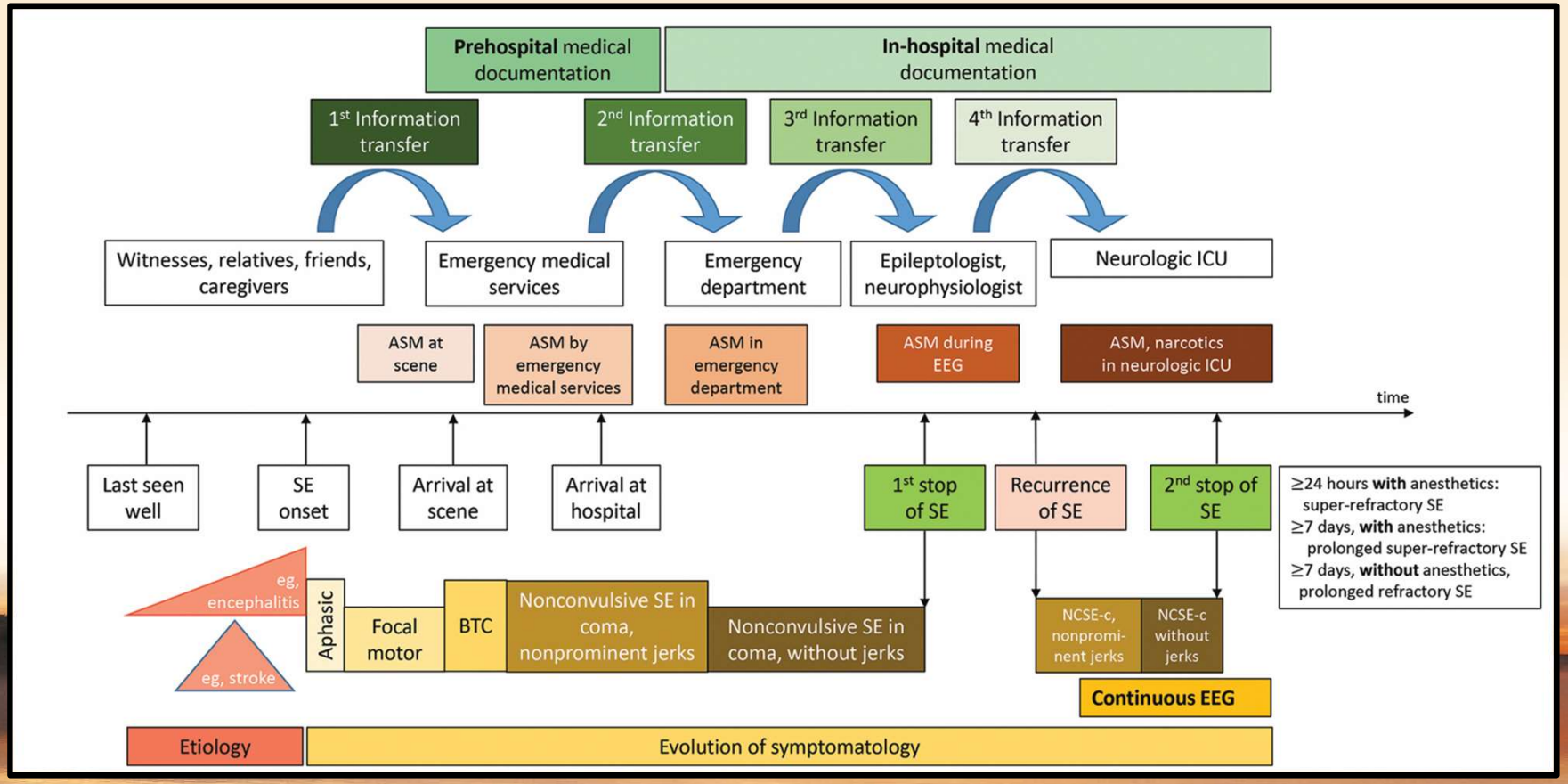
Betjemann JP, Lowenstein DH. Status epilepticus in adults. Lancet Neurol. 2015 Jun;14(6):615-24. doi: 10.1016/S1474-4422(15)00042-3. Epub 2015 Apr 10. PMID: 25908090
Chen JW, Wasterlain CG. Status epilepticus: pathophysiology and management in adults. Lancet Neurol. 2006 Mar;5(3):246-56. doi: 10.1016/S1474-4422(06)70574-X. PMID: 16488380

AMPAR & surrounding microenvironment in the adults and elderly



Huang et al., 2024, Archives of Geriatrics and Gerontology (accepted in revision)

