STATUS EPILEPTICUS CLINICAL PATHWAY

EXECUTIVE SUMMARY

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Primary Objective

Status epilepticus is a common pediatric neurological emergency with an estimated incidence of 1 to 6 per 10,000 per year and a mortality rate of 3-8%. **It is a disease process defined as a seizure longer than 5 minutes and can result in permanent neurological damage if it continues for longer than 30 minutes.**[16] With such a risk of permanent neurological damage, it is key that care be initiated quickly. Delay in initiation in benzodiazepine, the first line therapy, leads to failure to respond and status epilepticus becomes refractory to subsequent treatments and can result in a prolonged PICU stay.[7, 23] The purpose of this pathway is to standardize the treatment of patients with status epilepticus by ensuring prompt recognition and delivery of first and second line antiseizure medication and if needed third line therapy. Ultimately, (1) stopping the seizure rapidly by reducing time to ASM administration and (2) Reducing variability in choice, dose, and administration time of second line anti-seizure medication class.

Recommendations

Psychogenic Non-Epileptic Seizures (PNES) versus Status Epilepticus (SE)

All that shakes is not status epilepticus.[11] Misdiagnosis and treatment of prolonged psychogenic nonepileptic seizures (pPNES) as status epilepticus are a common and widespread problem with deleterious consequences. Among 980 patients aged 8 years or older diagnosed and treated for status epilepticus in RAMPART and ESETT, 79 (8.1%) were discharged with a final diagnosis of pPNES. **The relative incidence was highest in adolescents and young adults (20.1%).** Adverse effects, including respiratory depression and intubation, were documented in 26% of patients with pPNES receiving benzodiazepines in RAMPART and 33% of patients receiving additional second-line medication in ESETT. In ESETT, patients who were treated with BZD before hospital admission had higher rates of unresponsiveness and severe adverse effects than those treated after admission, suggesting cumulative effects of accelerated treatment momentum. Across trials, one in five patients with pPNES were admitted to an intensive care unit. [10]

PNES are attacks that may look like epileptic seizures but are not caused by abnormal brain electrical discharges. Instead, they are a manifestation of psychological distress. PNES are not a unique disorder but are a specific type of a larger group of psychiatric conditions that manifest as physical symptoms.

PNES can be regarded as involuntary experiential and behavioral responses to internal or external triggers.[6] As behaviors, they are not accompanied by EEG changes.

Psychiatric conditions associated with PNES include depression, anxiety, somatic symptoms and related disorders, post-traumatic stress disorder, dissociative disorders, and/or personality disorders.

The diagnosis of PNES is established by video-EEG monitoring, in which captured clinical events are examined in conjunction with EEG activity.

Main clinical features of tonic-clonic seizures compared with the convulsive type of psychogenic nonepileptic seizures (PNES). [25]* UpToDate 2022 Courtesy of Roderick Duncan MD PhD FRCP

	Generalized Tonic-Clonic Epileptic Seizures	Convulsive PNES
Frequency	Variable	Infrequent PNES are unusual
Duration	Usually, < 2 min excluding postictal phase	Brief PNES are unusual
Eyes	Open/half open	Usually closed
Motor Activity	Generalized tonus followed by generalized clonic activity	Alternating movement or tremor, occasionally trashing, back arching, side-side head movement; tonic features uncommon
Vocalization	Initial, inarticulate, no emotional features	During and after seizure, conveys distress
Autonomic signs	Signs of arousal and hyperventilation, flushed, pale	Cyanosis
Postictal phase	Drowsy, confused, sleeps, severe headache	Often back to alertness quickly; distress
Incontinence of urine	Reported and observed	Commonly reported
Sleep events	Commonly reported/observed, events may occur only during sleep	Commonly reported/observed, but not EEG verified; events reported to occur during sleep only highly unusual
Injury	Commonly reported/observed	Less commonly reported/observed
Burns	Thermal	Friction
Tongue/Mouth injury	Bite to lateral tongue or inside of cheek, observed injury	Reported bite to tip of tongue
Stereotypy	Usual	Common

First Line Medications

Convulsive Status Epilepticus Guidelines recommend that the first benzodiazepine be given within 5-10 minutes from seizure onset. Studies have noted that the slower treatment or delay in treatment is associated with longer seizure duration, increased need for continuous infusions, more frequent hypotension, and increased mortality.

