CRITICAL CARE MANAGEMENT OF STATUS EPILEPTICUS

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OBJECTIVES

- Review the latest guideline from the American Epilepsy Society on the treatment of status epilepticus.
- Discuss an algorithm for management.
- Explore novel approaches to SE treatment

DEFINITION

- Status epilepticus (SE)
  - A seizure that lasts longer than 5 minutes or two or more seizures without return to baseline
- Refractory status epilepticus (RSE)
  - Ongoing seizure despite treatment with a benzodiazepine and antiepileptic drug (AED)
- Super-refractory status epilepticus (SRSE)
  - Continuous or recurrent seizure lasting 24 hrs. or more following initiation of anesthetic medications, or recurrent seizure after weaning off the anesthetic agent

INTRODUCTION

- Medical Emergency
- Incidence of 60 cases per 100,000
- Mortality rate of 7 – 28%
  - Age
  - Medical comorbidities
  - Presence of nonconvulsive status epilepticus (NCSE)
  - Underlying cause

CAUSES

- Genetic influence
- Head trauma
- Brain conditions
- Infectious diseases
- Prenatal injury
- Developmental disorders

The new definition and classification of seizures and epilepsy

Jessica J. Falco-Walter [a], Ingrid E. Scheffer [b], Robert S. Fisher [a]

- Based on 3 key features
  - ✓Onset location
  - ✓Level of awareness
  - ✓Other features
    - ➢ Motor
    - ➢ Auras

Falco-Walter, JJ, et al., *Epilepsy Research 2017*

ONSET LOCATION

- Focal seizure
  - ✓Previously called partial seizure
  - ✓Begin in an area or network of cells on one side of the brain
- Generalized seizure
  - ✓Networks of cells on both sides of the brain
- Unknown onset seizure
- Focal to bilateral seizure
  - ✓Starts on one side and spreads to both sides

Falco-Walter, JJ, et al., *Epilepsy Research 2017*

LEVEL OF AWARENESS

- Focal aware
  - ✓Person remains aware, even if unable speak or respond
- Focal impaired awareness
  - ✓Complex partial seizure
  - ✓Awareness is impaired or affected
  - ✓Person may have a vague idea
- Awareness unknown
- Generalized seizure

Falco-Walter, JJ, et al., *Epilepsy Research 2017*

MOTOR SYMPTOMS

- Focal motor seizure
  - ✓ Some type of movement occurs
  - ✓ Twitching
  - ✓ Jerking
  - ✓ Stiffening of a body part
  - ✓ Automatisms
- Focal non-motor seizure
  - ✓ Changes in sensation
  - ✓ Emotions
  - ✓ Thinking
  - ✓ Experiences

- Generalized motor seizure
  - ✓ Generalized tonic-clonic
  - ✓ Grand mal
  - ✓ Stiffening (tonic) and jerking (clonic)
- Generalized non-motor seizure
  - ✓ Absence
  - ✓ Petit mal
  - ✓ Brief changes in awareness, staring
  - ✓ Automatic or repeated movements

Falco-Walter, JJ, et al., *Epilepsy Research 2017*

ILAE 2017 Classification of Seizure Types Expanded Version [1]

Focal Onset

Aware	Impaired Awareness

Motor Onset
- automatisms
- atonic [2]
- clonic
- epileptic spasms [2]
- hyperkinetic
- myoclonic
- tonic

Non-Motor Onset
- autonomic
- behavior arrest
- cognitive
- emotional
- sensory

focal to bilateral tonic-clonic

Generalized Onset

Motor
- tonic-clonic
- clonic
- tonic
- myoclonic
- myoclonic-tonic-clonic
- myoclonic-atonic
- atonic
- epileptic spasms

Non-Motor (absence)
- typical
- atypical
- myoclonic
- eyelid myoclonia

Unknown Onset

Motor
- tonic-clonic
- epileptic spasms

Non-Motor
- behavior arrest

Unclassified [3]

1 Definitions, other seizure types and descriptors are listed in the accompanying paper and glossary of terms

2 Degree of awareness usually is not specified

3 Due to inadequate information or inability to place in other categories

Falco-Walter, JJ, et al., *Epilepsy Research 2017*

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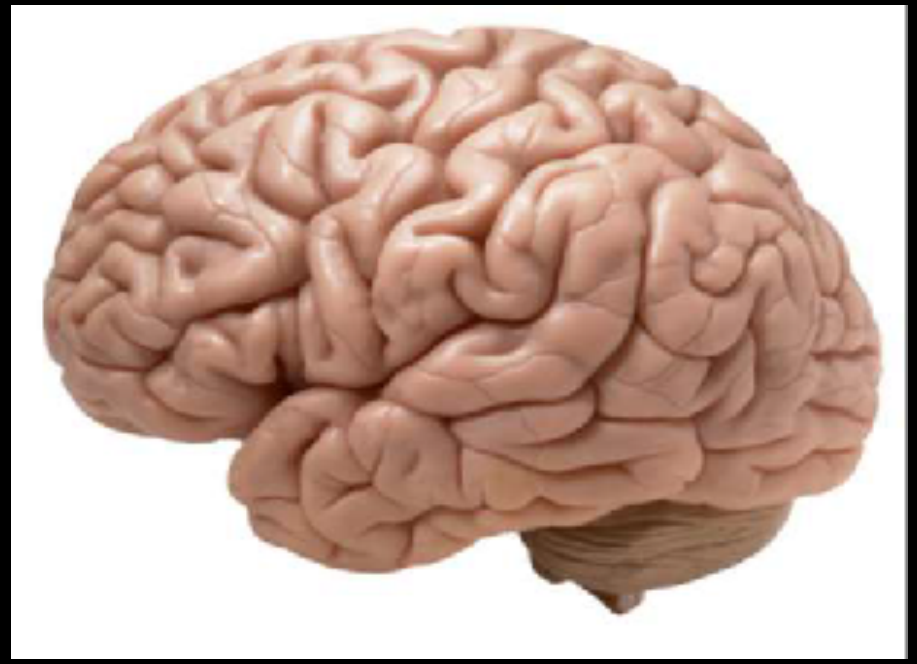