The process of management of status epilepticus



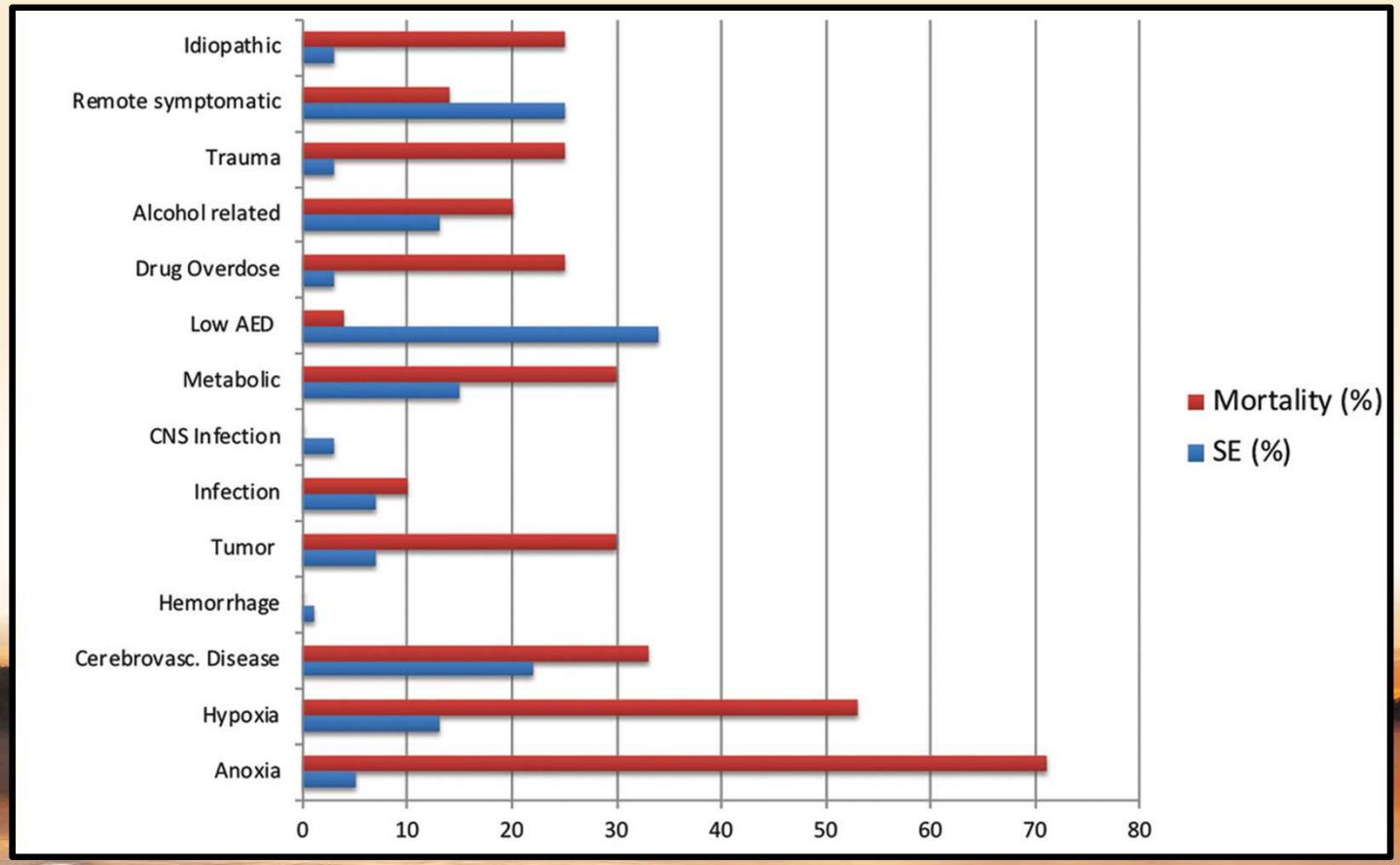
Trinka and Leitinger, 2022, Continuum

Taiwan epilepsy guidelines (2023)

Stage 1: stage of early status epilepticus (0-10/30 min)
Lorazepam (initial 4 mg slow IV push, may repeat once)
Midazolam (initial 10 mg IM, may repeat once)
Diazepam (10 mg slow IV push, may repeat once)
Stage 2: stage of established status epilepticus (10/30-60/90 min)
Phenytoin (initial 15-20 mg/kg IV infusion at 50 mg/min, additional Phenytoin 5-10 mg/kg/day IV infusion at 50-75 mg/min)
Valproic acid (initial 15-30 mg/kg IV infusion at 3-6 mg/kg/min, maintain dose 20-30 mg/kg/day IV infusion)
Levetiracetam (initial 30-60 mg/kg IV infusion, maintain dose 2000-4000 mg/day IV infusion)
Lacosamide (200-400 mg IV rapid loading dose over 3-5 min, followed by a daily dose of 200-400 mg)
Brivaracetam (200 mg IV rapid loading dose over 3-5 min, followed by 100 mg Q12H IV infusion)
Stage 3: stage of refractory status epilepticus (> 60/90 min)
Midazolam (0.1-0.3 mg/kg at 4 mg/min IV bolus, followed by a continuous IV infusion of 0.05-0.4 mg/kg/hr)
Phenobarbital (10-20 mg/kg IV infusion at 100 mg/min, maintain dose 1-3 mg/kg/day)
Propofol (1-2mg/kg IV bolus, followed by a continuous IV infusion of 5-10 mg/kg/hr)
Pentobarbital (10-20 mg/kg at 25 mg/min IV bolus, followed by a continuous iv infusion of 0.5-3 mg/kg/hr)
Thiopental (100-250 mg IV bolus over 20 s, followed by a continuous IV infusion of 3-5 mg/kg/hr)

* 較後期（如stage2或stage3）之處置應包含較前期（stage1或stage1與2）之處置
* 粗體字型為一般較為建議或方便換算的劑型、劑量。

Common and easily recognized causes of status epilepticus



Trinka and Leitinger, 2022, Continuum

Comparison of RSE and SRSE (2)

Criteria	RSE	SRSE
Treatment Strategies	Benzodiazepines followed by ASMs like phenytoin or levetiracetam.	Requires more complex treatment strategies, including continuous use of anesthetic agents, ketogenic diet, immunotherapy, and surgical interventions.
In-hospital Mortality	Varies but generally lower compared to SRSE.	High in-hospital mortality; studies report rates of around 24.1%.
Duration of Seizures	Persistent seizures despite first and second-line treatments.	Mean duration of 36.3 days with treatment often continuing beyond 28 days.
Prognostic Factors	Outcomes influenced by factors like age, etiology, and response to initial treatment.	Prognostic factors such as age and etiology are less predictive; longer treatment duration associated with higher chances of seizure cessation but increased risk of severe disability.
Etiologies	Can include a wide range of causes, often linked to acute symptomatic events, metabolic disturbances, or chronic epilepsy.	More likely to have acute or unknown etiologies; lower incidence of remote symptomatic causes and known epilepsy compared to RSE.

