**Supplemental Digital Appendix 1**

DATE: July 2015

# Medical University of South Carolina
# Center for Evidence-Based Practice and Outcomes Research
## *Management of Prolonged Seizure and Status Epilepticus in Infants & Children*
## Evidence-Based Practice Review Summary

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**Objective for the Review:** To critically review the evidence on strategies for diagnosis and management of prolonged seizure or status epilepticus in the pediatric population

**Inclusion Criteria:** infants/children aged >30 days and <18 years with prolonged seizures or status epilepticus in the ED and inpatient settings

**Exclusion Criteria:** neonates (≤30 days old), adults

**Target Order Set Users:** All clinicians caring for infants/children with prolonged seizures or status epilepticus in the ED or inpatient setting at MUSC

**Review Preparation**

1) In pediatric patients presenting with seizures characterized by tonic-clonic generalized movements, what laboratory studies are useful in diagnosing and managing patients?

*In infants/children with prolonged seizures/status epilepticus (SE):*

2) does routine use of diagnostic imaging studies impact emergent clinical management?
3) which benzodiazepine is most effective, timely, and safe as first-line therapy? And which route is most effective (e.g., IV, oral, intranasal)?
4) which anticonvulsant is most effective, timely, and safe as second-line therapy?
5) which anticonvulsant is most effective, timely, and safe as third-line therapy?

6) In pediatric patients with refractory status epilepticus, what is the optimal continuous EEG monitoring strategy to improve patient outcomes?

**Quality Measures:**

Outcome
- ED and IP LOS
- Direct variable cost
- Readmission rate

Process
- Utilization of ED, floor and IP order sets
- Utilization of the Seizure Drug Panel
- Time to POC glucose (from admission in ED)
- Time to POC glucose (from seizure initiation in IP)
- Time to appropriate initial emergent therapy (from admission in ED)
- Time to appropriate initial emergent therapy (from seizure initiation in IP)
- Time to appropriate urgent control therapy (from admission in ED)
- Time to appropriate urgent control therapy (from seizure initiation in IP)
- Time to appropriate refractory therapy (from admission in ED)
- Time to appropriate refractory therapy (from seizure initiation in IP)
- Rate of routine EEG
- Time to routine EEG (from seizure initiation)
- Rate of continuous EEG
- Time to continuous EEG (from seizure initiation)
- Rate of IV placement in ED (if admitted to IP)
- Rate of IV placement IP

## Existing External Guidelines/Pathways/Order Sets

**Existing External Guidelines**

| Title | Guideline Issuer | Year |
|---|---|---|
| The Epilepsies: the Diagnosis and Management of the Epilepsies in Adults and Children in Primary and Secondary Care | National Institute for Health and Care Excellence | 2012 |
| Guidelines for the Evaluation and Management of Status Epilepticus | Neurocritical Care Society (Brophy et al.) | 2012 |
| Practice Parameter: Diagnostic Assessment of the Child with Status Epilepticus | American Academy of Neurology (Rivello et al.) | 2006, reaffirmed 2013 |
| Practice Parameter: Use of Serum Prolactin in Diagnosis Epileptic Seizures | American Academy of Neurology (Chen et al.) | 2005, reaffirmed 2013 |
| Initial Management of Seizures (Status Epiliepticus) Evidence-based Clinical Guidelines | Texas Children's Hospital Evidence-based Outcomes Center (Macias et al.) | 2009 |
| Recommendations on the use of EEG monitoring in critically ill patients | European Society of Intensive Care Medicine (Claassen et al.) | 2013 |

The five published clinical guidelines have been evaluated for this review using the **University of Pennsylvania's Center for Evidence-Based Practice Trustworthy Guideline rating scale.** The scale is based on the Institute of Medicine's "Standards for Developing Trustworthy Clinical Practice Guidelines" (IOM), as well as a review of the AGREE Enterprise and Guidelines International Network domains.

### Guideline Ratings

| Guideline Issuer | NICE 2012 | NCS 2012 | AAN 2005 2006 | TCH 2009 | ESICM 2013 |
|---|---|---|---|---|---|
| 1. Transparency | A | B | B | A | A |
| 2. Conflict of interest | NR | NR | NR | NR | A |
| 3. Development group | A | C | C | A | A |
| 4. Systematic Review | A | B | B | B | A |
| 5. Supporting evidence | A | A | A | A | A |
| 6. Recommendations | A | A | B | A | A |
| 7. External Review | NR | NR | NR | NR | NR |

| | | | | | |
|---|---|---|---|---|---|
| 8. Currency and updates | A | B | C | A | |

See appendix B for full description of the Trustworthy Guideline grading system.

## Guideline Evidence Evaluation Systems

| | National Institute for Health and Care Excellence 2012 | Neurocritical Care Society 2012 | American Academy of Neurology 2005 & 2006 | Texas Children's Hospital 2009 | European Society of Intensive Care Medicine 2013 |
|---|---|---|---|---|---|
| **Evidence Evaluation** | The GRADE criteria were utilized to evaluate the body of evidence used to make clinical recommendations but levels of evidence were not provided for the individual practice recommendations STRONG recommendation: Desirable effects clearly outweigh undesirable effects or vice versa WEAK recommendation: Desirable effects closely balanced with undesirable effects High quality evidence: Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies Moderate quality evidence: Evidence from RCTs with important limitations (e.g., inconsistent results, methodological flaws, indirect evidence, or imprecise results) or unusually strong evidence from unbiased observational studies Low quality evidence: Evidence for at least 1 critical outcome from observational studies, from RCTs with serious flaws or indirect evidence Very Low quality evidence: Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence | The GRADE criteria and the standardized assessment methods from the American Heart Association were utilized to evaluate the body of evidence used to make clinical recommendations American Heart Association: Level A: Adequate evidence is available from multiple, large, randomized clinical trials or meta analyses Level B: Limited evidence is available from less rigorous data, including fewer, smaller randomized trials, | Class I: Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets a–d above or a randomized, controlled trial in a representative population that lacks one criteria Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment. Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion Level A: requires at least one convincing Class I study or at least two consistent, convincing Class II studies. Level B: requires at least one convincing Class II study or overwhelming Class III evidence. Level C: requires at least two convincing Class III studies. | Published clinical guidelines were evaluated for this review using the AGREE criteria - The Critical Appraisal Skills Program (CASP) criteria were used to evaluate the quality of articles reviewed. Application of the CASP criteria are completed by rating each reviewed study or review as: Strong study/systematic review - well designed, well conducted, adequate sample size, reliable measures, valid results, appropriate analysis, and clinically applicable/relevant. Study/systematic review with minor limitations - specifically lacking in one of the above criteria Study/systematic review with major limitations - specifically lacking in several of the above criteria | The GRADE criteria were used to evaluate the body of evidence used to make clinical recommendations. Quality of evidence was rated as high (grade A), moderate (grade B), low (grade C), or very low (grade D). Recommendations were also classified as strong (grade 1) or weak (grade 2). A strong recommendation reflects the possibility that following the given recommendation about EEG will result in more beneficial effects (detection and therapy of seizures, reduced injury associated with ongoing seizures, improved outcome, less burden on staff and patients, cost savings) than harm to ICU patients (inaccurate predictive value, useless antiepileptic drugs (AED), difficult EEG implementation). A weak recommendation reflects the opinion that the benefit/risk balance could be in favor of this recommendation, but the members of the task force were not confident because of limited evidence. |

## Review of Relevant Evidence: Search Strategies and Databases Reviewed

| Search Strategies | Document Strategies Used |
|---|---|
| **Search Terms Used:** | **1st line:** (status epilepticus [MeSH] OR "status epilepticus") AND (benzodiazepines [MeSH] OR benzodiazepines OR lorazepam OR Ativan OR midazolam OR diazepam OR Diastat OR Valium); **2nd line:** ("Status epilepticus"[MeSH] OR "status epilepticus") AND ("anticonvulsants"[MeSH] OR anticonvulsant OR antiepileptic OR Keppra OR Levetiracetam OR fosphenytoin OR Cerebyx OR phenytoin OR Dilantin OR Phenytek OR valproate sodium OR midazolam OR phenobarbital) AND ("second line" OR second-line OR "urgent control" OR longer-acting OR "benzodiazepine refractory"); **3rd line:** ("status epilepticus"[MeSH] OR "status epilepticus") AND ("anticonvulsants"[MeSH] OR anticonvulsant OR antiepileptic OR propofol OR Diprivan OR Fresenius OR Propoven OR midazolam OR phenobarbital OR thiopental OR pentobarbital OR Nembutal) AND ("third line" OR "third-line" OR refractory); **laboratory studies:** ("status epilepticus"[MeSH] OR "status epilepticus") AND ("clinical laboratory techniques"[MeSH] OR laboratory OR workup OR toxicology OR "serum glucose" OR "serum electrolytes" OR glucose OR magnesium OR calcium OR "renal function" OR "liver function" OR "Blood Cell Count"[MeSH] OR blood) AND ("diagnosis"[MeSH] OR diagnos* OR "differential diagnosis" OR "disease management"[MeSH] OR management); **imaging studies:** ("status epilepticus"[MeSH] OR "status epilepticus") AND ("diagnostic imaging"[MeSH] OR radiology OR imaging OR MRI OR "computed tomography" OR CT[tiab] OR electrocardiograph OR electrocardiography OR ECG OR electroencephalograph OR electroencephalogram OR electroencephalography OR EEG OR "cerebral ultrasound" OR "brain neuroimaging") AND ("diagnosis, differential"[MeSH] OR diagnos* OR "differential diagnosis" OR management); **continuous EEG monitoring:** ("Status Epilepticus"[Mesh] OR status epilepticus) AND (refractory OR uncontrolled) AND ("Electroencephalography"[Mesh] OR electroencephalogra* OR EEG OR cEEG) AND continuous |
| **Years Searched - All Questions** | 2000 - present (1st line therapy); 2005 - present (2nd line therapy, 3rd line therapy, laboratory studies, imaging studies) |
| **Language** | English |
| **Age of Subjects** | Infants and children (<18 years old) |
| **Search Engines** | PubMed, Scopus, CINAHL, PsychINFO, Cochrane Database of Systematic Reviews, National Guideline Clearinghouse |
| **Government/State Agencies** | National Institute for Health and Care Excellence |
| **Other** | Neurocritical Care Society, American Academy of Neurology, Texas Children's Hospital |

## Evidence Found with Searches

| Check type of evidence found | Summary of Evidence – All Questions | Number of articles obtained |
|---|---|---|
| ☒ | Systematic reviews/Meta-analysis | 2 |
| ☒ | Randomized controlled trials | 9 |
| ☒ | Non-randomized studies | 20 |
| ☐ | Government/State agency regulations | 0 |
| ☒ | Professional organization guidelines/white papers, etc. | 5 |

**Evaluating the Quality of the Evidence**

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. The table below defines how the quality of the evidence is rated and how a strong versus weak recommendation is established. For more detailed information, see Appendix A.

| Recommendation | |
|---|---|
| **STRONG** | Desirable effects clearly outweigh undesirable effects or vice versa |
| **WEAK** | Desirable effects closely balanced with undesirable effects |
| **Quality** | **Type of Evidence** |
| **High** | Further research is very unlikely to change our confidence in the estimate of effect. |
| **Moderate** | Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. |
| **Low** | Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. |
| **Very Low** | Any estimate of effect is very uncertain. |

**Question #1. In pediatric patients with prolonged seizures/status epilepticus (SE), which laboratory analysis studies are useful in diagnosing and managing the patient?**

**MUSC Clinical Practice Recommendation(s):** Point of care serum glucose should be taken as soon as possible for all actively seizing patients. Venous blood gas levels should be checked after the first and second doses of urgent control therapy. Additional laboratory test may be necessary after seizure cessation based on patient history and clinical indications. **Strong Recommendation, Low Quality Evidence**

## Guideline Recommendations:

***Laboratory Analysis:***

The Neurocritical Care Society guideline for evaluation and management of status epilepticus in adults and children (2012) recommends that a lumbar puncture (LP) is only warranted if a CNS infection is suspected. **(Expert Opinion)**

The National Institute of Health and Care Excellence guideline (2012) recommends measurement of serum prolactin is not recommended for the diagnosis of epilepsy. In children and young people, other investigations, including blood and urine biochemistry, should be undertaken at the discretion of the specialist to exclude other diagnoses, and to determine an underlying cause of the epilepsy.

