

# Asthma Medications



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# Asthma Guidelines

- NIH/NHLBI (USA) <http://www.nih.gov/guidelines/asthma/ashtgdln.pdf>.
- GINA (Global Initiative for Asthma) <http://www.ginasthma.com>
- Canadian <http://www.cma.ca/cmaj/vol-161/issue-11/asthma/consensus.pdf>
- National Asthma Council (Australia) <http://www.nationalasthma.org.au/publications.html>

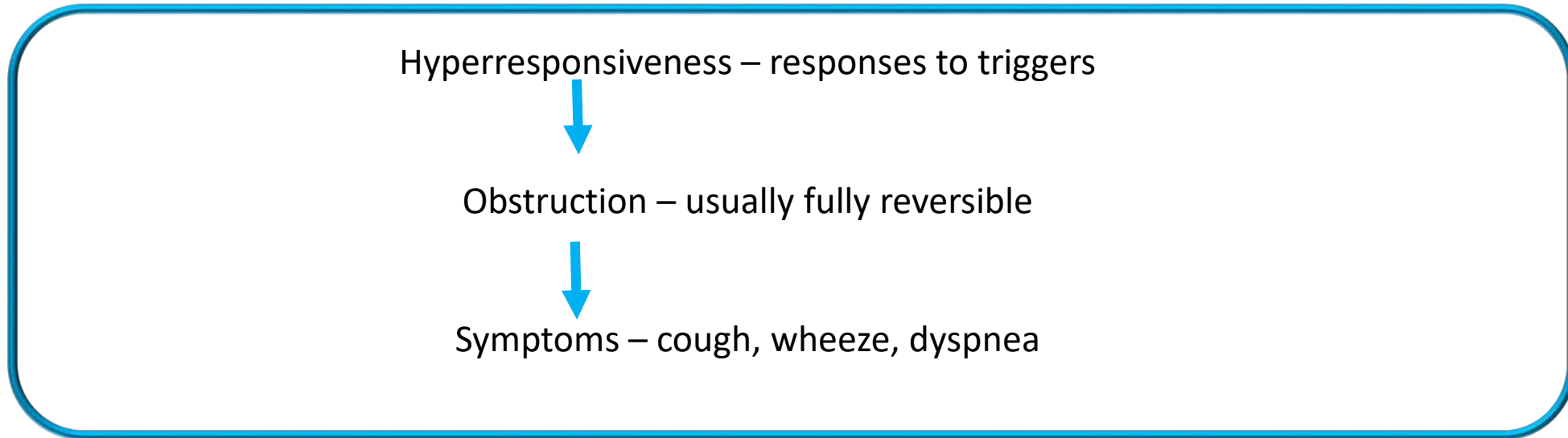
# Objectives

- Summarize current pharmacologic management of asthma.
- Identify key medications as being either long-term control medications or quick-relief medications.
- Given a stage of asthma, identify appropriate pharmacologic intervention.
- Given a case scenario, identify appropriate pharmacologic intervention.