MANAGEMENT

- Neurologic life support
- Peripheral intravenous access
- Medications
- Workup

AES ALGORITHM

Glauser T, et al. *Epilepsy Currents*. 2016

SHEN'S ALGORITHM

0 – 5 min
- Stabilization
- Labs, IV

5 – 15 min
- Initial Therapy
- Benzodiazepine x 1-2
- AED

15 – 30 min
- Intubation
- Propofol bolus -> gtt
- AED

THERAPY

- Initial Emergent Therapy
  - ✓Benzodiazepines
- Second Urgent-control Therapy
  - ✓Antiepileptic drug (AED)
- Third Refractory Therapy

INITIAL EMERGENT THERAPY

- Benzodiazepines
  - ✓Lorazepam
  - ✓Midazolam
  - ✓Diazepam
  - ✓Clonazepam

SECOND URGENT-CONTROL THERAPY

- Antiepileptic drug (AED)
  - ✓Phenytoin/fosphenytoin
  - ✓Valproic acid
  - ✓Levetiracetam (Keppra)
  - ✓Lacosamide (Vimpat)
  - ✓Phenobarbitol
  - ✓Carbamezapine (Tegretol)

THIRD REFRACTORY THERAPY

- Aggressive phase
- Continuous EEG
- Repeat second-line therapy
- Anesthetic dose
  - ✓Thiopental
  - ✓Midazolam
  - ✓Pentobarbital
  - ✓Propofol

BENZODIAZEPINES

- GABA receptor agonist
- Routes of administration
  - ✓Intravenous
  - ✓Nasal
  - ✓Buccal
  - ✓Rectal
- Respiratory depression

DIAZEPAM

- Higher brain concentration
- Onset of action 30 seconds
- Highly lipid soluble
- Rapid redistribution and decreased brain concentration
- Clinical effectiveness about 20 minutes

MIDAZOLAM

- Any route of administration
- Intramuscular, rectal, sublingual, intranasal
- Half life 1.5 to 2.5 hrs.

LORAZEPAM

- Onset of action 2 minutes
- Duration of action greater than 12 hrs.

WHY USE BENZO FIRST?

A Comparison of Four Treatments for Generalized Convulsive Status Epilepticus

- 5 year randomized, double blind
- 570 patients
- 16 Veterans Affairs medical centers and 6 affiliated university hospitals

Treiman DM, et al., JAMA 1998

A Comparison of Four Treatments for Generalized Convulsive Status Epilepticus

- Treatment regimen
  - ✓phenobarbital (15mg/kg)
  - ✓phenytoin (18mg/kg)
  - ✓diazepam (0.15mg/kg) plus phenytoin (18mg/kg)
  - ✓lorazepam (0.1mg/kg)

Treiman DM, et al., JAMA 1998

A Comparison of Four Treatments for Generalized Convulsive Status Epilepticus

- Treatment success
  - ✓Seizure cessation within 20 min
  - ✓No return of seizure activing for 40 min

Treiman DM, et al., JAMA 1998

A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus.

- Randomized, double-blind trial
- Intravenous benzodiazepines
- Prolonged seizure (> 5 min)
- Repetitive generalized convulsive seizure

Alldredge BK, et al., *N Eng J Med* 2001

A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus.

- 205 patients
  - ✓66 received 2mg lorazepam
  - ✓68 received 5mg diazepam
  - ✓71 received placebo

Alldredge BK, et al., *N Eng J Med* 2001

A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus.

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

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

*CI denotes confidence interval.

†Each odds ratio was adjusted for race or ethnic group, the intervals from the onset of status epilepticus to study treatment and from study treatment to arrival at the emergency department, and cause of status epilepticus within each prognostic group.

Alldredge BK, et al., *N Eng J Med* 2001

A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus.

- Benzodiazepines are safe and effective

Alldredge BK, et al., *N Eng J Med* 2001

Midazolam versus diazepam for the treatment of status epilepticus in children and young adults: a meta-analysis.