The Practice Parameter on diagnostic assessment of the child with status epilepticus from the American Academy of Neurology (2006) recommends:

1. There are insufficient data to support or refute whether blood cultures should be done on a routine basis in children in whom there is no clinical suspicion of infection. **(Level U)**
2. There are insufficient data to support or refute whether LP should be done on a routine basis in children in whom there is no clinical suspicion of infection. **(Level U)**
3. Antiepileptic drug (AED) levels should be considered when a child with epilepsy on AED prophylaxis develops SE. **(Level B, Class II & III)**

4. Toxicology testing may be considered in children with SE, when no apparent etiology is immediately identified, as the frequency of ingestion as a diagnosis was at least 3.6%. **(Level C, class III evidence)** To detect a specific ingestion, suspected because of the clinical history, it should be noted that a specific serum toxicology level is required, rather than simply urine toxicology screening.
5. Studies for inborn errors of metabolism may be considered when the initial evaluation reveals no etiology, especially if there is a preceding history suggestive of a metabolic disorder. The specific studies obtained are dependent on the history and the clinical examination. There is insufficient evidence to support or refute whether such studies should be done routinely. **(Level C, Class III)**
6. The specific studies obtained are dependent on the history and the clinical examination. There is insufficient evidence to support or refute whether such studies should be done routinely. **(Level U)**
7. There are insufficient data to support or refute whether genetic testing (chromosomal or molecular studies) should be done routinely in children with SE. **(Level U)**

The Practice Parameter on the use of serum prolactin in diagnosing epileptic seizures from the American Academy of Neurology (2005) recommends:

1. Elevated serum prolactin (PRL), when measured in appropriate clinical setting at 10 to 20 minutes after a suspected event, should be considered a useful adjunct to differentiate GTC or CPS from psychogenic NES among adults and older children. **(Level B)**
2. Serum PRL, when measured more than 6 hours after a suspected event, should be representative of the baseline PRL level. **(Level B)**
3. Serum PRL assay is not of utility to distinguish seizure from syncope. **(Level B)**
4. The utility of serum PRL assay has not been established in the evaluation of SE, repetitive seizures, or neonatal seizures. **(Level U)**

Texas Children's Hospital, Evidence-based Outcomes Center guideline for initial management of seizures (2009) recommends:

1. Blood cultures, LP, AED levels, and toxicology levels are not routinely recommended in children with SE.
2. AED levels should be considered in children with epilepsy currently being treated with antiepileptic medications.
3. Serum toxicology levels should be considered when no apparent etiology is identified.
4. LP should be considered based on history, clinical findings, and fever.
5. In otherwise healthy infants (≤ 12 months), laboratory tests could include: Blood glucose check (Accu-Chek®) and Chem 10 (includes sodium, potassium, chloride, CO2, BUN, creatinine, glucose, calcium, magnesium, phosphorus).

**Primary Literature:**

| **PICO Question #1: In pediatric patients with prolonged seizures/status epilepticus (SE), which laboratory analysis studies are useful in diagnosing and managing the patient?** | | | | | | Lower Quality Rating if: |
|---|---|---|---|---|---|---|
| *Author/Date/ Journal* | *Purpose of Study* | *Study Design* | *Sample& Setting* | *Outcomes* | *Design Limitations* | ☒ Studies inconsistent (*When there are differences in the direction of the effect, populations, interventions or outcomes between studies)*<br><br>☐ Studies are indirect *(Your PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*<br><br>☒ Studies are imprecise (*When studies include few patients and few* |
| Boyle & Sturm, 2013, *Pediatric Emergency Care* | To determine the clinical factors associated with a more extensive workup in a cohort of patients who present to the pediatric ED with Complex Febrile Seizures(CFS) | Retrospective observational cohort | 120,000 patients (6mo – 6 yrs) from 2 tertiary care centers reviewed from 2009-2011 | The only factor associated with having a Lumbar Puncture (LP) performed was whether empiric antibiotics were used (OR, 2.96; 95% CI, 1.28–6.8). In this patient population, history of a febrile seizure was associated with lower odds of an LP (OR, 0.29; 95% CI, 0.12–0.69). In addition, an older-age category was also associated with lower odds | Study Limitations =<br>☐ None<br>***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)***<br>☐ Insufficient sample size<br>☐ Sample not representative of patients in the population as a whole<br>☐ Variables (confounders, exposures, predictors) were not described<br>☒ Outcome criteria not objective or were not applied in blind fashion<br>☒ Insufficient follow-up, if applicable<br>☐ For prognostic study, sample not defined | |

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| | | | | of an LP (OR, 0.53; 95% CI, 0.31–0.91).<br><br>There was an association between previous febrile seizures and lower odds of an LP. A lower-age category was associated with an increased odds of an LP performed in our cohort of patients with CFS. If empiric antibiotics were given in the emergency department, an LP was more often performed. | at common point in course of disease/condition<br>☐ For diagnostic study, gold standard not applied to all patients<br>☐ For diagnostic study, no independent, blind comparison between index test and gold standard | *events and thus have wide confidence intervals and the results are uncertain)*<br><br>☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug)*<br><br>Increase Quality Rating if:<br>☐ Large Effect<br><br>Level of evidence for studies as a whole:<br><br>☐ High<br>☐ Moderate<br>☒ Low<br>☐ Very Low |
| Hardasmalani et al., 2012, *Pediatric Emergency Care* | To determine the yield of diagnostic workup in children presenting with complex febrile seizures (CFS) | Retrospective chart review | 71 children (6 mo – 6 yrs) with complex febrile seizures | Boys accounted for 59.2% of cases, and median age was1.5 years with SD of 1.13<br><br>70 patients had normal neurologic examination. In regards to the CBC, all 71 patients had serum chemistries; none with abnormal electrolytes. All patients had blood and urine cultures performed; none were positive. 67 Patients had lumbar puncture for CSF analysis. One patient (1/67) had abnormal findings for high protein and culture positive for Mycoplasma pneumonia.<br><br>**Conclusion was most patients with complex seizures do not require extensive diagnostic workup**, i.e. CSF analysis, CBC, blood culture, urinalysis, and chemistries. | Study Limitations =<br>☐ None<br>***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)***<br>☒ Insufficient sample size<br>☒ Sample not representative of patients in the population as a whole<br>☒ Variables (confounders, exposures, predictors) were not described<br>☒ Outcome criteria not objective or were not applied in blind fashion<br>☐ Insufficient follow-up, if applicable<br>☐ For prognostic study, sample not defined at common point in course of disease/condition<br>☐ For diagnostic study, gold standard not applied to all patients<br>☐ For diagnostic study, no independent, blind comparison between index test and gold standard | |
| Sutter et al., 2013, *Critical Care Medicine* | To elucidate an association of C-reactive protein and albumin with | Retrospective observational cohort | 135 patients analyzed from 2005 to 2009 in the ICU of a | Albumin level at SE onset was the only biomarker significantly associated with death after adjustment for | Study Limitations =<br>☐ None<br>***Non-Experimental/Observational Studies (case-control, cohort, cross sectional,*** | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | the course and outcome of SE | | University Hospital in Switzerland | confounders (SE severity, tumors, and infection). With every 1g/L increase in albumin risk of refractory SE (OR=0.92, 95%CI .86-.97, p=.004) and death (OR=0.86, 95%CI .79-.94, p=.001) decreased.<br><br>CRP levels were recorded daily for three days after SE onset. After adjusting for confounders only CRP recorded on the third day had a significant association with developing RSE (OR 1.01, 95%CI 1.00-1.02).<br><br>**Multivariable logistic regression for albumin and CRP found, only albumin at SE onset remained independently and significantly associated with refractory SE (OR .92, 95%CI .86-98) and death (OR .90, 95%CI .83-.97).** | ***longitudinal, descriptive, epidemiologic, case study/series, QI, survey)***<br>☐ Insufficient sample size<br>☒ Sample not representative of patients in the population as a whole<br>☐ Variables (confounders, exposures, predictors) were not described<br>☒ Outcome criteria not objective or were not applied in blind fashion<br>☐ Insufficient follow-up, if applicable<br>☐ For prognostic study, sample not defined at common point in course of disease/condition<br>☒ For diagnostic study, gold standard not applied to all patients<br>☐ For diagnostic study, no independent, blind comparison between index test and gold standard | |
| Sutter, Tschudin-Sutter, Grize, et al., 2011, *Critical Care* | To examine the reliability of C-reactive protein (CRP), procalcitonin (PCT), and WBC for diagnosis of infections during SE | Retrospective observational cohort | 160 patients from 1 hospital with SE confirmed by electroenceph alogram | 22.5% of the 160 SE patients had infections during SE. Single levels of CRP and WBC had no association with the presence of infections<br>**The linear changes WBC and CRP over the first three days after SE onset were significantly associated with the presence of infections (*P* = 0.0012 for CRP, *P* = 0.0137 for WBC)**<br><br>Levels of PCT were available for 31 patients and did not differ significantly in patients with and without | Study Limitations =<br>☐ None<br>***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)***<br>☐ Insufficient sample size<br>☐ Sample not representative of patients in the population as a whole<br>☐ Variables (confounders, exposures, predictors) were not described<br>☒ Outcome criteria not objective or were not applied in blind fashion<br>☐ Insufficient follow-up, if applicable<br>☐ For prognostic study, sample not defined at common point in course of disease/condition<br>☐ For diagnostic study, gold standard not applied to all patients<br>☐ For diagnostic study, no independent, | |

