Step Up Therapy in Children

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Disclosure Slide

- **Employment**  
  University of Wisconsin

- **Financial Interests**  
  Nothing to Disclose

- **Research Interests**  
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- **Gifts**  
  Nothing to Disclose

- **Other Interests**  
  Nothing to Disclose
## Step-up Approaches in Asthma

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Thomas, Lemanske & Jackson, JACI 128:915, 2011
Step-up Long Term

Adjusting therapy based on asthma CONTROL

Stepping down

Stepping up

Step 1

Step 2

Step 3

Step 4

Step 5

Step 6

BADGER

Intermittent Asthma

Persistent Asthma
Research Question: Children

**BADGER**

*Best Add-on Therapy Giving Effective Responses*

- In patients receiving daily low dose ICS treatment who are not well controlled, what are the next best treatment options?
EPR-3 Recommendations

Preferred:
EITHER:
Low-dose ICS + either LABA, LTRA, or Theophylline
OR
Medium-dose ICS

Step 1
Step 2
Step 3
Step 4
Step 5
Step 6

Intermittent Asthma
Persistent Asthma
EPR-3 Recommendations

In children, is there a best choice for Step 2 to Step 3 care?
BADGER: Research Question

- In children not satisfactorily controlled on low dose ICS (fluticasone 100 µg BID) therapy, what is the best next treatment approach?
  - Increased doses of ICS (fluticasone 250 µg BID)?
  - Add a LABA (salmeterol/fluticasone combination)?
  - Add a LTRA (montelukast)?

Lemanske RF et al. NEJM 362:975, 2010
Differential Response

At the end of the study, each child was identified as either a differential or non-differential treatment responder.

A differential responder was someone who exhibited significantly better outcomes on one treatment than on another.

Effective treatment response was based on (in order of importance):

1. Asthma exacerbations
2. Asthma control days (ACD)
3. Change in FEV\textsubscript{1}. 
Definitions for Differential Response: Asthma Exacerbations

- Differential response with respect to asthma exacerbations occurred when the total amount of prednisone prescribed to control asthma symptoms was at least 180 milligrams* greater on one treatment than on either of the other two treatments.

*Based on “prednisone burst” of 2 mg/kg/day for 2 days, 1 mg/kg/day for 2 days to a maximum of 60-60-30-30 mg
Definitions for Differential Response: Asthma Control Days

Differential response with respect to ACD occurred when the number of annualized ACD (AACD) achieved on one treatment was at least 31 days more than on either of the other two treatments.
Asthma Control Day (ACD)

- An ACD was defined as a day **without**:
  - Albuterol rescue use (pre-exercise treatment permitted)
  - Use of non-study asthma medications
  - Nighttime awakenings
  - Daytime asthma symptom score more than mild
  - Unscheduled health care provider visits for asthma
  - Yellow-zone PEF or Red-zone PEF
Definitions for Differential Response: \( FEV_1 \)

- Differential response with respect to \( FEV_1 \) occurred when the \( FEV_1 \) change on one treatment was at least 5% higher than on either of the other two treatments.

- The \( FEV_1 \) change for each treatment was defined as the percent difference between the \( FEV_1 \) from the end of the run-in to the end of the treatment period.

\[
\frac{FEV_{treatment} - FEV_{run-in}}{FEV_{run-in}}
\]
Inclusion Criteria

- Age 6-18 years
- Able to perform reproducible spirometry based on ATS criteria
- FEV$_1$ reversibility $\geq$ 12% OR
- Methacholine PC$_{20}$ $\leq$ 12.5 mg/ml

Lemanske RF et al. NEJM 362:975, 2010
BADGER Protocol: Overview

Three Treatment Period, Double blind, 3 way cross-over

Run-in period on 1xICS to demonstrate lack of control

Run-in Period 2-8 weeks
1xICS = fluticasone DPI 100 µg BID

Randomization

Period 1
Evaluation Period

2.5 x ICS or
1x ICS + LABA or
1 x ICS + LTRA

16 weeks

Period 2
Evaluation Period

2.5 x ICS or
1x ICS + LABA or
1 x ICS + LTRA

16 weeks

Period 3
Evaluation Period

2.5 x ICS or
1 x ICS + LABA or
1 x ICS + LTRA

16 weeks

2.5 x ICS = fluticasone DPI 250 µg BID
1xICS+LABA = fluticasone/salmeterol DPI 100/50 BID
1xICS+LTRA = fluticasone DPI 100 µg BID + montelukast
Primary Outcome
Stage 1

Was a differential response observed in $\geq 25\%$ of the participants?
Results: Differential Response

Differential response occurred in 161/165 participants (98%) (p<0.0001)
Primary Outcome
Stage 2

What was the direction of the best response?
Primary Outcome: Probability of BEST Response Based on Composite Outcome*

LABA step-up was more than 1.5 times as likely to produce the best response

LABA
ICS
LTRA

*(p = 0.002)
*(p = 0.004)

*Covariate adjusted model

Lemanske RF et al. NEJM 362:975, 2010
BADGER: Conclusions

Uncontrolled on low dose ICS at Step 2 care
A differential response to step-up therapy was demonstrated in nearly all subjects (≥ 95%) using a composite evaluation of components in both impairment and risk domains of asthma control.
BADGER: Conclusions

The probability of experiencing the best overall response was more than 1.5 times as likely with LABA step-up.
BADGER: Conclusions

Many children demonstrated a best response to either ICS or LTRA step-up, highlighting the need to regularly monitor and appropriately adjust each child’s asthma therapy.