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. 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. 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. 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.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Type of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>STRONG</td>
<td>Desirable effects clearly outweigh undesirable effects or vice versa</td>
</tr>
<tr>
<td>WEAK</td>
<td>Desirable effects closely balanced with undesirable effects</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quality</th>
<th>Type of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies</td>
</tr>
<tr>
<td>Moderate</td>
<td>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</td>
</tr>
<tr>
<td>Low</td>
<td>Evidence for at least 1 critical outcome from observational studies, from RCTs with serious flaws or indirect evidence</td>
</tr>
<tr>
<td>Very Low</td>
<td>Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence</td>
</tr>
</tbody>
</table>

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.

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. The meta-analysis, Hancock 2013, combined data from Hrachovy 1994 with Yanagaki 1999. The meta-analysis, Zeng 2011, combined data from Hrachovy 1994 with Shu 2009. 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). Similarly, the Zeng 2011 study...
(which used direct and indirect comparisons) showed no difference in efficacy between high- and low-dose ACTH (RR 0.93, 95% CI: 0.57-1.54). Both studies are of moderate quality of evidence. Ito 2002 analyzed the initial effects of a low-dose regimen for ACTH. The observational study found that the effect of ACTH was not dose dependent. A 2016 observational study found no difference in the response rate between children that received high- compared to low-dose ACTH (p=0.14). Yin 2017 evaluated three low-dose regimes (1 IU/kg/day, 1.1-1.9 IU/kg/day, and 2-4 IU/kg/day) of ACTH for treatment of infantile spasms utilizing retrospective data. The authors reported that by day 14, there was a statistical difference in the response rate for cessation of spasms favoring 2-4 IU/kg/day compared to the 1 IU/kg/day ACTH dosing regimen (p=0.004). There were not any differences seen in the other comparisons. Two national guidelines recommend that low-dose ACTH be considered as an alternative to high-dose treatment.

In a randomized controlled trial to study low-dose versus conventional dose ACTH, the authors reported no significant difference in adverse effects except for sleepiness and brain shrinkage (p=0.023). Hamano 2006 reported a statistical difference in the discontinuation of ACTH between high- and low-dose regimens with less frequency in the latter. However, the study resulted no significant difference in the occurrence of adverse effects.

**PICO Question 2:** In children diagnosed with infantile spasms, does the use of prednisolone compared to ACTH increase the likelihood of remission of infantile spasms and hypsarrhythmia?

**Recommendation:** Strong recommendation with low quality evidence to continue the use of ACTH over prednisolone for the initial treatment of infantile spasms. A review of the literature found one meta-analysis, two randomized controlled trials and one observational study addressing this question. The meta-analysis found on this topic included three randomized controlled trials. Lux 2004 compared ACTH 40-60 units on alternate days versus high-dose prednisolone 40-60 mg/day. Baram 1996 compared ACTH 150 units/m²/day versus prednisone 2 mg/kg/day, and Hrachovy 1994 compared ACTH 20-30 units/day versus prednisonel 2 mg/kg/day. The meta-analysis, Hancock 2013, reported that there was no difference found between ACTH and high-dose prednisolone for resolution of spasms (OR 1.36, 95% CI 0.41-4.53). Wanigasinghe 2014 compared ACTH 40 IU every other day versus prednisolone 40 mg/day. Initial response to treatment showed a higher likelihood of spasm freedom in the prednisolone group (OR 2.9, 95% CI 1.3-6.6, p=0.01). However, the six (OR 1.7; 95% CI 0.8-3.8, p=0.19) and twelve month (OR 1.9; 95% CI 0.8-4.2, p=0.13) review showed no statistical difference in spasm freedom. Knupp 2016 was a retrospective review that compared treatment with ACTH, oral corticosteroids, or vigabatrin in 230 children with new onset infantile spasms. The study found that the response rate was higher in the ACTH group compared to the vigabatrin treated group (p=0.038) and oral corticosteroids group (p=0.06). Due to small sample sizes and various dosing regimens of the treatment modalities, there is insufficient evidence at this time to conclude that prednisolone is as effective as ACTH.

This is in agreement to the recommendation of the American Academy of Neurology and Child Neurology Society that there is not enough evidence to recommend steroids as equally efficacious to ACTH for infantile spasms. The guideline from the International League of Epilepsy recommends ACTH as the preferable treatment for patients. The National Institute for Health and Clinical Excellence guideline from Europe recommends the use of steroids or vigabatrin as first-line treatment.

**Critical Points of Evidence**

**Evidence Supports**
- Administer high-dose ACTH for treatment of infantile spasms. — Strong recommendation, low quality evidence
- Continue the use of ACTH over prednisolone for the initial treatment of infantile spasms. — Strong recommendation, low quality evidence
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

Responds to Pyridoxine
- No
- Confirmed Infantile Spasms on EEG
- No
- OFF Algorithm Consider Repeat EEG
- Yes
- Treat with Pyridoxine

Confirmed Infantile Spasms on EEG
- No
- Etiology Unknown
- Yes
- If etiology is Tuberous sclerosis or lesional/structural, administer Vigabatrin
- No
- Administer ACTH
- Initiate H2RA as a gastric acid suppression during treatment
- Outpatient monitoring should include blood pressure and glucose screening 1-2 times per week
- 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
- Prescriber must be enrolled in Vigabatrin REMS program
- Complete patient-physician agreement form

Follow up in Neuro Clinic in two weeks of beginning medication

Treatment with intramuscular (IM) ACTH

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

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.

Treatment with Oral Vigabatrin

<table>
<thead>
<tr>
<th>Days</th>
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</tr>
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<tbody>
<tr>
<td>1–3</td>
<td>50 mg/kg/day divided two times daily</td>
</tr>
<tr>
<td>4–6</td>
<td>100 mg/kg/day divided two times daily</td>
</tr>
<tr>
<td>&gt;7</td>
<td>150 mg/kg/day divided two times daily</td>
</tr>
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Side effects (e.g. sedation, hypotonia) 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.

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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
   - American Academy of Neurology and Child Neurology Society
   - Evidence-based guideline update: medical treatment of infantile spasms; International League Against Epilepsy
   - Summary of recommendations for the management of infantile seizures; National Institute for Health and Clinical Excellence
   - The Epilepsies: The diagnosis and management of the epilepsies in adults and children in primary and secondary care

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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<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Comments</th>
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<tr>
<td>March 2018</td>
<td>First Iteration</td>
<td></td>
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