Convulsive Status Epilepticus

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Disclosure

Funding/research grants: ERF, PERF, NIH, EFA, ETP, Empatica, Upsher Smith.

Consulting: Upsher Smith, UCB, Engage.

Board Membership and related committees: ACNS, Pediatric Status Epilepticus Research Group (pSERG), NORSE Institute, CCERMC

Associate Editor: Wyllie's Treatment of Epilepsy, 6th & 7th editions

Device donations: Empatica, SmartWatch, Neuroelectrics

IP/Patents: Epilepsy/status diagnosis, Seizure detection, Seizure prediction, Epilepsy/disease visualization and management (Trivox)

Clinical care: Billing for electrophysiological studies and clinical care through BCH

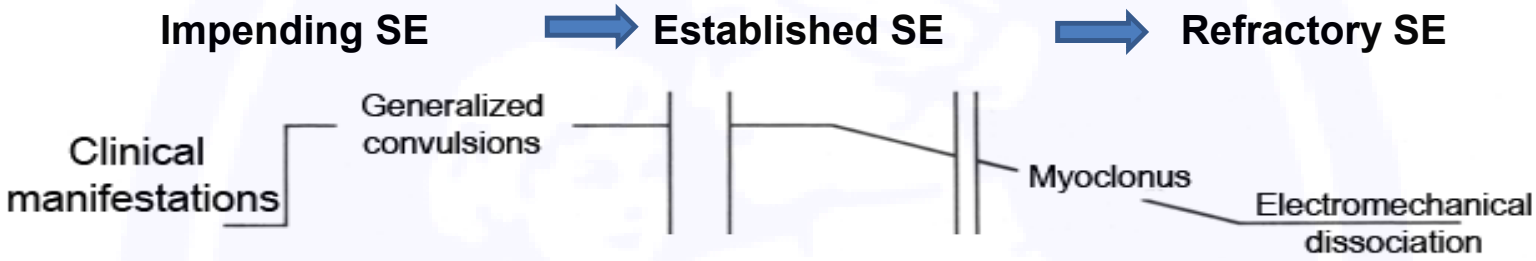
Spouse: Karen Stannard, MD, bills for electrophysiological studies and clinical care through BCH

Off-label discussion of seizure, epilepsy,
and status epilepticus diagnosis & treatment options

Learning Objectives

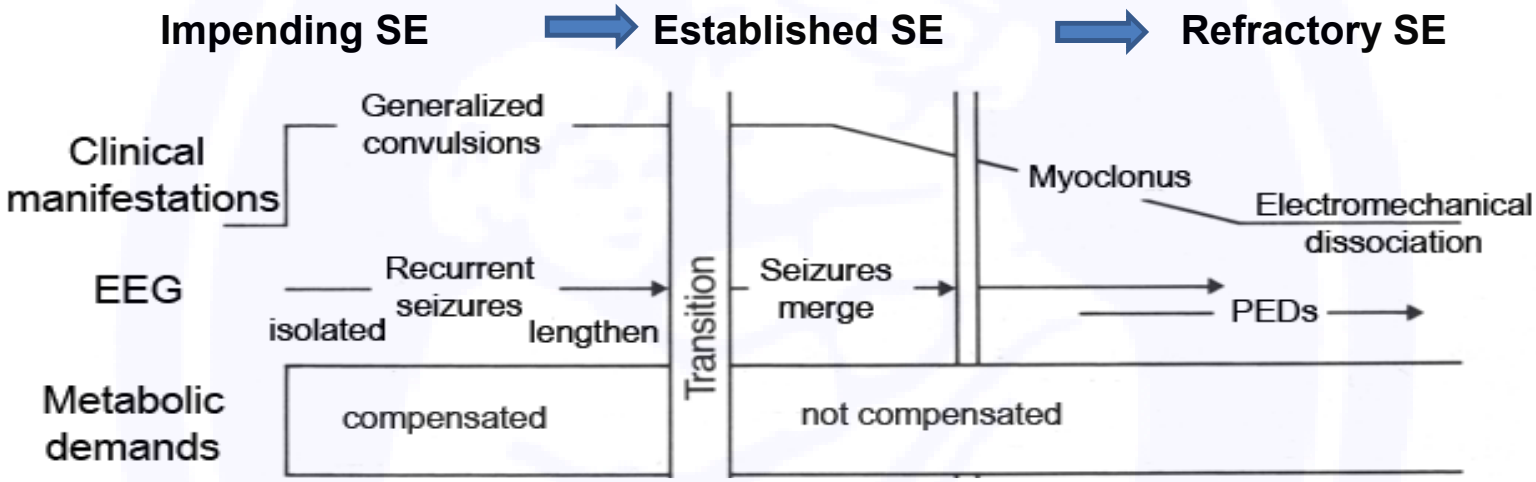
- Discuss current management approach to pediatric convulsive status epilepticus
  - Diagnosis
  - Treatment
  - Etiological workup
- Discuss gaps in pediatric convulsive status epilepticus care

Status Epilepticus Evolution



Modified from Lothman. Neurology, 1990

Status Epilepticus Evolution



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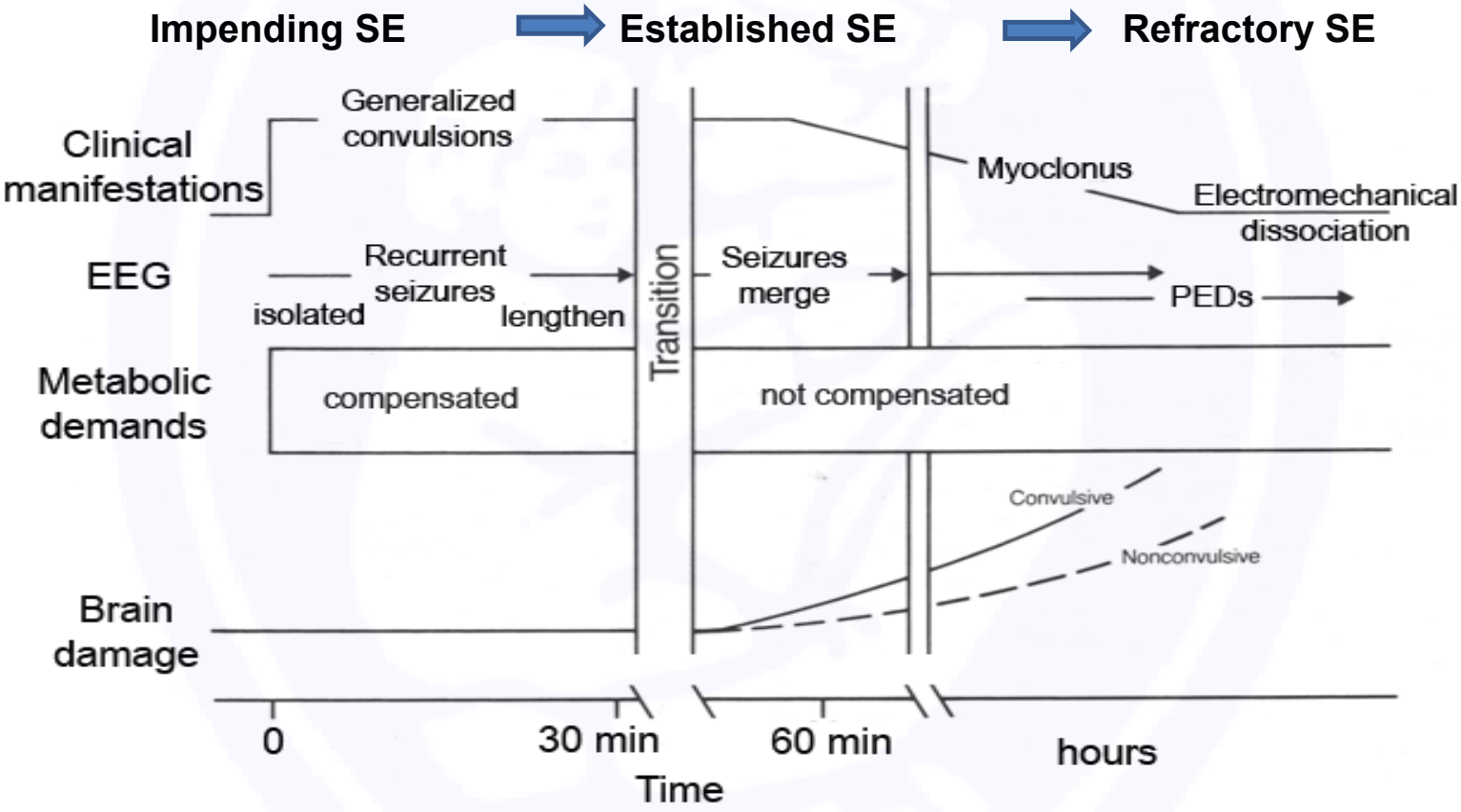
Status Epilepticus Evolution



Modified from Lothman. Neurology, 1990

Treatment

If no IV access available -

midazolam (IM 0.2 mg/kg OR IN 0.2 mg/kg OR Buccal 0.5 mg/kg; maximum 10 mg)

OR **diazepam** (PR 0.2-0.5 mg/kg; maximum 20 mg; OR IN 0.2-0.3 mg/kg; maximum 20 mg)

If IV access is available-

lorazepam IV 0.1 mg/kg (maximum 4 mg, can repeat once)

OR **diazepam** IV 0.15-0.2 mg/kg (maximum 10 mg, can repeat once)