Zhao-Zi-yu et al in 2016 did a meta-analysis and found 16 randomized controlled trials (n=1821 patients). [26] The review was a comparison of midazolam, lorazepam and diazepam and the following was found:
1-Non-intravenous midazolam and IV lorazepam were superior to intravenous or non-intravenous diazepam
2-Non-intravenous midazolam was as effective as IV lorazepam

Sheehan T et al. looked at benzodiazepine (BZD) administration patterns before escalation to second-line medications in pediatric refractory convulsive status epilepticus (n=293 patients, mean age 3.8y).[20]

1. > 1/3 patients received > 2 benzodiazepines before escalation to non-BZD antiseizure medications (ASM)
2. Patients with out-of-hospital seizure onset were more likely to receive more doses of BZDs beyond 30 minutes
3. Out-of-hospital seizure onset and intermittent status epilepticus were associated with the failure to escalate from BZDs to non-BZDs ASMs
4. Approximately ½ of patients who received 2 or more BZDs before hospital arrival, the rescue algorithm was restarted following patient handoff

Sheehan summarized that "delays in the implementation of medical guidelines could be reduced by initiating treatment and transitioning to second-line ASMs after 2 BZD doses during handoffs between pre-hospital and in-hospital settings." [20]

Research in the Pre-hospital arena:
Silbergleit R et al 2012 looked at the efficacy of intramuscular midazolam versus intravenous lorazepam in the prehospital setting.[22]
The RAMPART (Rapid Anticonvulsant Medication Prior to Arrival Trial) was a double-blind randomized noninferiority clinical trial. Designed and conducted by the NETT network. This study involved 4314 paramedics, 33 EMS agencies and 79 receiving hospitals across the US (n=893 subjects). The primary outcome was termination of seizures before arrival to the ED. They found that IM Midazolam is at least as safe and effective as IV lorazepam for prehospital seizure cessation.

	IM Midazolam	IV Lorazepam
% cessation of seizure on arrival to ED	73.4% (329/448)	63.4% (282/445
Need for intubation	14%	14.4%
Recurrence of seizure	11.5%	10.6%
Median Time to Active Treatment	1.2 min	4.8 min
Median Time from active treatment to cessation of convulsions	3.3 min	1.6 min
Total Estimated time	4.7 min	6.4 min

In 2014, a multidisciplinary panel was brought together to develop an evidence-based guideline for prehospital seizure management. Their recommendations were published in Prehospital

Emergency Care in 2014.[19] They recommended that non-IV route (buccal, IM or IN) benzodiazepine be used as first-line therapy for status epilepticus rather than IV or rectal routes. They went on to note that their drug of choice is Midazolam at 0.2 mg/kg.

Benzodiazepines

Benzodiazepine produces neurological effects through interaction with a particular receptor in the central nervous system known as GABAA receptor (GABAAR).[12] Under normal circumstances the interaction between GABA and $GABA_AR$ leads to the intracellular influx of Cl^- which causes cell membrane hyperpolarization. This is in turn responsible for inhibitory signaling against eventual depolarization, action potential or nerve impulses.[12, 17]
However, during the neonatal period, nerve cells are believed to have high concentrations of Cl^- to the point that GABA-gated Cl^- efflux sets up, as well as potential GABA-mediated neuro-excitation. As a result of this process, the neocortex shows the most delayed establishment of neuronal Cl^- homeostasis during development. [8, 14, 21] Therefore, when a benzodiazepine is administered to a neonate with seizure, neocortical enhancement of GABA-gated Cl^- efflux may occur with GABA-mediated neuro-excitation. This might produce paradoxical effects to those expected, with exacerbation of myoclonus, seizures, and abnormal movements. [8, 14, 21] The persistence of seizure might be explained by paradoxical neuro-excitation or reduced anticonvulsant activity of benzodiazepines in neonates. [2, 3, 9, 24]

Although some benzodiazepines such as clonazepam are recommended as second line anticonvulsants in neonatal seizure benzodiazepine should be avoided as much as possible in neonate infants as a general rule. [15, GPK)]

Phenobarbital (PB) is still the first-line antiseizure medication (ASM) for neonatal seizures. **It can not only control seizures but also reduce the metabolism of the brain**. PB can control 43–80% of electrical seizures (abnormal electroencephalograms) in newborns.

Second Line Medications

Where are we in 2022 in the treatment of convulsive status epilepticus (CSE)?
Three key studies have been published in the last 2 years comparing second line medications in the care of the child in CSE. The ConSEPT, EcLiPSE and ESETT studies which hold the evidence used to determine our clinical pathway.

ConSEPT study

- 13 centers in Australia and New Zealand (3/201-11/2017)
- 234 children between 3 months and 16 years with CSE
- Randomized to receive phenytoin or levetiracetam
- Primary outcome was clinical cessation of seizure activity 5 minutes after the completion of infusion of first trial medication
- Mean age 3.9 years

Clinical cessation of seizure activity 5 minutes after the completion of infusion of the first drug, assessed at 10 minutes (levetiracetam) and 25 minutes (phenytoin), repeated with opposite drug at 35 minutes, if necessary. One drug was not superior to the other in this clinical trial.

