Step-up and Step-down Strategies in the Treatment of Asthma

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Step-wise Approach to Asthma Therapy

Choosing the initial step in therapy based upon Asthma SEVERITY

<table>
<thead>
<tr>
<th>Intermittent Asthma</th>
<th>Persistent Asthma</th>
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<tbody>
<tr>
<td>Step 1</td>
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<tr>
<td>Step 2</td>
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<td>Step 3</td>
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<td>Step 5</td>
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<tr>
<td>Step 6</td>
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</tbody>
</table>
Step-wise Approach to Asthma Therapy

Adjusting therapy based on asthma CONTROL

Stepping down

Intermittent Asthma

Step 1

Persistent Asthma

Step 2

Step 3

Step 4

Step 5

Step 6

Stepping up
## Step-up Approaches in Asthma

<table>
<thead>
<tr>
<th>Step-up Long-term (SLT)</th>
<th>Step-up Short-term (SST)</th>
<th>Step-up Intermittent (SUI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in therapy for uncontrolled asthma (weeks)</td>
<td>Increase in therapy for brief loss of control (days)</td>
<td>Increase in therapy for variable symptoms (day-to-day)</td>
</tr>
<tr>
<td>Persistent loss of control</td>
<td>Brief loss of control (upper respiratory tract infections, pet exposure)</td>
<td>Mild symptoms</td>
</tr>
<tr>
<td>Step-down therapy when control achieved after 3-6 months</td>
<td>Step-down therapy when control achieved after 3-10 days</td>
<td>Intermittent use</td>
</tr>
</tbody>
</table>

Thomas, Lemanske & Jackson, JACI 128:915, 2011
EPR-3 Recommendations For Frequent Preschool Wheeze & + API

DAILY low-dose ICS at step-2 as preferred treatment

Step 1

Step 2

Step 3

Step 4

Step 5

Step 6
Prevention of Early Asthma in Kids

- Randomized, multicenter, double-blind, parallel group, placebo-controlled trial
- 285 two & three y/o kids at high-risk for asthma (mAPI +)
- Fluticasone 44 µg/puff vs. placebo (2 puffs b.i.d.)

Guilbert, *NEJM* 2006
PEAK – Outcomes

**Treatment Phase:**
- ↓ Exacerbations
- ↓ Supplemental medications (ICS and LTRA)
- = bronchodilator use and unscheduled visits

**Observation Phase:**
- = Exacerbations
- = Supplemental medications (ICS and LTRA)
- = Bronchodilator use and unscheduled visits

**EFD:** No cough or wheeze, unscheduled clinic, urgent care, ED or hospital visits; no use of asthma medications including bronchodilator pre-treatment before exercise

Guilbert, *NEJM* 2006
**Conundrum with Daily ICS Use**

- Most effective and guideline preferred controller for persistent pediatric and adult asthma as it improves day-to-day asthma control and prevents exacerbations.

- However, exacerbations occur yearly in about 30% of children with mild and 40% of children with mild-moderate asthma prescribed daily ICS in trials.

- Long-term adherence with daily ICS is consistently low: 30-50% in general pediatric practice.

- Growth effects small but may be permanent.
ICS Options for Preschool Children with Recurrent Wheeze and Past Year Exacerbations

- Daily
- Intermittent
## MIST Protocol: Overview

<table>
<thead>
<tr>
<th>Randomized Treatment Group</th>
<th>Nightly <strong>EXCEPT</strong> During Respiratory Tract Illnesses</th>
<th>During Respiratory Tract Illnesses <strong>ONLY</strong> for 7 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily low-dose Budesonide</td>
<td>Budesonide 0.5 mg PM</td>
<td>Placebo AM Budesonide 0.5 mg PM</td>
</tr>
<tr>
<td>Intermittent high-dose Budesonide</td>
<td>Placebo PM</td>
<td>Budesonide 1.0 mg AM 1.0 mg PM</td>
</tr>
</tbody>
</table>

Cohort (N=278): Ages 12-53 mo, frequent wheeze, modified API, past year exacerbation, intermittent illnesses

Run-in: placebo respule nightly + albuterol prn
Time to 1st Exacerbation Similar with Daily vs Intermittent ICS

% of Patients without a Course of Prednisolone

Days

0 50 100 150 200 250 300 350 400

Intermittent

Daily

p-value=0.87

(Rate 0.95/person yr)

(Rate 0.97/person yr)

Number at Risk

Intermittent 139 114 100 89 78 71 64 50

Daily 139 114 93 84 74 66 54 40
Lessons from MIST

In API positive preschoolers with frequent wheeze & prior year exacerbations

- Illness burden is substantial despite ICS therapy
- Intermittent high-dose budesonide started early during predefined respiratory tract illnesses and continued for 7 days, may be an alternative option to daily low-dose budesonide given its
  - similar outcomes
  - less frequent use
  - lower ICS exposure
Are there alternative approaches to daily ICS in school age asthma?
Is a Long Acting Beta Agonist Necessary for Control?