AES 2019

Effectiveness of Non-IV First Line Treatment

No treatment

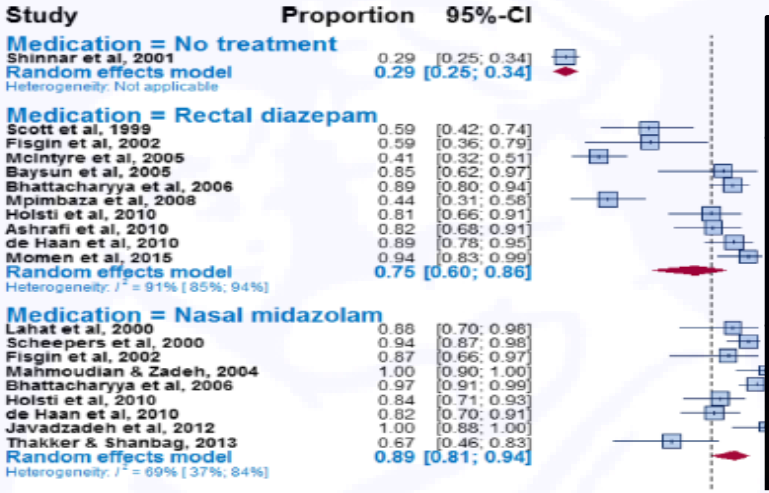
0.29

Sanchez Fernandez et al., Epilepsia 2017

AES 2019

Effectiveness of Non-IV First Line Treatment

No treatment	0.29
DZP PR	0.75
MDZ IN	0.89



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AES 2019

Effectiveness of Non-IV First Line Treatment

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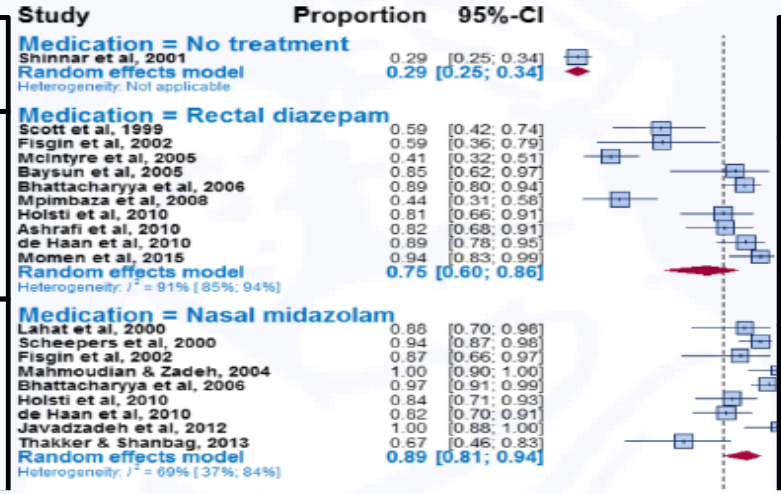
MDZ IN		0.89



Sanchez Fernandez et al., Epilepsia 2017

AES 2019

Effectiveness of Non-IV First Line Treatment

No treatment	Medication = No treatment Shinnar et al, 2001 0.29 [0.25; 0.34] Random effects model 0.29 [0.25; 0.34] Heterogeneity: Not applicable	0.29
DZP PR	Medication = Rectal diazepam Scott et al, 1999 0.59 [0.42; 0.74] Fisgin et al, 2002 0.59 [0.36; 0.79] McIntyre et al, 2005 0.41 [0.32; 0.51] Baysun et al, 2005 0.85 [0.62; 0.97] Bhattacharyya et al, 2006 0.89 [0.80; 0.94] Mpimbaza et al, 2008 0.44 [0.31; 0.58] Holsti et al, 2010 0.81 [0.66; 0.91] Ashrafi et al, 2010 0.82 [0.68; 0.91] de Haan et al, 2010 0.89 [0.78; 0.95] Momen et al, 2015 0.94 [0.83; 0.99] Random effects model 0.75 [0.60; 0.86] Heterogeneity: I^2 = 91% [85%; 94%]	0.75
MDZ IN	Medication = Nasal midazolam Lahat et al, 2000 0.88 [0.70; 0.96] Scheepers et al, 2000 0.94 [0.87; 0.98] Fisgin et al, 2002 0.87 [0.66; 0.97] Mahmoudian & Zadeh, 2004 1.00 [0.90; 1.00] Bhattacharyya et al, 2006 0.97 [0.91; 0.99] Holsti et al, 2010 0.84 [0.71; 0.93] de Haan et al, 2010 0.82 [0.70; 0.91] Javadzadeh et al, 2012 1.00 [0.88; 1.00] Thakker & Shanbag, 2013 0.67 [0.46; 0.83] Random effects model 0.89 [0.81; 0.94] Heterogeneity: I^2 = 69% [37%; 84%]	0.89
MDZ bucc	Medication = Buccal midazolam Scott et al, 1999 0.75 [0.59; 0.87] Baysun et al, 2005 0.78 [0.56; 0.93] McIntyre et al, 2005 0.65 [0.55; 0.74] Mpimbaza et al, 2008 0.73 [0.59; 0.85] Talukdar & Chakrabarty, 2009 0.85 [0.73; 0.93] Ashrafi et al, 2010 1.00 [0.93; 1.00] Tonekaboni et al, 2012 0.41 [0.24; 0.59] Random effects model 0.73 [0.60; 0.83] Heterogeneity: I^2 = 78% [54%; 89%]	0.73
MDZ IM	Medication = Intramuscular midazolam Chamberlain et al, 1997 0.92 [0.64; 1.00] Shah & Deshmukh, 2005 0.90 [0.78; 0.97] Momen et al, 2015 0.96 [0.86; 1.00] Portela et al, 2015 0.88 [0.62; 0.98] Welch et al, 2015 0.68 [0.55; 0.80] Random effects model 0.88 [0.73; 0.95] Heterogeneity: I^2 = 74% [37%; 90%]	0.88
LRZP IN	Medication = Nasal lorazepam Ahmad et al, 2006 0.75 [0.64; 0.84] Arya et al, 2011 0.83 [0.72; 0.91] Random effects model 0.79 [0.70; 0.86] Heterogeneity: I^2 = 32%	0.79
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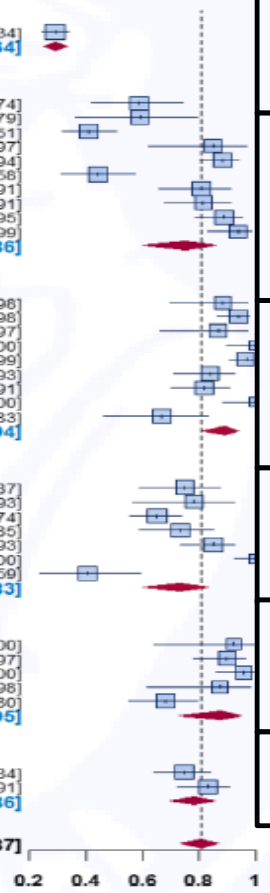

Sanchez Fernandez et al., Epilepsia 2017

Treatment

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midazolam (IM 0.2 mg/kg OR IN 0.2 mg/kg OR Buccal 0.5 mg/kg; maximum 10 mg)

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If IV access is available-

lorazepam IV 0.1 mg/kg (maximum 4 mg, can repeat once)

OR **diazepam IV** 0.15-0.2 mg/kg (maximum 10 mg, can repeat once)

fosphenytoin IV 20 mg PE/kg (maximum 1500 PE mg, can repeat 5-10 mgPE/kg if needed)

OR **levetiracetam IV** 30-60 mg/kg (maximum 4500 mg, can repeat 30 mg/kg if needed)

OR **valproic acid IV** 20 mg/kg (maximum 3000 mg, can repeat 20 mg/kg if needed)

OR **phenobarbital IV** 20 mg/kg (can repeat 5-10 mg/kg if needed)

can repeat the ASM above (as indicated in brackets) or give a different one if seizure persists

ConSEPT Trial

Open-label Randomized Trial of Two Anticonvulsant Medications for Pediatric Status Epilepticus

233 Children with benzodiazepine refractory SE (3 mos to 16 yrs) 	Levetiracetam 40 mg/kg 	Phenytoin 20 mg/kg 
Clinical seizure cessation 5 minutes after complete infusion	50% (60/119)	60% (68/114)

LEV is not superior to PHT for second line management of pediatric CSE.

Dalziel et al., Lancet, 2019

EcLiPSE Trial

Open-label Randomized Trial of Two Anticonvulsant Medications for Pediatric Status Epilepticus		
286 Children with benzodiazepine refractory SE 	Levetiracetam 40 mg/kg 	Phenytoin 20 mg/kg 
Time from randomization to clinical cessation of Convulsive Status Epilepticus	70% (106/152)	64% (86/134)
LEV is not superior to PHT for second line management of pediatric CSE.		

Lyttle et al., Lancet, 2019

Established Status Epilepticus Treatment Trial

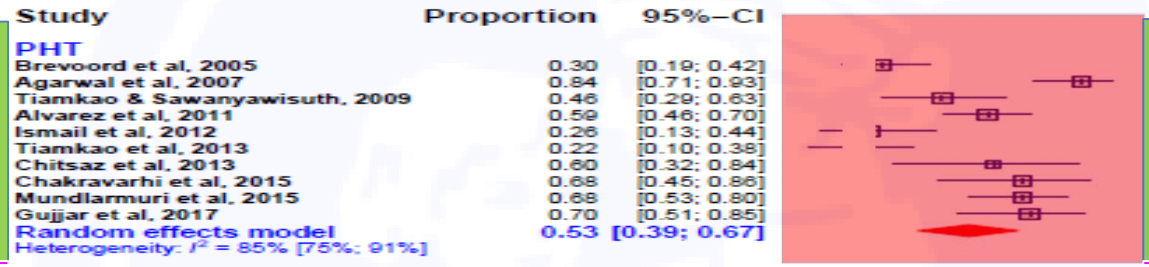
Trial of Three Anticonvulsant Medications for Status Epilepticus			
384 Children and adults with benzodiazepine refractory SE 	Levetiracetam 60 mg/kg 	Phenytoin 20 mg/kg 	Valproate 40 mg/kg 
No clinical seizures and improved responsiveness at 60 minutes	47% (68/145)	45% (53/118)	46% (56/121)

No significant differences in rates of seizure cessation or adverse events.