Trinka and Leitinger, 2022, Continuum

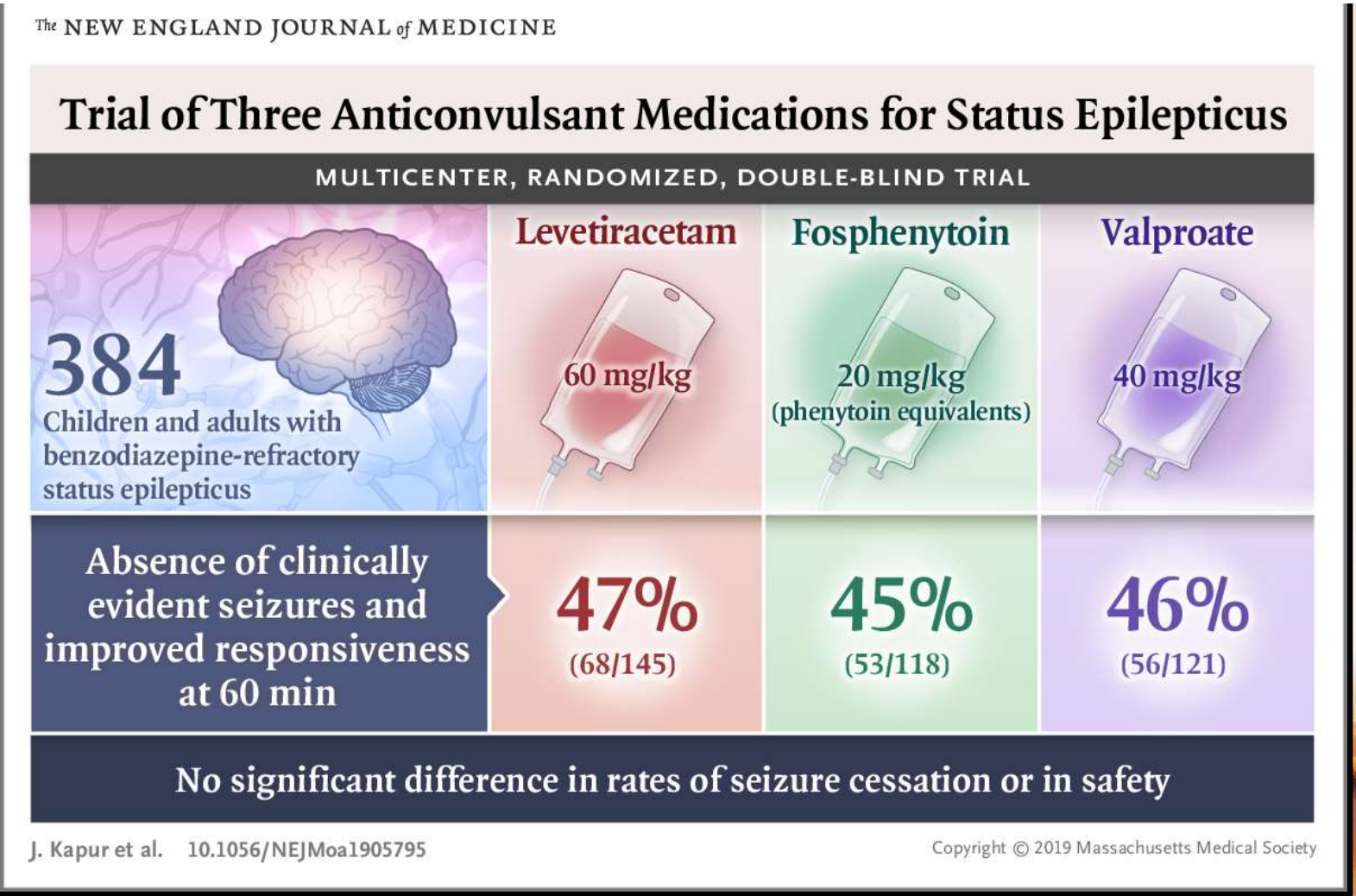
Consensus of 8th London-Innsbruck Colloquium on SE for 1st non-BZD

Recommendations for nonbenzodiazepine medication: initial doses, incremental doses, and maximum doses for a diagnostic intravenous antiseizure medication trial.

choice	Levetiracetam 1	Valproate 1	Lacosamide 1	Brivaracetam 1	Fosphenytoin[a] 2	Phenobarbital[b] 3
Starting dose	40 mg/kg	30mg/kg	6mg/kg	4mg/kg	15mg/kg	10mg/kg
Administration time	5 min	5 min	10 min	5 min	10 – 15 min(maximum 150 mg/min)	15+ min
With additional boluses up to a maximum dose of (whichever is lower):						
Maximum total loading dose, weight based	60 mg/kg	40 mg/kg	8 mg/kg	6 mg/kg	20 mg PE/kg	20 mg/kg
Maximum total loading dose, absolute	4500 mg	3000 mg	600 mg	450 mg	1500 mg PE	1500
Special measures	ECG monitoring					

Abbreviations: PE, phenytoin sodium equivalent.
[a]Phenytoin can be used where fosphenytoin is not available, at a maximum rate of 50 mg/min.
[b]In countries where only phenobarbital is available.