- 6 studies
- 774 subjects
- Midazolam by any route was superior to diazepam

McMullan J, et al., *Acad Emerg Med* 2010

RAMPART (Rapid Anticonvulsant Medication Prior to Arrival Trial): A double-blind randomized clinical trial of the efficacy of IM midazolam versus IV lorazepam in the pre-hospital treatment of status epilepticus by paramedics

- 4314 paramedics
- 33 EMS agencies
- 79 receiving hospitals

Silbergleit R, et al., *Epilepsia* 2011

ORIGINAL ARTICLE

Intramuscular versus Intravenous Therapy for Prehospital Status Epilepticus

Robert Silbergleit, M.D., Valerie Durkalski, Ph.D., Daniel Lowenstein, M.D., Robin Conwit, M.D., et al., for the NETT Investigators*

- Double-blind, randomized, noninferiority trial
- 893 patients
- Intramuscular midazolam 10mg
- Intravenous lorazepam 4mg

Silbergleit R, et al., *N Engl J Med* 2012

ORIGINAL ARTICLE

Intramuscular versus Intravenous Therapy for Prehospital Status Epilepticus

Robert Silbergleit, M.D., Valerie Durkalski, Ph.D., Daniel Lowenstein, M.D., Robin Conwit, M.D., et al., for the NETT Investigators*

- Result: Absent seizure without rescue therapy at ED arrival
  - ✓IM midazolam 73.4%
  - ✓IV lorazepam 63.4%

Silbergleit R, et al., *N Engl J Med* 2012

SHEN'S ALGORITHM

0 – 5 min
- Stabilization
- Labs, IV

5 – 15 min
- Initial Therapy
- Benzodiazepine x 1-2
- AED

15 – 30 min
- Intubation
- Propofol bolus -> gtt
- AED

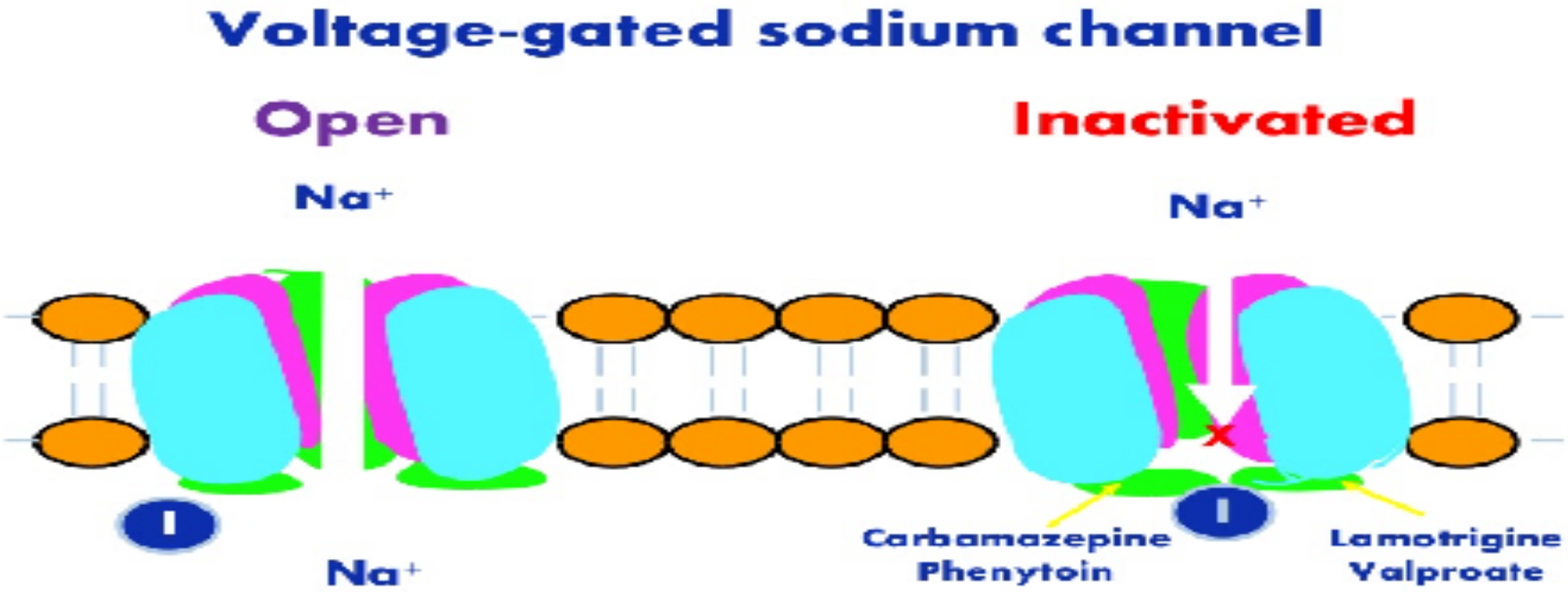
SECOND URGENT CONTROL THERAPY

- The Antiepileptic drugs (AED)
- No strong data supporting the use of one over another
- Use is dependent on availability, preference, side effect profile
- Emergent therapy fails to control 35 – 45% of patients

Glauser T, et al. *Epilepsy Currents*. 2016

AEDs:

