ICU Management of Status Epilepticus

Clio Rubinos MD MSCR
Director, Neurocritical Care Fellowship
Assistant Professor, Department of Neurology
Division of Neurocritical Care and Epilepsy

UNC SCHOOL OF MEDICINE Neurology

Disclosure

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- Speaker honoraria from the American Epilepsy Society

- Consulting honoraria from Quatro Consulting INC

- Azurity advisory committee

Outline

- Define the concepts and stages of Status Epilepticus
- Appraise the clinical evidence of systemic complication and brain damage after prolonged seizures and status epilepticus
- Review evidence of the management of Status Epilepticus
- Discuss the approach and management of the Ictal-Interictal Continuum patterns

Definition of Status Epilepticus

Status Epilepticus

Results from either the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms that lead to abnormally prolonged seizures **(after time point t_1)**

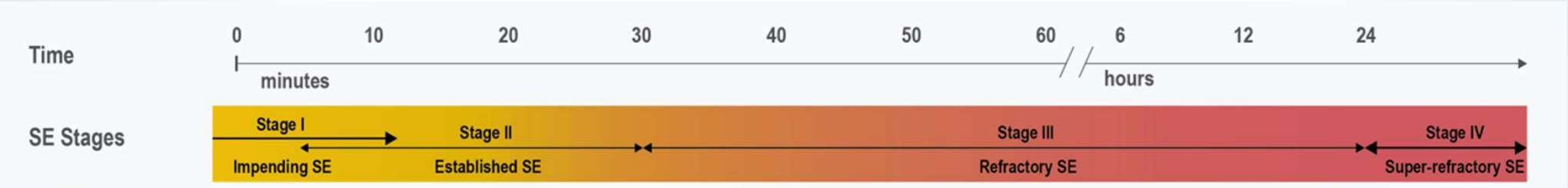
Can have long-term consequences **(after time point t_2),** including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures

Emergency treatment of SE should be started

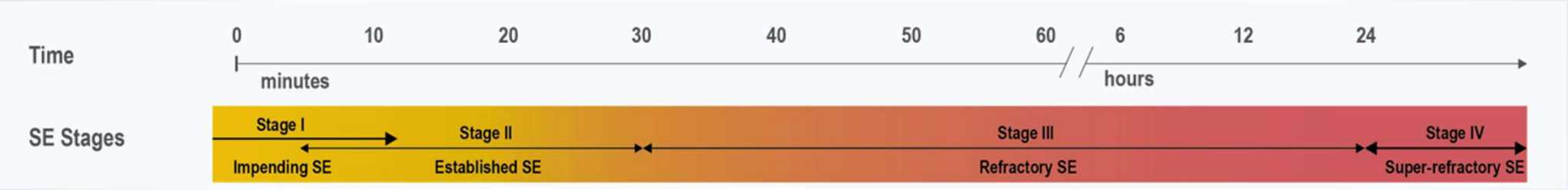
Long consequences may be expected

Type of SE	Time (t_1), when a seizure is likely to be prolonged leading to continuous seizure activity	Time (t_2), when a seizure may cause long-term consequences
Tonic-clonic SE	5 minutes	30 minutes
Focal SE with impaired consciousness	10 minutes	>60 minutes
Absence SE	10-15 minutes[a]	Unknown

Stages of Status Epilepticus



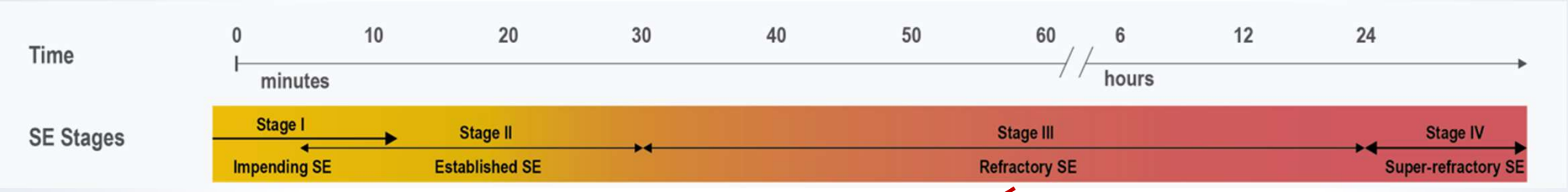
Stages of Status Epilepticus



Established SE

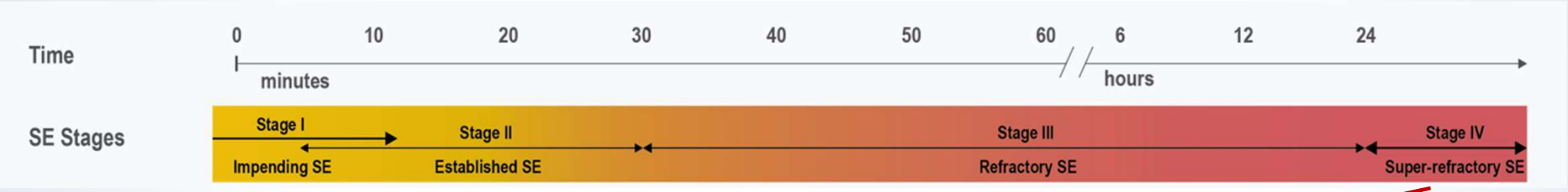
SE epilepticus that persists after treatment with benzodiazepine

Stages of Status Epilepticus



Refractory SE:
SE that persists despite the administration of at least two parenteral drugs that have been properly selected and dosed, including a benzodiazepine.
No specific seizure duration required

Stages of Status Epilepticus

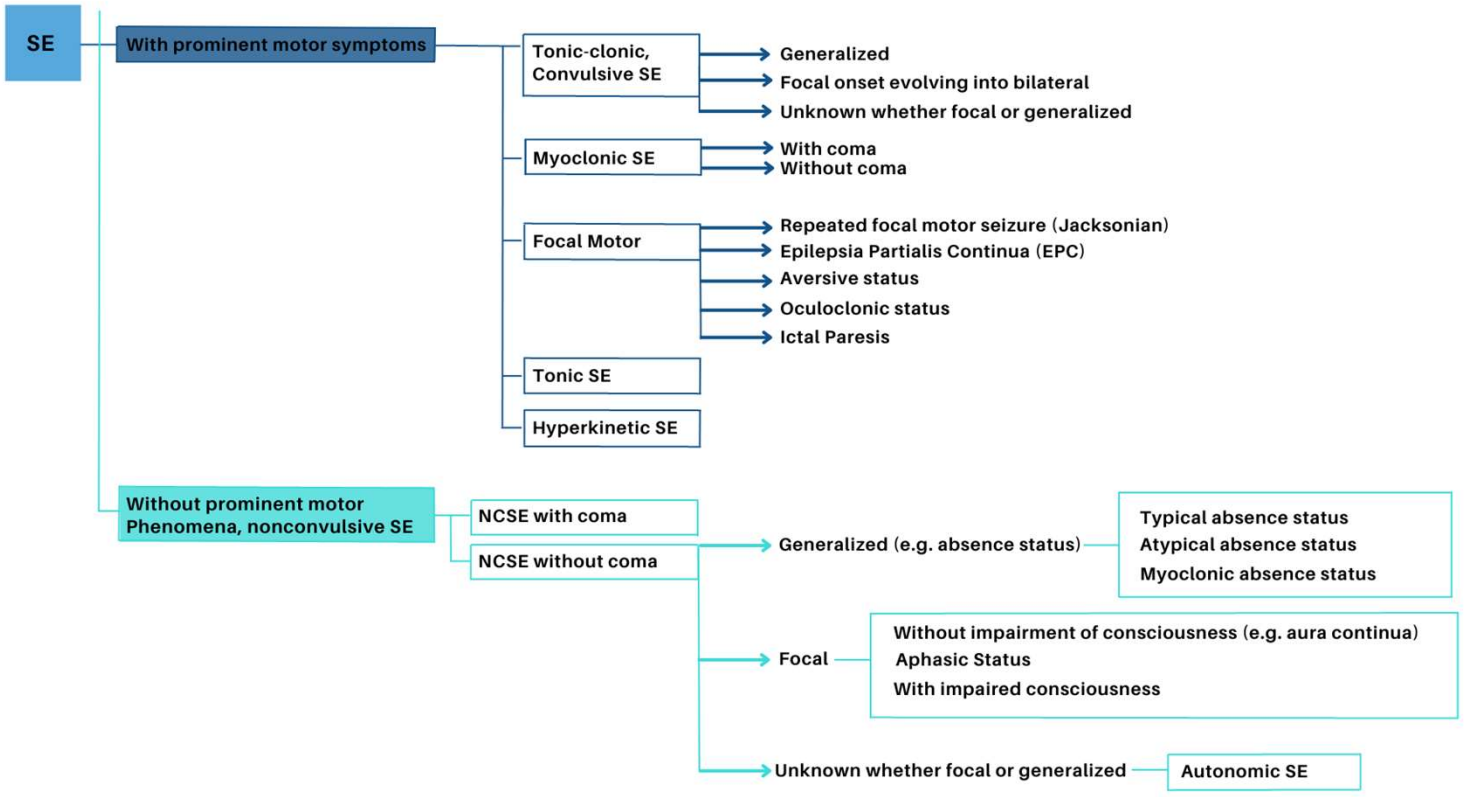


Super-refractory SE:

SE that persists for at least 24 hours after the start of anesthesia and other medications and these have not been discontinued and appropriately medicated, or if the seizures recur after withdrawal of anesthesia, for which reintroduction of anesthesia is required

"Anesthesia" includes commonly used agents such as Midazolam, Propofol, Pentobarbital, Thiopental, Ketamine, and others, provided they are used at anesthetic doses.

SE subtype is characterized by the presence or absence of motor symptoms and/or impaired consciousness.



Classification scheme for status epilepticus proposed by the International League Against Epilepsy Task Force on classification of status epilepticus. NCSE: nonconvulsive SE, SE: status epilepticus.

Altered mental status is a major symptom of nonconvulsive SE

Nonmotor symptoms (eg, nonconvulsive status epilepticus)[1,2]

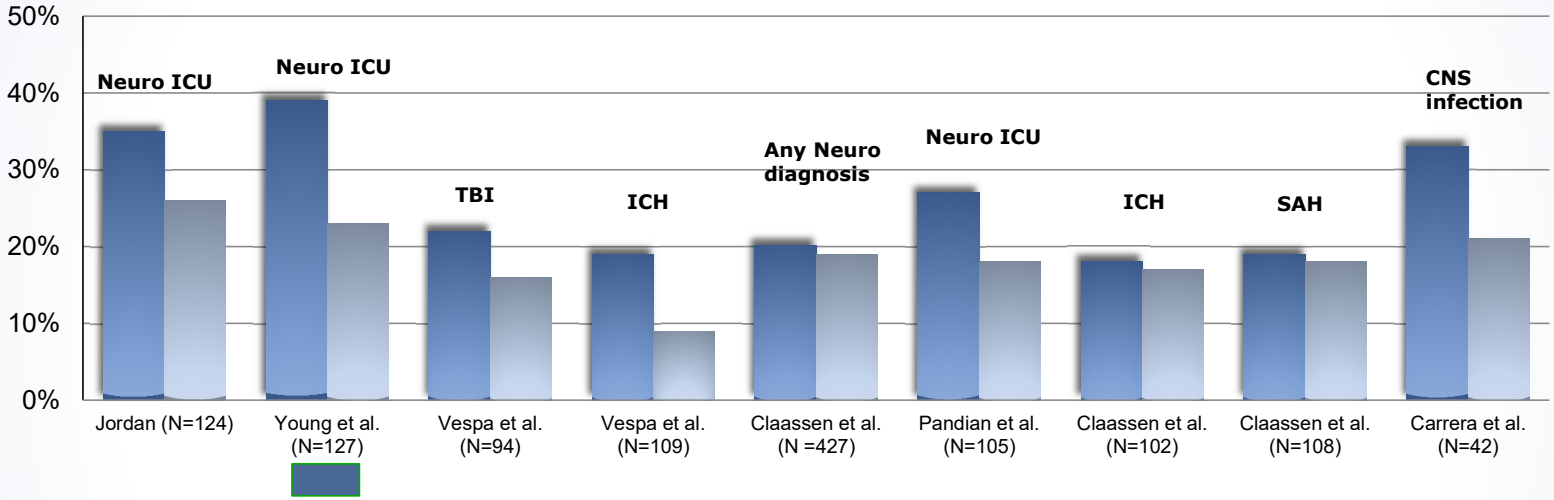
- **Altered mental status (82%)**
  - **Confusion (49%)**
  - **Coma (22%)**
  - **Lethargy (21%)**

  Altered mental status is a central clinical feature of NCSE
- Speech disturbance (15%)
- Myoclonus (13%)
- Unusual behavior (11%)
- Anxiety, agitation, and delirium (8%)
- Extrapyramidal signs (7%)
- Hallucinations (6%)

Motor symptoms

- Generalized tonic-clonic movements of the extremities[3]
- Localized tonic-clonic movements of the extremities[4-6]
- Oroalimentary automatisms (eg, lip smacking, repeated swallowing or chewing)[4-6]
- Abnormal eye movements (eg, rapid eye movements, gaze deviation, hippus)[4-8]
- Limb paralysis[5]

Non convulsive seizures: Prevalence in critically ill adults w/ primary neuro diagnosis



% of patients with NCSz

% of patients whose seizures were exclusively nonconvulsive

Courtesy of Dr. Lawrence Hirsch, MD

Nonconvulsive Status Epilepticus

Defined as electrographic seizures that last longer than *10 minutes or present for at least 20% of any 60-minute period* of recording.

