

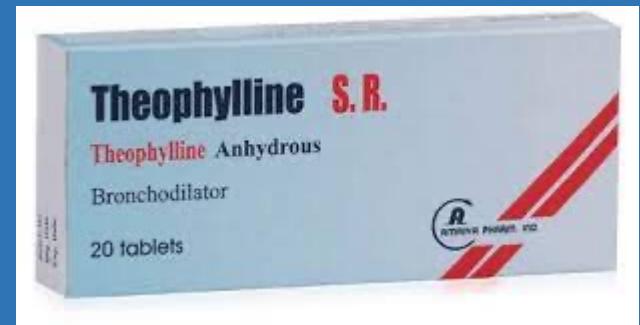
# Asthma and the CAC: What has changed

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# What has changed

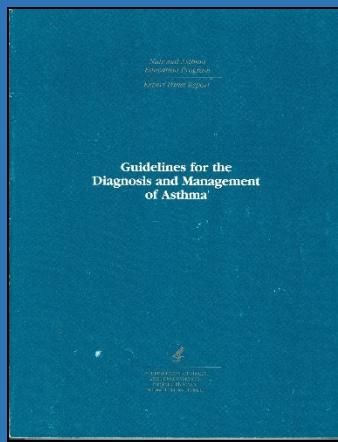
- Guidelines
  - 4 Expert Panel Reports
- Medications
  - Beta Agonists
  - Long Acting Muscarinic Agents
  - Propellants and spacers
  - Biologics
- Social Determinants of Health
  - Environment and Asthma
  - Adverse Childhood Experiences (ACES)