Leitinger M et al. Epilepsia, 2023

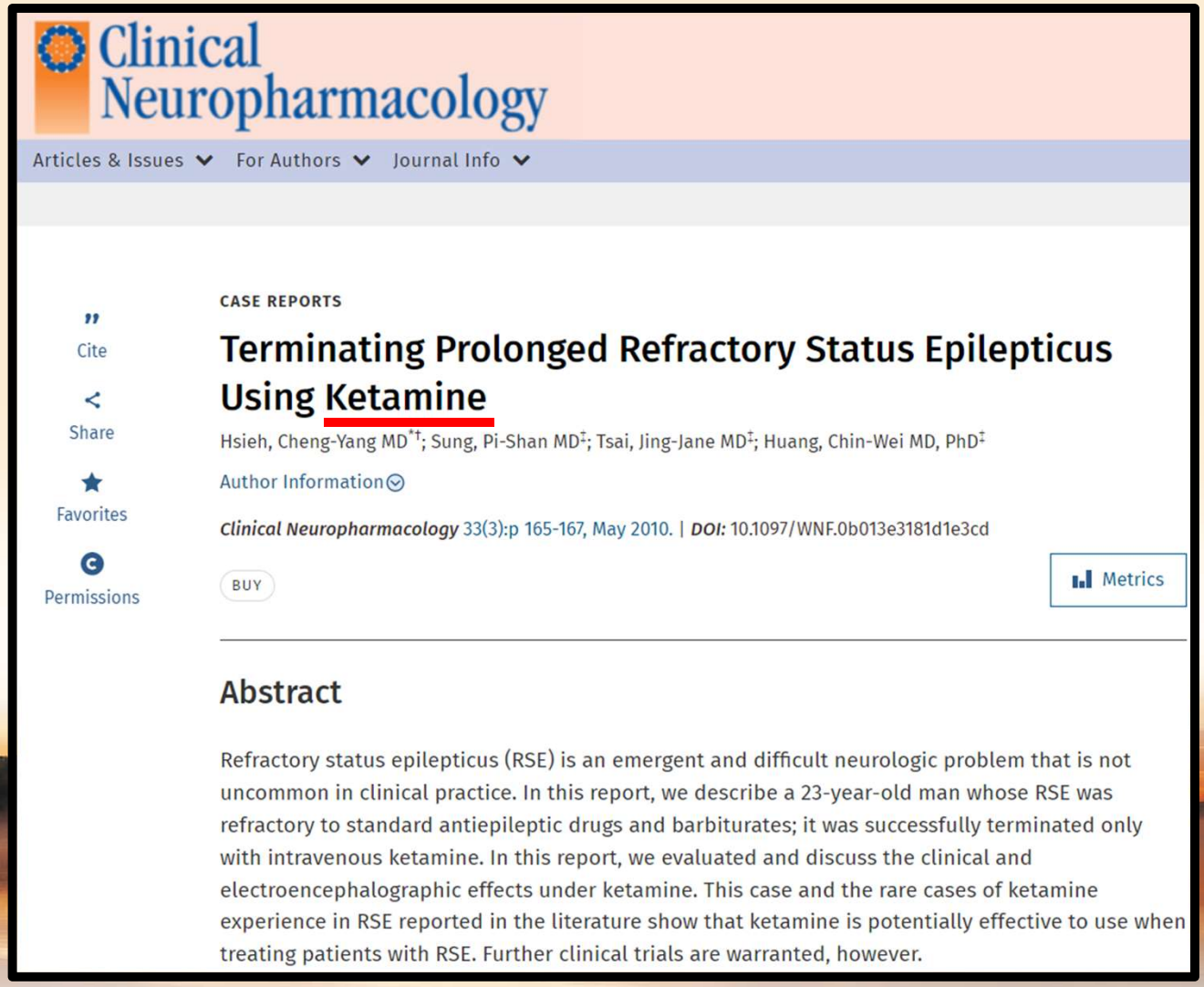


But whether this is also true for RSE is unknown.

Vossler et al., 2020, Epilepsy Currents

Status Epilepticus - Three Anticonvulsants Head-to-Head - ESETT RCT – JournalFeed Last accessed: May 2024

Hsieh et al., 2010, Clin Neuropharmacol.



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CASE REPORTS

Terminating Prolonged Refractory Status Epilepticus Using Ketamine

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Author Information

Clinical Neuropharmacology 33(3):p 165-167, May 2010. | **DOI:** 10.1097/WNF.0b013e3181d1e3cd

BUY

Metrics

Abstract

Refractory status epilepticus (RSE) is an emergent and difficult neurologic problem that is not uncommon in clinical practice. In this report, we describe a 23-year-old man whose RSE was refractory to standard antiepileptic drugs and barbiturates; it was successfully terminated only with intravenous ketamine. In this report, we evaluated and discuss the clinical and electroencephalographic effects under ketamine. This case and the rare cases of ketamine experience in RSE reported in the literature show that ketamine is potentially effective to use when treating patients with RSE. Further clinical trials are warranted, however.

Treatment	Description	Efficacy	Reference
Ketamine	NMDA receptor antagonist	varied efficacy, with some studies indicating it can be effective in terminating seizures in SRSE. 40-60% of patients showed positive responses, though it requires further validation.	Neurological Research and Practice, 2024
Ketogenic Diet	High-fat, low-carbohydrate diet designed to mimic fasting state and produce ketones.	has been found to be effective in 50-70% of cases, particularly in pediatric patients. It can reduce seizure frequency and intensity.	Frontiers in Neurology, 2023
Immunotherapy	Treatments like corticosteroids, IV immunoglobulins, and plasmapheresis to address autoimmune causes of SRSE.	Can be effective in SRSE due to autoimmune encephalitis or other immune-related etiologies. 30-50% response rate depending on the underlying cause.	JAMA Neurology, 2023
Responsive Neurostimulation (RNS)	Implantable device that monitors brain activity and delivers electrical stimulation to prevent seizures.	In a small case series, 70% of patients with focal SRSE experienced resolution of seizures after RNS implantation. This is considered a promising but still experimental approach.	Journal of Neurosurgery, 2023

An overview of the efficacy of various alternative treatments for SRSE, highlighting both their potential benefits and limitations

