A Contemporary Approach to Status Epilepticus

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- The annual incidence of Status epilepticus(SE) is estimated to be 17–23 episodes per 100,000 children per year

- 10% - 25% of patients presenting with SE will have Refractory Status epilepticus (RSE)

- Significant morbidity and mortality

Overview

- Changes and current recommendations
- Evidence
- Current practice
- Time to treatment and outcome

Definitions

neurocritical care society Neurocrit Care
DOI 10.1007/s12028-012-9695-z

REVIEW

Guidelines for the Evaluation and Management of Status Epilepticus

Neurocrit Care 17:3-23, 2012

EPILEPSY CURRENTS

American Epilepsy Society Guideline

Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society

Epilepsy Currents, Vol. 16, No. 1 (January/February) 2016 pp. 48–61

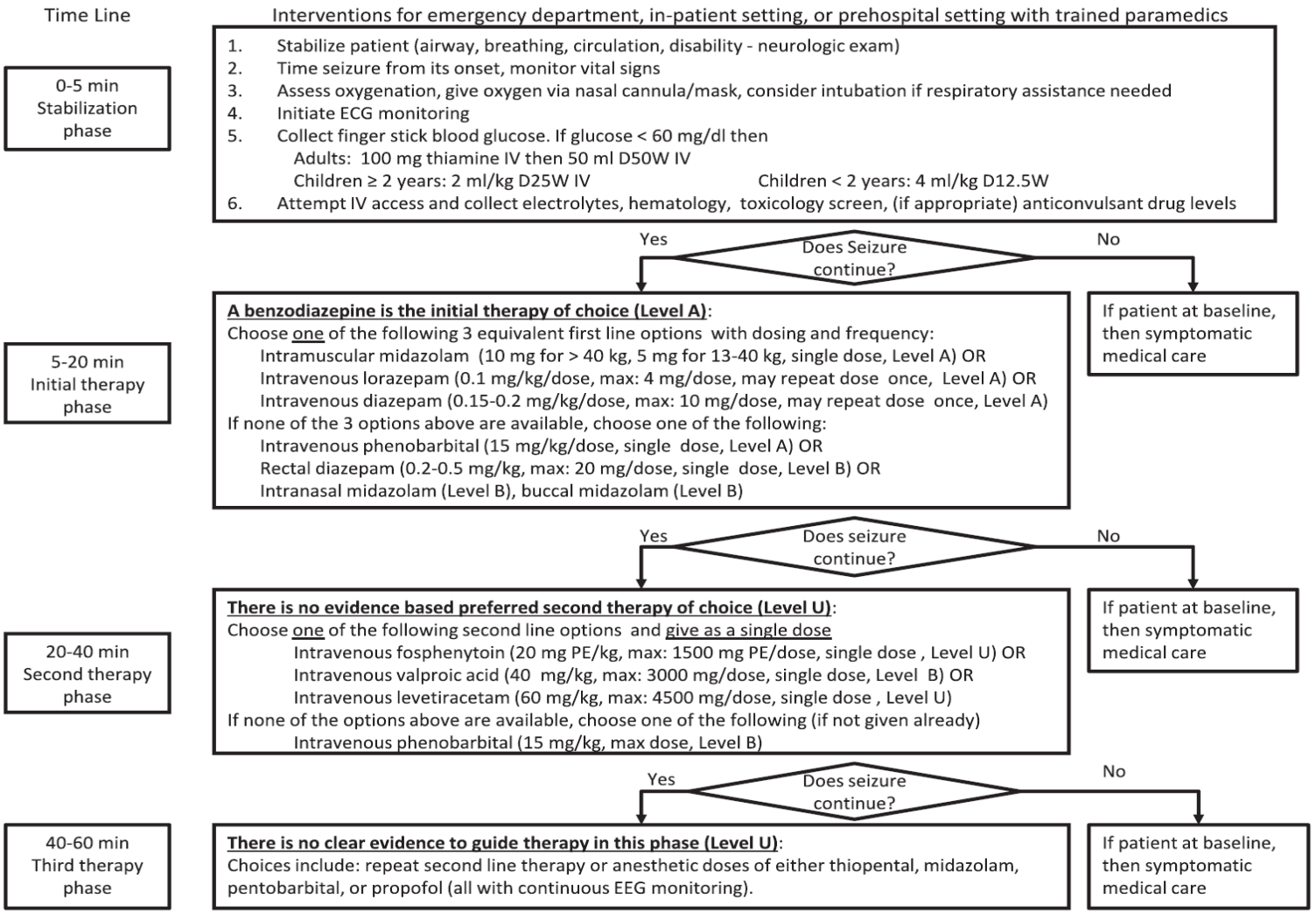
Status epilepticus:

