

Difficult Asthma Aged 12 & Over

- Lecture Objectives:
 - Difficult asthma 12 and over to include interpretation of PFT's
 - Discuss what makes a difficult asthma patient
 - Discuss the diagnosis, treatment and follow-up of a difficult asthma patient
 - Review PFT's and explain severe asthma
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 - President-Elect, American Academy of Physicians Assistants in Allergy, Asthma and Immunology

Difficult Asthma 12 & Over

- What is a difficult asthma patient?
- Expert Panel Report – 3 (EPR-3) guidelines and the recommended approach to difficult asthma
- Challenges and Opportunities in asthma management, especially as it applies to difficult asthma
- Ongoing research being conducted, integrated as appropriate when supported by literature
- PFT's and their use in asthma treatment

Difficult Asthma 12 & Over

- Why is difficult asthma, well, so difficult?
 - Difficult asthma can be any severity of asthma, mild, moderate or severe
 - Difficult asthma can be exacerbated by numerous co-morbidities including GERD, rhinitis, sinusitis, and/or medication sensitivity
 - Difficult asthma can be exacerbated by known environmental triggers, unknown irritants and allergens, viral respiratory infections or smoking
 - Difficult asthma might mean difficulty confirming the diagnoses of asthma
 - Difficult asthma might be the asthma variability that we have all come to know and love
 - Difficult asthma might be non-compliance with meds

Asthma Guidelines

- Expert Panel Report – 3 (EPR-3) guidelines for the diagnosis and treatment of asthma
- Published August 2007
- Ongoing research being conducted, integrated as appropriate when supported by literature

Implications of the Guidelines

- Large amount of asthma self-care required
- Need for a partnership with children and parents and adults to improve asthma care
- Best practices (including self-care education) differ by setting of care
 - ER and inpatient
 - Outpatient (PCP and specialists)
 - School and Child care
 - Home and community

Overview: Key components of Asthma Management from EPR-3

- Assessment & monitoring
- Control of environmental factors contributing to asthma & co-morbid conditions
- Medications
- Education for a partnership in care
- Each plays a role in treating difficult asthma

Definition of Asthma

- Asthma is a chronic inflammatory disease of the airway with:

Airway obstruction that may or may not be reversible, either spontaneously or with medication

Airway inflammation caused by many cellular components

Increased airway hyper responsiveness

- NHLBI

Pathological Definition of Asthma

- Chronic inflammation
- Infiltration of lymphocytes, eosinophils, neutrophils, together with epithelial desquamation, thickening and disorganization of the tissues of the airway wall
- Bronchial wall edema
- Excess mucous production
- Smooth muscle hypertrophy and fibroblast proliferation
 - Bronchial hyperresponsiveness
 - Smooth muscle contractions

Etiology of Asthma

- Atopy: Genetic predisposition to develop immunoglobulin E (IgE) mediated response to aeroallergens (seen most in children)
 Strongest factor for developing asthma
- Exposure to triggers

Hygiene Hypothesis

- Is based on the following observations:
 - Asthma is more common in urban areas than in rural areas
 - Children raised on farms have a lower incidence of asthma than children raised in cities
 - Infants raised in a large family with sibs are less likely to develop asthma than only children
 - Early life exposure to microbial products, e.g., endotoxins, promote the development of a Th1 lymphocyte cell line that appears to protect against the development of allergies and asthma

Development of Asthma

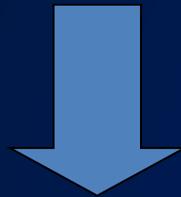
- Genetics and Environment interacting in ways not fully understood, leading to



Bronchoconstriction



Airway Inflammation



Asthma Symptoms

Dual Phase Response in Asthma

- Immediate (early) Response
 - Asthma reaction to stimulus
 - Occurs within minutes
 - Immediate bronchoconstriction
 - Resolves spontaneously or with Beta2 Agonist
- Late Phase (delayed or secondary) response
 - Airway inflammation
 - May occur 4-12 hours after immediate response
 - Influx of inflammatory cells and mediators
 - Often more severe and prolonged

Initial Assessment and Diagnosis of Asthma

- Does patient have history or presence of episodic symptoms of airflow obstruction?
 - Wheeze, shortness of breath, chest tightness, or cough
 - Asthma symptoms vary throughout the day
 - Absence of symptoms at the time of the examination does not exclude the diagnosis of asthma

Initial Assessment and Diagnosis of Asthma

- Is airflow obstruction at least partially reversible?
 - Use spirometry to establish airflow obstruction:
 - FEV1 <80% predicted;
 - FEV1/FVC ratio <65%
 - Use spirometry to establish reversibility:
 - FEV1 increases \geq 12% and at least 200ml after using a short acting inhaled Beta2-agonist

Initial Assessment and Diagnosis of Asthma

- Asthma Diagnosis (by history, the patient must meet three criteria):
 - Symptoms of asthma occur in response to an allergen trigger or airway irritant (airway hyperreactivity)
 - Repeated episodes of symptoms (recurrence)
 - Response to treatment (reversibility) measured objectively by spirometry with a significant increase post-bronchodilator or relief of symptoms

Initial Assessment and Diagnosis of Asthma

- Primary triggers that I see in practice
 - Strenuous exercise
 - Cold air exposure
 - Viral respiratory infections, colds, flu, sinus infections (either viral or bacterial)
 - Inhaled allergens
 - Rhinitis and Sinusitis

Initial Assessment and Diagnosis of Asthma

- Secondary triggers that I see in practice
 - Reflux or GERD
 - Medicines such as ASA or NSAIDs
 - Food additives such as sulfites used to preserve wine, beer and dried fruits
 - Hormonal changes
- Triggers will have an additive effect

Initial Assessment and Diagnosis of Asthma

- Cough, frequently the only asthma symptom
 - Can occur with exercise
 - Cold air exposure
 - At night
 - In smoky areas
 - After laughing or crying
- Difficult to differentiate an asthma cough from the cough of a regular cold
- Asthma medicines can help reduce or control an asthma cough

Co-morbidity Factors in Asthma

- Rhinitis
- Sinusitis
- GERD
- Aspirin Sensitivity

Rhinitis

- Strong association between asthma and sensitization to allergens
 - Sensitization to dust mites, animal dander, cockroach and alternaria increases asthma risk
 - Pollen sensitization carries less risk for asthma
 - Importance of inhalant sensitivity declines with advancing age
 - Exposure to seasonal outdoor fungal spores and indoor allergens has been implicated in fatal asthma exacerbations

Sinusitis and ASA sensitivity

- Strong association between asthma and sinusitis
 - Previously thought of as 2 separate systems
 - Currently discussed as “Unified Airway”
 - Sometimes called Sino-Pulmonary Syndrome
- ASA Sensitivity
 - Asthma exacerbations including anaphylaxis
 - Frequently includes sensitivity to other NSAIDs
 - When associated with nasal polyps this is known as Samter’s Triad

Stepwise approach to Therapy

- STEP 1: Quick-relief medication: PRN
- STEP 2: 1 Long-term-control medication:
anti-inflammatory
- STEP 3: > 1 Long-term-control medications
- STEP 4: Multiple long-term-control medications
- STEP 5 & 6 Multiple long-term-control medications, referral for allergy or pulmonary consult, intense educational effort, possibly allergy shots, oral steroids and Xolair

Classifying-Severity

- The level of severity is based on most life-threatening impairment or risk category
- Assess impairment domain based on patient's recall of previous 2-4 weeks

Components of Severity		Classifying Asthma Severity and Initiating Therapy in Children							
		Intermittent		Persistent					
				Mild		Moderate		Severe	
		Ages 0-4	Ages 5-11	Ages 0-4	Ages 5-11	Ages 0-4	Ages 5-11	Ages 0-4	Ages 5-11
Impairment	Symptoms	≤2 days/week		>2 days/week but not daily		Daily		Throughout the day	
	Nighttime awakenings	0	≤2x/month	1-2x/month	3-4x/month	3-4x/month	>1x/week but not nightly	>1x/week	Often 7x/week
	Short-acting beta ₂ -agonist use for symptom control	≤2 days/week		>2 days/week but not daily		Daily		Several times per day	
	Interference with normal activity	None		Minor limitation		Some limitation		Extremely limited	
	Lung Function • FEV ₁ (predicted) or peak flow (personal best) • FEV ₁ /FVC	N/A	Normal FEV ₁ between exacerbations >80%	N/A	>80%	N/A	60-80%	N/A	<60%
Risk	Exacerbations requiring oral systemic corticosteroids (consider severity and interval since last exacerbation)	0-1/year (see notes)		≥2 exacerbations in 6 months requiring oral systemic corticosteroids, or ≥4 wheezing episodes/1 year lasting >1 day AND risk factors for persistent asthma	≥2x/year (see notes)				
				Relative annual risk may be related to FEV ₁					
Recommended Step for Initiating Therapy (See "Stepwise Approach for Managing Asthma" for treatment steps.) The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.		Step 1 (for both age groups)		Step 2 (for both age groups)		Step 3 and consider short course of oral systemic corticosteroids	Step 3: medium-dose ICS option and consider short course of oral systemic corticosteroids	Step 3 and consider short course of oral systemic corticosteroids	Step 3: medium-dose ICS option OR step 4 and consider short course of oral systemic corticosteroids
		In 2-6 weeks, depending on severity, evaluate level of asthma control that is achieved. <ul style="list-style-type: none"> Children 0-4 years old: If no clear benefit is observed in 4-6 weeks, stop treatment and consider alternative diagnoses or adjusting therapy. Children 5-11 years old: Adjust therapy accordingly. 							

Classifying-Severity ≥ 12 yrs

Components of Severity		Classification of Asthma Severity (Youths ≥ 12 years of age and adults)			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment Normal FEV ₁ /FVC: 8-19 yr 85% 20-39 yr 80% 40-59 yr 75% 60-80 yr 70%	Symptoms	≤ 2 days/week	> 2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤ 2 x/month	3-4x/month	> 1 x/week but not nightly	Often 7x/week
	Short-acting beta ₂ -agonist use for symptom control (not prevention of EIB)	≤ 2 days/week	> 2 days/week but not > 1 x/day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	<ul style="list-style-type: none"> Normal FEV₁ between exacerbations FEV₁ $> 80\%$ predicted FEV₁/FVC normal 	<ul style="list-style-type: none"> FEV₁ $\geq 80\%$ predicted FEV₁/FVC normal 	<ul style="list-style-type: none"> FEV₁ $> 60\%$ but $< 80\%$ predicted FEV₁/FVC reduced 5% 	<ul style="list-style-type: none"> FEV₁ $< 60\%$ predicted FEV₁/FVC reduced $> 5\%$
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/year (see note)	≥ 2 /year (see note) 		
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. →			
		Relative annual risk of exacerbations may be related to FEV ₁			

Look how asthma severity affects lung function measurement



Assessing-Control

CONTROL: the degree to which the manifestations of asthma are minimized by therapeutic intervention and the goals are met.