The 10-minute cutoff matches the definition of focal status epilepticus with impaired consciousness by the International League Against Epilepsy.

The 20% cutoff, lowered from the previous 50%, is based on expert consensus and on one study in critically ill children in whom the risk of neurological decline was significantly greater when the maximum hourly seizure burden was >20%.

Acute systemic complication of Status Epilepticus

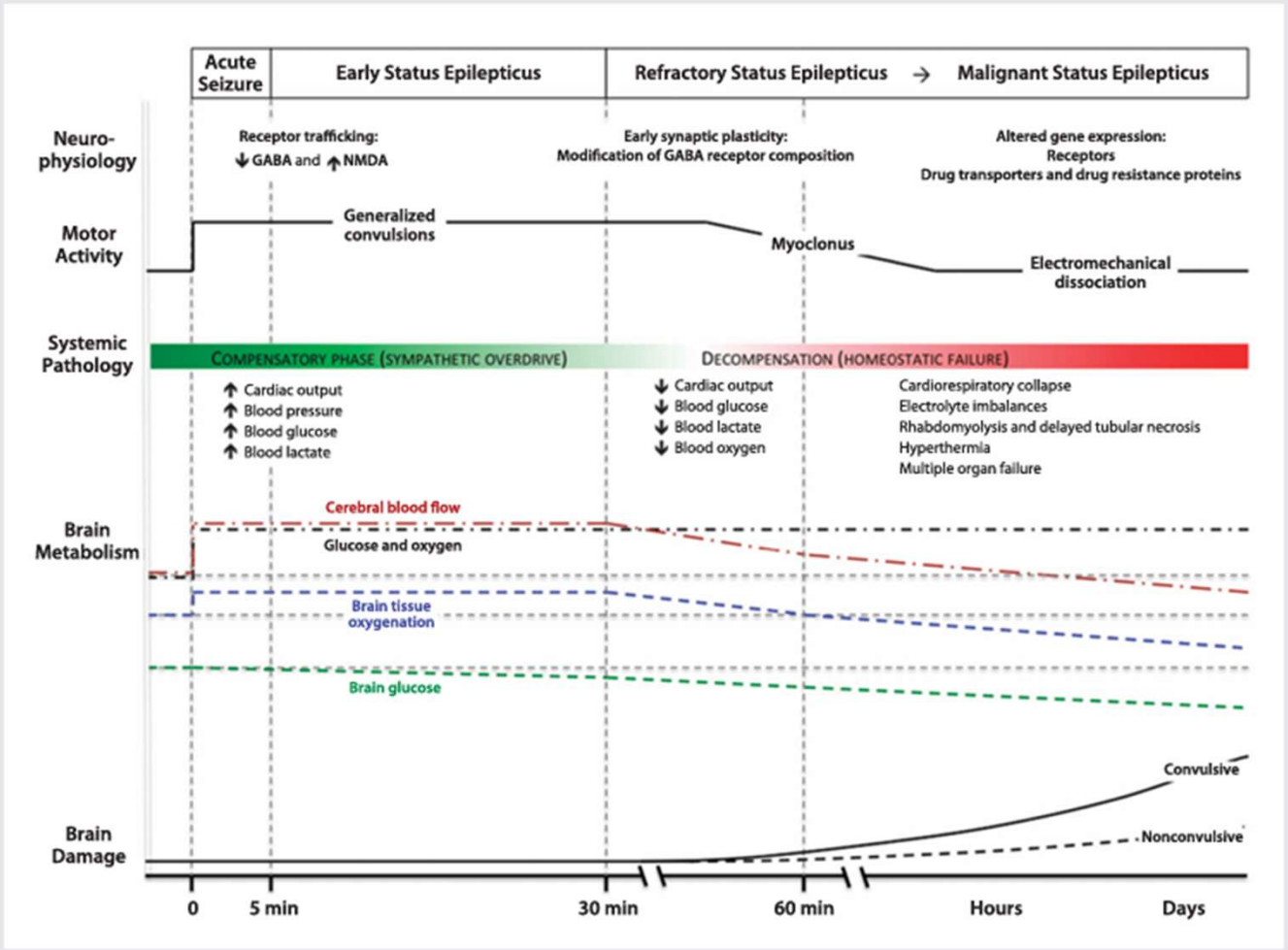
Systemic complications

- Altered mental Status:
  - Post Ictal State to coma, Underlying pathology, NCSE
- Hemodynamic instability:
  - First stage: Hypertension, tachycardia, arrhythmias, stress cardiomyopathy
  - Second stage:
- Hypoxemia:
  - Apnea, trismus, soft palate hypotonia, aspiration pneumonia, respiratory muscle, neurogenic pulmonary edema.
- Cardiac Arrest (1.1%)
  - Asystole (hypoxemia), bradycardia and conduction disorders, ventricular fibrillation

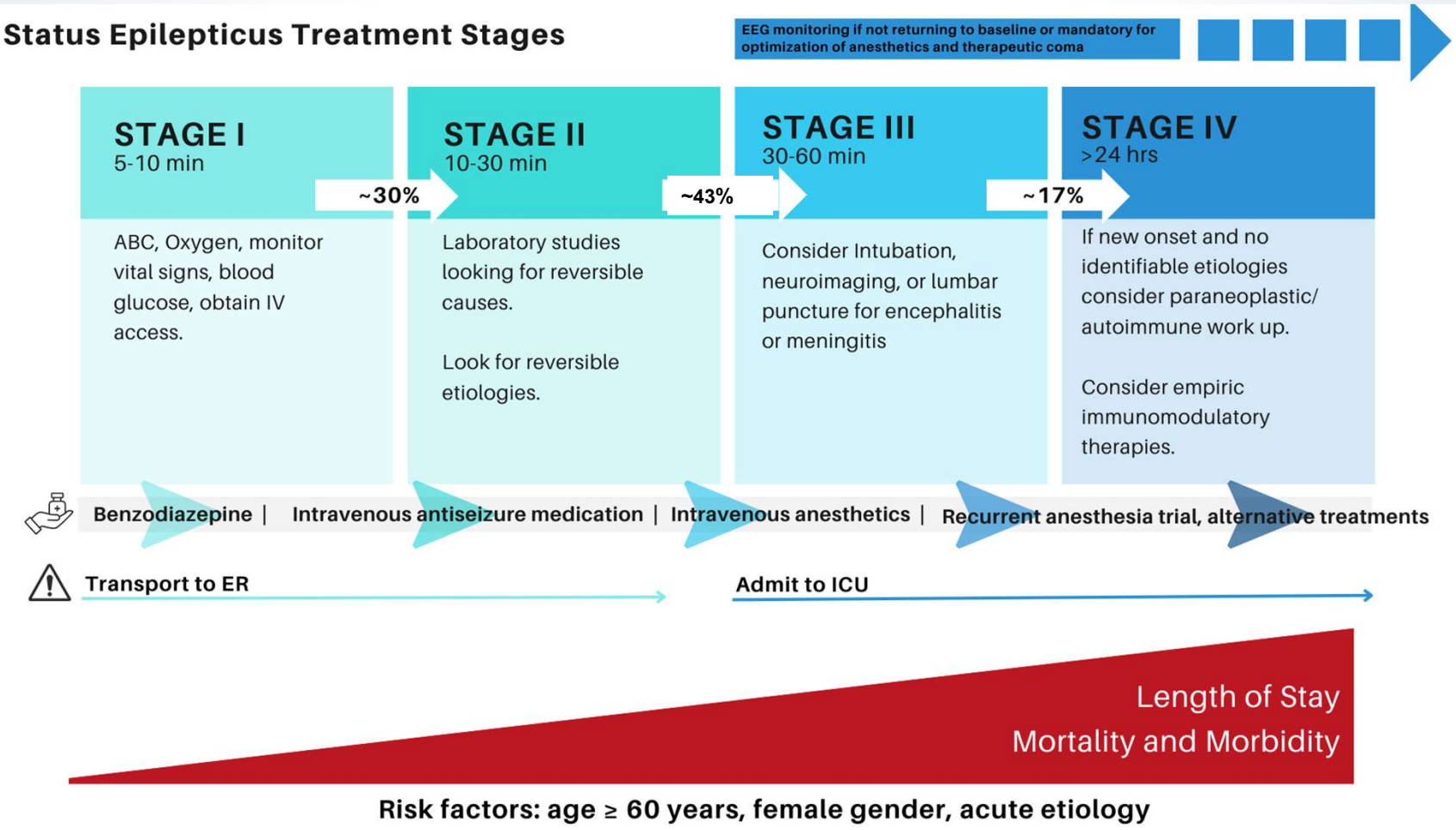
Treatment

- Admit in the ICU:
  - Urgent EEG and treatment of the underlying pathology
- Hypertension: treatment with anti-hypertensive medication (PRES)
- Hypotension: Fluid challenge, vasopressors, invasive monitoring of blood pressure
- Echocardiogram to look for stress cardiomyopathy
- Urgent oxygenation therapy and intubation
- Cardio-pulmonary resuscitation (slow infusion of ASM with cardiac effects)

Benghanem et al. Curr Opin Crit Care 2024


Acute Seizure
Early Status Epilepticus
Refractory Status Epilepticus → Malignant Status Epilepticus
Neuro-physiology
Receptor trafficking:
↓GABA and ↑NMDA
Early synaptic plasticity:
Modification of GABA receptor composition
Altered gene expression:
Receptors
Drug transporters and drug resistance proteins
Motor Activity
Generalized convulsions
Myoclonus
Electromechanical dissociation
Systemic Pathology
COMPENSATORY PHASE (SYMPATHETIC OVERDRIVE)
DECOMPENSATION (HOMEOSTATIC FAILURE)
↑ Cardiac output
↑ Blood pressure
↑ Blood glucose
↑ Blood lactate
↓ Cardiac output
↓ Blood glucose
↓ Blood lactate
↓ Blood oxygen
Cardiorespiratory collapse
Electrolyte imbalances
Rhabdomyolysis and delayed tubular necrosis
Hyperthermia
Multiple organ failure
Brain Metabolism
Cerebral blood flow
Glucose and oxygen
Brain tissue oxygenation
Brain glucose
Brain Damage
Convulsive
Nonconvulsive
0
5 min
30 min
60 min
Hours
Days