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| | | | | infections<br><br>Low levels of CRP and PCT rule out hospital-acquired infections in SE patients. | blind comparison between index test and gold standard | |
| Tobias et. al, 2007, *Southern Medical Journal* | To improve the treatment of status epilepticus through documenting any variability of initial stabilization, evaluation, and pharmacologic treatment of infants and children with SE | Retrospective observational cohort | 100 continuous patients with SE | Lack of laboratory evaluation was a potential issue of care. When serum glucose was measured, results were not available for 20 minutes or more in 37% of the patients. No measurement of serum sodium was obtained in 9 of the 100 patients during their initial evaluation. | Study Limitations =<br>☐ None<br>***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)***<br>☒ Insufficient sample size<br>☒ Sample not representative of patients in the population as a whole<br>☐ Variables (confounders, exposures, predictors) were not described<br>☐ Outcome criteria not objective or were not applied in blind fashion<br>☐ Insufficient follow-up, if applicable<br>☐ For prognostic study, sample not defined at common point in course of disease/condition<br>☐ For diagnostic study, gold standard not applied to all patients<br>☐ For diagnostic study, no independent, blind comparison between index test and gold standard | |

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**Question #2. In infants/children with prolonged seizures/status epilepticus (SE), does routine use of diagnostic imaging studies impact emergent clinical management?**

**MUSC Clinical Practice Recommendation(s):** Routine EEG is recommended in patients that do not return to functional baseline within 60 minutes from cessation of seizure activity. EEG may be considered in children with new onset status epilepticus and for children with an apparent first, unprovoked seizure. Continuous EEG is recommended for children with refractory status epilepticus, or if there is concern for non-convulsive status epilepticus. Notify neurology to facilitate continuous EEG. **Strong Recommendation, Low Quality Evidence**

**Guideline Recommendations:**

***Diagnostic Imaging:***

The National Institute for Health and Care Excellence Guideline on the Diagnosis and Management of the Epilepsies (2012) recommends:

1. An EEG should be performed only to support a diagnosis of epilepsy in children and young people. If an EEG is considered necessary, it should be performed after the second epileptic seizure but may, in certain circumstances, as evaluated by the specialist, be considered after a first epileptic seizure.
2. The EEG should not be used to exclude a diagnosis of epilepsy in a child, young person or adult in whom the clinical presentation supports a diagnosis of a non-epileptic event.
3. An EEG may be used to help determine seizure type and epilepsy syndrome in children, young people and adults in whom epilepsy is suspected. This enables them to be given the correct prognosis.
4. Neuroimaging should be used to identify structural abnormalities that cause certain epilepsies.
5. MRI should be the imaging investigation of choice in children, young people and adults with epilepsy. Computed tomography (CT) should be used to identify underlying gross pathology if MRI is not available or is contraindicated, and for children or young people in whom a general anaesthetic or sedation would be required for MRI but not CT. In an acute situation, CT may be used to determine whether a seizure has been caused by an acute neurological lesion or illness.
6. Neuroimaging should not be routinely requested when a diagnosis of idiopathic generalized epilepsy has been made. In children and young people, a 12-lead ECG should be considered in cases of diagnostic uncertainty.

The Practice Parameter on diagnostic assessment of the child with status epilepticus from the American Academy of Neurology (2006) recommends:

1. An EEG may be considered in a child presenting with new onset SE as it may determine whether there are focal or generalized abnormalities that may influence diagnostic and treatment decisions. **(Level C, Class III)**
2. Although non-convulsive SE occurs in children who present with SE, there are insufficient data to support or refute recommendations regarding whether an EEG should be obtained to establish this diagnosis. **(Level U)**
3. Neuroimaging may be considered for the evaluation of the child with SE if there are clinical indications or if the etiology is unknown. **(Level C, class III)** If neuroimaging is done, it should only be done after the child is appropriately stabilized and the seizure activity controlled.
4. There is insufficient evidence to support or refute recommending routine neuroimaging. **(Level U)**

Texas Children's Hospital, Evidence-based Outcomes Center guideline for initial management of seizures (2009) recommends:

1. Electroencephalograms (EEG) are not routinely recommended. EEG may be considered in children presenting with new onset SE.

2. Brain computed tomography (CT) or magnetic resonance imaging (MRI) is not routinely recommended. If there are no clinical indicators or etiology is unknown, neuroimaging may be considered once the child is stabilized.

European Society of Intensive Care Medicine 2013 recommends:

1. Urgent EEG in patients with SE that do not return to functional baseline within 60 min after administration of seizure medication **(strong recommendation, low quality of evidence—grade 1C)**.
2. Urgent (within 60 min) EEG in patients with refractory SE **(strong recommendation, low quality of evidence—grade 1C)**.

**Primary Literature:**

**PICO Question #2: In infants/children with prolonged seizures/status epilepticus (SE), does routine use of diagnostic imaging studies impact emergent clinical management?**

| *Author/Date/Journal* | *Purpose of Study* | *Study Design* | *Sample& Setting* | *Outcomes* | *Design Limitations* |
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| Fernandez et al., 2014, *Journal of Child Neurology* | To identify indications when EEG in the pediatric ED is most useful | Retrospective descriptive study | 68 children (mean age: 7.3 yrs) underwent emergent EEGs | An emergent EEG with sharp waves or spikes had a sensitivity of 0.83, a specificity of 0.96, a positive predictive value of 0.91, and a negative predictive value of 0.91.<br><br>Among the children who received the diagnosis of epilepsy,83.3% had an abnormal EEG in the ED. | Study Limitations =<br>☐ None<br>Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)<br>☒ Insufficient sample size<br>☐ Sample not representative of patients in the population as a whole<br>☐ Variables (confounders, exposures, predictors) were not described<br>☐ Outcome criteria not objective or were not applied in blind fashion<br>☐ Insufficient follow-up, if applicable<br>☐ For prognostic study, sample not defined at common point in course of disease/condition<br>☐ For diagnostic study, gold standard not applied to all patients<br>☒ For diagnostic study, no independent, blind comparison between index test and gold standard |
| Kalita et al., 2006, *Electromyography and Clinical Neurophysiology* | To evaluate the role of clinical, EEG and radiological changes in predicting the outcome of SE | Prospective cohort | 70 patients (children & adults) with status epilepticus and EEG results | EEG at 1 hour was abnormal in 51/53 patients. Clinical seizures recurred in 38 patients within 24 hours, and 15 of them had ictal discharges at 1 hour EEG. Duration of EEG was ≤1hr for 18 patients and >1hr for 52 patients. Duration was not found to correlate with | Study Limitations =<br>☐ None<br>Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)<br>☒Insufficient sample size<br>☐ Sample not representative of patients in the population as a whole<br>☐ Variables (confounders, exposures, |

Lower Quality Rating if:
☒ Studies inconsistent (*When there are differences in the direction of the effect, populations, interventions or outcomes between studies)*

☐Studies are indirect *(Your PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*

☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*

☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug)*

Increase Quality Rating if:
☐ Large Effect

Level of evidence for studies as a

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| | | | | prognosis (p=0.94).<br><br>The patients with ictal EEG abnormality at 1 hour had high frequency of seizure recurrence within 24 hours (p=0.01). 15/22 patients with ictal EEG discharges had recurrences of seizures within 24 hours. Only 10/33 patients without ictal abnormality had recurrence. **EEG is useful in monitoring status epilepticus and its abnormality at 1 hour predicts seizure recurrence within 24 hours.** | predictors) were not described<br>☐ Outcome criteria not objective or were not applied in blind fashion<br>☐ Insufficient follow-up, if applicable<br>☐ For prognostic study, sample not defined at common point in course of disease/condition<br>☐ For diagnostic study, gold standard not applied to all patients<br>☒For diagnostic study, no independent, blind comparison between index test and gold standard | whole:<br><br>☐ High<br>☐ Moderate<br>☒ Low<br>☐ Very Low |
| Nordli et al., 2012, *American Academy of Neurology* | To evaluate the relationships among serial EEG, MRI, and clinical follow-up in a cohort of children followed from the time of presentation with febrile SE | Prospective cohort | 199 children with febrile SE within 72 hours of presentation to the ED | 90/199 (45.2%) EEGs were abnormal with the most common abnormality being focal slowing (n=47) or attenuation (n=25); these were maximal over the temporal areas in almost all cases. Epileptiform abnormalities were present in 13 EEGs (6.5%). The odds of focal slowing were significantly increased by focal febrile SE (OR=5.08) and hippocampal T2 signal abnormality (OR=3.50), and significantly decreased with high peak temperature (OR= 0.18). Focal EEG attenuation was also associated with hippocampal T2 signal abnormality (OR= 3.3). | Study Limitations =<br>☐ None<br>Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)<br>☐ Insufficient sample size<br>☐ Sample not representative of patients in the population as a whole<br>☐ Variables (confounders, exposures, predictors) were not described<br>☐ Outcome criteria not objective or were not applied in blind fashion<br>☐ Insufficient follow-up, if applicable<br>☐ For prognostic study, sample not defined at common point in course of disease/condition<br>☐ For diagnostic study, gold standard not applied to all patients<br>☒For diagnostic study, no independent, blind comparison between index test and gold standard | |
| Yoong et al., 2012 *Developmental Medicine and Child Neurology* | To determine the yield of magnetic resonance imaging (MRI) after | Prospective cohort | 80 children (1mo–16yr) were enrolled and seen for clinical assessment | Structural abnormalities were found in 31% of patients. Abnormal neurological examination at assessment (OR=190.46), CSE that was | Study Limitations =<br>☐ None<br>Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey) | |

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| | an episode of childhood convulsive status epilepticus (CSE) and to identify the clinical predictors of an abnormal brain scan | | and brain MRI within 13 weeks of suffering from an episode of CSE | not a prolonged febrile seizure (OR= 77.12), and a continuous rather than an intermittent seizure (OR= 29.98) were all predictive of an abnormal scan. No children with previous neuroimaging had new findings that altered their clinical management. | ☒ Insufficient sample size<br>☒ Sample not representative of patients in the population as a whole<br>☐ Variables (confounders, exposures, predictors) were not described<br>☐ Outcome criteria not objective or were not applied in blind fashion<br>☐ Insufficient follow-up, if applicable<br>☐ For prognostic study, sample not defined at common point in course of disease/condition<br>☐ For diagnostic study, gold standard not applied to all patients<br>☒For diagnostic study, no independent, blind comparison between index test and gold standard | |

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**Question #3. In infants/children with prolonged seizures/status epilepticus (SE), which benzodiazepine is most effective, timely, and safe as first line therapy? Which route is most effective (e.g., IV, oral, intranasal)?**

**MUSC Clinical Practice Recommendation(s):** Benzodiazepines are recommended for use as first line therapy for treatment of SE. IV lorazepam (0.1 mg/kg; Max dose: 4mg) is recommended for patients with immediate IV access. Intranasal midazolam (0.2 mg/kg; Max: 10mg) or rectal diazepam (Age < 2 years: dosing not established; Age 2-5 years: 0.5 mg/kg; Age 6-11 years: 0.3 mg/kg; Age >= 12 years: 0.2 mg/kg (max 20 mg/dose) are recommended for use in patients without immediate IV access. If initial dose does not provide seizure cessation within 5 minutes, a 2nd dose should be administered. For patients admitted to the ED, proceed to urgent therapy if a benzodiazepine was administered pre-hospital. **Strong Recommendation, Moderate Quality Evidence**

## Guideline Recommendations:

***First-line therapies:***

The Neurocritical Care Society guideline for evaluation and management of status epilepticus in adults and children (2012) recommends:

1. Benzodiazepines should be given as emergent initial therapy. **(Strong recommendation, High quality evidence)**
2. Lorazepam is the drug of choice for IV administration. **(Strong recommendation, Moderate quality evidence)**
3. Midazolam is the drug of choice for IM administration. **(Strong recommendation, Moderate quality evidence)**
4. Rectal diazepam can be given when there is no IV access and IM administration of midazolam is contraindicated. **(Strong recommendation, Moderate quality evidence)**

The National Institute for Health and Care Excellence guideline for the diagnosis and management of epilepsies in adults and children (2012) recommends:

1. Administer intravenous lorazepam as first-line treatment in hospital in children, young people and adults with ongoing generalized tonic–clonic seizures (convulsive status epilepticus).
2. Administer intravenous diazepam if intravenous lorazepam is unavailable, or buccal midazolam if unable to secure immediate intravenous access.
3. Administer a maximum of two doses of the first-line treatment (including pre-hospital treatment).