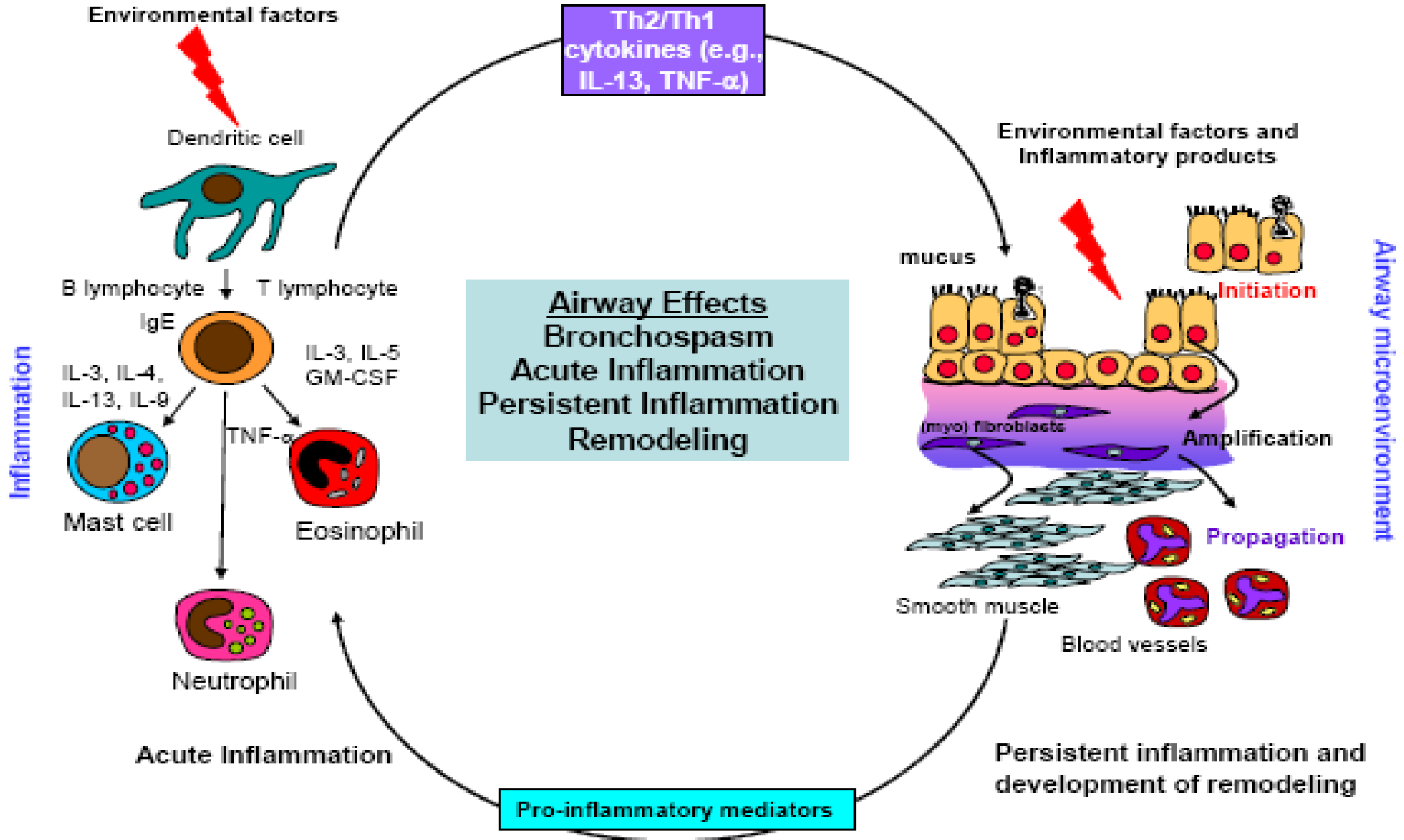
# Inflammation and Asthma

Asthma is a chronic inflammatory disorder

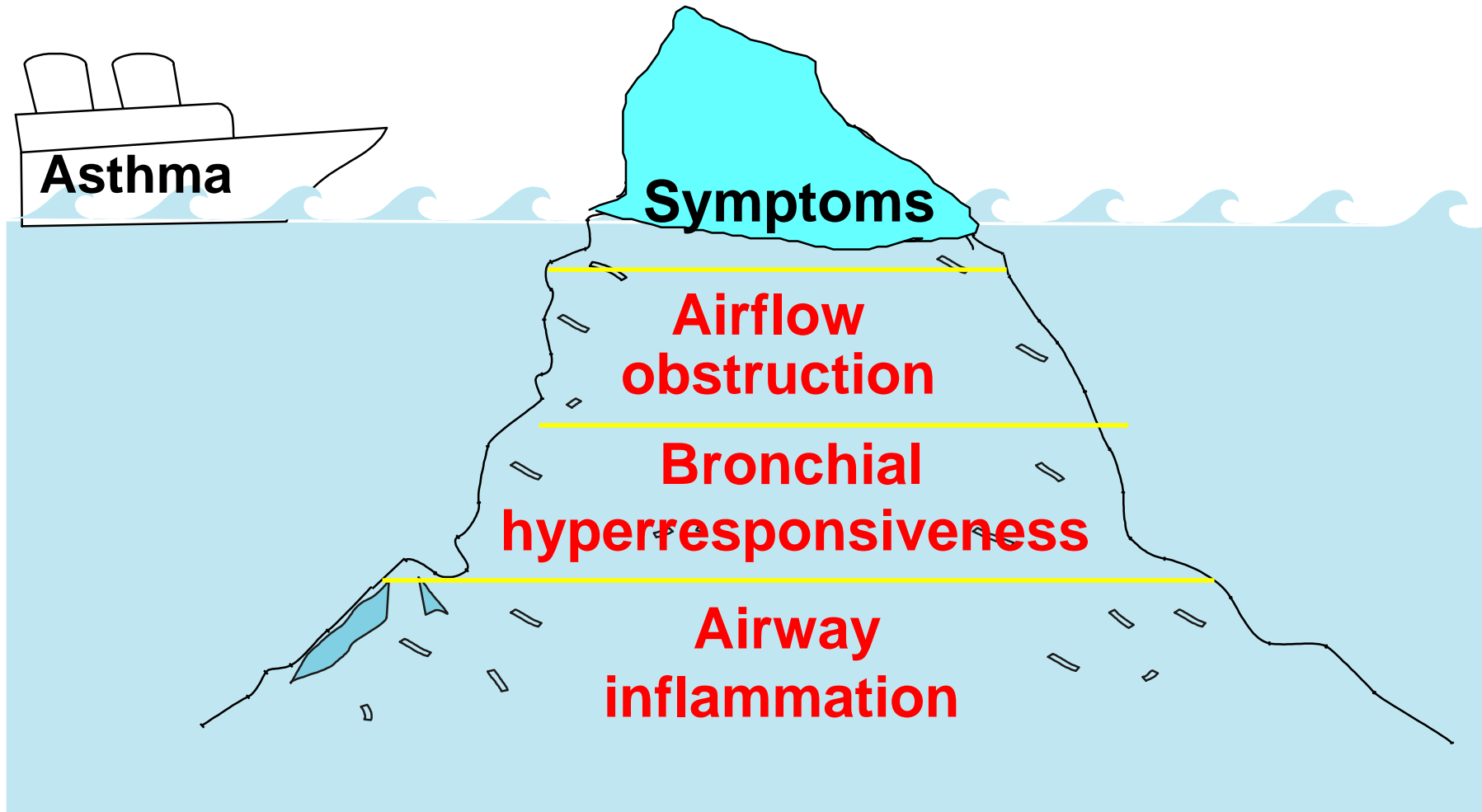
➤ Airway inflammation leads to



- While symptoms are easily appreciated, they are not the fundamental aspect of asthma
- Nor the only/final target of therapy

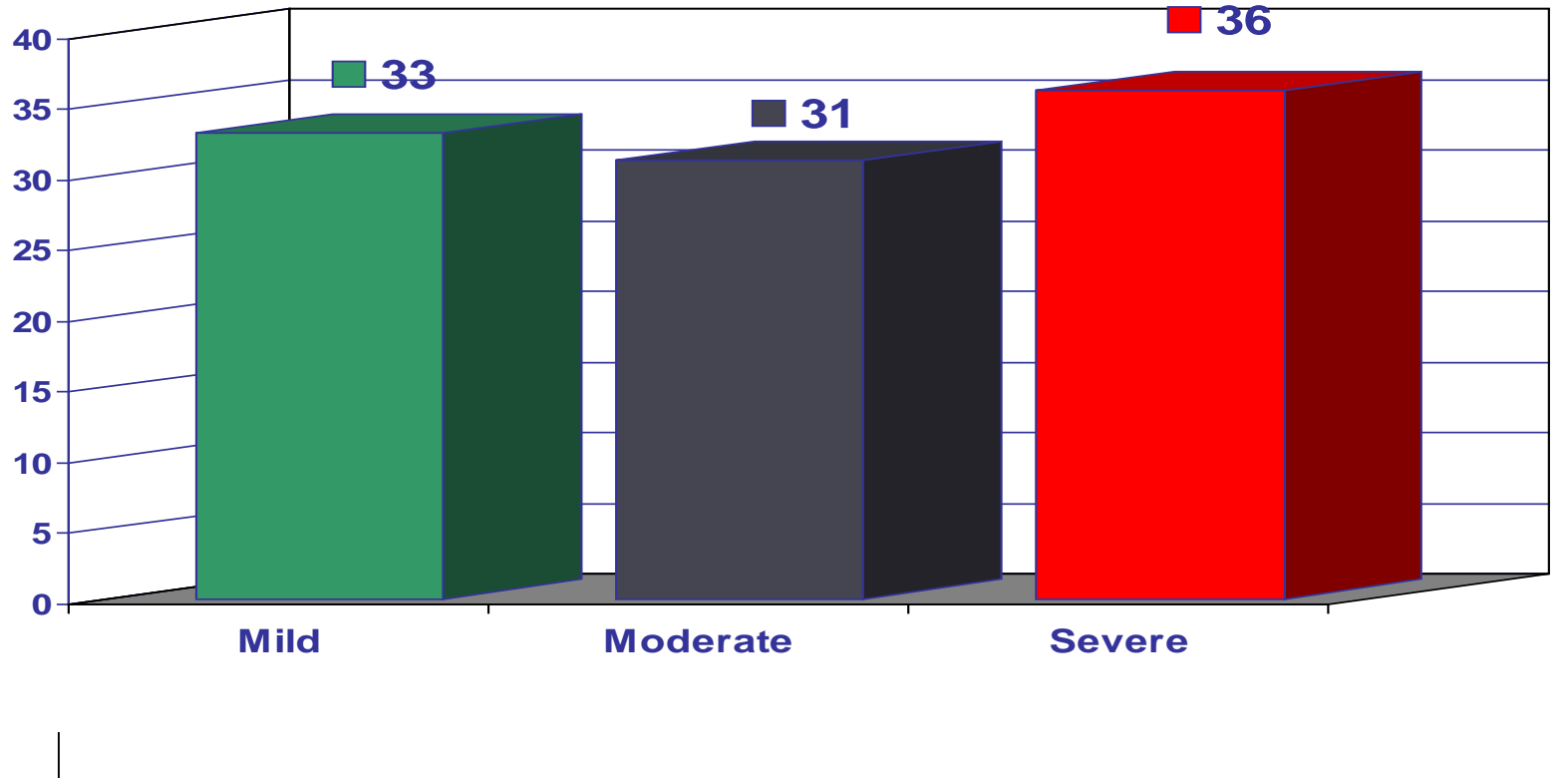


# What are we treating?



# Pediatric & Adolescent Asthma Deaths:

33% of asthma-related fatalities occurred in patients classified as having MILD disease.



