Problem Based Learning: Balancing Safety and Efficacy of Asthma Therapy

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LEARNING OBJECTIVES

1) Identify key clinical decisions that contributed to the development of a rare systemic side effect of ICS (growth/adrenal suppression) in a child with possible asthma.

2) Identify knowledge gaps related to ICS dosing and side effect recognition and treatment.

3) Discuss methods to promote prevention and early recognition of systemic side effects of ICS.
Activate Your Keypads and Do Not Remove From Room
Do you feel confident in your ability to detect and diagnose growth and adrenal suppression secondary to ICS in a child with asthma?

1. Yes
2. No

94%
6%
Which is NOT a common symptom/sign of adrenal crisis?

1. Lethargy
2. Nausea/vomiting
3. Diarrhea
4. Abdominal pain
5. Hypotension
6. Convulsion
7. Shortness of breath
8. Unexplained hypoglycemia
With which ICS do you have the greatest level of experience in treating 5-11 year old children with asthma?

1. Beclomethasone HFA MDI (Qvar)
2. Fluticasone MDI (Flovent)
3. Fluticasone DPI (Flovent)
4. Mometasone DPI (Asmanex)
5. Budesonide DPI (Pulmicort)
6. Ciclesonide HFA MDI (Alvesco)
7. Flunisolide HFA MDI
Which fluticasone MDI dosages are FDA-approved for asthma in children <12 years of age?

1. 44 mcg
2. 110 mcg
3. 220 mcg
4. All of the above
5. 1 and 2 only
What is the NHLBI Guideline-recommended “medium dose” of fluticasone MDI for 5-11 year old children with asthma?

1. 44 2 puffs bid
2. 110 2 puffs bid
3. 220 2 puffs bid
4. None of the above

62%
27%
4%
7%
History – ML, 6 Years, 7 Months Old

- Presented to Allergist on 11/23/09.
- 3-year history of runny nose, nasal congestion, posterior nasal drainage, and frequent bouts of cough.
- Cough during colds, the fall and winter, and occasionally with exercise (along with some increased respiratory rate).
- No recent history of shortness of breath, decreased exercise tolerance, difficulty breathing, sputum production, or wheezing.
- One oral steroid course at about 3 years of age.
- No oral steroids or ER visits in the past year.
• Recurrent sinusitis and otitis media and two sets of tympanostomy tubes.
• Osteomyelitis (knee, 2007), gastroenteritis (hospitalization, 2005).
• Sinuses normal on MRI (for headaches).
• Born 6 weeks early, in NICU (no ventilator), had GERD.
• RSV at 18 months, not hospitalized, received a short (~1 month) course of nebulized Pulmicort and albuterol p.r.n., but not needed in last 3 years.
• No history of food allergy.
• Lives in a smoke free environment, no indoor pets.
• Family history was positive for allergy/asthma in Mother.
• ROS was otherwise negative.
CURRENT MEDICATIONS (can’t tell if they helped):

- Zyrtec 10 mg qd
- Singulair 5 mg qd.
- Veramyst – 2 qd, started 1/09.
- Albuterol inhaler p.r.n.
- Multivitamin daily.
Physical Examination

- HR 118, RR 20, Ht 43.5 in (5\textsuperscript{th} %ile), Wt 41lbs (10\textsuperscript{th} %ile).
- Well-developed and well-nourished.
- Allergic shiners, pale, edematous nasal turbinates, watery nasal discharge, and lymphoid hyperplasia of the posterior pharyngeal wall.
- Lungs clear to percussion and auscultation
- Cardiac exam normal.
- Remainder normal.
Allergy Skin Testing

- Puncture skin tests positive to tree and grass pollen, mold and house dust mite.
- Chest Radiograph – not done.
### Spirometry Report

**Spirometry Report**

**Puritan-Bennett Renaissance II**

**S/N:** G060701489

**Version:** 1.1.11

<table>
<thead>
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<th>Measurement</th>
<th>OC</th>
<th>BEST</th>
<th>Trial</th>
<th>%Pred</th>
<th>Pred</th>
<th>LLN</th>
<th>OC</th>
<th>BEST</th>
<th>Trial</th>
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<th>%Cho</th>
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<td></td>
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<td>PEF(L/M)</td>
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<td>58.1</td>
<td>6</td>
<td>35</td>
<td>161.6</td>
<td>83.4</td>
<td>1</td>
<td>51</td>
<td>1</td>
<td>43</td>
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<tr>
<td>FIVC (L)</td>
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<td>1.24</td>
<td>0.58</td>
<td>1</td>
<td>47</td>
<td></td>
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</tbody>
</table>