# Asthma Medications in 1996

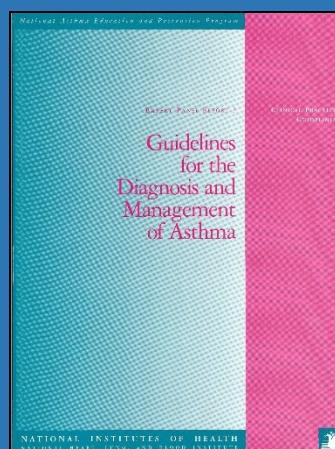


# Guidelines for Asthma

## National Asthma Education and Prevention Program (NAEPP)



1991



1997

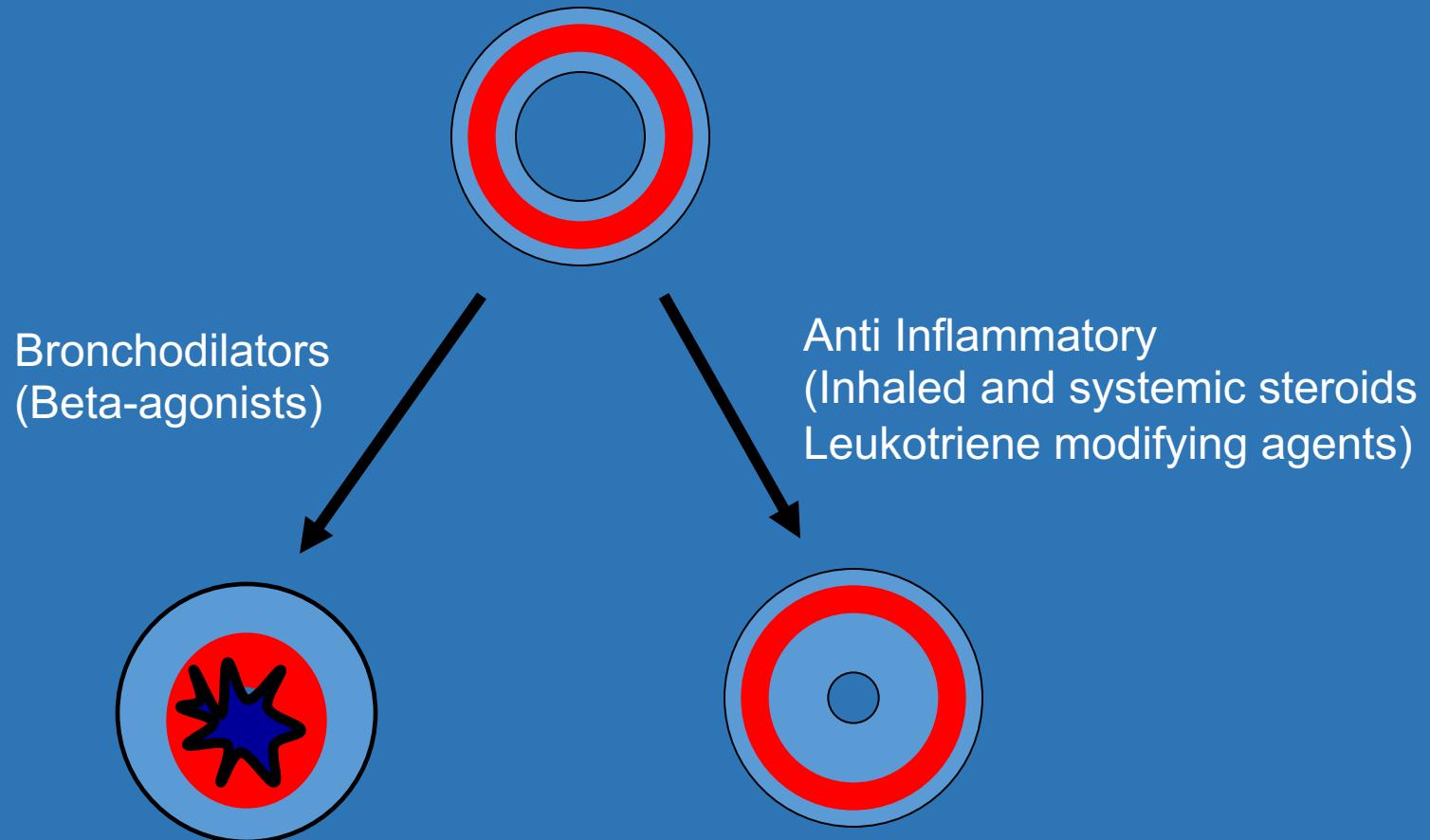


Increasing Complexity

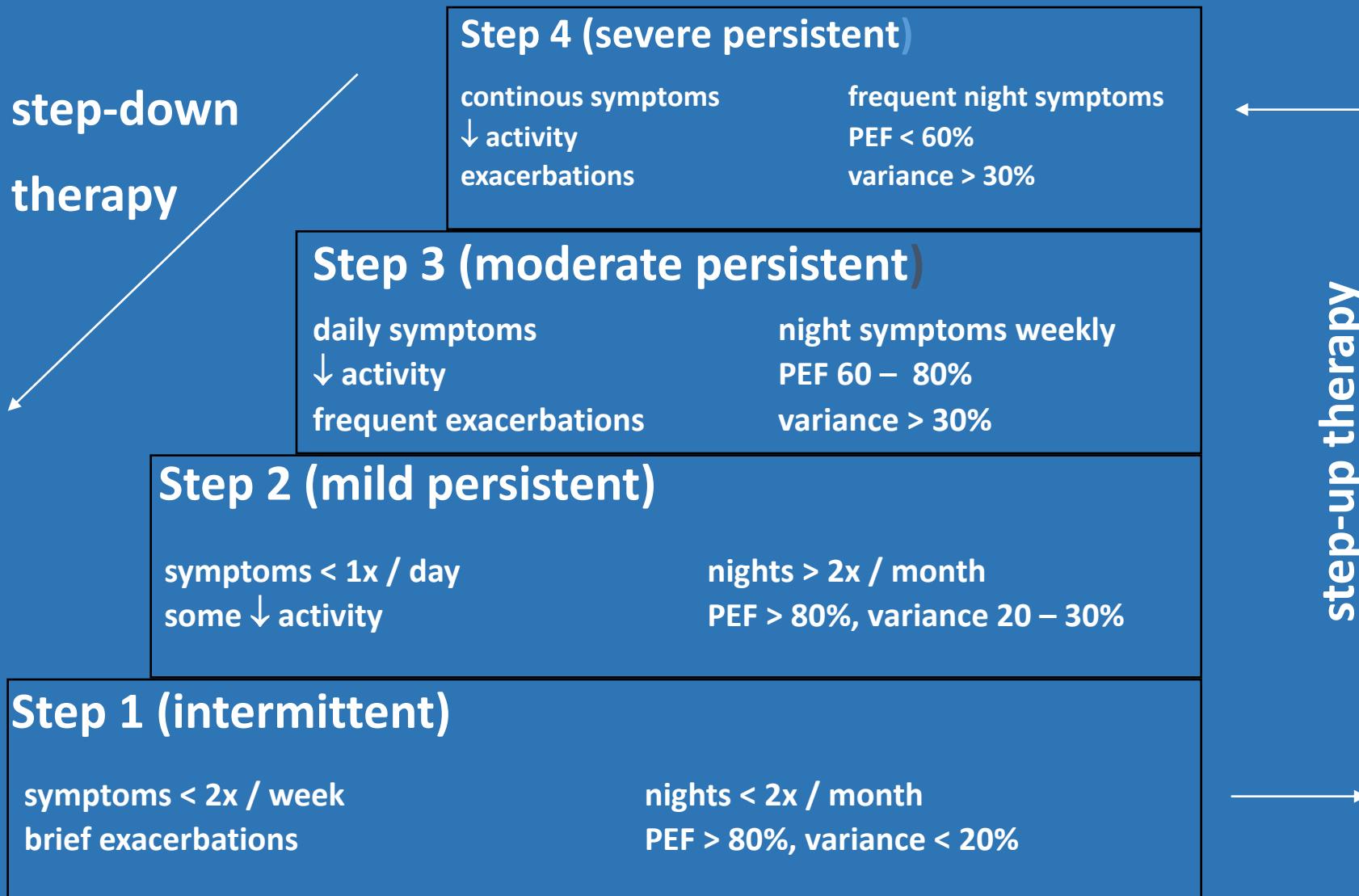
# NAEPP Guidelines: 1991-1997

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- 1991—Expert Panel Report-first edition provided evidence-based recommendations on:
  - Objective measures of lung function
  - Environmental control measures
  - Comprehensive pharmacologic therapy using a stepwise approach
  - Patient education (Partnership)
- 1997— EPR 2-updated and revised
  - Further defined the inflammatory basis of asthma
  - Recommended long-term controllers and quick-relief medications
  - Included newer controller medications