**Physician Assessment of Patient Asthma Severity**

# Pharmacologic therapy is used to...

- Prevent and control asthma symptoms,
- Improve the quality of life,
- Reduce the frequency and severity of asthma exacerbations,
- Reverse airflow obstruction.



# Types of Medications

- Quick-Relief Medications-Bronchodilators
  - Anticholinergics
  - SABAs
  - Systemic corticosteroids
  
- Long-term control medications-Anti-inflammatory
  - Corticosteroids
  - Cromolyn sodium and nedocromil
  - Immunomodulators
  - Leukotriene modifiers
  - LABAs
  - Methylxanthines

See medication Handout in Living Well with Asthma booklet.

# KEY POINTS

- Misinformation is sometimes worse than no information at all. If you are uncertain about the answer to a medication (or other) question, don't guess: look it up
- Epinephrine is a bronchodilator with alpha- and beta-adrenergic effects. It raises blood pressure when given systemically.
- Isoproterenol is a nonselective beta-adrenergic bronchodilator; it stimulates bronchi and cardiac tissue with equal potency. It does not raise blood pressure, but it speeds heart rate.
- Inhaled beta-2 selective adrenergic agonists (current beta-agonist bronchodilators) are potent bronchodilators with little cardiac stimulatory effects. Examples include albuterol (Ventolin, Proventil), pirbuterol (Maxair), metaproterenol (Alupent) and levalbuterol (xopenex).
- One reason why selective beta-2 agonist bronchodilators via metered-dosed inhaler (MDI) have so few side effects is the small amount of medication that is needed to achieve bronchodilation.

# Rescue Medications

## OR Quick Relief Medications

- Used to give fast relief of acute symptoms and exercise-induced bronchospasm. Quick relief for tight, narrowed airways and the symptoms of coughing, wheezing, and chest tightness.
- Inhaled Short Acting Beta2-Agonists: Proventil<sup>®</sup>, Ventolin<sup>®</sup>, Tornalate<sup>®</sup>, Maxair<sup>®</sup>, Maxair Autohaler<sup>®</sup>, Brethaire<sup>®</sup>, Xopenex<sup>®</sup>, Alupent<sup>®</sup>
- *Anticholinergics*- ipratropium (Atrovent) and tiotropium (Spiriva)
- *Systemic corticosteroids*

# β<sub>2</sub>-agonists

		Receptor Selectivity				
Agent	Dosage Forms <sup>a</sup>	β <sub>1</sub>	β <sub>2</sub>	β <sub>2</sub> Potency	Duration of Action (hrs)	
"short-acting"	Epinephrine <sup>d</sup>	Inj, AS, MDI	+++	+++	2	0.5-2
	Isoproterenol (Isuprel)	Inj, AS, MDI, SL	+++	++++	1	0.5-2
	Isoetharine (Bronkosol)	AS, MDI	++	+++	6	0.5-2
	Metaproterenol (Alupent)	AS, MDI, PO	++	++	10	3-4
	Terbutaline (Brethine)	Inj, MDI, PO, AS	+	++++	4	4-8
	Albuterol (Ventolin, Proventil)	AS, MDI, PO	+	+++	2	4-8
	Levalbuterol (Xopenex)					
"long-acting"	Bitolterol (Tornalate)	MDI	+	++++	4	4-8
	Pirbuterol (Maxair)	MDI	+	++++	4	4-8
	Formoterol (Foradil)	MDI	+	++++	0.24	8-12
	Salmeterol (Serevent)	MDI	+	++++	0.50	12

# Long-Term Control Medications: Inhaled Corticosteroids

## Actions:

- Most effective long term control medication for persistent asthma
- The most potent B-receptor responsiveness
  - ICS suppress reduce mucus production and hypersecretion
  - inhibit inflammatory response at all levels
  - the generation of chemical mediators (e.g. cytokines),
  - the recruitment of eosinophils
  - the release of inflammatory mediators
- ICS differ from systemic corticosteroids in their bioavailability and therefore the risk of potential side effects are minimized.
- Symptomatic and spirometry improvement with in 2 weeks.

# Long-Term Control Medications: Inhaled Corticosteroids

- Potential but small risk for adverse events at usual doses is well balanced by efficacy.
  - Risk can be reduced even further by:
    - Using spacer and rinsing mouth
    - Using lowest effective dose
    - Add long-acting  $\beta_2$ -agonist to a low or medium dose of ICS rather than a higher dose of ICS
    - Consider calcium supplements and vitamin D in postmenopausal women.
    - Monitoring growth in children

# Growth Risks and Inhaled Corticosteroids

- Risks of ICSs are well balanced by their benefits.
- As children grow at variable rates, short-term evaluations are poorly predictive of final adult height.
- Poorly controlled asthma may delay growth in children.

# Growth Risks and Inhaled Corticosteroids

- Dose dependent: Low- to medium-dose ICS therapy may be associated with a possible, but not predictable, adverse effect on linear growth. The clinical significance of this potential systemic effect has yet to be determined. High doses of ICS have greater potential for growth suppression.
- Use of high doses of ICS not as bad as the use of oral systemic corticosteroids.
- In general, the efficacy of ICSs is sufficient to outweigh any concerns about growth or other systemic effects. However, ICSs, as with any medications, should be titrated to as low a dose as needed to maintain good control of the child's asthma.



# Long-Term Corticosteroids

- Use the lowest possible dose (single dose daily or on alternate days).
- Monitor patients closely for corticosteroid adverse side effects
- When well-controlled asthma is achieved, make persistent attempts to reduce oral systemic corticosteroids. High-dose ICS therapy is preferable to oral systemic corticosteroids.
- Recommend consultation with an asthma specialist.
- *Systemic corticosteroids* can provoke confusion, agitation, and changes in glucose metabolism in older adults.