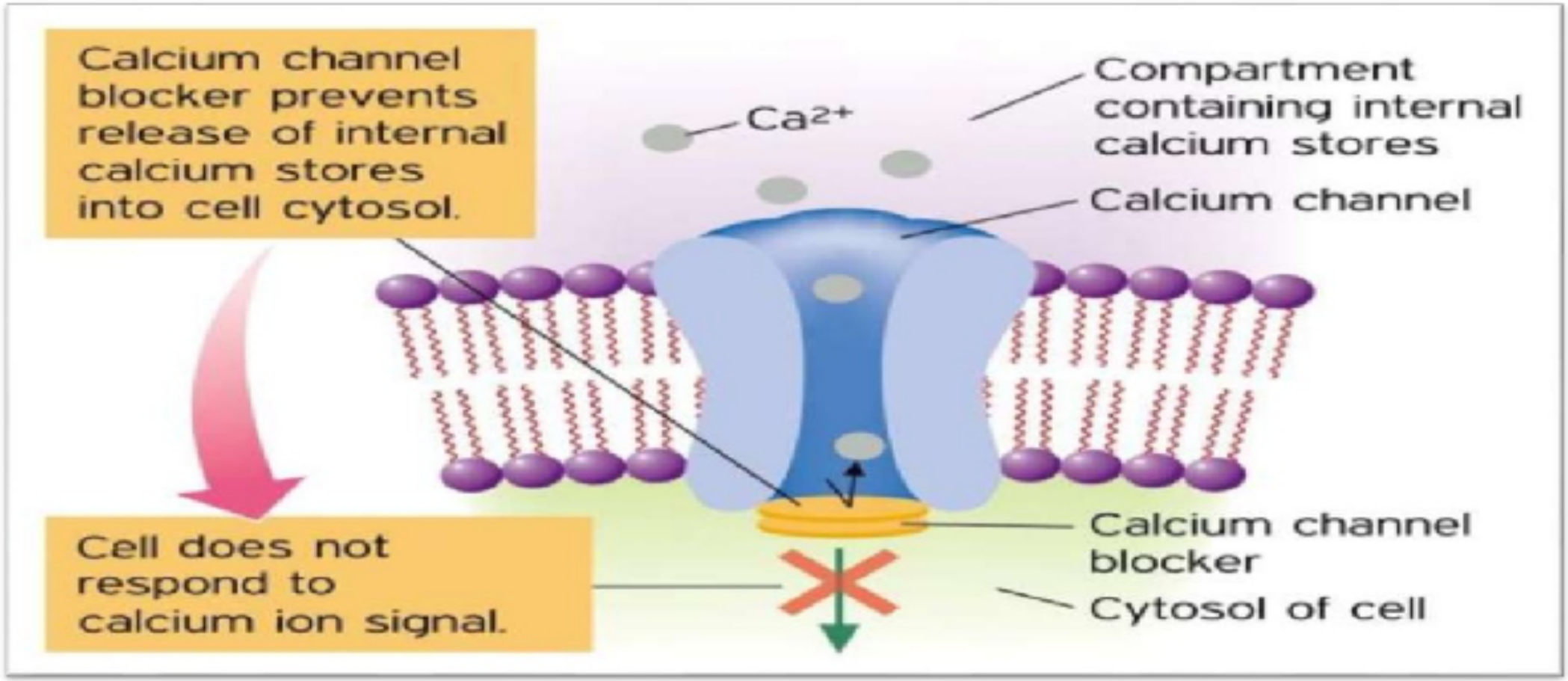
Mechanisms of Action



AEDs:

Mechanisms of Action

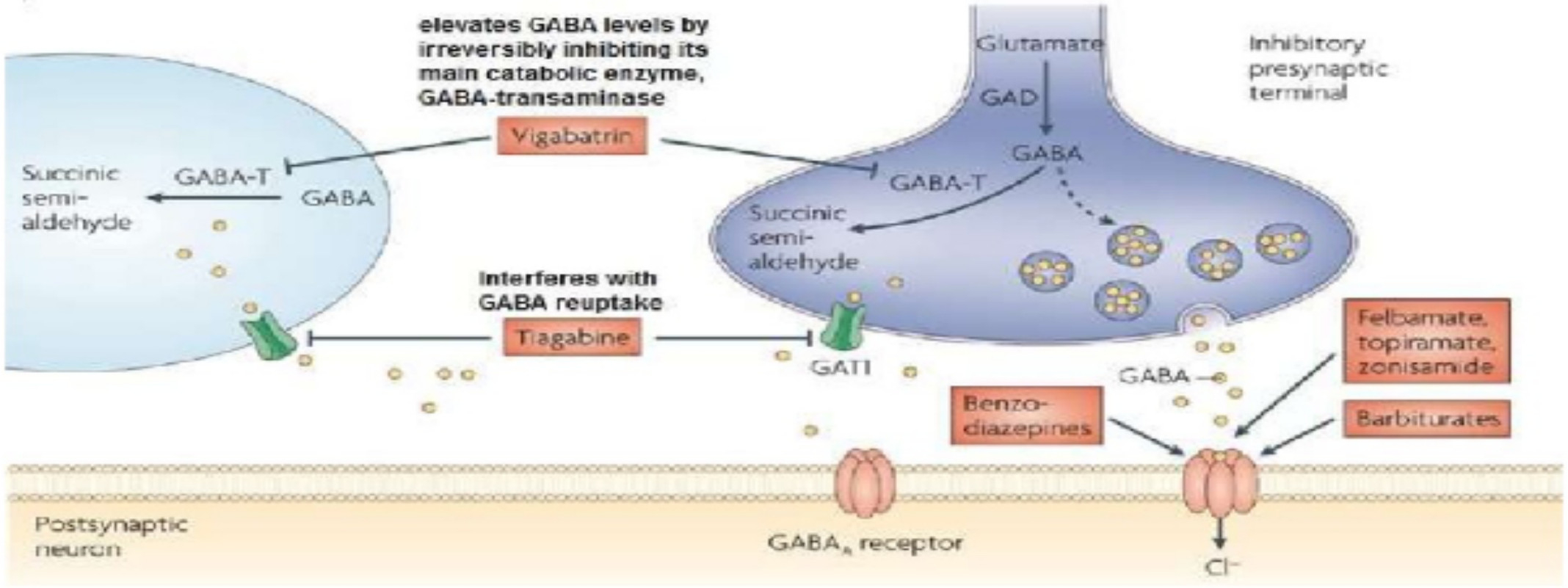
- **Calcium channel blockade**



AEDs:

