# OPTIMAL PREHOSPITAL MANAGEMENT OF SEIZURE EMERGENCIES

## CLINICAL INSIGHT

### 1. Overview of Care for Seizure Emergencies

Seizure emergencies are set apart by their duration. A typical, brief seizure lasts less than 5 minutes, whereas prolonged seizures last 5-30 minutes. Status epilepticus is defined as continuous seizure activity for over 30 minutes, or at least 2 sequential seizures without recovery in between them. Acute repetitive seizures (ARS) are a type of seizure emergency where patients have at least 3 seizures within 24 hours (if not characteristic of the patient's habitual seizure frequency). Both status epilepticus and ARS place the patient at risk for neurological morbidity and mortality.

The 5-minute threshold that separates brief from prolonged seizures is based on the increased risks that emerge in patients after 5 minutes of seizing. Crossing this threshold increases risk for a prolonged seizure and status epilepticus. Adverse physiological changes begin to present after 30 minutes—hyperthermia, acidosis, hypotension, and rhabdomyolysis, for example—leading to neuronal damage. Thus, this definition of prolonged seizures seeks a balance between unnecessary interventions and the risk of poor outcomes for patients who go on to have prolonged seizures.

| | Duration | Criteria |
|---|---|---|
| **Brief seizures** | <5 minutes | |
| **Status epilepticus (SE)** | >30 minutes | • Continuous seizure activity<br>• ≥2 sequential seizures without full recovery of consciousness<br>• Cerebral autoregulation and neuronal damage after 30 minutes |
| **Prolonged seizures** | Last 5-30 minutes | |
| **Acute repetitive seizures** | | • Mental status preserved between seizures<br>• ≥3 within 24 hours (in patients whose habitual seizure frequency is ≤3 per day)<br>• Increased risk of prolonged seizures<br>• Physically and socially disabling<br>• Common concern for patients with intractable epilepsy |

### 2. Morbidity, Mortality, and Status Epilepticus

Status epilepticus causes about 55,000 deaths per year out of between 102,000 and 150,000 episodes. Alongside the seizure type and patient age, seizure duration is related to mortality risk: patients whose seizures lasted 10-29 minutes had a 30-day mortality risk of 2.6%, compared to 19% in those whose seizures lasted >30 minutes. The Rochester population-based studies found a 10-year mortality rate of 43%, with those who had myoclonic status epilepticus, acute symptomatic status epilepticus, or seizures lasting >24 hours, being at highest risk. In another cohort, only 11% of patients with generalized status epilepticus were considered healthy after 7 months of follow-up, while 42% died and 31% were left with lasting disability.

### 2. Evidence-based Guidelines from the American Epilepsy Society

In 2016, the American Epilepsy Society (AES) published guidelines for treating status epilepticus. The overall goal of treatment is the rapid termination of clinical and electrical seizure activity to reduce associated mortality and morbidity. The AES notes that basic critical care and emergency principles have been widely accepted, but that pharmacologic management varies, either because the therapy patients received is aimed at reducing seizure activity rather than terminating it, inefficient therapies are used, or insufficient anticonvulsant doses are used. Prehospital care is also neglected, and acute rescue medications are

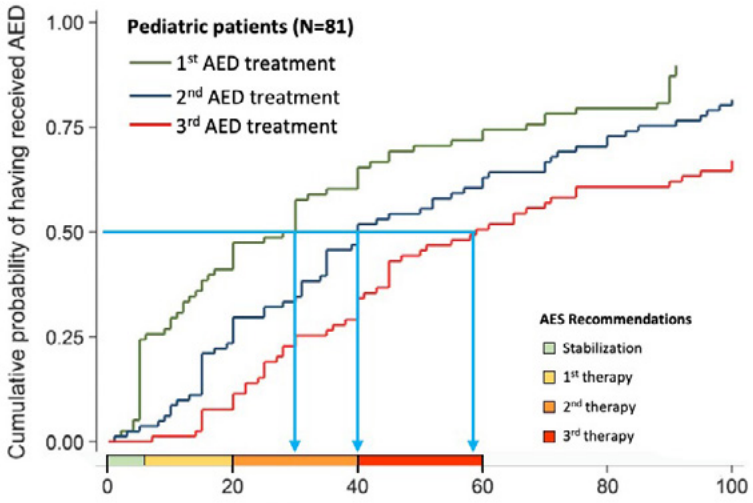
underutilized. A link to these guidelines is included in the *Clinical Resources* section, along with the results of the Established Status Epilepticus Treatment Trial (which found that levetiracetam, fosphenytoin, and valproate were essentially equivalent second-phase treatments) and the Treatment of Recurrent Electrographic Nonconvulsive Seizures Trial (which found that lacosamide was noninferior to fosphenytoin as a second-phase treatment).

### 3. Pediatric Perspective

Status epilepticus in childen can be more difficult to treat and is of more varied etiology than in adults. From a technical standpoint, younger children have more rapid metabolism, which may require dosing adjustments and precautions with specific therapies (eg, propofol); at the same time, there is less direct clinical research to support clinical decision making. The AES guidelines do offer safety and efficacy data to support application of the guidelines to pediatric cases of status epilepticus.

### 4. Importance of Prehospital Care

Most patients (87%) have a rescue medication, but only a fraction (38%) receive it in the prehospital setting. This is true even in patients with an established epilepsy diagnosis. Those patients who do not receive prehospital treatment are at risk of treatment delays and an increased need for third-phase treatments: the risk of a seizure lasting >60 minutes was 2.4 times greater in patients who did not receive prehospital treatment. The duration of status epileptics was also doubled, and the risk of recurrent status epilepticus was 85%, compared to 58% in those who did receive prehospital treatment. The Pediatric Status Epilepticus Research Group Trial found evidence of other negative outcomes in patients who received delayed benzodiazepine treatment, including an increased risk of death (odds ratio 11.0) and risk of hypotension (odds ratio 2.3). The barriers to timely prehospital treatment include suboptimal preventive care, infrequent use of rescue medications, delayed EMS activation, and inappropriately dosed medications.




