Texas Children's Hospital

DATE: July 2018

TEXAS CHILDREN'S HOSPITAL
EVIDENCE-BASED OUTCOMES CENTER
Initial Management of Status Epilepticus
Evidence-Based Guideline

Definition: Status Epilepticus (SE) is a disease process resulting in prolonged seizures of longer than 5 minutes. [1] The cause of SE can stem from the malfunction of the response to terminate a seizure or from the commencement of the mechanisms that result in prolonged seizures. [2] If SE continues for longer than 30 minutes, there can be permanent neurological damage, including neuronal death, neuronal injury, and alteration of neuronal networks. [2,3]

Epidemiology: Convulsive status epilepticus (CSE) is the most common neurological emergency seen in childhood. [4] It is also among the top five reasons for admission to the PICU at Texas Children's Hospital and is the third most common reason for transport calls. SE is a medical emergency and is associated with an overall mortality rate of 8% in children and 30% in adults. [4,5] Among children, the overall incidence of SE is approximately 1 to 6 per 10,000/year. [4-6] The incidence appears to be higher in children under 1 year of age with over 50% of cases occurring in children under 3 years. SE represents the first seizure of subsequent epilepsy in approximately ⅓ of patients. [5]

Etiology: Remote symptomatic is the most common classification of SE in children, followed by acute symptomatic and febrile status epilepticus. [6]

Table I. Status Epilepticus Etiologic Classification [6]

Type	Definition
Remote symptomatic (33%)	Occurring without an acute provocation with a prior history of CNS insult
Acute symptomatic (26%)	Occurring during an acute illness; acute CNS insult
Febrile (22%)	Occurring when the only provocation is febrile illness
Cryptogenic (15%)	Occurring in the absence of an acute precipitating CNS insult, systemic metabolic disturbances, or both
Progressive encephalopathy (3%)	Occurring with an underlying progressive CNS disorder
Remote symptomatic with an acute precipitant (1%)	Occurring with chronic encephalopathy with an acute provocation

Inclusion Criteria
- Age ≥1 month (or 44 weeks postmenstrual age if the infant was premature)
- Clinical findings of convulsive SE

Exclusion Criteria
- Premature infants who have not been discharged from the NICU

Differential Diagnosis
- Movement disorders (e.g., spasticity, clonus, dystonia)
- Nonepileptic seizures (e.g., pseudoseizures)

Diagnostic Evaluation

NOTE: Central nervous system (CNS) infection should be excluded.

History: Assess for
- Seizure onset
- Known seizure disorder
- Ingestion
- Fever (e.g., signs of serious infection)
- Medications
  - Received prior to presentation (e.g., type, dose, dosage, route)
  - Current anticonvulsant medications
  - Use of psychopharmacologic medications
  - Toxic/Subtherapeutic anticonvulsant levels
  - Nonadherence and/or recent change
- Vagus Nerve Stimulation (VNS)
- Metabolic abnormalities
- Trauma (e.g., history of head trauma >24 hours)
- Dietary therapies

Physical Examination
- Airway, breathing, circulation
- Evidence of prior neurological impairment; altered mental status
- Duration of seizure
- Evidence of trauma (e.g., head, oral-lingular)
- Physical manifestations of the seizure (e.g., limb movement, symmetry/laterality, eyes open/closed, pupillary response, eyes straight ahead/deviated)

NOTE: As seizures continue in time, the clinical manifestations (e.g., rhythmic eye fluttering, asymmetrical tone) may decrease or disappear leading to SE being unrecognized/untreated. This can also be known as minimally-convulsive SE.

Laboratory Tests

Blood cultures, lumbar puncture (LP), antiepileptic drug (AED) levels, and toxicology levels are not routinely recommended in children with SE.

In select populations, the laboratory tests below may considered.
- Consider AED levels in children with epilepsy currently being treated with antiepileptic medications.
- Consider serum toxicology levels when no apparent etiology is identified.
- Consider LP based on history, clinical findings, and fever.
- In otherwise healthy infants (≤12 months), laboratory tests could include:
  - Blood glucose check (Accu-Chek®)
  - Chem 10 (includes sodium, potassium, chloride, CO_2, BUN, creatinine, glucose, calcium, magnesium, phosphorus)

Diagnostic Imaging Studies:

- An EEG should be obtained in patients not returning to baseline neurologic evaluation after treatment for status epilepticus. (6-14)
- A continuous EEG should be obtained in patients treated for refractory status epilepticus. (6-14)
- Brain computed tomography (CT) or magnetic resonance imaging (MRI) are not routinely recommended. If there are no clinical indicators or etiology is unknown, neuroimaging should be considered once the child is stabilized. (15)

Diagnostic Assessment

The diagnostic assessment for patients with a history of epilepsy should be determined by history and clinical findings.