Kapur et al., NEJM, 2019

Effectiveness of Second Line Treatment

PHT



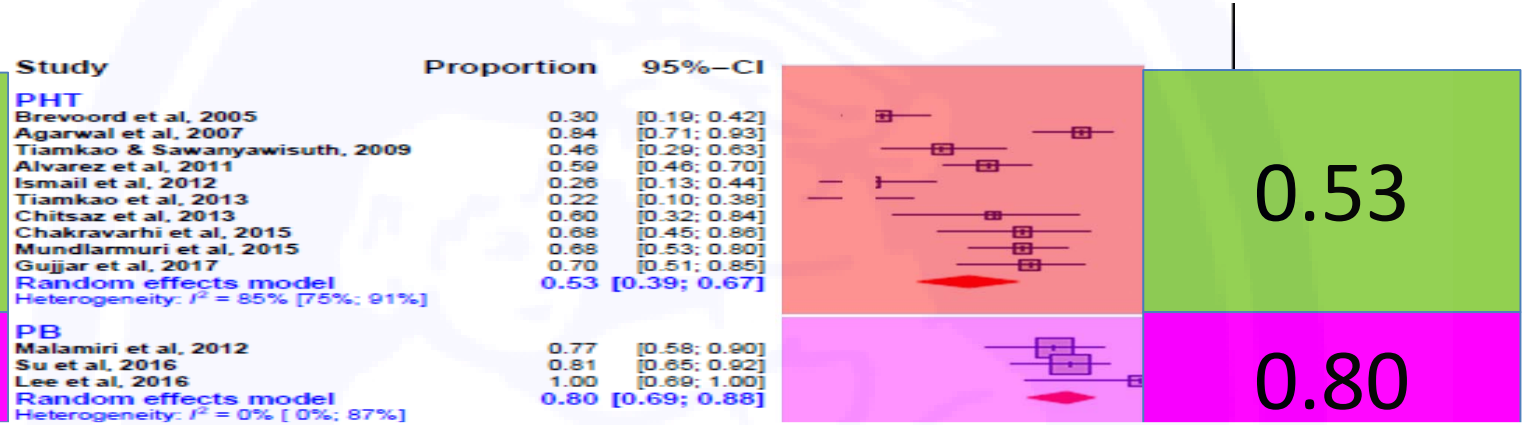
0.53

Sanchez Fernandez et al., Neurology 2019

Effectiveness of Second Line Treatment

PHT

PB



0.53

0.80

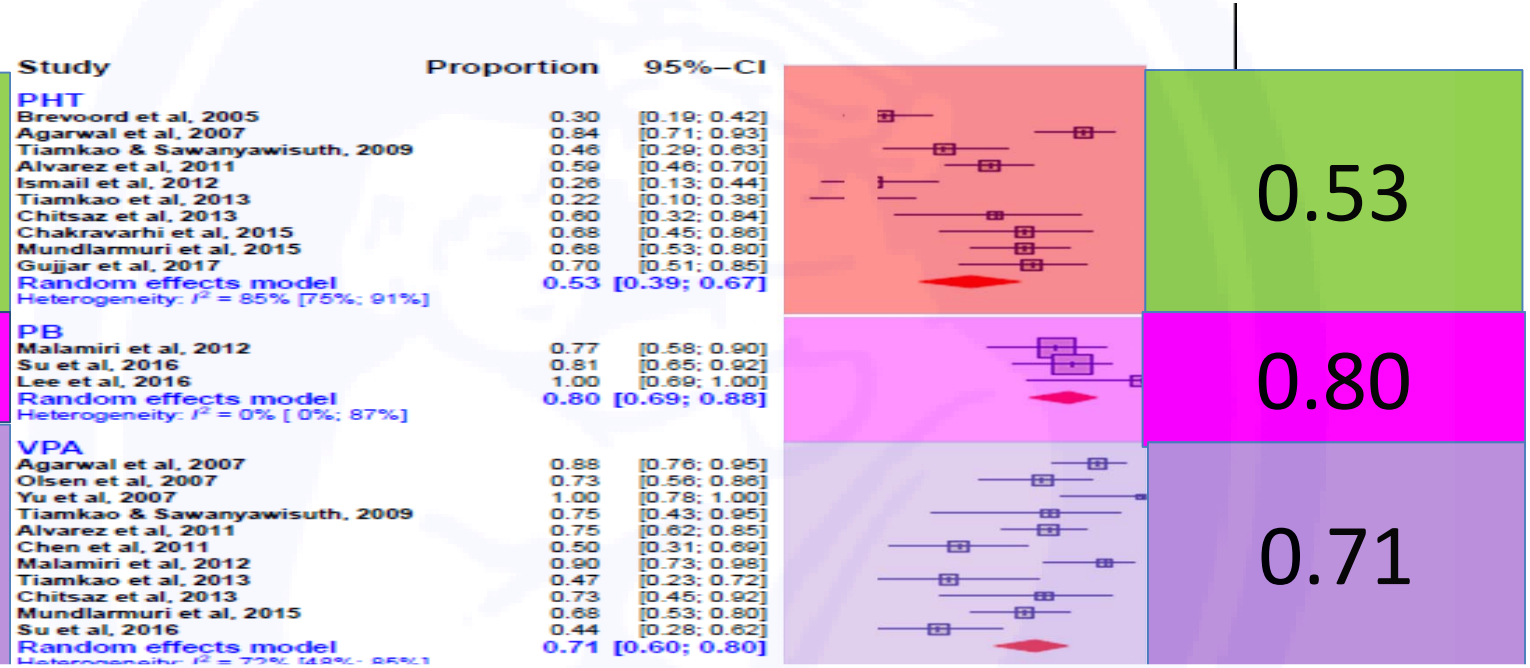
Sanchez Fernandez et al., Neurology 2019

Effectiveness of Second Line Treatment

PHT

PB

VPA



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Sanchez Fernandez et al., Neurology 2019

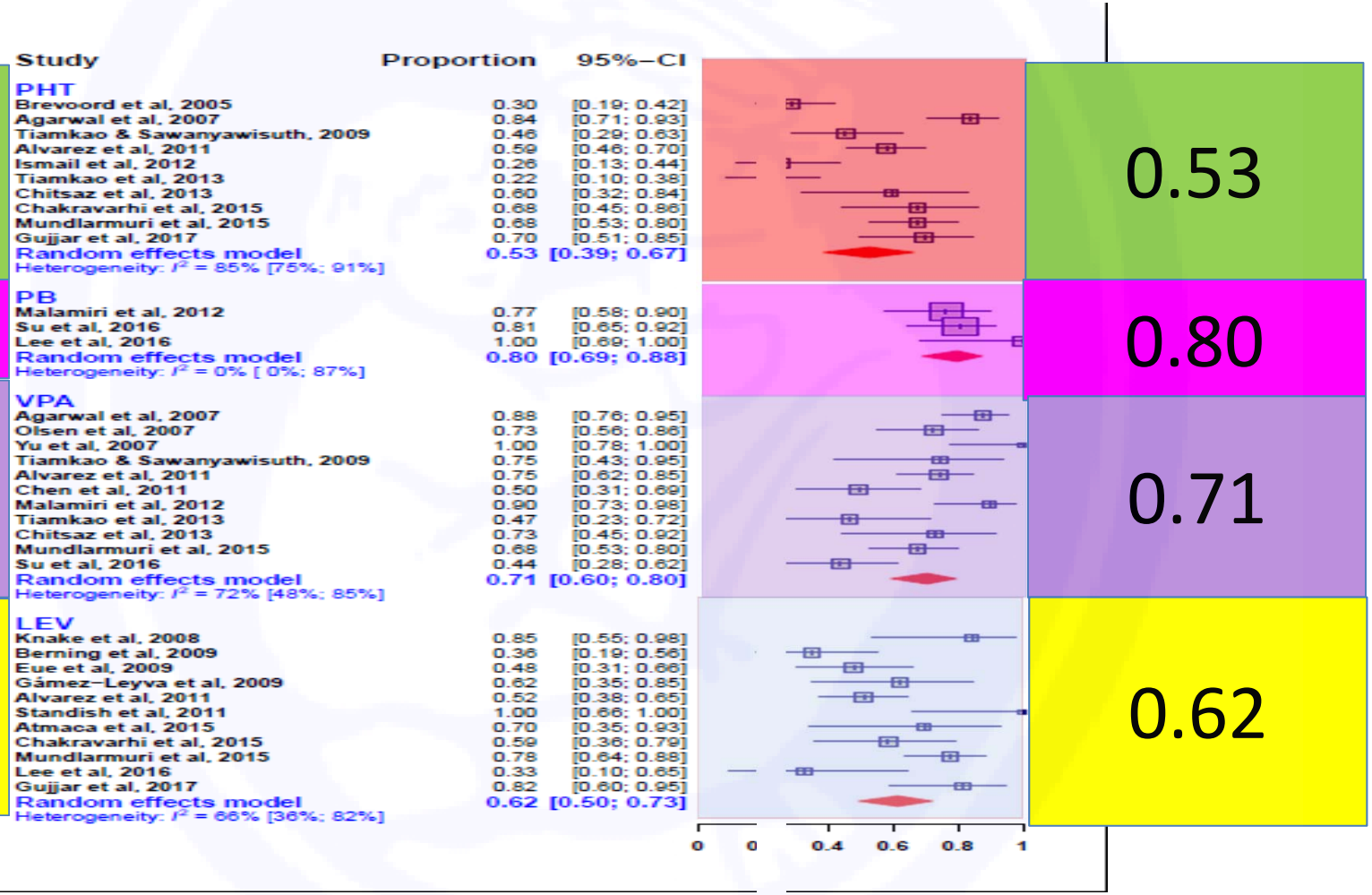
Effectiveness of Second Line Treatment

PHT

PB

VPA

LEV



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Sanchez Fernandez et al., Neurology 2019

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OR **levetiracetam IV** 30-60 mg/kg (maximum 4500 mg, can repeat 30 mg/kg if needed)

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can repeat the ASM above (as indicated in brackets) or give a different one if seizure persists

midazolam (IV load with 0.2 mg/kg at 2 mg/min infusion, titrate with EEG, maximum 2 mg/kg/h)

OR **pentobarbital** (IV load with 5– 15 mg/kg at 50 mg/min, titrate with EEG, maximum 5 mg/kg/h)

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OR **propofol** (IV load with 1-2 mg/kg at 20 mcg/kg/min, caution with doses >65 mcg/kg/min and prolonged application due to propofol infusion syndrome)

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Treatment

Early Status Epilepticus

IV fosphenytoin 20 mg PE/kg (maximum 1500 PE mg, can repeat 5-10 mgPE/kg if needed)
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Treatment