### 5. Advances in Prehospital Management of Acute Repetitive Seizures

Rectal diazepam (PR diazepam) has been the most commonly prescribed rescue medication, but most families would prefer an alternative. Intranasal midazolam and diazepam have both been recently approved by the FDA for treatment of intermittent, stereotypic episodes of frequent seizure activity (ie, seizure clusters and acute repetitive seizures). Midazolam nasal spray (MDZ-NS) is approved for patients 12 and older, and diazepam nasal spray (DZP-NS) is approved for patients 6 and older.

MDZ-NS was compared to placebo in the ARTEMIS 1 phase 3 trial, which showed that MDZ-NS terminated seizures within 10 minutes in 54% of patients (compared to 34% in the placebo group, $P$=0.01), and prevented seizure recurrence (38% in the MDZ-NS group had a recurrent seizure, compared to 60% in the placebo group, $P$=0.004). The treatment emergent adverse events (TEAEs) were consistent with those seen with benzodiazepines or expected with the intranasal administration. In an extension trial, 80% of patients did not have additional seizure activity after receiving up to 2 doses of MDZ-NS.

DZP-NS was approved based on pharmacokinetic studies demonstrating comparable bioavailability between the intranasal and PR formulations. In these studies, the TEAEs were consistent with those associated with benzodiazepines and expected with intranasal administration. A follow-up phase 3 trial compared adverse events in patients with moderate (1-2 doses/month) or frequent (>2 doses/month) DZP-NS exposure. There were no additional safety or tolerability concerns in patients with frequent DZP-NS exposure, and nasal irritation was mild and transient.

### 6. Focus on Caregivers and Healthcare Providers

Delays in treatment with benzodiazepine rescue medication are frequent, even in patients with a prior epilepsy diagnosis. In a group of 27 patients, only 12 received their first-line benzodiazepine before arriving at the hospital, and only 7 of these patients received treatment from a family member. This suggests that families are reluctant to administer rescue medications, and EMS may not consider administering non-IV treatments. A Seizure Action Plan (SAP) improves caregiver knowledge of when to administer a rescue medication, improves rescue medication access at school, and informs caregivers of when to activate EMS. However, only 45% of parents recalled having an SAP (and the use of SAPs is less widely accepted in adults with epilepsy). A link to the Epilepsy Foundation SAP is included in the Clinical Resources, but Penovich et al have recently proposed a succinct, single-page, graphic seizure action plan.

Patients prefer rescue medication training from a neurologist, but also accept training from other medical staff. They want more hands-on training and refresher training after several years. Parents want SAPs as well. Critical junctures—at diagnosis, in the first year after diagnosis, or following changes in the patient's seizure pattern, or developmental, health, employment, or social status—provide training opportunities and are good times to update SAPs. This update is important both to refresh caregiver training, but also because the majority of patients have an out-of-date rescue medication prescription that is below the accepted guideline range.

Finally, caregiver training cannot be overlooked. In a study conducted before the approvals of MDZ-NS and DZP-NS, 84% of school nurses were trained to administer PR diazepam, compared to 63% who were comfortable administering compounded intranasal midazolam.

## CLINICAL RESOURCES

**Optimal Prehospital Management of Seizure Emergencies Patient and Caregiver Training Video**

- Video 1 – Unsuccessfully Managing Seizure Emergencies
- Video 2 – Successfully Treating Seizure Emergencies

**Epilepsy Foundation Rescue Medication Resources**

- Seizure Rescue Therapies

**Relevant Studies Published Since 2016 Guidelines**

- Lyttle MD, Rainford NEA, Gamble C, et al. Levetiracetam versus phenytoin for second-line treatment of paediatric convulsive status epilepticus (EcLiPSE): a multicentre, open-label, randomised trial. Lancet 2019;25;393:2125-2134. PubMed citation with links to Full Text: https://pubmed.ncbi.nlm.nih.gov/31005385/
- Kapur J, Elm J, Chamberlain JM, et al. Randomized trial of three anticonvulsant medications for status epilepticus. N Engl J Med. 2019;381:2103-2113. New England Journal of Medicine Full Text link: https://www.nejm.org/doi/full/10.1056/NEJMoa1905795
- Husain AM, Lee JW, Kolls BJ, et al. Randomized trial of lacosamide versus fosphenytoin for nonconvulsive seizures. Ann Neurol. 2018;83:1174-1185. PubMed citation with links to Full Text: https://pubmed.ncbi.nlm.nih.gov/29733464/

**American Epilepsy Society**

- Guidelines

**American Academy of Neurology**

- Guidelines

**American Academy of Pediatrics**

- Rescue Medicine for Epilepsy in Education Settings

**Child Neurology Foundation Seizure Action Plan**

- School Action Plan
- Seizure Action Plan

**Epilepsy Action**

- My Epilepsy Care Plan
- Epilepsy in Schools: How to Deal With a Tonic Seizure (Video)

**Epilepsy Ontario**

- Tonic Clonic Seizure (Video)

**Epilepsy Foundation Seizure Action Plan Patient Video**

- What is a Seizure Action Plan?

**Epilepsy Association of Western and Central PA**

- Seizure Action Plan Template

**Epilepsy Foundation Videos and Downloadable Seizure Action Plan**

- Seizure Action Plan Template
- What Is a Seizure Action Plan? (With Template)
- Seizures in School