Texas Children's Hospital, Evidence-based Outcomes Center guideline for initial management of seizures (2009) recommends:

1. Drug treatment should be initiated without delay once the diagnosis of early SE has been determined, and children with early SE should be treated with lorazepam as 1st line therapy.
2. If seizures continue AND a benzodiazepine was NOT administered prehospital, a second dose of lorazepam can be given.
3. With seizure cessation following 1st line therapy, children with new onset seizures should be observed.

## Primary Literature:

| **PICO Question #3: In infants/children with prolonged seizures/status epilepticus (SE), which benzodiazepine is most effective, timely, and safe as first-line therapy? Which route is most effective (e.g., IV, oral, intranasal)?** | | | | | | Lower Quality Rating if: ☒ Studies inconsistent *(When there are differences in the direction of the effect, populations, interventions or outcomes between studies)* ☐ Studies are |
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| *Author/Date/Journal* | *Purpose of Study* | *Study Design* | *Sample* | *Outcomes* | *Design Limitations* | |
| Brigo et al., 2015, *Epilepsy Behav* | To determine in non-IV midazolam (MDZ) is as effective and safe as IV or rectal diazepam (DZP) in terminating early SE seizures in children and adults | Systematic review & meta-analysis | 19 studies with 1933 seizures in 1602 patients (18 were conducted in children) | **Non-IV MDZ was as effective as DZP by any route (RR=1.03, 95% CI 0.98-1.08; p=0.29; $I^2$=65%). Non-IV MDZ and DZP by any route had similar risk of adverse effect (RR=0.87, 95% CI 0.50-1.50; p=0.6; $I^2$=0%).** These remained the same when sub- | Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised or studies were of low quality | |

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| | | | | grouped for children only.<br><br>Non-IV MDZ had a **shorter time from arrival to drug administration (RR=-3.56 min, 95% CI -5.00 to -2.11; p<0.00001; $I^2$=97%) and time from administration to seizure cessation (RR=0.56, 95% CI 0.15-0.98; p=0.008; $1^2$=66%) than DZP by any route**. Buccal MDZ was more effective than rectal DZP in terminating SE in children, but only when expressed as an odds ratio (OR=1.67, 95% CI 0.89-3.14). There were no significant differences in seizure cessation and adverse effects for other route comparisons. | ☒ Methods and/or results were inconsistent across studies | indirect *(Your PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*<br><br>☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*<br><br>☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug)*<br><br><u>Increase Quality Rating if:</u><br>☐ Large Effect<br><br>Level of evidence for studies as a whole:<br><br>☐ High<br>☒ Moderate |
| McMullan et al., 2010, *Academic Emergency Medicine* | To determine by systematic review if non-intravenous (non-IV) midazolam is as effective as diazepam, by any route, in terminating SE seizures in children and adults | Systematic review & meta-analysis | 6 studies with 774 subjects, all RCT's ages 0-22 years | **Midazolam, by any route, was superior to diazepam, by any route (RR = 1.52, 95% CI 1.27-1.82; number needed to treat [NNT] = 7).** There is no apparent difference between non-IV midazolam and IV diazepam in achieving seizure cessation (RR = 0.79, 95% CI 0.19-3.26).<br><br>Buccal midazolam is more successful in achieving seizure cessation than rectal diazepam (RR = 1.54, 95% CI 1.29-1.85; $I^2$= 0%; NNT = 6).<br><br>There is no apparent difference between the safety of midazolam and diazepam with respect to respiratory complications (RR = 1.49, 95% CI 0.25-8.72). | Study Limitations =<br>☐ None<br>***Systematic Review***<br>☐ Review did not address focused clinical question<br>☐ Search was not detailed or exhaustive<br>☐ Quality of the studies was not appraised or studies were of low quality<br>☒ Methods and/or results were inconsistent across studies | |

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| Ahmad et al., 2006, *The Lancet* | To determine the efficacy and safety of intranasal lorazepam versus intramuscular (IM) paraldehyde for protracted convulsions in children | RCT | 160 patients (2 mo -12 yrs) with generalized convulsions continuing for a minimum of 5 minutes presenting to a pediatric ED in Malawi | Presenting seizures stopped within 10 minutes in 60 patients (70%) who received intranasal lorazepam (absolute risk [AR] = 0.75, 95% CI 0.64-0.84) and 49 patients (61%) who received IM paraldehyde (AR= 0.61, 95% CI 0.49-0.72).<br><br>8 patients (10%) who received intranasal lorazepam and 21 patients (26%) who received IM paraldehyde needed 2+ rescue anticonvulsive agents (OR= 6.33, 95% CI 1.64–24.45, p>0.007).<br><br>**Intranasal lorazepam is effective, safe, and provides a less invasive alternative to intramuscular paraldehyde in children with protracted convulsions.** | Study Limitations =<br>☐ None<br>***RCT & Quasi-Experimental Studies***<br>☐ Insufficient sample size<br>☐ Lack of randomization<br>☒ Lack of blinding<br>☐ Stopped early for benefit<br>☐ Lack of allocation concealment<br>☐ Selective reporting of measures<br>☐ Large losses to F/U | ☐ Low<br>☐ Very Low |
| Chamberlain et al., 2014, *JAMA* | To determine if the validity of hypothesis that IV lorazepam has better efficacy and safety than IV diazepam for treating pediatric SE | RCT | 273 patients (3mo-18yo) with convulsive status epilepticus randomized to lorazepam (n=133) or diazepam (n=140) | Cessation of SE for 10 minutes without recurrence within 30 minutes was 72.1% for patients given diazepam and 72.9% for patients given lorazepam (absolute efficacy difference =0.8%; 95% CI, -11.4% to 9.8%).<br><br>26 patients in each group required assisted ventilation, accounting for 16.0% of patients given diazepam and 17.6% of patients given lorazepam (absolute risk difference = 1.6%, 95% CI, -9.9% to 6.8%). Sedation rate was higher after lorazepam administration versus diazepam (66.9% vs 50.0% respectively, absolute risk difference =16.9%, 95% CI, 6.1-27.7%).<br><br>**Overall, treatment with lorazepam did not result in improved efficacy or safety, compared with diazepam.** | Study Limitations =<br>☒ None<br>***RCT & Quasi-Experimental Studies***<br>☐ Insufficient sample size<br>☐ Lack of randomization<br>☐ Lack of blinding<br>☐ Stopped early for benefit<br>☐ Lack of allocation concealment<br>☐ Selective reporting of measures<br>☐ Large losses to F/U | |
| Momen et al., | To evaluate the | RCT | 100 children with | 96% of cases were successful with | Study Limitations = | |

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| 2015, *Eur J Paediatr Neurol* | efficacy and safety of intramuscular (IM) midazolam in controlling convulsive SE in children versus rectal diazepam | | convulsive SE (1mo -16y) randomly assigned to IM midazolam or rectal diazepam at a children's hospital in Iran | IM midazolam administration, and 94% of cases were successful with rectal diazepam administration with **no significant difference between successful treatments (p=0.061). Time from arrival to seizure cessation was significantly lower with midazolam versus diazepam (127, 95% CI 83-320 vs 243, 95% CI 115-725 respectively; p<0.001) with no difference in adverse effects.** | ☐ None<br>***RCT & Quasi-Experimental Studies***<br>☐ Insufficient sample size<br>☐ Lack of randomization<br>☒ Lack of blinding<br>☐ Stopped early for benefit<br>☐ Lack of allocation concealment<br>☐ Selective reporting of measures<br>☐ Large losses to F/U | |
| Sreenath et al., 2010, *European Journal of Paediatric Neurology* | To determine whether IV lorazepam is as efficacious as diazepam-phenytoin combination in the treatment of convulsive status epilepticus in children | RCT | 178 children (1-12 years old) were randomly assigned to IV lorazepam (n=90) or diazepam+ phenytoin (n=88) at a pediatric emergency department in North India. If IV access not possible, the drug was given rectally | Success of therapy was 100% in both groups, with no significant difference in the median time taken to stop seizure (p=0.29). **Patients given diazepam were more likely to require additional doses to stop seizure (RR =0.377, 95% CI 0.377-1.046; p=0.061).** No patients had seizure recurrence in the 18hr follow-up period. | Study Limitations =<br>☐ None<br>***RCT & Quasi-Experimental Studies***<br>☐ Insufficient sample size<br>☐ Lack of randomization<br>☒ Lack of blinding<br>☐ Stopped early for benefit<br>☒ Lack of allocation concealment<br>☐ Selective reporting of measures<br>☐ Large losses to F/U | |
| Chin et al., 2008, *The Lancet Neurology* | To determine the most effective treatment for childhood convulsive SE to minimize the length of seizures, treat the causes, and reduce adverse outcomes | Prospective observational study | 182 Children (median = 3.24yrs) with 240 episodes of convulsive SE started in the community in London | **IV lorazepam in the accident and ED was associated with greater likelihood of seizure termination than was treatment with rectal diazepam (OR=3.7; 95% CI 1.7–7.9)**<br><br>No treatment prehospital (OR=2.4, 95% CI 1.2–4.5) and more than two doses of benzodiazepines (OR=3.6, 95% CI 1.9–6.7) were associated with seizure episodes that lasted for more than 60 min.<br><br>Treatment with more than two doses of benzodiazepines was associated with respiratory depression (OR=2.9, 95% CI 1.4– | Study Limitations =<br>☐ None<br>***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)***<br>☒ Insufficient sample size<br>☒ Sample not representative of patients in the population as a whole<br>☒ Variables (confounders, exposures, predictors) were not described<br>☐ Outcome criteria not objective or were not applied in blind fashion<br>☐ Insufficient follow-up, if applicable<br>☐ For prognostic study, sample not defined at common point in course of disease/condition<br>☐ For diagnostic study, gold standard | |