- defined as 5 minutes or more of:
  - continuous clinical and/or electrographic seizure activity or
  - recurrent seizure activity without recovery (returning to baseline) between seizures

Refractory Status epilepticus :

- defined as clinical or electrographic seizures that persist after administration of an adequate dose of initial benzodiazepine and a second appropriate anti-seizure medication

American Epilepsy Society Guideline



American Epilepsy Society Guideline

Time Line	Interventions for emergency department, in-patient setting, or prehospital setting with trained paramedics
0-5 min Stabilization phase	1. Stabilize patient (airway, breathing, circulation, disability - neurologic exam) 2. Time seizure from its onset, monitor vital signs 3. Assess oxygenation, give oxygen via nasal cannula/mask, consider intubation if respiratory assistance needed 4. Initiate ECG monitoring 5. Collect finger stick blood glucose. If glucose < 60 mg/dl then Adults: 100 mg thiamine IV then 50 ml D50W IV Children ≥ 2 years: 2 ml/kg D25W IV Children < 2 years: 4 ml/kg D12.5W 6. Attempt IV access and collect electrolytes, hematology, toxicology screen, (if appropriate) anticonvulsant drug levels

American Epilepsy Society Guideline

5-20 min
Initial therapy
phase

A benzodiazepine is the initial therapy of choice (Level A):

Choose one of the following 3 equivalent first line options with dosing and frequency:

- Intramuscular midazolam (10 mg for > 40 kg, 5 mg for 13-40 kg, single dose, Level A) OR
- Intravenous lorazepam (0.1 mg/kg/dose, max: 4 mg/dose, may repeat dose once, Level A) OR
- Intravenous diazepam (0.15-0.2 mg/kg/dose, max: 10 mg/dose, may repeat dose once, Level A)

If none of the 3 options above are available, choose one of the following:

- Intravenous phenobarbital (15 mg/kg/dose, single dose, Level A) OR
- Rectal diazepam (0.2-0.5 mg/kg, max: 20 mg/dose, single dose, Level B) OR
- Intranasal midazolam (Level B), buccal midazolam (Level B)

American Epilepsy Society Guideline

20-40 min
Second therapy
phase

There is no evidence based preferred second therapy of choice (Level U):

Choose one of the following second line options and give as a single dose

- Intravenous fosphenytoin (20 mg PE/kg, max: 1500 mg PE/dose, single dose , Level U) OR
- Intravenous valproic acid (40 mg/kg, max: 3000 mg/dose, single dose, Level B) OR
- Intravenous levetiracetam (60 mg/kg, max: 4500 mg/dose, single dose , Level U)

If none of the options above are available, choose one of the following (if not given already)

- Intravenous phenobarbital (15 mg/kg, max dose, Level B)

American Epilepsy Society Guideline

40-60 min Third therapy phase	**There is no clear evidence to guide therapy in this phase (Level U)**: Choices include: repeat second line therapy or anesthetic doses of either thiopental, midazolam, pentobarbital, or propofol (all with continuous EEG monitoring).

- Treatment to be guided by cEEG monitoring

- Goal is termination of all clinical and electrographic seizure activity as early as possible

- In patients with RSE

  “a period of 24-48 hours of electrographic control is recommended before slow withdrawal of continuous infusion of anticonvulsants ”

Choice of Anti epileptic drug: first line

- Only the first line treatment with benzodiazepine (BZD) has strong evidence

- RAMPART trial included 120 children randomized to IM midazolam (*n* = 60) or IV lorazepam (*n* = 60)

- Pediatric Emergency Care Applied Research Network (PECARN). Lorazepam vs diazepam for pediatric status epilepticus: *JAMA* 2014;311:1652–1660