- Based on Impairment and Risk

- ▣ Classifications of control
 - Well controlled

 - Not well controlled

 - Very poorly controlled

Assessment \geq 12 yrs

Components of Control		Classification of Asthma Control (\geq 12 years of age)		
		Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Symptoms	\leq 2 days/week	$>$ 2 days/week	Throughout the day
	Nighttime awakenings	\leq 2x/month	1–3x/week	\geq 4x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting beta ₂ -agonist use for symptom control (not prevention of EIB)	\leq 2 days/week	$>$ 2 days/week	Several times per day
	FEV ₁ or peak flow	$>$ 80% predicted/ personal best	60–80% predicted/ personal best	$<$ 60% predicted/ personal best
	Validated questionnaires ATAQ ACQ ACT	0 \leq 0.75* \geq 20	1–2 \geq 1.5 16–19	3–4 N/A \leq 15
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	\geq 2/year (see note)	
		Consider severity and interval since last exacerbation		
	Progressive loss of lung function	Evaluation requires long-term followup care		
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Recommended Action for Treatment (see figure 4–5 for treatment steps)		<ul style="list-style-type: none"> • Maintain current step. • Regular followups every 1–6 months to maintain control. • Consider step down if well controlled for at least 3 months. 	<ul style="list-style-type: none"> • Step up 1 step and Reevaluate in 2–6 weeks. • For side effects, consider alternative treatment options. 	<ul style="list-style-type: none"> • Consider short course of oral systemic corticosteroids, • Step up 1–2 steps, and Reevaluate in 2 weeks. • For side effects, consider alternative treatment options.

Look how **asthma control** affects lung function measurement



Stepwise Approach to Therapy

- Step 1, Intermittent Asthma – Use SABA
- Step 2, Mild asthma – Use low dose ICS
- Step 3, Moderate asthma – Use low dose ICS and LABA, LTRA, or Theophylline, or Med dose ICS
- Step 4, Severe Asthma – Use medium dose ICS + LABA or add Singulair, LTRA, or theophylline
- Step 5 & 6, Use High dose ICS and LABA, refer to allergy or pulmonology. These Pts may need additional meds, allergy immunotherapy, oral steroids, or Xolair

Goals of Asthma Therapy

- Prevent chronic and troublesome symptoms
- Baylor's rules of 2
 - Require infrequent use (\leq 2 days a week) of inhaled SABA for quick relief of symptoms (not including prevention of exercise induced bronchospasm EIB)
- Maintain (near-) “normal” pulmonary function
- Maintain normal activity levels (including exercise and other physical activity)
- Meet patients' and families' expectations of and satisfaction with asthma care

Goals of Asthma Therapy

- Prevent recurrent exacerbations of asthma and minimize the need for ED visits or hospitalizations
- Prevent loss of lung function; for children, prevent reduced lung growth
- Provide optimal pharmacotherapy with minimal or no adverse effects of therapy
- Don't forget asthma action plan and your long-term relationship with your asthmatic patients

Monitoring Patients Asthma

- Recognition of signs and symptoms
- Spirometry and peak flow
- Quality of life/functional status
- Patient self-monitoring and health care utilization
- Adherence, beta2-agonist use, oral corticosteroid bursts, side effects
- Satisfaction with asthma control and quality of care

Monitoring Symptoms

- Symptom history should be based on a short (2 to 4 weeks) recall period
- Symptom history should include:
 - Daytime asthma symptoms
 - Nocturnal wakening as a result of asthma symptoms
 - Exercise-induced symptoms
 - Exacerbations

Monitoring Quality of Life and Functional Status

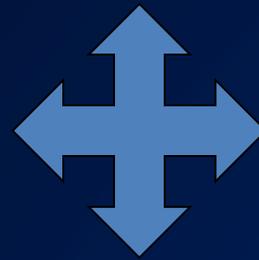
- Periodically assess:
 - Missed work or school due to asthma
 - Reduction in usual activities due to asthma
 - Sleep disturbances due to asthma
 - Change in caregiver activities due to child's asthma

Pharmacologic Therapy

Environmental risk factors (causes)

↓
INFLAMMATION

Airway
hyperresponsiveness



Precipitants

Airflow
limitation

Symptoms

Adapted with permission from Stephen T. Holgate, M.D., D.Sc.

- **Asthma is a chronic inflammatory disorder of the airways.**
- **A key principle of therapy is regulation of chronic airway inflammation.**

Goals for Medication Therapy

- Maintain normal activity levels to include exercise
- Maintain near normal pulmonary function tests
- Prevent chronic and troublesome symptoms
- Prevent recurrent exacerbations of asthma
 - Require rescue medications less than or equal to 2x/week
- Avoid adverse effects from asthma medications

Pharmacotherapy

- Antiinflammatory (controller/maintenance)
- Bronchodilators (rescue/quick relief meds)
- Others including theophylline, mast cell stabilizers, oral Beta-2 agonists, Anti-IgE biologic agent, and allergen immunotherapy

Medication Classification

Long-Term Control

- Inhaled corticosteroids
- Inhaled long-acting β 2-agonists
- ICS/LABA combinations
- Leukotriene modifiers
- Cromolyn sodium/ Nedocromil
- Methylxanthines
- Oral long-acting β 2-agonists
- Immunomodulators
- Anti-IgE biologic agent
- Allergen Immunotherapy

Quick Relief

Short-acting β 2-agonists

Anticholinergics

Oral Corticosteroids

Long-Term Control Medications

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

Pharmacologic Therapy

“Airway inflammation is a major factor in the pathogenesis and pathophysiology of asthma. The importance of inflammation to central features of asthma continues to expand and underscore this characteristic as a primary target of treatment...

Corticosteroids block late-phase reaction to allergen, reduce airway hyperresponsiveness, and inhibit inflammatory cell migration and activation. They are the most potent and effective anti-inflammatory medication currently available.”

- NAEPP EPR-3, 2007

Most Effective Long-Term Controller Inhaled Corticosteroids (ICS):

- The daily use of ICS results in the following:
- Asthma symptoms will diminish. Improvement will continue gradually
- Occurrence of severe exacerbations is greatly reduced
- Use of quick-relief medication decreases
- Lung function improves significantly, as measured by PEF, and FEV1
- Increased number of B2 adrenergic receptors and improved receptor responsiveness to B2 adrenergic stimulation
- Reduced mucus production and hypersecretion
- Reduced bronchial hyper-responsiveness
- Reduced airway edema and exudation

Problems due to asthma may return if patients stop taking ICS

ICS: local adverse effects

- Oral candidiasis (thrush)
 - 45-58% of patients have + cultures (clinical thrush 0-34%)
 - Not as common with lower doses (5%)
- Dysphonia
 - 5-50% of patients
- Reflex cough and bronchospasm

ICS: systemic adverse effects

- Linear growth:
 - Low-med dose ICS may have potential to decrease growth velocity in children
 - Affects are small and may be reversible
 - Studies show improved asthma outcomes in children
 - Expert Panel statements:
 - Risk is well balanced by benefits
 - Effects may be dose dependent
 - Poorly controlled asthma may delay growth in children
 - Effect typically occurs in first several months
 - Growth should be monitored

Underutilization of ICS

- Inadequately prescribed by providers
- Inaccurate determination of persistent disease
- Safety concerns
- Inadequately taken by patients
- Reluctance to use daily therapy
- Fear of “steroids” and confusion with anabolic steroids
- Lack of perception of effect

Generic	Brand	Dose/actuation	notes
Fluticasone	Flovent	44, 110, 220 mcg 100, 250, 500 mcg	HFA MDI Discus
Triamcinolone acetonide	Azmacort	100 mcg	MDI with built in spacer
Beclomethasone dipropionate	QVAR	40 mcg 80 mcg	HFA MDI
Flunisolide	Aerobid	250 mcg	HFA MDI
Budesonide Nebulizer suspension	Pulmicort	200 mcg 0.25, 05 mg	DPI, Turbuhaler Only available product for neb
Mometasone furoate	Azmanex twisthaler	110 mcg 220 mcg	Breath-activated Once daily dosing
Ciclesonide	Alvesco	80 mcg, 160mcg,	MDI, once daily dosing

Combo products

Product	Dosage Form	Dose	
Fluticasone/Salmeterol (Advair®)	DPI: 100/50; 250/50; 500/50	1 blister q 12 hours	Discus approved for kids ≥ 4
	HFA: 45/21; 115/21; 230/21	2 inhalations q 12 hours	HFA approved for kids ≥ 12
Budesonide/Formoterol (Symbicort®)	HFA: 80/4.5; 160/4.5	Two inhalations twice daily	Approved for kids ≥ 12
Mometasone/Formoterol (Dulera®)	HFA: 100/5; 200/5	Two inhalations twice daily	Approved for kids ≥ 12

Inhaled corticosteroids

- Teach patient:
 - About delay of onset
 - Importance of taking every day
 - Proper technique
 - Use spacer for MDI
 - RINSE and SPIT after each use
 - Decrease oral thrush, dysphonia
 - When to change canister
 - Fear of steroids is common/need to provide accurate counseling/education to pts
- Be proactive teaching your patients about the merits of ICS and to decrease steroid phobia

Stepwise approach to Therapy

- STEP 1: Quick-relief medication: PRN
- STEP 2: 1 Long-term-control medication:
anti-inflammatory
- STEP 3: > 1 Long-term-control medications
- STEP 4: Multiple long-term-control medications
- STEP 5 & 6 Multiple long-term-control medications, referral for allergy or pulmonary consult, intense educational effort, possibly allergy shots, oral steroids and Xolair

Evolving Patterns in Asthma Management

Period	Goal of Management	Medications
1960s	Relieve bronchospasm	Short-acting β -agonists
1970s	Prevent bronchospasm	Albuterol, theophylline
1980s	Prevent allergen-induced bronchospasm	Cromolyn
1990s	Prevent and resolve inflammation	Inhaled glucocorticoids, leukotriene modifiers, long-acting β -agonists, combination therapy
2000s	Asthma control	Anti IgE
2010s	Personalized medicine; Early intervention	Patient characteristics, biomarkers, genetics; Immunomodulators

Current Approaches to “Personalizing” Asthma Care

- **Initiating therapy** – medication, dose and formulation
- **Stepping up and stepping down therapy** – primarily symptom-based
- **Monitoring** – Periodic follow-up
- **Immunomodulators** – introduced in late stage of disease

Approaches to Advance Asthma Management

- Early intervention to prevent and control asthma
- Anticipate and prevent asthma exacerbations
- Apply biomarkers to monitor disease activity
- Use genetics/epigenetics to identify risk category for disease onset/severity
- Immunomodulators to alter course of disease

Developing New Approaches to “Personalize” Asthma Management

- **Early intervention strategies** – Who? What treatment? What outcomes?
- **Biomarkers** – Which ones? What application?
- **Combination therapy** – How soon? What type?
- **Genetics/epigenetics** – Can we move discovery to application?
- **Immunomodulators** – Benefit-risk? Do we have the right ones?

Which Biomarkers?

