Inclusion Criteria
Age 1-36 months
Diagnosis of infantile spasms

Exclusion Criteria
Prior failure of treatment for infantile spasms
Diagnosis of tuberous sclerosis or Lennox-Gastaut
Concurrent use of steroids for indications other than infantile spasms

Background
Epilepsy is a common neurological disorder affecting 1 out of 26 people in the United States at some point in their lifetime.\(^1\) Childhood epilepsy can cause severe injury to the developing brain. One particularly catastrophic childhood epileptic encephalopathy is infantile spasms. Although infantile spasms may appear subtle, the neurodevelopmental consequences are devastating including intellectual disability, autism, and subsequent epilepsy in up to 70% of children.\(^2\) Over 200 different etiologies may cause infantile spasms leading to delayed recognition and treatment. Recent studies have shown that early diagnosis and initiation of effective treatment for infantile spasms may improve neurodevelopmental outcomes.\(^3\) However, along with a lack of standardized diagnostic workup, medication regimens are highly variable, some of which are quite costly. Creating an evidence-based treatment protocol of infantile spasms at Texas Children’s Hospital will help with standardization.

Critically Analyze 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 evidence is rated and how a strong versus a weak recommendation is established.

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PICO Question 1: In children diagnosed with infantile spasms, does the use of high dose ACTH compared to low dose ACTH increase the likelihood of remission of infantile spasms and hypsarrhythmia?

Recommendation: Strong recommendation with low quality evidence to administer high-dose ACTH for treatment of infantile spasms.\(^4,5\)

Two studies reviewed (Hancock 2013 and Zeng 2011) completed a meta-analysis of other randomized control trials to determine preferred ACTH dose. Both studies used the randomized controlled trial from Hrachovy 1994 but pooled these results with data from different studies.\(^4,5\) The meta-analysis, Hancock 2013, combined data from Hrachovy 1994 with Yanagaki 1999.\(^6\) The meta-analysis, Zeng 2011, combined data from Hrachovy 1994 with Shu 2009.\(^5\) Low-dose ACTH ranged from 0.4-20 IU/day and high-dose 50-150 IU/m2/day. The Hancock 2013 study showed a nonstatistical difference in the rate of spasm cessation between high-doses of ACTH (79.5% of patients) compared to low-dose ACTH (76.5% of patients) (OR 1.1, 95% CI 0.4 to 2.6).\(^4\) Similarly, the Zeng 2011 study
Evidence Supports

- Administer high-dose ACTH for treatment of infantile spasms. (4-12) – Strong recommendation, low quality evidence
- Continue the use of ACTH over prednisolone for the initial treatment of infantile spasms. (4,7,9,10,13-15) – Strong recommendation, low quality evidence
Texas Children's Evidence Based Outcomes Center
Clinical Algorithm for Epileptic Spasms (Infantile Spasms)

Diagnostic Evaluation
- Admit to Neurology
- Neurological Exam
- Video EEG
- Brain MRI
- No determined etiology, add patient specific metabolic, genetic, and chromosomal evaluations
- Pyridoxine Challenge (100mg IV for two doses 20 minutes apart)

Patient presenting with suspected infantile spasms

Treat with Pyridoxine

Follow up in Neuro Clinic in two weeks of beginning medication

Responds to Pyridoxine

Confirmed Infantile Spasms on EEG

OFF Algorithm Consider Repeat EEG

Etiology Unknown

Tuberocest sclerosis or lesional/structural, administer Vigabatrin
- Prescriber must be enrolled in Vigabatrin REMS program
- Complete patient-physician agreement form

If no response to ACTH treatment or seizures recur, consult Epileptologist for further treatment (or surgical workup)

If etiology is Tuberous sclerosis or lesional/structural, administer Vigabatrin

Days
1 – 14
15 – 17
18 – 20
21 – 23
24 – 29
Dose – ACTH
75 Units/m2 twice daily
30 Units/m2 in the morning
15 Units/m2 in the morning
10 Units/m2 in the morning
10 Units/m2 every other morning (3 total doses)

If there is no clinical response by day 14, consider alternative treatment.

*If ACTH is not tolerated, unable to be obtained or there is a lack of adherence to regimen, consider treatment with high dose prednisolone.

Days
1 – 3
4 – 6
>7
Dose – Vigabatrin
25 mg/kg/dose two times daily
50 mg/kg/dose two times daily
75 mg/kg/dose two times daily

Side Effects (e.g. sedation, hyptonia) may necessitate slower titration.
If no response by day 14, consider alternative treatment

Other Treatments
- Topiramate or Zonisamide
- Ketogenic Diet
- Low-Dose ACTH
- Prednisolone
References

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.

Infantile Spasm Content Expert Team
Anne Anderson, MD, Neurology
Rohini Coorg, MD, Neurology
Irfan Ali, MD, Neurology
Laura Masters, MD, Neurology
Michael Quach, MD, Neurology
Elaine Seto, MD, Neurology
Jim Riviello, MD, Neurology
Gary Clarke, MD, Neurology

EBP Course Participant and EBOC Support
Aderonke Igbekele, BSN
Mindl Weingarten, PharmD, Pharmacy
Andrea Jackson, MBA, CCRN
Charles Macias, MD, MPH, Director

Additional EBOC Support
Tom Burke, Research Assistant
Sherin Titus, Research Assistant
Karen Gibbs, MSN/MPH, RN, Research Specialist
Jennifer Loveless, MPH, Research Specialist
Sheesha Porter, MS, RN, Research Specialist
Ellis Arjmand, MD, PhD, MMM, Associate Medical Director
Christina Davidson, MD, MFM, Associate Medical Director
Annie Dykes, MSN, RN, ACNS-BC, Assistant Director
Kathy Carberry, MPH, RN, Director

No relevant financial or intellectual conflicts to report.

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

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

4. Critically Analyze the Evidence
   - 2 meta-analyses, 3 randomized controlled trials, 4 nonrandomized studies and 3 professional organization guidelines

5. Summarize the Evidence
   - Materials used in the development of the guideline, evidence summary, and order sets are maintained in a Treatment of Infantile Spasms 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.

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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 treatment of infantile spasms 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 guideline 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 family, to make the ultimate judgment regarding care.

Version History

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<tr>
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