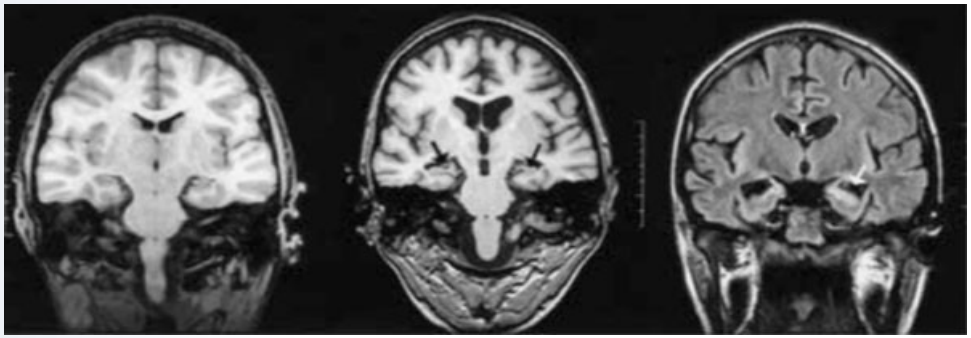
Status Epilepticus Treatment Stages



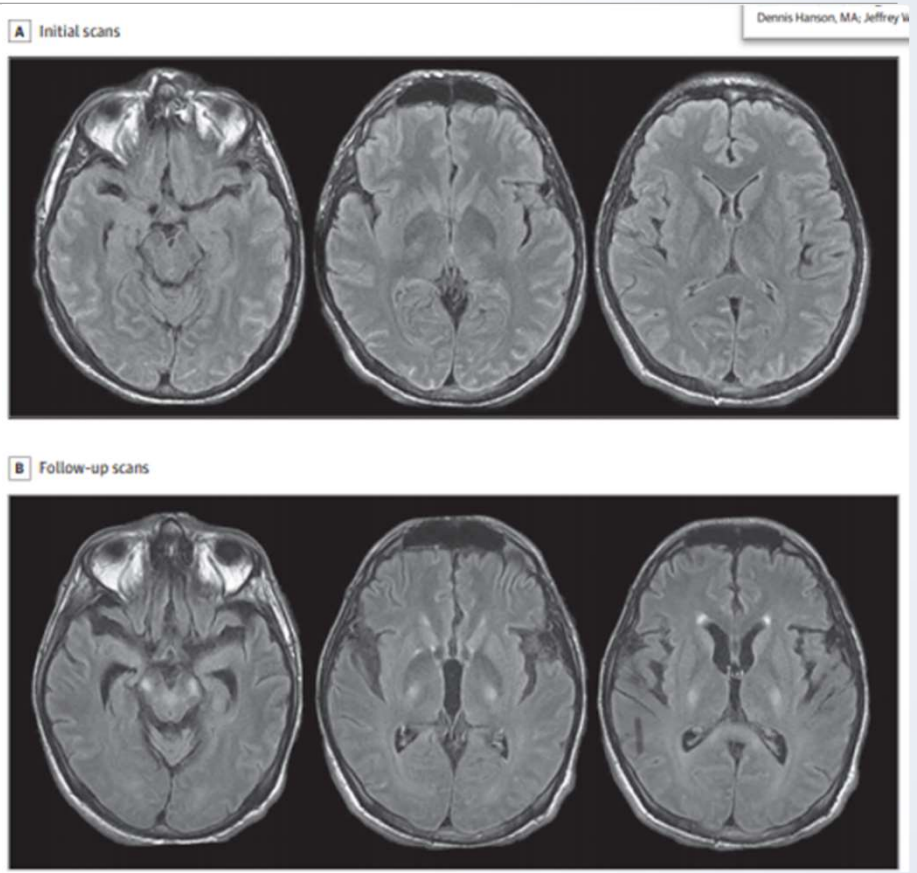
Risk factors: age ≥ 60 years, female gender, acute etiology

Preclinical and clinical studies show that SE leads to widespread neuronal

- Decreased neuronal density in the hippocampi
- Focal atrophy in several brain regions: hippocampi, subcortical white matter, basal ganglia, corpus callosum cerebellum
- Increased Neuron-Specific enolase



Coronal sections of T1-weighted magnetic resonance images at onset of (left) and 6 weeks after (middle) a prolonged episode of status epilepticus in a 19-year-old man. Note overall brain and hippocampal atrophy (arrows, middle). Fluid-attenuated inversion recovery (FLAIR) imaging 6 weeks after a prolonged episode of status epilepticus reveals evidence of the development of mesial temporal sclerosis (arrow, right). Images are not concordant because they were obtained at different facilities.



Slovitter and Damiano 1981, Meldrum et al 1973, DeGiorgio et al 1992, Manno Mayo clnic Proc 2003, Hocker JAMA

Management of Status Epilepticus

The goal of immediate treatment is seizures control!

Time is brain

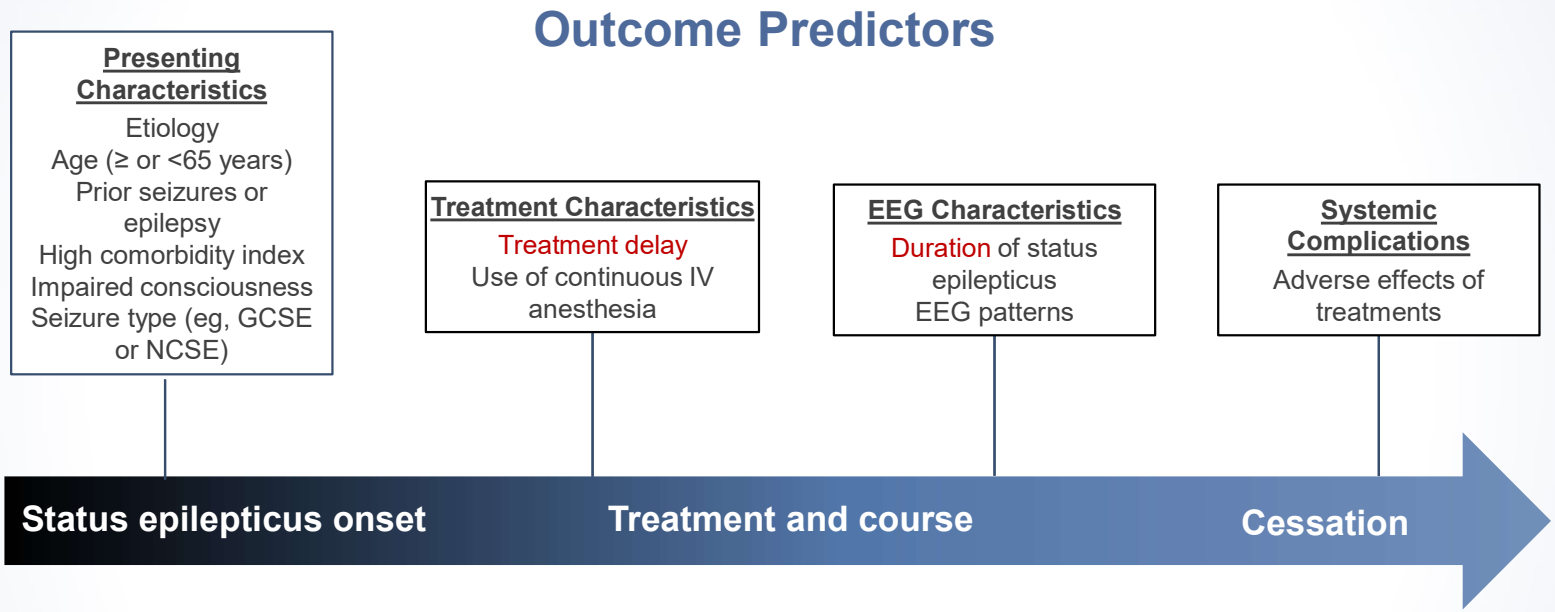
Preclinical and clinical studies show that SE leads to widespread neuronal damage and cell death due to excessive neuronal firing.

- Decreased neuronal density in the hippocampi
- Increased Neuron-Specific enolase

Manno. Mayo Clin Proc 2003

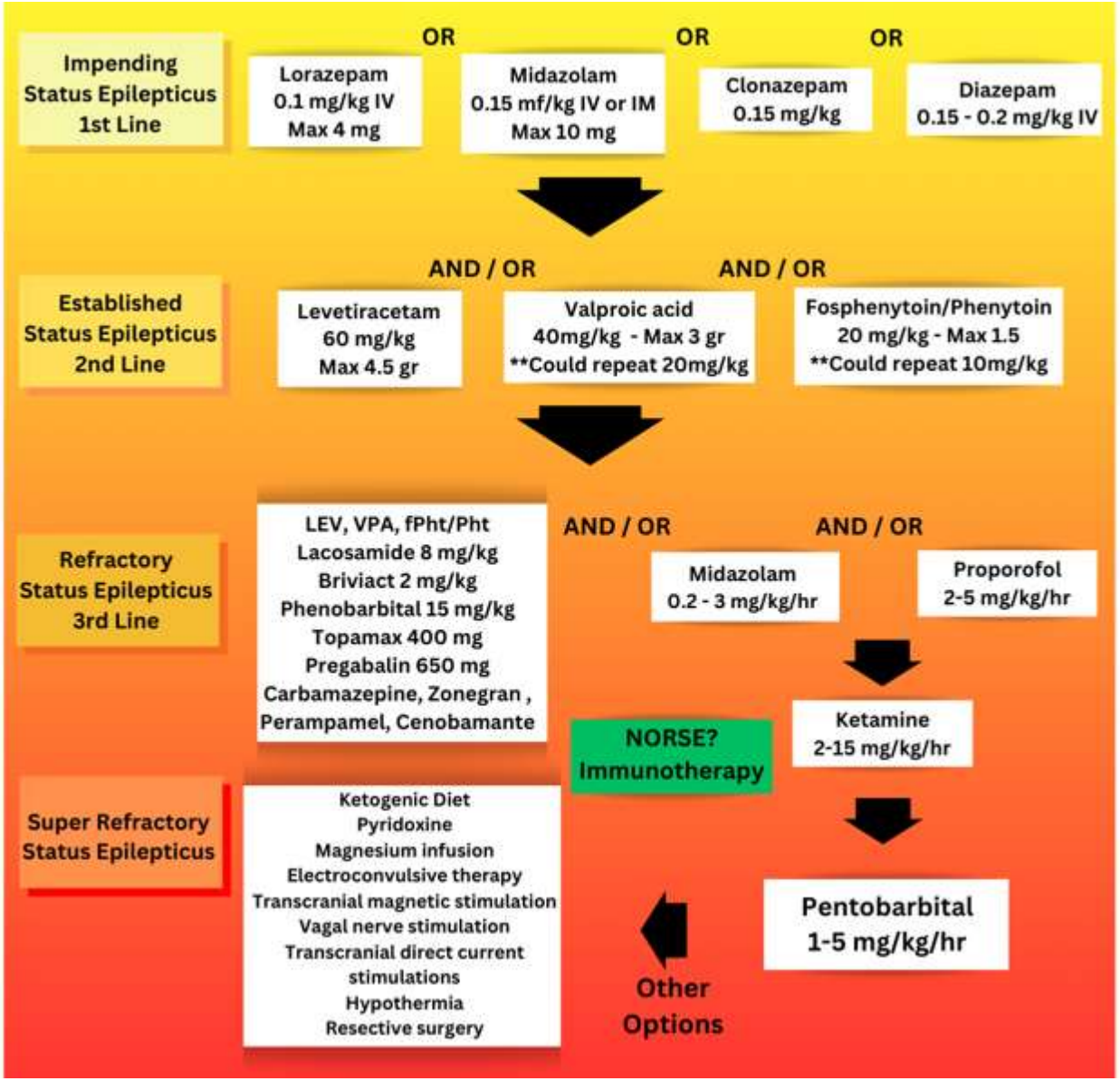
Slovitter and Damiano 1981, Meldrum et al 1973, DeGiorgio et al 1992, Manno May clnic Proc 2003, Hocker JAMA

Multiple factors may influence outcomes in SE



How can we help?

