General

Guideline Title

Bibliographic Source(s)

Guideline Status
This is the current release of the guideline.


The American Academy of Neurology (AAN) reaffirmed the currency of the guideline in July 2015.

This guideline meets NGC’s 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations
Definitions of the levels of the recommendations (A, B, C, U) and classification of the evidence (Class I-IV) are provided at the end of the "Major Recommendations" field.

Are Other Forms of Corticosteroids as Effective as Adrenocorticotropic Hormone (ACTH) for Treatment of Infantile Spasms?

Conclusion
Data are insufficient regarding the equivalence of other corticosteroids to ACTH (Class III and IV evidence).

Recommendation
The evidence is insufficient to recommend the use of prednisolone, dexamethasone, and methylprednisolone as being as effective as ACTH for short-term treatment of infantile spasms (Level U).

Are Low-Dose ACTH Regimens Effective for Short-term Treatment of Infantile Spasms?
Conclusion

A Class I study showed similar efficacy between low-dose (20–30 IU) and high-dose (150 IU/m²) natural ACTH, and a Class II study using the same low-dose natural ACTH showed clinical and electroencephalographic (EEG) response rates of >40%. The evidence suggests that low-dose ACTH is probably as effective as high-dose ACTH for short-term treatment of infantile spasms (Class I and II evidence).

Recommendation

Low-dose ACTH should be considered as an alternative to high-dose ACTH for treatment of infantile spasms (Level B).

Is ACTH More Effective Than Vigabatrin (VGB) for Short-term Treatment of Infantile Spasms?

Conclusion

Two Class III studies (1 from the 2004 parameter and a later study) demonstrated that ACTH is more effective than VGB for short-term treatment of children with infantile spasms (excluding those with tuberous sclerosis complex [TSC]). A small Class III study and a Class IV study found no difference in short-term outcome between ACTH and VGB.

Recommendation

ACTH (Level B) or VGB (Level C) may be offered for short-term treatment of infantile spasms. Evidence suggests that ACTH may be offered over VGB (Level C).

What Other Agents Are as Effective as ACTH for Treatment of Infantile Spasms?

Conclusions

Data from previously reviewed and updated evidence are insufficient to determine whether valproic acid (VPA), vitamin B6, nitrazepam (NZP), levetiracetam (LEV), zonisamide (ZNS), topiramate (TPM), the ketogenic diet, sulthiame, or other novel therapies (e.g., intravenous immunoglobulin [IV Ig], thyrotropin-releasing hormone [TRH]) are effective in the treatment of infantile spasms (Class III and IV evidence). A single Class III study showed better outcome for combination therapy with ACTH and magnesium sulfate (MgSO₄).

Recommendation

The evidence is insufficient to recommend other therapies (VPA, vitamin B6, NZP, LEV, ZNS, TPM, the ketogenic diet, or novel/combination therapies) for treatment of infantile spasms (Level U).

Does Successful Early Treatment of Infantile Spasms Lead to Long-term Improvement of Neurodevelopmental Outcomes or Decreased Incidence of Epilepsy?

Conclusions

A Class II study showed that hormonal therapy (ACTH or prednisolone) relative to VGB therapy leads to better neurodevelopmental outcome in children with cryptogenic spasms. One previous Class III study and 1 newer Class II study showed that shorter lag time to treatment improves long-term cognitive outcomes.

Recommendations

1. Hormonal therapy (ACTH or prednisolone) may be considered for use in preference to VGB in infants with cryptogenic infantile spasms, to possibly improve developmental outcome (Level C).
2. A shorter lag time to treatment of infantile spasms with either hormonal therapy or VGB may be considered to improve long-term cognitive outcomes (Level C).

Definitions:

Classification of Recommendations

Level A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.*)

Level B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified
population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

Level C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

Level U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

* In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2).

Classification of Evidence for Therapeutic Intervention

Class I: A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. The following are also required:

a. Concealed allocation
b. Primary outcome(s) clearly defined
c. Exclusion/inclusion criteria clearly defined
d. Adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias.
e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*

1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority.
2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose and dosage adjustments are similar to those previously shown to be effective).
3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.
4. The interpretation of the results of the study is based upon a per protocol analysis that takes into account dropouts or crossovers.

Class II: A randomized controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e above or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e above. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.**

Class IV: Studies not meeting Class I, II, or III criteria including consensus or expert opinion.

*Note that numbers 1-3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.