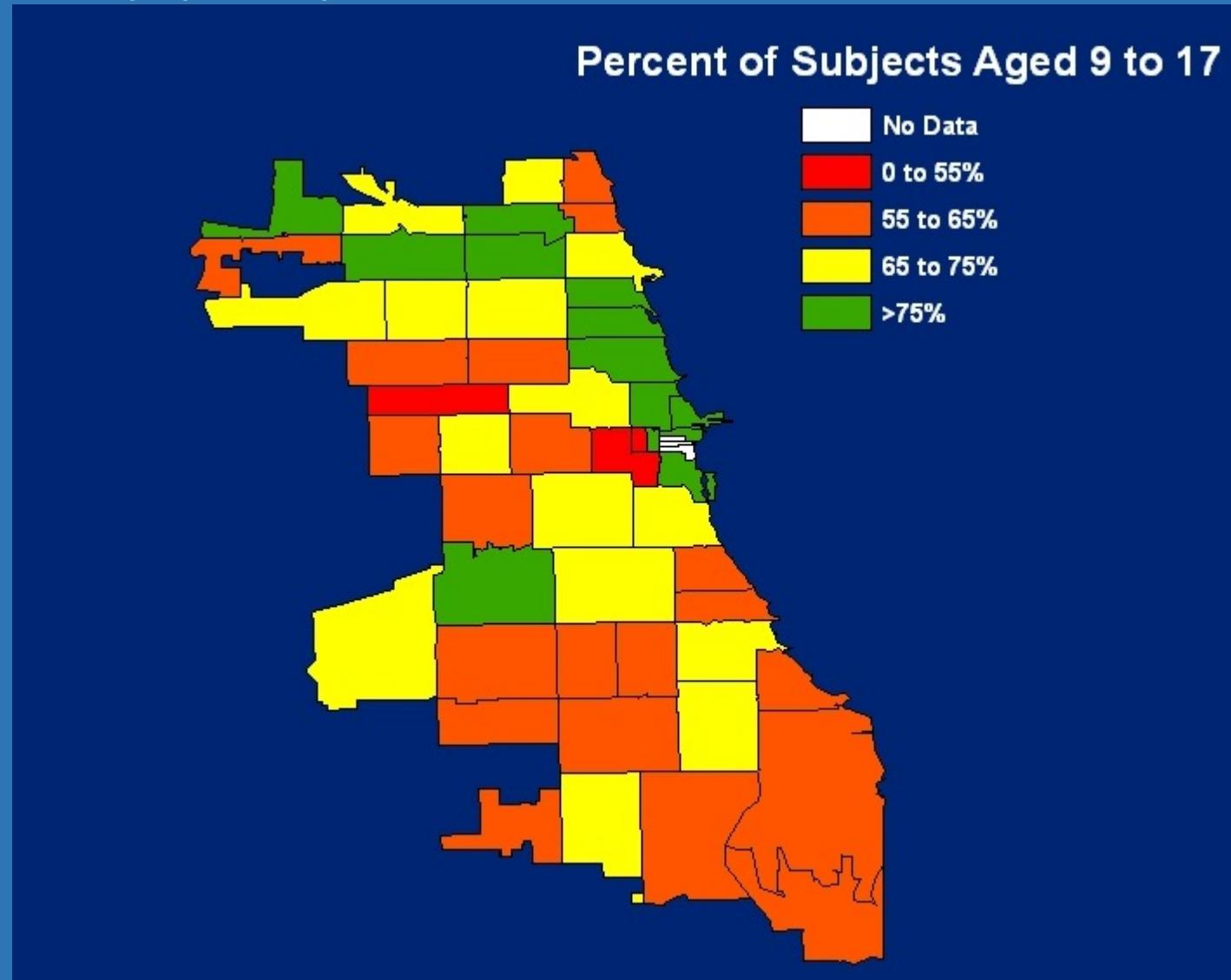
# *Approaches to the Control of Asthma*



	<b>Long Term Controller</b>	<b>Quick Relief</b>	<b>Education</b>
<b>STEP 2 Mild Persistent</b>	<p>One Daily Medication:</p> <ul style="list-style-type: none"> <li>-Anti-Inflammatory: either Inhaled Corticosteroid (Low Dose) or cromolyn or nedocromil (Children usually begin with a trial of cromolyn or nedocromil)</li> <li>-Sustained release theophylline to serum concentrations of 5-15 mc/ml is an alternative but not preferred strategy.) Zafilukast or zileuton also may be considered for patients &gt; 12 years of age, although their position in therapy is not fully established</li> </ul>	<ul style="list-style-type: none"> <li>-Short acting bronchodilator: Inhaled beta-agonist as needed for symptoms.</li> <li>-Intensity of treatment will depend on severity of exacerbation</li> <li>-Use of short acting beta-agonists on a daily basis or increasing use indicates the need for additional long term controller therapy</li> </ul>	<p>Step 1 actions plus:</p> <ul style="list-style-type: none"> <li>-Teach self monitoring</li> <li>-Refer to group education if available</li> <li>-Review and update self management plan</li> </ul>
<b>STEP 1 Mild Intermittent</b>	-No daily medication needed	<ul style="list-style-type: none"> <li>-Short acting bronchodilator: Inhaled beta-agonist as needed for symptoms.</li> <li>-Intensity of treatment will depend on severity of exacerbation</li> <li>-Use of short acting beta-agonists on a daily basis or increasing use indicates the need for additional long term therapy</li> </ul>	<ul style="list-style-type: none"> <li>-Teach basic facts about asthma</li> <li>-Teach inhaler/spacer/holding chamber technique</li> <li>-Discuss roles of medications</li> <li>-Develop self-management plan for when and how to take rescue actions especially in patients with a history of severe exacerbations</li> <li>-Discuss appropriate environmental control measures to avoid exposure to known allergens and irritants.</li> </ul>

	<b>Long Term Controller</b>	<b>Quick Relief</b>	<b>Education</b>
<b>STEP 4 Severe Persistent</b>	<p>Daily Medication:</p> <ul style="list-style-type: none"> <li>-Anti-Inflammatory: Inhaled Corticosteroid (High Dose) AND</li> <li>-Long-acting bronchodilator: Either long acting inhaled beta agonist, sustained release theophylline, or long acting beta agonist tablets.</li> <li>AND</li> <li>-Corticosteroid tablets or syrup Long term (make repeat attempts to reduce systemic steroids and maintain control with high dose inhaled steroids)</li> </ul>	<ul style="list-style-type: none"> <li>-Short acting bronchodilator: Inhaled beta-agonist as needed for symptoms.</li> <li>-Intensity of treatment will depend on severity of exacerbation</li> <li>-Use of short acting beta-agonists on a daily basis or increasing use indicates the need for additional long term therapy</li> </ul>	<p>Steps 2 and 3 actions plus:</p> <ul style="list-style-type: none"> <li>-Refer to individual education/counseling</li> </ul>
<b>STEP 3 Moderate Persistent</b>	<p>Daily Medications:</p> <ul style="list-style-type: none"> <li>-Either</li> <li>Anti-Inflammatory: Inhaled Corticosteroid (Medium dose)</li> <li>OR</li> <li>Inhaled corticosteroid (low-medium dose) and add a Long acting bronchodilator especially for nighttime symptoms; either long acting Inhaled beta2-agonists, sustained-release theophylline or long acting beta2 agonist tablets</li> </ul> <p>-If needed</p> <ul style="list-style-type: none"> <li>Ant-Inflammatory: Inhaled corticosteroids (medium-high dose)</li> <li>AND</li> <li>Long-acting bronchodilator, especially for nighttime symptoms; either long acting Inhaled beta2-agonists, sustained-release theophylline or long acting beta2 agonist tablets.</li> </ul>	<ul style="list-style-type: none"> <li>-Short acting bronchodilator: Inhaled beta-agonist as needed for symptoms.</li> <li>-Intensity of treatment will depend on severity of exacerbation</li> <li>-Use of short acting beta-agonists on a daily basis or increasing use indicates the need for additional long term therapy</li> </ul>	<p>Step 1 actions plus:</p> <ul style="list-style-type: none"> <li>-Teach self monitoring</li> <li>-Refer to group education if available</li> <li>-Review and update self management plan</li> </ul>