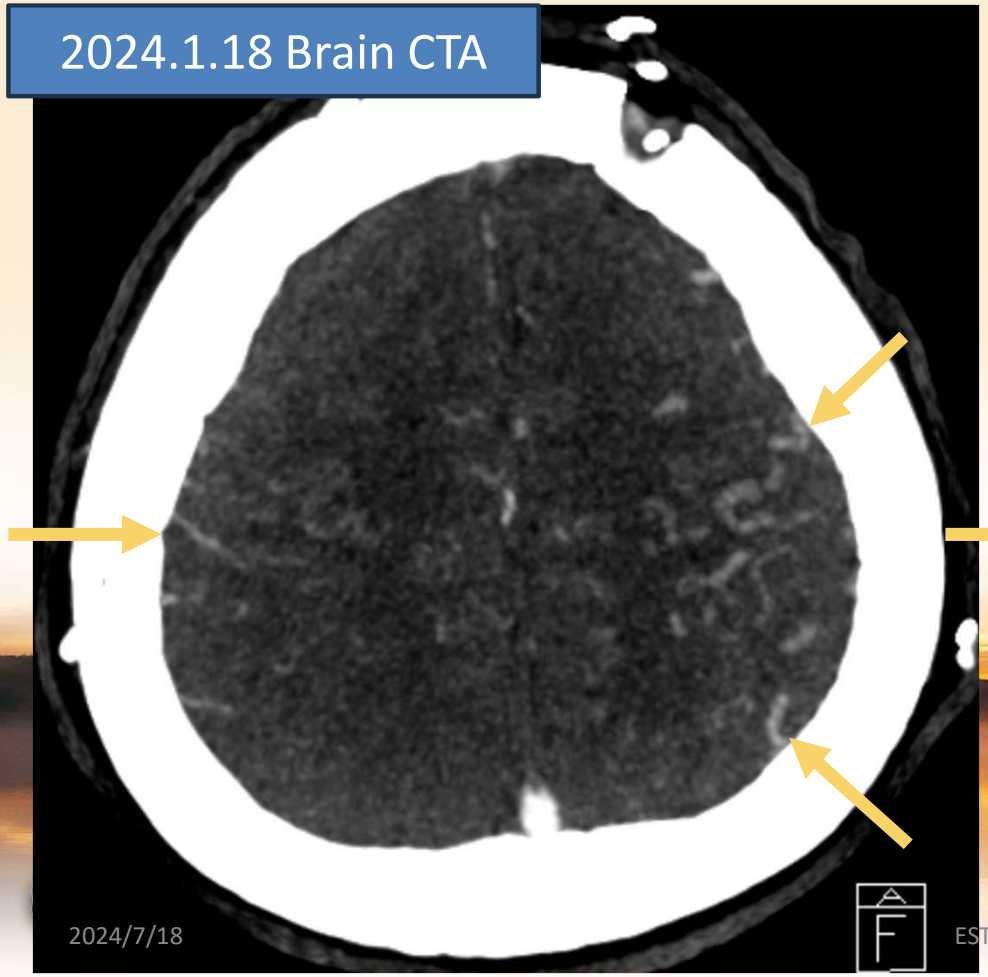
Treatment	Description	Efficacy	Reference
Vagus Nerve Stimulation (VNS)	Device implanted to stimulate the vagus nerve, which can help reduce seizure frequency and intensity.	Has shown efficacy in reducing seizures in about 50-60% of SRSE patients. It is less invasive than RNS.	JAMA Neurology, 2023
Deep Brain Stimulation (DBS)	Surgical treatment involving the implantation of electrodes in specific brain areas to modulate neural activity.	Has shown effectiveness in a subset of patients with SRSE, particularly those with well-localized seizure foci. However, it is highly invasive and considered when other treatments fail.	Brain, 2011
High-dose Barbiturates	Continuous infusion of barbiturates like pentobarbital to induce a coma and control seizures.	High-dose barbiturates can be effective in controlling seizures in SRSE, but they come with significant risks, including hypotension and immunosuppression.	Epilepsia, 2019
Magnesium Sulfate	Administered in cases of eclampsia or suspected magnesium deficiency-related seizures.	Limited data suggest that magnesium sulfate can be beneficial in specific contexts such as eclampsia. It is not broadly effective for all cases of SRSE.	Crit Care Clin, 2023

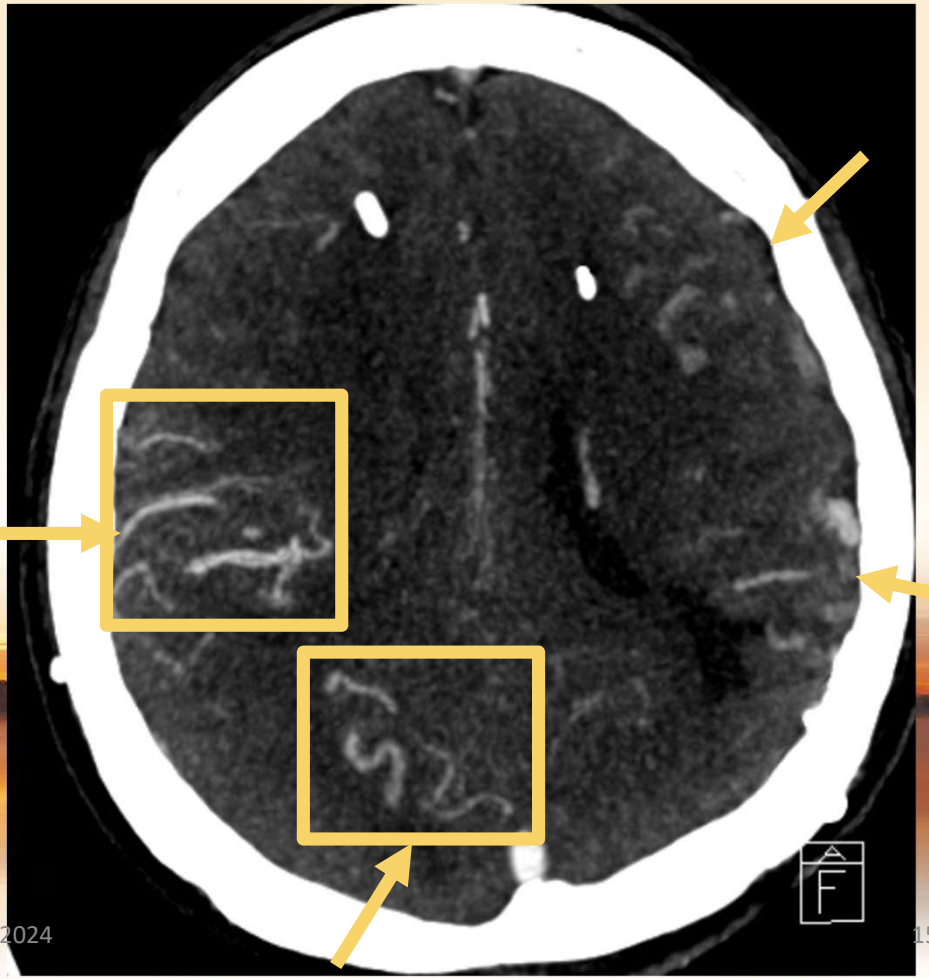
An overview of the efficacy of various alternative treatments for SRSE, highlighting both their potential benefits and limitations