- PC20 with methacholine
- FeNO – Fraction exhaled nitrous oxide
- Asthma Control Tests
- Genetic mapping

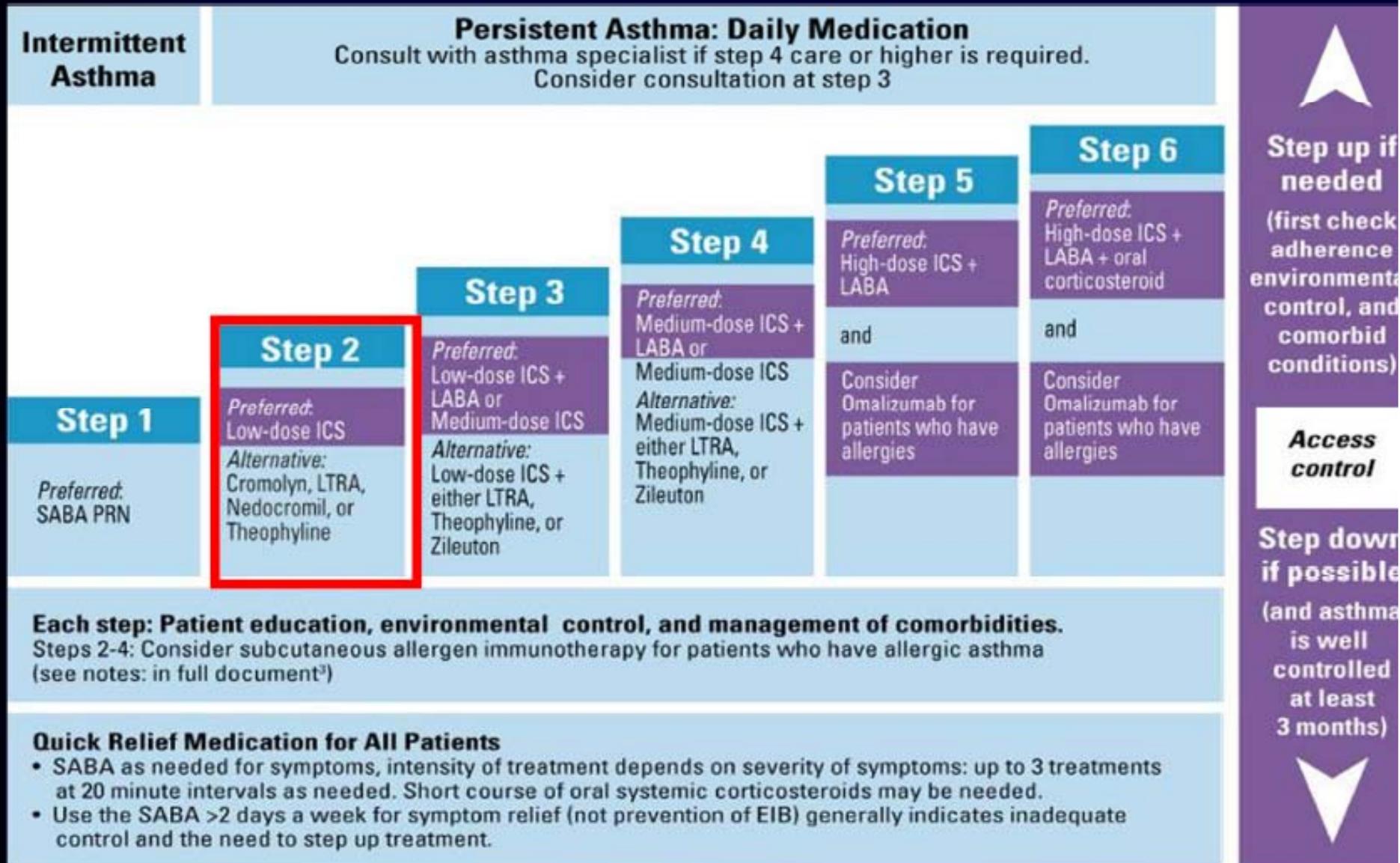
Primary Goal of Therapy: Achieving and Maintaining Asthma Control

- Primary goal of asthma therapy is to enable a patient to achieve and maintain **control** over their asthma
 - Eliminate **impairments** including symptoms, functional limitations, poor quality of life, and other manifestations of asthma
 - Reduce **risk** of exacerbations, ED visits, and hospitalizations
- Treatment goals are identical for all levels of **asthma severity**

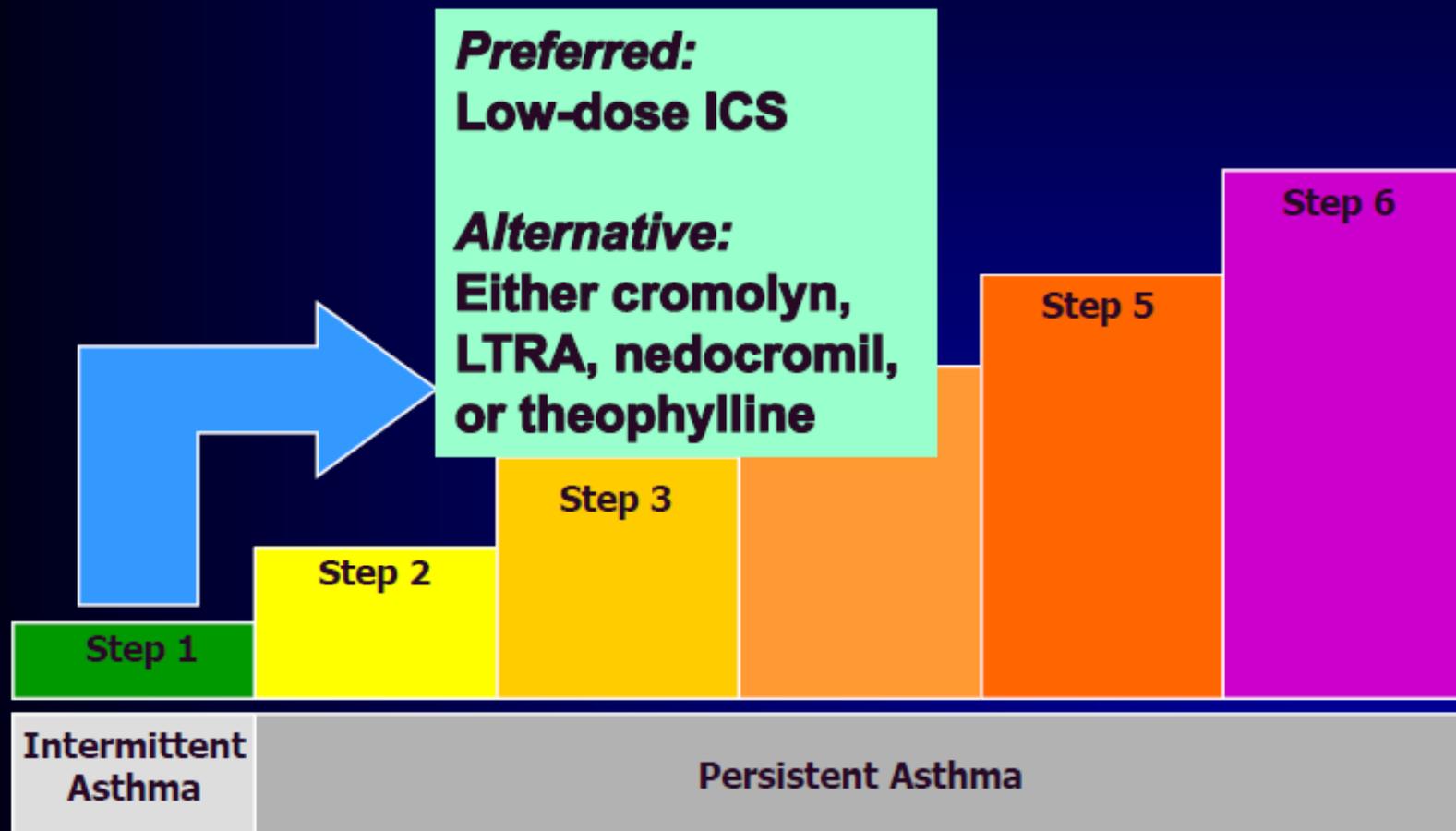
Assessing Asthma Control and Adjusting Therapy in Youths 12 Years of Age and Adults

Components of Control		Classification of Asthma Control ≥12 years of age		
		Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Symptoms	≤ 2 days/week	> 2 days/week	Throughout the day
	Nighttime awakenings	≤ 2 x/month	1-3 x/week	≥ 4x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short acting beta ₂ -agonist use for symptom control (not prevention of EIB)	≤ 2 days/week	> 2 days/week	Several times per day
	FEV ₁ or peak flow	> 80% predicted/ personal best	60-80% predicted/ personal best	< 60% predicted/ personal best
	Validated questionnaires ATAQ ACQ ACT	0 ≤ 0.75 ≥ 20	1-2 ≥ 1.5 16-19	3-4 N/A ≤ 15
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/year 2/year (see note) Consider severity and interval since last exacerbation		
	Progressive loss of lung function	Evaluation requires long-term followup care		
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to vary troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Recommended Action for Treatment		<ul style="list-style-type: none"> • Maintain current step • Regular followups every 1-6 months to maintain control. • Consider step down if well controlled for at least 3 months. 	<ul style="list-style-type: none"> • Step up 1 step, and • Reevaluate in 2-6 weeks. • For side effects, consider alternative treatment options. 	<ul style="list-style-type: none"> • Consider short course of oral systemic corticosteroids, • Step up 1-2 steps, and • Reevaluate in 2 weeks. • For side effects, consider alternative treatment options.

Stepwise Approach for Managing Asthma in Youths ≥ 12 Years of Age and Adults



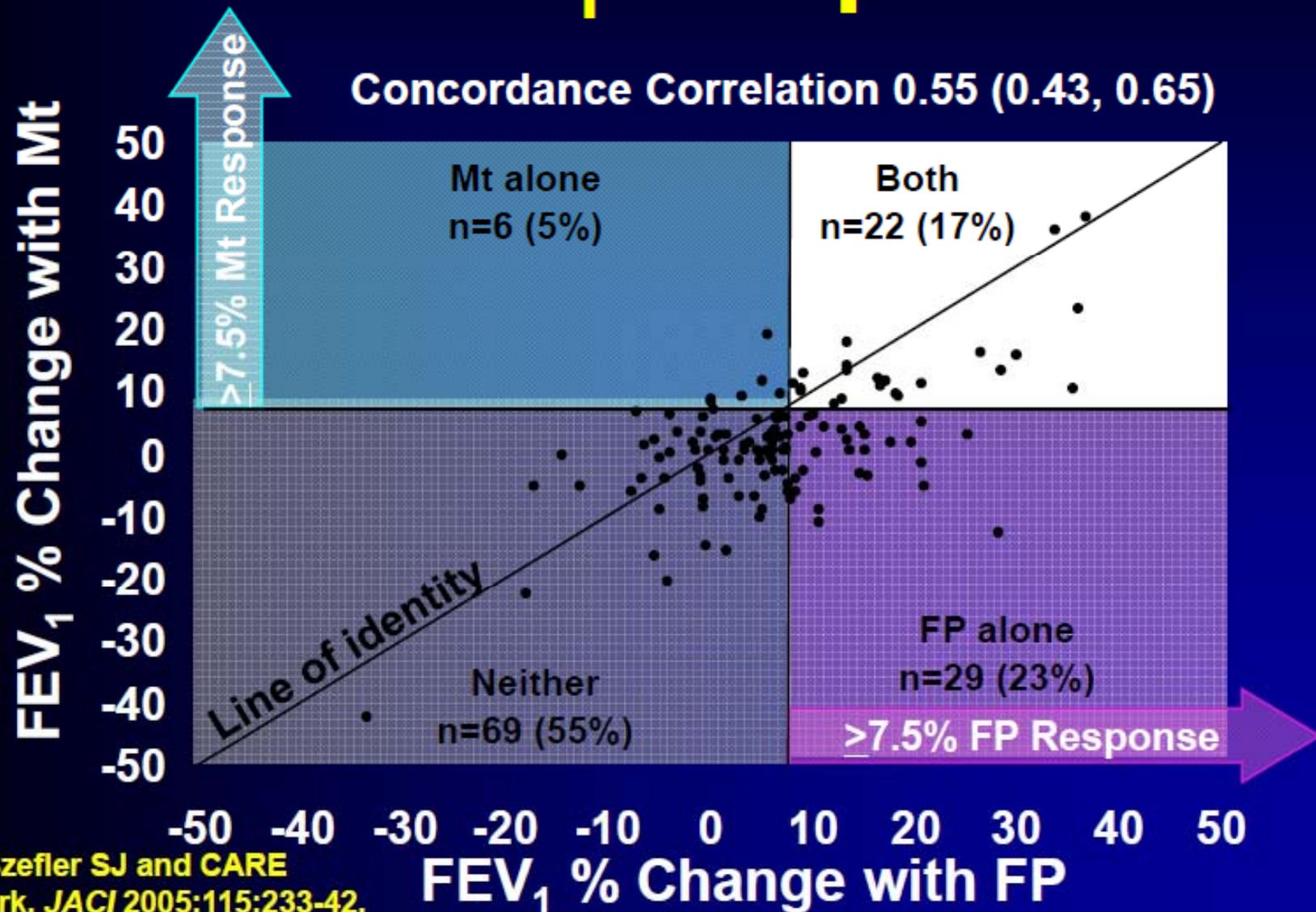
EPR-3 Recommendations: Step-Up Therapy



Do we treat everyone the same?