Mechanisms of Action

- **GABA**



PHENYTOIN

- Decreases the recovery rate of voltage-activated sodium channel
- pKa 8.3, highly lipid soluble but insoluble in water
- Highly protein bound, one free portion is active
- Mixed in polypropylene glycol pH 12
- Metabolized by liver, has saturable pharmacokinetics
- Slow infusion rate 50mg/min
- Delayed onset of action
- Complications include hypotension and cardiac arrhythmia
- If extravasation occurs, causes local irritation, thrombophlebitis, compartment syndrome, “purple glove syndrome”

FOSPHENYTOIN

- Water-soluble precursor which is rapidly transformed to phenytoin
- Faster rate of infusion 150mg/min, can also be given IM
- Higher cost

VALPROIC ACID

- Is most prescribed AED worldwide
- Maximum plasma concentration reached within minutes
- Highly protein bound to plasma protein (>90%)
- Metabolized extensively in liver
- Half-life 12 h
- Non-sedating, No cardiac toxicity
- Low adverse event rate (<10%) dizziness, thrombocytopenia, mild hypotension, pancreatitis, hyperammonia

LEVETIRACETAM

- Minimal hepatic metabolism and low plasma protein binding
- Excreted renally and needs to be adjusted for renal failure
- Low rate of adverse effects
  - ✓Somnolence and sedation
  - ✓Agitation
  - ✓Thrombocytopenia

Misra UK, et al., *J Neurol* 2012

LACOSAMIDE

- Acts as a sodium channel blocker, by enhancing slow inactivation
- Slightly bound to plasma protein (<15%)
- 95% is excreted in the urine, 30% as inactive metabolite

Second-line status epilepticus treatment: Comparison of phenytoin, valproate, and levetiracetam

Vincent Alvarez, Jean-Marie Januel, Bernard Burnand, Andrea O. Rossetti

- Single tertiary care hospital
- 187 patients
- Treatment with intravenous benzodiazepines followed by:
  - ✓ Phenytoin 20 mg/kg
  - ✓ Valproate 20 mg/kg
  - ✓ Levetiracetam 20 mg/kg

✓ Valproate was most effective

Alvarez V, et al., *Epilepsia* 2011

The relative effectiveness of five antiepileptic drugs in treatment of benzodiazepine-resistant convulsive status epilepticus: A meta-analysis of published studies

- 27 studies
- Mean efficacy termination of seizure within 30 min
  - ✓ valproate 75.7%
  - ✓ phenobarbital 73.6%
  - ✓ levetiracetam 68.5%
  - ✓ phenytoin 50.2%
- Lacosamide was excluded due to insufficient data

Yasiry Z & SD Shorvon, *Seizure* 2014

REFRACTORY THERAPY

- Anesthetic
  - ✓Propofol
  - ✓Midazolam
  - ✓Thiopental
  - ✓Pentobarbital
- Ketamine
- Ketogenic diet
- Immunologic therapy
- Electroconvulsive therapy (ECT)
- Surgery

PROPOFOL

- Potentiation of GABA receptor binding
- NMDA antagonism
- Lipid-soluble emulsion that results in rapid onset and offset
- Hypotension and bradycardia
- Propofol infusion syndrome (PRIS)

MIDAZOLAM

- Used to induce coma
- Lacks propylene glycol diluent
- Hepatic metabolism, active metabolite is renally eliminated

PENTOBARBITAL

- Long acting barbiturate
- Causes significant cardiovascular and respiratory depression and hypotension
- Needs vasopressor support
- Half-life of 15-48 hrs, but may take days to weeks for complete elimination

KETAMINE

- NMDA receptor antagonist
- Stable hemodynamic profile
- Potential for increasing intracranial pressure

Ketamine use in the treatment of refractory status epilepticus.

Synowiec AS[1], Singh DS, Yenugadhati V, Valeriano JP, Schramke CJ, Kelly KM.

- Retrospective review
- 11 patients
- Dose 0.45 to 2.1 mg/kg/h

Synowiec AS et al., *Epilepsy Res* 2013

Ketamine use in the treatment of refractory status epilepticus.

Synowiec AS[1], Singh DS, Yenugadhati V, Valeriano JP, Schramke CJ, Kelly KM.

- Adverse reactions
  - ✓Psychiatric symptoms
  - ✓Increased ICP
  - ✓Increased secretion of saliva
  - ✓Increased intraocular pressure
  - ✓Arrhythmia
  - ✓Neurotoxicity

Synowiec AS et al., *Epilepsy Res* 2013

ALTERNATIVE THERAPY

- Therapeutic hypothermia
- Immunomodulatory therapy
- Deep brain stimulation
- Ketogenic diet
- Surgery
- Electroconvulsive therapy
- Vagal nerve stimulation

ORIGINAL ARTICLE

Hypothermia for Neuroprotection in Convulsive Status Epilepticus

Stephane Legriel, M.D., Virginie Lemiale, M.D., Maleka Schenck, M.D., Jonathan Chelly, M.D., et al., for the HYBERNATUS Study Group*

- 11 French ICU
- 270 patients
- Treatment:
  - ✓32 to 34^{0}C for 24 hours in addition to standard care
  - ✓standard care

Legriel S, et al., *NEJM* 2016

ORIGINAL ARTICLE

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- Functional Outcome at 90 days
  - ✓ Glasgow Outcome Scale (GOS) of 5
- Hypothermia group 49%
- Control group 43%