# Geocoding: Appropriate use of ICS



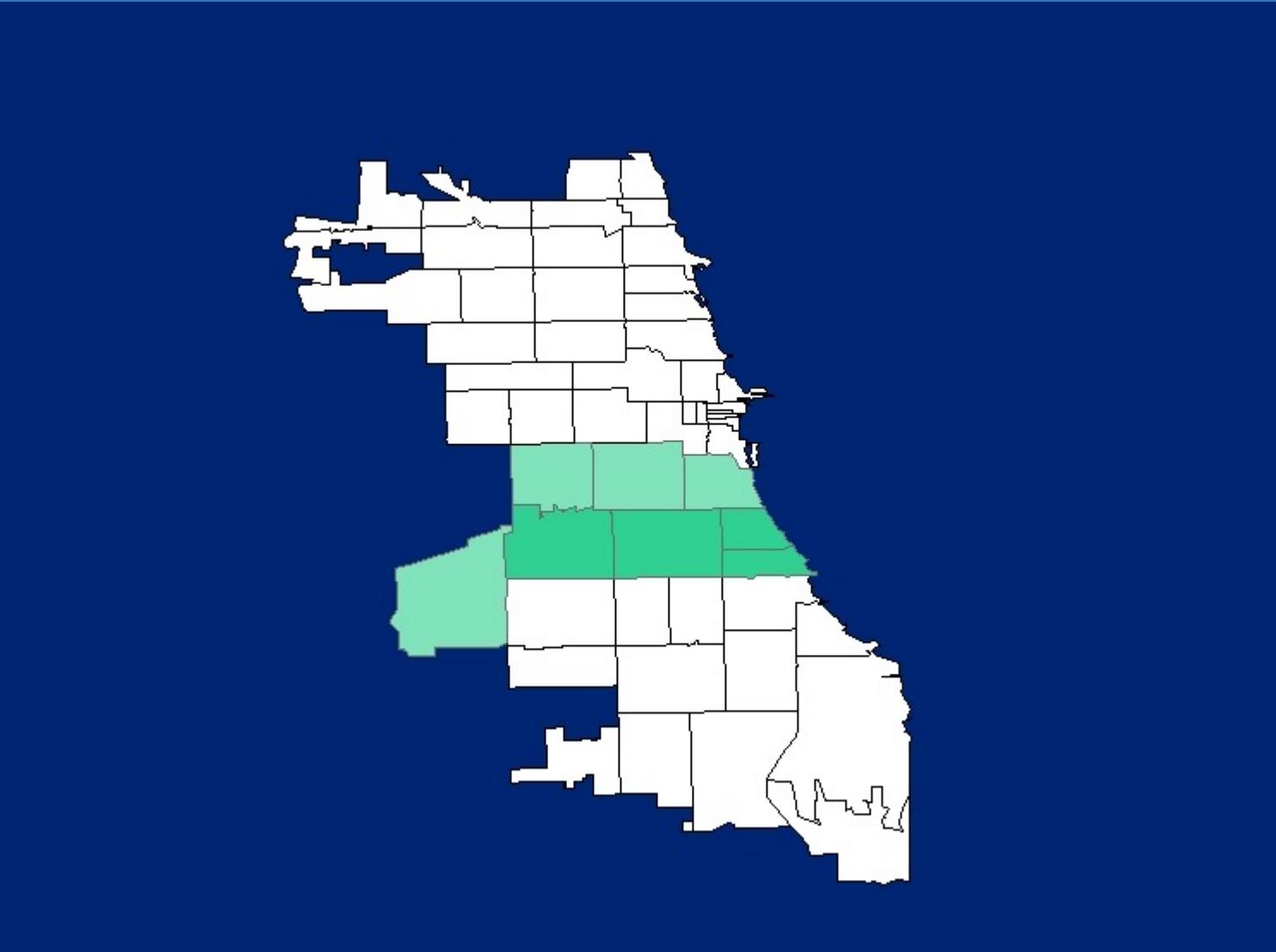
Source: Walgreens Health Initiatives

# Chicago Community Asthma Program (CAPP)

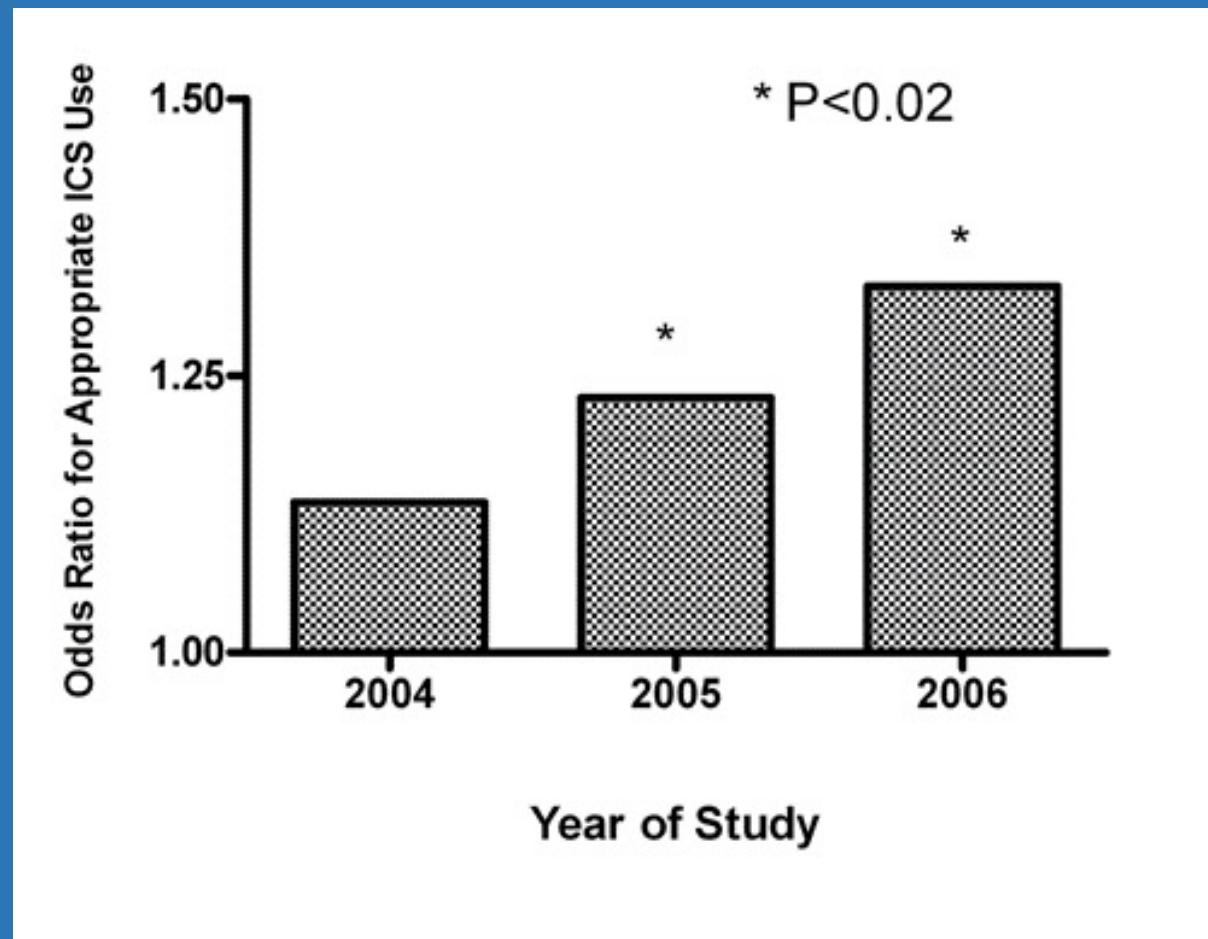
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- Multifaceted Program Aimed at:
  - Improving Identification of Individuals with Asthma
  - Introduction of Interventions Designed to Better Manage Asthma Care