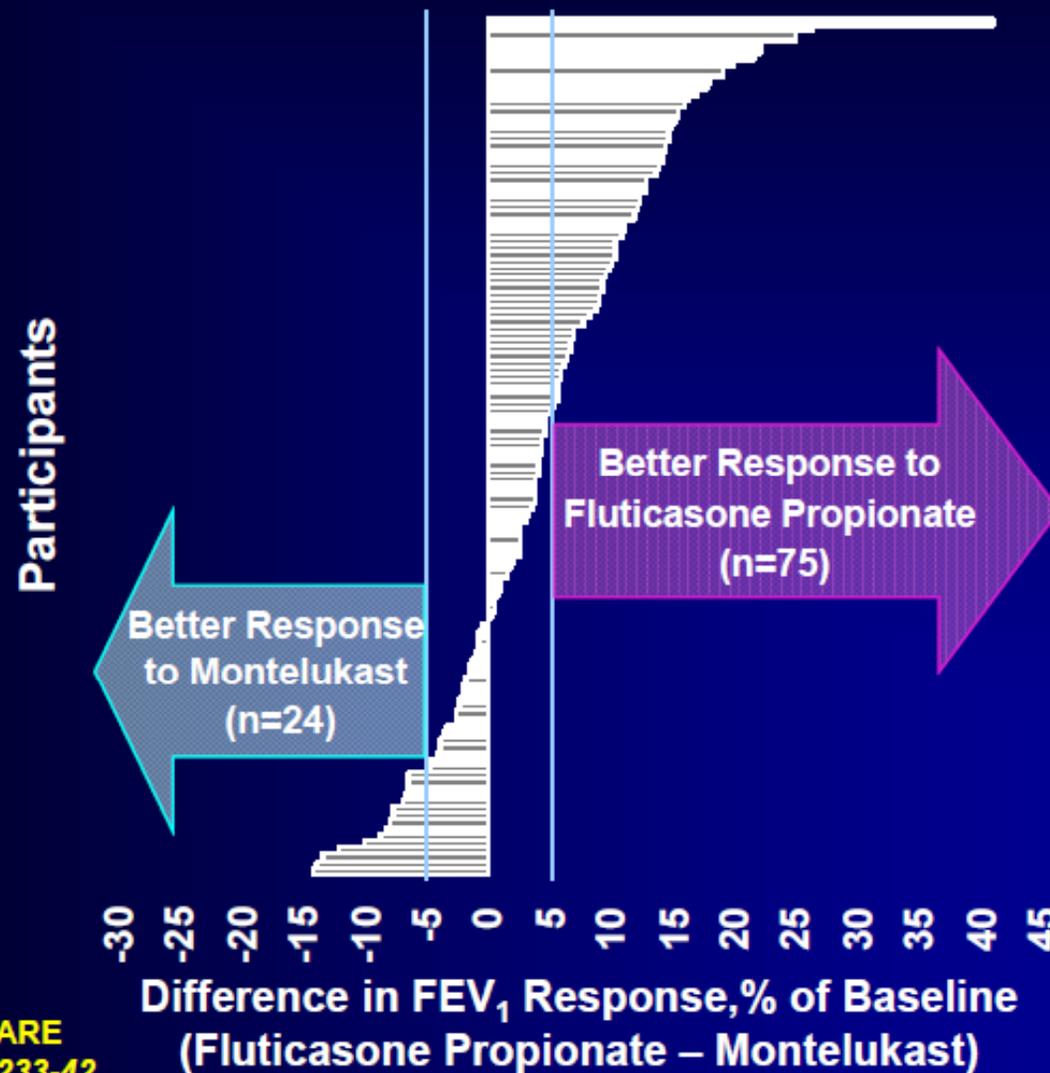
- Personalize your treatment approach
 - Anticipate variability in treatment response
 - Past exacerbations HX – consider pre-treatment
 - Intervention early is the best approach
- Follow the guidelines
 - Maintain control
 - Eliminate impairments
 - Reduce risk

Primary Outcome: FEV₁ Response

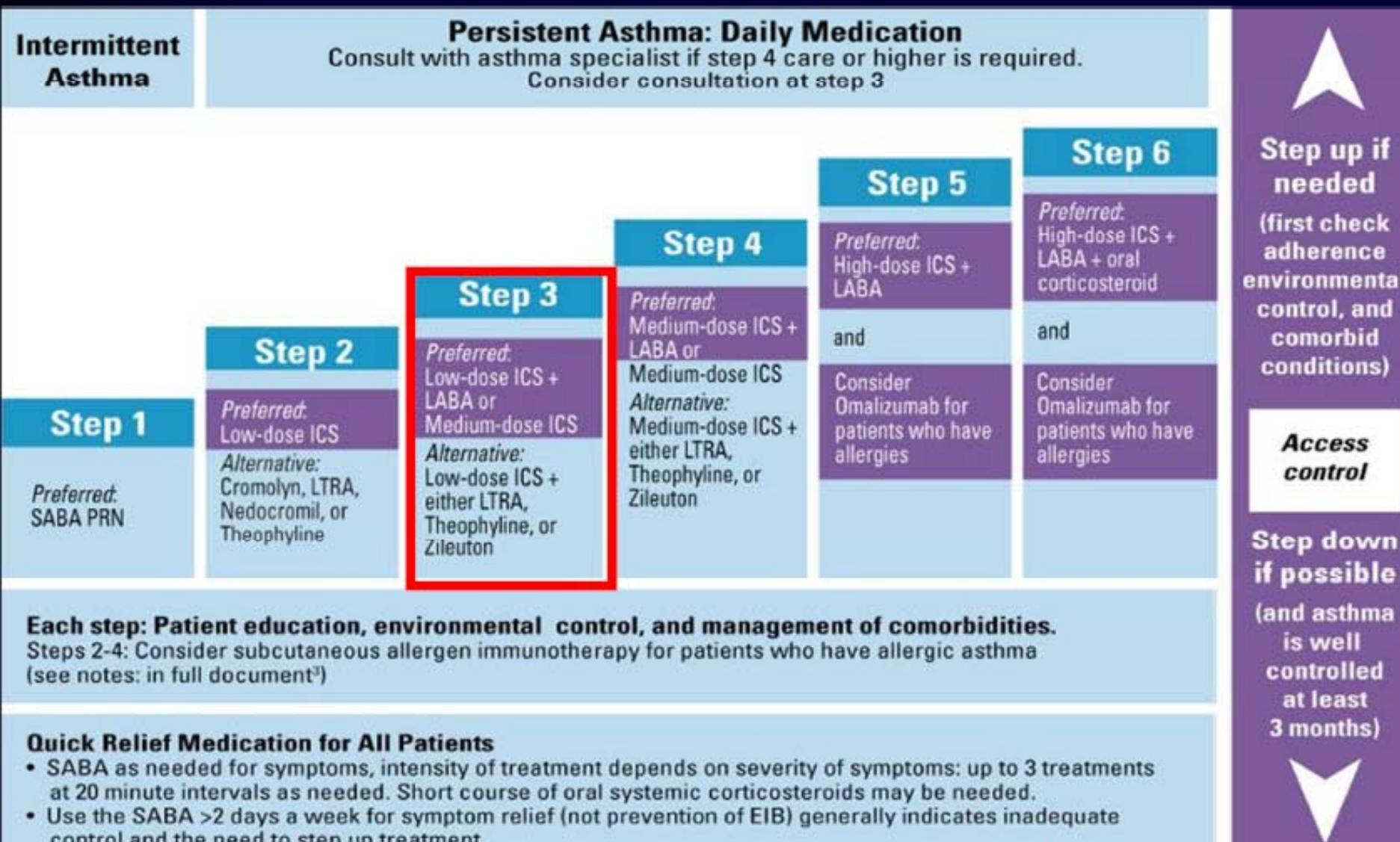


Ref. Szefer SJ and CARE
Network. JACI 2005;115:233-42.

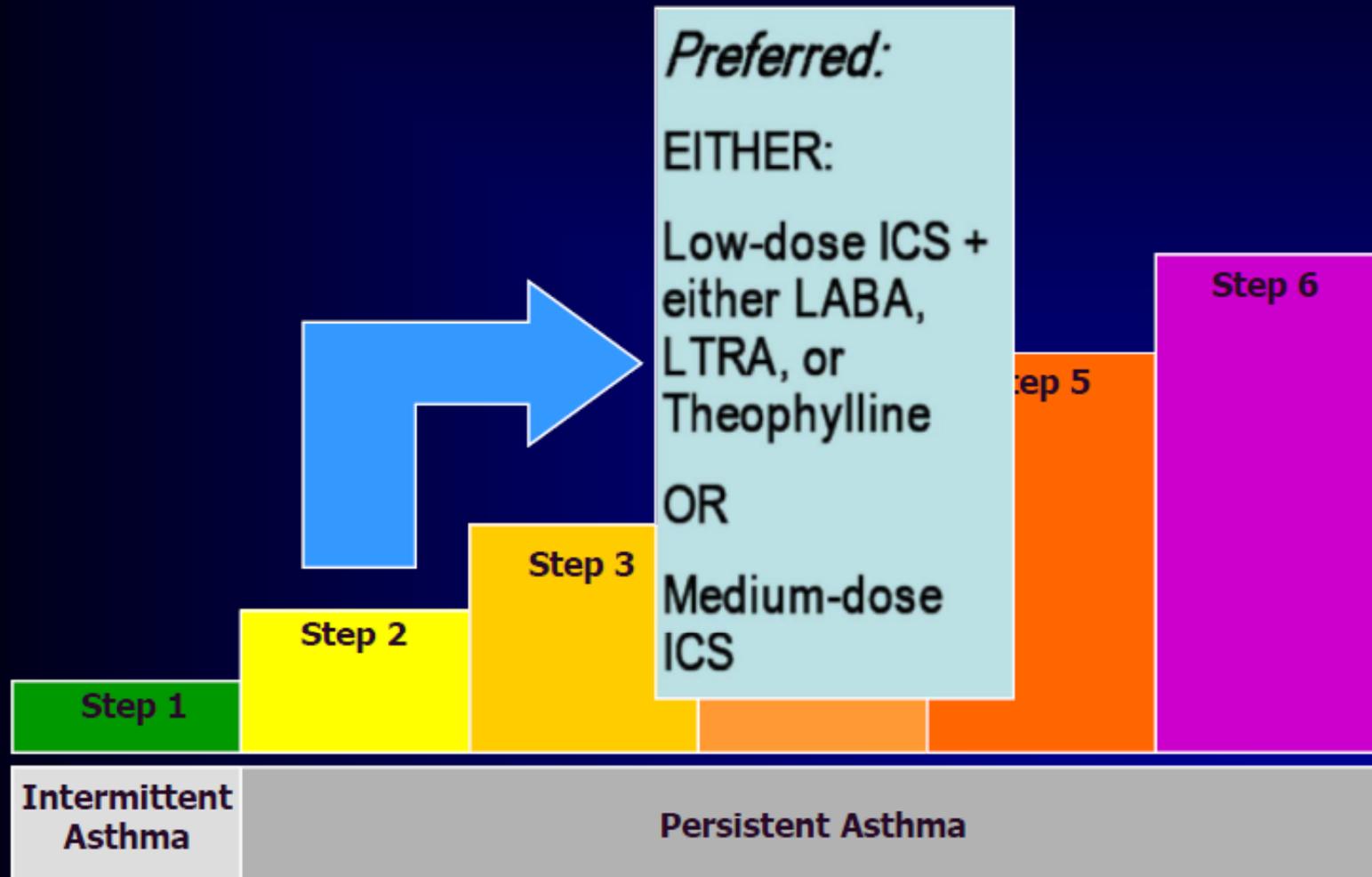
Individual Difference in FEV₁ Response



Stepwise Approach for Managing Asthma in Youths ≥ 12 Years of Age and Adults



EPR-3 Recommendations



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. Szeffler, 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 μ g BID) therapy, what is the next best treatment approach?
 - Increased doses of ICS (fluticasone 250 μ g 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** 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 FEV₁.