Early Status Epilepticus

Established Status Epilepticus

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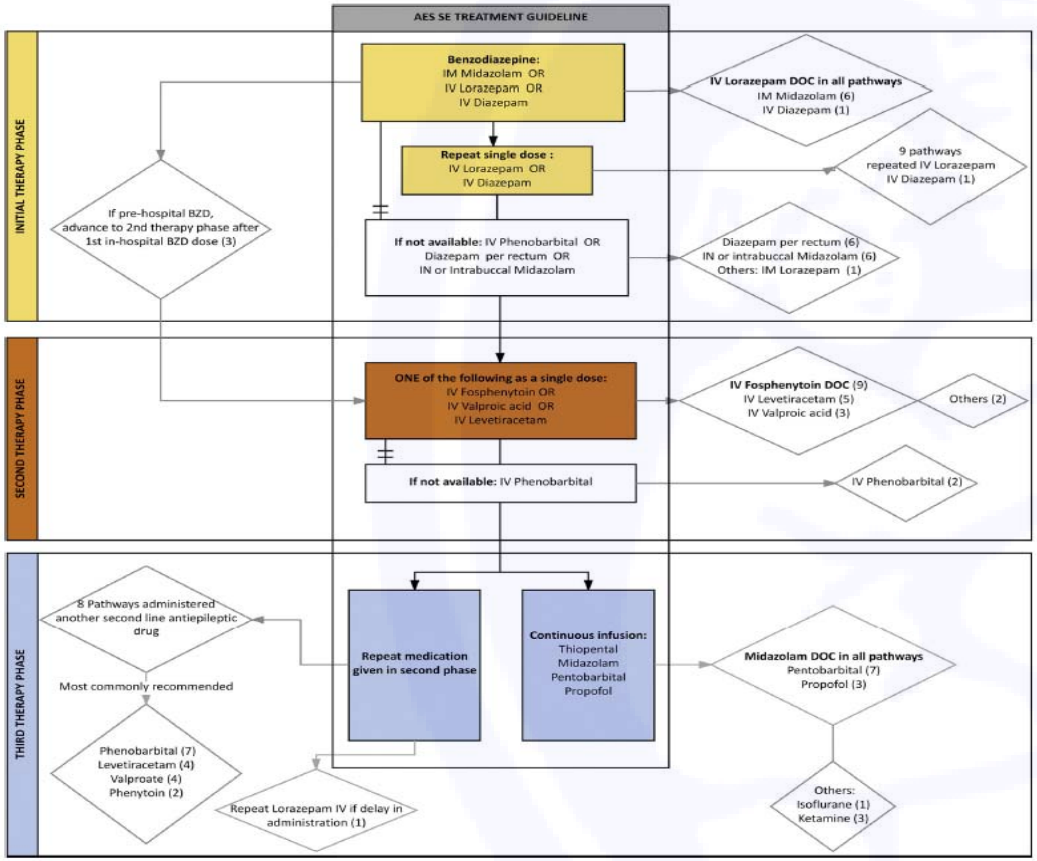
Refractory Status Epilepticus

AES Guideline



Modified based on Glauser et al., Epilpesia, 2016
AES Treatment Guideline

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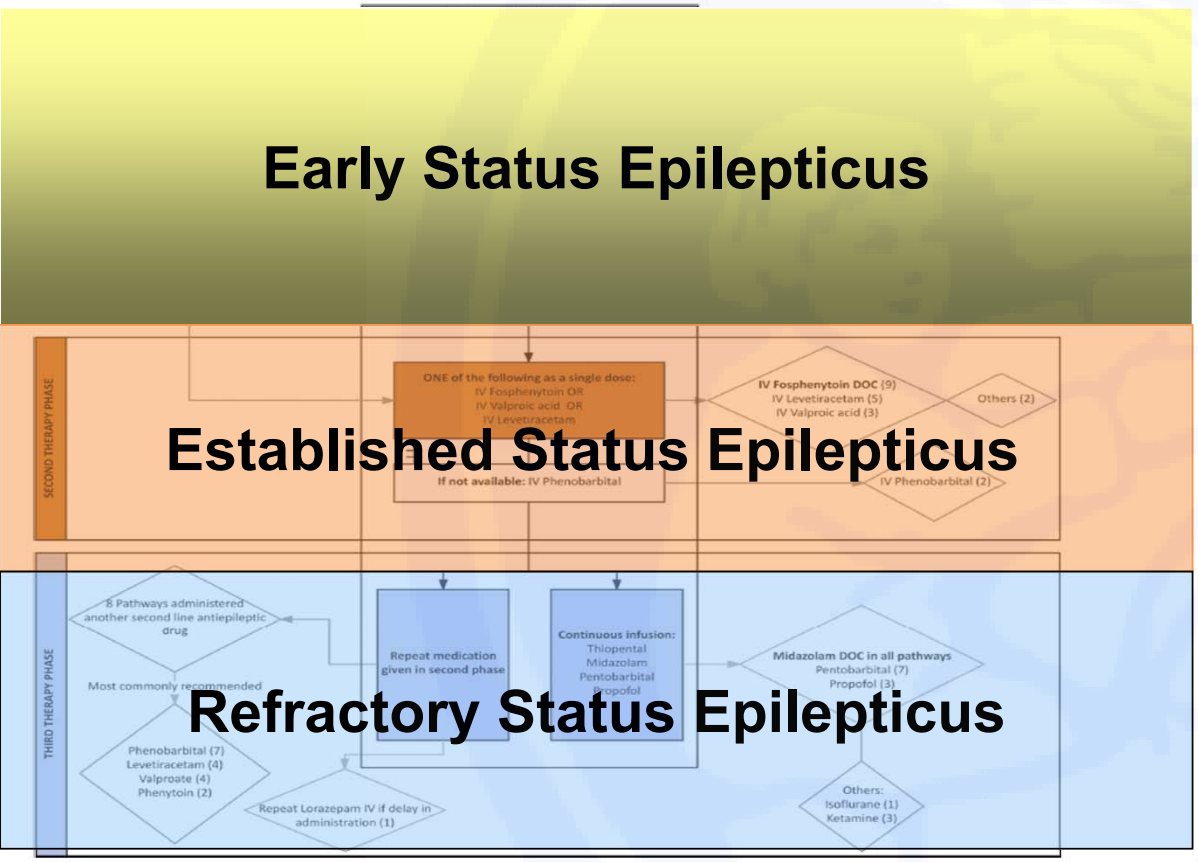

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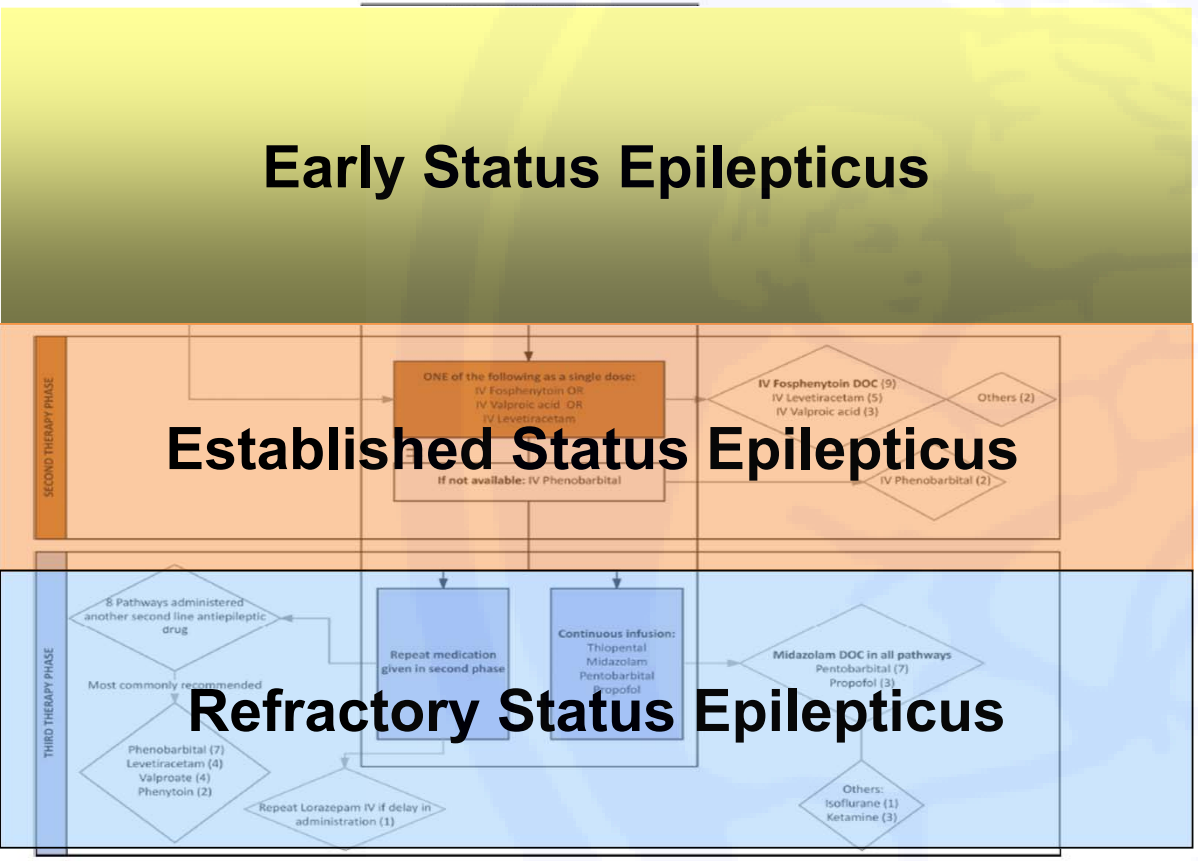
AES Treatment Guideline