Choice of Anti epileptic drug: second line

Seizure 23 (2014) 167–174

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Review

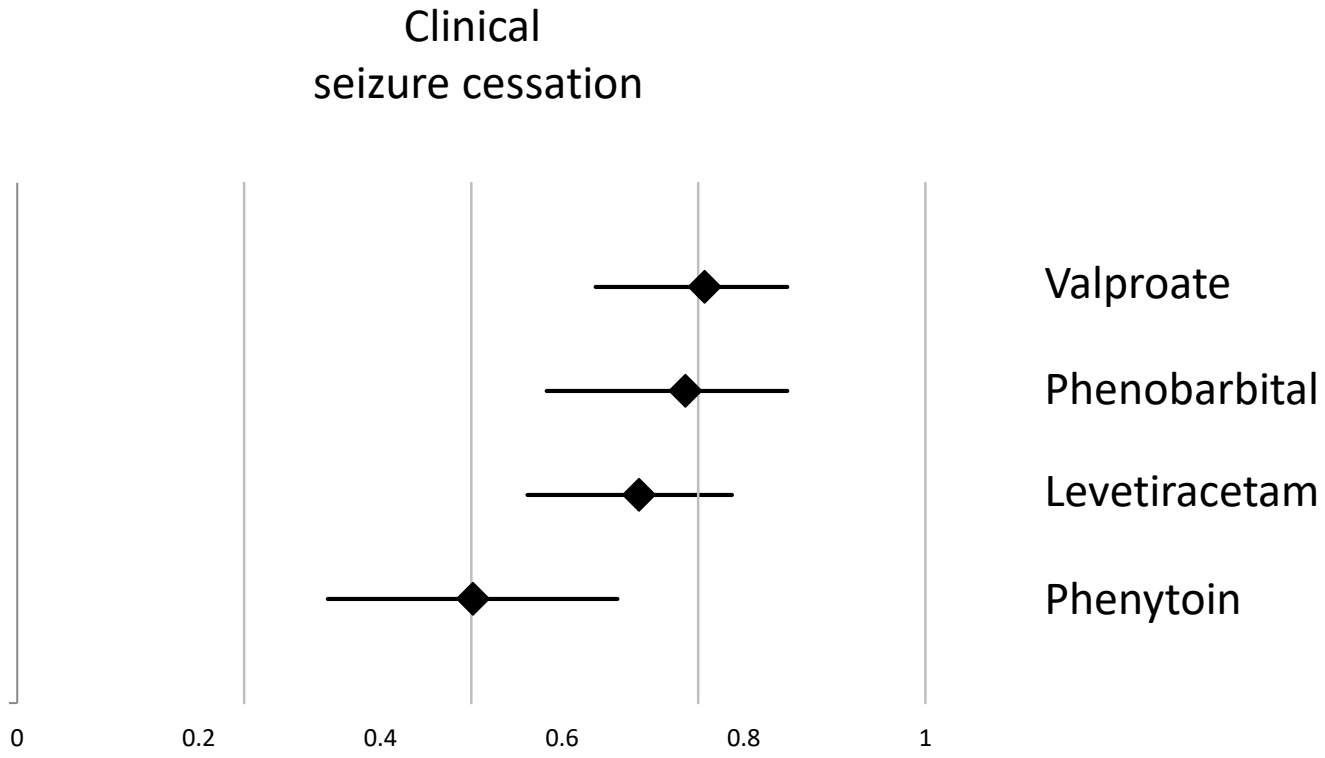
The relative effectiveness of five antiepileptic drugs in treatment of benzodiazepine-resistant convulsive status epilepticus: A meta-analysis of published studies

Zeid Yasiry [a,*], Simon D. Shorvon [b]

[a] Department of Medicine, University of Babylon/College of Medicine, Babil, Iraq
[b] Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, London, UK

Summary

Meta-analysis Estimates of efficacy



Yasiry et al 2014

Second line agent: upcoming trials

- The Convulsive Status Epilepticus Paediatric Trial (ConSEPT)

- Emergency treatment with Levetirecetam or Phenytoin in Status Epilepticus in children- the EcLIPSE study

- The Established Status Epilepticus Treatment Trial (ESETT) – comparing valproate, levetiracetam, and phenytoin (or fosphenytoin)

Third line: Pharmacological Coma

- Two most commonly used- Midazolam, Thiopentone
- No evidence that one is better than other in RSE
- Midazolam most commonly used initial agent
- Midazolam likely have less adverse effects

Midazolam infusion

- If seizures persist or recur: bolus and increase infusion by 2mcg/kg/min every 5 minutes
- Dose range: upto 30mcg/kg/min
- If no response- rapid escalation to second agent

Other Drugs:

- Ketamine

  KETASER01- Efficacy of ketamine in refractory convulsive status epilepticus in children

- Lignocaine
- Magnesium Sulphate
- Propofol
- Inhaled Anaesthetics

Alternative therapies

- Immunomodulatory therapy
- Ketogenic Diet
- Therapeutic Hypothermia
- Vagal Nerve stimulation
- Epilepsy surgery