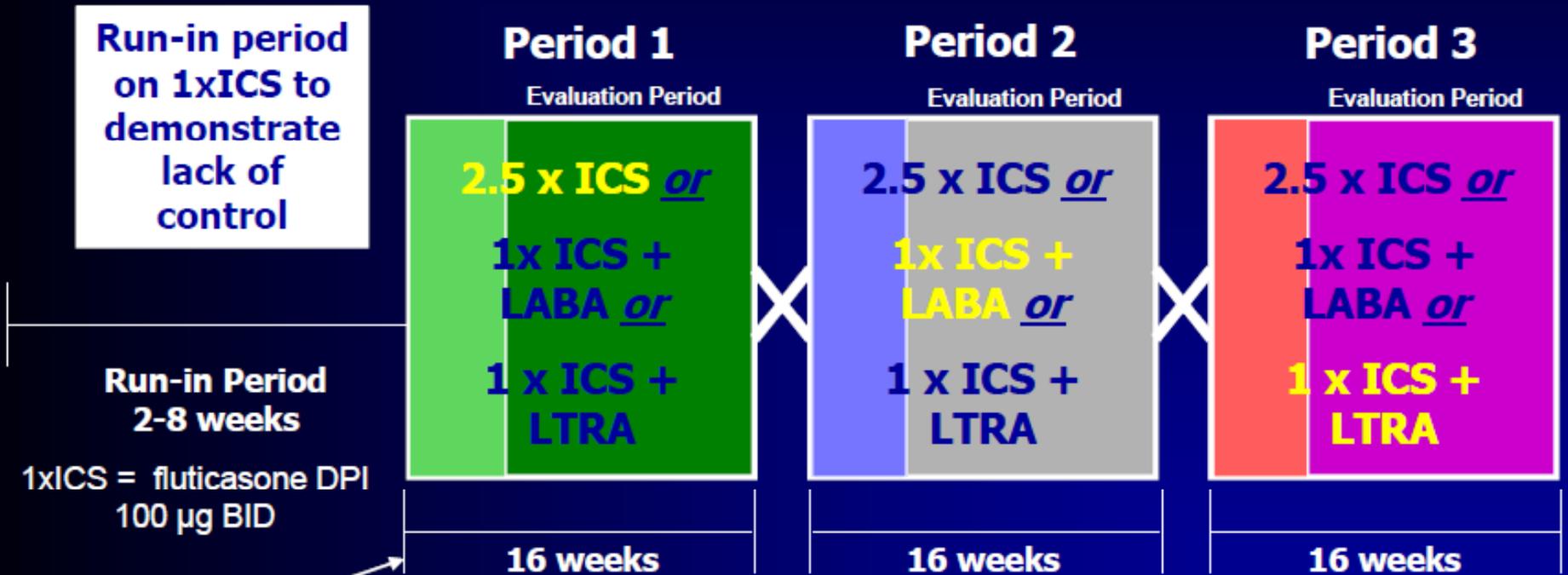
BADGER: Outcome measures to determine differential response

- 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
 - FEV₁:
 - 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

BADGER Protocol: Overview



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



Randomization

2.5 x ICS = fluticasone DPI 250 µg BID

1xICS+LABA = fluticasone/salmeterol DPI 100/50 BID

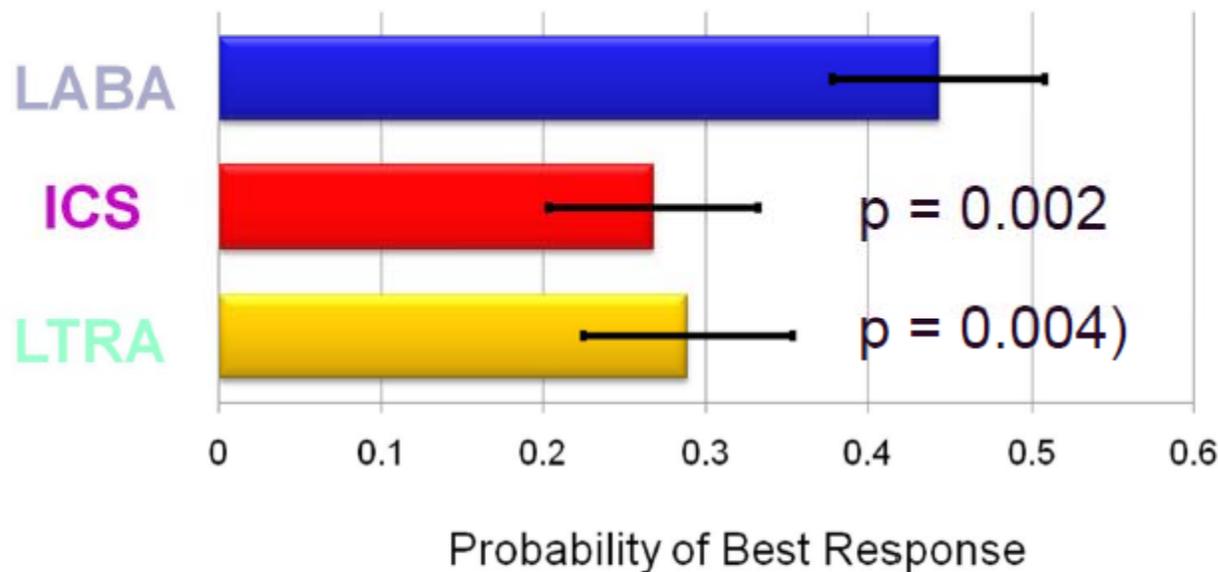
1xICS+LTRA = fluticasone DPI 100 µg BID + montelukast

Results: Differential Response

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

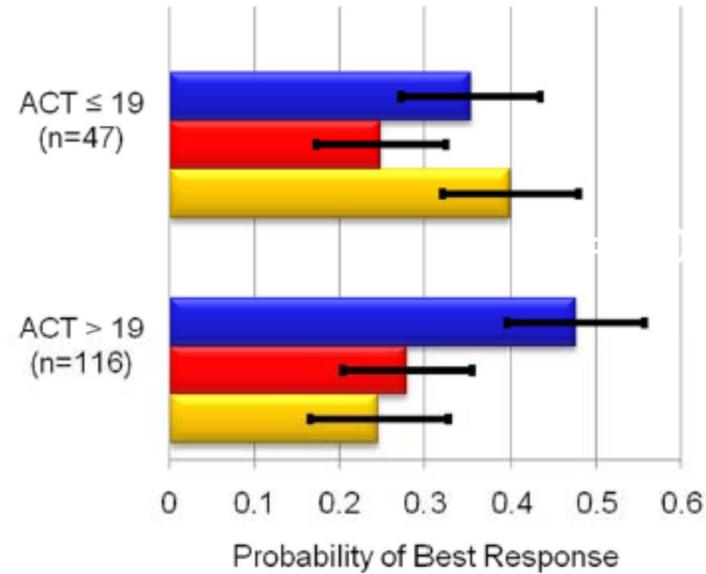
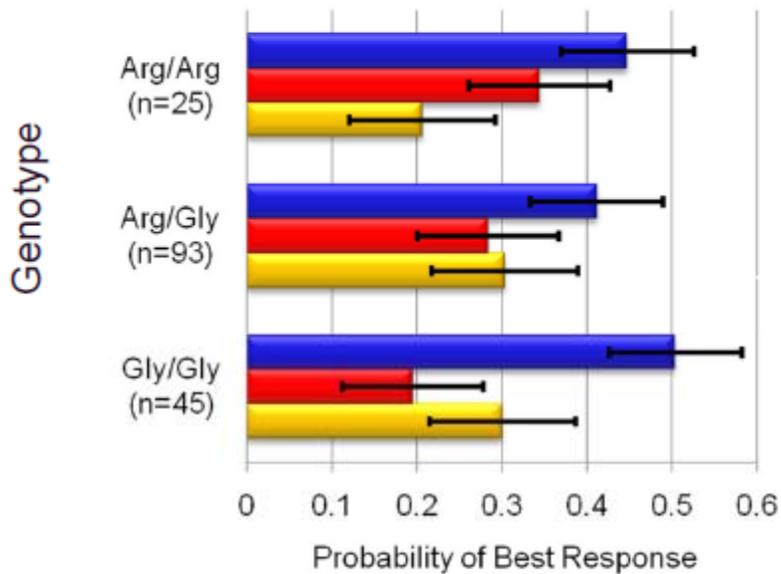
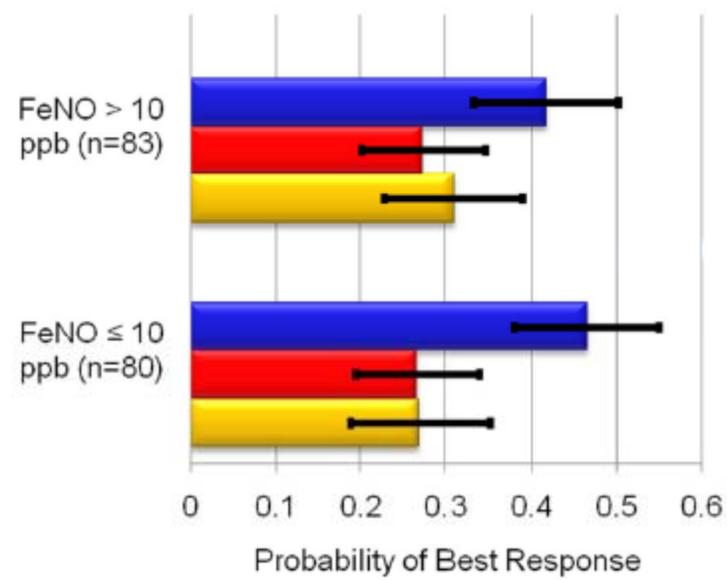
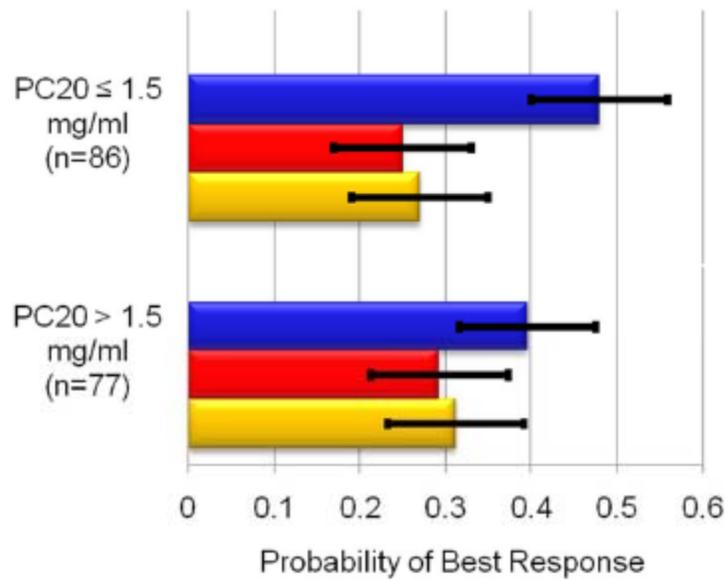
Primary Outcome: Probability of BEST Response Based on Composite Outcome*