**Report Summary:**

- **Pre Med:** Tests 7 Acceptable 0 Reproducible 5
- **Post Med:** Tests 4 Acceptable 0 Reproducible 2

- **FVC VAR:** 27ML
- **FEV1 VAR:** 10ML
- **PEF VAR:** 8.5L/M
- **PEF VAR:** 16.4L/M

**NONE Interpretation:**
- **PREMED - Undetermined**
- **POSTMED - No Sig. Improv. in FVC FEV1**

**Comment:**
Spirometry

Legend:
- Pre
- Post
- Pred

Pre PF: 130
Post PF: 110
Bronchodilator Used: **Prufes**

+ FA = A*C

Effort/Technique: Good/Fair

Initials: C G P F
Does ML Have Asthma?

1. Yes (explain)
2. No (explain)
3. Uncertain (explain)

56% Yes (explain)
31% No (explain)
13% Uncertain (explain)
• Allergic rhinitis.
• Asthma (cough-variant).
• Cough.
• Recurrent sinusitis.
What Daily Therapy Would You Prescribe For ML?

1. None
2. Add trial of low-dose ICS
3. Add trial of low-dose ICS + LABA
4. Add trial of medium-dose ICS
5. Add trial of PPI
6. Other (explain)
Recommendations and Dosages

- Nasonex - 2 squirts in each nostril qd.
- Zyrtec 10 mg qd.
- Singulair 5 mg qhs.
- Flovent 110 mcg 2 puffs bid with Aerochamber.
- Ventolin HFA 2-4 puffs q4-6 hours p.r.n.
- Immunotherapy when older.
- H1N1 flu shot.
- Asthma action plan using symptoms.
- Follow-up visit in 6 weeks.
ML’s Mother Asks if the Inhaled Steroid Will Make ML Short? Your Reply?

1. No.
2. Yes, but only temporarily and no effect on adult height.
3. Yes, and ½ inch short as an adult.
4. Other (explain).
Your Thoughts on the Dose of Nasonex Used?

1. Too high
2. Just right
3. Too low
4. Doesn’t matter, since not systemically bioavailable

66% Too high
22% Just right
5% Too low
8% Doesn’t matter, since not...
Your Thoughts on the Dose of Flovent Used?

1. Too high
2. Just right
3. Too low
4. Doesn’t matter, since not systemically bioavailable

- Too high: 82%
- Just right: 15%
- Too low: 3%
- Doesn’t matter, since not...: 0%
Followup

Next Office Visit (1/14/10, age 6 years, 9 months, month #2)

• One ear infection

• No asthma symptoms including exertional, ER visits, or prednisone.

• Medication compliance good.

• Physical examination unchanged. Ht 43.5 in, Wt 44 lbs, HR 80, RR 18.

• ACT score 23.

• FVC 60%, FEV1 63%, FEF25-75 95%, PEF 67% predicted, interpreted as poor technique.

• Continue medications. Return visit 6 months.
Next Telephone Communication (4/8/10):

- Red and itchy eyes.
- Diagnosis allergic conjunctivitis.
- Antihistamine eyedrops p.r.n.
Next Office Visit (8/3/10, age 7 years, 4 months, month #9).

- No asthma symptoms, emergency visits, prednisone courses, albuterol use or exercise-induced symptoms.
- Reacted to penicillin.
- Physical examination unchanged. Ht 44 in, Wt 47 lbs, HR 100, RR 18.
- FVC 74%, FEV1 75%, FEF25-75 97%, PEF 75% predicted, interpreted as improved effort and mild obstruction.
What should be done with ML’s ICS dosage?

1. Step up (explain)
2. Step-down (explain)
3. No change (explain)
4. Other (explain)
Office Visit (8/3/10), continued.

- Recommendation made to continue medications.
Followup

Next Office Visit (2/21/11, age 7 years, 10 months, month #15).

