

JOHNS HOPKINS ALL CHILDREN'S HOSPITAL

Status Epilepticus Clinical Pathway

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This pathway is intended as a guide for physicians, physician assistants, nurse practitioners and other healthcare providers. It should be adapted to the care of specific patient based on the patient's individualized circumstances and the practitioner's professional judgment.

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Status Epilepticus Clinical Pathway

Rationale

This clinical pathway was developed by a consensus group of JHACH neurologists/epileptologists, emergency physicians, advanced practice providers, hospitalists, intensivists, nurses, and pharmacists to standardize the management of children treated for status epilepticus. The following clinical issues are addressed:

- When to evaluate for status epilepticus
- When to consider admission for further evaluation and treatment of status epilepticus
- When to consult Neurology, Hospitalists, or Critical Care Team for further management of status epilepticus
- When to obtain further neuroimaging for status epilepticus
- What ongoing therapy patients should receive for status epilepticus

Background:

Status epilepticus (SE) is the most common neurological emergency in children¹ and has the potential to cause substantial morbidity and mortality. Incidence among children ranges from 17 to 23 per 100,000 annually.² Prevalence is highest in pediatric patients from zero to four years of age.³ Ng³ acknowledges the most current definition of SE as a continuous seizure lasting more than five minutes or two or more distinct seizures without regaining awareness in between. This shift from the definition of SE being 30 or more minutes of continuous seizure activity has been supported by the American Epilepsy Society and the American Neurocritical Care Society.

Brophy⁴ reports that pharmacoresistance and permanent neuronal injury have been suggested by animal data from the effects of SE occurring before the traditional definition. When comparing several different pediatric SE protocols, Vasquez⁵ found that more timely SE treatment is recommended since prior studies have shown that appropriate escalation of medications and prompt administration may increase the probability of seizure cessation. In fact, there is a 5% cumulative increase for the episode to last longer than 60 minutes with each minute that passes between the onset of SE and arrival to the emergency center.⁶

Within the first five minutes, it should be determined if seizures are epileptic or nonepileptic as well as whether or not a benzodiazepine has been administered en route to the emergency center. There is level A evidence that IV lorazepam and IV diazepam are successful at stopping seizures within five minutes. There is level B evidence that IM midazolam, intranasal midazolam, rectal diazepam, and buccal midazolam are most likely efficacious at stopping SE. There is inadequate evidence to support the use of sublingual, rectal, and intranasal lorazepam, valproic acid, levetiracetam, phenytoin, and phenobarbital as first line agents.⁷

As a second line therapy, IV levetiracetam, fosphenytoin, or valproic acid should be considered, followed by IV phenobarbital. Recent data have shown that levetiracetam could be a suitable alternative to phenytoin with a good safety profile for pediatric status epilepticus.⁸ However, levetiracetam was not superior to phenytoin for stopping seizures. IV phenobarbital has been

found to be more sedating than IV valproic acid. Overall valproic acid is better tolerated than phenobarbital with similar efficacy.⁷

Possible long-term complications of SE other than death affect 15-50% of pediatric patients and include cognitive and behavioral problems, secondary epilepsy, and focal neurological deficits. With more adequately treated SE over the last three decades, there has been an improvement in mortality outcomes. More recent studies report mortality rates of 5% in patients less than one year and 2% in patients 1 to 19 years of age, compared to 11% of children younger than 15 years previously.³ Inadequately or untreated SE can result in changes in motor activity, progressive changes in the electroencephalogram (EEG) pattern, as well as an increased resistance to treatment and more severe consequences.⁴

Diagnosis

Diagnosis is made clinically, however, EEG can be diagnostic and some laboratory findings are indicative. The recent Neurocritical Care Society guideline indicates initial etiologic testing should include bedside finger stick blood glucose.

Lab tests

Initial laboratory tests:

Blood glucose, complete blood count with differential, comprehensive metabolic panel, magnesium, phosphorus, and anti-epileptic medication levels for established seizure patients

Depending on the clinical scenario, other diagnostic testing may be required:

- Neuroimaging or lumbar puncture
- Other laboratory testing (coagulation studies, toxicology screen, HcG, inborn errors of metabolism screening, chromosomal microarray, genetic epilepsy panel)
- Continuous EEG

Radiologic Studies

Neuroimaging abnormalities have been reported in 30% of children with SE and are described to alter acute management in 24%. Computed Tomography (CT) scan is fast, and is able to detect blood and masses. MRI brain is superior and should be considered when the CT scan is negative.