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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LABA **ICS** **LTRA**

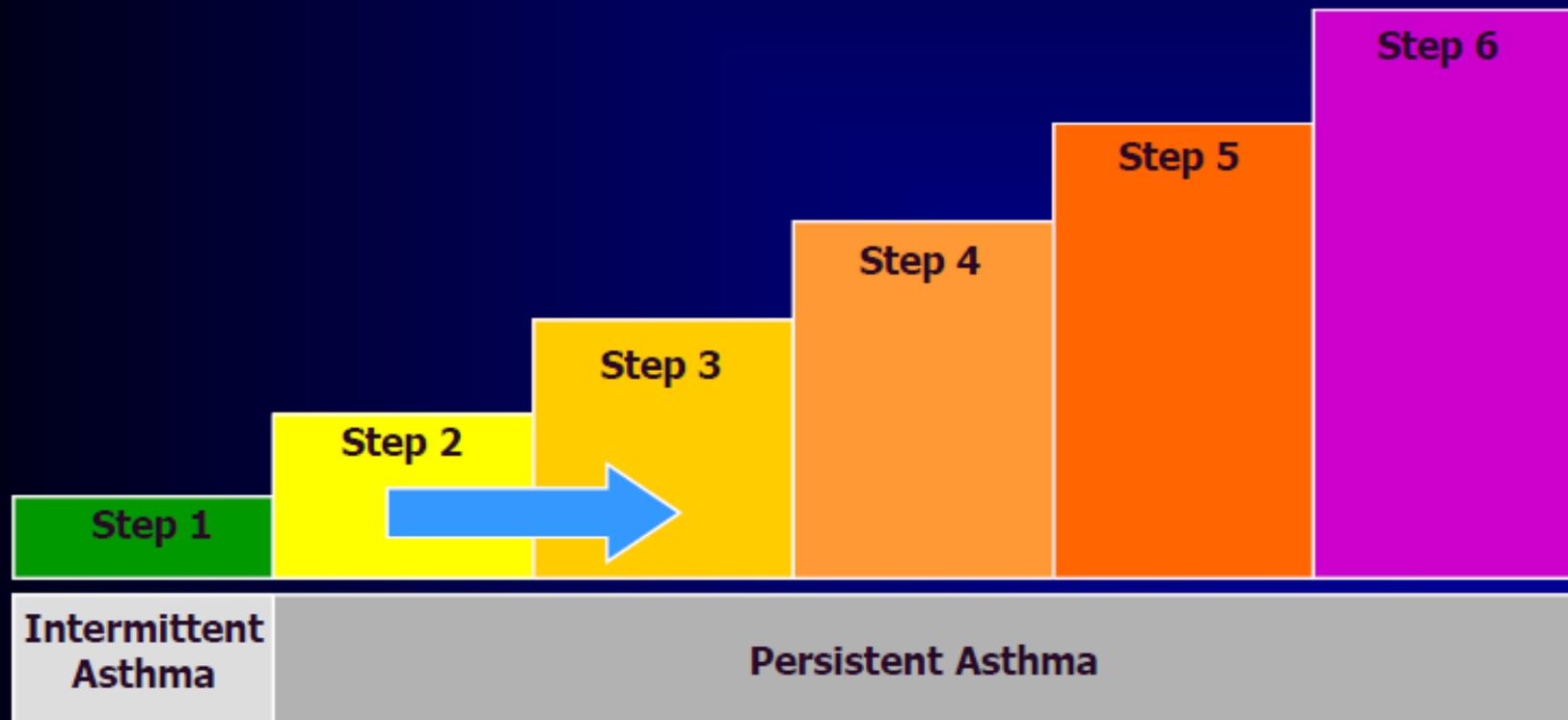
Ref. Lemanske R and CARE Network NEJM 2010;362:975-985.

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BADGER: Conclusions

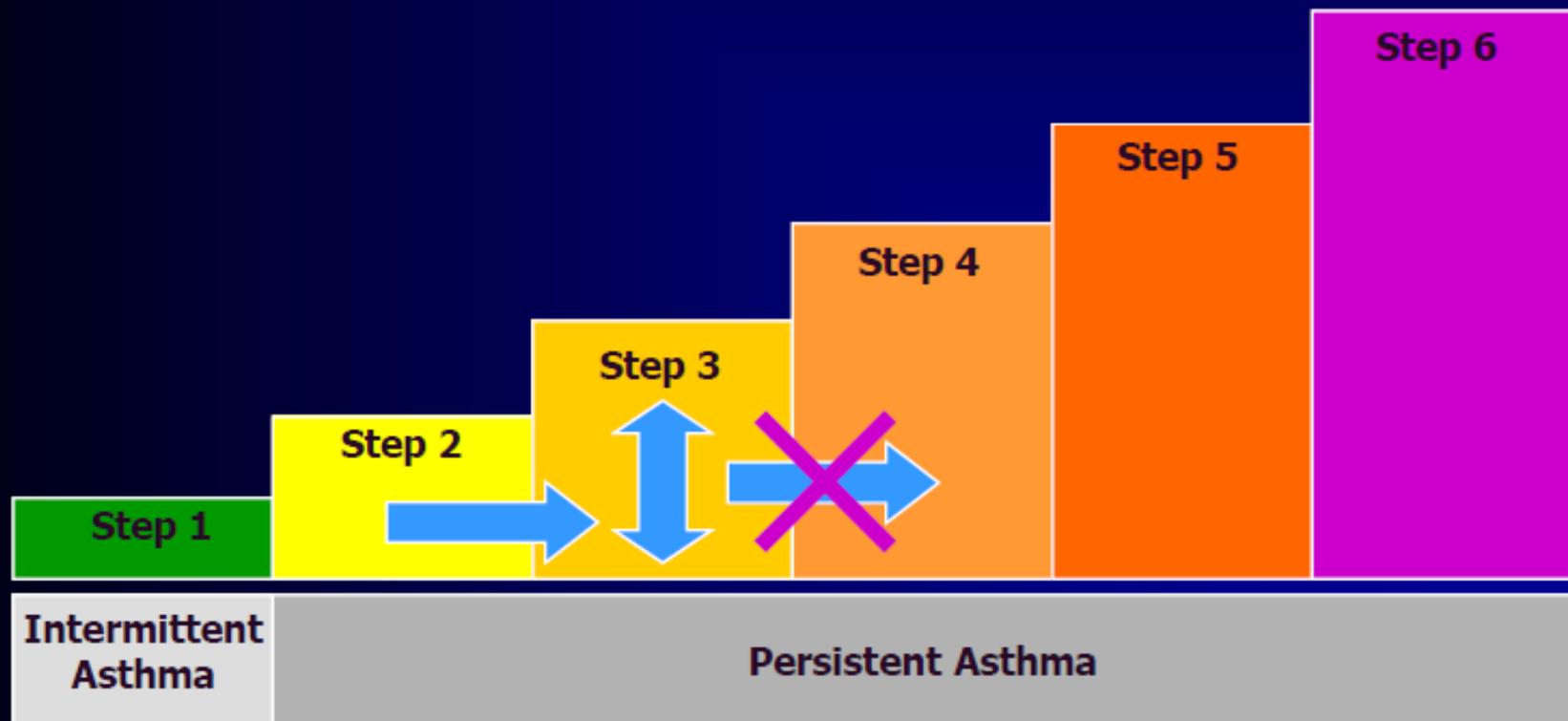
The probability of experiencing the best overall response was more than 1.5 times as likely with LABA step-up.



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.



Eight Critical Clinical Strategies

(Adapted from "Partners Putting Guidelines Into Action", 2008)

- 1) EPR3-compliant care in the medical home
- 2) Use better measures of airflow- FEV1, ratio
- 3) Deliver effective asthma education (record)
- 4) Increase inhaled corticosteroid (ICS) use
- 5) Assess & improve inhalation technique
- 6) Reduce triggers & manage co morbidities
- 7) Disseminate written asthma action plans
- 8) Collaborate across settings, actionable data

Who needs special asthma education?

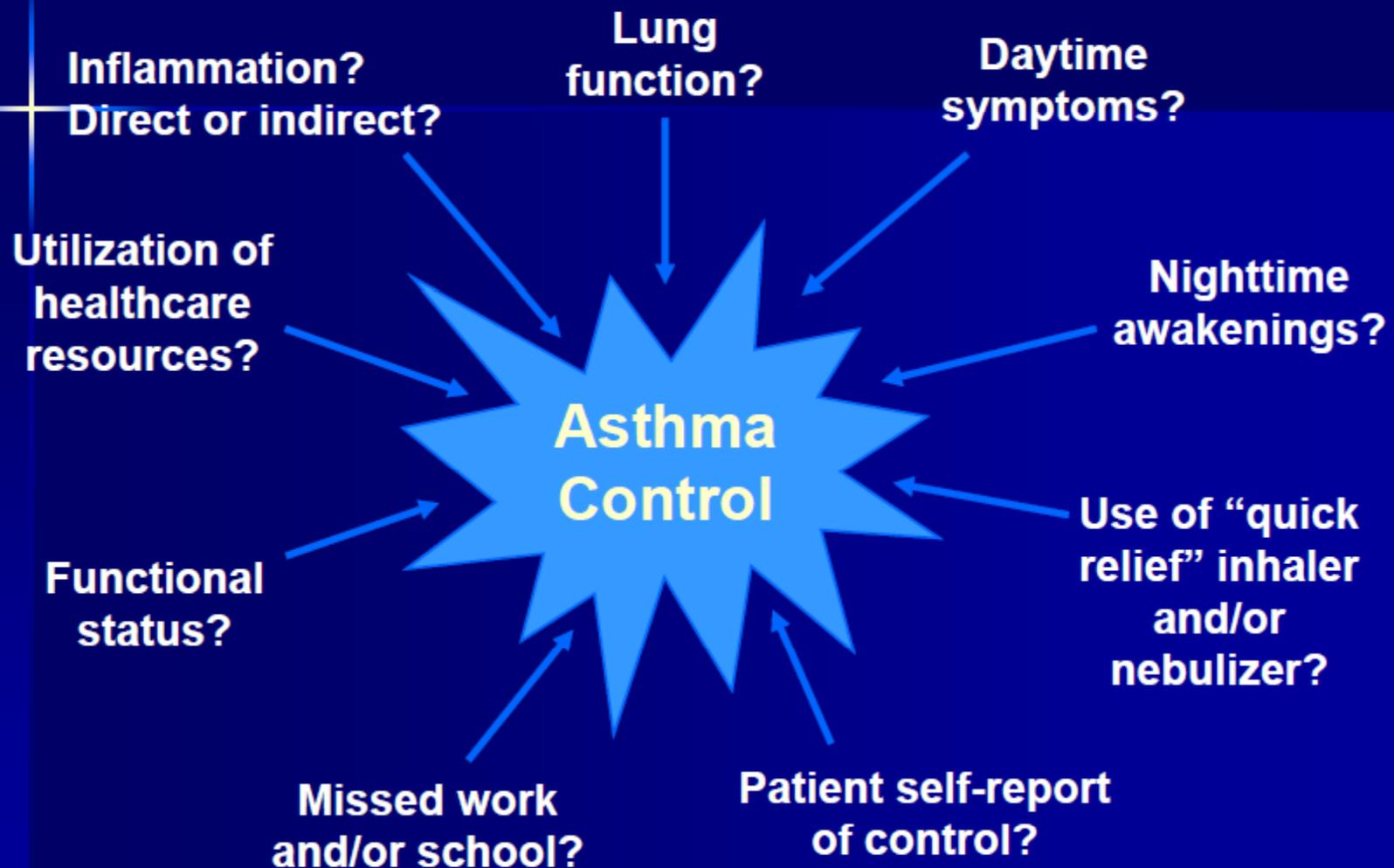
- High level of impairment
(how will you measure this?)
 - FEV1 < 80% of predicted
 - Activity impairment
 - Sleep disruption
- High risk
 - ED, hospital and oral steroid bursts
 - CARAT (Childhood Asthma Risk Assessment Tool)

