Update on Corticosteroid Safety in Children

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Conflict of Interest Disclosures for David P. Skoner

<table>
<thead>
<tr>
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<th>Greer Laboratories, Novartis, Genentech, Merck, GlaxoSmithKline, Sanofi, Teva, Boston Scientific</th>
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<tr>
<td>Consultant</td>
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<td>Speaker's Bureau</td>
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Growth and Adrenal Effects Of ICS and INCS In Children

Objectives

• Describe the onset and offset.
• Discuss clinical implications.
Growth and Adrenal Effects Of ICS and INCS In Children

- What is the onset?
Comparison of Growth When Not Recieving BDP With Growth During Treatment Segregated by Six Week Divisions in Asthma (Stadiometry)

<table>
<thead>
<tr>
<th>Period</th>
<th>Growth (mm/week)</th>
<th>Difference Between Treatment/Non-Treatment</th>
<th>p Value</th>
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<tbody>
<tr>
<td>No treatment</td>
<td>0.140</td>
<td>--</td>
<td></td>
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<tr>
<td>Weeks 0-6</td>
<td>0.073</td>
<td>-0.067</td>
<td>0.011</td>
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<tr>
<td>Weeks 7-12</td>
<td>0.094</td>
<td>-0.046</td>
<td>0.076</td>
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<tr>
<td>Weeks 13-18</td>
<td>0.095</td>
<td>-0.047</td>
<td>0.079</td>
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<tr>
<td>Weeks 19-24</td>
<td>0.138</td>
<td>-0.002</td>
<td>0.935</td>
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<tr>
<td>Weeks 25-30</td>
<td>0.120</td>
<td>-0.02</td>
<td>0.607</td>
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Arch Dis Child 1998;78:172-173

Study Design - Lower-leg Growth Rates in Children With Asthma During Treatment With Ciclesonide And Fluticasone Propionate

Kneumometry

Primary Endpoint: Lower Leg Growth Rate

ITT analysis: mean lower leg growth rate (mm/week) ±1-SEM. N=28 for each group.

Detection of Growth Suppression in Children During Treatment With Intranasal Beclomethasone Dipropionate

Stadiometry

![Graph showing mean change from baseline (cm) over months with *p < .05 and **p < .01](image)


The Study Design of the FDA Guidance Was Sufficiently Sensitive to Find a Small Growth Effect of the INCS TAA (OTC approval by FDA to 2 years of age)

**Early Onset**

P = .01

![Graphs showing growth effect](image)

Growth effect of combination INCS and ICS is unknown!


Change From Baseline in AUC at Day 29

![Graph showing change from baseline in AUC with means at baseline](image)

Growth and Adrenal Effects Of ICS and INCS In Children

What is the onset?
- The effects begin within 2 weeks of starting therapy.

What is the offset?

Side Effects of Systemically-Active ICS Can Be Permanent in Children

Maci’s Case Illustrates an Unmet Need for Greater Attention to Safety in Children with Mild Allergy and Asthma

- Maci, 6 years old, developed Cushing’s Syndrome, with growth and life-threatening adrenal gland suppression. Doctors diagnosed allergies, misdiagnosed asthma, prescribed higher-than-recommended and unapproved doses of both inhaled (Fluticasone MDI 110 2 bid) and intranasal (Mometasone INCS 2/nostril) corticosteroids, failed to follow guideline recommendations to reduce doses over about 16 months, and then failed to recognize and acknowledge that the systemic side effects were corticosteroid-related despite the parent’s strong belief and frequent assertions otherwise.
- Maci’s adrenal suppression reversed 4 weeks after stopping ICS/INCS, but she continues to be treated with growth hormone.
- Led to the formation of a non-profit organization called Maci’s TEAMs (Teaching Everyone About Medication Safety), which will keep children on allergy and asthma medications safe by educating physicians and parents about proper diagnosis, doses and side effects.
Growth and Adrenal Effects Of ICS and INCS In Children

What is the offset?
- Best evidence indicate that the growth effect is permanent, but adrenal suppression is reversible within several months.

What are the clinical implications?

Carefully Balance Safety And Efficacy of INCS/ICS in Children

(Skoner DP Pediatrics 2002; 109(2):381-392)
- Make sure that the diagnosis is correct before exposing children to ICS/INCS.
- Make safety a priority, especially if pre-pubertal, mild disease, using both INCS and ICS, high adherence.
- Choose INCS/ICS with the best safety profile, low systemic activity, and at least one negative growth study designed per FDA guidance.
- Recommend spacer/chamber and mouth rinsing.
- Follow FDA/NHLBI Asthma Guideline dosing recommendations, insuring that starting doses align with disease severity, and stepping-down to lowest effective dose.
- Optimize steroid-sparing strategies.
- Be proactive and have a safety discussion with parent.
- Listen to parents who report changes in their child.
- Monitor frequently (e.g. every 2-3 months):
  — Growth and changes in behavior or physical appearance at all doses.
  — Other systemic side effects at high doses (e.g. eyes).
**Growth Effect Of Topical Corticosteroid Therapy In Children**

- The onset of ICS side effects is in the first 3 months.
  - Plan a 2 or 3 month follow-up visit after starting ICS to evaluate for hypercorticism, such as changes in physical appearance and growth percentiles.
- The small growth effect is permanent without offset. Adrenal suppression is reversible within several months.
  - Focus efforts on prevention by carefully balancing benefit and risk. Use lowest effective dose, aggressively practice step down dosing.

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**We Need to Step-Down ICS Doses When Possible**

[Outcomes Of Stepping Down Asthma Medications In A Guideline-based Pediatric Asthma Management Program (Mayo Clinic)]

Retrospective study of 5- to 18-year-old children with asthma in an integrated primary care practice. Criteria for step down and success based on NAEPP-3 guideline definition of control (≥ 3 months).

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