The table below gives details on the diagnostic tests that may be considered for patients without a previous diagnosis of epilepsy.

Diagnostic Assessment for Patients Without Epilepsy

Patient Category	Diagnostic Assessment to Consider
Patient Without Epilepsy and Fever	Blood glucose check (Accu-Chek®) Chem 10 Toxicology Screen
Febrile Patient Without Epilepsy	Blood glucose check (Accu-Chek®) Chem 10 CBC UA, culture Viral Cultures Lumbar Puncture (LP) Note: Acute symptomatic SE is common in children <2 years

Critical Points of Evidence*

Evidence Supports

- Fosphenytoin should be used as urgent therapy in infants and children with prolonged seizures/SE after initial administration of benzodiazepines. For patients with a history of cardiac disease, that are hemodynamically unstable or with an allergy to fosphenytoin, levetiracetam may be used as urgent therapy. (1,3,16-26) – Strong recommendation, moderate quality evidence
- Intranasal (IN) midazolam should be used as treatment for prolonged seizures/status epilepticus in infants and children without intravenous access. If IN midazolam is not available, intramuscular (IM) midazolam can be used. (27-32) – Strong recommendation, moderate quality evidence
- Continuous IV midazolam infusion should be used as treatment for patients with refractory status epilepticus. Phenobarbital may be administered if IV midazolam is not immediately available. (1,3,17,19,24-26,33-39) – Strong recommendation, very low quality evidence
- A continuous EEG should be obtained in patients treated for refractory status epilepticus. The continuous EEG should be continued for at least 24 hours. (6-14) – Strong recommendation, low quality evidence.
- An EEG should be obtained in patients not returning to baseline neurologic evaluation after treatment for status epilepticus. (6-14) – Strong recommendation, low quality evidence

*NOTE: The references cited represent the entire body of evidence reviewed to make each recommendation.

Condition-Specific Elements of Clinical Management

General: Children with SE are often unresponsive and usually have obvious seizures. With time, the clinical manifestations often become subtle and difficult to determine. (40)

Treatment Recommendations: Drug treatment should be initiated without delay once the diagnosis of SE has been determined. SE of longer duration is less responsive to treatment. (40-42) This guideline utilizes an aggressive anticonvulsant treatment sequence based on the rapid onset and extended duration of the effects of lorazepam and the presumed value of an additional long-acting medication. During this sequence, the patency of the child's airway should be continually assessed.

Initial treatment for status epilepticus will preferably consist of IV lorazepam. (32) If the patient does not have IV access, intranasal midazolam should be administered. (27-32)

If seizure persists after two doses of initial treatment, IV fosphenytoin should be administered. Levetiracetam can be considered in patients with a history of cardiac disease, hemodynamically unstable or with an allergy to fosphenytoin. (1,3,16-26)

For patients with refractory status epilepticus, IV continuous midazolam infusion should be titrated to induce seizure cessation. (1,3,17,19,24-26,33-39) A continuous EEG should be utilized with continuous midazolam infusion. (6-14) A dose of phenobarbital may be given if the midazolam infusion is not available. (1,3,17,19,24-26,33-39)

Admission Criteria

Consider admission to observation or inpatient status for patients with resolved status epilepticus who have not returned to baseline neurologic examination.

Intensive Care Unit Admission Criteria

Children who received treatment for refractory status epilepticus AND/OR have respiratory distress should be admitted to the ICU.

Caregiver Education

Seizure precautions, children should not be allowed:

- In or around water, unsupervised (e.g., bath tubs, swimming pools, lakes)
- To climb to high places (e.g., jungle gyms)
- To ride a bicycle without a helmet
- To participate in full contact sports

Discharge Criteria

- Seizure cessation
- Return to baseline mental status
- Appropriate support system (e.g., primary care physician [PCP], caregiver/family)

Consults/Referrals

Consultation and follow up with a Neurology specialist is appropriate for:

- New focal neurological defects
- Children with epilepsy
- Following administration of antiepileptic drugs therapy
- Refractory status epilepticus
- Unprovoked seizure (no known etiology)

Follow-Up Care

Children diagnosed with simple febrile seizures should follow up with their PCP.