Central nervous system infections are a common cause for acute symptomatic SE. Lumbar puncture should be performed whenever there is a clinical suspicion for infection. Children who are less than two years old, immunosuppressed or compromised, or have received recent antibiotics may present with status epilepticus prior to other clear signs of central nervous system infection.

EEG should be considered early to guide treatment and establish that seizures have stopped both electrographically as well as clinically.

- There is increasing data that after convulsive SE terminates some children have persisting electrographic seizures.

- Continuous EEG monitoring should be initiated within one hour of SE onset if ongoing seizures are suspected
- Diagnosing paroxysmal non epileptic attacks (PNEA) by EEG monitoring may avoid continued exposure to anticonvulsants and pharmacologic coma induction with potential adverse effects. Clinical signs that should increase suspicion of PNEA include:
 - Eyes tightly closed, side to side head movements (often fixed to one side in seizures), alternating limb shaking, arching, rotation of the body in multiple directions, and fluctuating course or “stop and go”⁹

General Management

1. Vital signs assessment (0 – 2 minutes)
2. Non-invasive airway protection and gas exchange with head positioning (0–2 minutes)
3. Neurologic examination (0 – 5 minutes)
4. Placement of peripheral intravenous access for administration of emergent anti-seizure medication therapy and fluid resuscitation (0 – 5 minutes)
5. Intubation if airway or gas exchange is compromised or intracranial pressure is elevated (0– 10 minutes)

Status Epilepticus Pathway

Having a stepwise plan, that is well known, will help abort episodes of status epilepticus earlier and more efficiently. This common pathway will help inform admitting providers of the recommended management and treatment that should be initiated for a patient that is found to have a seizure > 5 minutes.

If the admitting provider determines that some portion of the pathway could be detrimental to the patient (i.e. valproic acid contraindicated due to metabolic abnormality or neurologist requests viewing continuous EEG before certain medications beyond benzodiazepines are administered) then that provider will need to arrange an alternative pathway that will be clearly outlined and communicated to nursing and the admitting team.

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Status Epilepticus Clinical Pathway
 (First 60 Minutes)

Inclusion Criteria:

- Patients with seizure > 5 minutes

Exclusion Criteria:

- Neonates < 30 days
- Patients with epilepsy that have baseline EEG on the Ictal-interictal continuum
- Patients with psychogenic non-epileptic attacks

0 – 5 min

Emergency Center Pathway

- Determine prior history of seizures from EMS or caregiver
- Determine if benzodiazepines were given en route to EC

Inpatient Pathway

- Nurse should notify provider that patient is seizing. Patient should be evaluated at the bedside.
- If nurse is unable to contact provider, initiate a rapid response or code.

- Initiate ABCDE, oxygen, continuous pulse oximetry, and cardiorespiratory monitoring
- Obtain IV access, glucose POC, CBC w/diff and CMP with Mg and Phos
- Obtain anticonvulsant levels for established seizure patients
- Determine if seizure is epileptic or non-epileptic
- Concurrently, consider obtaining further labs (toxicology screen, HcG) & imaging with fast brain MRI or CT head if MRI unavailable
- Correct reversible causes like hyponatremia & hypoglycemia

5 – 10 min

Administer lorazepam IV 0.1 mg/kg/dose (max 4 mg/dose)
 If no IV access, consider midazolam (IM or IN) 0.2 mg/kg/dose (max 10 mg/dose)

**Reassess in 5 Minutes:
 Seizure Stopped?**

YES

NO

10 – 20 min

Repeat second dose of benzodiazepine **AND** administer second line medication
(second line medication should be administered even if the seizure stops after the second benzodiazepine dose)

ESTABLISHED SEIZURE PATIENT:

Consider loading dose of home medication if IV formulation is available **OR** initiate second line medication

OR

NEW ONSET SEIZURES:

Second Line Medications:

- Levetiracetam 60 mg/kg/dose IV (max 2500 mg)
- OR**
- Fosphenytoin 20 mg/kg/dose IV (max 1500 mg)
(Excluding Dravet syndrome)
- OR**
- Valproic acid 40 mg/kg/dose IV (max 3000 mg)
(Only patients > 2 years old or patients with known Dravet syndrome)

If above unavailable, consider phenobarbital 20 mg/kg/dose IV (max 1000 mg)

Consider ordering 2 second line medications

**Reassess in 5 minutes:
 Seizure Stopped?**

YES

NO

- Monitor patient
- Airway protection
- Consult Neurology
- Continue diagnostic work up from previous step
- Obtain video EEG if subclinical or focal seizure is suspected
- Consider LP if encephalitis or meningitis is suspected
- Consider initiation of maintenance therapy