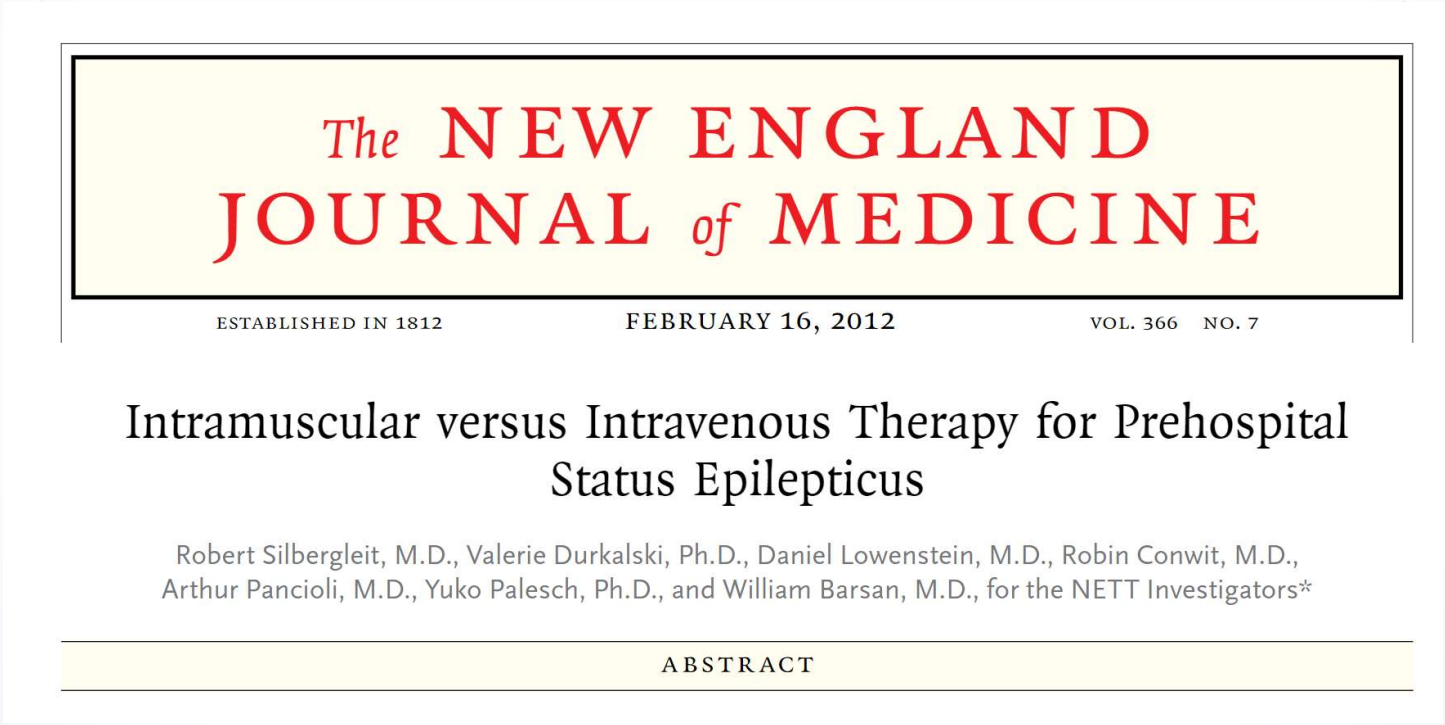
MODIFIABLE factors: Time to treatment and duration of SE



Clio Rubinos.
Continuum 2024

Importance of Early Treatment of Seizure Emergencies

Four controlled, double-blind clinical studies of initial treatment of status epilepticus have been published:



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*

ABSTRACT

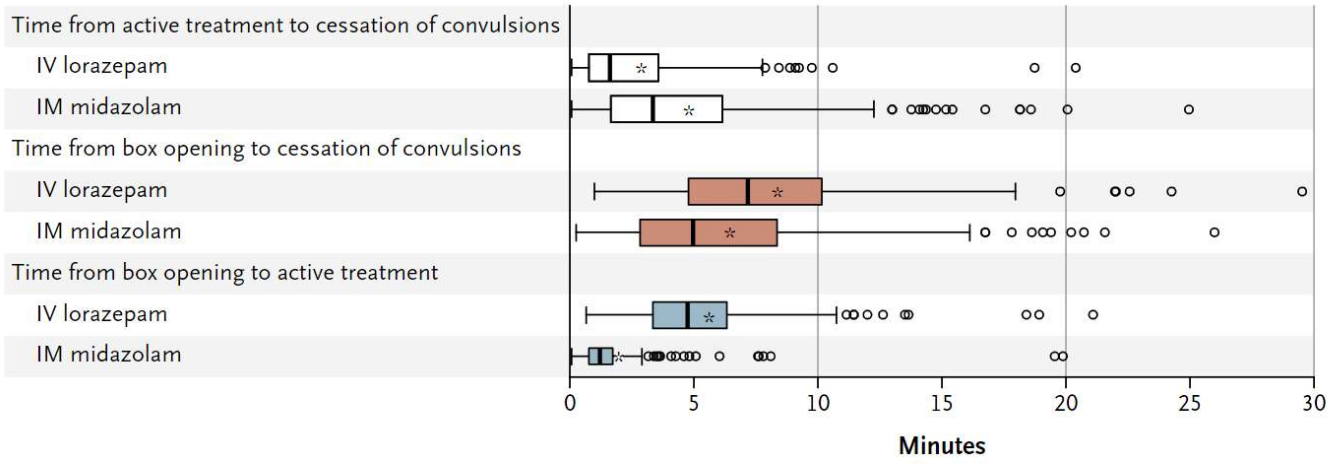


Figure 3. Intervals between Active Treatment and Cessation of Convulsions, Box Opening and Cessation of Convulsions, and Box Opening and Active Treatment.

The shorter time to IM drug administration was offset by the faster onset of action after IV drug administration, resulting in similar latency periods until convulsions were terminated. Time to IV administration includes the nominal time (about 20 seconds) needed to administer the drug by means of IM autoinjector. Asterisks indicate means, boxes interquartile ranges, bold vertical lines within boxes medians, I bars 1.5 times the interquartile range, and circles outliers.

Randomized, double-blind, phase III, adaptive trial design
nt SE (N=384)
A

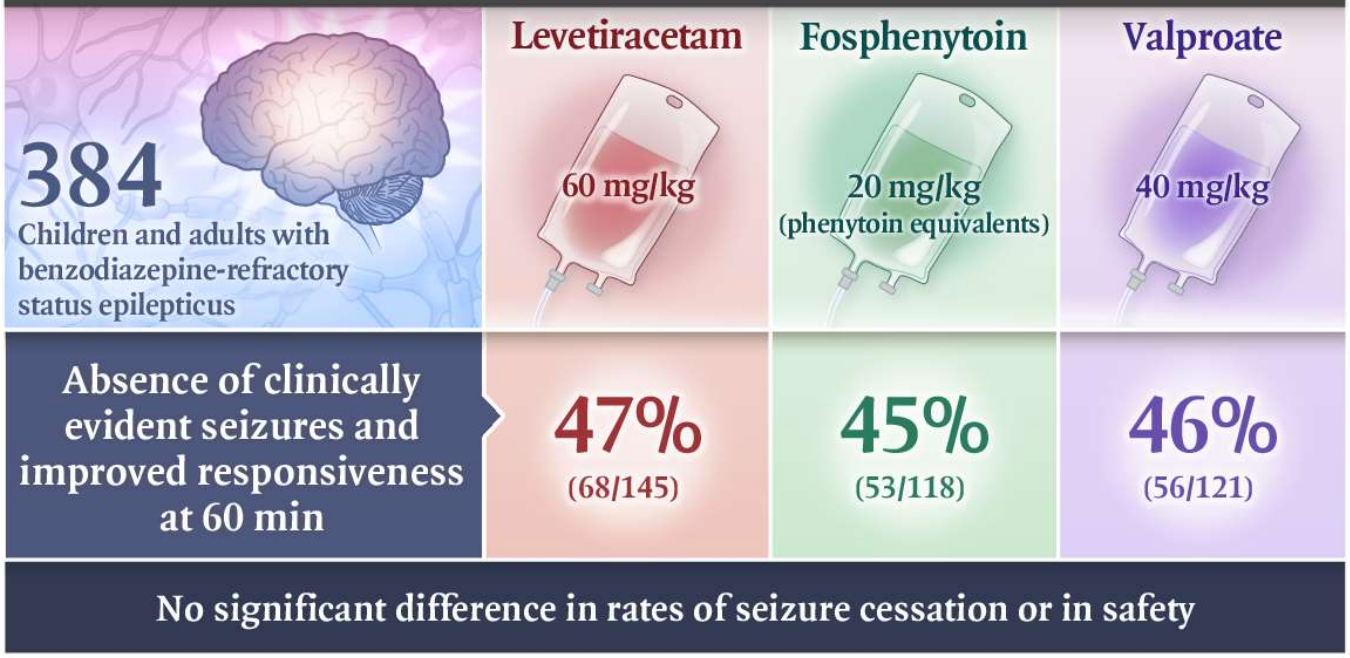
ing one drug to be

eing stopped

The NEW ENGLAND JOURNAL of MEDICINE

Trial of Three Anticonvulsant Medications for Status Epilepticus

MULTICENTER, RANDOMIZED, DOUBLE-BLIND TRIAL



No significant difference in rates of seizure cessation or in safety

J. Kapur et al. 10.1056/NEJMoa1905795

Randomiz
Medic

Jaideep Kapur, M.B., William Barsan, Shlomo Shinnar, Hannah Cock, and Robert Silb

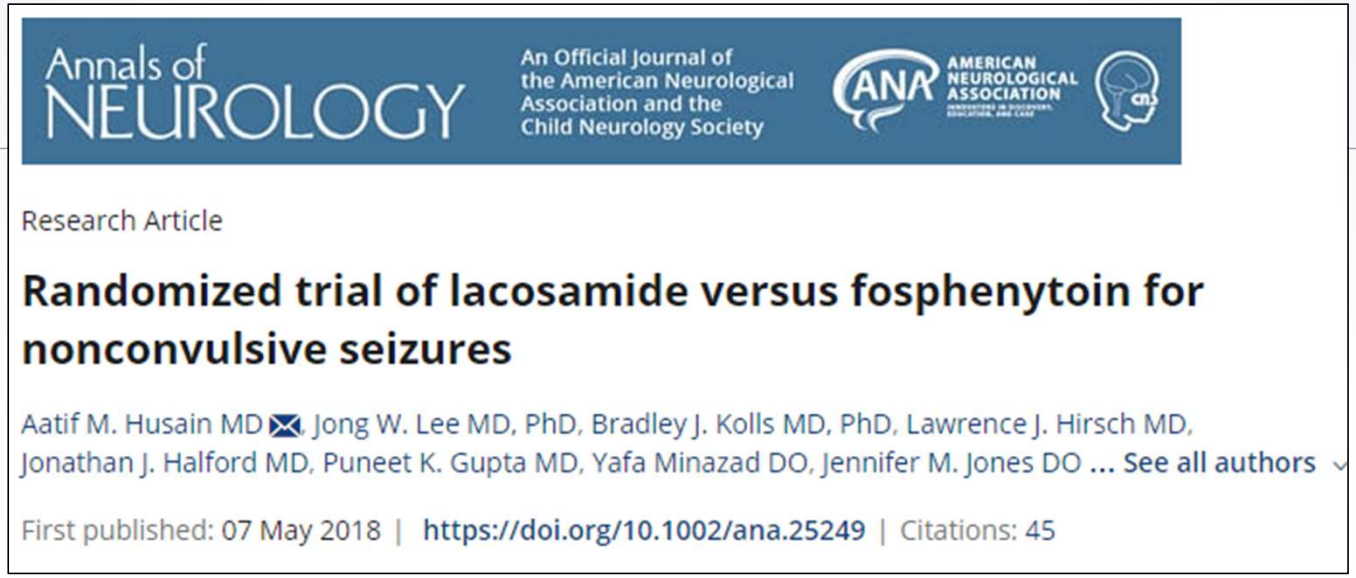
Outcome and Pop

Primary efficacy ou sciousness			
Intention-to-treat			
No. with outc			
Percent of pat			
Probability tha			
Probability tha			
Per-protocol popu			
No. with outc			
Percent of pati			
Probability tha			
Probability that treatment is the least effective	0.34	0.35	0.31

ytoin Levetiracetam Valproate

0 40 50 60 70 80 90 100

nts with Treatment Success (%)



Annals of NEUROLOGY

An Official Journal of the American Neurological Association and the Child Neurology Society

AMERICAN NEUROLOGICAL ASSOCIATION

Research Article

Randomized trial of lacosamide versus fosphenytoin for nonconvulsive seizures

Aatif M. Husain MD, Jong W. Lee MD, PhD, Bradley J. Kolls MD, PhD, Lawrence J. Hirsch MD, Jonathan J. Halford MD, Puneet K. Gupta MD, Yafa Minazad DO, Jennifer M. Jones DO ... See all authors

First published: 07 May 2018 | https://doi.org/10.1002/ana.25249 | Citations: 45

Randomized, nonblinded, multicenter, noninferiority trial
Adults with NCSz on EEG (N=74)
IV LCM vs. IV fPHT

- Seizures were controlled in 19 of 30 (63.3%) subjects in the LCM arm and 16 of 32 (50%) subjects in the fPHT arm.
  - LCM was noninferior to fPHT

SYSTEMATIC REVIEW

Intravenous Brivaracetam in the Treatment of Status Epilepticus: A Systematic Review

Francesco Brigo[1,2] · Simona Lattanzi[3] · Raffaele Nardone[1,4] · Eugen Trinka[4,5]

- 37 patients aged 22 to 85 years (21 woman) with various types of SE
- Number of drugs prior to BRV ranged from 1 to 8. Time from SE onset to BRV ranged from **0.5 hour to 105 days**
- Initial BRV dose ranged from **50 to 400 mg**
- Success rate varied from **27% to 100%**
- The time from BRV administration to SE cessation ranged from 15 minutes to 94 hours
- No serious adverse effects were reported