**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Infantile spasms

Guideline Category
Assessment of Therapeutic Effectiveness

Management

Clinical Specialty
Neurology
Pediatrics

Intended Users
Physicians

Guideline Objective(s)
To update the 2004 American Academy of Neurology (AAN)/Child Neurology Society (CNS) practice parameter on treatment of infantile spasms in children

Target Population
Children aged 1 to 36 months with infantile spasms

Note: The subcommittee did not consider studies (1) of children with Lennox-Gastaut syndrome, (2) of children aged <1 month or >36 months at study entry, (3) wherein EEG not initially performed to confirm hypsarrhythmia

Interventions and Practices Considered

Management/Treatment

1. Adrenocorticotropic hormone (ACTH) regimens (low dose, high dose)
2. Prednisolone and prednisone
3. Vigabatrin

The following treatments were considered but there was insufficient evidence to make recommendations concerning their use:

1. Corticosteroids (prednisolone, dexamethasone, and methylprednisolone) for short-term use
2. Benzodiazepines including nitrazepam
3. Valproic acid
4. Vitamin B6
5. Levetiracetam
6. Zonisamide
7. Topiramate
8. Ketogenic diet
9. Other novel/combination therapies

Major Outcomes Considered

- Complete cessation of spasms
- Resolution of hypsarrhythmia
- Normalization of electroencephalography (EEG)
- Relapse rate
Methodology

Methods Used to Collect/Select the Evidence

Description of Methods Used to Collect/Select the Evidence

2012 Guideline

An updated literature search of MEDLINE and EMBASE databases (2002–August 2011) using the OVID interface was conducted using the process described in the 2004 parameter (see appendix e-3 of the Data Supplement [see the "Availability of Companion Documents" field]). The combined MEDLINE and EMBASE text word searches identified 1,935 articles. All search titles and abstracts were analyzed for content. English-language articles on therapy, prognosis, and adverse effects (AEs) were selected. Sixty-eight articles were chosen for detailed review; 26 were included in the analysis.

Articles selected for detailed review required a clearly stated diagnosis of infantile spasms, an electroencephalogram (EEG) demonstrating hypsarrhythmia or modified hypsarrhythmia (articles using routine electroencephalography (EEG) recording were included because not all articles used prolonged video-EEG monitoring), and inclusion of children aged 1–36 months. Infantile spasms were classified as either symptomatic (i.e., of known cause) or cryptogenic (of unknown cause but presumably genetic in many infants) as defined by the International League Against Epilepsy. Cases described as idiopathic were included in the cryptogenic group for analysis.

The subcommittee excluded studies of children with Lennox-Gastaut syndrome, studies of children aged <1 month or >36 months at the time of study entry, and studies wherein an EEG was not initially performed to confirm the presence of hypsarrhythmia or modified hypsarrhythmia. Also excluded were retrospective studies with single case reports, case series containing fewer than 4 infants, studies on long-term prognosis that were uncontrolled for treatment, letters, abstracts, unpublished data, and review articles.

2015 Reaffirmation

MEDLINE was searched from January 2010 to July 2015 using the search terms infantile spasms, spasm, hypsarrhythmia, hypsarrhythmia, cryptogen, infant, spasm, jackknife seizure, noddling spasm, salaam seizure, spasms nutans, symptomatic infant: spasm, west syndrome, lightning attack, salaam attack and blitznicksalaamkrampfe, petit mal quadrette, massive myoclon: spasm, and minor motor epilepsy. Inclusion/exclusion criteria for the search included humans only, relevant to clinical questions; criteria used to screen search results were the same as described in the 2012 published guideline.

Number of Source Documents

Sixty-eight articles were selected for detailed review; 26 were included in the analysis

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Classification of Evidence for Therapeutic Intervention
Class I: A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. The following are also required:

a. Concealed allocation
b. Primary outcome(s) clearly defined
c. Exclusion/inclusion criteria clearly defined
d. Adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias.
e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*
   1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority.
   2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose and dosage adjustments are similar to those previously shown to be effective).
   3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.
   4. The interpretation of the results of the study is based upon a per protocol analysis that takes into account dropouts or crossovers.

Class II: A randomized controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e above or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e above. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.**

Class IV: Studies not meeting Class I, II, or III criteria including consensus or expert opinion.

*Note that numbers 1-3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.

**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

Methods Used to Analyze the Evidence

Meta-Analysis

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Two panelists independently reviewed, abstracted, and classified the articles, to assess the quality of data related to study design and treatment effect. A third panelist arbitrated any disagreements in ratings. For each question, evidence is sequentially analyzed and then summarized to determine the overall strength of the evidence and to formulate recommendations.

Analysis included short-term, intermediate, and long-term outcome measures. Short-term outcome measures were defined as complete spasms cessation; hypsarrhythmia resolution and, where documented, electroencephalogram (EEG) normalization; and relapse rate. Adverse effects (AEs) and mortality were documented. For studies with a mean follow-up of >12 months, intermediate to long-term outcome measures were EEG without epileptiform abnormalities, absence of seizures, and normal development. Data recorded included the number of patients entering and completing the trial, age at spasms onset, age at study entry, treatment lag (time of spasms onset to treatment initiation with the agents described herein), gender, etiology, drug dosage, therapy duration, co-interventions, and follow-up duration.

