

# An Evidence-Based Framework for the Treatment of Status Epilepticus

RHEA BATTLE, PHARM.D.  
NEUROCRITICAL CARE PHARMACY SPECIALIST  
EMORY UNIVERSITY HOSPITAL

## Disclosures

- I do not have (nor does any immediate family member have) a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation.
- There was no Financial Support obtained for this CPE Activity

## Objectives

- Identify initial and subsequent pharmacologic agents for Status Epilepticus
- Describe a time dependent treatment strategy for Status Epilepticus
- Describe anticonvulsant medication limitations
- Define refractory Status Epilepticus
- Identify treatment options for refractory Status Epilepticus

## Defining Status Epilepticus (SE)

### Traditional (old) definition:

- A continuous seizure that last for 30 minutes or more  
or
- Intermittent seizures without full recovery of consciousness between seizures

### New definition:

- A seizure that lasts for 5 minutes or more, or recurrent seizure activity without an interictal return to baseline

Teran, F, Harper-Kirksey, K. Clinical Decision making in Seizures and Status Epilepticus. E. Med Practice 2015; 17(1)

## Epidemiology

- An estimated 180,000 cases/yr of status epilepticus in the US
- Mortality rates up to 30%
  - Estimated 55,000 deaths annually
- 35% do not respond to benzodiazepines

Siven, J, Waterhouse, E. Management of Status Epilepticus. Am Fam Physicians 2003;68:469-76

## Etiology

- Acute brain insults/head trauma
- Meningitis
- Encephalitis
- Hypoxia
- Hypoglycemia
- CVA
- Drug toxicity (Cefepime, Carbapenems)
- Withdrawal
- AED noncompliance
- Infection
- CNS tumor

Teran, F, Harper-Kirksey, K. Clinical Decision making in Seizures and Status Epilepticus. E. Med Practice 2015; 17(1)

## Classification of Status Epilepticus (SE)

- ▶ Generalized convulsive status epilepticus (GCSE)
- ▶ Generalized non-convulsive status epilepticus
- ▶ Simple partial status epilepticus
- ▶ Complex partial status epilepticus

Toran, T, Harper-Kirksey, K. Clinical Decision making in Seizures and Status Epilepticus. E. Med Practice 2015: 17(1)

## Generalized Convulsive Status Epilepticus (GCSE)

- ▶ Untreated or inadequately treated SE Increase risk of:
  - ▶ Neuronal damage
  - ▶ Cognitive dysfunction
  - ▶ Intractable to treatment
  - ▶ Poor prognosis

Browne, Thomas, Holmes, Gregory. Handbook of Epilepsy 4th ed. Lippincott Williams & Wilkins, Philadelphia, PA 2008. Google books Web 5 Feb 2017. www.books.google.com

## SE Treatment Guidelines

- ▶ American Epilepsy Society guideline and treatment algorithm for convulsive status epilepticus (2016)
  - ▶ 38 relevant randomized controlled trials and 4 meta analysis
  - ▶ Streamlined therapies into an evidence based framework
  - ▶ No new treatment options presented
  - ▶ Focus on generalized convulsive status epilepticus
    - ▶ Most common
    - ▶ Associated with substantial mortality

Glauser, T, ShiAdults: Report of the Guideline Committee of the American Epilepsy Society. Epilepsy Currents, Vol. 16, No. 1 (January/February) 2016 pp. 48-61

## Time Dependent Treatment Strategy

- ▶ **Stabilize Phase (0-5 min)**
- ▶ Initial Therapy Phase (5-20 min)
- ▶ Second Therapy Phase (20-40 min)
- ▶ Third Therapy Phase (40+ min of seizure activity)

Glauser, T et. Al. Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults. Report of the Guideline Committee of The American Epilepsy Society. Epilepsy Curr. 2016; 16:48-61

## Stabilize Phase (0-5 min)

- ▶ First aid for seizures (ABCDE)
  - ▶ **M**aintain **A**irway- Risk of aspiration
  - ▶ **B**reathing- place O<sub>2</sub>
  - ▶ **C**irculation - Obtain IV access
  - ▶ **D**extrose - Check BGL
  - ▶ **E**lectrolytes - **Na**, Ca, Mg, anticonvulsant level, tox screen, troponin
- ▶ Monitor vital signs
- ▶ EEG