Variability in Care



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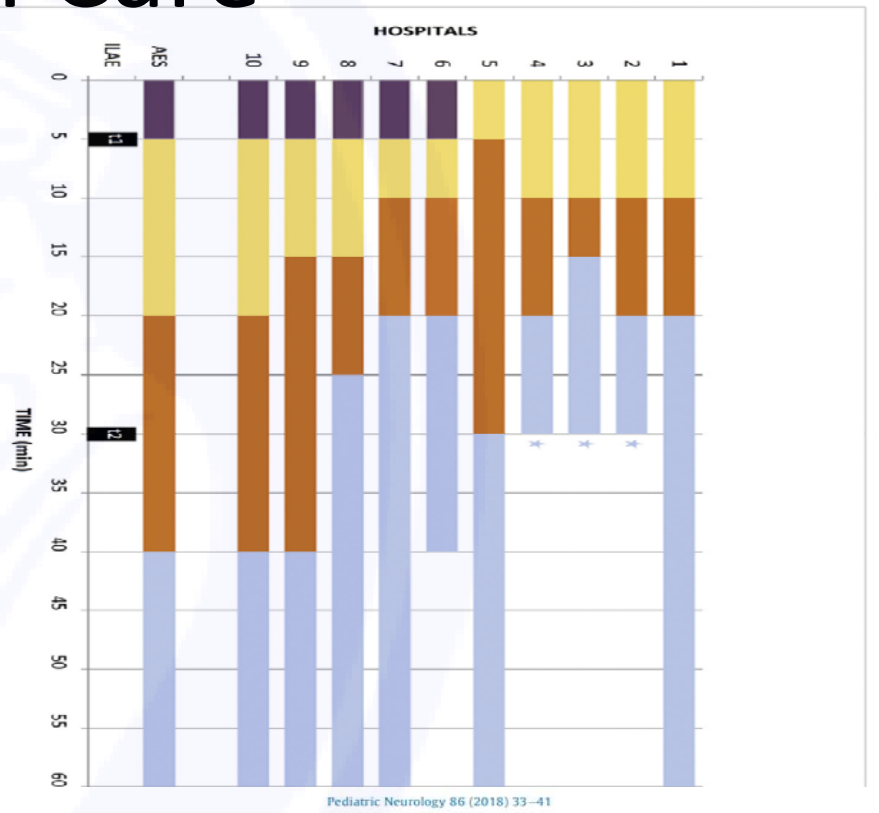
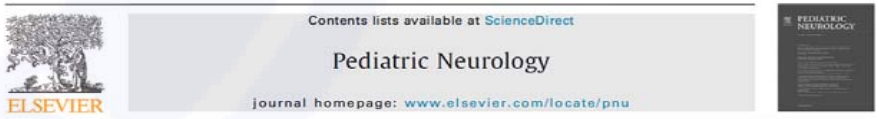


Pediatric Neurology 86 (2018) 33–41



Original Article

Hospital Emergency Treatment of Convulsive Status Epilepticus: Comparison of Pathways From Ten Pediatric Research Centers

Alejandra Vasquez, MD[a], Marina Gaínza-Lein[a,b],

Etiology and related workup

CABs

Hypoxia
Hemodynamics
Hyperthermia
Hypoglycemia
Hyponatremia

If no IV access available -
midazolam (IM 0.2 mg/kg OR IN 0.2 mg/kg OR Buccal 0.5 mg/kg; maximum 10 mg)
OR rectal diazepam (0.2-0.5 mg/kg; maximum 20 mg)
If IV access is available-
IV lorazepam 0.1 mg/kg (maximum 4 mg, can repeat once)
OR diazepam (PR 0.2-0.5 mg/kg; maximum 20 mg; OR IN 0.2-0.3 mg/kg; maximum 20 mg)

IV fosphenytoin 20 mg PE/kg (maximum 1500 PE mg, can repeat 5-10 mgPE/kg if needed)
OR IV levetiracetam 30-60 mg/kg (maximum 4500 mg, can repeat 30 mg/kg if needed)
OR IV valproic acid 20 mg/kg (maximum 3000 mg, can repeat 20 mg/kg if needed)
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can repeat the ASM above (as indicated in brackets) or give a different one if seizure persists

Labs
EKG
Imaging

midazolam (load with 0.2 mg/kg at 2 mg/min infusion, titrate with EEG, maximum 2 mg/kg/h)
OR pentobarbital (load with 5– 15 mg/kg at 50 mg/min, titrate with EEG, maximum 5 mg/kg/h)
OR thiopental (load with 2–7 mg/kg at 50 mg/min, titrate with EEG, maximum 5 mg/kg/h)
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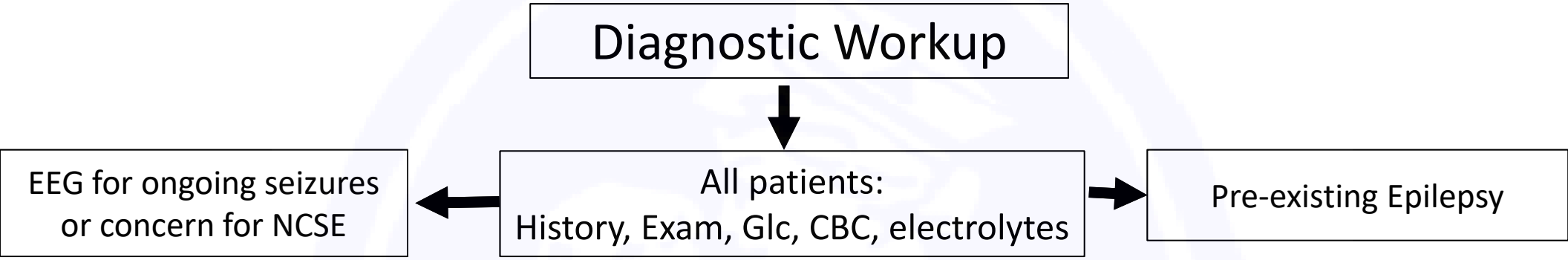
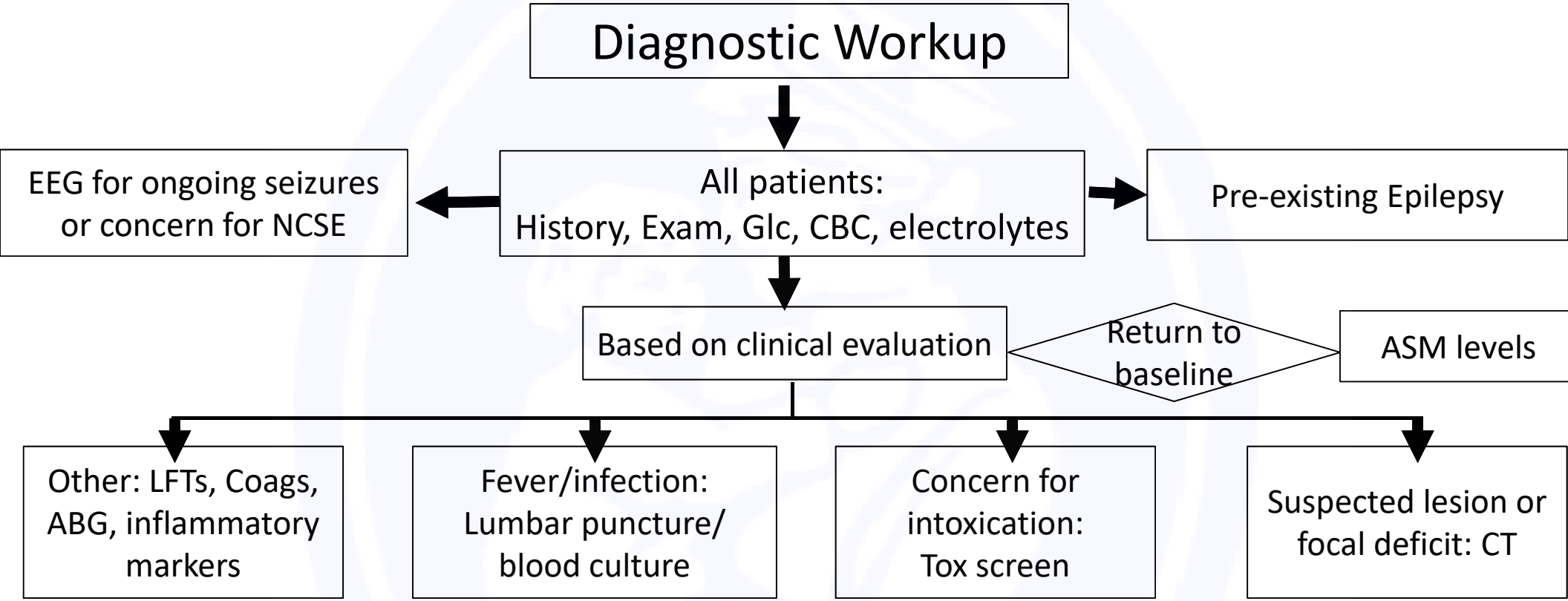
EEG Monitoring

Diagnostic Workup



Modified after Sculier et al. 2019;
Courtesy of Barcia, Sanchez Fernandez, et al. 2019



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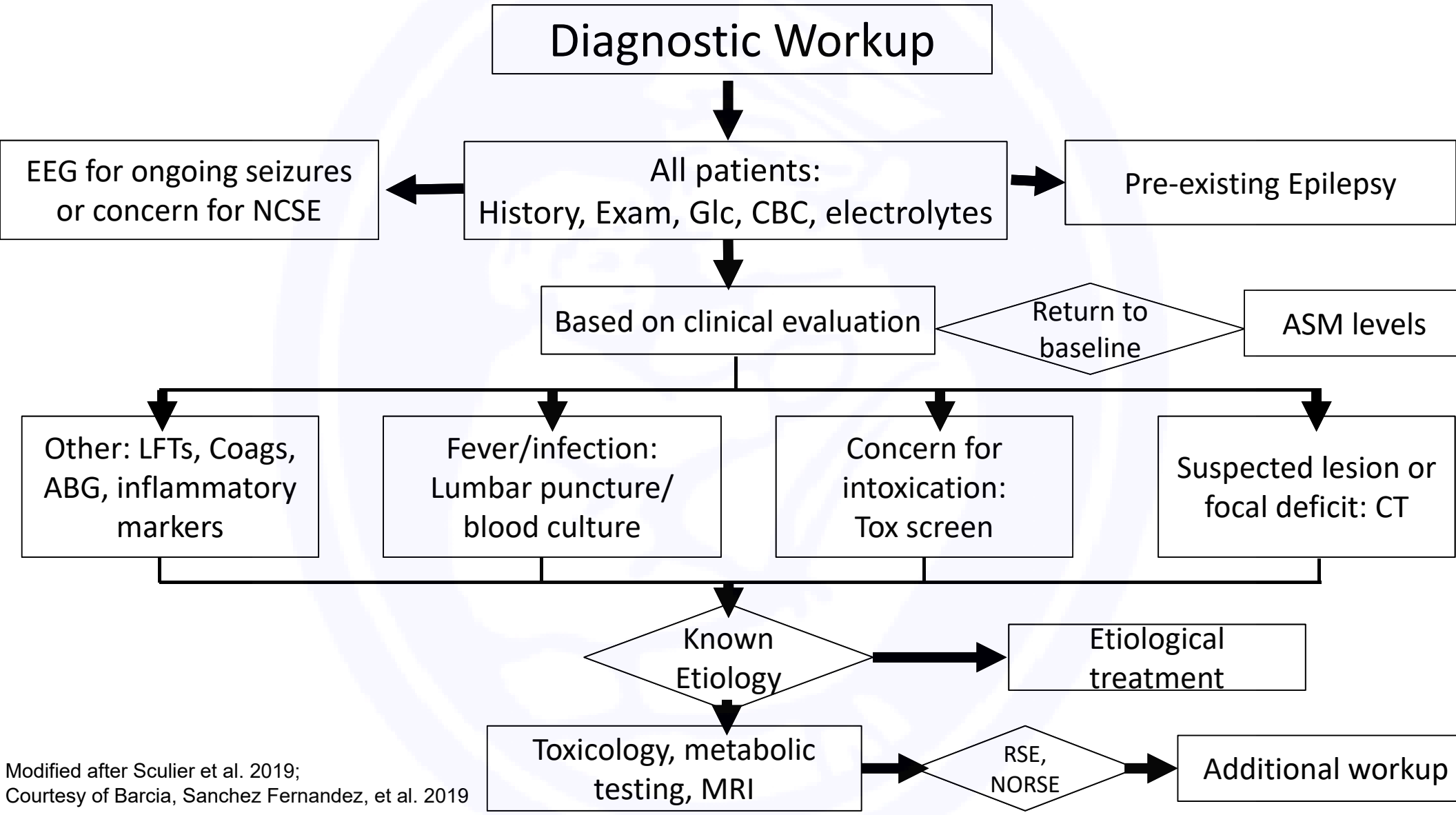