Legriel S, et al., *NEJM* 2016

ORIGINAL ARTICLE

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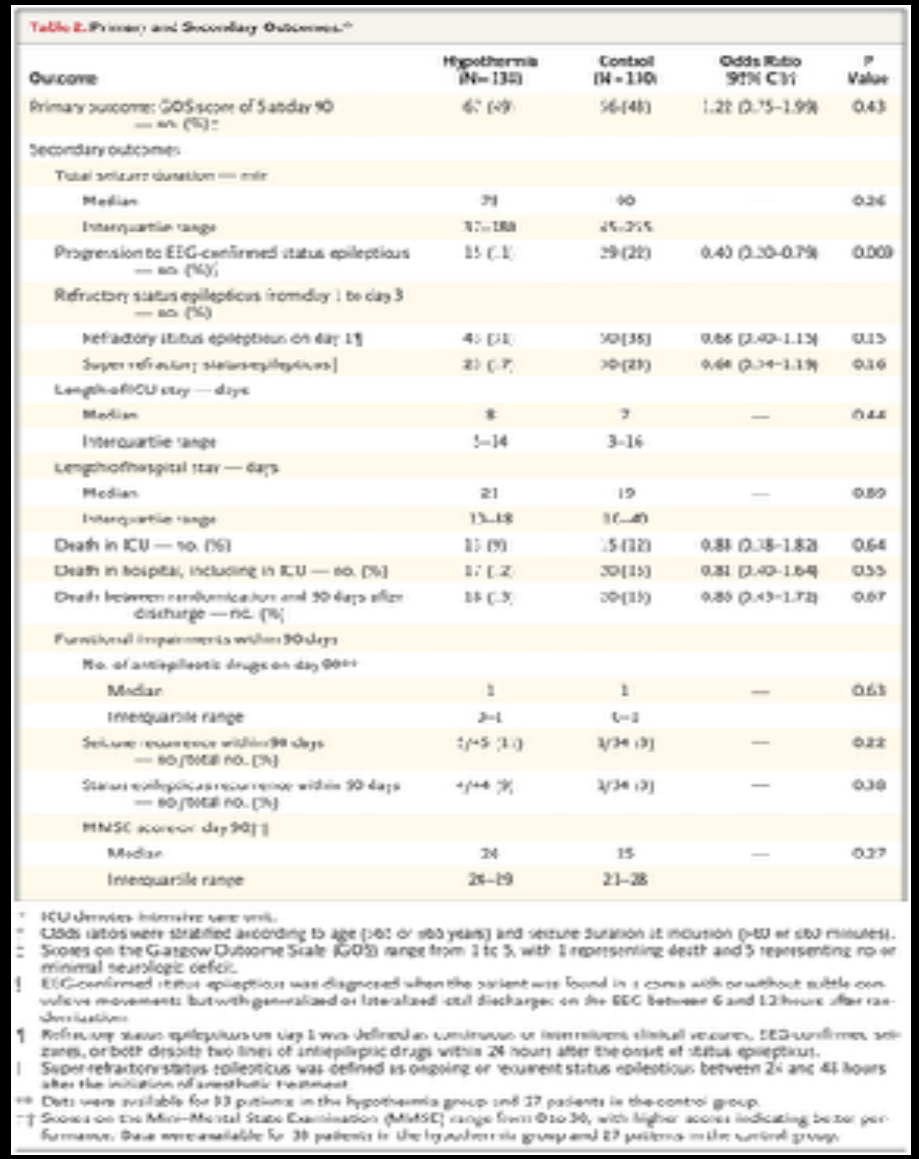


Table 2. Primary and Secondary Outcomes.*

Outcome	Hypothermia (N=130)	Control (N=130)	Odds Ratio 95% CI†	P Value
Primary outcome: GOS score of 5 at day 90 — no. (%)‡	67 (49)	56 (48)	1.22 (0.75–1.99)	0.43
Secondary outcomes				
Total seizure duration — min				
Median	79	90	—	0.26
Interquartile range	37–188	45–255		
Progression to EEG-confirmed status epilepticus — no. (%)§	15 (11)	29 (22)	0.40 (0.20–0.79)	0.009
Refractory status epilepticus from day 1 to day 3 — no. (%)¶				
Refractory status epilepticus on day 1¶	43 (33)	50 (38)	0.86 (0.49–1.53)	0.15
Super-refractory status epilepticus‖	21 (16)	30 (23)	0.64 (0.34–1.19)	0.16
Length of ICU stay — days				
Median	8	7	—	0.44
Interquartile range	5–14	3–16		
Length of hospital stay — days				
Median	21	19	—	0.89
Interquartile range	13–38	10–46		
Death in ICU — no. (%)	11 (9)	15 (12)	0.88 (0.38–1.82)	0.64
Death in hospital, including in ICU — no. (%)	17 (13)	30 (23)	0.81 (0.40–1.64)	0.55
Death between randomization and 90 days after discharge — no. (%)	16 (13)	20 (15)	0.86 (0.43–1.73)	0.67
Functional impairments within 90 days				
No. of antiepileptic drugs on day 90**				
Median	1	1	—	0.63
Interquartile range	0–1	0–2		
Seizure recurrence within 90 days — no./total no. (%)	17/45 (38)	3/34 (9)	—	0.22
Status epilepticus recurrence within 90 days — no./total no. (%)	4/44 (9)	3/34 (9)	—	0.39
MMSE score on day 90††				
Median	24	25	—	0.27
Interquartile range	20–29	23–28		