# Intervention Area: The Region Formerly Known as 4



# Odds Ratio for Individuals Aged 5-9

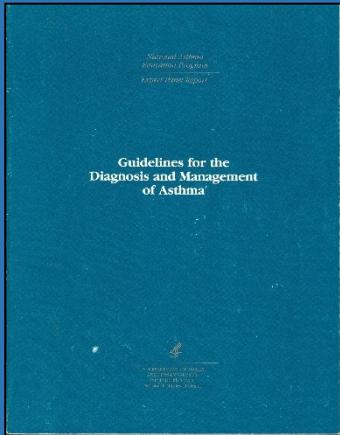


*Journal of Urban Health; 2011; 88 S1:144-155*

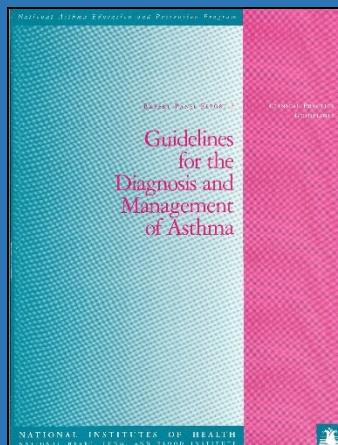
# Guidelines for Asthma

## National Asthma Education and Prevention Program (NAEPP)

Evidence from the  
medical literature



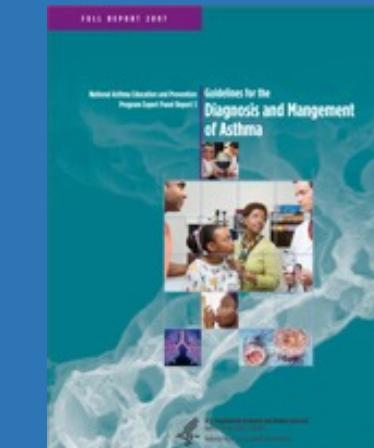
1991



1997



2002



2007

Increasing Complexity

# NAEPP Guidelines: 2002-2007

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- 2002—Update on selected topics
  - Use of ICS in children
  - Combination therapies
  - Use of antibiotics
  - Monitoring and prevention
- 2007—EPR3
  - Better understanding of pathophysiology
    - Emphasizes importance of allergens in morbidity and control of asthma
    - Outlines testing methods for allergen detection
  - Includes newer asthma therapies, such as anti-IgE therapy, for defined roles in treatment
  - Emphasizes control over severity assessment

# Asthma Assessment and Monitoring: Key Differences from 1997 and 2002 Expert Panel Reports

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- Key elements of assessment and monitoring
  - Severity
  - Control
  - Responsiveness to treatment
- Severity emphasized for initiating therapy
- Control emphasized for monitoring and adjusting therapy
- Severity and control defined in terms of 2 domains
  - Impairment
  - Risk

# Severity, Control and Responsiveness

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- **Severity**

- Intrinsic intensity of the disease process
- Guides clinical decisions during initial evaluation and before the start of controller therapy
- Most easily measured when not on long-term therapy

- **Control**

- Degree to which symptoms, impairment, and risk of exacerbations are minimized and the goals of therapy are met
- Used to guide whether to maintain or adjust therapy

- **Responsiveness**

- Ease with which asthma control is achieved by therapy
- Responsiveness to asthma treatment is highly variable

# Long Term Management of Asthma

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- Incorporate four components of care
  - Assessment and monitoring
  - Education
  - Intervention on environment and comorbid conditions
  - Medications
- Initiate therapy based on asthma severity
- Adjust therapy on asthma control

# Additional Modification in the Stepwise Approach

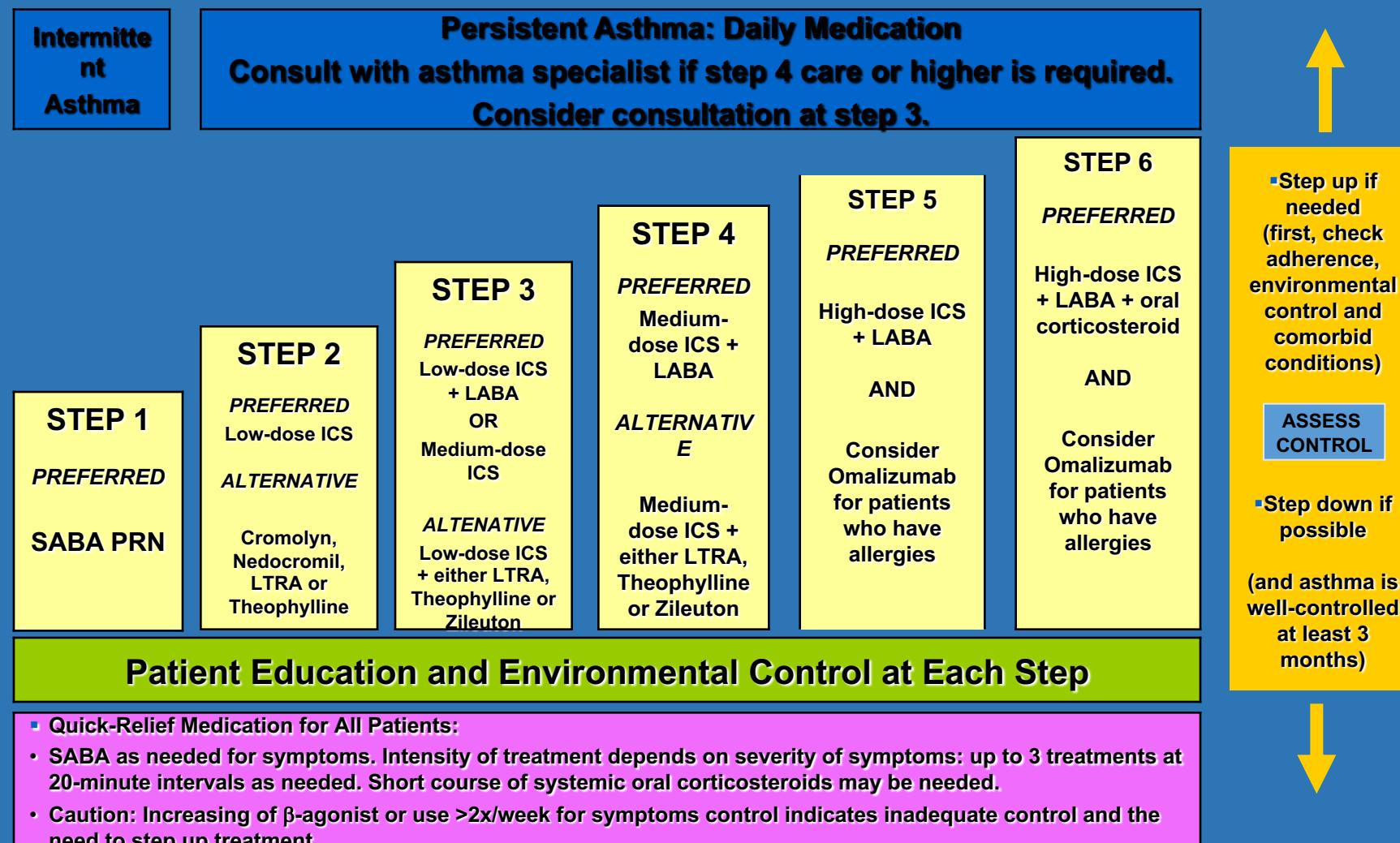
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- New Age Groups
  - 0-4
  - 5-11
  - 12 and up
- Increase in the number of steps: 6 vs. 4
- Elimination of “Mild” when describing intermittent patients
- Redefinition of preferred medications within each step
  - ICS remains preferred long term control therapy
  - Despite LABA fears combined LABA/ICS is equally preferred to increasing ICS dose
  - Anti-IgE therapy added at steps 5 and 6 in those with clear allergic component