- Mild asthma subjects (n=455)
- Six months treatment
- Primary outcome: AM PEF

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Scheduled</th>
<th>As needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Placebo</td>
<td>BDP 250 mcg + Albuterol 100 mcg</td>
</tr>
<tr>
<td>B</td>
<td>Placebo</td>
<td>Albuterol 100 mcg</td>
</tr>
<tr>
<td>C</td>
<td>BDP 250 mcg</td>
<td>Albuterol 100 mcg</td>
</tr>
<tr>
<td>D</td>
<td>BDP 250 mcg + Albuterol 100 mcg</td>
<td>Albuterol 100 mcg</td>
</tr>
</tbody>
</table>

Results:

- AM PEF and Exacerbations:
  Group A = C = D > B
- Cumulative dose of ICS lower in Group A compared to C and D

Is rescue ICS (step-up intermittent) a better approach as step-down care to ICS discontinuation?
The TReating Of Children To Prevent EXacerbations Of Asthma (TREXA) Trial

Martinez FD for the CARE Network
Lancet 2011; 377:650-7
TREXA Trial Design

Cohort (N=288): ages 5 – 18 years

Controlled mild persistent asthma after 4-week run-in on beclomethasone 40 ug BID with placebo rescue + albuterol

<table>
<thead>
<tr>
<th>Randomization groups</th>
<th>Rescue Therapy + albuterol</th>
<th>Daily Therapy (BID)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined ICS</td>
<td>Beclomethasone (80 ug)</td>
<td>Beclomethasone (40 ug)</td>
</tr>
<tr>
<td>Daily ICS</td>
<td>Placebo</td>
<td>Beclomethasone (40 ug)</td>
</tr>
<tr>
<td>Rescue ICS</td>
<td>Beclomethasone (80 ug)</td>
<td>Placebo</td>
</tr>
<tr>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
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TREXA: Regimens on Exacerbations Requiring Oral Corticosteroids

Time to 1st Exacerbation

Daily ICS \( p=0.03 \)
Combined ICS \( p=0.07 \)
Rescue ICS \( p=0.07 \)
Placebo

\( p \) values adjusted for multiple comparisons (Hochberg-Bonferroni)

(Martinez F, Lancet 2011;377:650-7)
TREXA: Regimens on Treatment Failures

- Combined: P=0.012, 5.6%
- Daily: P=0.009, 2.8%
- Rescue: P=0.024, 8.5%
- Placebo: 23.0%

N=71, N=71, N=71, N=74

(Martinez F, Lancet 2011;377:650-7)
TREXA: Regimens on Linear Growth

(Martinez F, Lancet 2011;377:650-7)
TREXA - Conclusions

- Discontinuing ICS causes an unacceptable increase in exacerbations in children with well-controlled, mild persistent asthma.

- Daily ICS is the most effective treatment for preventing exacerbations; adding rescue ICS to daily ICS does not add benefit.

- Rescue ICS with albuterol (step-up intermittent therapy) demonstrates benefits over albuterol alone and avoids daily ICS administration and its growth effects.
Combination Therapy
More ICS or add a LABA?

  - Improved impairment; no difference in risk domain

  - Improved impairment; no difference in risk domain
FACET Study: Formoterol and Budesonide in Moderate Asthma

Budesonide 100mcg/400mcg BID
Formoterol 12mcg BID

**p=0.01

Beta Agonists + ICS: Maintenance and Reliever Therapy?
Combination Therapy as both Maintenance and Reliever Therapy

O’Byrne PM et al. AJRCCM 171: 129, 2005
Combination Therapy: STAY Study

Severe Asthma Exacerbations

O’Byrne PM et al. AJRCCM 171:129, 2005
In patients receiving daily low dose ICS treatment who are not well controlled, what are the next best treatment options?

Lemanske RF et al. NEJM 362:975, 2010
Unanswered Questions in Childhood Asthma

Uncontrolled on low dose ICS at Step 2 care

Step 1

Intermittent Asthma

Step 2

Step 3

Step 4

Step 5

Step 6

Persistent Asthma
EPR-3 Recommendations

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

OR
Medium-dose
ICS

**Steps:**

1. Intermittent Asthma
2. Persistent Asthma
3.
4.
5.
6.
BADGER: Research Question

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

- Each participant would receive all 3 treatment options

- Determine the presence or absence of a differential response among those treatments using a composite outcome that evaluated 3 components in defining asthma control:
  - Impairment domain
    - Asthma control days
    - Pulmonary function (FEV$_1$)
  - Risk domain
    - Asthma exacerbations
Research Questions

- Could a **differential response** be demonstrable in at least 25% of participants?
- If so, what was the **direction of the response** (i.e., which therapy had the greatest probability of producing the best response?)
- Were there baseline characteristics that could **predict the probability of a differential response**?
  - Methacholine PC$_{20}$
  - FeNO
  - Asthma Control Test (ACT®) scores
  - B16 genotype (Arg/Arg)
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$_1$. 

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: FEV1

- 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.

\[
\text{FEV}_{\text{treatment}} - \frac{\text{FEV}_{\text{run-in}}}{\text{FEV}_{\text{run-in}}}
\]
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

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 1x ICS + LABA or 1 x ICS + LTRA

16 weeks

Randomization

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: Probability of **BEST** Response Based on Composite Outcome*

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

* Covariate adjusted model

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

A differential response to step-up therapy was demonstrated in nearly all subjects (≥ 95%) and more than 1.5 times as likely with LABA step-up. 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.