Modified after Sculier et al. 2019;
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Survival

- Short-term mortality of SE ranges from:
  - **0-4%** in children
  - **2-40%** in adults
- Long-term mortality after an episode of SE, including in-hospital deaths:
  - **0 to 22%** in children
  - **0 to 57%** in adults
- Risk factors include:
  - Etiology
  - Older age
  - SE duration
  - Development of subsequent epilepsy

Sculier et al., 2017

Recurrence of (SR)SE

- Recurrent SE range:
  - 10-56% in children
  - 13-37% in a mixed population of adults and children

- Predictors of recurrent SE:
  - Age <4 years
  - Female gender
  - Lack of response to the first ASM for SE
  - Remote symptomatic and progressive etiologies

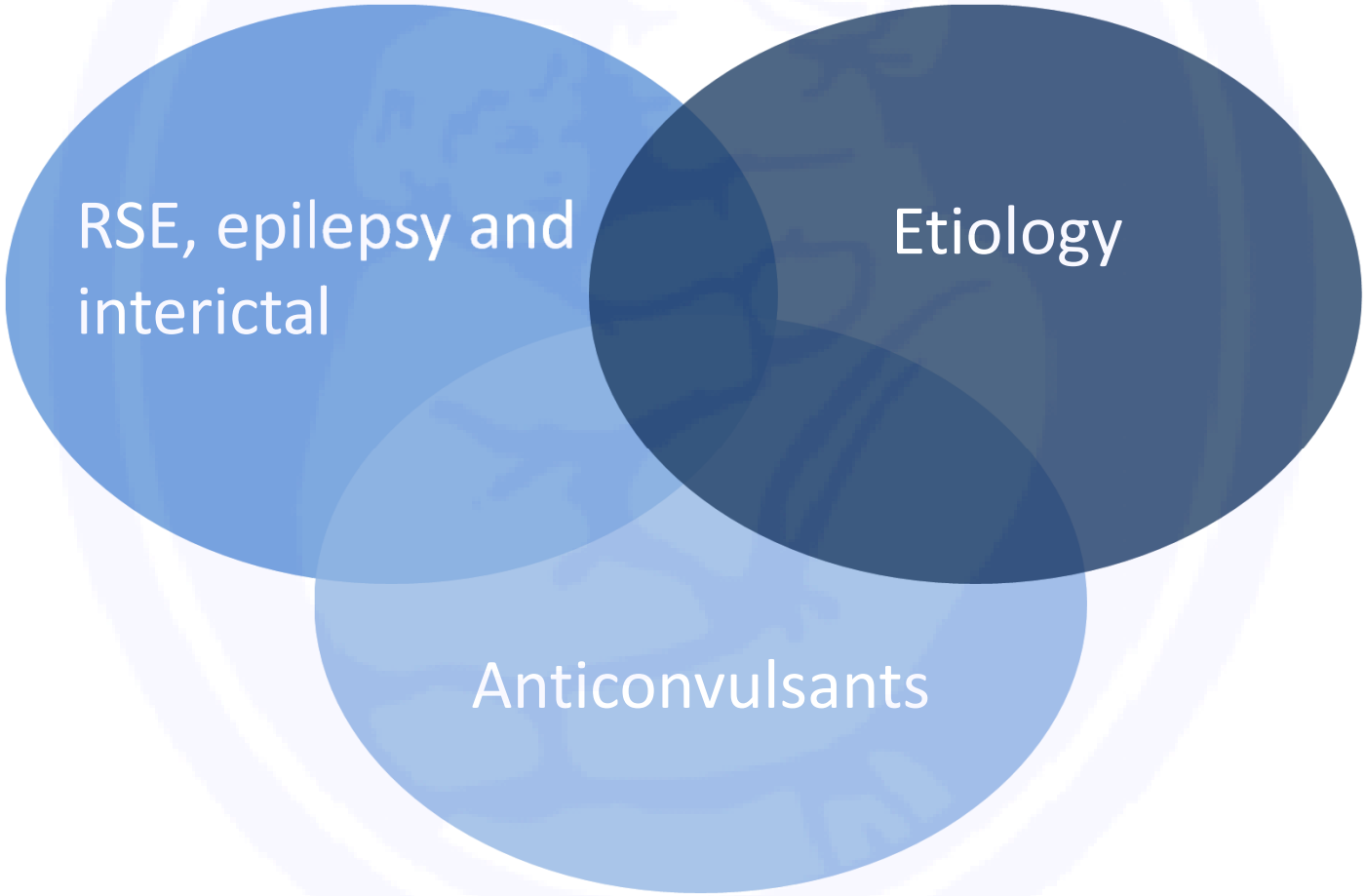
Sculier et al., 2017

Subsequent Epilepsy

- RSE is associated with 87.5% risk of subsequent epilepsy
- Highest onset risk of epilepsy/epilepsy worsening during the first year of follow-up:
  - Pediatric patients 5 to 36%
  - Adults 22 to 41%
- Patients with epilepsy after SE have lower rates of epilepsy remission (66.4 to 80%) than those without SE (55 to 61.5%)

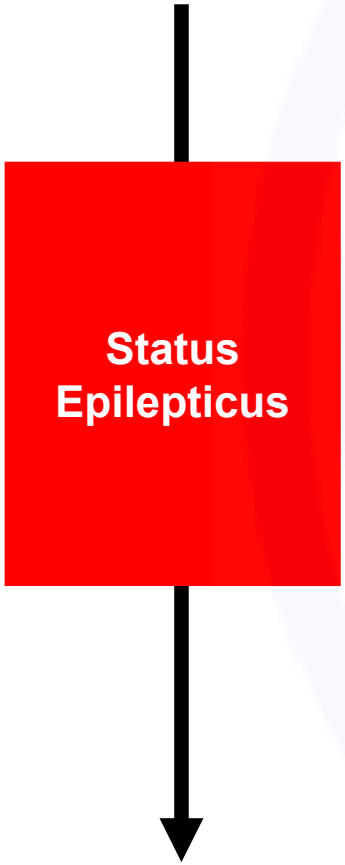
Sculier et al., 2017

Intellectual impairment in RSE



Challenges

Timeline



Identification of Patients at Risk and Prediction

Detection and Warning Systems

Early Status Epilepticus Treatment

Refractory Status Treatment

Etiology and Comorbities

Medication Weaning

Follow up (Epilepsy, Cognition, Quality of life)

pSERG

- Pediatric RCSE was based on little evidence and extrapolated from adult studies and case reports/series in children
- Gaps
  - Risk factors for SE
  - Biomarkers
  - 2nd & 3rd line treatment options
  - Long term outcomes

Sánchez Fernandez et al, Seizure 2014

pSERG Inclusion Criteria

Inclusion Criteria

- ✓ Age 1 month to 21 years old
- ✓ Convulsive seizures at onset (focal or generalized)
- ✓ Seizure duration of 5 minutes or longer
- ✓ Case (Refractory SE)
  - ✓ Failure of 2 or more types ASMs and/or use of Continuous Infusion
- ✓ Control
  - ✓ Cessation of seizure after treatment with one 2nd line ASM

Sánchez Fernandez et al, Seizure 2014

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- ✓ Control
  - ✓ Cessation of seizure after treatment with one 2nd line ASM

Exclusion Criteria

- ✗ Non Convulsive at onset
- ✗ Unclear Seizure onset
- ✗ Nonconvulsive SE with motor manifestations limited to infrequent myoclonic jerks