Glauser, T et. Al. Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults. Report of the Guideline Committee of The American Epilepsy Society. Epilepsy Curr. 2016;16:48-61

## Time Dependent Treatment Strategy

- ▶ Stabilize Phase (0-5 min)
- ▶ **Initial Therapy Phase (5-20 min)**
- ▶ Second Therapy Phase (20-40 min)
- ▶ Third Therapy Phase (40+ min of seizure activity)

Glauser, T et. Al. Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults. Report of the Guideline Committee of The American Epilepsy Society. Epilepsy Curr. 2016;16:48-61

## Initial Therapy Phase (5-20 min)

**Ideal Drug Characteristics:**

- ▶ Rapid CNS penetration
- ▶ Rapid onset of action
- ▶ Long duration of action

**Goal of Therapy:**

- ▶ Prevents neuronal injury
- ▶ Maximizes cerebral O<sub>2</sub> supply
- ▶ Decrease morbidity/mortality
- ▶ Cessation of seizure activity

Teram, F. Harper-Kirksey, K. Clinical Decision making in Seizures and Status Epilepticus. E. Med Practice 2015: 17(1)

The New England Journal of Medicine

### A COMPARISON OF FOUR TREATMENTS FOR GENERALIZED CONVULSIVE STATUS EPILEPTICUS

DAVID M. TREMAN, M.D., PATTI D. MYERS, M.P.A., NANCY Y. WALTON, Ph.D., JOSEPH F. COLLINS, Sc.D., CHERY COLLING, R.Ph., M.S., A. JAMES RONAN, M.D., ADRIAN HANSFORTH, M.D., EDWARD FASSITT, M.D., VINCENT P. CALABRESE, M.D., BASIM M. UTHMAN, M.D., R. EUGENE RAMSAY, M.D., AND MEENAL B. MAMSIANI, M.D., FOR THE VETERANS AFFAIRS STATUS EPILEPTICUS COOPERATIVE STUDY GROUP\*

- ▶ 5 year Multi-centered, Double-blinded, randomized comparison of four different IV treatments (class I trial)
- ▶ Convulsive (384 patients) and non-convulsive (134 patients)
- ▶ Overt status epilepticus: Continuous GTC seizure lasting 10 minutes or longer, or two or more GTC seizures without full recovery of consciousness
- ▶ Successful treatment: SE stopped within 20 minutes after the start of infusion with no recurrence prior to 60 minutes

## What is the Best Initial Agent For Seizure Termination?

**Veteran's Affairs Status Epilepticus Cooperative Study Group (continued):**

- ▶ Primary Outcomes: no significant difference between groups
  - ▶ Lorazepam 0.1 mg/kg: (65%)
  - ▶ Phenobarbital 18 mg/kg: (58%)
  - ▶ Diazepam 0.15 mg/kg followed by phenytoin 18 mg/kg: (56%)
  - ▶ Phenytoin alone 18 mg/kg: (44%)
- ▶ One head-to-head comparison met the pre-specified statistically significant difference: lorazepam was superior to phenytoin as an initial agent ( $p = 0.002$ )

Reisman DM et al. A Comparison of Four Treatments for Generalized Convulsive Status Epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. N Engl J Med 1998; 239:792-798.

## Initial Therapy Phase (5-20 min)

- ▶ Benzodiazepines are recommended as initial therapy (Level A recommendation)
  - ▶ Lorazepam
    - ▶ Onset: 3-8 min
    - ▶ Duration of action: 4-6 hr
  - ▶ Diazepam
    - ▶ Onset: 1-3 min
    - ▶ Duration of action: 15-30 min
  - ▶ Midazolam
    - ▶ Onset: 1-5 min (IV)
    - ▶ Duration of action: IV: < 2 hrs
    - IM: up to 6 hrs

Glauser, T et al. Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults. Report of the Guideline Committee of The American Epilepsy Society. Epilepsy Curr. 2016;16:48-61

