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.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Type of Evidence</th>
</tr>
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<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>
<tr>
<td>Quality</td>
<td></td>
</tr>
<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>
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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. (5, 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. (5, 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.
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
   - 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.

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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
<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Comments</th>
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<td>Apr 2014</td>
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