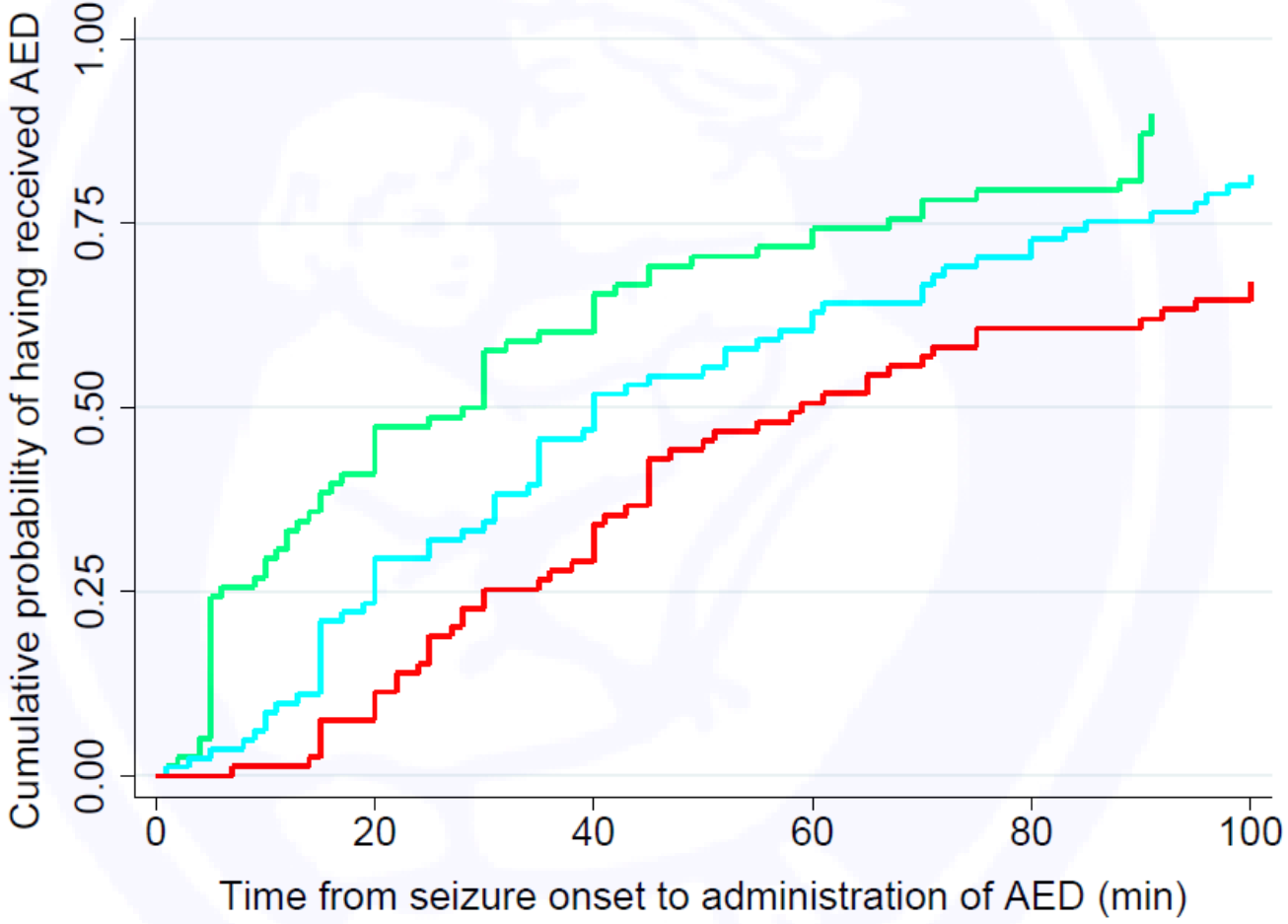
Sánchez Fernandez et al, Seizure 2014

Goals of pSERG

- Foster an evidence based approach to **assessing the current variation in care** and **converting that information to knowledge** for improving the management and prognosis of children with RCSE.
  - Collaboration between pediatric hospitals that care for children with RCSE.
  - Prospective computerized database that provides valuable information on current acute care of children with RCSE.
  - Observational data on the follow-up of children with RCSE and identify biomarkers and predictors of treatment response and long-term outcomes.

Sánchez Fernandez et al, Seizure 2014

Time to Treatment



Sánchez Fernández, I et al. Neurology 2015

What is causing the delay?

- **Intermittent RSE**
- **Out of hospital onset**
- 38% did not receive any ASM prior to hospital arrival
- 1st BZD given (median time)
  - 24.1% at home (5 minutes)
  - 32.6% by EMS (18.5 minutes)
  - 24.8% non-pSERG hospital (55 minutes)
  - 18.4% at pSERG hospital (50 minutes)

ARTICLE

Factors associated with treatment delays in pediatric refractory convulsive status epilepticus

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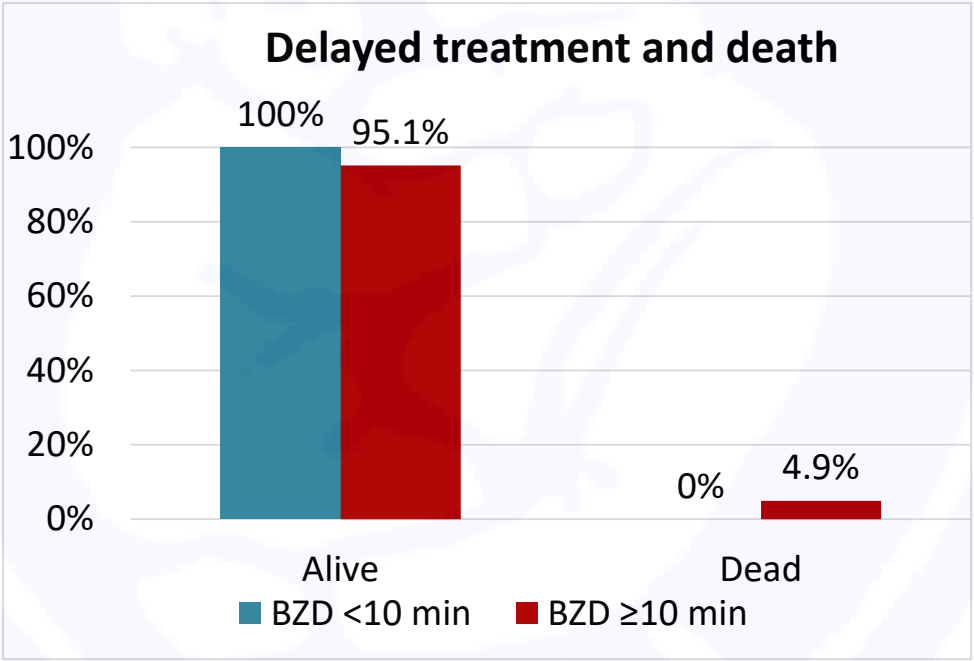
Sánchez Fernández, I et al. Neurology 2018

Delayed first BZD (≥10 min) and association with death

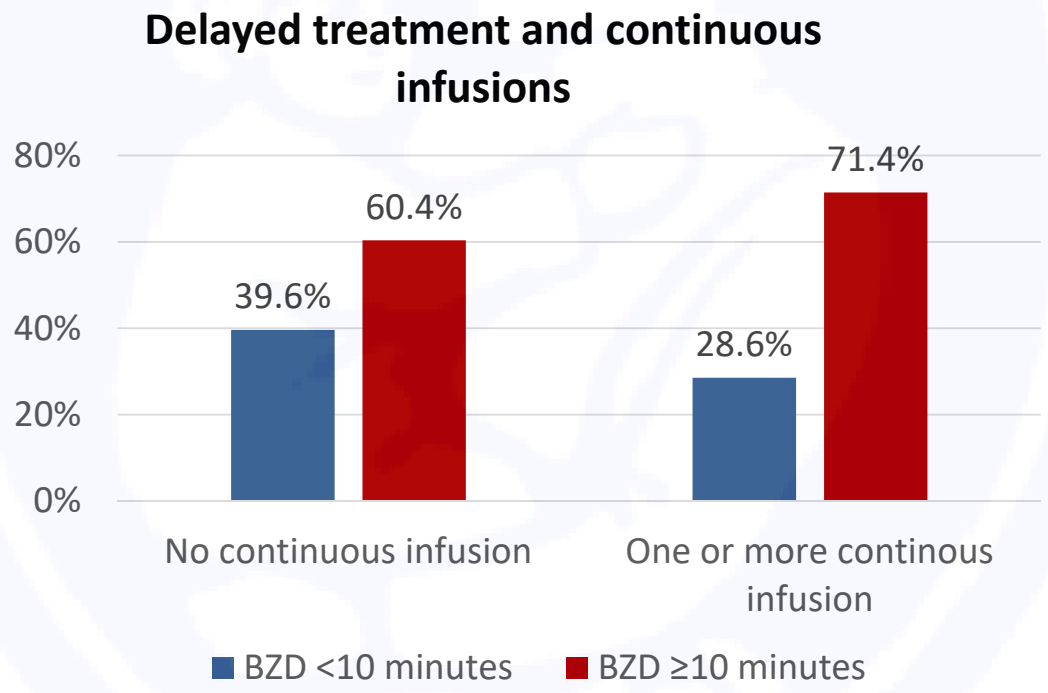
All patients who died prior to hospital discharge (n=7) received the first BZD ≥ 10 minutes (OR 7.33; p<0.05).



Gaínza-Lein M, et al. JAMA Neurology 2018

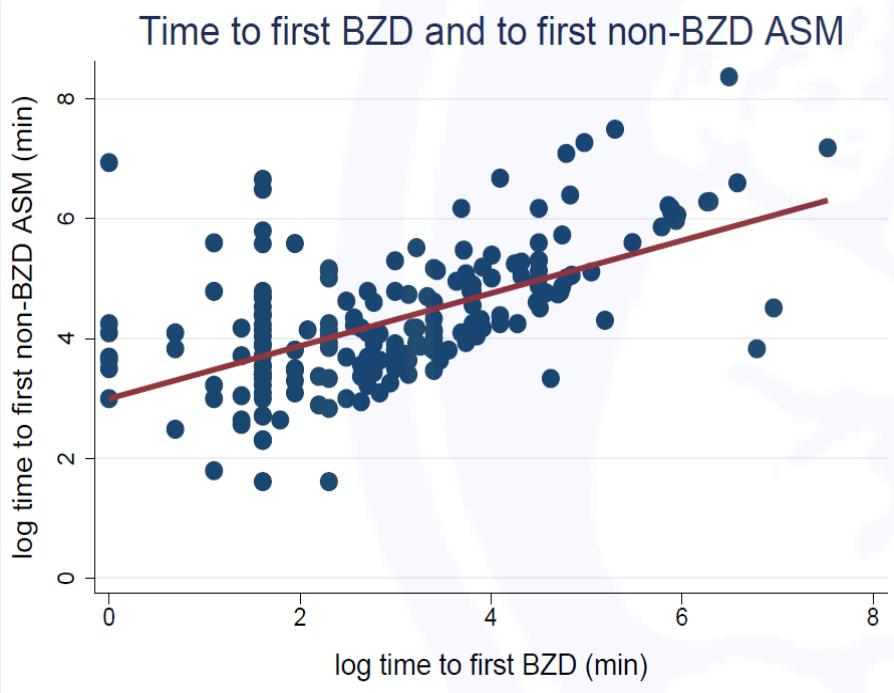
Delayed first BZD (≥10 minutes) and the use of continuous infusion

Out of the 112 (51%) patients who received a continuous infusion for RSE treatment, 80 (71%) were treated with the first BZD ≥ 10 minutes (OR 1.83; p<0.05).