# Classifying Severity in Patients $\geq$ 12 Years Not Currently Taking Long-Term Controllers

Components of Severity		Classification of Asthma Severity			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment	Symptoms	$\leq 2$ days/week	$>2$ days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	$\leq 2$ /month	3-4/month	$>1$ /week but not nightly	Often 7/week
	Short-acting beta <sub>2</sub> -agonist use for symptom control (not prevention of EIB)	$\leq 2$ days/week	$>2$ days/week but not $>1$ /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"> <li>▪ Normal FEV<sub>1</sub> between exacerbations</li> <li>▪ FEV<sub>1</sub> <math>&gt;80\%</math> predicted</li> <li>▪ FEV<sub>1</sub>/FVC normal</li> </ul>	<ul style="list-style-type: none"> <li>▪ FEV<sub>1</sub> <math>&lt;80\%</math> pred</li> <li>▪ FEV<sub>1</sub>/FVC reduced 5%</li> </ul>	<ul style="list-style-type: none"> <li>▪ FEV<sub>1</sub> <math>&gt;60-80\%</math> but <math>&lt;80\%</math> pred</li> <li>▪ FEV<sub>1</sub>/FVC reduced 5%</li> </ul>	<ul style="list-style-type: none"> <li>▪ FEV<sub>1</sub> <math>&lt;60\%</math> predicted</li> <li>▪ FEV<sub>1</sub>/FVC reduced <math>&gt;5\%</math></li> </ul>
Risk	Exacerbations (consider frequency and severity)	0-2/year $>2$ in 1 year Frequency and severity may fluctuate over time for patients in severity category Relative annual risk of exacerbations may be related to FEV <sub>1</sub>			
Recommended Step for Initiating Therapy		Step 1	Step 2	Step 3	Step 4 or 5
		← and consider short course of systemic oral corticosteroids			
		In 2-6 weeks, evaluate level of asthma control, and adjust therapy accordingly.			

# Stepwise Approach for Managing Asthma in Patients $\geq$ 12 Years of Age

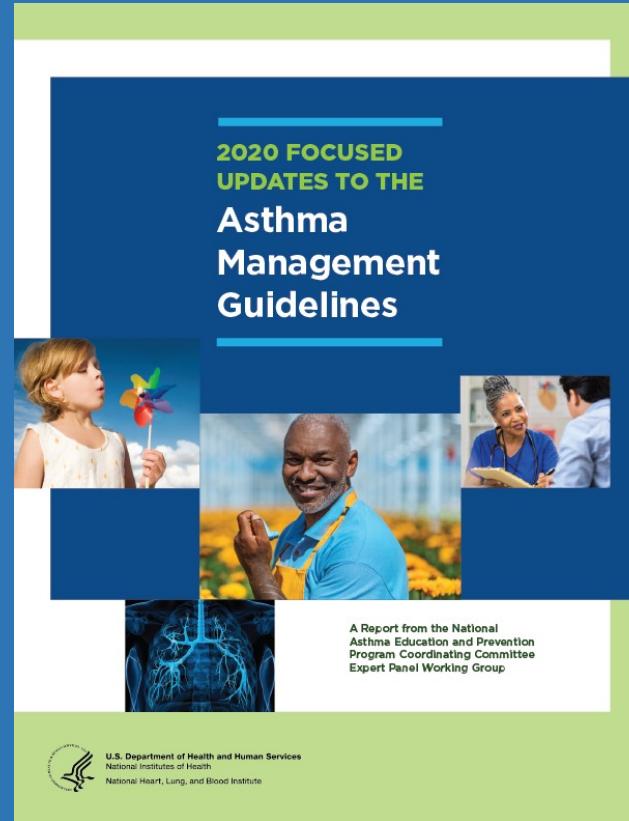


Components of Severity		Classification of Asthma Control		
		Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Nighttime awakenings	≤2/month	1-3/month	≥4/month
	Short-acting beta <sub>2</sub> -agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
	Interference with normal activity	None	Some limitation	Extremely limited
	FEV <sub>1</sub> 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	0-1 per year	2-3 per year	>3 per year
	Reduction in lung growth	Evaluation requires long-term follow-up 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 overall assessment of risk.		
Recommended Action for Treatment		<ul style="list-style-type: none"> <li>▪ Maintain current step.</li> <li>▪ Consider step down if well controlled for at least 3 months.</li> </ul>	<ul style="list-style-type: none"> <li>▪ Step up at least 1 step and</li> <li>▪ Reevaluate in 2-6 weeks.</li> <li>▪ For side effects: consider alternative treatment options.</li> </ul>	<ul style="list-style-type: none"> <li>▪ Consider short course of systemic oral corticosteroids</li> <li>▪ Step up 1-2 steps and</li> <li>▪ Reevaluate in 2 weeks.</li> <li>▪ For side effects: consider alternative treatment options</li> </ul>

# EPR-4

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- Initially met 2018
- Report Released 2020
- Update on six specific topics
- Used GRADE methodology
- Some overlap with GINA



# Specific recommendations 12+ years old

Step	NAEPP 2020 Guideline Update	GINA 2020 Report
1	<i>Not reviewed</i>	PRN low-dose ICS-formoterol
2	Daily low-dose ICS and PRN SABA <i>or</i> PRN low-dose ICS and PRN SABA	Daily low-dose ICS and PRN SABA <i>or</i> PRN low-dose ICS-formoterol
3	Daily low-dose ICS-formoterol ( <i>maintenance + reliever</i> )	Daily low-dose ICS and PRN SABA <i>or</i> Daily low-dose ICS-formoterol ( <i>maintenance + reliever</i> )
4	Daily medium-dose ICS-formoterol ( <i>maintenance + reliever</i> )	Daily medium-dose ICS-LABA and PRN SABA <i>or</i> Daily medium-dose ICS-formoterol ( <i>maintenance + reliever</i> )
5	Daily medium- to high-dose ICS-LABA + LAMA and PRN SABA	Daily high-dose ICS-LABA and refer for phenotypic assessment and add-on therapy
6	<i>Not reviewed</i>	N/A

# Long Acting Beta Agonists: Black Box Warning!

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## WARNING: ASTHMA-RELATED DEATH

See full prescribing information for complete boxed warning.