Adhikari A et al. Neurol Res Pract, 2024; Nabbout R et al. Front Neurol, 2023; Cornwall CD et al. JAMA Neurol. 2023; Ernst LD et al. J Neurosurg, 2023; Shorvon S and Ferlisi M. Brain, 2011; Coppler PJ and Elmer J. Crit Care Clin, 2023

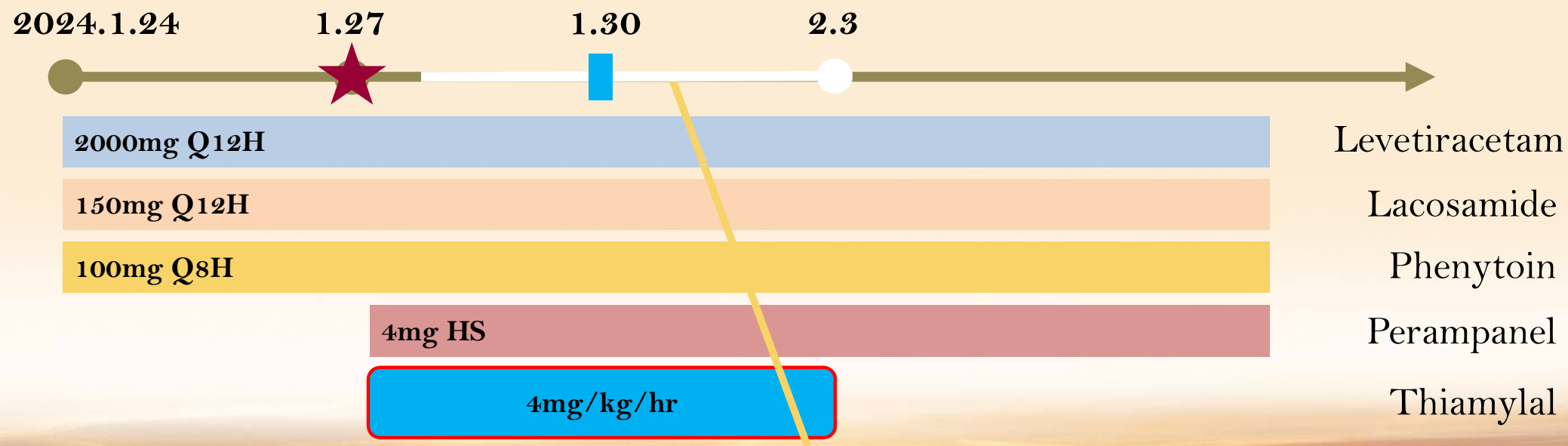
A 29 year-old female with SRSE
Etiology: Multiple arteriovenous fistulas at bilateral hemispheres

2024.1.18 Brain CTA





Present Illness and Management



✓ Intervention: 5th TAE/TVE at right middle meningeal artery & TVE at right sigmoid sinus significantly beneficial in reducing the seizures

healthcare

MDPI

Article

Status Epilepticus Mortality Risk Factors and a Correlation Survey with the Newly Modified STESS

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Abstract: Background: Status epilepticus (SE) is a neurological emergency and is usually associated with significant morbidity and mortality rates. Several clinical scales have been proposed to predict the clinical outcome of such incidents, including the Status Epilepticus Severity Score (STESS), the modified STESS (mSTESS), and the Encephalitis-Nonconvulsive Status Epilepticus-Diazepam Resistance-Image Abnormalities-Tracheal intubation (END-IT). Nevertheless, there is still a need for a more practical and precise predictive scale. Methods: This is a retrospective cohort study which examines data from patients with SE in our Department of Neurology between 2009 and 2020. Based on the outcome of each case, the patients were divided into survivor and non-survivor groups. We analyzed the independent factors and adjusted the STESS to achieve a better prediction of prognosis. The predictive accuracy of our new STESS scale was then compared with that of the mSTESS and the END-IT. Results: Data on a total of 59 patients were collected, with 6 of them classified as non-

Components of Newly Modified STESS (nSTESS)

Clinical Features	Score
Consciousness	
Alert or somnolent/confused	0
Stuporous or comatose	1
Worst seizure type	
Simple-partial, complex-partial, absence, myoclonic	0
Generalized-convulsive	1
Nonconvulsive status epilepticus in coma	2
Age	
<65 years old	0
≥65 years old	2
History of previous seizures	
Yes	0
Not or unknown	1
Use of thiobarbiturate	
Yes	1
No	0
Numbers of used AEDs within 1st week	
≤2	0
3	1
≥4	2
Total	0–9

Clinical characteristics of the survivors and non-survivors hospitalized in NCKU Hospital from 2009 to 2020.

AED, antiepileptic drug; SD, standard deviation; STESS, Status Epilepticus Severity Score.