Current practice

ARTICLES

Time from convulsive status epilepticus onset to anticonvulsant administration in children

Iván Sánchez Fernández, MD
Nicholas S. Abend, MD
Satish Agadi, MD
Sookee An, BA
Ravindra Arya, MD, DM
James Nicholas Brenton, MD
Jessica L. Carpenter, MD
Kevin E. Chapman, MD
William D. Gaillard, MD
Tracy A. Glauser, MD
Howard P. Goodkin, MD, PhD
Kush Kapur, PhD
Mohamad A. Mikati, MD
Katrina Peariso, MD
Margie Ream, MD
James Riviello, Jr., MD
Robert C. Tasker, MBBS, MD
Tobias Loddenkemper, MD
And the Pediatric Status Epilepticus Research Group (pSERG)

ABSTRACT

Objective: To describe the time elapsed from onset of pediatric convulsive status epilepticus (SE) to administration of antiepileptic drug (AED).

Methods: This was a prospective observational cohort study performed from June 2011 to June 2013. Pediatric patients (1 month–21 years) with convulsive SE were enrolled. In order to study timing of AED administration during all stages of SE, we restricted our study population to patients who failed 2 or more AED classes or needed continuous infusions to terminate convulsive SE.

Results: We enrolled 81 patients (44 male) with a median age of 3.6 years. The first, second, and third AED doses were administered at a median (p_{25}–p_{75}) time of 28 (6–67) minutes, 40 (20–85) minutes, and 59 (30–120) minutes after SE onset. Considering AED classes, the initial AED was a benzodiazepine in 78 (96.3%) patients and 2 (2–3) doses of benzodiazepines were administered before switching to nonbenzodiazepine AEDs. The first and second doses of nonbenzodiazepine AEDs were administered at 69 (40–120) minutes and 120 (75–296) minutes. In the 64 patients with out-of-hospital SE onset, 40 (62.5%) patients did not receive any AED before hospital arrival. In the hospital setting, the first and second in-hospital AED doses were given at 8 (5–15) minutes and 16 (10–40) minutes after SE onset (for patients with in-hospital SE onset) or after hospital arrival (for patients with out-of-hospital SE onset).

Conclusions: The time elapsed from SE onset to AED administration and escalation from one class of AED to another is delayed, both in the prehospital and in-hospital settings. ***Neurology*®** **2015;84:2304–2311**

GLOSSARY

AED = antiepileptic drug; **BZD** = benzodiazepine; **EMS** = Emergency Medical Services; **ICU** = intensive care unit; **pSERG** = pediatric Status Epilepticus Research Group; **RCSE** = refractory convulsive status epilepticus; **SCC** = Spearman correlation coefficient; **SE** = status epilepticus.

Key findings:

- Only 38% patients receive anti-epileptic drug (AED) before arrival to hospital

- Significant delay in administration of AED

  The median time until administration of the first, second, and third AED doses were 28 (6–67) minutes, 40 (20–85) minutes, and 59 (30–120) minutes

- Once in the hospital, patients received repeated doses of BZDs

Current practice

Refractory Status Epilepticus in Children: Intention to Treat With Continuous Infusions of Midazolam and Pentobarbital*

Robert C. Tasker, MD, FRCP[1,2]; Howard P. Goodkin, MD, PhD[3]; Iván Sánchez Fernández, MD[2,4]; Kevin E. Chapman, MD[5]; Nicholas S. Abend, MD, MSCE[6]; Ravindra Arya, MD, DM[7]; James N. Brenton, MD[3]; Jessica L. Carpenter, MD[8]; William D. Gaillard, MD[8]; Tracy A. Glauser, MD[7]; Joshua Goldstein, MD[9]; Ashley R. Helseth, MD, PhD[10]; Michele C. Jackson, BA[2,4]; Kush Kapur, PhD[4]; Mohamad A. Mikati, MD[10]; Katrina Peariso, MD[7]; Mark S. Wainwright, MD, PhD[9]; Angus A. Wilfong, MD[11]; Korwyn Williams, MD, PhD[12]; Tobias Loddenkemper, MD[2,4]; on behalf of the Pediatric Status Epilepticus Research Group (pSERG)

Pediatr Crit Care Med 2016; 17:968–975

Key findings:

- median of 5 doses of AED given before the infusion started

- prolonged duration of seizure activity before initiation of midazolam infusion (median of 145 min)