- Long-acting beta<sub>2</sub>-adrenergic agonists (LABA), such as salmeterol, the active ingredient in SEREVENT DISKUS, as monotherapy (without inhaled corticosteroids [ICS]) increase the risk of asthma-related death. A U.S. trial showed an increase in asthma-related deaths in subjects receiving salmeterol (13 deaths out of 13,176 subjects treated for 28 weeks on salmeterol versus 3 out of 13,179 subjects on placebo). When LABA are used in fixed -dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone. (5.1)
- Prescribe SEREVENT DISKUS only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on an ICS. Do not use SEREVENT DISKUS for patients whose asthma is adequately controlled on low- or medium-dose ICS. (1.1, 5.1)
- Available data from controlled clinical trials suggest that LABA as monotherapy increase the risk of asthma-related hospitalization in pediatric and adolescent patients. (5.1)

# As needed ICS: ICS-formoterol

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- SYGMA 1&2
  - Participants: mild persistent asthma 12+ years old
  - Intervention: PRN budesonide-formoterol 200/6 µg
  - Outcomes: ↓ exacerbations, ↓ ICS dose

# Single inhaler therapy: ICS-formoterol

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- Numerous studies in school-age children (6+ years old), adolescents, and adults examining fixed dosing versus adjustable maintenance dosing (“SMART” therapy)

# Role of tiotropium

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# Tiotropium – The Basics

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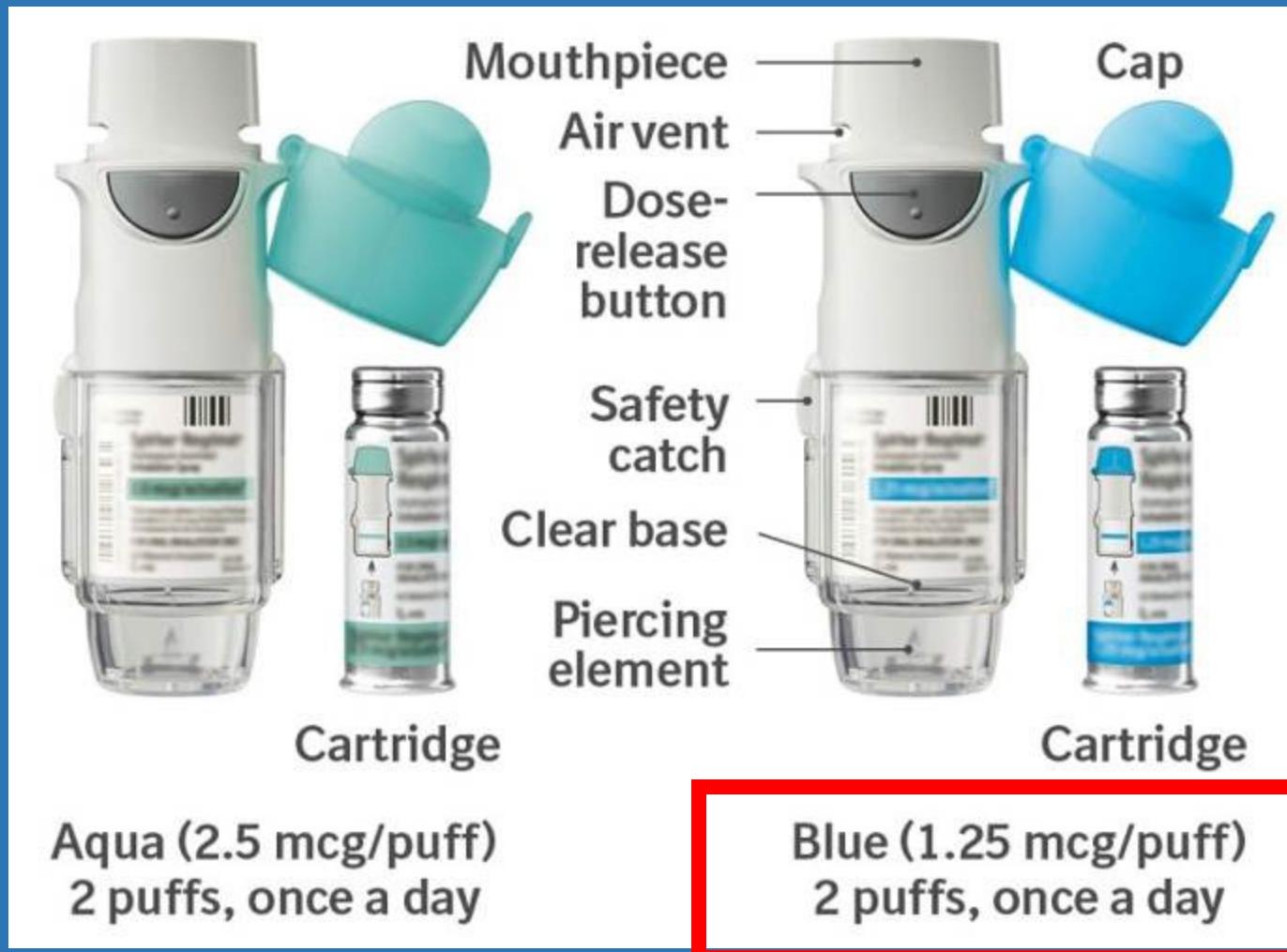
- Oldest LAMA agent, blocks acetylcholine at M<sub>3</sub> receptor on bronchial smooth muscle
- Guidelines
  - Step 4/5 in GINA 2016
  - Not included in EPR-3 2007

LAMA = long-acting muscarinic antagonist

EPR-3 = Third Expert Panel Report of the National Heart, Lung, and Blood Institute

GINA = Global Initiative for Asthma

DPI: dry powder inhaler



# Tiotropium in Pediatrics

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- FDA approved for ages 6 years and older
- Primary literature in adolescents demonstrates the following
  - Lack of dose dependent response
  - Inconsistent outcomes from study to study
  - Added benefit in severe asthma, but perhaps not at the FDA approved 1.25 mcg strength

Respir Med. 2014;108:1268-76.  
Ann Allergy Asthma Immunol. 2015; 115(3):211-6.  
J Allergy Clin Immunol. 2016; 138:441-450.  
Eur Respir J. 2017; 11;49(1) pii: 1601100.

# Tiotropium in Adults

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- Response may be predicted by:
  - Pharmacogenetic data (Arg/Arg or 16 Arg/Gly polymorphism of the *ADRB2* gene)
  - Sputum neutrophils
- Expected outcomes:
  - Reduced exacerbation frequency in those on medium to high dose ICS + LABA
  - Improved peak and trough FEV<sub>1</sub> at week 12 in those on low to medium dose ICS

N Engl J Med. 2012. 367:1198-207.

Ann Pharmacother. 2013. 47:704-13.