- No asthma symptoms (except slight cough today), no albuterol use no nasal symptoms.
- Mother worried about weight gain.
- Easy bruising of skin.
- Physical examination unchanged. Ht 45.5 in (3rd %ile compared to 5th %ile on 11/23/09), Wt 52 lbs. (slightly >25th %ile compared to 10th %ile on 11/23/09). HR 112, RR 22. PEFR 140 l/m.
- ACT score 25.
- PFT (14 total attempts): FVC 66%, FEV1 66%, FEF25-75 99%, PEF 58% predicted, interpreted as poor technique.
Height/weight Plot Changes Not Viewed as Significant

- Began treatment at 6.5 yrs

[Graph showing body mass index for age percentiles with a black square highlighting the change in growth pattern after 6.5 years.]

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**Notes:**
- The changes in growth pattern are marked by a black square. The graph shows the body mass index for age percentiles from 2 to 20 years.
- The vertical red line represents the beginning of treatment, indicated with the text "Began treatment at 6.5 yrs."
Followup

Office Visit (2/21/11, continued).

- Considering Mom’s concerns and ML’s improvement, “it was time to wean the Flovent anyway”.
- Continue medications, except decrease Flovent 110 to 2 puffs qhs after the cough resolves.
- Rinsing, gargling, spitting and brushing after use appeared for the first time in the asthma action plan.
- Return visit 6 months.
Do you see a problem with the management at this juncture?

1. Yes (explain)
2. No (explain)
Endocrinology Visit (4/5/11, age 8 years, 0 months, month #17).

- Mother requested endocrine referral from pediatrician for short stature and fast weight gain.
- Always small and thin at about the 5th percentile on growth curves, but recently had fallen off her height curve and jumped up on her weight curve.
- Noted to be very active with outdoor play and in dance.
- Still on Flovent 110 2 puffs bid and Nasonex.
- Family history negative for diabetes, thyroid disease, and growth problems.
- Physical examination: Ht 113.9 cm, Wt 23.4kg, BMI 18. Round facies and cheek fullness, a fat pad on the back of the neck, and centripetal deposit of adiposity.
Endocrinology Evaluation

- Normal bone age.
- CBC normal except for WBC elevated 17.4, lymphocytes low 21%, and PMN high 69%.
- Serum cortisol <2 mcg/dL (normal 2.5-22.9), ACTH <5 pg/mL (normal 5-46).
- Urinary free cortisol <1 mcg/L (low).
- TSH 9.1 uIU/mL (normal 0.47-4.68), normal levels of free T4, IGF-1, and IGF binding protein.
- No anti-thyroid antibodies.
- Serum glucose 71 mg/dL (normal 74-100).
- Serum electrolyte levels normal.
What Is The Diagnosis?

1. Addison’s Disease
2. Congenital Adrenal Hyperplasia
3. Hypothalamic, Pituitary or Adrenal Tumor
4. Autoimmune polyendocrine syndrome
5. Iatrogenic Cushing’s Syndrome
6. Polyglandular Deficiency Syndrome
7. Other
Types of Cushing’s Syndrome

ACTH-Dependent

ACTH-Independent

ECTOPIC ACTH

IATROGENIC CUSHING’S SYNDROME

Cortisol Medications
Suppressed ACTH and cortisol levels, in the context of fast weight gain and short stature, confirmed the diagnosis of Iatrogenic Cushing's Syndrome, which is HPA axis suppression secondary to exogenous glucocorticoid use. But, there was still reluctance to attribute this to the inhaled steroids because no one had ever seen it before. So, her mother didn’t know if the adrenal gland would recover or not, and was concerned that her daughter would die (my involvement).
What Changes in Therapy Would You Recommend?

1. Abruptly stop all corticosteroids
2. Gradually taper all corticosteroids
3. Recommend “stress” Cortef doses
4. Stop inhaled steroids, add and then gradually wean prednisone
5. Change Flovent to Alvesco and taper Alvesco
6. Combination of above
7. Other
Resolution

- Discontinue Flovent and Nasonex.
- Begin Alvesco 80 2 puffs q.h.s. and Patanase p.r.n.
- Continue with Singulair, now viewed as potentially “steroid-sparing” therapy for asthma.
- Labs on 5/13/11 (after being off Flovent for 4 weeks): Cortisol level 9.1 (normal 2.5-22.9), ACTH 20 (normal 5-46), Free T4 1.74 and TSH 0.059 (normal 0.47-4.68).
- Serum immunoglobulin levels normal, except for IgE 231 IU/mL (0-90).
- On 7/1/11, reported stopping the Alvesco about 4 days earlier with success so far.
Bone fracture (9/11): minor fall while attempting to get on a high balance gymnastics beam → broken left elbow.

