Study Findings and LABA Update

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Conflict of Interest

- No conflict of interest

Objectives:

- AHRQ report
  - Explain the importance of health care provider adherence to asthma guidelines
  - Determine the use of clinical pharmacy support in prescribing asthma controller and rescue medications
- Evaluate the recent recommendations for use of LABA in 5-11 year old children
- Optimize step-down treatment for well controlled mild to moderate persistent asthma

Agency for Healthcare Research and Quality

- AHRQ sponsors systematic reviews to assist public and private sector organizations improve health care in the United States. This study is titled and was undertaken to assess:

- Interventions to Modify Health Care Provider Adherence to Asthma Guidelines

AHRQ Review of Published Literature

- Objectives of literature review: To assess the effect of interventions designed to improve health care provider's adherence to asthma guidelines on 3 key questions:
  - 1. Health care process outcomes
  - 2. Clinical outcomes
  - 3. Health care processes that subsequently impact clinical outcomes (How does question 1 impact question 2)
  - 73 of 4,217 citations were eligible, 68 addressed one or more of the critical outcomes and were included
    - None of the studies evaluated considered how question 1 impacted question 2

Asthma Guideline Usage by HCP's

- EPR-3 and GINA have been in place 20+ years
- HCP's do not routinely follow asthma guidelines
- Multiple reasons for lack of adherence include:
  - Lack of awareness of guidelines
  - Disagreement with guideline recommendations
  - Doubts about effectiveness of guideline recommendations
  - Lack of confidence in carrying out best practices
  - Inability to overcome previous practice behavior inertia
  - External barriers such as time constraints during visits, lack of user friendly guidelines, patient preferences

Asthma Guideline Usage by HCP's

- Asthma guidelines are not avidly followed by HCP's, but why?
- A growing understanding of the shortcomings of asthma guidelines is the limited tools and resources available to HCP's to follow the recommended care
- Multiple reasons for lack of adherence include:
  - Lack of confidence in carrying out best practices
  - Inability to overcome inertia of previous practice behavior
  - External barriers such as time constraints during visits, lack of user friendly guidelines, and patient preferences

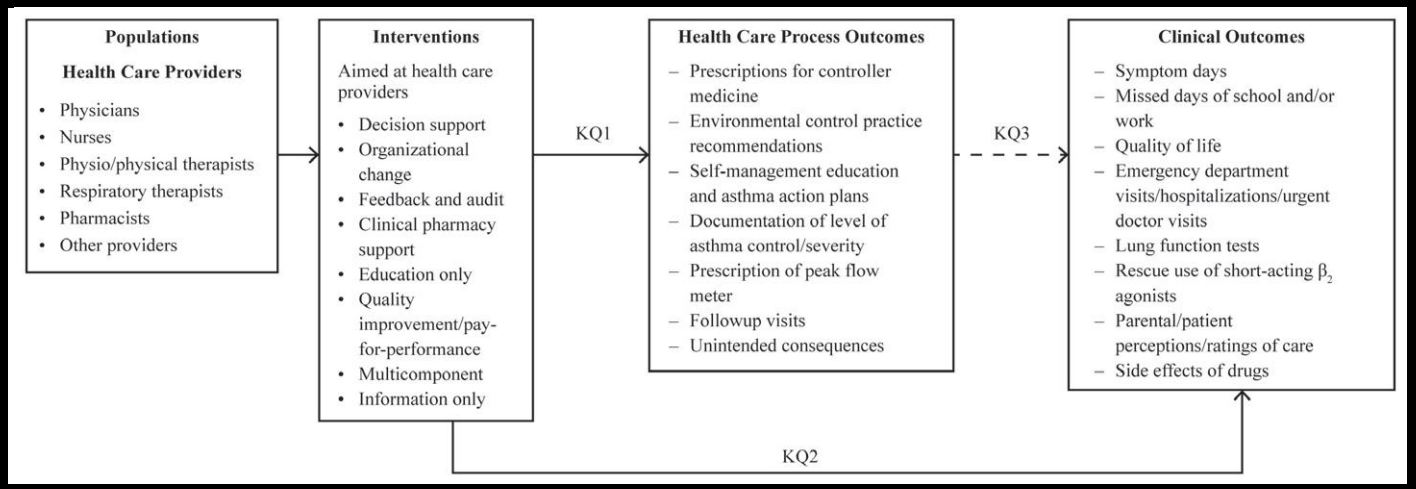
Interventions to improve Asthma outcomes