- timing to escalate to second anesthetic (pentobarbital) – 24 hours

- endpoint for seizure termination used – Clinical seizure in 48%

Research

JAMA Neurology | Original Investigation

Association of Time to Treatment With Short-term Outcomes for Pediatric Patients With Refractory Convulsive Status Epilepticus

Marina Gaínza-Lein; Iván Sánchez Fernández, MD, MPH; Michele Jackson, MS; Nicholas S. Abend, MD; Ravindra Arya, MD, DM; J. Nicholas Brenton, MD; Jessica L. Carpenter, MD; Kevin E. Chapman, MD; William D. Gaillard, MD; Tracy A. Glauser, MD; Joshua L. Goldstein, MD; Howard P. Goodkin, MD, PhD; Kush Kapur, PhD; Mohamad A. Mikati, MD; Katrina Peariso, MD, PhD; Robert C. Tasker, MBBS; Dmitry Tchapyjnikov, MD; Alexis A. Topjian, MD, MSCE; Mark S. Wainwright, MD, PhD; Angus Wilfong, MD; Korwyn Williams, MD, PhD; Tobias Loddenkemper, MD; for the Pediatric Status Epilepticus Research Group

JAMA Neurol. 2018;75(4):410-418.

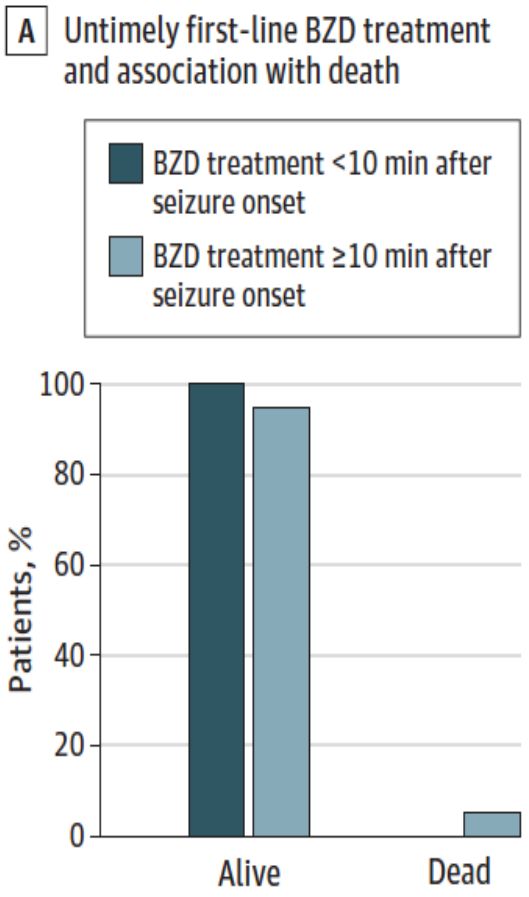
- pSERG multicentre prospective study
- 218 pts from 11 hospitals
- Patients divided in 2 cohorts:
  - received initial BZD in < 10 minutes or at 10 or more minutes after seizure onset (untimely)
- Primary outcome - death during hospital admission
- Secondary outcome - need for continuous infusion for seizure termination

Results

- 66.1% received untimely first-line BZD treatment

- On multivariate analysis after controlling for structural etiology, febrile RCSE, age, and no neurological history:

  Adjusted odds ratio (AOR) of death was 11 for patients with untimely first-line BZD treatment