Unanswered questions:

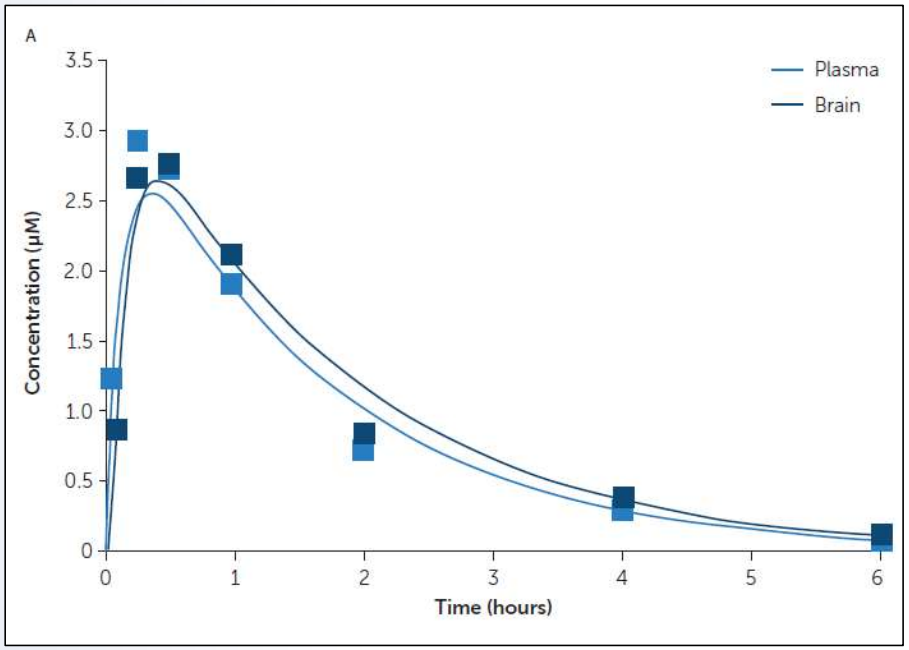
- Optimal bolus dose and rate not explored → safety in high dose/high rate
- EEG response not well determined, spectrum of efficacy is unknown

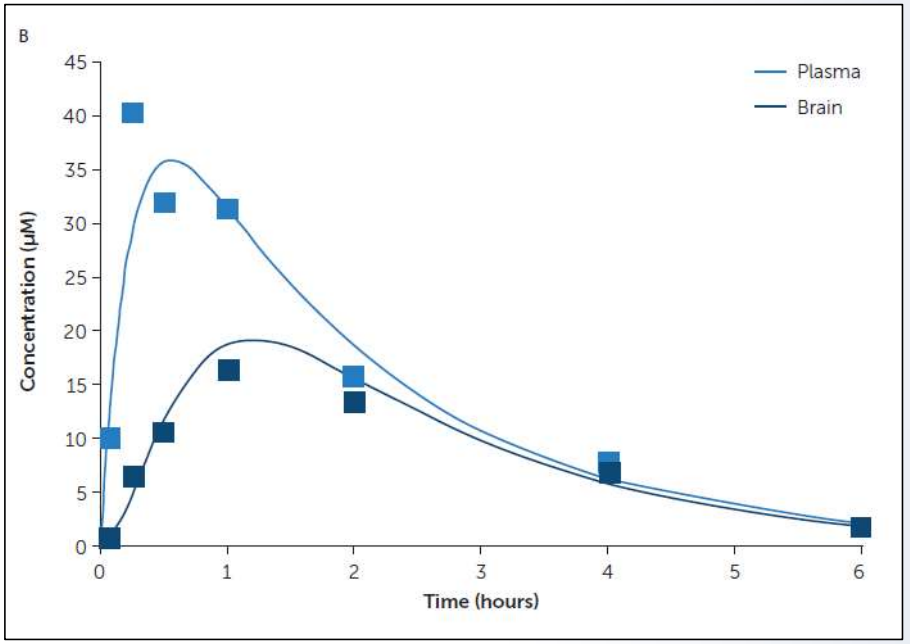
→ RCT is needed

1: Brigo, Lattanzi, Nardone and Trinka *CNS Drugs*. 2019; 33(8):771-781

BRV enters the brain faster than levetiracetam (LEV) following oral administration

Audiogenic mice: single oral doses of BRV and LEV (0.82 mg/kg BRV and 6.5 mg/kg LEV)





The more rapid brain-blood-barrier penetration of BRV may into a more rapid anti-seizure effect compared with LEV

Nicolas JM, et al. *Epilepsy Curr 2014;14* (Suppl.S1):224, Abstract No: 2.156.

Therapeutic Principles– 2

Table 5. Suggested treatment for status epilepticus Stage I

Medication	Dose	Route of administration	Elimination half life
Diazepam	0.15 – 0.2 mg/kg/dose May repeat once	IV administration Other options: Rectal diazepam (0.2 – 0.5 mg/kg, max: 15 - 20 mg per dose, Single dose) Intranasal 0.2 mg/kg (via special delivery device) 28- 50 kg: 10 mg (1, 10 mg device) 51 to 75 kg: 15 mg (2, 7.5 mg devices) 76 kg+: 20 mg (2, 10 mg devices)	48 hours (rapidly redistributes out of brain, so short duration in status)
Lorazepam	0.1mg /kg/dose, can repeat once Max: 4 mg/dose	Preferred IV administration Can give IM in the absence of IV access, but this can be painful and absorption is reduced to 70%	12 – 24 hours
Midazolam	0.2 mg/kg Max dose of 10 mg	IV or IM (IM has good absorption) Other options: Intranasal 5 mg x1 (may repeat in 10 min in opposite nostril) Buccal 0.5 mg/kg	90 – 150 min

IV: intravenous, IM: intramuscular

Therapeutic Principles– 2

Table 6. Suggested treatment for status epilepticus Stage II

Medication	Loading dose	Maintenance dose	Note
Fosphenytoin	20 mg PE/kg IV (max 1500 mg) Max rate 150 mg/min **5–10 mg PE/Kg IV	See phenytoin	Side Effects: Hypotension Blood levels: see phenytoin
Lacosamide	200 – 400 mg IV	200 – 300 mg every 12 hours	Dose adjustment in severe renal and/or hepatic impairment (max 300 mg/day) Side Effects: May prolonged PR interval (do not use PR >200), hypotension
Levetiracetam	60 mg/kg IV (max 4500 mg)	1000 – 6000 mg/d in 2 – 3 doses	Correct for kidney function Side Effects: Sedation, agitation, aggression

Therapeutic Principles– 2 (cont')

Phenobarbital	20 mg/kg IV -Max rate 60 mg/min **5 – 10 mg/kg Max rate 60 mg/min	1-3 mg/kg/day in 2 – 3 divided doses	Side Effects: Hypotension, respiratory depression, metabolic acidosis Blood levels goal: - 15 – 40 mcg/ml
Phenytoin	20 mg/kg IV -Max rate 50 mg/min ** 5 – 10 mg/kg	5 – 7 mg/kg/day IV or PO in 2 – 4 divided doses	Side Effects: Pain, phlebitis, purple glove syndrome, hypotension, bradycardia, Ventricular arrhythmias, cardiac nodal depression, metabolic acidosis Blood levels: - Total Phenytoin 15–25 mcg/mL - Free Phenytoin 1.5 -2.5 mcg/ml
Valproic Acid	40 mg/kg IV over 10 min (max 3000 mg) -Max rate 60 mg/kg/min **20 mg/Kg IV	Start 10 –15 mg/kg/d in 3 -4 divided doses	Beware of carbapenem use – drastically lowers blood levels Avoid concomitant administration with phenytoin/phenobarbital due to drug interactions. Side Effects: Tremor, hyperammonemia, thrombocytopenia, hepatic toxicity, pancreatitis Blood levels goal: - 50 – 140 mcg/mL
**Second dose if seizures persist			

Therapeutic Principles– 2 additional ASMS

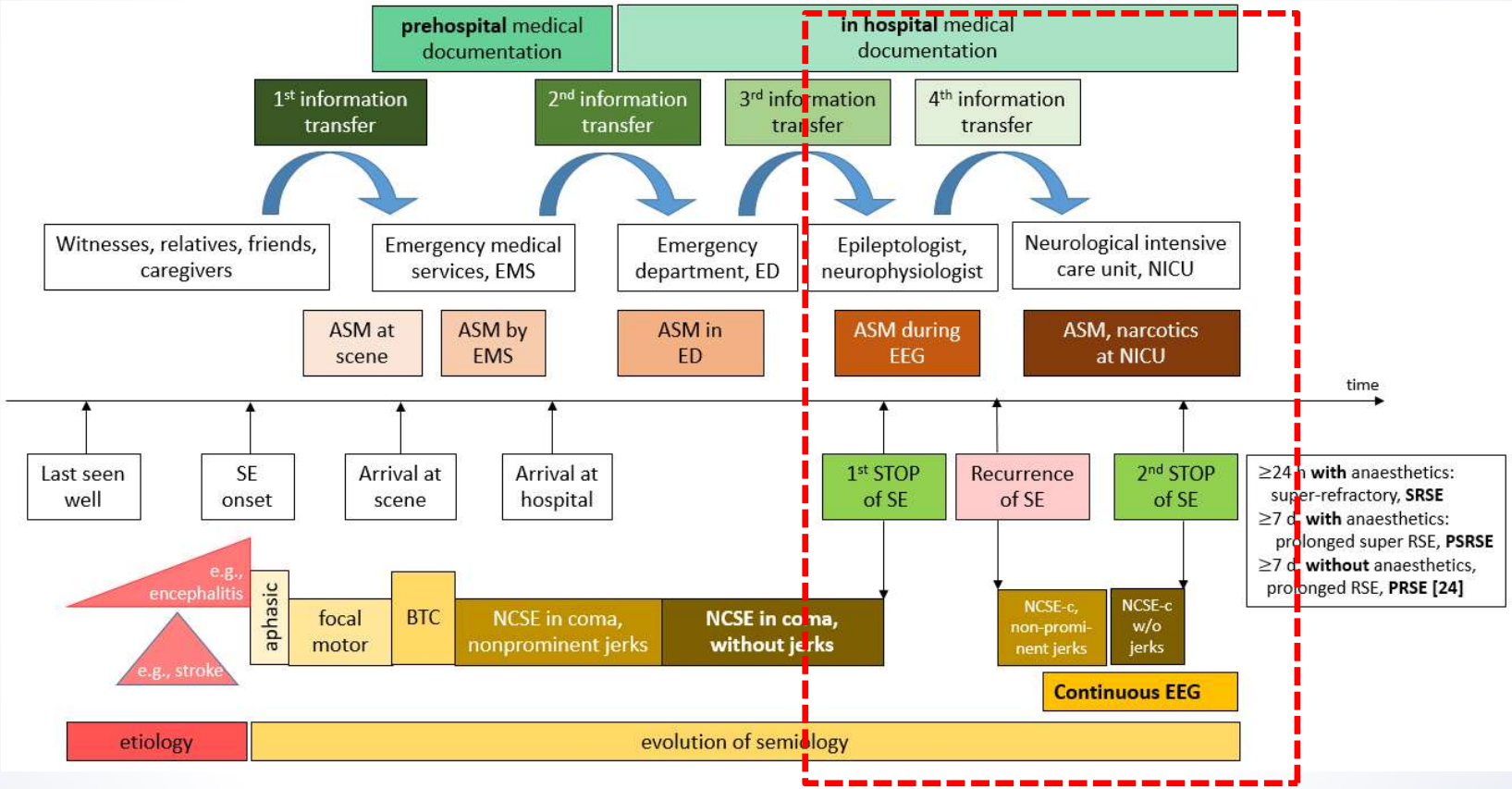
Table 7 – Additional antiseizure medication agents for any stage

Medication	Loading dose	Maintenance dose	Note
Brivaracetam	100 – 200 mg (Oral of IV)	100 mg every 12 hours	Intravenous use only for 3 days after status epilepticus, then change to oral Higher doses have been used, but is not recommended Side Effects: Sedation
Clobazam	60 mg oral	20 mg/d BID (10 – 60 mg/d)	Oral / enteral administration only Load only in patients with protected oral airway Side Effects: Sedation, respiratory depression
Perampanel	Variable (up to 32 mg)	2 - 12 mg/d in divided doses	Major substrate o CYP 3A4 so higher doses may be required with inducers such as carbamazepine, phenytoin, or oxcarbazepine