- Most interventions targeting improvement of asthma care and outcomes have been patient-focused
- There have been some provider-targeted interventions to improve adherence to guidelines including:
  - Educational seminars
  - CME conferences and articles
  - Office prompts and MT initiatives such as:
  - Asthma care monitoring system
  - Emergency room quality improvement projects
- However, there is no consensus on the most effective provider-targeted interventions that improve adherence to guidelines

Interventions to improve Asthma outcomes

- This review looked at interventions targeting HCP's adherence to asthma guidelines, and whether those interventions improved patient outcomes
- Secondly, this review looked at whether changes in asthma care process improved clinical outcomes
- Successful interventions were those showing statistically significant improvement in outcomes
- Cost assessments for the interventions were not included in this review

Framework for HCP Interventions



Framework for HCP Interventions

Interventions → Populations: Health Care Providers → Health Care Process Outcomes → Clinical Outcomes

Analytical Framework AHRQ Review

Health care providers (HCP'S)	Interventions aimed at HCP's	Health Care Process Outcomes	Clinical Outcomes
Physicians	Decision Support	Rx for Controller Meds	Symptom Days
Nurses	Organizational Change	Environmental control recommendations	Missed days of school or work
Physio/Physical Therapists	Feedback & Audit	Self management education and AAP's	ED visits/Urgent Doc visits/hospitalizations
Respiratory Therapists	Clinical Pharmacy Support	Documentation of level of control/severity	Lung Function Tests
Pharmacists	Education only	Rx of Peak Flow Meter	Rescue use of Short Acting Beta-2 drugs
Other Providers	Quality Improvement/ Pay-for-Performance	Follow-up visits	Parental/Patient perception/rating of care
	Multicomponent	Unintended Consequences	Side effects of drugs

Presentation of select AHRQ data

- The outcomes selected for evaluation were those most commonly used in practice
- Specifically, those outcomes that are relied upon by clinicians to guide their decision making
- And, those endorsed by the NIH Workshop on Asthma Outcomes
  - Prescription of Asthma Controller medicines
  - Provision of asthma action plan/self-management education
  - ED visit or hospitalization
  - Missed days of school or work

Prescriptions of asthma controller meds

- Moderate evidence supports helping HCP's decision making process such as classifying asthma severity
- Moderate evidence supports providing performance data to HCP's about the quality of care they provide
- Moderate evidence supports targeting pharmacists' delivery of asthma care
- Low grade evidence supports changing the way an organization provides asthma care
- Low grade evidence supports using multi-component interventions

Asthma Action Plans
Self-Management Education

- Moderate evidence supports helping HCP's decision making process such as classifying asthma severity
- Moderate evidence supports targeting pharmacists' delivery of asthma care
- Low grade evidence supports providing performance data to HCP's about the quality of care they provide
- Low grade evidence supports changing the way an organization provides asthma care
- Low grade evidence supports using education only, quality improvement/pay for performance efforts and multi-component interventions

ED/Urgent Care Visits/Hospitalizations

- Moderate evidence supports helping HCP's decision making process such as classifying asthma severity
- Low grade evidence suggests no benefit by changing the way an organization provides asthma care
- Low grade evidence suggests no benefit by providing educational information only to HCP's
- Low grade evidence suggests no benefit by providing quality improvement/pay for performance data to HCP's

Lost Days of Work or School

- The evidence suggests there is no benefit by helping HCP's decision making process such as classifying asthma severity
- Evidence for the remaining interventions was insufficient or low in strength

Conclusions

- Low to Moderate evidence supports helping HCP's decision making process such as classifying asthma severity
- Low to Moderate evidence supports targeting pharmacists' delivery of asthma care
- Low to Moderate grade evidence supports providing performance data to HCP's about the quality of care they provide
- Further research is needed to evaluate HCP targeted interventions with a focus on standardized measures of outcomes and more rigorous study designs

Further Study Conclusions

- There is more information about the interventions on improving health care process outcomes than for clinical outcomes.
- Further evaluation of how these interventions may improve clinical outcomes for patients is needed.
- Low to moderate evidence supports helping HCP's decision making process, improved pharmacy support and feedback to providers about the quality of care they provide.
- Standardized measures of outcomes, more rigorous study design and addition of cost measures is needed

LABAs: Where Do We Stand?