Characteristics	Survivors (*N* = 53)	Non-Survivors (*N* = 6)	All	*p*-Value
Age–year (mean ± SD)	55.04 ± 21.33	56.67 ± 18.98	55.20 ± 20.95	0.859
Male sex–no. (%)	32 (60.4%)	4 (66.7%)	36 (61%)	0.769
Underlying diseases				
Meningioencephalitis–no. (%)	8 (15.09%)	0 (0%)	8 (13.6%)	0.583
Intracranial hemorrhage–no. (%)	15 (28.3%)	3 (50%)	18 (30.51%)	0.357
Seizure types				0.115
Focal impaired awareness	29 (54.72%)	4 (66.67%)		
Focal to generalized	4 (7.55%)	2 (33.33%)		
Generalized	18 (33.96%)	0 (0%)		
Nonconvulsive status epilepticus	2 (3.77%)	0 (0%)		
Categories of AEDs				
Valproic acid–no. (%)	31 (58.49%)	3 (50%)	34 (58.62%)	0.696
Levetiracetam–no. (%)	38 (71.7%)	6 (100%)	44 (75.86%)	0.157
Phenytoin–no. (%)	22 (41.51%)	3 (50%)	25 (43.1%)	0.696
Topiramate–no. (%)	11 (20.75%)	3 (50%)	14 (24.14%)	0.114
Lacosamide–no. (%)	1 (1.89%)	1 (16.67%)	2 (3.45%)	0.418
Perampanel–no. (%)	5 (9.43%)	2 (33.33%)	7 (12.07%)	0.313
Numbers of AEDs used in 1st week				0.016
1	15 (28.3%)	0 (0%)	15 (25.86%)	
2	25 (47.17%)	2 (33.34%)	27 (46.55%)	
3	10 (18.87%)	2 (33.34%)	12 (20.69%)	
4	2 (3.77%)	2 (33.34%)	4 (6.9%)	
5	1 (1.89%)	0 (0%)	1 (1.72%)	
Continuous infusion of sedatives				
Midazolam–no. (%)	31 (58.49%)	4 (66.67%)	35 (60.34%)	0.530
Propofol–no. (%)	4 (7.55%)	2 (33.34%)	6 (10.34%)	0.108
Thiobarbiturate–no. (%)	0 (0%)	2 (33.34%)	2 (3.45%)	0.009
STESS				0.117
0	1 (1.89%)	0 (0%)	1 (1.72%)	
1	10 (18.87%)	0 (0%)	10 (17.24%)	
2	16 (30.19%)	2 (33.34%)	18 (31.03%)	
3	19 (35.85%)	1 (16.67%)	20 (34.48%)	
4	5 (9.43%)	3 (50%)	8 (13.79%)	
5	2 (3.77%)	0 (0%)	2 (3.45%)	

Huang et al.Healthcare.2021

Capacity of the new scale (nSTESS) versus the STESS, mSTESS, and END-IT to predict mortality.

Scale	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Overall Accuracy (%)	OR (CI 95%)	*p*-Value
STESS≥3	66.70%	50.90%	13.30%	93.10%	69.20%	2.077 (0.35–12.325)	0.352
mSTESS≥4	50.00%	56.60%	11.50%	90.90%	56.60%	1.304 (0.241–7.069)	0.543
END-IT≥3	50.00%	66.00%	14.30%	92.10%	57.70%	1.944 (0.356–10.625)	0.361
nSTESS≥4	83.30%	77.40%	29.40%	97.60%	86.80%	17.083 (1.816–160.683)	0.006

CI, confidence interval;
nSTESS, newly modified Status Epilepticus Severity Score;
mSTESS, modified Status Epilepticus Severity Score;
NPV, negative predictive value;
OR, odds ratio;
PPV, positive predictive value;
STESS, Status Epilepticus Severity Score;
END-IT, Encephalitis-NCSE-Diazepam Resistance-Image Abnormalities-Tracheal Intubation.

Huang et al. Healthcare, 2021

Epilepsy & Behavior 140 (2023) 109110

Contents lists available at ScienceDirect

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Clinical scores and clusters for prediction of outcomes in status epilepticus

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Prognostic scores of in-hospital mortality in status epilepticus.

Predictors of outcome in scoring systems				
Status Epilepticus Severity Score (STESS) [Rossetti et al. 2008]	**Modified STESS (mSTESS) [González-Cuevas et al. 2016]**	**Newly Modified STESS (nSTESS) [Huang et al. 2021]**	**Epidemiology-based Mortality score in Status Epilepticus (EMSE) [Leitinger et al. 2015]**	**Risk score predictive of mortality in status epilepticus [Tiamkao et al. 2018]**
Level of consciousness	Level of consciousness	Level of consciousness	Aetiology	Age
Worst seizure type	Worst seizure type	Worst seizure type	Age	Comorbidities
Age	Age	Age	Comorbidities	Complications of SE
History of previous seizures	History of previous seizures	History of previous seizures	EEG	
	Baseline disability (modified Rankin Scale)	Use of thiobarbiturate		
		Number of antiseizure medicines used within the first week		

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External validation of newly modified status epilepticus severity score for predicting mortality in patients with status epilepticus in a regional hospital in Taiwan