# Oral Corticosteroid Doses - Children

Medication	Dosage/Form	0 to 4 yrs	5 to 11 yrs
Methylprednisolone	2, 4, 8, 16, or 32 mg tablets	0.25–2 mg/kg daily in single dose in a.m. or every other day as needed.	0.25–2 mg/kg daily in single dose in a.m. or every other day as needed.
Prednisolone	5 mg tablets, 5 mg/5 cc, 15 mg/5 cc		
Prednisone	1, 2.5, 5, 10, 20, 25 mg tablets; 5 mg/cc, 5 mg/5 cc		

# Oral Corticosteroid Doses – Adolescents and Adults

Medication	Dosage/Form	0 to 4 yrs
Methylprednisolone	2, 4, 8, 16, or 32 mg tablets	7.5 to 60 mg daily in single dose in a.m. or every other day as needed.  Short-course “burst”: to achieve control, 40 to 60 mg per day as a single or 2 divided doses for 3-10 days.
Prednisolone	5 mg tablets, 5 mg/5 cc, 15 mg/5 cc	
Prednisone	1, 2.5, 5, 10, 20, 25 mg tablets; 5 mg/cc, 5 mg/5 cc	

# Alternatives to ICS

➤ Cromolyn Sodium

➤ Leukotriene Modifiers

➤ Theophylline

# Cromolyn (Intal)

- Mast cell stabilizers
- Inhibit both early and late asthmatic response
- Little to no side-effects
  - least toxic drug to treat asthma
  - safe for use in pregnancy or breast feeding
- Several weeks to maximum effect
- Dose (frequency) may be reduced eventually

# Cromolyn (Intal)

- Place(s) in therapy:
  - maintenance for mild persistent asthma in children
  - allergy/exercise induced bronchospasm
  - ? decrease dose of corticosteroids

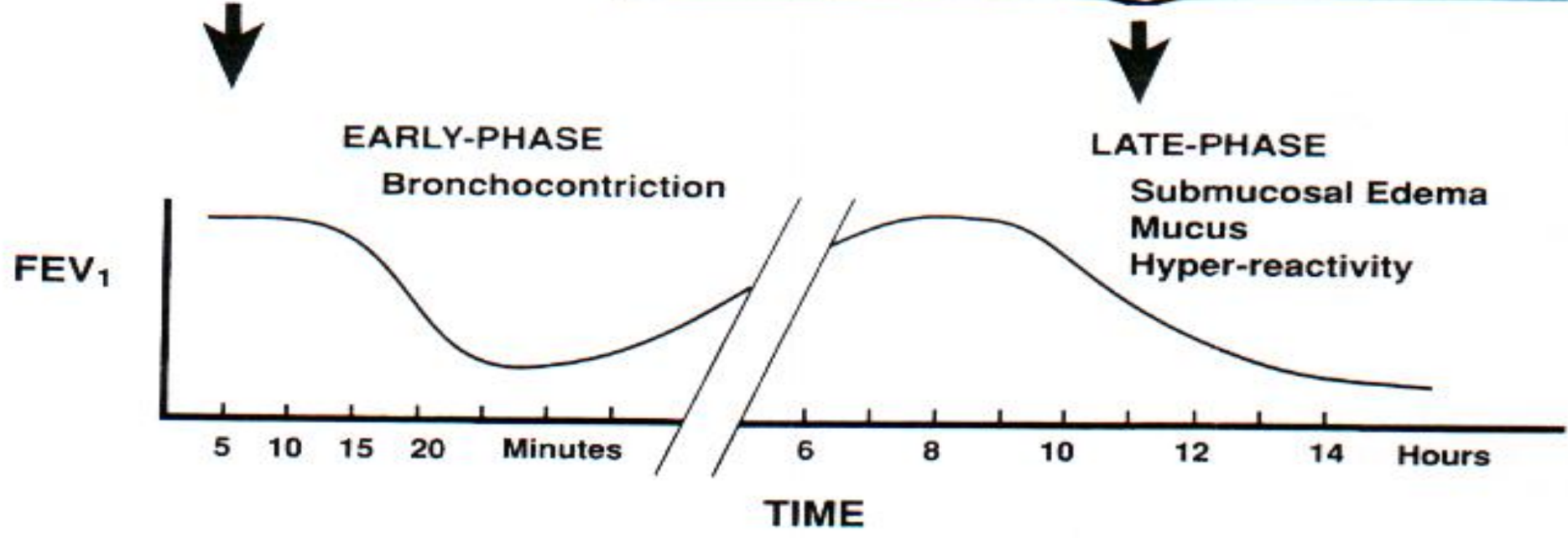
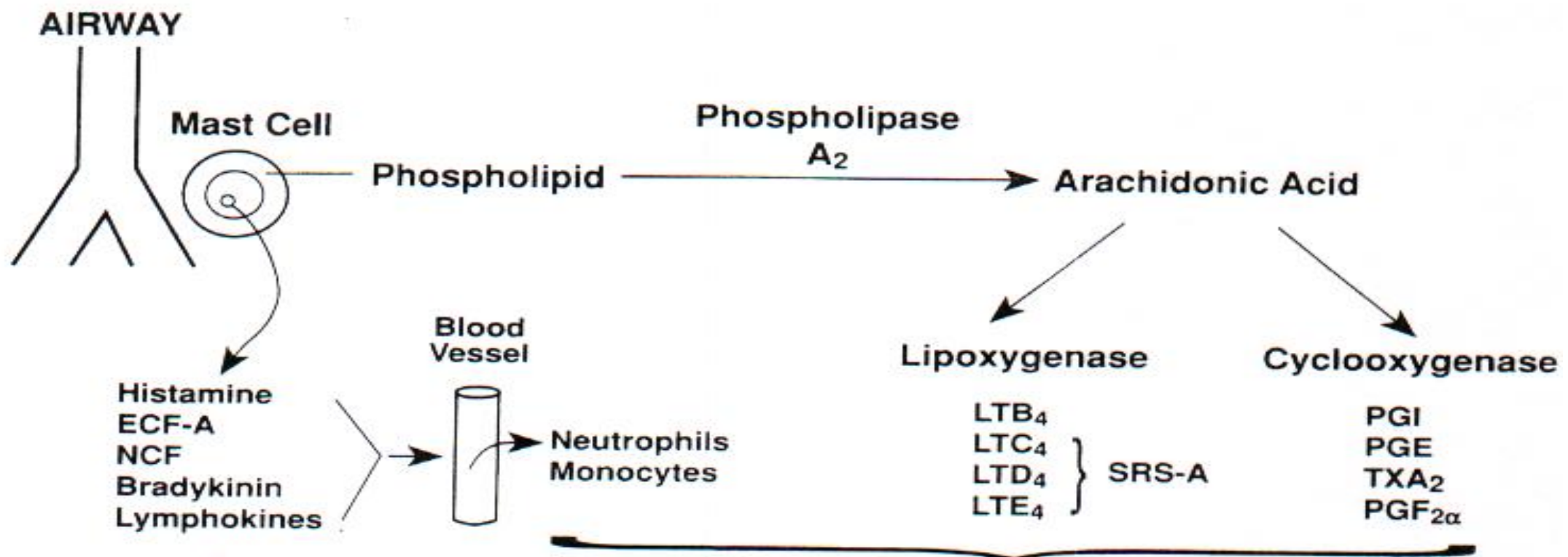
# Leukotriene Modifiers

## ➤ Two mechanisms

- 5-lipoxygenase inhibitors
  - zileuton (Zyflo)
- Cysteinyl leukotriene receptor antagonists
  - zafirlukast (Accolate), montelukast (Singulair)

## ➤ Indications

- Generally, long-term therapy in mild persistent asthma or as add-on in higher stages of management
- Improve lung function
  - Decrease short-acting  $\beta_2$ -agonist use
  - Prevent exacerbations





# Methylxanthines (Theophylline)

## ➤ Places in therapy:

- primary therapy when inhaled corticosteroids not possible
  - toddlers, etc.
- patient's who can't/won't use inhalers
- additive therapy at later Stages

## ➤ ADR's/Serum Levels/Drug Interactions

- Therapeutic Range 5-15 mcg/mL, or 10-20 mcg/mL
  - levels > 20 mcg/mL: N/V/D, HA, irritability, insomnia, tachycardia
  - levels > 30 mcg/mL: seizures, toxic encephalopathy, hyperthermia, brain damage
- Drug Interactions
  - PLENTY!!