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| | | | | 6.1). | not applied to all patients<br>☐ For diagnostic study, no independent, blind comparison between index test and gold standard | |
| Riviello et al., 2012, *Neurocritical Care* | To determine the emergent initial therapy, urgent control therapy, and refractory therapy administered by physicians for SE in children and adults | Survey | 120 physicians with expertise in treatment of SE were asked to complete a survey addressing acute treatment of SE. SE experts were identified based on suggestions from members of the NCS SE Guideline Writing Committee | Benzodiazepines are the agent of choice for emergent initial treatment. Lorazepam is the preferred drug for IV use and Diazepam for rectal administration. | Study Limitations =<br>☐ None<br>***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)***<br>☒ Insufficient sample size<br>☒ Sample not representative of patients in the population as a whole<br>☒ Variables (confounders, exposures, predictors) were not described<br>☒ Outcome criteria not objective or were not applied in blind fashion<br>☐ Insufficient follow-up, if applicable<br>☐ For prognostic study, sample not defined at common point in course of disease/condition<br>☐ For diagnostic study, gold standard not applied to all patients<br>☐ For diagnostic study, no independent, blind comparison between index test and gold standard | |
| Qureshi et. al., 2002, *Seizure* | To compare the effect of IV lorazepam with IV diazepam as first line treatment of CSE in children. | Prospective observational study | 85 children with prolonged seizures arriving to the ER were given either standard treatment with IV diazepam (0.3 mg/kg) or IV lorazepam (0.1 mg/kg)<br><br>Diazepam group: 17 out of 26 patients (0.5mo-8yo)<br><br>Lorazepam group: 31 out of 59 patients (1-11yo) | Children who received lorazepam vs diazepam were not statistically different with respect to: 1) Median seizure duration before treatment, 2) Median total seizure duration, 3) Number who successfully stopped seizing after iv dose, 4) Median (range) time seizure stopped after siting iv cannula (min) in all patients, 5) Number requiring 2nd dose, 6) Median (range) latency to stopping of seizure after a single iv dose only (min) or 7) Number (%) requiring PICU (p>0.05).<br><br>**Lorazepam seems at least as safe and effective as diazepam in the treatment of convulsive status epilepticus.** | Study Limitations =<br>☐ None<br>***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)***<br>☒ Insufficient sample size<br>☐ Sample not representative of patients in the population as a whole<br>☒ Variables (confounders, exposures, predictors) were not described<br>☐ Outcome criteria not objective or were not applied in blind fashion<br>☐ Insufficient follow-up, if applicable<br>☐ For prognostic study, sample not defined at common point in course of disease/condition<br>☐ For diagnostic study, gold standard not applied to all patients<br>☐ For diagnostic study, no independent, blind comparison between | |

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**Question #4. In infants/children with prolonged seizures/status epilepticus (SE), which anticonvulsant (e.g., Keppra, fosphenytoin, phenytoin) is most effective, timely, and safe as second-line therapy?**

**MUSC Clinical Practice Recommendation(s):** IV Fosphenytoin (20 mg PE/kg given over 7-10 min; Max: 1g) is recommended as the preferred second line therapy for urgent control of SE. If seizure does not stop within 5-10 minutes of infusion completion, give an additional 10mg PE/kg dose of fosphenytoin. If seizure does not stop within 5-10 minutes of infusion completion for second dose, administer IV valproate (25 mg/kg given over 7-15 min) or, if not available, IV Keppra (20 mg/kg given over 5-15 min; Max: 2g). Inpatient consult to neurology is recommended for patients requiring second line therapies. MET code activation is recommended. Venous blood gas checks are recommended. **Strong Recommendation, Low Quality Evidence**

**Guideline Recommendations:**

***Second-line therapies:***

The Neurocritical Care Society guideline for evaluation and management of status epilepticus in adults and children (2012) recommends urgent control AED therapy recommendations include use of IV fosphenytoin/phenytoin, valproate sodium, or levetiracetam. **(Strong recommendation, Moderate quality evidence)**

The National Institute for Health and Care Excellence (2012) guideline for the diagnosis and management of epilepsies in adults and children recommends that if seizures continue, administer intravenous phenobarbital or phenytoin as second-line treatment in hospital in children and young people with ongoing generalized tonic-clonic seizures (convulsive status epilepticus).

Texas Children's Hospital, Evidence-based Outcomes Center guideline for initial management of seizures (2009) recommends:

1. Children should be treated with fosphenytoin as 2nd line therapy.
2. Obtain phenytoin level 2 hours after last bolus, if fosphenytoin is to be continued. If levels are low and seizures reoccur or continue, consider additional dosing to achieve therapeutic levels.
3. With seizure cessation following 2nd line therapy, children should be admitted to Observation/Inpatient and managed as appropriate to clinical findings.

**Primary Literature:**

| **PICO Question #4: In infants/children with prolonged seizures/status epilepticus (SE), which anticonvulsant (e.g., Keppra, fosphenytoin, phenytoin) is most effective, timely, and safe as second-line therapy?** | | | | | | Lower Quality Rating if:<br>☒ Studies inconsistent (*When there are differences in the direction of the effect, populations, interventions or outcomes between studies)*<br><br>☐ Studies are indirect *(Your PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*<br><br>☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*<br><br>☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug)* |
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| *Author/Date /Journal* | *Purpose of Study* | *Study Design* | *Sample& Setting* | *Outcomes* | *Design Limitations* | |
| Malamiri et al., 2012, *European Journal of Peadiatric Neurology* | To determine the safety and efficacy of IV sodium valproate versus phenobarbital in controlling convulsive status epilepticus and acute prolonged convulsive seizures in children | RCT | 60 children (median =5yo) presenting in ER with convulsions and seizures that were not controlled by bolus of IV diazepam in 5 min were randomly assigned to IV sodium valproate rapid loading or IV phenobarbital | In the valproate group 90% (27/30) had their seizures controlled in less than 20 minutes after beginning infusion compared to the 77% (23/30) of phenobarbital group. **Seizure recurrence within 24 hours after termination was significantly lower for patients given valproate vs. phenobarbital (51% vs. 15%; p=0.007).**<br><br>**Overall success rate was significantly higher with valproate than phenobarbital (77% vs 37%; p=0.004).** Overall occurrence of adverse effects was also lower in the valproate group (24% vs 74%; p< 0.001). | Study Limitations =<br>☐ None<br>***RCT & Quasi-Experimental Studies***<br>☒ Insufficient sample size<br>☐ Lack of randomization<br>☐ Lack of blinding<br>☐ Stopped early for benefit<br>☐ Lack of allocation concealment<br>☐ Selective reporting of measures<br>☐ Large losses to F/U | |
| Vyas et al., 2013, *British Association for* | To compare efficacy and adverse effects of IV Valporate and | RCT | 42 patients (6 mo-12 yrs) presenting with | **IV levetriacetam and IV valproate were found to have better clinical efficacy than IV** | Study Limitations =<br>☐ None<br>***RCT & Quasi-Experimental*** | |

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| *Pediatric Nephrology* | IV Levetiracetam as second line anti-epileptic drugs in SE to IV Phenytoin | | SE were randomly distributed into 3 groups depending on the day of admission and each group was assigned a different second-line antiepileptic | **phenytoin, but the difference was not statistically significant.** 57% patients receiving phenytoin, 63% receiving valproate and 80% receiving levitracetam became non convulsive.<br><br>The average time to stop convulsions was not significantly different between the 3 groups (10-11 min)<br><br>2/42 (4.7%) developed minor adverse effects from phenytoin in the form of excessive drowsiness and irritability. | ***Studies***<br>☒ Insufficient sample size<br>☐ Lack of randomization<br>☐ Lack of blinding<br>☐ Stopped early for benefit<br>☐ Lack of allocation concealment<br>☐ Selective reporting of measures<br>☐ Large losses to F/U | <u>Increase Quality Rating if:</u><br>☐ Large Effect<br><br>Level of evidence for studies as a whole:<br>☐ High<br>☐ Moderate<br>☒ Low<br>☐ Very Low |
| Chin et al., 2008, *The Lancet Neurology* | To determine the most effective treatment for childhood convulsive SE to minimize the length of seizures, treat the causes, and reduce adverse outcomes | Prospective, population-based study | 182 Children (median = 3.24yrs) with 240 episodes of convulsive SE started in the community in London | Of the 127 episodes that continued beyond 10 min after the first benzodiazepine was given, 107 (84%) were treated with further doses of benzodiazepines and 20 (16%) were treated with second-line treatment. A mean dose of 0.08 mg/kg IV lorazepam was the most common second-line benzodiazepine given in hospital, and this treatment led to 17 seizure terminations. Only 1/16 episodes that were treated with a second dose of rectal diazepam had seizure termination.<br><br>Of 82 episodes treated with a second-line antiepileptic drug, only 42 episodes were treated initially with the APLS-recommended antiepileptic drug, rectal paraldehyde 32/82 episodes were treated with IV phenytoin. | Study Limitations =<br>☒ None<br>***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)***<br>☐ Insufficient sample size<br>☐ Sample not representative of patients in the population as a whole<br>☐ Variables (confounders, exposures, predictors) were not described<br>☐ Outcome criteria not objective or were not applied in blind fashion<br>☐ Insufficient follow-up, if applicable<br>☐ For prognostic study, sample not defined at common point in course of disease/condition<br>☐ For diagnostic study, gold standard not applied to all patients<br>☐ For diagnostic study, no independent, blind comparison between index test and gold standard | |
| Ismail et al., 2012, *The American Journal of* | To determine the efficacy of phenytoin, a sodium channel blocker, in | Retrospective chart review | 56 children with 62 episodes of febrile seizure lasting longer | 9/62 episodes (14.5%) of phenytoin administration resulted in a positive response. 25 episodes (40.3%) resulted in | Study Limitations =<br>☐ None<br>***Non-Experimental/Observational Studies (case-control, cohort,*** | |

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| *Emergency Medicine* | the treatment of febrile SE in children | | than 15 minutes; the efficacy of phenytoin was classified into 3 categories: positive, negative, and non-evaluable responses | a negative response, and 28 episodes (45.2%) resulted in a non-evaluable response because phenytoin was given simultaneously with a GABAergic drug.<br><br>The mean seizure duration for a positive response was 52.8 minutes, 109.9 minutes for a negative response, and 52.6 minutes for the non-evaluable response. | ***cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)***<br>☒ Insufficient sample size<br>☐ Sample not representative of patients in the population as a whole<br>☐ Variables (confounders, exposures, predictors) were not described<br>☒ Outcome criteria not objective or were not applied in blind fashion<br>☐ Insufficient follow-up, if applicable<br>☐ For prognostic study, sample not defined at common point in course of disease/condition<br>☐ For diagnostic study, gold standard not applied to all patients<br>☐ For diagnostic study, no independent, blind comparison between index test and gold standard | |
| Lewena & Young, 2006, *Paediatric Emergency Medicine* | To define the characteristics and management of children presenting to the ED of a major tertiary paediatric hospital with CSE, and determine the timing and efficacy of therapeutic interventions, and identify factors that influence effectiveness of treatment | Retrospective data review | 37 patients with convulsive SE (mean 3.7 yrs) were identified w/ a balanced sex distribution | History of seizures was present in 65% of patients. Prehospital treatment with a benzodiazepine occurred in 51% of episodes. Average seizure duration at the time of hospital presentation was 48 min.<br><br>Second-line treatment with phenytoin (n=18), phenobarbitone (n=17) or both (n=7) was administered, on average, 24 min after hospital presentation. 6/32 patients had seizure termination after second-line therapy. Uncomplicated seizure control was achieved in 30% of patients with the combination of first and second line therapy. | Study Limitations =<br>☐ None<br>***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)***<br>☒ Insufficient sample size<br>☐ Sample not representative of patients in the population as a whole<br>☐ Variables (confounders, exposures, predictors) were not described<br>☒ Outcome criteria not objective or were not applied in blind fashion<br>☐ Insufficient follow-up, if applicable<br>☐ For prognostic study, sample not defined at common point in course of disease/condition<br>☐ For diagnostic study, gold standard not applied to all patients<br>☐ For diagnostic study, no independent, blind comparison between index test and gold standard | |