20 – 60 min

Administer loading dose of an alternative second line medication

**Reassess in 5 minutes:
 Seizure Stopped?**

YES

NO

Contact Critical Care Team for transfer to PICU and treatment of refractory SE with continuous midazolam or pentobarbital infusion all with continuous EEG monitoring

* Guidelines should not replace clinical judgement; individual patients' co-morbidities and situation will influence treatment

Pharmacologic Management:

First Line Medications:

- The first line medication for SE is a benzodiazepine.
 - Administer lorazepam IV 0.1 mg/kg/dose (max 4 mg/dose)
 - If no IV access:
 - Midazolam IN 0.2 mg/kg/dose (max 10 mg/dose)
 - Midazolam IM 0.2 mg/kg/dose (max 10 mg/dose)
- Assess for the administration of previous doses of benzodiazepines prior to arrival by parent or rapid response/code team.
- Repeat benzodiazepine dose in 5 minutes if seizure has not resolved.

*****Second Line medication should be administered even if the seizure stops after the second benzodiazepine dose*****

Second Line Medications (administer within 5-10 minutes of continued seizure activity):

- Levetiracetam 60 mg/kg/dose IV (max 2500 mg) over 12 minutes
- Fosphenytoin 20 mg/kg/dose IV (max 1500 mg) over 30 minutes (excluding Dravet syndrome)
- Valproic acid 40 mg/kg/dose IV (max dose 3000 mg) over 60 minutes
 - Only for patients > 2 years OR with known Dravet Syndrome
- If above unavailable, consider phenobarbital 20 mg/kg/dose (max dose 1000 mg) over 30 minutes

*****If patient has received 2 second line medications, continue to continuous infusion*****

- For persistent seizures, initiate continuous IV medication titrating to cessation of electrographic seizures on EEG or burst suppression
 - Midazolam continuous infusion:
 - Bolus: 0.2 mg/kg IV once followed by:
 - Continuous infusion: Initiate at 0.1 mg/kg/hr
 - Titration: Increase by 0.1 mg/kg/hr every 15 minutes as needed for cessation of electrographic seizures on EEG or burst suppression to a max dose of 2 mg/kg/hr

OR

- Pentobarbital continuous infusion

Therapeutic Drug Monitoring:

Therapeutic drug monitoring is defined as the use of assay procedures for determination of drug concentrations in plasma, and the interpretation and application of the resulting concentration data to develop safe and effective drug regimens. If performed properly, this process allows for the achievement of therapeutic concentrations of a drug more rapidly and safely than can be attained with empiric dose changes.

Therapeutic ranges are typically established at the following timed blood collections after SS (steady state) concentrations have been reached (generally 5-7 half-lives after initiation or change in dosing).

- Trough - 0-60 minutes before dose administration
- Peak - generally 1-2 hours after drug administration; however, this is highly drug dependent
- Random levels

Medication	Peak	Trough	Steady State (SS)	Therapeutic Range (mcg/mL)	Other Labs
phenobarbital	Obtain 2 hours after loading dose	Obtain 1 hour prior to dose when at SS	3 – 5 weeks	15 – 40	
fosphenytoin*			3 – 4 days	10 – 20 (total) 0.8 – 1.6 (free)	Albumin
			valproic acid	2 – 4 days	50 - 100

*Phenytoin correction for hypoalbuminemia:

- Corrected Phenytoin = Total Phenytoin Level / ((0.2 x albumin) + 0.1)

Additional Considerations:

The following diagnostic codes should be used in known epilepsy patients:

1. Generalized epilepsy, intractable, with status epilepticus G40.311
2. Generalized epilepsy, not intractable, with status epilepticus G40.301
3. Focal epilepsy, intractable, with status epilepticus, G40.211
4. Focal epilepsy, not intractable, with status epilepticus G40.201