Clinicians Assess Impairment & Risk

FIGURE 4-3a. ASSESSING ASTHMA CONTROL AND ADJUSTING THERAPY IN CHILDREN 4-4 YEARS OF AGE

Components of Control		Classification of Asthma Control (4-4 years of age)		
		Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Daytime symptoms	Less than once weekly	More than once weekly	More than once weekly
	Nighttime symptoms	None	Two or more times per month	Two or more times per month
	Rescue inhaler use for symptom control (not prevention of PE)	Less than once per week	Two or more times per month	Two or more times per month
Risk	Exacerbations requiring oral corticosteroids	0-1 times per year	2-3 times per year	4 or more times per year
	Future risk of asthma-related morbidity	Low	Intermediate	High
Recommended Action for Treatment (See Figure 4-3a for treatment steps.)		<ul style="list-style-type: none"> • Continue current treatment • Reassess in 1-3 months • Consider oral corticosteroids for at least 2 weeks 	<ul style="list-style-type: none"> • Step up to step 2 treatment • Reassess in 1-3 months • Step up to step 3 or 4 treatment (depending on clinical response) • For side effects, consider alternate treatment options 	<ul style="list-style-type: none"> • Consider step-up to step 4 treatment • Step up to step 5 treatment • Consider oral corticosteroids for at least 2 weeks • For side effects, consider alternate treatment options

How Can Asthma Control Be Measured?



Asthma control test is a trademark of Quality Metric Incorporated.

Asthma Control Test™ (ACT)

1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?

Score

All of the time **1** Most of the time **2** Some of the time **3** A little of the time **4** None of the time **5**

2. During the past 4 weeks, how often have you had shortness of breath?

More than once a day **1** Once a day **2** 3 to 6 times a week **3** Once or twice a week **4** Not at all **5**

3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night, or earlier than usual in the morning?

4 or more nights a week **1** 2 or 3 nights a week **2** Once a week **3** Once or twice **4** Not at all **5**

4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?

3 or more times per day **1** 1 or 2 times per day **2** 2 or 3 times per week **3** Once a week or less **4** Not at all **5**

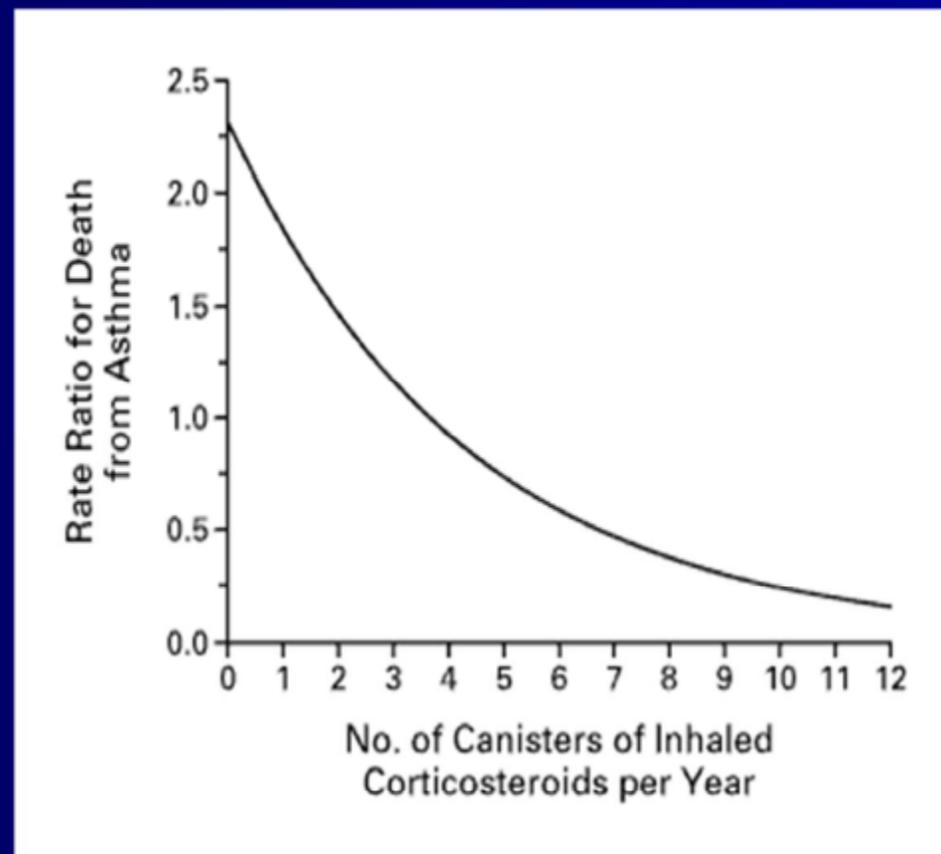
5. How would you rate your asthma control during the past 4 weeks?

Not controlled at all **1** Poorly controlled **2** Somewhat controlled **3** Well controlled **4** Completely controlled **5**

Asthma Control Test is a trademark of QualityMetric Incorporated.
Copyright 2002, QualityMetric Incorporated.

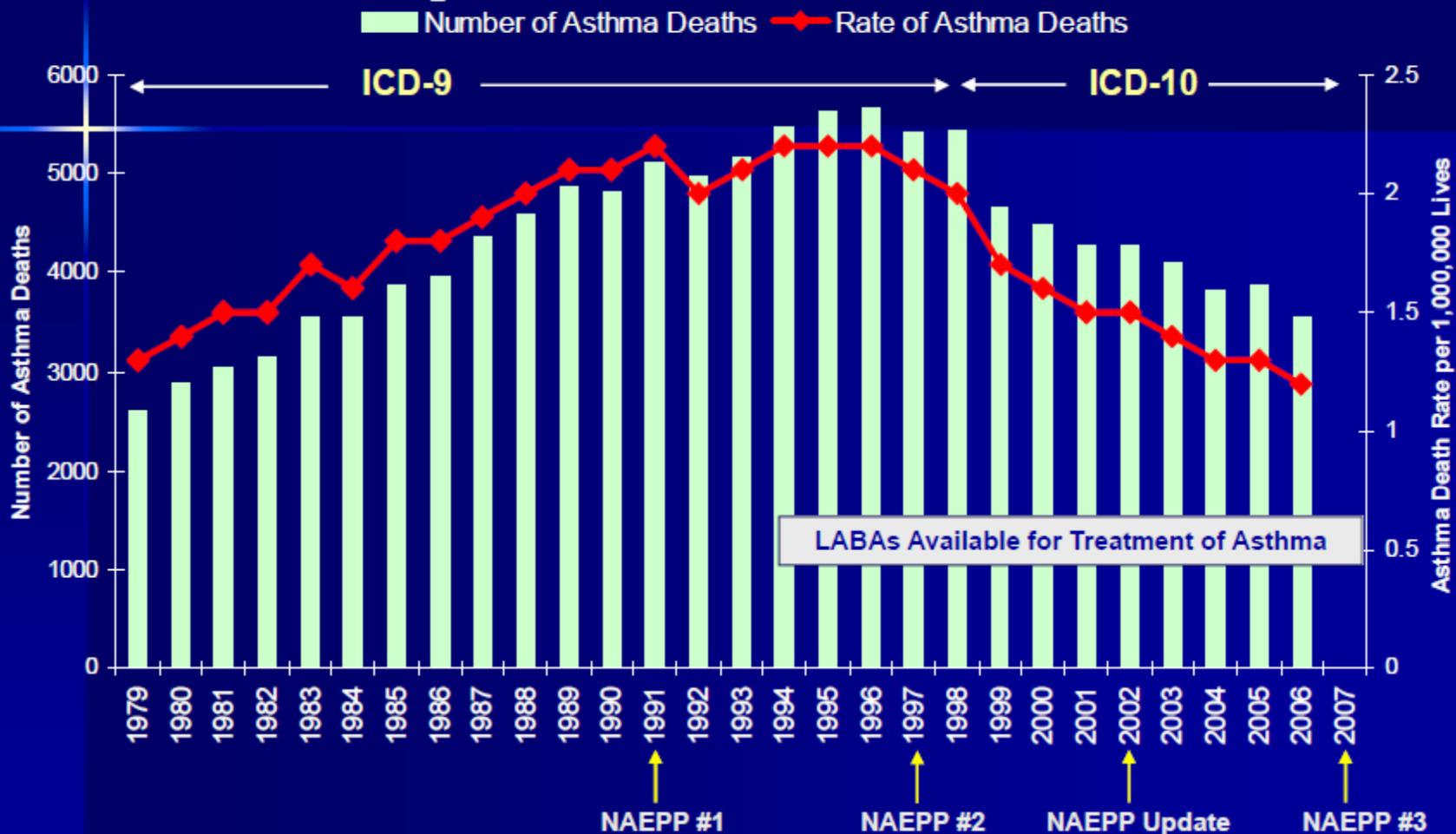
Patient Total Score

Low-Dose Inhaled Corticosteroids And The Prevention Of Death From Asthma



Suissa S, et al. *N Engl J Med* 2000;343:332-336

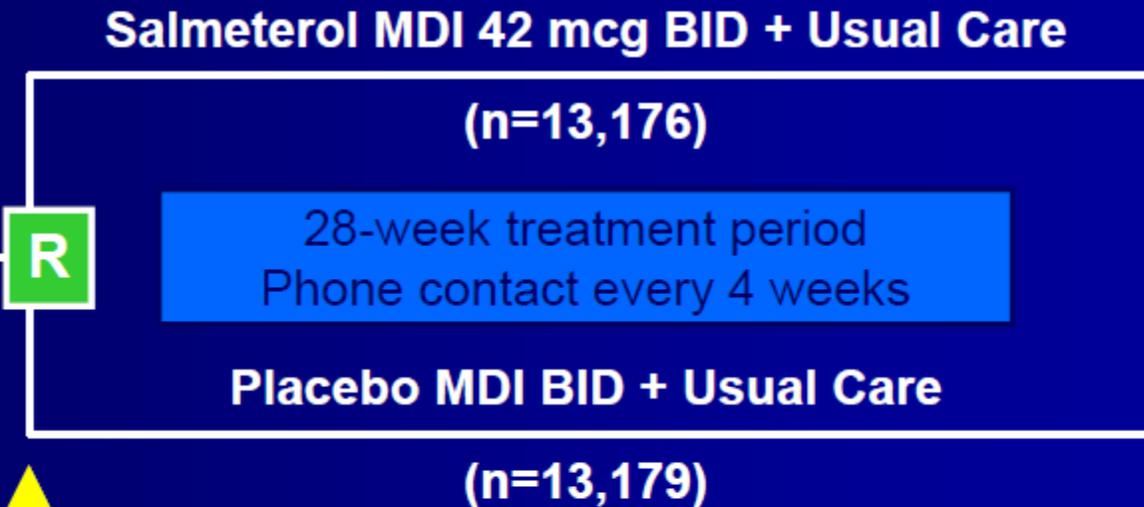
Changing Pattern in Asthma Mortality in the US



American Lung Association Epidemiology & Statistics Unit Research Program Services. *Trends in Asthma Morbidity and Mortality*. November 2007. Available at: www.lungusa.org. Accessed October 2, 2008.
 Heron MP et al. *Natl Vital Stat Rep*. 2008;56(16):1-52. (preliminary data)

SMART Study Design

- No inhaled long-acting beta₂-agonist
- ≥12 years of age



Clinic Visit

28-week supply of study medication provided

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

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)

Why Pulmonary Function Testing???