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| Riviello et al., 2012, *Neurocritical Care* | To determine the emergent initial therapy, urgent control therapy, and refractory therapy administered by physicians for status epilepticus (SE) in children and adults | Survey | 120 physicians with expertise in treatment of SE were asked to complete a survey, experts were identified based on suggestions from members of the NCS SE Guideline Writing Committee | Valproate sodium is the drug of choice for urgent therapy, followed by phenytoin, midazloam, and phenobarbital. | Study Limitations =<br>☐ None<br>***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)***<br>☒ Insufficient sample size<br>☒ Sample not representative of patients in the population as a whole<br>☒ Variables (confounders, exposures, predictors) were not described<br>☒ Outcome criteria not objective or were not applied in blind fashion<br>☐ Insufficient follow-up, if applicable<br>☐ For prognostic study, sample not defined at common point in course of disease/condition<br>☐ For diagnostic study, gold standard not applied to all patients<br>☐ For diagnostic study, no independent, blind comparison between index test and gold standard | |

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**Question #5. In infants/children with prolonged seizures/status epilepticus (SE) in the ED, which anticonvulsant is most effective, timely, and safe as third-line therapy?**

**MUSC Clinical Practice Recommendation(s):** If seizure has not stopped within 60 minutes of initiation, continuous IV midazolam or pENTObarbitol infusion is recommended. Advanced airway placement is recommended PRIOR to initiation of these therapies. Adequate monitoring of AED levels is recommended for patients receiving continuous AED therapy. **Strong Recommendation, Low Quality Evidence**

## Guideline Recommendations:

***Third-line therapies:***

The Neurocritical Care Society guideline for evaluation and management of status epilepticus in adults and children (2012) recommends:

1. Refractory SE therapy recommendations should consist of continuous infusion AEDs, but vary by the patient's underlying condition. **(Strong recommendation, Low quality evidence)**
2. Dosing of continuous infusion AEDs for refractory SE should be titrated to cessation of electrographic seizures or burst suppression. **(Strong recommendation, Very low quality evidence)**
3. Alternative therapies can be considered if cessation of seizures cannot be achieved; however, it is recommended to reserve these therapies for patients who do not respond to RSE AED treatment and consider transfer of the patient if they are not being managed by an ICU team that specialize in the treatment of SE and/or cannot provide cEEG monitoring. **(Weak recommendation, Very low quality)**

The National Institute for Health and Care Excellence guideline for diagnosis and management of status epilepticus (2012) recommends:

1. IV midazolam or thiopental for refractory status epilepticus in children and young people with refractory convulsive status epilepticus. Adequate monitoring, including blood levels of antiepileptic drugs and critical life systems support are required.
2. As the treatment pathway progresses, the expertise of an anaesthetist/intensivist should be sought.
3. Regular AEDs should be continued at optimal doses and the reasons for status epilepticus should be investigated.

Texas Children's Hospital, Evidence-based Outcomes Center guideline for initial management of seizures (2009) recommends:

1. Children should be treated with PHENObarbital as 3rd line therapy. Obtain PHENObarbital level 2 hours after last infusion, if PHENObarbital is to be continued. If levels are low and seizures reoccur or continue, consider additional dosing to achieve therapeutic levels.
2. With seizure cessation following 3rd line therapy, children should be admitted to appropriate level of care and managed as appropriate to clinical findings.
3. Children should be treated with midazolam as 4th line therapy. If midazolam does not suppress the seizures, PENTObarbital is currently the treatment of choice for refractory SE. PENTObarbital is associated with respiratory depression, myocardial depression, hypotension, and low cardiac output and practitioners must be prepared to treat these complications.
4. Additional adjunct therapy options include treatment with diazepam, valproic acid, levetiracetam, propofol, or ketamine.

## Primary Literature:

| **PICO Question #5: In infants/children with prolonged seizures/status epilepticus (SE), which anticonvulsant is most effective, timely, and safe as third-line therapy?** | Lower Quality Rating if:<br>☒ Studies inconsistent |
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| *Author/Date/ Journal* | *Purpose of Study* | *Study Design* | *Sample& Setting* | *Outcomes* | *Design Limitations* | (*When there are differences in the direction of the effect, populations, interventions or outcomes between studies)*<br><br>☐ Studies are indirect *(Your PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*<br><br>☒ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*<br><br>☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug)*<br><br><u>Increase Quality Rating if:</u><br>☐ Large Effect<br><br>Level of evidence for studies as a whole:<br><br>☐ High<br>☐ Moderate<br>☒ Low<br>☐ Very Low |
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| Mahvelati et al., 2011, *Journal Med Science* | To compare the efficacy and safety of propofol and midazolam in treatment of children's refractory status epilepticus | RCT | 32 patients were admitted and treated for refractory status epilepticus by randomization to midazolam (n=16) or propofol (n=16) | In the midazolam group, 6 patients (37.5%) had complete seizure control, 2 (12.5%) had recurrence after drug administration and 8 (50%) had no response.<br><br>In the propofol group, 10 patients (62.5%) had complete seizure control, 2 (12.5%) had recurrence after drug administration, and 4 (25%) had no response.<br><br>Apnea, bradycardia, hypotension acidosis, CPK, rising, serum TG and cholesterol increased in both groups. | Study Limitations =<br>☐ None<br>***RCT & Quasi-Experimental Studies***<br>☒ Insufficient sample size<br>☐ Lack of randomization<br>☒ Lack of blinding<br>☐ Stopped early for benefit<br>☒ Lack of allocation concealment<br>☐ Selective reporting of measures<br>☐ Large losses to F/U | |
| Mehata, Singhi & Singhi, 2007, *Journal of Neurology* | To compare the efficacy and safety of intravenous sodium valproate versus diazepam infusion for control of refractory status epilepticus. | RCT | 40 patients with refractory SE were randomized to receive either intravenous sodium valproate or diazepam infusion | Refractory SE was controlled in 80% of the valproate and 85% of the diazepam patients. The median time to control refractory status epilepticus was less with valproate than diazepam group (5 min vs 17 min; P < .001).<br><br>None of the patients on valproate required ventilation or developed hypotension, whereas 60% on diazepam required ventilation and 50% developed hypotension after starting infusion | Study Limitations =<br>☐ None<br>***RCT & Quasi-Experimental Studies***<br>☒ Insufficient sample size<br>☐ Lack of randomization<br>☐ Lack of blinding<br>☐ Stopped early for benefit<br>☐ Lack of allocation concealment<br>☐ Selective reporting of measures<br>☐ Large losses to F/U | |
| Singhi et al., 2001, *Journal of Childhood Neurology* | To compare the efficacy of continuous midazolam and | RCT | 40 patients were randomly assigned to midazolam (n=21) | 85.7% (n=18) of patients with refractory SE were controlled with continuous midazolam | Study Limitations =<br>☐ None<br>***RCT & Quasi-Experimental Studies***<br>☒ Insufficient sample size | |

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| | diazepam infusion for control of refractory SE in a Pediatric Emergency and Intensive Care Service | | vs. diazepam (n=19) in a Pediatric Emergency and Intensive Care Services at a tertiary care teaching and referral hospital | infusion and 89.5% (n=17) were controlled with continuous diazepam infusion | ☐ Lack of randomization<br>☐ Lack of blinding<br>☐ Stopped early for benefit<br>☐ Lack of allocation concealment<br>☒ Selective reporting of measures<br>☐ Large losses to F/U | |
| Akyildiz & Kumandas, 2011 *Childs Nervous System* | To evaluate a topimerate (TPM) regimen for treating refractory SE in the largest pediatric series compared to standard of care | Prospective Observational Study | 14 patients received TPM by the nasogastric route at a PICU in Turkey | The median time to seizure cessation after TPM was 5.5 h (range 2–48 h). 9 patients had complete termination (responders), 3 patients were partial responders within 72 h after TPM, and 2 patients were non-responders. The median TPM dose in responders was 5 mg/kg/day and 19 mg/kg/day (range 15–20 mg/kg/day) in partial responders | Study Limitations =<br>☐ None<br>***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)***<br>☒ Insufficient sample size<br>☒ Sample not representative of patients in the population as a whole<br>☐ Variables (confounders, exposures, predictors) were not described<br>☐ Outcome criteria not objective or were not applied in blind fashion<br>☐ Insufficient follow-up, if applicable<br>☐ For prognostic study, sample not defined at common point in course of disease/condition<br>☐ For diagnostic study, gold standard not applied to all patients<br>☐ For diagnostic study, no independent, blind comparison between index test and gold standard | |
| Barberio et al., 2012, *Journal of Child Neurology* | To describe dosing regimens and outcomes in children receiving continuous pentobarbital therapy for refractory SE | Retrospective chart review | 30 patients (aged 6.5±5.1 years) receiving continuous infusion of pentobarbital for the management of refractory SE from 2007-11 in a metropolitan teaching hospital | 33% (n=10) of patients achieved sustained burst suppression without relapse, and 60% of those experiencing relapse eventually re-achieved burst suppression (n=12). The mean time to achieve suppression was 22.6±17.5 hours, and was maintained for 13.9±21.1 hours before de-escalation. Patients with a known seizure | Study Limitations =<br>☐ None<br>***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)***<br>☒ Insufficient sample size<br>☒ Sample not representative of patients in the population as a whole<br>☐ Variables (confounders, exposures, predictors) were not described<br>☒ Outcome criteria not objective or were not applied in blind fashion<br>☐ Insufficient follow-up, if applicable<br>☐ For prognostic study, sample not | |

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| | | | | disorder were most likely to experience positive outcomes (seizure control at discharge or return to baseline) | defined at common point in course of disease/condition<br>☐ For diagnostic study, gold standard not applied to all patients<br>☐ For diagnostic study, no independent, blind comparison between index test and gold standard | |
| Gallentine, et al., 2009 *Epilepsy and Behavior* | To investigate the utility of levetiracetam (LEV) in children with refractory SE | Correlation study | 93 cases | 45% of children had a favorable response to the drug treatment of LEV | Study Limitations =<br>☐ None<br>***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)***<br>☒ Insufficient sample size<br>☒ Sample not representative of patients in the population as a whole<br>☒ Variables (confounders, exposures, predictors) were not described<br>☒ Outcome criteria not objective or were not applied in blind fashion<br>☐ Insufficient follow-up, if applicable<br>☐ For prognostic study, sample not defined at common point in course of disease/condition<br>☐ For diagnostic study, gold standard not applied to all patients<br>☐ For diagnostic study, no independent, blind comparison between index test and gold standard | |
| Gaspard et al., 2013 *Epilepsia* | To examine patterns of use, safety, and efficacy of intravenous ketamine for the treatment of refractory SE | Retrospective record review | 58 subjects representing 60 seizure episodes from 10 academic medical centers in North America and Europe | Ketamine was seen as a positive contributor to permanent SE control, which was achieved in 34 out of 60 cases (56.7%) | Study Limitations =<br>☐ None<br>***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)***<br>☒ Insufficient sample size<br>☒ Sample not representative of patients in the population as a whole<br>☐ Variables (confounders, exposures, predictors) were not described<br>☒ Outcome criteria not objective or were not applied in blind fashion<br>☒ Insufficient follow-up, if applicable<br>☐ For prognostic study, sample not defined at common point in course of disease/condition<br>☐ For diagnostic study, gold standard not applied to all patients | |