Drug n=234	Dose	# terminated	Cessation of seizure at 2h	Need for additional AED
Levetiracetam (Keppra) n=120	40 mg/kg over 5 minutes	60 (50%)	61 (51%)	48 (40%)
Phenytoin n= 114	20 mg/kg over 20 min	68 (60%)	62 (54%)	42 (37%)

EcLiPSE study

- Levetiracetam vs Phenytoin for the second line treatment of pediatric convulsive status epilepticus
- Multicenter, open label, randomized trial
- 30 UK and Ireland emergency departments (7/2015-4/2018)
- 6 months to under 18 years of age
- 286 patients: 152 (L); 134 (P)
- Primary outcome: time to cessation of clinical convulsive activity

Drug n=234	Dose	# terminated	Cessation of seizure at 2h	Need for additional AED
Levetiracetam (Keppra) n=120	40 mg/kg over 5 minutes	60 (50%)	61 (51%)	48 (40%)
Phenytoin n= 114	20 mg/kg over 20 min	68 (60%)	62 (54%)	42 (37%)

The results of this study, together with previously reported safety profiles and relative ease of administration of Levetiracetam, suggest that it could be an appropriate alternative to phenytoin as the first-choice AED for second line tx of pediatric convulsive status epilepticus

ESETT (Established Status Epilepticus Treatment Trial) study

- Efficacy and safety of levetiracetam, fosphenytoin and sodium valproate
- Management of those patients with benzodiazepine-resistant SE
- Age > 2yrs <18y; 18-65y; > 65y
- Multicenter, double-blind, randomized controlled trial
- 58 hospital EDs in the US (11/2015-12/2018)
- Primary outcome: absence of clinical apparent seizures and improving responsiveness at 60 min after start of infusion

- Secondary efficacy outcomes: time to termination of seizures, admission to ICU, length of ICU and hospital stays

Variable	Levetiracetam (Keppra) n=175 (38%)	Fosphenytoin n=142 (31%)	Valproate n=145 (31%)
% achieving primary outcome (<1h)	52% children 44% adults 37% older adults	49% children 46% adults 35% older adults	52% children 46% adults 47% older adults
Median time to seizure cessation	10.5 min	7.5 min	7.0 min
% seizure recurrence (1-12 h post-infusion)	10.7%	11.2%	11.2%
Life-threatening hypotension	0.7%	3.2%	1.6%
Arrythmia	0.7%	0	0
Intubation	20.0%	26.4%	16.8%

No differences were detected in efficacy or primary safety outcome by drug in each group

Summary of the use of Levetiracetam (LEV, Keppra)

- First approved in 2006
- Can be administered quickly as an IVP, minimal drug interactions, reliable pharmacokinetics and few serious side effects
- Use of LEV is recommended as second-line treatment for CSE, when use of a BZD was unsuccessful
- Dose: 60 mg/kg (max 4.5 g)

Editorial published by Suresh Pujar & Rod C Scott Arch Dis Child 2021:106(5)[18]

"As LEV offers practical advantage of ease of drug preparation and administration, shorter infusion time and option to continue as maintenance therapy, we prefer to use LEV as first choice therapy for BZD-resistant CSE in children"

Where do these studies leave us with treatment recommendations?

- Demonstrate when timing of CSE was recorded, majority of patients still face treatment delays for both early and established CSE
- Underscore the need for ongoing awareness and education for swift intervention
- Adequate initial BZD dosing

- Timely initiation of second-line treatment in BZD-resistant cases
- Strategy of successive use of IV anti-seizure medications, before recourse to anesthetic agents
- Levetiracetam is a viable alternative to phenytoin/fosphenytoin

Rationale

Status Epilepticus is a neurologic emergency. It requires rapid identification and treatment to manage and prevent long term injuries. The literature supports having a pre-determine plan, as it will expedite management and avoid delays.[1]

The literature published to date recommends that benzodiazepine dosage is as follows: Lorazepam dosing of 0.1mg/kg (max 4mg) IV/IM or Midazolam 0.2mg/kg IV/IN/IM (max 5mg for 13-40 kg or 10mg >40 kg) as first line for status epilepticus management.[23] Based on a chart review of 31 patients treated in the emergency department at CHMC, there was a significant variation in dosages for first- and second-line antiepileptic medications. Ativan (Lorazepam) ranged from 0.05mg/kg to 0.1mg/kg with a maximum dose of 2mg. With 1/3 of these patients being dosed at the lower end at 0.05mg/kg which may have led to the need for repetitive doses to attempt termination with 1st line benzodiazepines. When looking at the administration of Keppra as the 2nd line agent, 23 of the 31 patients received Keppra in our emergency department. There was dosing variation for Keppra utilized at Children's Hospital and Medical Center ranging from 20-60 mg/kg with only 9/23 (39%) patients receiving Keppra at 60 mg/kg. Literature recommendations from ConSEPT, EcLiPSE, and ESETT studies put Keppra dosing at 60 mg/kg.[4, 5,13]

Metrics

- Outcome Metric:
  1. Increase percentage of time that loading dose based on table was within recommended range for age/weight to 65% by May/June 2023.
  2. Increase percentage of time that correct Keppra dose was administered to 65% by May/June 2023.
- Process Metric:
  1. Increase utilization of ED Status Epilepticus order set to 50% by May/June 2023.
  2. Utilization of triage status epilepticus flowsheet to 50% by May/June 2023.
- Balancing Metric:
  1. Monitor for increasing rate of intubation.

Team Members

Champion(s):

- Donna Moro-Sutherland, MD (Emergency Medicine)
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Evidence

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