Diabetes care requires measurements of serum glucose and hemoglobin A1c

Care for hypertension requires measurements of a patients blood pressure

Treatment for dyslipidemia requires measurements of serum lipids

Lung disease care requires measurement of pulmonary function tests (PFT's)

What do PFT's measure?

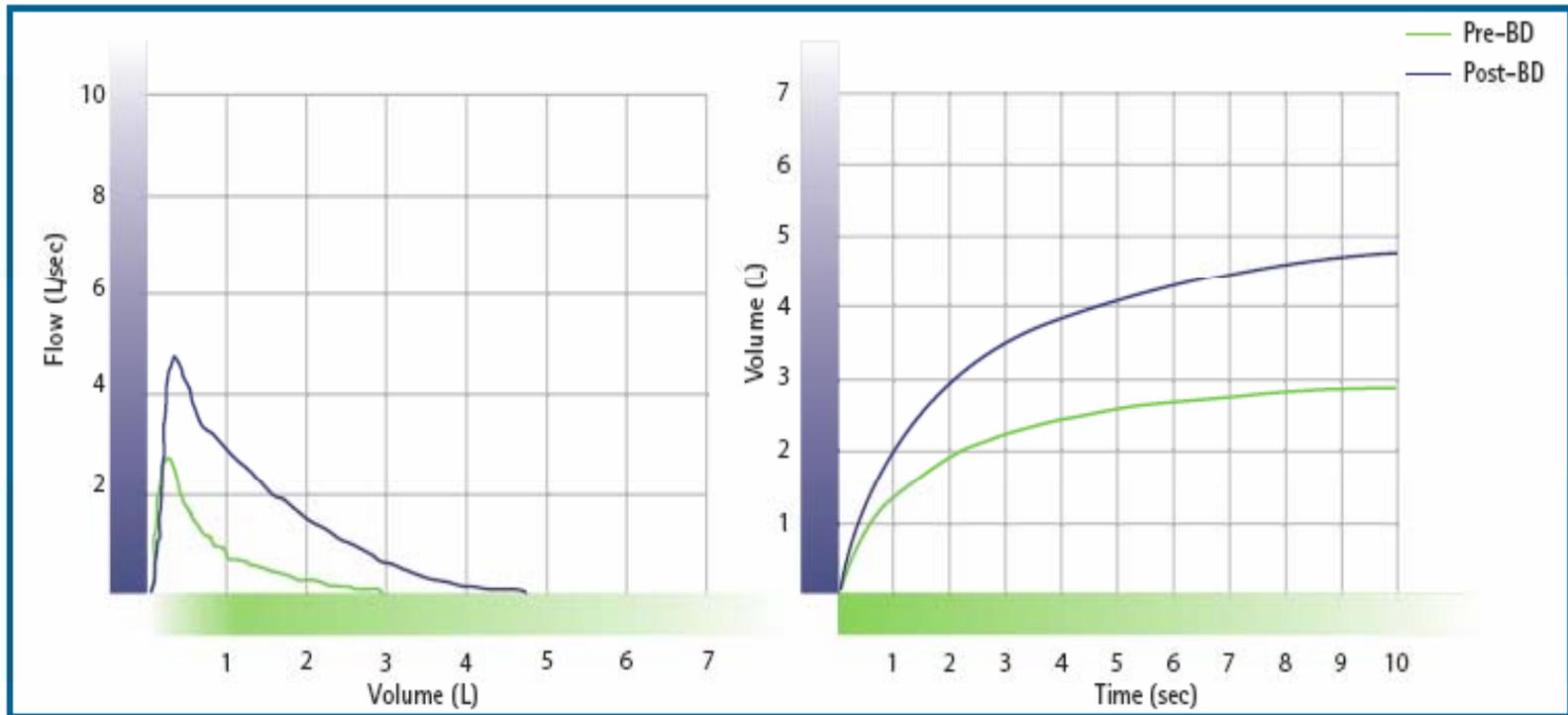
- Forced Vital Capacity (FVC)
- Forced Expiratory Volume measured over 1 second (FEV1).
- Airway obstruction is characterized by a decrease in the FEV1/FVC ratio.
- FEF 25-75 or MMEF

FEF 25-75 or MMEF

- ▣ Measures flow generated during the middle portion of expiratory effort
- ▣ Controversial value
- ▣ Indicates small airway function
- ▣ Least effort dependent result
- ▣ Also known as Maximal Mid Expiratory Flow (MMEF)
- ▣ May be more valuable in children than the FEV₁/FVC ratio

45 yo female with chronic cough, mostly at night for more than 2 years

- Occasional SOB while climbing stairs
- more recently has had cough, chest tightness and SOB walking on level ground
- 1 Pack/day smoker age 18-40, quit when her brother was diagnosed with emphysema
- Another brother had asthma in childhood, but outgrew it in high school
- Denies allergies or workplace exposures
- Lung sounds are clear



	Pre- BD*	% of Predicted	Post- BD	% of Predicted
FVC	2.9 L	57	4.7 L	92
FEV1	1.2 L	28	2.3 L	53
FEV1/FVC		41%		49%

Pattern: Obs, BD+

History is consistent with COPD, asthma, GERD, or a combination

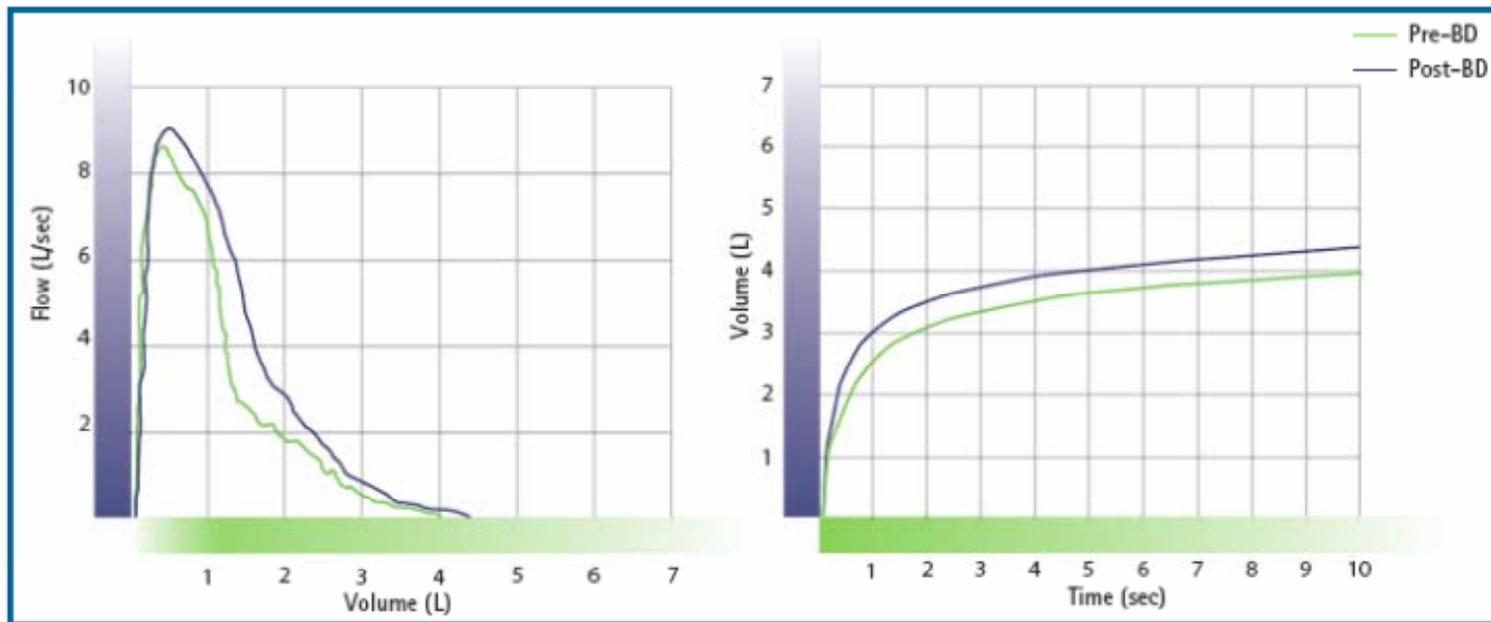
- Severe airways obstruction shown by drooping/scooping pattern of F-V curve
- Low FEV1/FVC ratio of 41% verifies this
- Consistent with COPD or asthma
- FEV1 almost doubles post B-D, confirming diagnosis of asthma
- She is likely to do well with use of an asthma controller medication

Categorizing asthma severity

- PFT's can help to determine severity of asthma and the degree of disease control
- FEV1 above 80% indicates mild asthma, or reasonable control for those on an asthma controller medication
- FEV1 between 60-80% suggests moderate persistent or poorly controlled asthma
- FEV1 below 60% suggests severe persistent or uncontrolled asthma

32 yo school teacher with lifelong HX of mild, intermittent asthma, occasional rescue inhaler needed

- URI 2 months ago with chest tightness and wheezing, responded promptly to inhaled albuterol, QID for 1 week
- Since then she reports awakening with cough and mild SOB about once per week
- PE results are normal, lungs are clear
- HX sounds like intermittent asthma, but you decide to proceed with spirometry, just to be sure



	Pre-BD	% of Predicted	Post-BD	% of Predicted
FVC	4.0 L	93	4.4 L	102
FEV1	2.5 L	71	3.0 L	86
FEV1/FVC	63%		68%	

Pattern: Obs, BD+

High peak flow of 8.5L/sec

- Bowl shaped F-V curve is characteristic of airways obstruction verified by low FEV1/FVC
- FEV1 is 71% pre-BD, increasing to 86% post-BD, a full 20% and 500ml
- Pre-BD test indicates moderate, persistent asthma
- 2 month F/U she reports exercising without coughing or chest tightness, no rescue inhaler use and PFT's are normal

Difficult Asthma 12 & Over

- Difficult cases in asthma (>12 y/o) to include interpretation of PFT's
 - Discuss what makes a difficult asthma patient
 - Discuss the treatment and follow-up of a difficult asthma patient
 - Review PFT's and explain severe asthma
- Dewey Hahlbohm, hahlbohmd@earthlink.net
- (406) 442-6934