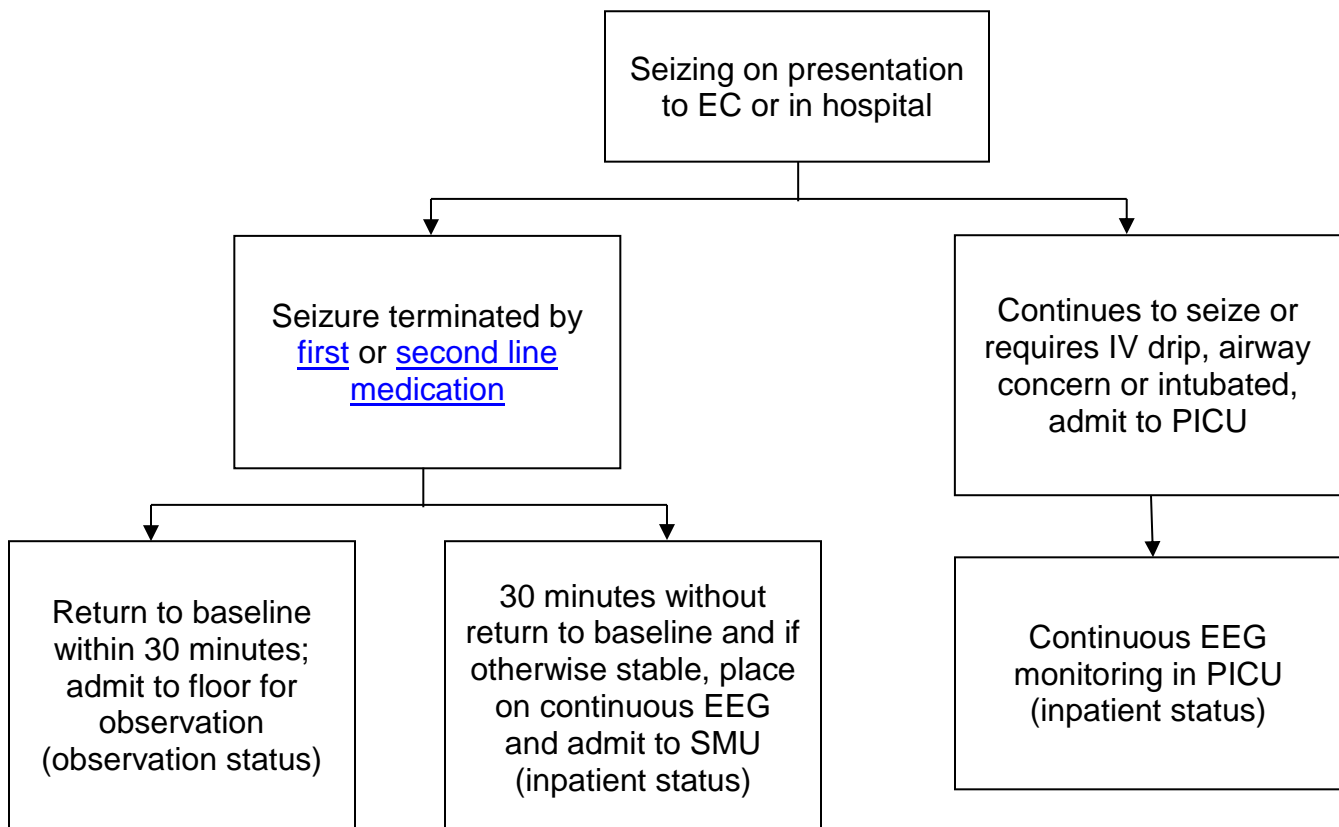
Additional codes that can be considered include:

5. Status epilepticus G40.901
6. Infantile spasms with status epilepticus G40.821
7. Intractable epilepsy with status epilepticus G40.911
8. Absence epileptic syndrome, not intractable, with status epileptics, G40.A01
9. Absence epileptic syndrome, intractable, with status epilepticus, G40. A11
10. Other generalized epilepsy and epileptic syndromes, not intractable, with status epilepticus, G40.401
11. Conversion disorder with seizures or convulsions, F44.5

Inpatient Status Admission Criteria:

1. **New onset seizure disorder** (≥ 2 in 24 hours) and a new antiepileptic medication (AED) is started, routine EEG or continuous EEG, Neuro checks q4h, and seizure precautions with anticipated stay > 24 hours
2. **Known seizure disorder** on AED therapy with good compliance and a therapeutic level who has breakthrough seizures greater than 2 in 24 hours or change in seizure type or duration. Intervention would require change in AED or dose adjustments, routine or continuous EEG, neuro checks q4h, and seizure precautions with anticipated stay > 24 hours
3. Patient with seizure qualifying as status epilepticus (i.e. seizure >5 minutes and having a seizure on arrival) with anticipated stay > 24 hours
4. Patient with seizure who has not returned to baseline mental status with anticipated stay > 24 hours

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Discharge Considerations

- No seizure activity in >24 hours
- Patient has returned to baseline mental status
- Tolerating antiepileptic medication
- Outpatient laboratory testing and neurology follow up appointment established

EC/PICU OUTCOME MEASURES:

1. Time to cessation of clinical seizures
2. Time to first line medication
3. Time to second and third line medication
4. Time to continuous EEG placement
5. Time to continuous IV midazolam or pentobarbital infusion, if needed

FLOOR OUTCOME MEASURES:

1. Time to cessation of clinical seizures
2. Time to first line medication
3. Time to second and third line medication
4. Time to transfer to PICU

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