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 Connell, M.D., Arthur Pancicci, M.D., Yuko Palesch, Ph.D., and William Barsan, M.D., for the NETT Investigators\*

**RAMPART Trial (Class I trial)**

- ▶ Multi-center, double-blinded, randomized, noninferiority clinical trial (n = 893)
- ▶ Primary outcome: Termination of seizure at ED arrival with no rescue therapy given
- ▶ Midazolam 10 mg IM (73%) and lorazepam 4 mg IV (63%)
- ▶ Conclusion: Midazolam non-inferior and demonstrated superiority 10% difference (95% CI: 4.0-16.1)

## Which Benzodiazepine Is Most Effective?

Equivalent first line options: (Level A recommendation)

IV Access

Lorazepam  
Diazepam  
(IV)

No significant difference in effectiveness between lorazepam and diazepam (level A)

No IV Access

Midazolam  
(IM)

No IV access, IM midazolam is more effective compared with IV lorazepam (level A)

Silbergleit R, Durkalski V, Lowenstein D, Connell R, Pancicci A, Palesch Y, Barsan W. NETT Investigators. Intramuscular Versus Intravenous Therapy for Prehospital Status Epilepticus. N Engl J Med 2012; 366:591-600.

### Initial Therapy Phase (5-20 min)

Drug	Loading Dose (LD)	Notes
Lorazepam	IV: 0.1 mg/kg (max 4 mg/dose) May repeat once in 5-10 min	<ul style="list-style-type: none"> <li>Longer anticonvulsant duration</li> <li>Direct glucuronidation</li> <li>Preferred IV agent</li> <li>Respiratory depression</li> <li>Hypotension</li> </ul>
Diazepam	IV: 0.15-0.2 mg/kg (max 10 mg/dose) May repeat once in 5-10 min	<ul style="list-style-type: none"> <li>Sedation (active metabolites)</li> <li>Rectal formulation available</li> <li>Respiratory depression</li> <li>Hypotension</li> </ul>
Midazolam	IM: 5-10 mg IM Single dose	<ul style="list-style-type: none"> <li>DOC for IM administration</li> <li>Intranasal/buccal formulations</li> <li>Respiratory depression</li> <li>Less hypotension</li> </ul>

Brophy, G. et al. Guidelines for the Evaluation and Management of Status Epilepticus. Neurocrit Care 2012

### Time Dependent Treatment Strategy

- ▶ Stabilize Phase (0-5 min)
- ▶ Initial Therapy Phase (5-20 min)
- ▶ **Second Therapy Phase (20-40 min)**
- ▶ Third Therapy Phase (40+ min of seizure activity)

Glauser, T et. Al. Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults. Report of the Guideline Committee of The American Epilepsy Society. Epilepsy Curr. 2016;16:48-61

### Second Therapy Phase (20-40 min)

Options for second phase therapy

- ▶ Fosphenytoin
- ▶ Valproic Acid
- ▶ Levetiracetam
- ▶ Lacosamide
- ▶ If none of the above options are available
  - ▶ Phenobarbital 15 mg/kg IV (Level B recommendation)

Glauser, T et. Al. Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults. Report of the Guideline Committee of The American Epilepsy Society. Epilepsy Curr. 2016;16:48-61

### Second Therapy Phase (20-40 min)

ESETT trial results

- ▶ Randomized, blinded, adaptive trial
- ▶ Primary Outcomes: Cessation of seizures and improvement in level of consciousness at 60 min

	Levetiracetam (n=145)	Fosphenytoin (n= 118)	Valproate (n=121)
Primary outcome	68 (47%)	53 (45%)	56 (46%)

Kapur, J, Elm J, et al. Randomized Trial of Three Anticonvulsant Medications for Status Epilepticus. N Engl Med 2019 Nov 28;381:22