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| | | | | | ☐ For diagnostic study, no independent, blind comparison between index test and gold standard | |
| Grosso et al., 2014, *European Journal of Pediatric Neurology* | To assess the efficacy and tolerability of IV lacosamide in children affected by refractory SE | Retrospective Case Series | 11 pediatric patients (mean age: 9.4yrs) with convulsive and non-convulsive refractory SE and SE etiology was symptomatic in 7 patients (63%). | In the convulsive refractory SE group (n=6), seizure cessation occurred in 3 patients as result of IV lacosamide and 3 were non-responders.<br><br>In the non-convulsive SE group (n=5), seizure cessation occurred in 2 patients as result of IV lacosamide, persistency of electrographic seizures occurred in 2, and 1 was a non-responder. | Study Limitations =<br>☐ None<br>***Non-Experimental/Observational Studies***<br>☒ Insufficient sample size<br>☒ Sample not representative of patients in the population as a whole<br>☐ Variables (confounders, exposures, predictors) were not described<br>☒ Outcome criteria not objective or were not applied in blind fashion<br>☐ Insufficient follow-up, if applicable<br>☐ For prognostic study, sample not defined at common point in course of disease/condition<br>☐ For diagnostic study, gold standard not applied to all patients<br>☐ For diagnostic study, no independent, blind comparison between index test and gold standard | |
| Morrison et al., 2006, *Intensive Care Medicine* | To assess the effectiveness of high-dose midazolam in pediatric refractory status epilepticus | Retrospective Case Series | 17 consecutive patients from May 2000 to October 2001 | Midazolam controlled seizures in 13 patients (76%) within 30 minutes of treatment imitation and a total of 15 patients overall (88%) with only 1 relapse (6%). No significant adverse outcomes were connected to midazolam use. 3 patients died due to other causes. | Study Limitations =<br>☐ None<br>***Non-Experimental/Observational Studies***<br>☒ Insufficient sample size<br>☐ Lack of randomization<br>☒ variables were not described<br>☐ Stopped early for benefit<br>☒ Outcome criteria not objective or were not applied in blind fashion<br>☐ Insufficient follow-up, if applicable<br>☐ For prognostic study, sample not defined at common point in course of disease<br>☐ For diagnostic study, gold standard not applied to all patients<br>☐ For diagnostic study, no independent, blind comparison between index test and gold standard | |
| Ozdemir et. al., 2005, *Seizure* | To assess the efficacy of midazolam and mortality in childhood refractory generalized convulsive SE | Retrospective Case Series | 27 children consecutively admitted to a Children's Hospital in Turkey from 1997 to 2000 | 26 children had complete control of seizures with midazolam infusion within 65 min; at a mean midazolam infusion rate of 3.1 μg/kg/min. 1 patient with acute | Study Limitations =<br>☐ None<br>***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)***<br>☒ Insufficient sample size | |

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| | | | | meningoencephalitis was not controlled and 5 (19%) patients died. | ☒ Sample not representative of patients in the population as a whole<br>☐ Variables (confounders, exposures, predictors) were not described<br>☒ Outcome criteria not objective or were not applied in blind fashion<br>☐ Insufficient follow-up, if applicable<br>☐ For prognostic study, sample not defined at common point in course of disease/condition<br>☐ For diagnostic study, gold standard not applied to all patients<br>☐ For diagnostic study, no independent, blind comparison between index test and gold standard | |
| Riviello, et al., 2012, *Neurocritical Care* | To determine the emergent initial therapy, urgent control therapy, and refractory therapy administered by physicians for SE in children and adults | Survey | 120 physicians with expertise in treatment of SE were asked to complete a survey addressing acute treatment of SE. SE experts were identified based on suggestions from members of the NCS SE Guideline Writing Committee | Midazloam, valproate sodium, propofol, phenobarbital are recommended for refractory therapy. | Study Limitations =<br>☐ None<br>***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)***<br>☒ Insufficient sample size<br>☒ Sample not representative of patients in the population as a whole<br>☒ Variables (confounders, exposures, predictors) were not described<br>☒ Outcome criteria not objective or were not applied in blind fashion<br>☐ Insufficient follow-up, if applicable<br>☐ For prognostic study, sample not defined at common point in course of disease/condition<br>☐ For diagnostic study, gold standard not applied to all patients<br>☐ For diagnostic study, no independent, blind comparison between index test and gold standard | |
| Rosati, et al., 2012, *Neurology* | To demonstrate the efficacy and safety of ketamine (KE) in the management of convulsive refractory SE in children | Retrospective Case Series | 9 children with refractory SE in the Pediatric Neurology Unit and ICU of Children's Hospital in Italy | Use of KE was associated with resolution of refractory SE in 6 children; a burst-suppression EEG pattern was obtained in 5.<br><br>KE was ineffective for 3 children. In 2 of the 3 non-responders, refractory SE, became | Study Limitations =<br>☐ None<br>***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, QI, survey)***<br>☒ Insufficient sample size<br>☒ Sample not representative of patients in the population as a whole<br>☒ Variables (confounders, exposures, predictors) were not described | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | life-threatening, but treated successfully with surgical removal of focal cortical dysplasia.<br><br>No patients experienced serious side effects as a result of ketamine. | ☒ Outcome criteria not objective or were not applied in blind fashion<br>☐ Insufficient follow-up, if applicable<br>☐ For prognostic study, sample not defined at common point in course of disease/condition<br>☐ For diagnostic study, gold standard not applied to all patients<br>☒ For diagnostic study, no independent, blind comparison between index test and gold standard | |
| van Gestel, et al., 2005, *Neurology* | To assess the effectiveness and safety profiles of propofol and thiopental in pediatric refractory status epilepticus | Retrospective Case Series | 33 consecutive patients (34 seizure events) from 1993-2004 | Propofol controlled seizures in 14/22 (64%) patients. No significant adverse outcomes were connected to midazolam. 2 patients died due to other causes. Thiopental controlled seizures in 11 out of 20 children (55%). 1 patient died as a result of thiopental and 2 patients may have died as a result of thiopental. 6 children died due to other causes. | Study Limitations =<br>☐ None<br>***Non-Experimental/Observational Studies***<br>☒ Insufficient sample size<br>☐ Lack of randomization<br>☒ variables were not described<br>☐ Stopped early for benefit<br>☒ Outcome criteria not objective or were not applied in blind fashion<br>☐ Insufficient follow-up, if applicable<br>☐ For prognostic study, sample not defined at common point in course of disease<br>☐ For diagnostic study, gold standard not applied to all patients<br>☐ For diagnostic study, no independent, blind comparison between index test and gold standard | |

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## Question #6. In pediatric patients with refractory status epilepticus, what is the optimal continuous EEG monitoring strategy to improve patient outcomes?

**MUSC Clinical Practice Recommendation(s):** Continuous EEG monitoring is recommended for children with refractory status epilepticus, or if there is concern for non-convulsive status epilepticus. Notify neurology to facilitate continuous EEG. **Strong Recommendation, Low Quality Evidence**

### Guideline Recommendations:

***Continuous EEG monitoring:***

The Neurocritical Care Society guideline for evaluation and management of status epilepticus in adults and children (2012) recommends:

1. The use of cEEG is usually required for the treatment of SE. **(Strong recommendation, Very low quality)**
2. Continuous EEG monitoring should be initiated within 1 h of SE onset if ongoing seizures are suspected. **(Strong recommendation, Low quality)**
3. The duration of cEEG monitoring should be at least 48 h in comatose patients to evaluate for nonconvulsive seizures. **(Strong recommendation, Low quality evidence)**
4. For patients with refractory SE, cEEg should continue until one of the following endpoints: 1) cessation of non-convulsive seizures (ClassI, level B), 2) diffuse beta activity (Class IIb, level C), 3) burst suppression 8-20 second intervals (Class IIb, level C), or 4) complete suppression of EEG (Class IIb, level C).
5. A period of 24–48 h of electrographic control is recommended prior to slow withdrawal of continuous infusion AEDs for refractory SE. **(Weak recommendation, Very low quality evidence)**
6. During the transition from continuous infusion AEDs in refractory SE, it is suggested to use maintenance AEDs and monitor for recurrent seizures by cEEG during the titration period. If the patient is being treated for refractory SE at a facility without cEEG capabilities, consider transfer to a facility that can offer cEEG monitoring. **(Strong recommendation, Very low quality evidence)**
7. The person reading EEG in the ICU setting should have specialized training in cEEG interpretation, including the ability to analyze raw EEG as well as quantitative EEG tracings. **(Strong recommendation, Low quality evidence)**

The National Institute for Health and Care Excellence Guideline on the Diagnosis and Management of the Epilepsies (2012) recommends:

1. EEG monitoring is necessary for refractory status. Consider the possibility of non-epileptic status.
2. In refractory convulsive status epilepticus, the primary end-point is suppression of epileptic activity on the EEG, with a secondary end-point of burst-suppression pattern (that is, short intervals of up to 1 second between bursts of background rhythm).

Texas Children's Hospital, Evidence-based Outcomes Center guideline for initial management of seizures (2009) recommends:

1. EEG is recommended for children with RSE.
2. Continuous EEG monitoring may be considered for children at risk for NCSE.