Pediatric Neurology 000 (2018) 1–9

Contents lists available at ScienceDirect

Pediatric Neurology

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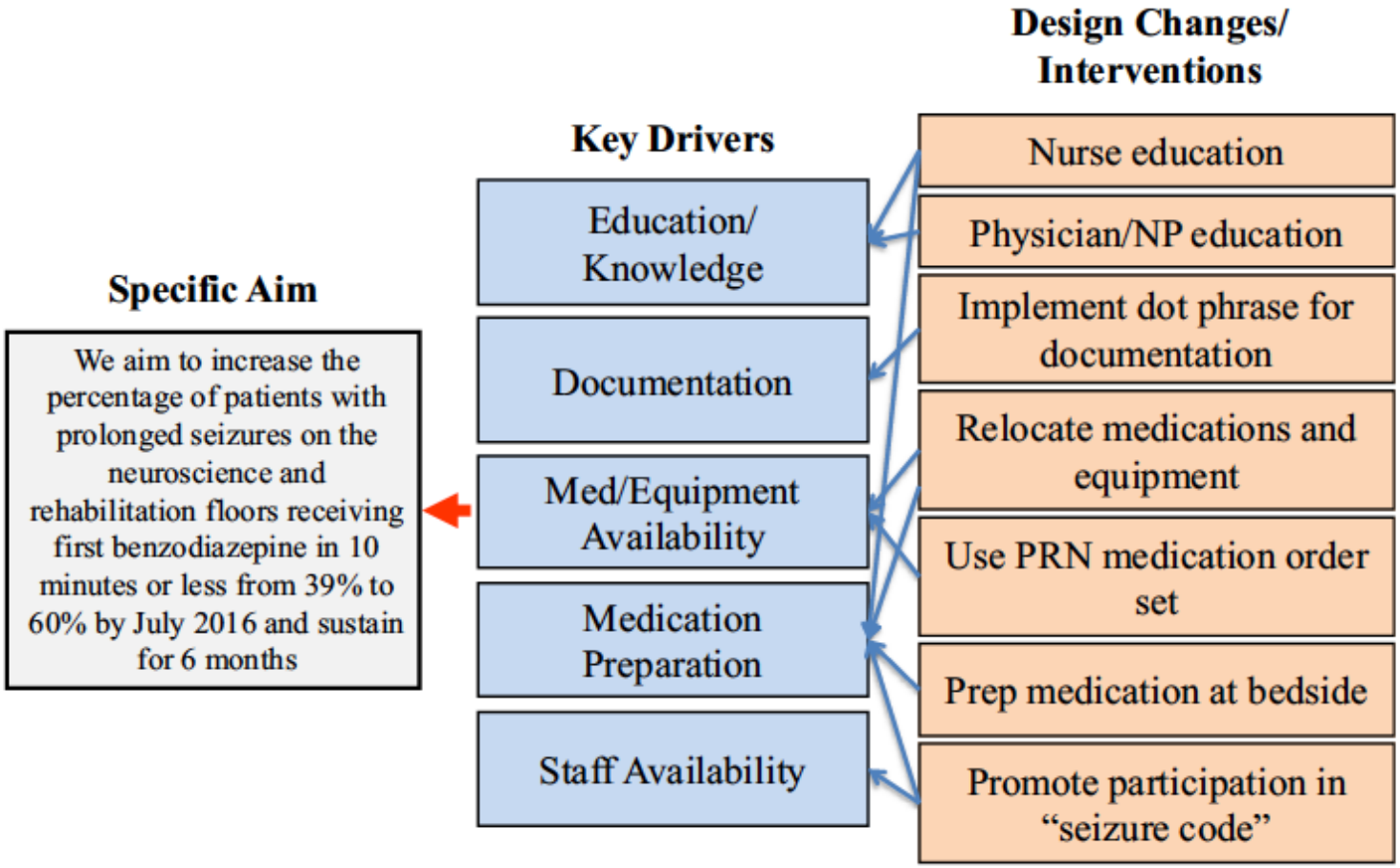
Original Article

Decreasing Seizure Treatment Time Through Quality Improvement Reduces Critical Care Utilization

Adam P. Ostendorf, MD [a,b*], Kelsey Merison, MD [b],
T. Arthur Wheeler, MS, MSES, MBA [b], Anup D. Patel, MD [a,b]


Specific Aim
We aim to increase the percentage of patients with prolonged seizures on the neuroscience and rehabilitation floors receiving first benzodiazepine in 10 minutes or less from 39% to 60% by July 2016 and sustain for 6 months
Key Drivers
Education/ Knowledge
Documentation
Med/Equipment Availability
Medication Preparation
Staff Availability
Design Changes/ Interventions
Nurse education
Physician/NP education
Implement dot phrase for documentation
Relocate medications and equipment
Use PRN medication order set
Prep medication at bedside
Promote participation in "seizure code"

Seventeen months after starting the project:

- median time to treat seizures decreased from a baseline of 14 minutes to 7.5 minutes($P = 0.01$)
- The proportion of patients transferred to ICU decreased from a baseline of 39% to 9%($P < 0.005$)
- An estimated $2.1 million of hospital charges were mitigated.

Summary

- Status epilepticus is a neurological emergency
- Treatment should be started early and escalated rapidly
- Time to treatment is critical in improving management and outcome

Seizure 58 (2018) 133–140

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Review

Towards acute pediatric status epilepticus intervention teams: Do we need "Seizure Codes"?

Coral M. Stredny[a,*], Nicholas S. Abend[b], Tobias Loddenkemper[a]

Thanks