Children diagnosed with complex febrile seizures, epilepsy OR SE should follow up with a Neurologist within 14 days.

Children diagnosed with new onset seizures should follow up in the New Onset Seizure Clinic within 4 weeks.

Prevention:

- Seizure precautions
- Prescribe rectal diazepam.

Measures

Process

- Utilization of clinical guideline in the EC and Acute Care
- Dose and timing of AED administration

Outcome

- Number of children administered antibiotics without concurrent infectious disease
- Frequency and outcome of diagnostic laboratory tests (e.g., electrolytes, blood glucose, LP, blood cultures)
- Frequency and outcome of diagnostic radiographic tests (e.g., MRI, CT)
- Incidence and venue of seizure cessation with 1st, 2nd, 3rd, and 4th line therapy

Status Epilepticus Medication Dosing Table

Medication	Route	Dose	Notes
Initial Therapy			
LORazepam	Intravenous (IV)	0.1 mg/kg/dose; **MAX** dose 4 mg/dose	Initial Treatment
Midazolam	Intranasal (IN)	0.2 mg/kg/dose; **MAX** dose 10 mg/dose Divide dose between both nares	May be given as initial treatment in patients without intravenous (IV) access
Urgent Therapy			
Fosphenytoin	IV	30 mg PE/kg; **MAX** dose 1500 mg	Dose is only for patients in Status epilepticus needing urgent treatment
LevETIRAcetam	IV	Usual initial range: 60 mg/kg; dose should not exceed adult initial range: **MAX** dose 4500 mg	May be used as urgent therapy in patients with a history of cardiac disease, hemodynamically unstable or with an allergy to fosphenytoin
Refractory Therapy			
Midazolam	IV Continuous Infusion	Administer 0.2 mg/kg bolus and begin continuous infusion at 0.1 mg/kg/hour	Refractory Treatment
PHENobarbital	IV	20 mg/kg; **MAX** 1000 mg/dose	May be administered for refractory status epilepticus if IV continuous midazolam is not immediately available
Adjunct Treatment for Refractory Status Epilepticus *Consult Epilepsy Service if administering any of the medications below as adjunct treatment for status epilepticus			
Valproate Sodium*	IV	40 mg/kg/dose; **MAX** dose 3000 mg	
Pentobarbital*	IV	5 – 10 mg/kg bolus dose (rate <50 mg/min) followed by 0.5 – 5 mg/kg/hr continuous infusion	
Ketamine*	IV	2 – 3 mg/kg/dose; infusion rate 10 µg/kg/min	