Gaínza-Lein M, et al. JAMA Neurology 2018

Workflow delay



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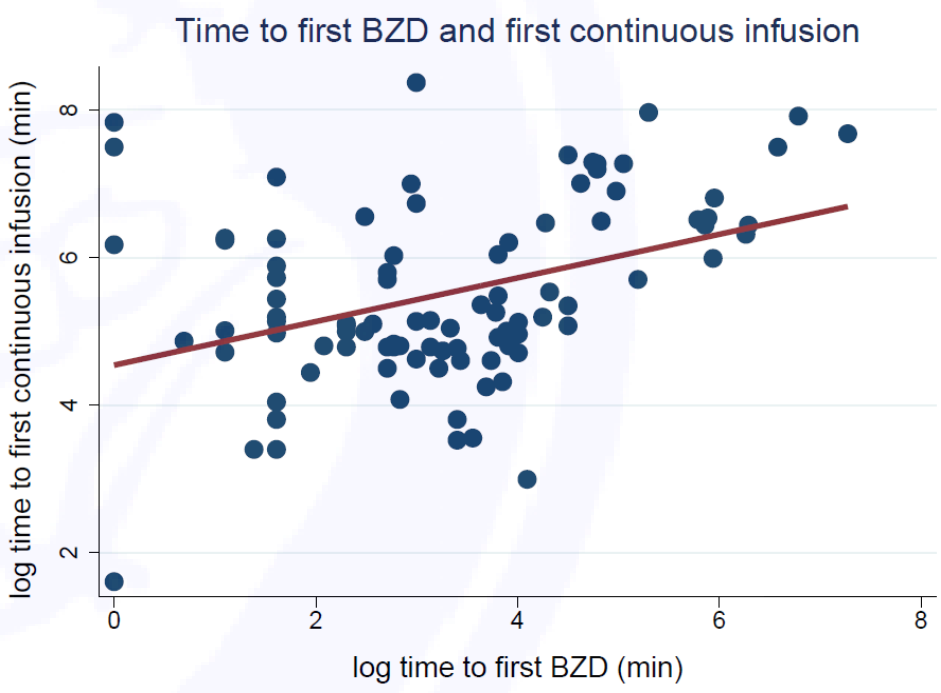

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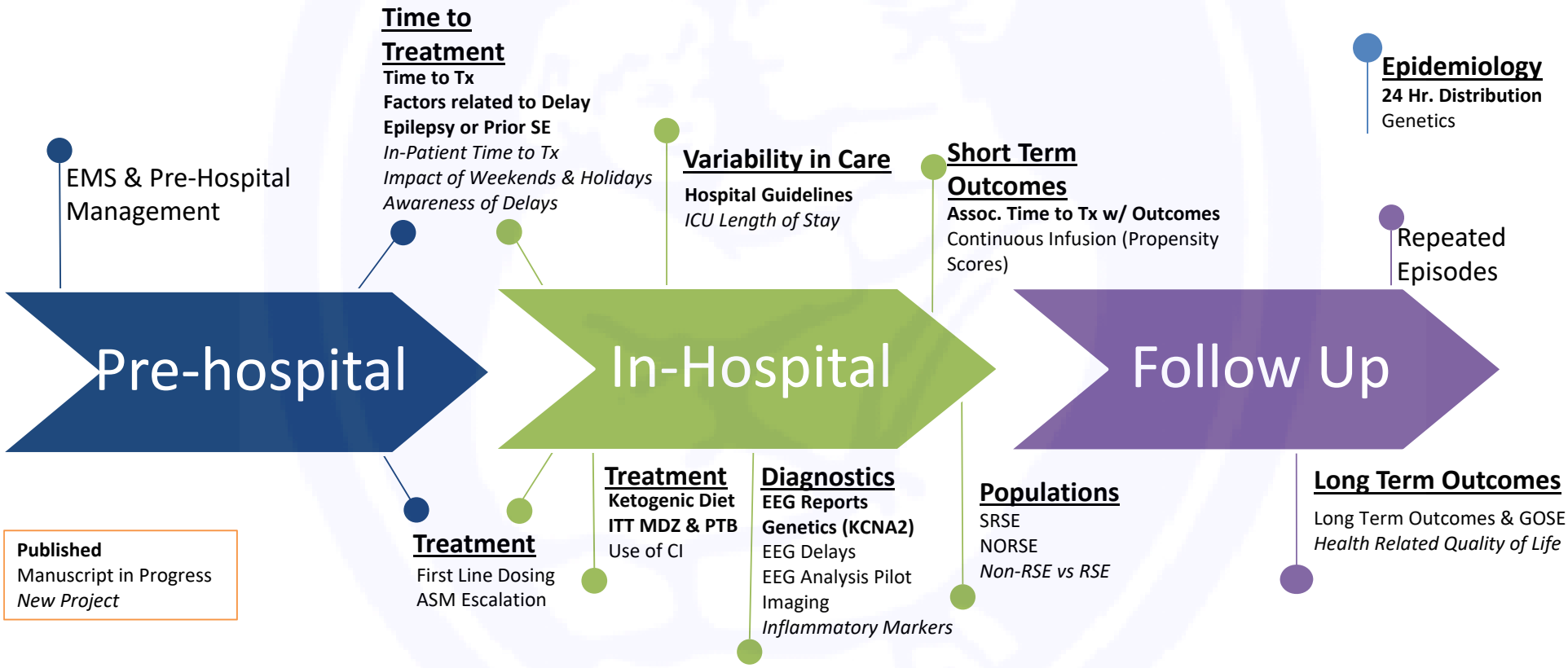
Gaínza-Lein M, et al. JAMA Neurology 2018

pSERG Body of Work

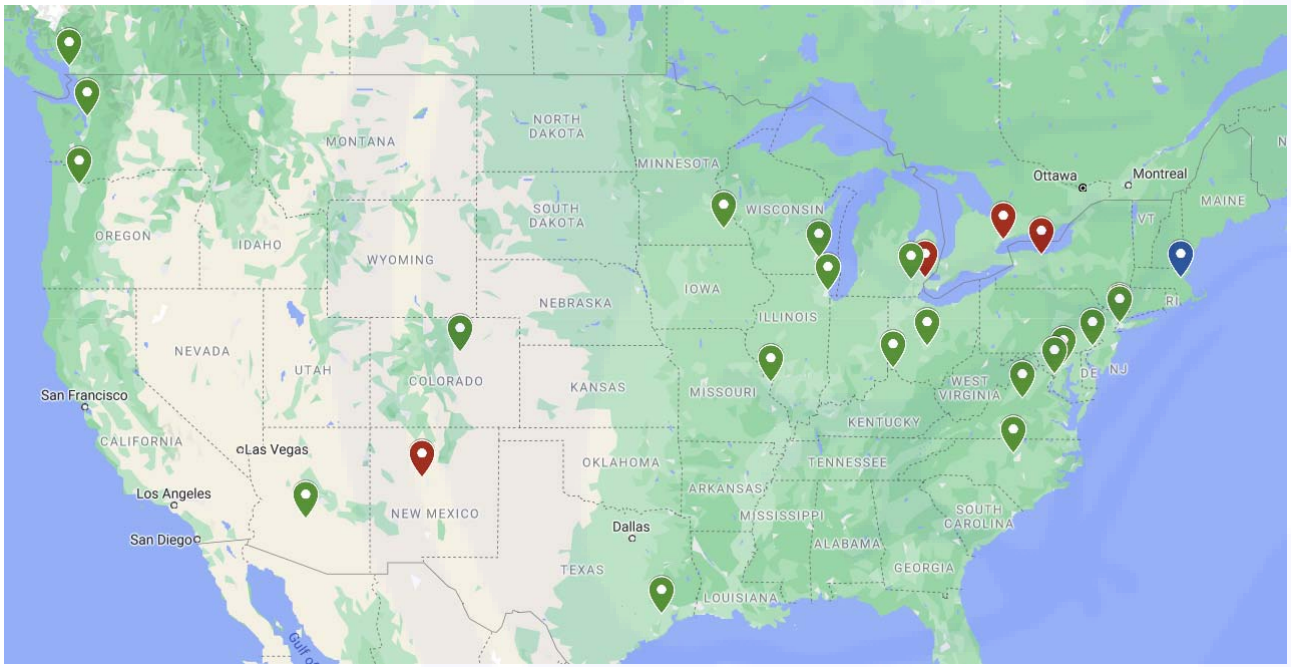


Courtesy of Justice Clark & pSERG team

Next steps

- Improved care and risk factor monitoring
- Implementation work & Interventions
- Biomarker analysis & Novel tools

Pediatric Status Epilepticus Research Group (pSERG)



pSERG Sites

University of New Mexico Health Science Center
Mott Children's Hospital
Johns Hopkins Hospital
Boston Children's Hospital (BCH)
University of Virginia
Lurie Children's Hospital
Cincinnati Children's Hospital
Nationwide Children's Hospital
Colorado Children's Hospital
Children's Hospital of Michigan
Duke University Medical Center
Texas Children's Hospital
Children's Hospital of Wisconsin
Columbia University Medical Center
Weill Cornell Medical Center
Children's Hospital of Philadelphia
Phoenix Children's Hospital
OHSU-Doernbecher Children's Hospital
Mayo Clinic
Strong Memorial Hospital
Seattle Children's Hospital
St. Louis Children's Hospital
British Columbia Children's Hospital
The Children's National Medical Center
The Hospital for Sick Children

Thank you

- **The pSERG Team**
  - Justice Clark, Coral Stredny, Marta Amengual-Gual, Cristina Barcia-Aquilar, Latania Reece, Teddy Sheehan,
- **The MultiModal Team**
  - Michele Jackson, Xiaofan Wang, Solveig Vieluf, Rima El Atrache, Sarah Cantley,
  - Previous Fellows: Fatemeh
- **Our Admin Staff**
  - Michael Kelly
- **Our Interns**
  - Many previous intern cohorts
  - Current Interns: Cepideh Razavi, Emily Peter, Meher Mathur, SM Shariar, Suporna Chaudhuri
- **Previous Loddenkemper Lab members:**
  - Ivan Sanchez Fernandez, Alejandra Vasquez, Marina Gaínza-Lein, Fatemeh Mohammadpour Touserkani, Saba Jafarpour, Ersida Buraniqi, Sarah Hammond, Claudine Sculier, Samuel Lewis, Francesca Coughlin, Robert Benjamin, Shannon Cary, and many more

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