# Long-acting $\beta_2$ -agonists

- Not a substitute for anti-inflammatory therapy
- Not appropriate for monotherapy



RED FLAG

- Literature supporting role in addition to inhaled corticosteroids
- Not for acute symptoms or exacerbations
- salmeterol (Serevent) first of class in US

# Long-acting $\beta_2$ -agonists - Salmeterol

- Trade Name – Serevent
- DPI – 50 mcg/blister
- Dose: 1 blister every 12 hours

# Long-acting $\beta_2$ -agonists- Formoterol

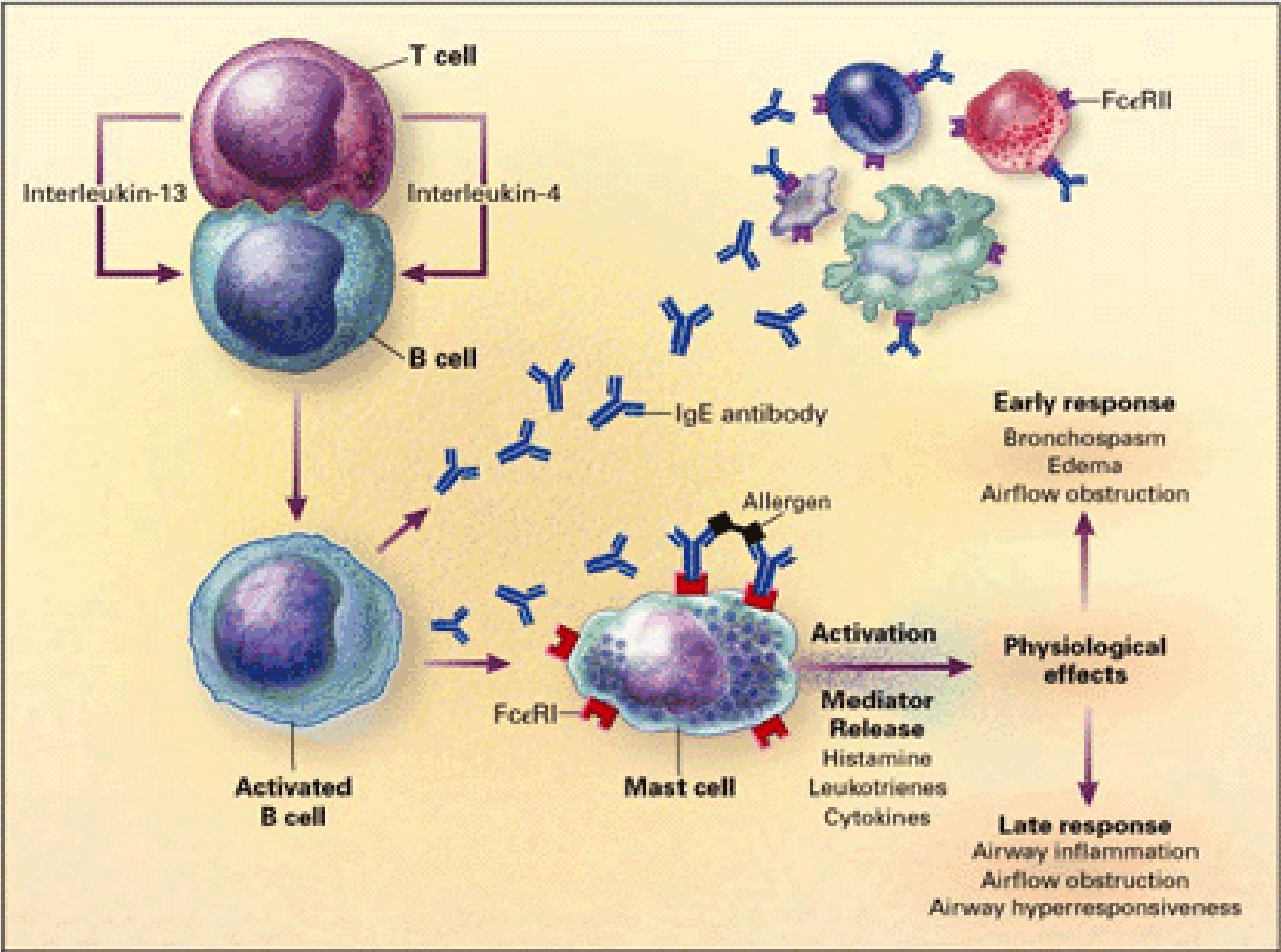
- Trade name: Foradil
- Newest long-acting beta-agonist
- Has *rapid* onset and long duration
- DPI – 12 mcg/capsule
- Dose: 1 capsule every 12 hours

# Combination Therapies

- Fluticasone + Salmeterol
  - Trade: Advair
  - DPI: 100 mcg + 50 mcg, 250 mcg + 50 mcg, or 500 mcg + 50 mcg.
  - HFA MDI: 45 mcg + 21 mcg, 115 mcg + 21 mcg, or 230 mcg + 21 mcg.
- Budesonide + Formoterol
  - Trade: Symbicort
  - HFA MDI: 80 mcg + 4.5 mcg or 160 mcg + 4.5 mcg

# IgE

- One of five classes of Immunoglobulin
- Binds to high-affinity (FcεRI) receptors on mast cells, basophils, alveolar macrophages, antigen-presenting cells
- Triggers the release of inflammatory mediators
- Strong association between IgE and asthma