- FDA Black Box Warning
  - "These medicines may increase the chance of severe asthma episodes, and death when those episodes occur"
- SMART Study was not designed to assess the effect of ICS on the endpoints
- At this time, guidelines and clinical trial data continue to support the use of LABAs *ONLY* as an add-on to ICS

National Asthma Education and Prevention Program (NAEPP) Guidelines for the Treatment of Asthma 3rd Expert Panel Report (EPR-3)

Stepwise Approach for Managing Asthma in Children Aged 5 to 11 Years

Intermittent

Mild Persistent

Moderate Persistent

Severe Persistent

Step 1

Preferred: SABA PRN

Step 2

Preferred: Low-Dose ICS

Alternative: LTRA, Cromolyn, Nedocromil, or Theophylline

Step 3

Preferred: Medium-Dose ICS

or Low-Dose ICS **and either** LABA, LTRA, or Theophylline

Step 4

Preferred: Medium-Dose ICS + LABA

Alternative: Medium-Dose ICS ***and either*** LTRA or Theophylline

Step 5

Preferred: High-Dose ICS + LABA

Alternative: High-Dose ICS ***and either*** LTRA or Theophylline ***and*** Omalizumab May Be Considered For Patients Who Have Allergies

Step 6

Preferred: High-Dose ICS + LABA + Oral Corticosteroid

Alternative: High-Dose ICS ***and either*** LTRA or Theophylline + Oral Corticosteroid ***and*** Omalizumab May Be Considered For Patients Who Have Allergies

LTRA = leukotriene re

Stepwise Approach for Managing

Asthma in Patients Aged ≥12 Years:

Intermittent	Mild Persistent	Moderate Persistent	Severe Persistent			
Step 1 ***Preferred***: SABA PRN	**Step 2** ***Preferred***: Low-Dose ICS ***Alternative***: Cromolyn, Nedocromil, LTRA, or Theophylline	**Step 3** ***Preferred***: Medium-Dose ICS ***or*** Low-dose ICS + LABA ***Alternative***: Low-Dose ICS ***and either*** LTRA, Theophylline, or Zileuton	**Step 4** ***Preferred***: Medium-Dose ICS + LABA ***Alternative***: Medium-Dose ICS ***and either*** LTRA, Theophylline, or Zileuton	**Step 5** ***Preferred***: High-Dose ICS + LABA ***and*** Consider Omalizumab For Patients Who Have Allergies	**Step 6** ***Preferred***: High-Dose ICS + LABA + Oral Corticosteroid ***and*** Consider Omalizumab For Patients Who Have Allergies	

Goal of Asthma Therapy: Achieve Control

Reduce Impairment

- Prevent chronic and troublesome symptoms
- Require infrequent use of inhaled SABA (≤2 days/week)
- Maintain (near) “normal” pulmonary function
- Maintain normal activity levels
- Meet patients’ expectations of, and satisfaction with, asthma

Reduce Risk

- Prevent recurrent exacerbations
- Minimize need for emergency department visits or hospitalizations
- Prevent progressive loss of lung function
- Provide optimal pharmacotherapy, with minimal or no adverse effects

Available at: http://www[illegible]lines/asthma/epr3/resource.pdf.

ICS + LABA Combinations

- Greater efficacy in combination products versus ICS alone:
  - Improved daytime and nighttime symptoms
  - Improved lung function
  - Decreased SABA need
  - Reduced frequency of exacerbations
  - Improved asthma control
  - Reduced ICS dose
- Increased convenience
- May improve adherence
- U.S. combinations:
  1. Budesonide + formoterol (HFA)
  2. Fluticasone + salmeterol (DPI & HFA)
  3. Mometasone+formoterol (HFA)

Long-Term Control Medications

- EPR-3 recommends long-term control medications be taken on a daily basis for treatment of persistent asthma
- Inhaled corticosteroids (preferred)
- Inhaled long-acting bronchodilators (LABA)
- Leukotriene modifiers (Singulair)
- Mast cell stabilizers (Cromolyn and nedocromil or Tilade)
- Theophylline
- Immunomodulators

LABAs: Where Do We Stand?