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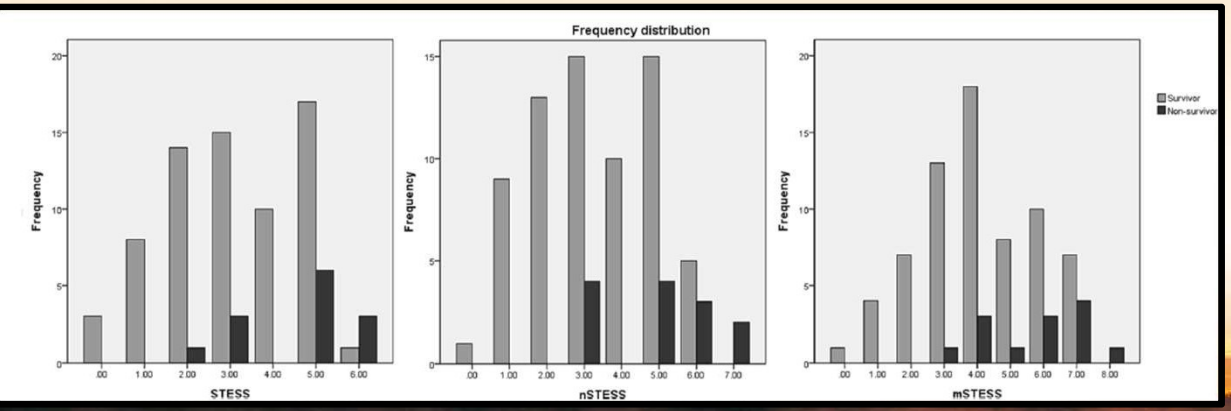
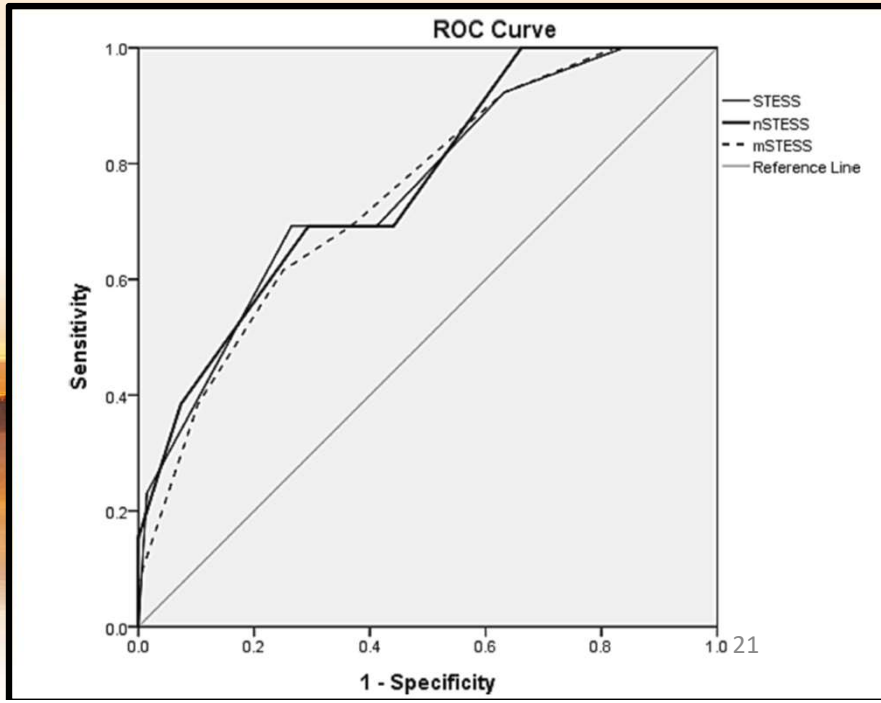
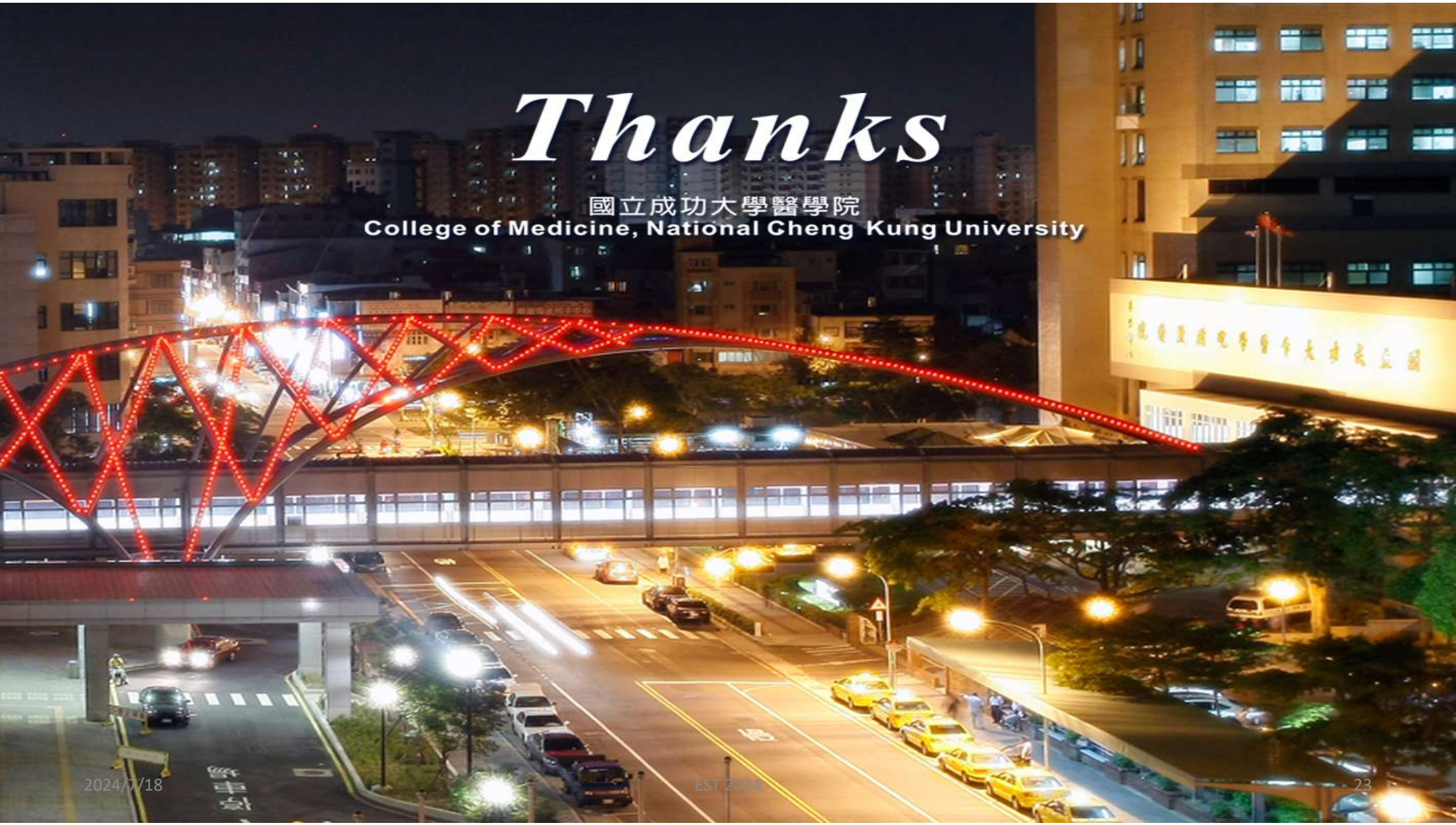
Huang et al., Epilepsy Behav, 2023





Conclusion

- Recent advancements in the understanding of status epilepticus have led to more accurate diagnoses, earlier interventions, and enhanced cerebral imaging of its effects.
- While the introduction of various alternative treatments for SRSE shows promise, further validation and research are necessary to tailor these therapies effectively.
- Outcome prediction serves as a practical tool for estimating the need for intensive care resources.
- Despite the high rates of successful treatment, the chances of surviving SRSE with only minor disabilities remain low, even with prolonged treatment.


Thanks
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College of Medicine, National Cheng Kung University