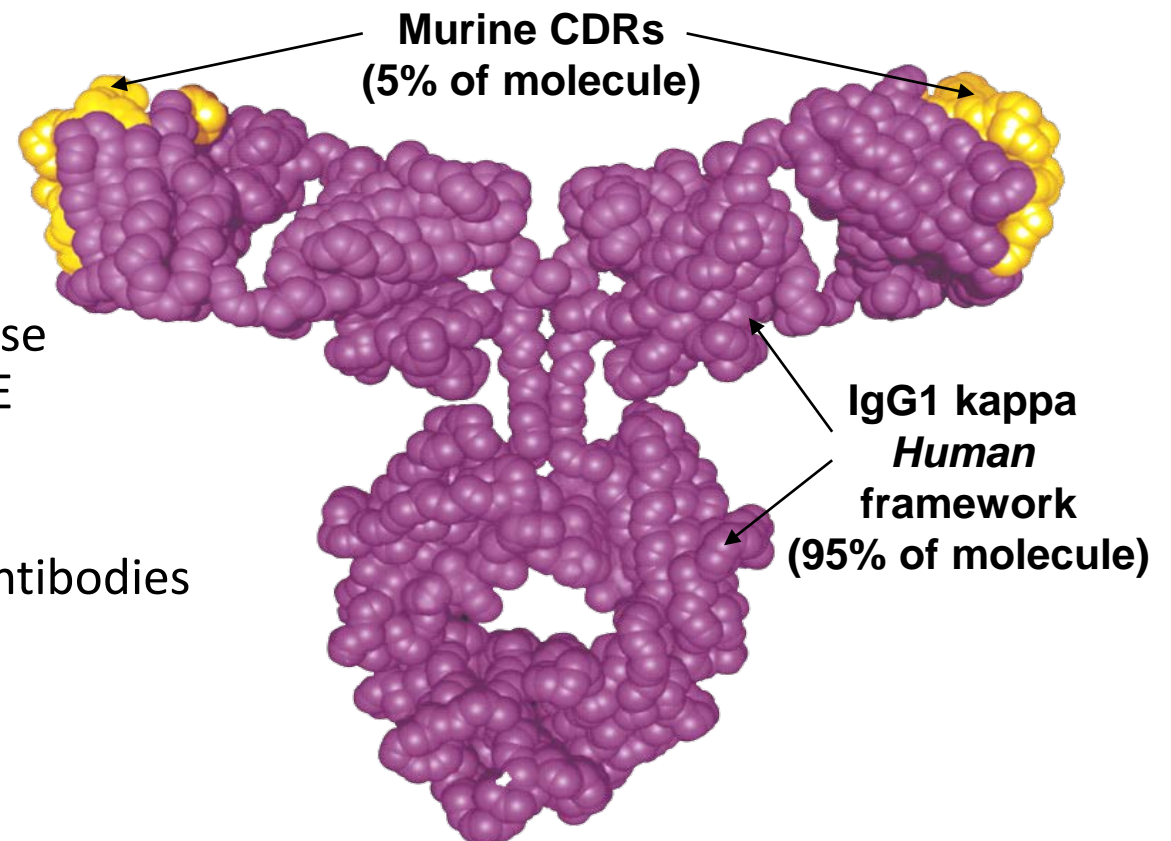
# Omalizumab (Xolair)

- MOA (mechanism of action) and effects-
  - Receptors are down regulated
  - IgE levels are affected
  - Eosinophilia is affected
  - Early and late phase are affected
- Given as subcutaneous injection every 2 to 4 weeks
- Dose depends on patient weight and IgE level



# Xolair™ Characteristics

- Humanized mAb against IgE
- Binds circulating IgE regardless of specificity
- Forms small, biologically inert omalizumab:IgE complexes
- Does not cause anaphylaxis because it does not crosslink cell-bound IgE
- Does not activate complement
- Does not elicit anti-omalizumab antibodies (HAHA; nonimmunogenic)



HAHA, Human anti-human antibody

Adapted with permission from Boushey H. J Allergy Clin Immunol. 2001;108:S77-S83.

# Efficacy Conclusions

- Reduction of asthma exacerbations requiring steroid interventions
- All other endpoints are positive, including steroid reduction, symptoms, and pulmonary function
- Supporting studies show similar reductions demonstrating a consistent drug effect in a variety of clinical settings

# Xolair Candidates

- Greater than 12 years old with moderate to severe allergic asthma
- Daily inhaled steroids for at least one year (at reasonable dose)
- Positive test for perennial allergen
- IgE 30 IU/mL-700 IU/mL
- Consideration of immunotherapy or failure of same

# Complementary Therapies

Expert panel concludes that there is insufficient evidence to support the effectiveness and does not recommend the use of acupuncture, chiropractic therapy, homeopathy, herbal therapy, breathing techniques, relaxation techniques, or yoga for the treatment of asthma.

Ernst E. J Asthma 1998;35:667-71. N= 3837 U.K. patients

# Herbal Therapies: A Few Points

## ➤ *Ginko biloba*

- used to treat cough in traditional Chinese medicine
  - has platelet-activating factor inhibiting properties
- appears to lack clinical value in treating asthma

## ➤ *Ma huang*

- “natural” form of ephedrine
  - can produce bronchodilation at some doses
  - adverse effects make it obsolete given modern pharmaceutical preparations

# Herbal Therapies: A Few Points

## ➤ *Tylophora asthmatica*

- used in Naturopathy, Ayurveda, Unani, and Homeopathy
  - relative of ipecac
- historically used to treat conditions of “excess mucus”

## ➤ *Datura stramonium*

- has bronchodilating properties
  - historically administered by smoking it

# Over-the-Counter (OTC) Therapies Cough and Cold

- OTC bronchodilators should be avoided!!
  - e.g., Primatene
- Cough Suppressants
  - Generally discouraged, but may be used safely in certain circumstances
    - e.g., dextromethorphan products, opiate products
- Expectorants
  - may be used safely
  - evidence of effectiveness lacking
- Antihistamines
  - OTC antihistamines generally safe in asthmatics

# Quick Reference Charts for the Classification and Stepwise Treatment of Asthma

(Adapted from 2007 NHLBI Guidelines for the Diagnosis and Treatment of Asthma Expert Panel Report 3)

Asthma *severity* is the intrinsic intensity of the disease process and dictates which step to initiate treatment.

Asthma *control* is the degree to which the goals of therapy are met (e.g., prevent symptoms/exacerbations, maintain normal lung function and activity levels).

**The classification of severity or level of control is based on the *most* severe impairment or risk category in which any feature occurs.**

Assess impairment domain by patient's recall of previous 2–4 weeks and/or by spirometry or peak flow measures.