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- At this point, guidelines and clinical trial data continue to support the use of LABAs *ONLY* as an add-on to ICS

The NEW ENGLAND JOURNAL of MEDICINE

Step-up Therapy for Children with Uncontrolled Asthma While Receiving Inhaled Corticosteroids

Robert F. Lemanske, Jr., M.D., David T. Mauger, Ph.D., Christine A. Sorkness, Pharm.D., Daniel J. Jackson, M.D., Susan J. Boehmer, M.S., Fernando D. Martinez, M.D., Robert C. Strunk, M.D., Stanley J. Szefler, M.D., Robert S. Zeiger, M.D., Ph.D., Leonard B. Bacharier, M.D., Ronina A. Covar, M.D., Theresa W. Guilbert, M.D., Gary Larsen, M.D., Wayne J. Morgan, M.D., Mark H. Moss, M.D., Joseph D. Spahn, M.D., and Lynn M. Taussig, M.D., for the Childhood Asthma Research and Education (CARE) Network of the National Heart, Lung, and Blood Institute

nejm.org

N Engl J Med 2010;362:975-985.

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

Differential Response

- At the end of the study, each child was identified as either a differential or non-differential treatmen 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 FEV1

BADGER: Outcome measures to determine differential response

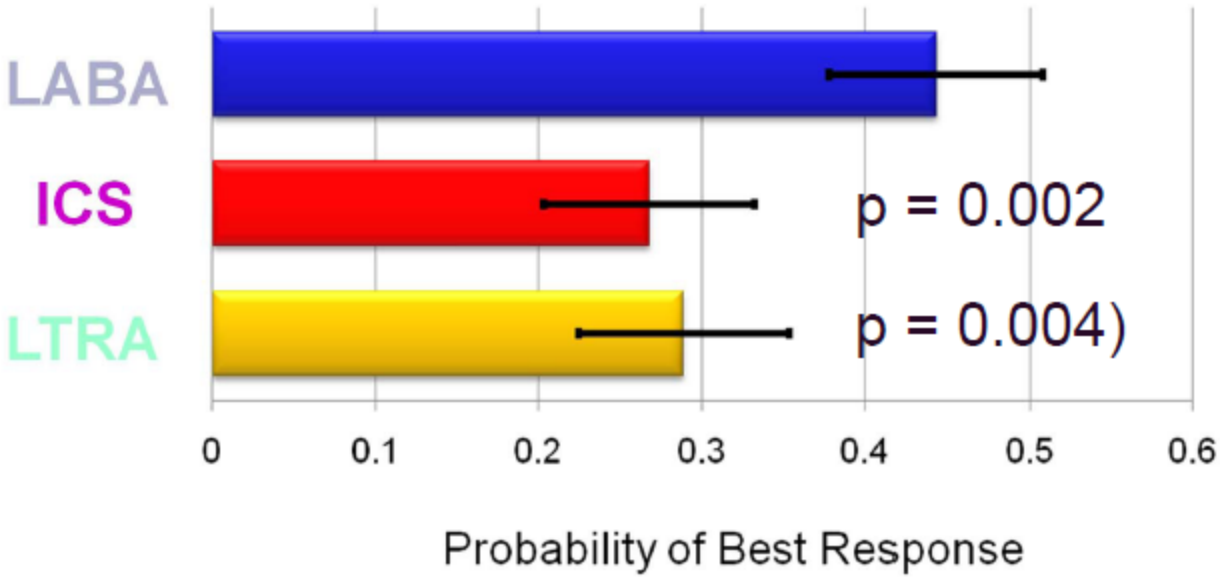
- 3 outcome measures:
  - Exacerbations:
    - occurs when the total amount of prednisone prescribed to control asthma symptoms is at least 180 milligrams less on one treatment than on either of the other two treatments
  - FEV_1:
    - occurs when the FEV1 change is at least 5.0% higher on one treatment than on either of the other two treatments
  - Asthma Control Days:
    - occurs when the number of annualized ACD (AACD) achieved is at least 31 days more on one treatment than on either of the other two treatments

Results: Differential Response

- Differential response occurred in 161/165 participants (98%) ($p<0.0001$)

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 Ref. Lemanske R and CARE Network NEJM 2010;362:975-985.