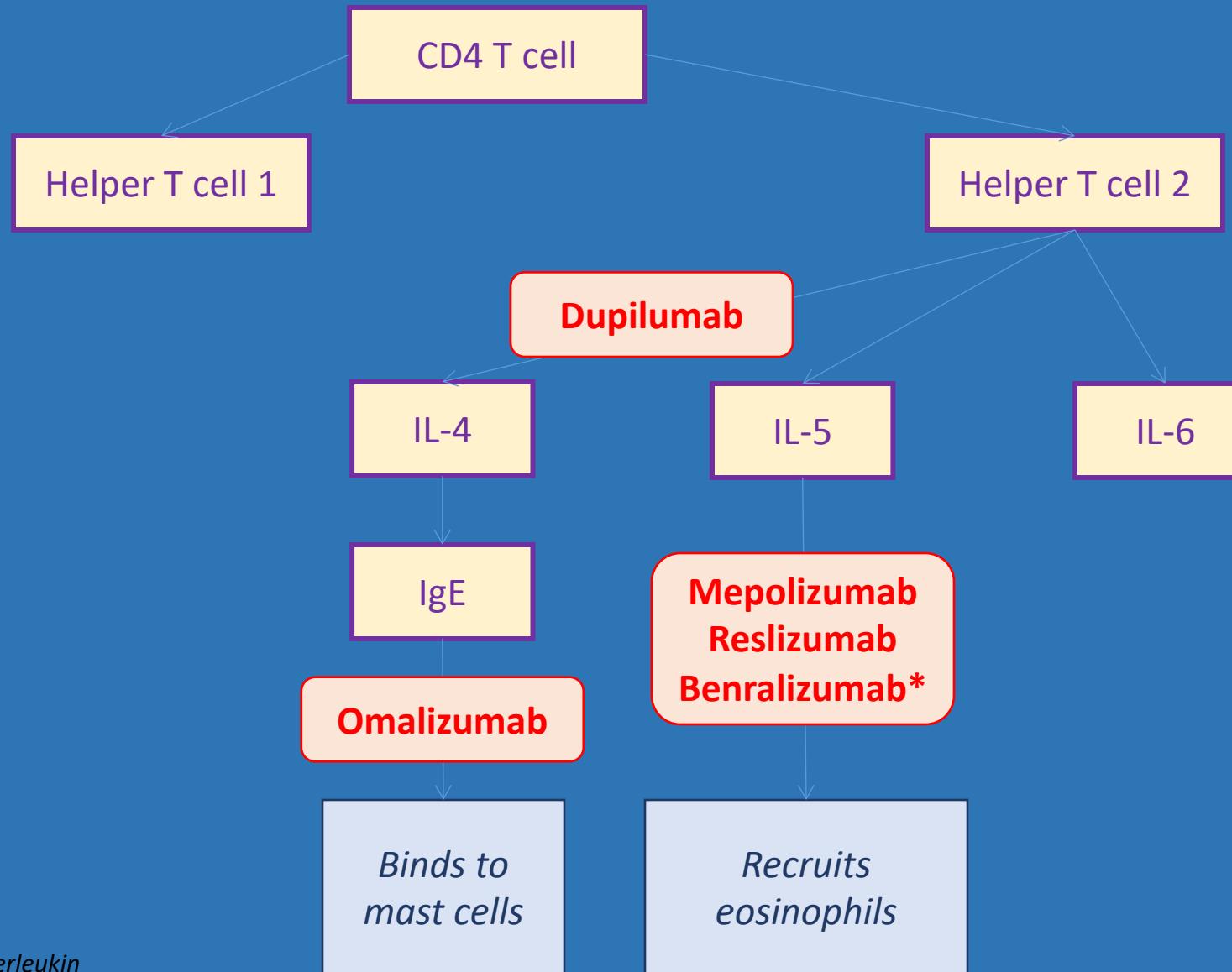
J Allergy Clin Immunol Pract. 2016. 4:104-13.

# Biologics at a Glance

**Table 5.** Safety and Efficacy Comparison Among Current Biologics

Medication	Asthma Control	AAER	FEV <sub>1</sub>	Eosinophil Count	Quality of Life	OCS	Affected Phenotype
Omalizumab <sup>13,31</sup>	↑	↓	--	—	↑	↓	Allergic asthma
Mepolizumab <sup>16-18,31</sup>	↑	↓	↑/--*	↓	--	↓	Eosinophilic asthma
Benralizumab <sup>21-23,31</sup>	--	↓	↑/--†	↓	--	↓	Eosinophilic asthma
Reslizumab <sup>6,31,32</sup>	↑	↓	↑	↓	↑	↓	Eosinophilic asthma
Dupilumab <sup>25-28,31</sup>	↑	↓	↑	↓‡	↑	↓	Allergic asthma§ Eosinophilic asthma OCS-dependent asthma

# Mechanisms of Action



# CFC Inhalers

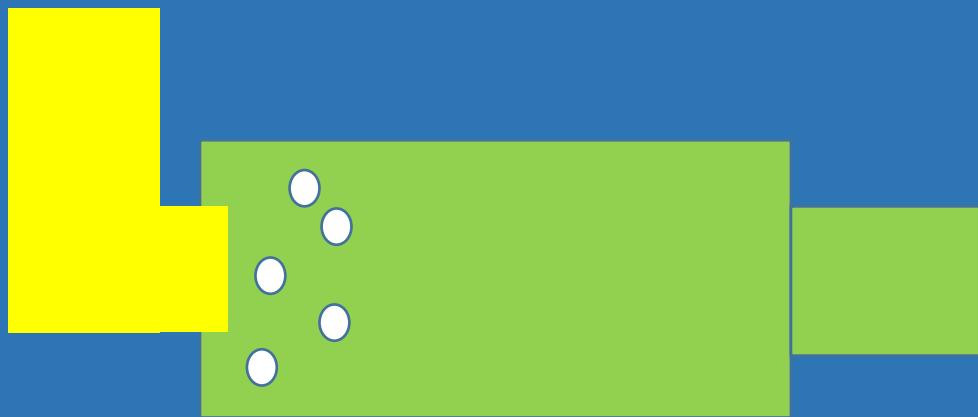
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- Chlorofluorocarbons (CFCs) traditionally used in inhalers
- 1987 Banned by the Montreal Protocol for most applications
- Metered dose inhalers given a grace period
- 2009 FDA bans the use of CFC inhalers
- HFA replaced CFCs as the propellant for inhalers
- Generic Albuterol disappears from the market.

# Spacer Devices and HFA Inhalers

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- CFC inhalers with relatively large droplet size
- Spacers provided time and space for droplets to evaporate
- HFA inhalers re-designed with a smaller particle size
- Spacers no longer universally required



# A Multiplicity of Dry Powder Inhalers

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# Asthma and the Environment

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- All of the NAEPP Guidelines Emphasized Allergy Interventions
- Home Environmental Intervention
- Outdoor environment
  - Ozone
  - Particulates

# Adverse Childhood Experiences (ACE)

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- ACES results in changes in inflammation
- Correlation with ACE exposure and Childhood Asthma
- Additive to Environmental Factors
- Approaches to mitigate ACEs have been identified

# What has changed?

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- Treatment approaches
- Medications
- Devices
- But the need for the CAC has not changed!