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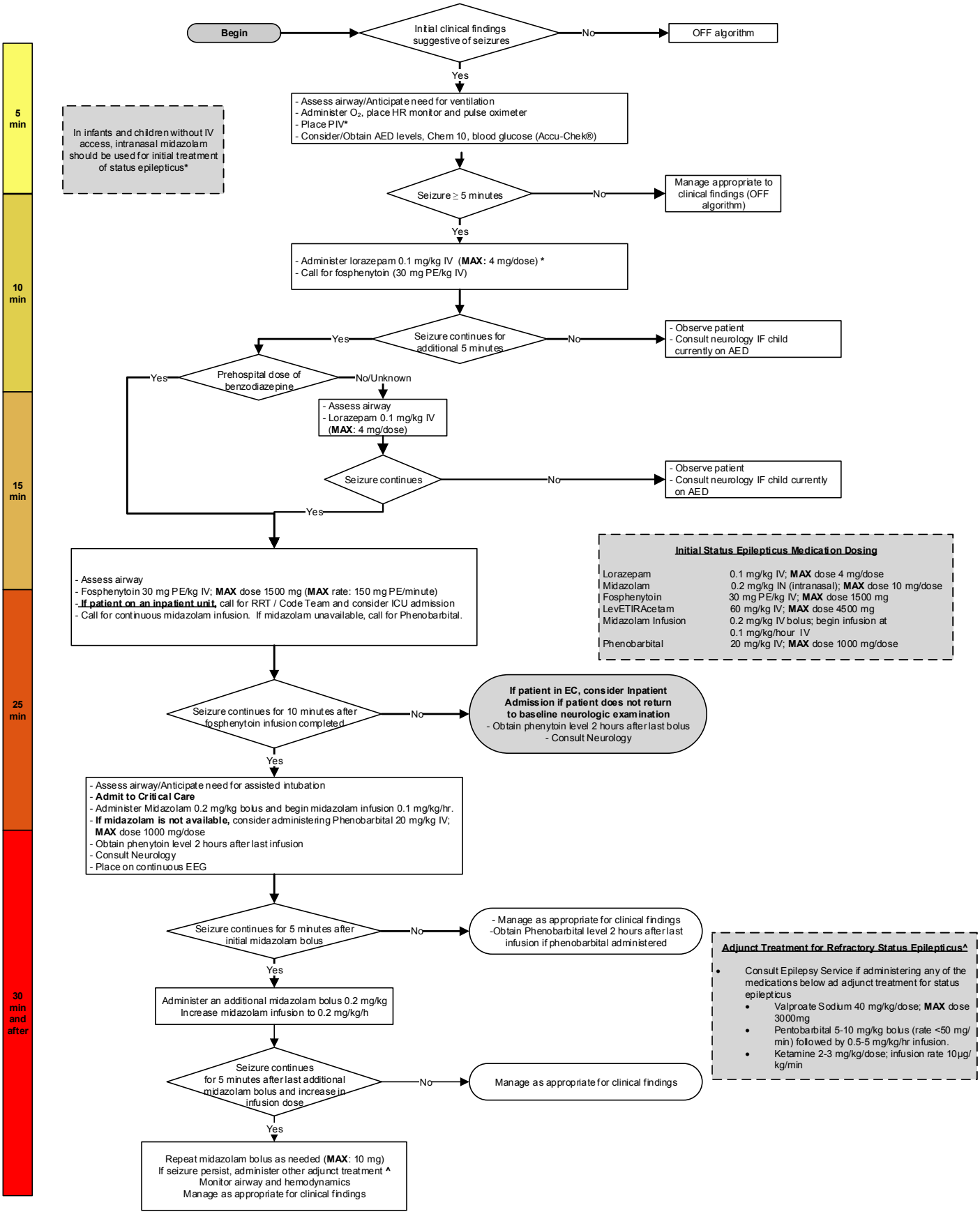
TCH Evidence-Based Outcomes Center
Clinical Algorithm for Initial Management of Status Epilepticus



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Clinical Standards Preparation

This clinical standard was prepared by the Evidence-Based Outcomes Center (EBOC) team in collaboration with content experts at Texas Children's Hospital. Development of this clinical standard supports the TCH Quality and Patient Safety Program initiative to promote clinical standards and outcomes that build a culture of quality and safety within the organization.

Status Epilepticus Content Expert Team
Karla Abela, RN, Pediatric Intensive Care Unit
Irfan Ali, MD, Neurology
Anne Anderson, MD, Neurology
Teri Baierlipp, PA, Neurology
Anthony Bodnar, RN, Acute Care
Kimberly Castrillon, RN, Acute Care
Rohini Coorg, MD, Neurology
Lindsay Day, MD, Emergency Medicine
Jennifer Erklauer, MD, Neurology
Dana Foradori, MD, Pediatric Hospital Medicine
Jessica Frontiero, NP, Neurology
Kelly Frost, NP, Neurology
Bryan Greenfield, MD, Emergency Medicine
Suzanne Iniguez, RT, Respiratory
Alexander Injac, MD, TCP
YiChen Lai, MD, Critical Care
Stephanie Marton, MD, Community Pediatrics
Laura Masters, MD, Neurology
Mindl Messinger, PharmD, Pharmacy
Erika Moore, RN, Acute Care
Angela Morgan, RN, Pediatric Intensive Care Unit
Brent Mothner, MD, Pediatric Hospital Medicine
Michael Quach, MD, Neurology
James Riviello, MD, Neurology
Elaine Seto, MD, Neurology
Laura Whittaker, PA, Neurology
Elizabeth Wuestner, RN, Emergency Center
Shabana Yusuf, MD, Emergency Medicine

EBOC Team
Andrea Jackson, MBA, CCRN-K, Evidence-Based Practice Specialist
Charles Macias, MD, MPH, Medical Director

Additional EBOC Support
Tom Burke, Research Assistant
Sherin Titus, Research Assistant
Karen Gibbs, MSN/MPH, RN, Evidence-Based Practice Specialist
Betsy Lewis, MSN, RN, Evidence-Based Practice Specialist
Jennifer Loveless, MPH, Evidence-Based Practice Specialist
Sheesha Porter, MS, RN, Evidence-Based Practice Specialist
Ellis Arjmand, MD, PhD, Associate Medical Director
Christina Davidson, MD, Associate Medical Director
Anne Dykes, MSN, RN, Assistant Director

The following financial and/or intellectual conflict was identified and addressed to ensure objectivity: James Riviello – member of national guideline committee.