Bone fractures (2/4/12): significant fall while coming down stairs of tree house → right supracondylar humerus and right distal radius radius fractures.

Bone fracture (2/19/13): fell off monkey bars and broke left arm, worst break yet requiring surgery.

DEXA (5/7/12): osteopenia

Eye Examination: normal

Began Growth Hormone (7/1/12) and Vitamin D

Normal genetics study
Rationale for Choosing Alvesco (Ciclesonide) for ML

No Adrenal Effect


No Growth Effect

Flovent 44 2 puffs bid (176 µg/day) is the ONLY FDA-approved dose for children, indicating that higher doses (110 and 220) either weren’t studied or were unsafe!
**NHLBI Guidelines on ICS Dosages**

**Flovent (5-11 year olds):**

2 bid of 44 = 176 (low dose);

2 bid of 110 = 440 (high dose).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low Daily Dose Child 0–4</th>
<th>Low Daily Dose Child 5–11</th>
<th>Medium Daily Dose Child 0–4</th>
<th>Medium Daily Dose Child 5–11</th>
<th>High Daily Dose Child 0–4</th>
<th>High Daily Dose Child 5–11</th>
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<tr>
<td>Beclomethasone HFA</td>
<td>NA</td>
<td>80–160 mcg</td>
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<td>&gt;160–320 mcg</td>
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<td>Budesonide DPI 90, 180, or 200 mcg/inhalation</td>
<td>NA</td>
<td>160–400 mcg</td>
<td>NA</td>
<td>&gt;400–800 mcg</td>
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<td>&gt;800 mcg</td>
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<tr>
<td>Budesonide inhaled Inhalation suspension for nebulization (child dose)</td>
<td>0.25–0.5 mg</td>
<td>0.5 mg</td>
<td>&gt;0.5–1.0 mg</td>
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<td>2.0 mg</td>
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<tr>
<td>Flunisolide 250 mcg/puff</td>
<td>NA</td>
<td>500–750 mcg</td>
<td>NA</td>
<td>1,000–1,250 mcg</td>
<td>NA</td>
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<tr>
<td>Flunisolide HFA 80 mcg/puff</td>
<td>NA</td>
<td>160 mcg</td>
<td>NA</td>
<td>220 mcg</td>
<td>NA</td>
<td>≥640 mcg</td>
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<td>Fluticasone HFA/MDI: 44, 110, or 220 mcg/puff</td>
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Effect of ICS Dosage on Therapeutic and Systemic Corticosteroid Effects

**Drug Inhaler Rx (~mcg/day)**

- **BDP without spacer**
  - Low-dose: 200
  - Medium-dose: 1,000

- **BDP with spacer**
  - Low-dose: 200
  - Medium-dose: 1,200

- **BUD MDI**
  - Low-dose: 200
  - Medium-dose: 1,600

- **BUD dry powder**
  - Low-dose: 100
  - Medium-dose: 800

- **FP**
  - Low-dose: 100
  - Medium-dose: 800

**Benefit/risk**

**Therapeutic benefit**

**Adverse effect**

**Clinical relevance**

**Step-up**
Effects of ICS on Childhood Growth Using Stadiometry
(Mild disease, ≥ 1 yr, DB-PC, various ages)

BUD=CAMP study, *NEJM*, 2000;343:1054-1063 (not primary growth study)
CIC=Skoner et al, *Pediatrics*. 2008;121:e1-14 (FDA: Conclusions cannot be drawn from this study because compliance could not be assured)

* LOW DOSE

**NO EFFECT**
Comparative Systemic Effects of Inhaled Corticosteroids

Martin et al, Am J Resp Crit Care Med 2002;165:1377-83 (ACRN study)

(ACRN study)

Highest approved dose for children 88 µg bid (FDA)

Highest medium dose for children 176 µg bid (NHLBI)

44 µg bid

(hourly plasma 8PM–8AM)
Decreased Serum Cortisol Levels in Children with Asthma Treated with Inhaled Fluticasone

% with Morning Serum Cortisol <5.5 μg/dl

62 children with moderate to severe asthma followed for two years.