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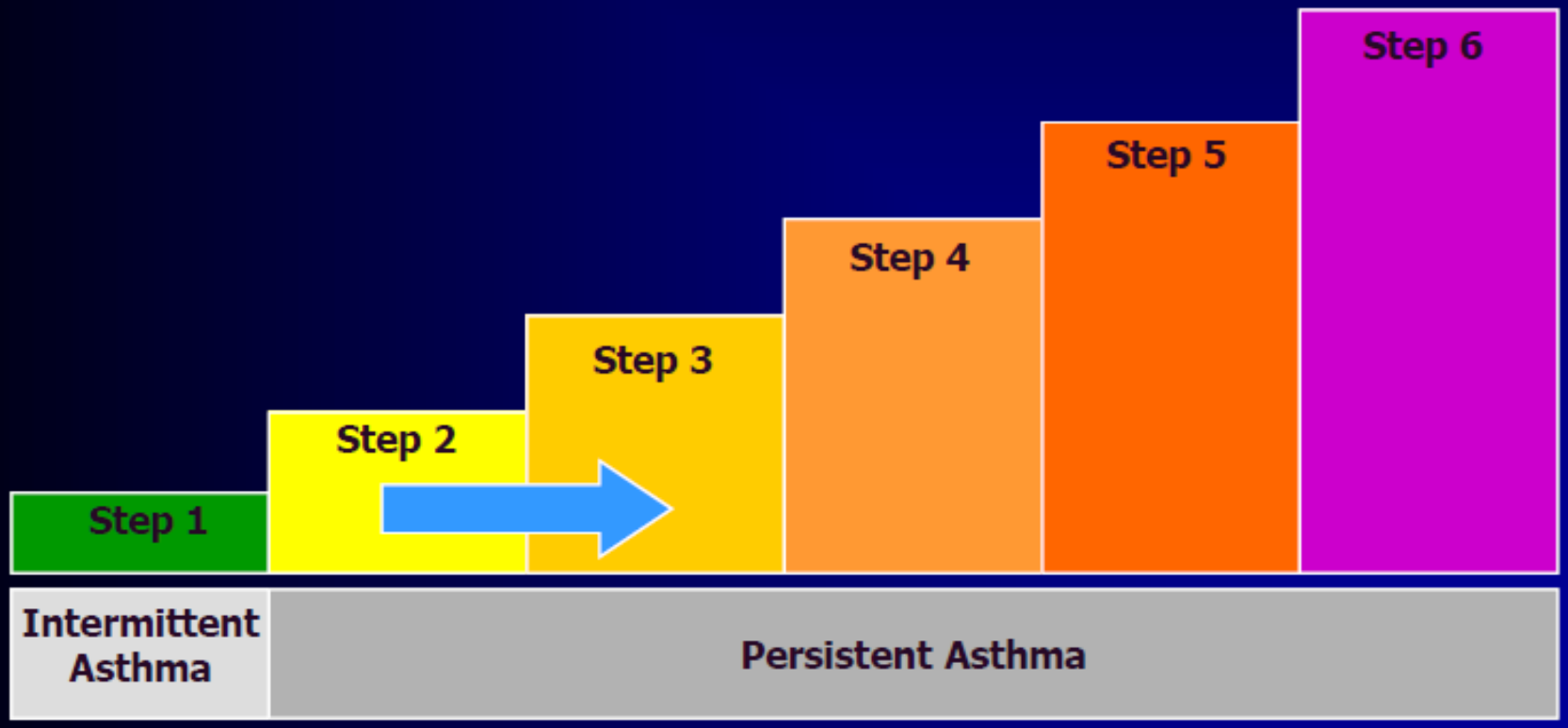
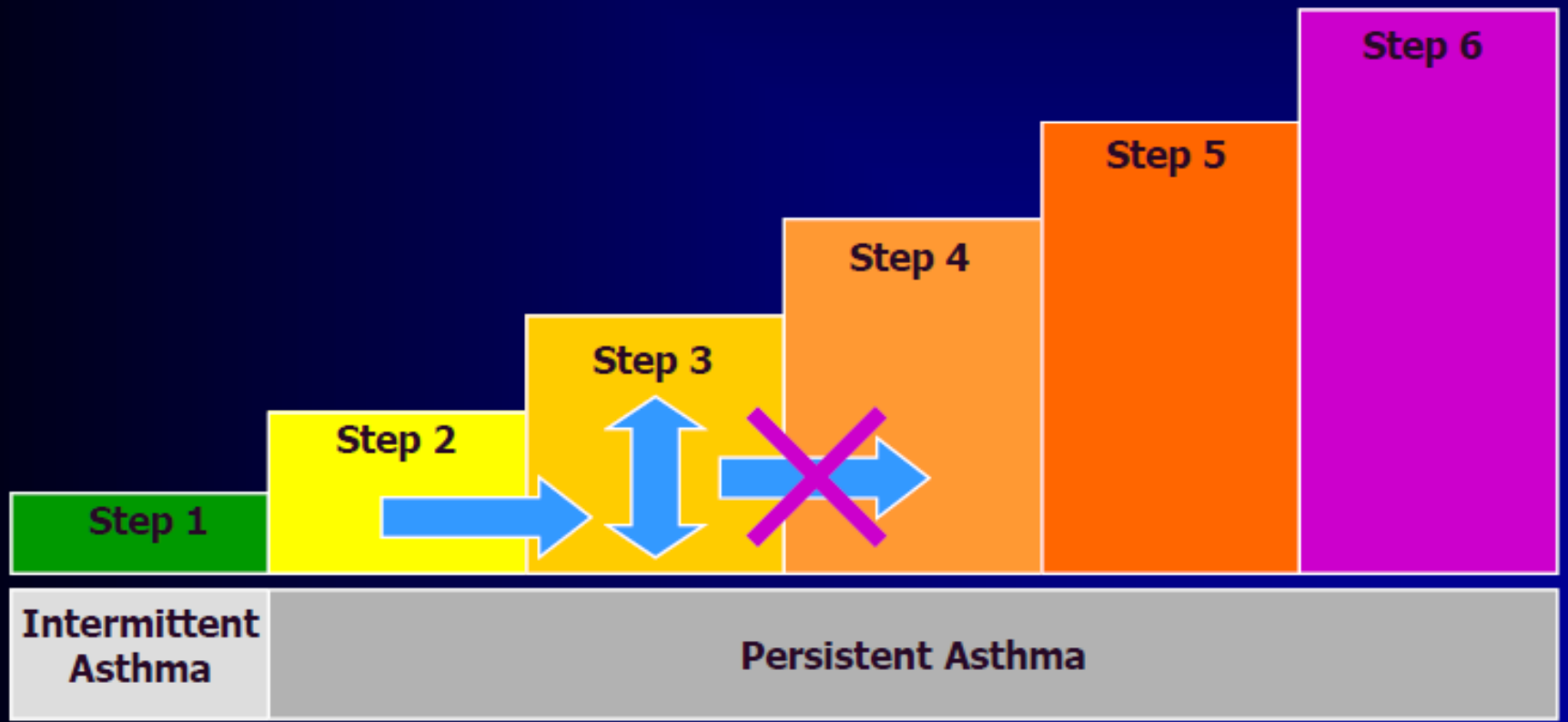
BADGER: Conclusions