Therapeutic Principles– 2 additional ASMS cont'

Pregabalin	450 – 600 mg oral	75 – 100 mg/d	- Studied for cyclic seizures Side Effects: Sedation, respiratory depression
Topiramate	200 - 400 mg oral	300 – 1600 mg/d every 12 hours	Oral / enteral administration only Side Effects: Metabolic Acidosis, kidney stones
Zonisamide	3x times the maintenance dose administered in two divided doses, 6 h apart.	100 – 300 mg/d	Side Effects: Kidney stones, gastrointestinal disorders

The Process of Management of Status Epilepticus



Trinka and Leitinger *Continuum* 2022 Apr 1;28(2):559-602

Anaesthetics used in refractory SE: Overview

	BARB	PRO	MDZ	KET
Mechanisms	$GABA_A$ (NMDA, Ca)	$GABA_A$ (NMDA?, Ca)	$GABA_A$	NMDA DA, NA, 5HTAA, Substance P
Loading dose	THP 2-7mg/kg PTB 5-15 mg/kg	1-2 mg/kg	0.1-0.3 mg/kg	1.5 – 2 mg/kg
Maintenance	THP 0.5-5 mg/kg/h PTB 0.5-5 mg/kg/h	2-5(12) mg/kg/h	0.05-2 mg/kg/h	1 – 10 mg/kg/h
Elimination $t_{1/2}$	**THP 36h, PTB 22h**	**2h**	**0.5-50h**	**2.5 – 3 h**
Disadvantages	Long wash-out	PRIS: check lactate, add BDZ	Increase dose with time	Respiratory stimulation, metabolic acidosis

Management of Refractory Status Epilepticus

cIV MIDAZOLAM

- Initial loading dose 0.2 mg/kg over 5 minutes
  - Repeat 0.2 boluses every 5 - 10 minutes until seizures stop
  - Maximum loading dose 2 mg/kg

- Maintenance dose 0.1- 2 mg/kg/hr (NCS Guidelines)
  - Doses up to 2.9 mg/kg/hr have been reported as safe and effective

- Taper: start when seizure free for 24 to 48 hours, taper under cEEG control for 4 to 24 hours

Management of Refractory Status Epilepticus

cIV PROPOFOL

- Initial loading dose 1-2 mg/kg IV over 3-5 min
  - Repeat 1-2 mg/kg boluses every 3-5 min until seizures stop
  - Maximum loading dose 10 mg/kg

- Maintenance dose 30–200 mcg/kg/min

- It is formulated in a 10% fat emulsion containing 1.1 kcal/mL:
  - Monitor triglycerides and dietary caloric intake
- Propofol infusion syndrome: Bradycardia, acidosis, cardiovascular collapse, rhabdomyolysis, renal failure, and hepatomegaly:
  - Monitor kidney and liver function, triglycerides, CK, bicarbonate in blood

Management of Refractory Status Epilepticus

cIV PENTOBARBITAL

- Loading dose 1 - 2 mg/kg
- Maximum dose 5 mg/kg

- Maintenance dose 1 – 5 mg/kg/hr

- Prolonged coma (half-life 15-60 hours)

- Hypotension usually requires pressor
- Caution can cause: paralytic ileus, immunosuppression, hemodynamic instability, intestinal perforation, hypokalemia, and hypothermia.

Which one is the best?

- **Propofol** is an option but its safety profile needs to be considered as it can cause propofol infusion syndrome:
  - **Propofol Infusion Syndrome: metabolic acidosis, rhabdomyolysis, cardiac arrest); use caution when using high doses (> 80 mcg/kg/min) for long durations (>48 hours)**

- **Midazolam** may cause less hypotension as it does not contain the solvent propylene glycol and may be preferred in selected clinical situations.
  - Tachyphylaxis and delayed awakening due to long-term duration in ICU

- **Pentobarbital** may have a higher rate of successfully controlling RSE acutely than midazolam, but may have more adverse effects:
  - Hypotension, hypokalemia, immune suppression, paralytic ileus, cardiotoxicity, hepatic dysfunction and propylene glycol toxicity

Anesthetic drugs in status epilepticus: which one is the best?

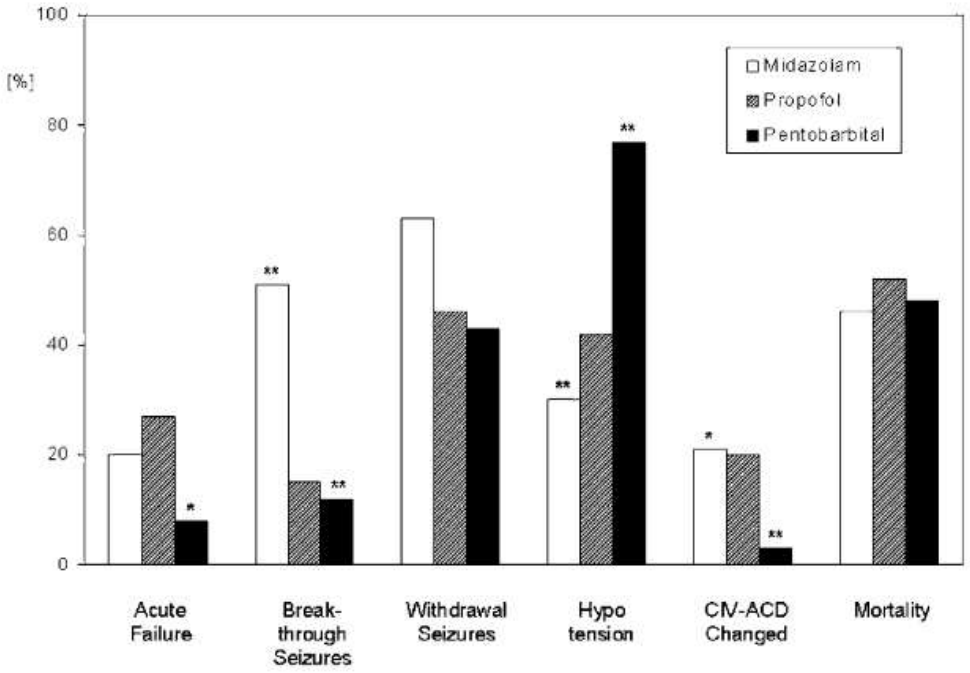


FIG. 1. Treatment response and outcome in patients with refractory status epilepticus treated with midazolam, propofol, or pentobarbital. Significance was tested with the χ^2 or Fisher's exact test of each treatment against the other two. *$p < 0.01$; **$p < 0.001$.

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)

Data are presented as % (N with available data), mean ± standard deviation (N with available data), or median (N with available data) if not normally distributed. If doses were reported only as mg or mg/h, mg/kg and mg/kg/h were calculated with given or estimated body weights: for male subjects divided by 80 kg; for women, divided by 60 kg.

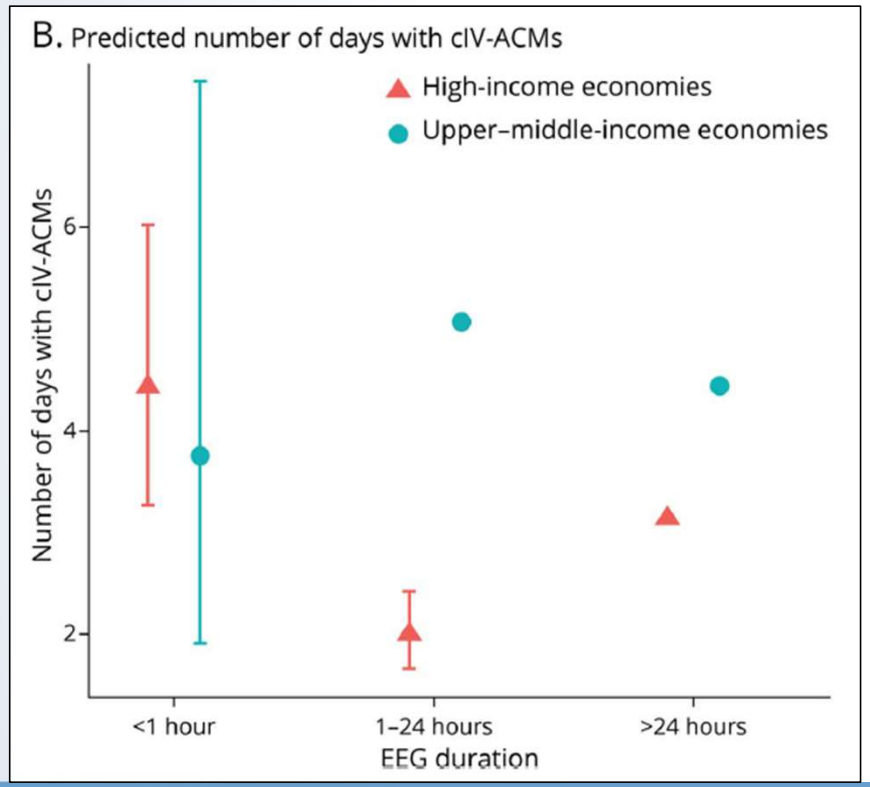
Management of Refractory Status Epilepticus

An International Cohort Study (MORSE CODe) Analysis of Patients Managed in the ICU

Wei-Ting Chiu, MD, Vanessa Campozano, MD, Alois Schiefecker, MD, Dannys Rivero Rodriguez, MD, Daniel Ferreira, MD, Amy Headlee, MD, Sinead Zeidan, MD, Alexandra Grinea, MD, Yao-Hsien Huang, MD, Kevin Doyle, BA, Qi Shen, PhD, Diana Gómez, MD, Sara E. Hocker, MD, Benjamin Rohaut, MD, Romain Sonneville, MD, Chien-Tai Hong, MD, Sophie Demeret, MD, Pedro Kurtz, MD, Nelson Maldonado, MD, Raimund Helbok, MD, Telmo Fernandez, MD, and Jan Claassen, MD

Correspondence
Dr. Claassen
jc1439@columbia.edu

Neurology® 2022



Retrospective, international, multicenter study, n=387

Aim to determine whether Propofol and midazolam were equally effective in controlling RSE in the ICU

A good functional outcome define as mRS score 0-2 at hospital discharge

- Comparable outcomes, including efficacy and complications between the two anesthetic agents.
- Patients initially managed with propofol were more likely to require the addition of second anesthetic infusion than those started with midazolam

EEG-guided therapy has been associated with **shorter duration** or anesthetic exposure

Management of Refractory Status Epilepticus

KETAMINE

- Loading dose: 1 - 1.5 mg/kg q 3-5 min until seizures stop
  - Maximum loading dose of 5 mg/kg
- Maintenance dose: 1 – 10 mg/kg/hr
- High doses can cause metabolic acidosis, tachycardia and bradycardia, and hypersalivation.