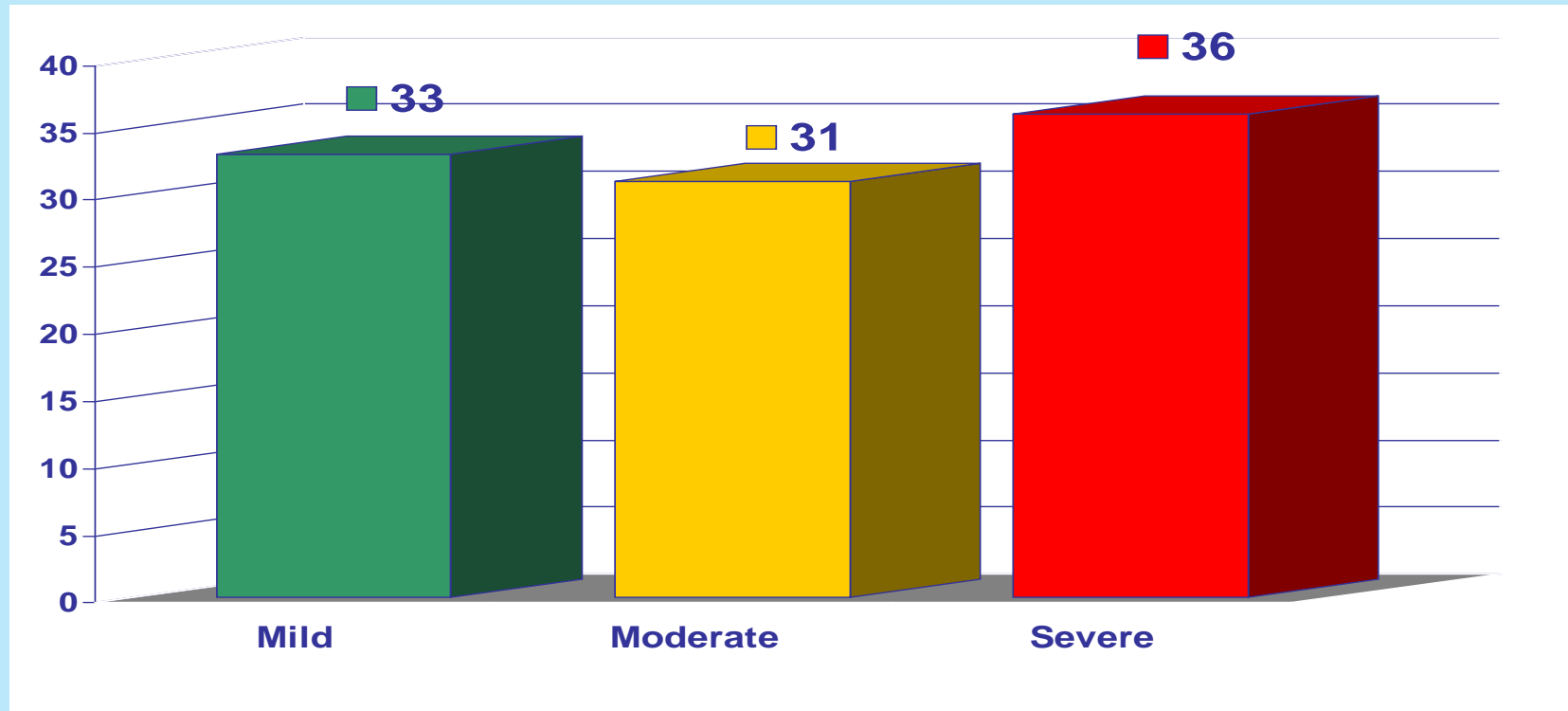
Symptom assessment for longer periods should reflect a global assessment, such as inquiring whether the patient's asthma is better or worse since last visit. *(See handout)*



# NIH Goals of Asthma Therapy

- Minimal or no chronic symptoms day or night
- Minimal or no exacerbations
- No limitations on activities; no missed school/work
- Maintain (near) normal pulmonary function
- Minimal use of inhaled short-acting beta<sub>2</sub>-agonists
- Minimal or no adverse effects from medications

# Pediatric & Adolescent Asthma Deaths: 33% of asthma-related fatalities occurred in patients classified as having MILD disease.



Physician Assessment of Patient Asthma Severity




**FIGURE 4–2a. CLASSIFYING ASTHMA SEVERITY AND INITIATING TREATMENT IN CHILDREN 0–4 YEARS OF AGE**

Assessing severity and initiating therapy in children who are not currently taking long-term control medication

Components of Severity		Classification of Asthma Severity (0–4 years of age)			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	0	1–2x/month	3–4x/month	>1x/week
	Short-acting beta <sub>2</sub> -agonist use for symptom control (not prevention of EIB)	≤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
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥2 exacerbations in 6 months requiring oral systemic corticosteroids, or ≥4 wheezing episodes/1 year lasting >1 day AND risk factors for persistent asthma		
		<p style="text-align: center;">← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time. →</p> <p>Exacerbations of any severity may occur in patients in any severity category.</p>			
Recommended Step for Initiating Therapy		Step 1	Step 2	Step 3 and consider short course of oral systemic corticosteroids	
(See figure 4–1a for treatment steps.)		In 2–6 weeks, depending on severity, evaluate level of asthma control that is achieved. If no clear benefit is observed in 4–6 weeks, consider adjusting therapy or alternative diagnoses.			



**FIGURE 4–2b. CLASSIFYING ASTHMA SEVERITY AND INITIATING TREATMENT IN CHILDREN 5–11 YEARS OF AGE**

Assessing severity and initiating therapy in children who are not currently taking long-term control medication

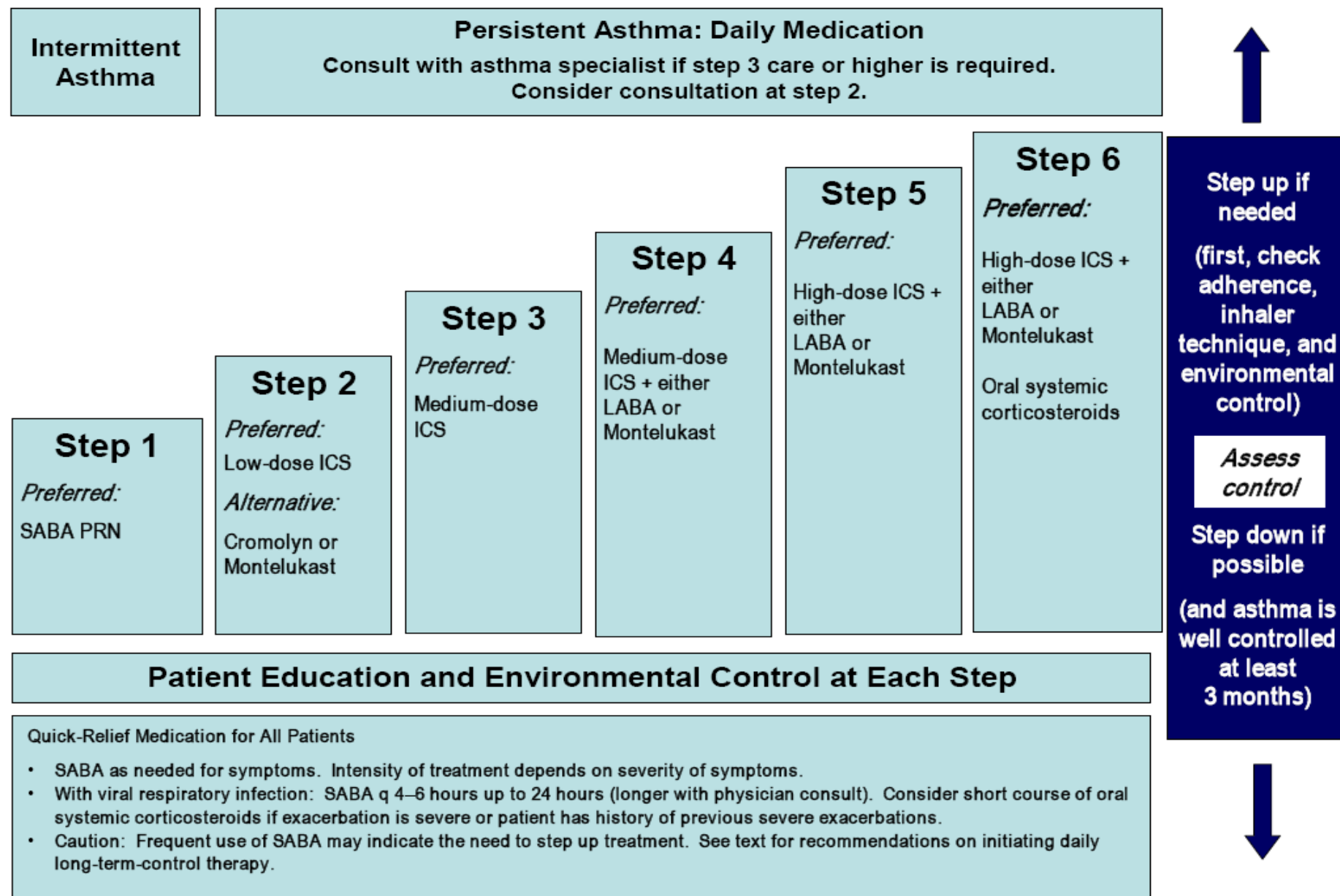
Components of Severity		Classification of Asthma Severity (5–11 years of age)			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting beta <sub>2</sub> -agonist use for symptom control (not prevention of EIB)	≤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	<ul style="list-style-type: none"> <li>• Normal FEV<sub>1</sub> between exacerbations</li> <li>• FEV<sub>1</sub> &gt;80% predicted</li> <li>• FEV<sub>1</sub>/FVC &gt;85%</li> </ul>	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub> = &gt;80% predicted</li> <li>• FEV<sub>1</sub>/FVC &gt;80%</li> </ul>	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub> = 60–80% predicted</li> <li>• FEV<sub>1</sub>/FVC = 75–80%</li> </ul>	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub> &lt;60% predicted</li> <li>• FEV<sub>1</sub>/FVC &lt;75%</li> </ul>
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 <sub>1</sub> .			
Recommended Step for Initiating Therapy		Step 1	Step 2	Step 3, medium-dose ICS option	Step 3, medium-dose ICS option, or step 4
(See figure 4–1b for treatment steps.)		In 2–6 weeks, evaluate level of asthma control that is achieved, and adjust therapy accordingly.			