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.



SMART Study Design

- No inhaled long-acting beta$_2$-agonist
- ≥12 years of age

R

Salmeterol MDI 42 mcg BID + Usual Care

(n=13,176)

28-week treatment period
Phone contact every 4 weeks

Placebo MDI BID + Usual Care

(n=13,179)

Clinic Visit

28-week supply of study medication provided

Nelson HS et al. *Chest*. 2006;129:15-26. Adapted with permission.

SMART Study Endpoints

- Primary Endpoint
  - Combined respiratory-related deaths or life-threatening experiences (intubation and ventilation)
- Key Secondary Endpoints
  - Respiratory-related deaths
  - Combined asthma-related deaths or life-threatening experiences
  - Asthma-related deaths

Ne

Baseline Characteristics

	Salmeterol (n=13,176)	Placebo (n=13,179)
Age, mean	**39.2**	**39.1**
Sex, n (%)		
Female	8334 (64)	8337 (64)
Male	4703 (36)	4686 (36)
Ethnic origin, n (%)		
Caucasian	9281 (71)	9361 (72)
African American	2366 (18)	2319 (18)
Hispanic	996 (8)	999 (8)
Asian	173 (1)	149 (1)
Other	230 (2)	224 (2)
Peak expiratory flow (% predicted)	84.0	83.8

Nelson HS et al. *Chest*. 2006;129:15-26. Adapted with permission.