### Second Phase (40+ min)

Drug	Loading Dose	Time to Peak	ADE / Notes
Fosphenytoin	20 mg PE/kg IV	30-60 min	<ul style="list-style-type: none"> <li>Max infusion rate 150 mg PE/min</li> <li>Hypotension</li> <li>Cardiac arrhythmias</li> <li>Many drug interactions</li> </ul>
Lacosamide	400 mg IV	End of infusion	<ul style="list-style-type: none"> <li>Cardiac arrhythmias</li> <li>Requires renal dose adjustment</li> </ul>
Levetiracetam*	60 mg/kg IV Max dose: 4500 mg	5-30 min	<ul style="list-style-type: none"> <li>Minimal drug interaction</li> <li>Requires renal dose adjustment</li> </ul>
Valproic Acid	40 mg/kg IV Max dose: 6000 mg	End of infusion (60 min)	<ul style="list-style-type: none"> <li>Hepatotoxic</li> <li>Pancreatitis</li> <li>Teratogenic</li> <li>Monitor BP</li> </ul>

Brophy, G. et al. Guidelines for the Evaluation and Management of Status Epilepticus. Neurocrit Care 2012

### Levetiracetam To Push or Not To Push

Rapid Infusion of undiluted levetiracetam

- ▶ N = 199 patients
- ▶ Total number of doses: 1626

Levetiracetam	# doses	Peripheral
500 mg	317	.....
1000 mg	858	64.6%
500/1000 mg	354	.....
250/750 mg	97	.....

- ▶ No documented injection site pain, erythema, extravasation or line replacements
- ▶ No side effects 98.5%
  - ▶ 3 patients (1.5%) experienced agitation, delirium, confusion, lethargy
  - ▶ Not an infusion related issue

Morgan O, Medendorp, B. Safety and Tolerability of Rapid Administration of Undiluted Levetiracetam. Neurocrit Care 2020 Feb;32(1): 131-134.

## Lacosamide to Push or Not to Push

IV Push Lacosamide Safety outcomes

- ▶ N = 166
- ▶ Single center retrospective cohort study
- ▶ No infusion site reactions reported

	IV Push (n = 78)	IVPB (n = 88)	P value
Hypotension	8 (10.3%)	7	0.61
Bradycardia	2 (2.6%)	2	>0.99
Lowest SBP	115 (21)	116 (24)	0.71
Lowest HR	74 (16)	78 (18)	0.14

Davidson KE, Newell J, et al. Safety and Efficacy of Intravenous Push Lacosamide Administration. Neurocrit Care. 2018 Dec;29(3): 491-495.

## Improving Time to Administration

**Lacosamide**

- ▶ All doses of lacosamide are undiluted via IV push
- ▶ Vials available in automated dispensing cabinet

**Levetiracetam**

- ▶ All doses of levetiracetam  $\leq$  1000 mg are given undiluted via IV push
- ▶ Levetiracetam doses > 1000 mg
  - ▶ Consecutive IV push doses of 1000 mg are given to equate total loading dose
- ▶ Vials available in automated dispensing cabinet

## Refractory Status Epilepticus

Impending SE

- 1<sup>st</sup> line BZDP

Established SE

- 2<sup>nd</sup> line agent

Refractory Status Epilepticus

- Persists after: 1<sup>st</sup> line BZDP and 2<sup>nd</sup> line agent

*Mortality approaches 50%, few return to pre-morbid baseline*

## Time Dependent Treatment Strategy

- ▶ Stabilize Phase (0-5 min)
- ▶ Initial Therapy Phase (5-20 min)
- ▶ Second Therapy Phase (20-40 min)
- ▶ **Third Therapy Phase (40+ min of seizure activity)**

Glauser, T et al. Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults. Report of the Guideline Committee of the American Epilepsy Society. Epilepsy Curr. 2016;16:48-61

## Third Therapy Phase (40+ min)

- ▶ Repeat second line therapy (Level U recommendation) or
- ▶ Midazolam, pentobarbital, or propofol (Level U recommendation)
  - ▶ All with continuous EEG monitoring
  - ▶ Require intubation

Glauser, T et al. Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults. Report of the Guideline Committee of the American Epilepsy Society. Epilepsy Curr. 2016;16:48-61