Ketamine to treat super-refractory status epilepticus

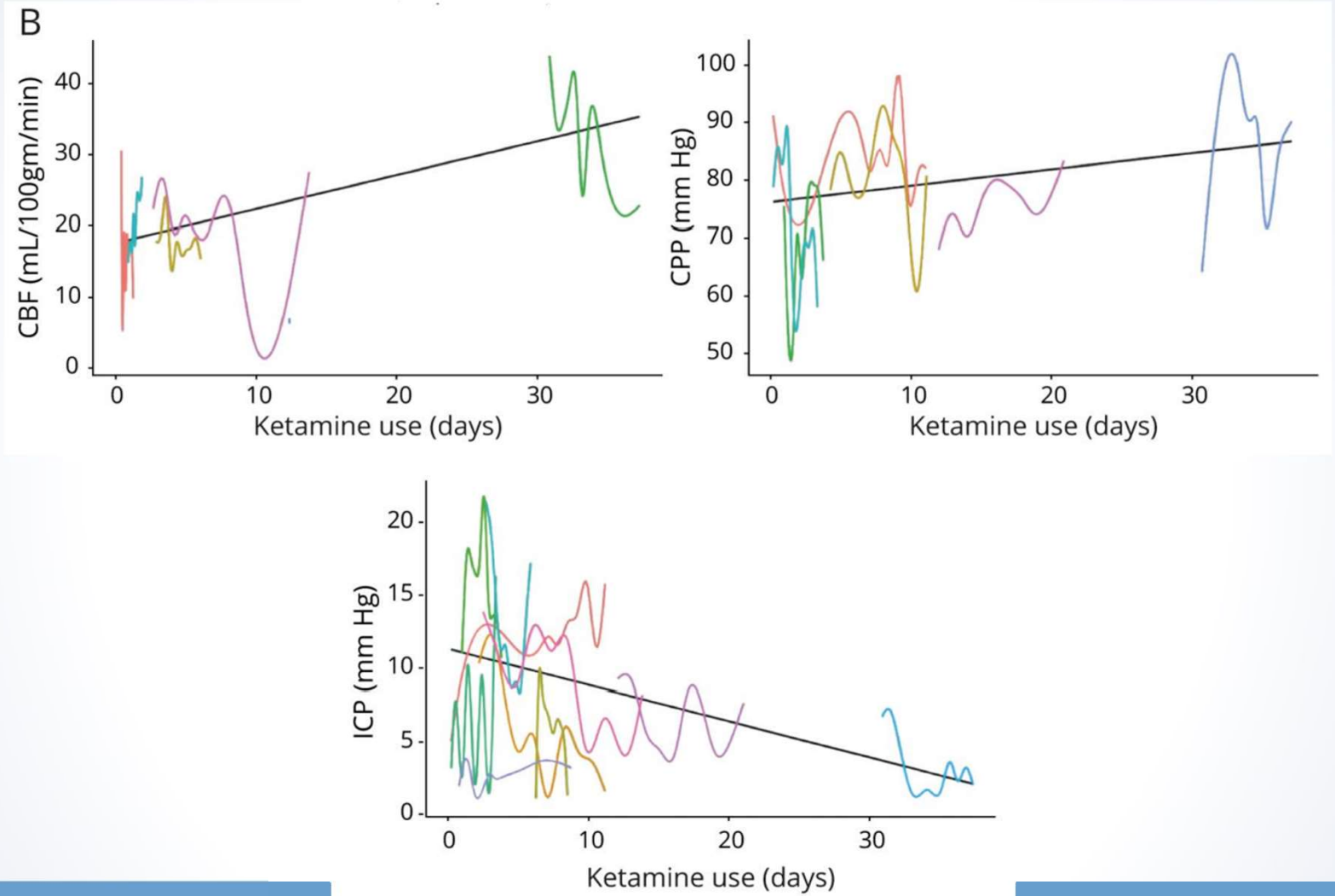
Neurology® 2020;

Ayham Alkhachroum, MD, Caroline A. Der-Nigoghossian, PharmD, BCCCP, Elizabeth Mathews, MD, Nina Massad, MD, Riva Letchinger, BS, Kevin Doyle, MA, Wei-Ting Chiu, MD, Julie Kromm, MD, Clio Rubinos, MD, Angela Velazquez, MD, David Roh, MD, Sachin Agarwal, MD, Soojin Park, MD, E. Sander Connolly, MD, and Jan Claassen, MD

Correspondence
Dr. Claassen
jc1439@columbia.edu

- Retrospective study, N = 68
- Mean dose of midazolam 1.0 ± 0.8 mg/kg/h when ketamine was started
- Ketamine was started a mean of 0.4 (0.1–1.0) days after starting midazolam
  - Mean ketamine infusion dose was 2.2 ± 1.8 mg/kg/h

- Within 24 hours of starting ketamine:
  - 81% of patients had a 50% decrease in seizure burden
  - 63% of patients had complete seizure cessation

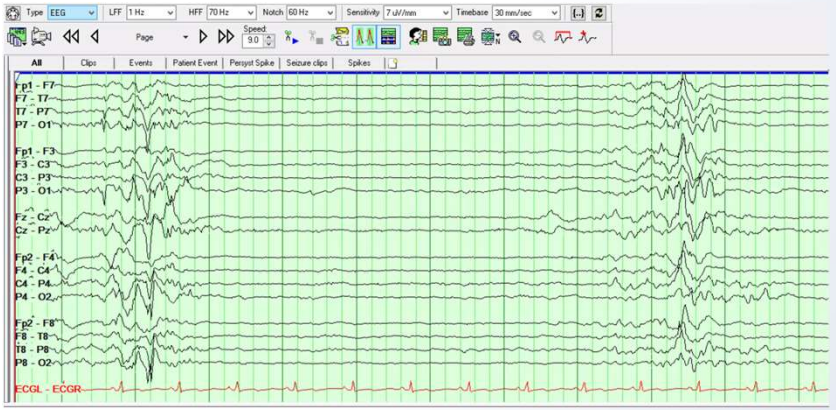

B
CBF (mL/100gm/min)
0
10
20
30
40
0
10
20
30
Ketamine use (days)
CPP (mm Hg)
50
60
70
80
90
100
0
10
20
30
Ketamine use (days)
ICP (mm Hg)
0
5
10
15
20
0
10
20
30
Ketamine use (days)

Anesthetics treatment goal

Treatment Goal: Seizure suppression?

- No data to support the superiority of burst suppression over seizure suppression
- Burst suppression has a lower incidence of sporadic crises
- Some experts allow for breakthrough seizures.

- **The duration of the seizure freedom is ambiguous and not well defined, typically between 24 and 48 hours.**



Claassen et al. Epilepsia 2002
Muhlhofer et al. Epilepsia 2019
Das et al. Seizure 2019

FULL-LENGTH ORIGINAL RESEARCH

Epilepsia

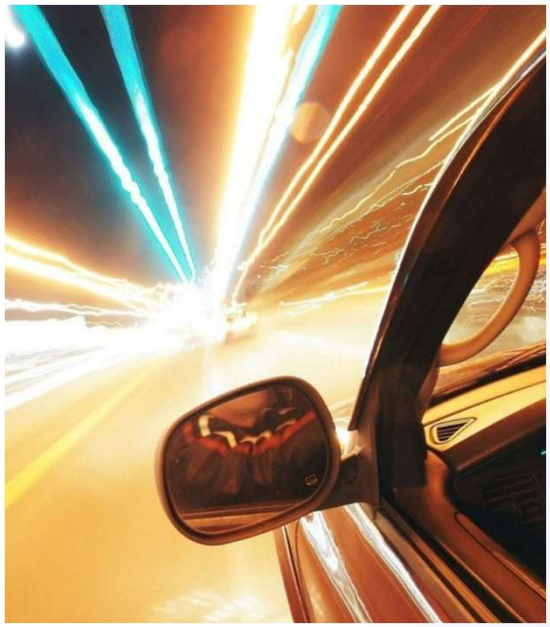
Duration of therapeutic coma and outcome of refractory status epilepticus

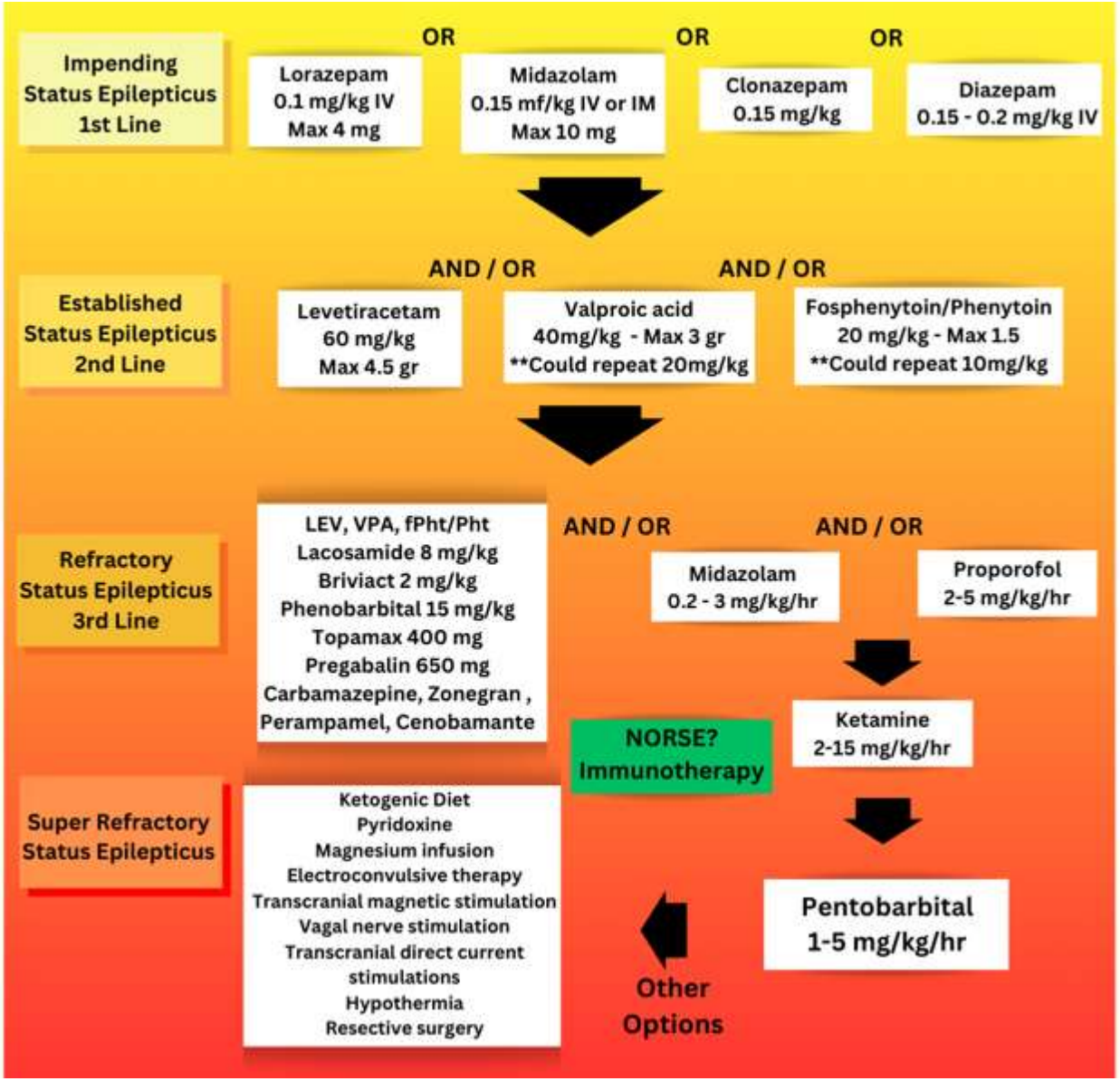
Wolfgang G. Muhlhofer[1] | Stephen Layfield[2] | Daniel Lowenstein[3] | Chee Paul Lin[4] | Robert D. Johnson[5] | Shalini Saini[6] | Jerzy P. Szaflarski[1]

Examine the association of duration of therapeutic coma (TC) with seizure recurrence, morbidity, and mortality in refractory status epilepticus (RSE). Define an optimal window for TC that provides sustained seizure control and minimizes complications.

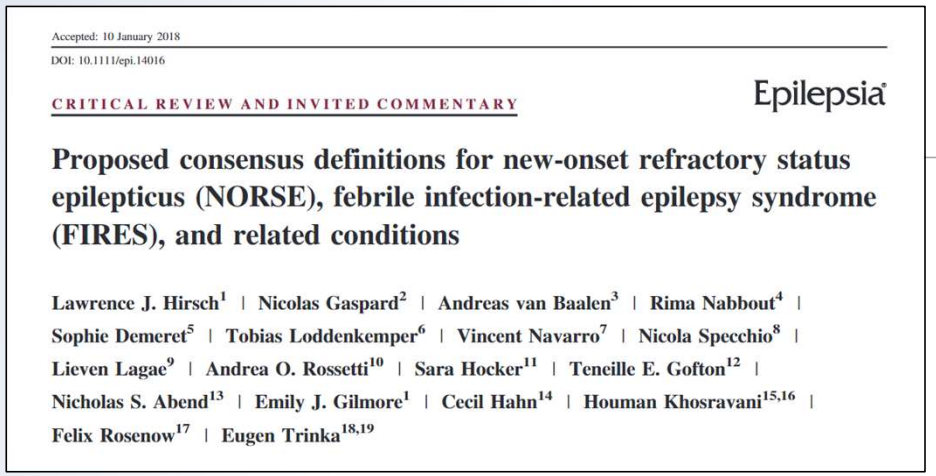
Results: Multivariable analysis of clinical and treatment characteristics of 182 patients who were treated predominantly with propofol as anesthetic agent showed that longer duration of the first trial of TC (27.2 vs 15.6 hours) was independently associated with a higher chance of seizure recurrence following the first weaning attempt ($P = 0.038$) but not with poor functional neurologic outcome upon discharge, in-hospital complications, or mortality. Furthermore, higher doses of anesthetic utilized during the first trial of TC were independently associated with fewer in-hospital complications ($P = 0.003$) and associated with a shorter duration of mechanical ventilation and total length of stay. Duration of TC was identified as an independent predictor of seizure recurrence with an optimal cutoff point at 35 hours.