UK Survey of Adrenal Crisis With Inhaled Corticosteroids

• Postal survey of 2912 pediatricians and endocrinologists
  – 24% (n=709) response rate with 55 positive replies
  – 33 cases met diagnostic criteria for acute adrenal crisis

• Diagnostic criteria for acute adrenal crisis included
  – ≥1 of the following signs: lethargy, nausea, vomiting, diarrhea, abdominal pain, hypotension, convolution, or unexplained hypoglycemia
  – Abnormal HPA axis function

BDP = beclomethasone dipropionate; BUD = budesonide; FP = fluticasone propionate; HPA = hypothalamic pituitary adrenal.

Survey of Adrenal Crisis* Associated With Inhaled Corticosteroids in the United Kingdom

*Based on a total of 11.85 million prescriptions for beclomethasone, budesonide, and fluticasone in England in 1998; †Defined as: lethargy, nausea, vomiting, diarrhea, abdominal pain, hypotension, or hypoglycemia associated with abnormal hypothalamic pituitary adrenal axis function; ‡Patient was also receiving fluticasone.


# ICS Dose 500–2000 μg/day
Clinical Presentation of Adrenal Crisis in UK Survey

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<th>Presentation</th>
<th>Children (n=28)</th>
<th>Adults (n=5)</th>
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<tbody>
<tr>
<td>Acute hypoglycemia*</td>
<td>23</td>
<td>1</td>
</tr>
<tr>
<td>Decreased levels of consciousness or coma</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Coma and convulsions</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Insidious</td>
<td>5</td>
<td>4</td>
</tr>
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</table>

*Acute adrenal insufficiency was believed to have contributed to the death of 1 child with cushingoid appearance and abdominal striae who presented with fulminent pneumococcal septicemia.

Guidelines Recommendations on Stepping Up and Stepping Down Asthma Therapy

- Step up to gain control
- Consider step down if well controlled for at least 3 months (including 25-50% ICS dose reduction)
- Gradually step down and closely monitor to determine the minimal amount of medication required to maintain control and/or reduce the risk of side effects

Retrospective study of 5- to 18-year-old children with asthma in an integrated primary care practice in the United States (Mayo Clinic).

Criteria for step down and success based on NAEPP-3 guideline definition of control (≥ 3 months).

Stepping down asthma medication based on NAEPP-3 guidelines is frequently successful, but not frequently done!!!
Could Poor Adherence Both Hurt (Bad Disease Outcomes) and Help (No Side Effects) Us?

Adherence to Inhaled Asthma Therapy Decreases Over Time

- Adults with moderate-to-severe asthma (N=50)
- Treated with BID ICS
- Actuation of inhaler monitored electronically

~30% after 1 year!


Asthma Morbidity Now Versus a Decade Ago

- Acute care for asthma in the past 12 months (1998 vs 2009)
  - AIA 1998 (n = 1708)
  - AIM 2009 (n = 2234)

- Hospitalized overnight
- Emergency room
- Other unscheduled emergency visit
- Any of these

Have you ever seen growth or adrenal suppression secondary to ICS in a child with asthma?

1. Yes
2. No
Of all the 5-11 year old children with asthma that you treat with fluticasone MDI, what percentage receive the 110 strength?

1. 0-20
2. 21-40
3. 41-60
4. 61-80
5. 81-100
Do you feel confident in your ability to detect and diagnose growth and adrenal suppression secondary to ICS in a child with asthma?

1. Yes
2. No

Yes: 74%
No: 26%
In a typical office visit, do you have time to adequately inform the parent about the risk of ICS-induced growth and adrenal suppression in a child with asthma?

1. Yes
2. No
SUMMARY

• Make sure the diagnosis is correct and that the severity warrants ICS treatment.

• ICS, commonly used to treat childhood asthma, can cause potentially-deadly systemic side effects if higher-than-approved doses are used for longer-than-recommended time periods (or, less commonly, at approved doses in highly susceptible individuals). This case uniquely WAS NOT complicated by oral GCS.

• Following FDA dosing and NHLBI asthma guideline recommendations minimizes the risk of developing ICS side effects (use lowest effective dose, consider ICS alternatives, monitor for side effects, “rinse and spit” after use, don’t exceed approved doses without careful monitoring, step down when possible). Listen/respond to parental concerns.

• Health care practitioners have wide variations and gaps in knowledge of proper asthma treatment in children with regard to:
  1) detection and treatment of systemic side effects of ICS.
  2) dosing of the ICS with which they have had the most experience, Flovent.

• There is often insufficient time to adequately inform parents about the risk of ICS systemic side effects during a typical office visit.

• Education about ICS dosing and systemic side effects can be effective.