Baseline Asthma Characteristics in Caucasians and African Americans

	Caucasian (n=18,642)	African American (n=4685)
Peak expiratory flow (% predicted)	85%	78%
Nocturnal symptoms present	59%	67%
≥ 1 ER visit last 12 months	22%	41%
≥ 1 ER visit lifetime	59%	72%
≥1 hospitalization last 12 months	6%	15%
≥1 hospitalization lifetime	30%	44%
≥1 intubation for asthma lifetime	4%	8%
Baseline ICS use	49%	38%

Nelson HS et al. *Chest*. 2006;129:15-26. Adapted with permission.

Asthma-Related Deaths in the 28-Week Salmeterol Multicenter Asthma Research Trial (SMART)

	Salmeterol n (%)	Placebo n (%)	Relative Risk (95% confidence interval	Excess Death Exp. Per 10,000 pts. (95% confidence interval)
Population **Salmeterol: N = 13,176** **Placebo: N = 13,179**	13 (0.10%)	3 (0.02%)	4.37 (1.25, 15.34)	8 (3,13)
Caucasian **Salmeterol: N = 9281** **Placebo: N = 9361**	6 (0.7%)	1 (0.01%)	5.82 (0.70, 48.37)	6 (1,10)
African American **Salmeterol: N = 2366** **Placebo: N = 2319**	7 (0.31%)	1 (0.04%)	7.26 (0.89, 58.94)	27 (8,46)

Prescribing Information for ADVAIR DISKUS.

LABA's or NOT?

- FDA Black Box Warning provides another scare for asthmatics, and parents of asthmatic children to not use ICS
- Pre-emptive and proactive discussion of the pros and cons of LABA use in combination with long-term controller meds is appropriate
- Developing that collaborative, mutually agreed upon treatment plan with patients is crucial

Step Down Treatment for Mild Persistent Asthma That is Well Controlled

- Most ICS meds recommend BID dosing
- EPR-3 recommends reduction from low-dose ICS to PRN SABA
- Continuous monitoring is stressed by EPR-3 with the understanding that asthma is a variable disease
- Most providers will use BID or QD dosing, whichever achieves control
- Patients often prefer QD dosing over BID dosing

GINA Step-down recommendations

- GINA 2012 Guidelines discuss Once daily dosing in greater detail, providing evidence based recommendations when available
- A scarcity of experimental data exists for the ideal timing, sequence and magnitude of treatment reductions in asthma
- Patient to patient approach is indicated, based on medications and dosages used to achieve control
- Discussion and agreement between patient and HCP is the ideal approach
- A full discussion of potential consequences including reappearance of SX and increased exacerbations should be discussed with patient

Considerations when Stepping-down

- 1st and foremost, asthma is a variable disease and may present with seasonal variations including allergic and viral induced symptoms
- Getting to know your patients and tracking their previous HX and SX can often provide indicators for increasing or decreasing meds at certain times of the year
- Regular follow-ups, even when patients are well controlled, improve QOL and patients well-being
- Opportunities to assess control and review asthma teaching points potentially reduce exacerbations

GINA Step-down recommendations

- When patient is on low dose ICS and well controlled, most patients can we switched to once daily dosing
- If patient's asthma remains controlled on the lowest dose of controller with no recurrence of SX for a year, controller treatment may be stopped
- When medium to high dose ICS is used alone, a 50% reduction in dose at 3 month intervals should be attempted

GINA Step-down recommendations

- When patient is controlled with a combination ICS and LABA, reducing ICS dose by 50% and continuing LABA is recommended (Evidence B)
- If control is maintained, continue reducing ICS until low dose ICS is reached, when LABA may be stopped (Evidence D)
- When patient is controlled with ICS and another controller not LABA, reduce ICS dose by 50% until low dose ICS is reached, when other controller may be stopped (Evidence D).

LABA's and FDA initiatives

- FDA has directed that 4 adult and 1 pediatric study be conducted by ICS/LABA manufacturers to try to further clarify the risk of adding LABA's to ICS
- 1 article in Thorax, and a commentary in Chest journals have questioned the potential of possible false results from these studies and asked the FDA to reconsider the study design they have mandated Study results expected in 2017
- For the present, we must still be aware and work within the guidelines, including the black box warning on LABAs.

Questions???

- Thanks for your attention!
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