Significance: This study suggests that a shorter duration yet deeper TC as treatment for RSE may be more effective and safer than the currently recommended TC duration of 24-48 hours. Prospective and randomized trials should be conducted to validate these assertions.





Clio Rubinos.
Continuum 2024



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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]

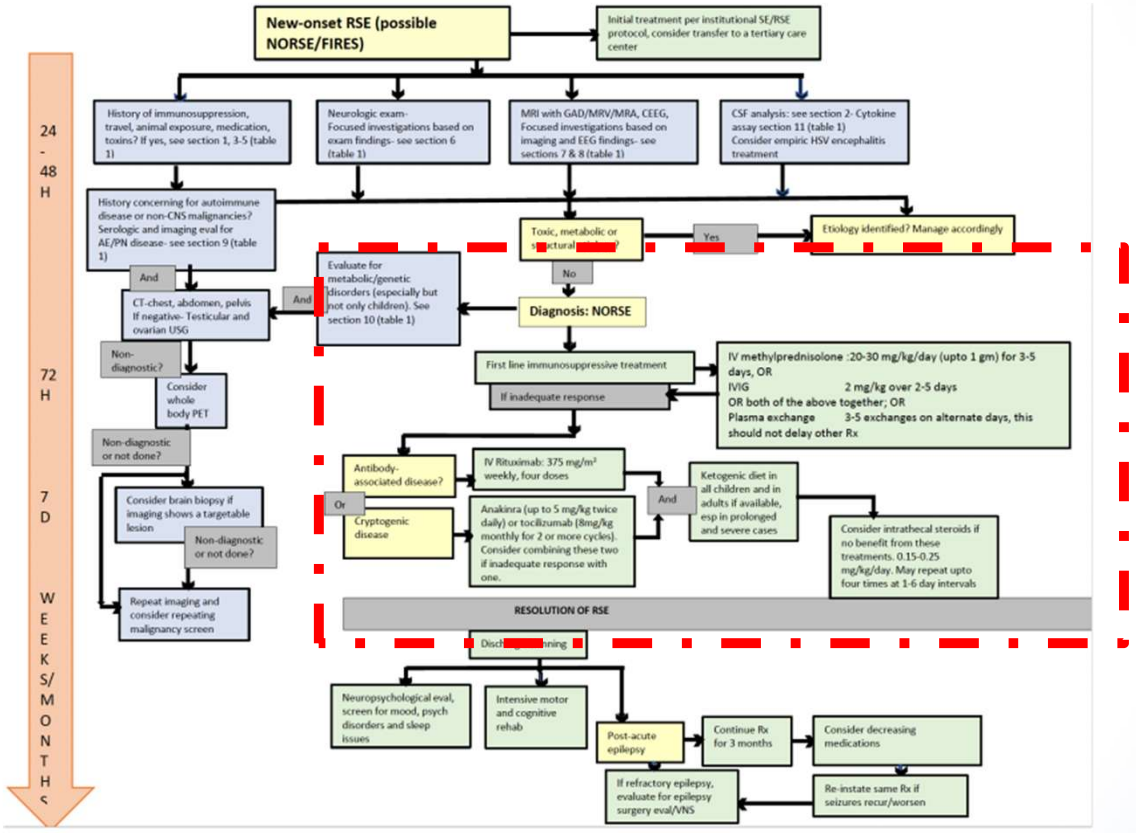
A clinical presentation, not a specific diagnosis, in a patient without active epilepsy of other preexisting relevant neurological disorder, with new onset of refractory status epilepticus without a clear acute or active structural, toxic or metabolic cause.

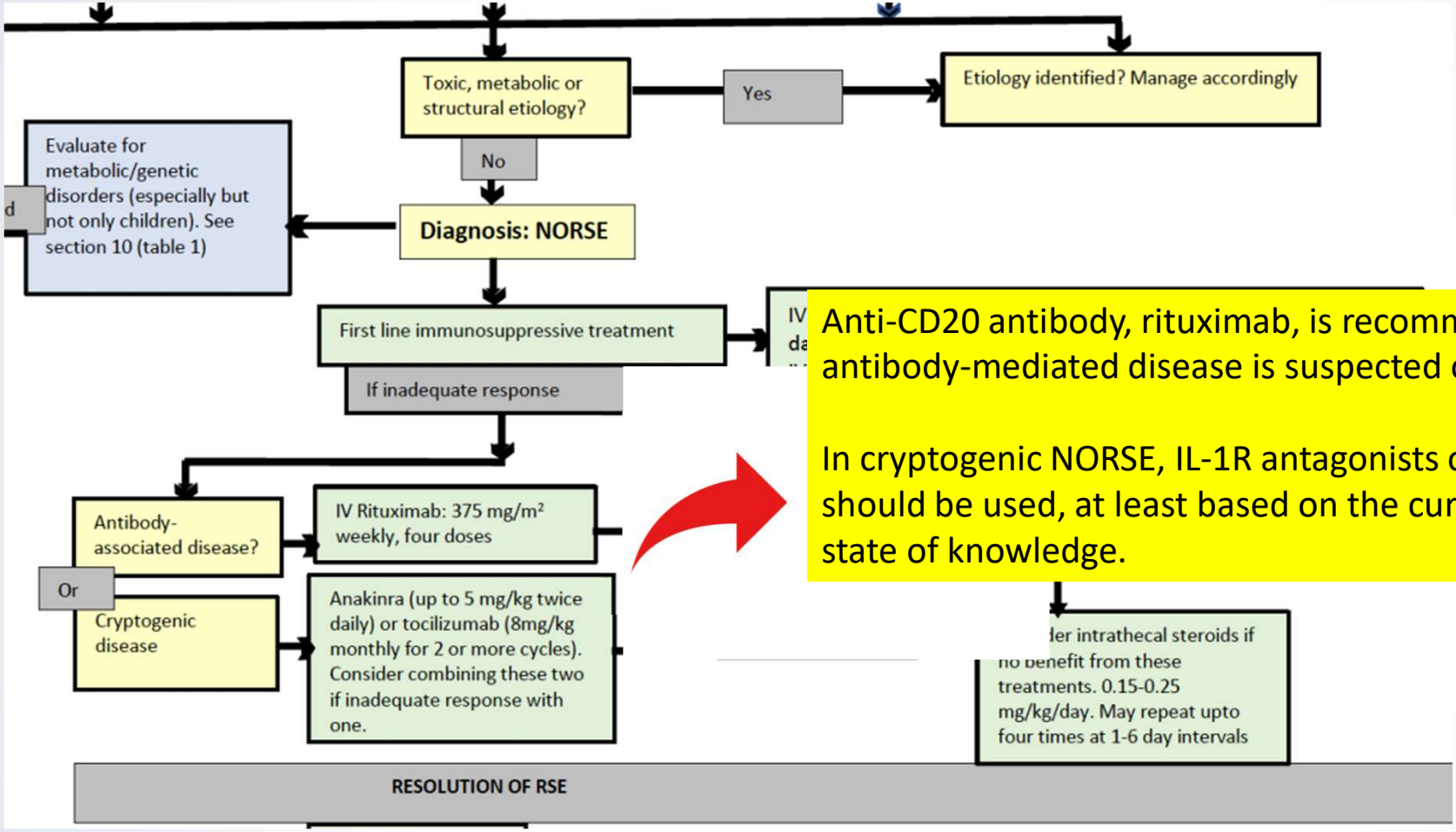
- Typically presents as super-refractory status epilepticus (SRSE), but this is not required for the diagnosis of NORSE
- Subgroup: Cryptogenic after extensive workup; referred to as “cryptogenic NORSE’ or “NORES of unknown etiology”
- NORSE does not include RSE with fully retained consciousness such as epilepsia partialis continua
- Includes viral infections and autoimmune síndromes – these may present as NORSE
- Allows remote brain injuries or resolved epilepsy (sz-free 10y, off ASMs 5y)
- Requiring imaging, CSF análisis, toxicology and blood tests as recommended for evaluation of SE in other guidelines)

FIRES: Febrile infection-related epilepsy syndrome

- **A subcategory of NORSE that requires a prior febrile infection, with fever starting between 2 weeks and 24 hrs prior to onset of refractory status epilepticus**
  - Has to be refractory SE
  - No age cutoff: can be infant, child or adult
  - Can be with or without fever at the time of onset of SE (About 50$ have fever in prior literature)
  - Excludes most cases of “prolonged febrile convulsions” (also known as febrile status epilepticus), as fever in those cases is usually acute onset (few hours or less, or discovered after the seizure)
    - If fever is present for > 24 hrs, perhaps this is an overlapping scenario with NORSE

A practical approach to the management of NORSE/FIRES





Anti-CD20 antibody, rituximab, is recommended if an antibody-mediated disease is suspected or confirmed.

In cryptogenic NORSE, IL-1R antagonists or IL-6 antagonists should be used, at least based on the current (limited) state of knowledge.

Other Treatment

Table 9. Alternative treatments for super refractory status epilepticus (41,65–68)

Treatment	Comments
Immunomodulatory agents	- Includes: adrenocorticotropic hormone, intravenous immunoglobulin, plasma exchange, steroids - Consider early in the treatment of NORSE (especially if suspected autoimmune encephalitis) - The STATUS (SAGE-547 Treatment as Adjunctive Therapy Utilized in Status Epilepticus) trial studied allopregnanolone, a positive allosteric modulator of GABA receptors, use in status epilepticus and found no significant difference in efficacy for seizure cessation between the control and intervention groups - The Randomized Therapy in Status Epilepticus (RAISE) trial is an ongoing study evaluating IV ganaxolone, an allopregnanolone analog, in patients with refractory status epilepticus
Ketogenic diet	- An anticonvulsant effect may be attributed to increased synthesis of glutamine and GABA - A multidisciplinary approach should be instituted when using the ketogenic diet, since the introduction of hidden carbohydrates can cease ketosis
Magnesium infusion	- Unclear mechanism, but thought to inhibit NMDA receptors - Suggested regimen: initial bolus of 4 grams followed by continuous infusion at 2 – 6 g/h targeting serum level of 3.5 mmol/L - Limited evidence

Other Treatment (cont)

Neuromodulation techniques	***Electroconvulsive therapy:*** - Widely applied in refractory psychiatric diseases - Unclear mechanism of action in SRSE, but may stimulate activation of endogenous GABAergic pathways
	Transcranial magnetic stimulation: - Pulsed electrical current is induced by electromagnetic induction to suppress cortical activity at low frequencies (≤ 1 Hz) and cortical excitability at high frequencies (≥ 5 Hz) - Possible cortical excitably modification when applied repetitively - There is no consensus on what protocol is most effective
	Vagal nerve stimulation (VNS): - Not widely used - A systematic review found that 74% of 38 patients with RSE/SRS had seizure cessation after acute VNS implantation
	Deep brain stimulation: - Limited evidence - Some data this can control seizures in patients with epilepsy - Target the anterior thalamic nucleus in SRSE

Other Treatment (cont')

Resective neurosurgery	- Consider when an epileptogenic zone has been identified - Can include focal, lobar, or multilobar resection; corpus callosotomy; hemispherectomy; or multiple subpial transections, either alone or in combination with focal resection
Therapeutic hypothermia	- HYBERNATUS multicenter RCT failed to show any benefit in functional outcome at 3 months - ASM levels should be followed as hypothermia reduces drug clearance
Transcranial direct current stimulation (tCDs)	- Emerging data for use in SRSE - Recent pilot study showed that ten patients with RSE benefited from 2-mA, 20-min tCDS sessions (reduction of 50% of median ictal epileptiform discharge rate per patient per session, and a reduction of 25% in the immediate period after the intervention)

Conclusions

- Currently available ASMs (BDZs) used for SE, allow also earlier seizure interruption, and prevention of recurrence
- Time is brain: earlier interruption is more often successful than later one
- Pharmacologic properties of the ASM determine the speed of brain entry and clinical efficacy
- Future: Combination with reliable seizure prediction tools
- Guidelines based on expert opinion suggest 24 – 48 hrs of sedation, but anecdotal evidence supports that shorter therapy, at higher infusion rates, might be as effective and safer
- EEG-guided therapy has been associated with a shorter duration of anesthetic exposure

Questions?

Email: crubinos@unc.edu

@Rubinorth