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TEXAS CHILDREN'S HOSPITAL
EVIDENCE-BASED OUTCOMES CENTER
Hydrocortisone Treatment in Non-Classical Congenital Adrenal Hyperplasia (CAH)
Evidence Summary

Inclusion Criteria
- Children with non-classical CAH

Background

Non-classical CAH is a common autosomal recessive disorder that can affect a child's growth and development. Therefore, it is important to understand the best treatment option to improve final adult height and clinical outcomes.

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.

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, from RCTs with serious flaws or indirect evidence
Very Low	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence

PICO Question 1: In patients with non-classical CAH, does treatment with maintenance steroids improve final adult height?

Recommendation(s): Strong recommendation with low quality evidence for treating patients with hydrocortisone to improve final adult height. [3,5,9,10]

A review of the literature revealed 4 retrospective observational studies that specifically addressed the use of hydrocortisone in patients with non-classical CAH. Two studies compared patients that received hydrocortisone to another group that did not and showed that the final adult height was closer to the midparental height in the group that received treatment. [5,10] One of these studies looked at the timing of initiation of hydrocortisone treatment and observed that patients who were treated ≥1 year before the onset of puberty achieved final height within their genetic potential. [10] Two additional studies that looked at only patients who were treated with hydrocortisone showed that their final adult height was comparable to their target height, although they did not specify at what age patients began treatment. [3,9]

PICO Question 2: In children with non-classical CAH, does treatment with stress steroids improve clinical outcome in stress situations?

Recommendation(s): Weak recommendation with very low quality evidence against the need for stress dose steroids. [1,2,4,6-8,11,12]

A review of the literature revealed no studies specifically evaluating the use of stress dose steroids in nonclassical CAH children in stress situations. However, there are multiple studies that find that in most cases, patients with nonclassical CAH have adequate baseline cortisol production as well as adequate production of cortisol when stimulated with ACTH, which mimics the body's response stress situations. [1,2,4,7] Only one prospective case control study found lower basal and stimulated cortisol values. [11] Expert opinion in multiple review articles do not recommend maintenance or stress dose steroids unless there is inadequate cortisol production upon ACTH stimulation or the patient is placed on glucocorticoid therapy for other reasons. [6,8,12]

Critical Points of Evidence*

Evidence Supports

- Maintenance hydrocortisone therapy should be considered in patients with non-classical CAH starting ≥1 year prior to the onset of puberty to improve final adult height. [3,5,9,10] – Strong recommendation, low quality evidence
- Stress dose steroids are not needed in patients with adequate response on ACTH stimulation test who are not on glucocorticoid therapy. [1,2,4,6-8,11,12] – Weak recommendation, very low quality evidence

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

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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.

Hydrocortisone Treatment in Non-Classical Congenital Adrenal Hyperplasia Content Expert Team
Bonnie McCann-Crosby, MD
Min-Jye Chen, MD

EBOC Team
Janelle Smith, MSN, RN, Research Specialist
Charles Macias, MD, MPH, Medical Director

EBP Sponsor
Esther Sampayo, MD

Additional EBOC Support
Tom Burke, Research Assistant
Sherin Titus, Research Assistant
Karen Gibbs, MSN/MPH, RN, Research Specialist
Andrea Jackson, MBA, RN, Research Specialist
Betsy Lewis MSN, RN, CNL, Research Specialist
Jennifer Loveless, MPH, Research Specialist
Sheesha Porter, MS, RN, Research Specialist
Anne Dykes, MSN, RN, 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
   - N/A
3. Literature Review of Relevant Evidence
   - Searched: PubMed, Google Scholar
4. Critically Analyze the Evidence
   - 4 randomized **controlled** trials, and 4 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 Hydrocortisone Treatment in Non-Classical Congenital Adrenal Hyperplasia (CAH) 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
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High	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies
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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 management of Hydrocortisone Treatment in Non-Classical Congenital Adrenal Hyperplasia (CAH) 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	Action	Comments
Apr 2014	Originally completed	