The Cochran-Mantel-Haenszel statistical method was used in the meta-analysis to quantify the clinical efficacy of adrenocorticotropic hormone (ACTH) versus vigabatrin (VGB). This method is used to perform a stratified analysis when comparing odds ratios (OR) across studies. It combines the ORs while maintaining the group from which the data came. The Breslow-Day (BD) statistic is then applied to test the homogeneity of the OR across the strata. When the BD statistic is nonsignificant, all studies in the meta-analysis are pointing in the same direction, signifying
concordance.

The American Academy of Neurology's 4-tiered article classification scheme for therapeutic evidence was used (see the "Rating Scheme for the Strength of the Evidence" field); the strength of the recommendations was linked to the evidence (see the "Rating Scheme for the Strength of the Recommendation").

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

2012 Guideline
Not stated

2015 Reaffirmation

A Guideline Development, Dissemination, and Implementation (GDDI) member who had expertise in neurologic disease conducted a targeted literature search for high quality studies using the same criteria as presented in the original guideline. The GDDI reviewer and the subcommittee reviewed the new evidence and determined that the following three criteria were met: 1. There is no new evidence that would alter conclusions or recommendations in the guideline since the last literature search, 2. Guideline methodology is sound and current methodology is not substantially different, and 3. No significant practice variation relevant to the guideline currently exists.

Rating Scheme for the Strength of the Recommendations

Classification of Recommendations

Level A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.*)

Level B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

Level C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

Level U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

* In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2).

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Drafts of the guideline have been reviewed by at least 3 American Academy of Neurology (AAN) committees, a network of neurologists,
Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate treatment of infantile spasms

Potential Harms

- The adverse effects of hormonal therapy most commonly reported are hypertension (0%-37%), irritability (37%-100%), infection (14%), and cerebral atrophy (62%)(see tables e-1–e-3 of the original guideline document).
- In August 2009, the US Food and Drug Administration (FDA) approved vigabatrin (VGB) for use in infantile spasms and as add-on therapy for refractory seizures, with a black box warning for potential permanent visual impairment; the drug is available only through the Lundbeck Inc. restricted Support, Help and Resources for Epilepsy (SHARE) program. Although concerns persist regarding visual field constriction and retinal toxicity with VGB use, the risk appears to be lower with short-term use. There are also recent reports of abnormal magnetic resonance imaging (MRI) signal intensity or restricted diffusion-weighted imaging affecting the thalamus, basal ganglia, dentate nucleus, and brainstem in patients receiving VGB for infantile spasms. However, these changes are reversible when therapy is discontinued, and the clinical significance of the MRI abnormalities is currently unknown.

Qualifying Statements

Qualifying Statements

This statement is provided as an educational service of the American Academy of Neurology (AAN) and the Child Neurology Society (CNS). It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN and CNS recognize that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all circumstances involved. The clinical context section is made available in order to place the evidence-based guideline(s) into perspective with current practice habits and challenges. No formal practice recommendations should be inferred.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.
Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need
Getting Better
Living with Illness

IOM Domain
Effectiveness
Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)


Adaptation
Not applicable: The guideline was not adapted from another source.

Date Released
2012 Jun 12 (reaffirmed 2015 Jul 18)

Guideline Developer(s)
American Academy of Neurology - Medical Specialty Society
Child Neurology Society - Medical Specialty Society
Source(s) of Funding

American Academy of Neurology (AAN) and the Child Neurology Society

Guideline Committee

Guideline Development Subcommittee of the American Academy of Neurology

Practice Committee of the Child Neurology Society

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

*Disclosure*

Dr. Go reports no disclosures. Dr. Mackay has received honoraria from UCB Pharma, Jansen Cilag, and Sanofi-Aventis for presentations at industry-sponsored symposia. Dr. Weiss, T. Adams-Webber, D. Stephens, Dr. O.C. Snead III, and Dr. Ashwal report no disclosures. Go to Neurology.org for full disclosures.

*Conflict of Interest*

The American Academy of Neurology (AAN) and Child Neurology Society (CNS) are committed to producing independent, critical and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN and CNS keep separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN and CNS limit the participation of authors with substantial conflicts of interest. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com.

Guideline Status

This is the current release of the guideline.


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This guideline meets NGC’s 2013 (revised) inclusion criteria.

Guideline Availability
Availability of Companion Documents

The following are available:


In addition, Continuing Medical Education (CME) material for this guideline is available at the AAN Web site [link].

Patient Resources

The following is available:


Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI on August 17, 2004. The information was verified by the guideline developer on September 9, 2004. This summary was updated by ECRI Institute on May 1, 2009 following the U.S. Food and Drug Administration advisory on antiepileptic drugs. This NGC summary was updated by ECRI Institute on July 27, 2012. The currency of the guideline was reaffirmed by the developer in July 2015 and the summary was updated by ECRI Institute on January 18, 2017.

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