* ICU denotes intensive care unit.
† Odds ratios were stratified according to age (≤65 or >65 years) and seizure duration at induction (≤60 or >60 minutes).
‡ Scores on the Glasgow Outcome Scale (GOS) range from 1 to 5, with 1 representing death and 5 representing no or minimal neurologic deficit.
§ EEG-confirmed status epilepticus was diagnosed when the patient was found in a coma with or without subtle convulsive movements but with generalized or lateralized ictal discharges on the EEG between 6 and 12 hours after randomization.
¶ Refractory status epilepticus on day 1 was defined as continuous or intermittent clinical seizures, EEG confirmed seizures, or both despite two lines of antiepileptic drugs within 24 hours after the onset of status epilepticus.
‖ Super-refractory status epilepticus was defined as ongoing or recurrent status epilepticus between 24 and 48 hours after the initiation of anesthetic treatment.
** Data were available for 33 patients in the hypothermia group and 27 patients in the control group.
†† Scores on the Mini–Mental State Examination (MMSE) range from 0 to 30, with higher scores indicating better performance. Data were available for 38 patients in the hypothermia group and 27 patients in the control group.

Legriel S, et al., *NEJM* 2016

Pediatric super-refractory status epilepticus treated with allopregnanolone.

Broomall E[1], Natale JE, Grimason M, Goldstein J, Smith CM, Chang C, Kanes S, Rogawski MA, Wainwright MS.

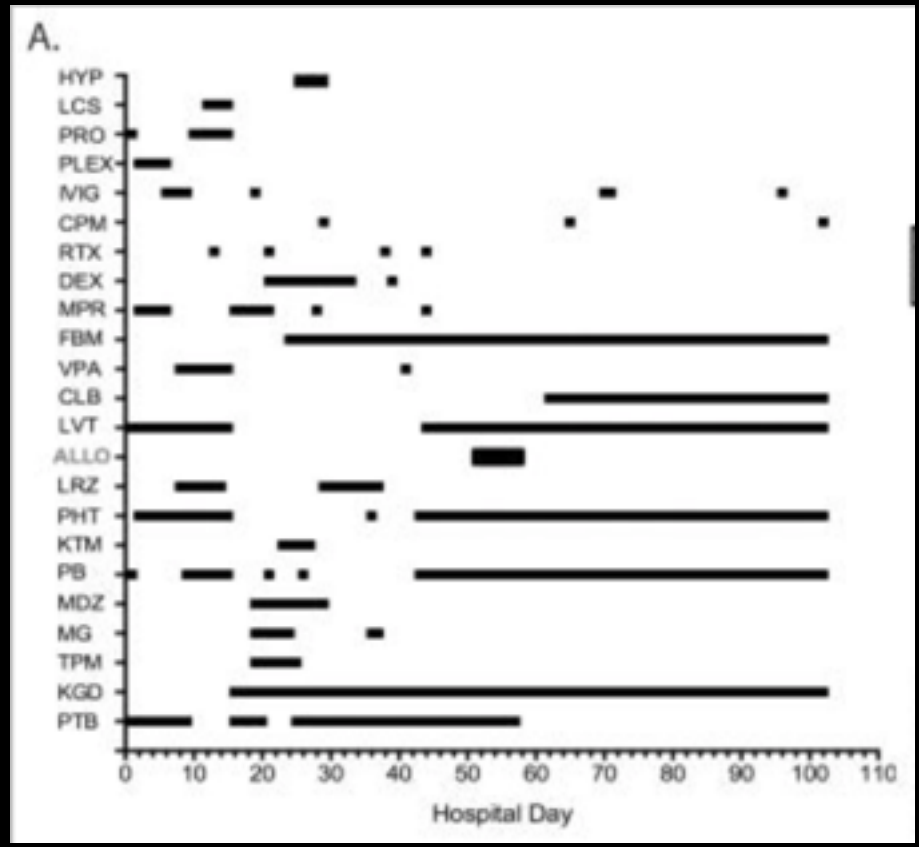
- Neurosteroid allopregnanolone
  - Metabolite of progesterone
- Acts as a positive modulator of synaptic and extrasynaptic $GABA_A$ receptors

Broomall E, et al., *Ann Neurol* 2014

Pediatric super-refractory status epilepticus treated with allopregnanolone.

Broomall E[1], Natale JE, Grimason M, Goldstein J, Smith CM, Chang C, Kanes S, Rogawski MA, Wainwright MS.

- Patient 1
- Reading
- Learning to play the piano



Broomall E, et al., *Ann Neurol* 2014

Pediatric super-refractory status epilepticus treated with allopregnanolone.

Broomall E[1], Natale JE, Grimason M, Goldstein J, Smith CM, Chang C, Kanes S, Rogawski MA, Wainwright MS.