## Third Phase (40+ min) continued

Drug	Loading Dose	Continuous Infusion rate	Notes
Propofol	1-2 mg/kg IV (up to 5 mg/kg)	20 mcg/kg/min Titrate 5-10 mcg q5min Range: 30-200 mcg/kg/min	• Hypotension w/ LD • Requires mech ven • PRIS: >80 mcg/kg/minute for >48 hr
Midazolam	0.2 mg/kg IV (max 10 mg)	0.05-2 mg/kg/hr Titrate 0.05-.1mg q3-4 hrs	• Tachyphylaxis • NO propylene glycol
Pentobarbital	5-15 mg/kg IV (max rate 50 mg/min)	0.5-10 mg/kg/hr Titrate 0.5-1 mg q12h	• Elimination half life 15-60 hrs • Hypotension • Myocardial depression

Brophy, G. et al. Guidelines for the Evaluation and Management of Status Epilepticus. Neurocrit Care 2012

## Molecular Changes in Prolonged SE

- ▶ Number and activity of GABA receptors gradually decrease
  - ▶ BZDP
- ▶ Upregulation of p-glycoprotein molecular transporters at the level of the BBB occurs
  - ▶ Phenytoin, phenobarbital
- ▶ Numbers and activities of glutamatergic NMDA receptors increase
  - ▶ Ketamine

Teran, F, Harper-Kirksey, K. Clinical Decision making In Seizures and Status Epilepticus. E. Med Practice 2015; 17(1)

## Ketamine For Refractory SE

- ▶ Loading dose: 3 mg/kg IV (may repeat 1.5 mg/kg)
- ▶ Continuous infusion: 0.5-2 mg/kg/hr titrate (range 1-10 mg/kg/hr)
- ▶ Monitor CPK, Liver enzymes
- ▶ Adverse Effect: Psychosis
  - ▶ Give with benzodiazepines to decrease psychosis

Glauser, T et al. Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults. Report of the Guideline Committee of the American Epilepsy Society. Epilepsy Curr. 2016;16:48-61

## Summary

- ▶ Time is brain (30 min)
- ▶ Seizure physical symptoms can be subtle
- ▶ Remember your ABCs and to treat the underlying cause
- ▶ Literature supports BZDP use as initial agent
- ▶ Time dependent loss of synaptic GABA receptors
- ▶ When selecting an agent keep in mind the different pharmacologic profiles of AEDs medication (pharmacokinetic properties, propensity for drug-drug interactions, side effect profiles and toxicities)
- ▶ 24-48 h of electrographic control is recommended prior to slow withdrawal of continuous infusion

## References

- ▶ Teran, F, Harper-Kirksey, K. Clinical Decision making In Seizures and Status Epilepticus. E. Med Practice 2015; 17(1)
- ▶ Siven, J, Waterhouse, E. Management of Status Epilepticus. Am Fam Physicians 2003;68:469-76
- ▶ Browne, Thomas, Holmes, Gregory. Handbook of Epilepsy 4<sup>th</sup> ed. Lippincott Williams & Wilkins. Philadelphia, PA, 2008. Google books Web 5 Feb 2017. [www.books.google.com](http://www.books.google.com)
- ▶ Glauser, T, ShiAdults: Report of the Guideline Committee of the American Epilepsy Society. Epilepsy Currents. Vol. 16, No. 1 (January/February) 2016 pp. 48-61
- ▶ Silbergliet R, Durkalski V, Lowenstein D, Cornitt R, Pancioli A, Palesch Y, Barsan W : NETT Investigators. Intramuscular Versus Intravenous Therapy for Prehospital Status Epilepticus. N Engl J Med 2012;366:591-600.
- ▶ Brophy, G, et al. Guidelines for the Evaluation and Management of Status Epilepticus. Neurocrit Care 2012
- ▶ Kapur J, Elm J, et al. Randomized Trial of Three Anticonvulsant Medications for Status Epilepticus. N Engl J Med 2019 Nov 381:22.
- ▶ Morgan, O, Medenwald, B. Safety and Tolerability of Rapid Administration of Undiluted Levetiracetam. Neurocrit Care 2020 Feb;32(1): 131-134.
- ▶ Davickson KE, Newell J, et al. Safety and Efficacy of Intravenous Push Lacosamide Administration. Neurocrit Care. 2018 Dec;29(3): 491-495.

Questions?