**Primary Literature:**

**PICO Question #6: In pediatric patients with refractory status epilepticus, what is the optimal continuous EEG monitoring strategy to improve patient outcomes?**

| *Author/Date/ Journal* | *Purpose of Study* | *Study Design* | *Sample& Setting* | *Outcomes* | *Design Limitations* |
|---|---|---|---|---|---|
| Hyllienmark & Amark, 2007, *European Journal of Paediatric Neurology* | To describe the indications for and outcomes of continuous EEG (cEEG) monitoring in children in adolescents in the pediatric ICU | Descriptive | 54 patients (29 days – 18 years old) monitored with continuous EEG from 2002-2006 in Sweden<br><br>-EEG evaluated at least 2 times per day<br><br>-online review performed by specialist in clinical neurophysiology<br><br>-necessary night reviews were performed remotely or at bedside within 2 hours | 44.4% (24/54) of patients classified as having SE.<br><br>Timing from suspicion of SE to cEEG onset was <6 hours in 20 patients and >6 hours in 34.<br><br>On average, the SE patients (n=24) were monitored with cEEG for 145 hours (range 22-620 hours), and 11 patients were intubated.<br><br>75% (18/24) of patients were treated successfully during cEEG. cEEG findings directly influenced titration of antiepileptic drugs for these patients. | Study Limitations =<br>☐ None<br>***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, survey)***<br>☒ Insufficient sample size<br>☒ Sample not representative of patients in the population as a whole<br>☒ Variables (confounders, exposures, predictors) were not described<br>☐ Outcome criteria not objective or were not applied in blind fashion<br>☐ Insufficient follow-up, if applicable<br>☐ For prognostic study, sample not defined at common point in course of disease/condition<br>☐ For diagnostic study, gold standard not applied to all patients<br>☐ For diagnostic study, no independent, blind comparison between index test and gold standard |
| Patel et al., 2015, Seizure | To determine current clinical practice in the management of convulsive refractory SE among adult ICU patients | Survey | 75 randomly-selected healthcare trusts in the UK<br><br>-55 responded | 23/55 trusts responded they did not have access to continuous EEG for refractory SE management.<br><br>Of the 18 trusts with access to EEG, 15 would use the equipment as soon as the patient was intubated and transferred to ICU. 2 would use the EEG as soon as general anesthesia was given, and 1 would use EEG as soon as convulsive refractory SE began. | Study Limitations =<br>☐ None<br>***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, survey)***<br>☒ Insufficient sample size<br>☒ Sample not representative of patients in the population as a whole<br>☒ Variables (confounders, exposures, predictors) were not described<br>☐ Outcome criteria not objective or were not applied in blind fashion<br>☐ Insufficient follow-up, if applicable<br>☐ For prognostic study, sample not defined |

*Lower Quality Rating if:*

☐ Studies inconsistent (When there are differences in the direction of the effect, populations, interventions or outcomes between studies)

☒ Studies are indirect (Your PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)

☐ Studies are imprecise (When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)

☐ Publication Bias (e.g. pharmaceutical company sponsors study on effectiveness of drug)

*Increase Quality Rating if:*

☐ Large Effect

Level of evidence for studies as a whole:

☐ High
☐ Moderate
☒ Low

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | There is great inconsistency in the management of convulsive refractory SE, and the majority of ICU units do not have a protocol in place or access to continuous EEG monitoring despite guidelines considering it fundamental for management. | at common point in course of disease/condition<br>☐ For diagnostic study, gold standard not applied to all patients<br>☐ For diagnostic study, no independent, blind comparison between index test and gold standard | ☐ Very Low |
| Sanchez et al., 2013, *Epilepsia* | To describe the clinical utilization of continuous EEG (cEEG) in critically ill children at a tertiary care hospital | Retrospective cohort study | 550 consecutively critically ill children at 11 hospitals in North America who underwent cEEG<br><br>-50 from each center<br><br>-almost all cEEG was performed with time-locked video and notations from bedside caregivers<br><br>-each center had own their encepholagrapher, no central reader | The number of subjects undergoing cEEG monitoring for refractory SE and seizure other indications was significantly different across centers ($p < 0.001$) as was mortality ($p < 0.001$).<br><br>cEEG duration across all seizure indications was: <12h in 88 subjects (16%), 12–24h in 187 subjects (34%), 24–48h in 129 subjects (23%), 48–72h in 44 subjects (8%), >72 h in 94 subjects (17%), unknown in 8 subjects (1%).<br><br>cEEG was initiated outside of regular work hours in 47% of cases.<br><br>The number of subjects with short (<24 h) or long (≥24 h) cEEG duration was significantly different across centers ($p < 0.001$).<br><br>The mean cEEG duration was longer in children who were comatose (41±24 hrs) than in those who were obtunded (32±22 hrs) or had normal mental status (25±21 hrs) ($p < 0.001$). | Study Limitations =<br>☐ None<br>***Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, survey)***<br>☐ Insufficient sample size<br>☐ Sample not representative of patients in the population as a whole<br>☐ Variables (confounders, exposures, predictors) were not described<br>☒ Outcome criteria not objective or were not applied in blind fashion<br>☐ Insufficient follow-up, if applicable<br>☐ For prognostic study, sample not defined at common point in course of disease/condition<br>☐ For diagnostic study, gold standard not applied to all patients<br>☐ For diagnostic study, no independent, blind comparison between index test and gold standard | |

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# Appendix A. GRADE criteria for rating a body of evidence on an intervention

Developed by the GRADE Working Group

***Grades and interpretations:***

| |
|---|
| High: Further research is very unlikely to change our confidence in the estimate of effect. |
| Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. |
| Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. |
| Very low: Any estimate of effect is very uncertain. |

***Type of evidence and starting level***

| |
|---|
| Randomized trial–high |
| Observational study–low |
| Any other evidence–very low |

***Criteria for increasing or decreasing level***

| |
|---|
| **Reductions** |
| Study quality has serious (–1) or very serious (–2) problems |
| Important inconsistency in evidence (–1) |
| Directness is somewhat (–1) or seriously (–2) uncertain |
| Sparse or imprecise data (–1) |
| Reporting bias highly probable (–1) |
| **Increases** |
| Evidence of association† strong (+1) or very strong (+2) |
| Dose-response gradient evident (+1) |
| All plausible confounders would reduce the effect (+1) |
| †Strong association defined as significant relative risk (factor of 2) based on consistent evidence from two or more studies with no plausible confounders |
| Very strong association defined as significant relative risk (factor of 5) based on direct evidence with no threats to validity. |

# Appendix B. Trustworthy Guideline rating scale

The University of Pennsylvania's Center for Evidence-Based Practice Trustworthy Guideline rating scale is based on the Institute of Medicine's "Standards for Developing Trustworthy Clinical Practice Guidelines" (IOM), as well as a review of the AGREE Enterprise and Guidelines International Network domains.

The purpose of this scale is to focus on the weaknesses of a guideline that may reduce the trust a clinical user can have in the guideline, and distinguish weaknesses in documentation (e.g. guide-line does not have a documented updating process) from weaknesses in the guidance itself (e.g. recommendations are outdated). Current quality scales like AGREE emphasize documentation. They are important checklists for developers of new guidelines, but are less useful for grading existing guidelines. These scales also are harder for clinicians and other persons who are not methodology experts to apply, and their length discourages their use outside formal technology assessment reports. This new scale is brief, balanced, and easy and consistent to apply.

We do not attempt to convert the results of this assessment into a numeric score. Instead we present a table listing the guidelines and how they are rated on each standard. This facilitates qualitative understanding by the reader, who can see for what areas the guideline base as a whole is weak or strong as well as which guidelines are weaker or stronger.

## 1. Transparency

| | |
|---|---|
| A | Guideline development methods are fully disclosed. |
| B | Guideline development methods are partially disclosed. |
| C | Guideline development methods are not disclosed. |

The grader must refer to any cited methods supplements or other supporting material when evaluating the guideline. Methods should include:
Who wrote the initial draft
How the committee voted on or otherwise approved recommendations

Evidence review, external review and methods used for updating are not addressed in this standard.

## 2. Conflict of interest

| | |
|---|---|
| A | Funding of the guideline project is disclosed, disclosures are made for each individual panelist, and financial or other conflicts do not apply to key authors of the guideline or to more than 1 in 10 panel members). |
| B | Guideline states that there were no conflicts (or fewer than 1 in 10 panel members), but does not disclose funding source. |
| C | Lead author, senior author, or guideline panel members (at least 1 in 10) have conflict of interest, or guideline project was funded by industry sponsor with no assurance of independence. |
| NR | Guideline does not report on potential conflict of interests. |

For purposes of this checklist, conflicts of interest include employment by, consulting for, or holding stock in companies doing business in fields affected by the guideline, as well as related financial conflicts. This definition should not be considered exclusive. As much as anything, this is a surrogate marker for thorough reporting, since it may be assumed that guideline projects are funded by the sponsoring organization and many authors think it unnecessary to report a non-conflict.

## 3. Guideline development group

| | |
|---|---|
| A | Guideline development group includes 1) methodological experts and clinicians and 2) representatives of multiple specialties. |
| B | Guideline development group includes one of the above, but not both. |

| | |
|---|---|
| C | Guideline developers all from one specialty or organization, and no methodologists. |
| NR | Affiliations of guideline developers not reported |

The purpose of this standard is to ensure that supporters of competing procedures, or clinicians with no vested interest in utilization of one procedure or another, are involved in development of the guideline. Both AGREE II and IOM call for patient or public involvement: very few guideline panels have done so to date, so this is not necessary for guidelines to be rated A. Involvement of methodologists or HTA specialists in the systematic review is sufficient involvement in the guideline development group for our purposes. In the absence of any description of the guideline group, assume the named authors are the guideline group.

## 4. Systematic review

| | |
|---|---|
| A | Guideline includes a systematic review of the evidence or links to a current review. |
| B | Guideline is based on a review which may or may not meet systematic review criteria. |
| C | Guideline is not based on a review of the evidence. |

In order to qualify as a systematic review, the review must do all of the following:
Describe itself as systematic or report search strategies using multiple databases
Define the scope of the review (including key questions and the applicable population)
Either include quantitative or qualitative synthesis of the data or explain why it is not indicated

Note: this element does not address the quality of the systematic review: simply whether or not it exists. Concerns about quality or bias of the review will be discussed in text, where the analyst will explain whether the weaknesses of the review weaken the validity or reliability of the guideline.
Note: a guideline may be rated B on this domain even if the review on which it is based is not available to us. This potential weakness of the guideline should be discussed in text of the report.

## 5. Grading the supporting evidence

| | |
|---|---|
| A | Specific supporting evidence (or lack thereof) for each recommendation is cited and graded |
| B | Specific supporting evidence (or lack thereof) for each recommendation is cited but the recommendation is not graded. |
| C | Recommendations are not supported by specific evidence. |

To score a B on this domain there should be specific citations to evidence tables or individual references for each relevant recommendation in the guideline, or an indication that no evidence was available. Any standardized grading system is acceptable for purposes of this rating. If a guideline reports that there is no evidence available despite a thorough literature search, it may be scored B on this domain, or even A if evidence for other recommendations is cited and graded.

## 6. Recommendations

| | |
|---|---|
| A | Considerations for each recommendation are documented (i.e. benefits and harms of a particular action, and/or strength of the evidence); and recommendations are presented in an actionable form. |
| B | Either one or the other of the above criteria is met. |
| C | Neither of the above criteria are met |

In order to be actionable, the guideline should specify the specific population to which the guideline applies, the specific intervention in question, and the circumstances under which it should be carried out (or not carried out). The language used in the recommendations should also be consistent with the strength of the recommendation (e.g. directive and active language like “should” or “should not” for strong recommendations, and passive language like “consider” for weak recommendations). A figure or algorithm is considered actionable as long as it is complete enough to incorporate all the applicable patients and interventions. Please see the forthcoming NICE manual (24) for a good discussion of actionability in guidelines.

## 7. External review

| | |
|---|---|
| A | Guideline was made available to external groups for review. |
| B | Guideline was reviewed by members of the sponsoring body only. |
| C | Guideline was not externally reviewed. |
| NR | No external review process is described. |

## 8. Updating and currency of guideline

| | |
|---|---|
| A | Guideline is current and an expiration date or update process is specified. |
| B | Guideline is current but no expiration date or update process is specified. |
| C | Guideline is outdated. |

A guideline is considered current if it is within the developers' stated validity period, or if no period or expiration data is stated, the guideline was published in the past three years (NOTE: the specific period may be changed at the analyst's discretion, based on whether the technology is mature and whether there is a significant amount of recent evidence). A guideline must address new evidence when it is updated. A guideline which is simply re-endorsed by the panel without searching for new evidence must be considered outdated.