Development Process

This clinical standard was developed using the process outlined in the EBOC Manual. The literature appraisal documents the following steps:

1. Review Preparation
   - PICO questions established
   - Evidence search confirmed with content experts

2. Review of Existing External Guidelines
   - Neurocritical Care Society, Guidelines for the Evaluation and Management of Status Epilepticus, 2012; National Institute of Health and Clinical Excellence, The Epilepsies: The Diagnosis and Management of the Epilepsies in Adults and Children in Primary and Secondary Care, 2012; Italian League Against Epilepsy, Treatment of Convulsion Status Epilepticus in Childhood: Recommendations of the Italian League Against Epilepsy, 2013; European Federation of Neurological Societies, EFNS Guideline on the Management of Status Epilepticus in Adults, 2010; American Academy of Neurology and the Practice Committee of the Child Neurology Society, Practice Parameter: Diagnostic Assessment of the Child With Status Epilepticus (An Evidence-Based Review, 2007; American Academy of Neurology and the American Epilepsy Society, Practice Parameter: Evaluating an Apparent Unprovoked First Seizure in Adults (An Evidence-Based Review), 2007; American Epilepsy Society, Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults; 2016

3. Literature Review of Relevant Evidence
   - Searched: PubMed, Cochrane Collaboration

4. Critically Analyze the Evidence
   - 10 meta-analyses, 5 randomized controlled trials, and 14 nonrandomized studies

5. Summarize the Evidence
   - Materials used in the development of the clinical standard, literature appraisal, and any order sets are maintained in a Status Epilepticus evidence-based review manual within EBOC.

Evaluating the Quality of the Evidence

Published clinical guidelines were evaluated for this review using the **AGREE II** criteria. The summary of these guidelines are included in the literature appraisal. AGREE II criteria evaluate Guideline Scope and Purpose, Stakeholder Involvement, Rigor of Development, Clarity and Presentation, Applicability, and Editorial Independence using a 4-point Likert scale. The higher the score, the more comprehensive the guideline.
This clinical standard specifically summarizes the evidence *in support of* or *against* specific interventions and identifies where evidence is *lacking/inconclusive*. The following categories describe how research findings provide support for treatment interventions.
"Evidence Supports" provides evidence to support an intervention
"Evidence Against" provides evidence against an intervention.
"Evidence Lacking/Inconclusive" indicates there is insufficient evidence to support or refute an intervention and no conclusion can be drawn *from the evidence*.
The **GRADE** criteria were utilized to evaluate the body of evidence used to make practice recommendations. The table below defines how the quality of the evidence is rated and how a strong versus weak recommendation is established. The literature appraisal reflects the critical points of evidence.

Recommendation	
STRONG	Desirable effects clearly outweigh undesirable effects or vice versa
WEAK	Desirable effects closely balanced with undesirable effects
Quality	**Type of Evidence**
High	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies
Moderate	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	Evidence for at least 1 critical outcome from observational studies, RCTs with serious flaws or indirect evidence
Very Low	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence

Recommendations

Practice recommendations were directed by the existing evidence and consensus amongst the content experts. Patient and family preferences were included when possible. The Content Expert Team and EBOC team remain aware of the controversies in the initial management of status epilepticus in children. When evidence is lacking, options in care are provided in the clinical standard and the accompanying order sets (if applicable).

Approval Process

Clinical standards are reviewed and approved by hospital committees as deemed appropriate for its intended use. Clinical standards are reviewed as necessary within EBOC at Texas Children's Hospital. Content Expert Teams are involved with every review and update.

Disclaimer

Practice recommendations are based upon the evidence available at the time the clinical standard was developed. Clinical standards (guidelines, summaries, or pathways) do not set out the standard of care and are not intended to be used to dictate a course of care. Each physician/practitioner must use his or her independent judgment in the management of any specific patient and is responsible, in consultation with the patient and/or the patient's family, to make the ultimate judgment regarding care.

Version History

Date	Comments
Jul 2018	Originally completed