- Patient 2
- HD 15
- Meeting milestones

- No adverse effects of treatment
- Allowed withdrawal of all general anesthetic infusions

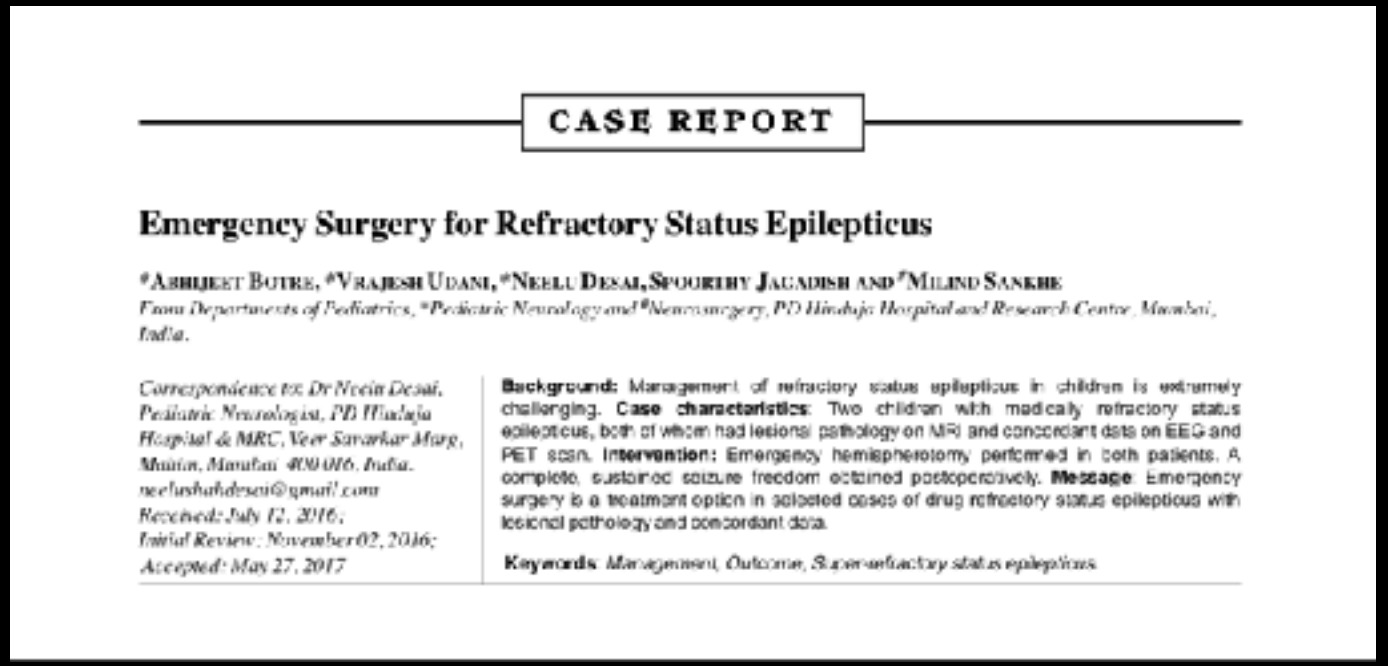
Broomall E, et al., *Ann Neurol* 2014

Successful management of super-refractory status epilepticus with thalamic deep brain stimulation.

Lehtimäki K[1], Långsjö JW[2], Ollikainen J[1], Heinonen H[3], Möttönen T[1], Tähtinen T[1], Haapasalo J[1], Tenhunen J[4], Katisko J[5], Öhman J[1], Peltola J[1].

- 17 y.o. not resolved with propofol, thiopental, midazolam, or ketamine coadministered with multiple AEDs and IVig
- Centromedian nucleus of thalamus

Lehtimaki K, et al., *Ann Neurol* 2017



CASE REPORT

Emergency Surgery for Refractory Status Epilepticus

*Abhijeet Botre, *Vrajesh Udani, *Neelu Desai, Spoorthy Jagadish and †Milind Sankhe
*From Departments of Pediatrics, *Pediatric Neurology and †Neurosurgery, PD Hinduja Hospital and Research Centre, Mumbai, India.*

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Received: July 12, 2016; Initial Review: November 02, 2016; Accepted: May 27, 2017

Background: Management of refractory status epilepticus in children is extremely challenging. **Case characteristics:** Two children with medically refractory status epilepticus, both of whom had lesional pathology on MRI and concordant data on EEG and PET scan. **Intervention:** Emergency hemispherotomy performed in both patients. A complete, sustained seizure freedom obtained postoperatively. **Message:** Emergency surgery is a treatment option in selected cases of drug refractory status epilepticus with lesional pathology and concordant data.

Keywords: *Management, Outcome, Super-refractory status epilepticus.*

- 4.5 month old boy with right hemispheric cortical dysplasia
- Right hemispherotomy was done after 10 days
- 7 y.o. boy with 3 yr. history of right-sided focal motor seizure
- Progressive left cerebral atrophy
- Hemispherotomy done after 7 days

Seizure. 2017 Apr;47:1-4. doi: 10.1016/j.seizure.2017.02.011. Epub 2017 Feb 24.

New-onset refractory status epilepticus treated with vagus nerve stimulation: A case report.

Yamazoe T[1], Okanishi T[2], Yamamoto A[3], Yamada T[4], Nishimura M[5], Fujimoto A[1], Enoki H[1], Yokota T[1], Sato K[1], Yamamoto T[1].

Author information

KEYWORDS: Anti-glutamate receptor encephalitis; Autoimmune encephalitis; New-onset refractory status epilepticus; Rapid titration; Status epilepticus; Vagus nerve stimulation

- 24 yr. old man presented with delirium and shouting of meaningless words, 2 days after fever related to URI
- Pt developed clonic seizure on left side of his face that sometimes evolved into generalized tonic0clonic seizure
- At 14 months, pt. was bedridden, unable to communicate verbally, required a PEG, on IV midazolam
- 1 yr. seizure free after VNS

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