**FIGURE 4-6. CLASSIFYING ASTHMA SEVERITY AND INITIATING TREATMENT IN YOUTHS ≥12 YEARS OF AGE AND ADULTS**

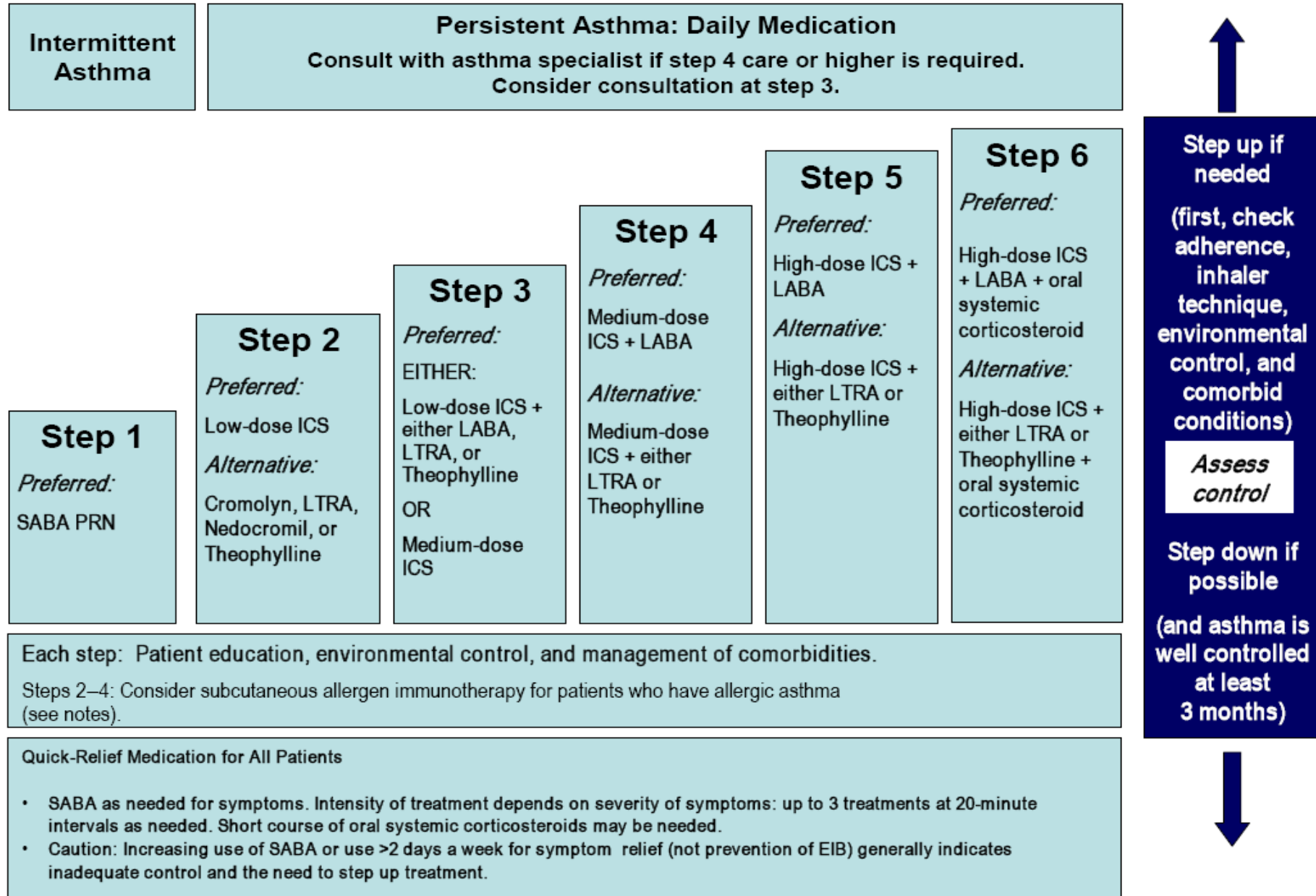
— Assessing severity and initiating treatment for patients who are not currently taking long-term control medications

Components of Severity		Classification of Asthma Severity ≥12 years of age			
		Intermittent	Persistent		
			Mild	Moderate	Severe
<b>Impairment</b>  Normal FEV <sub>1</sub> /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	≤2x/month	3–4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting beta <sub>2</sub> -agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily, and not more than 1x on any 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> &gt;80% predicted</li> <li>• FEV<sub>1</sub>/FVC normal</li> </ul>	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub> &gt;80% predicted</li> <li>• FEV<sub>1</sub>/FVC normal</li> </ul>	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub> &gt;60% but &lt;80% predicted</li> <li>• FEV<sub>1</sub>/FVC reduced 5%</li> </ul>	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub> &lt;60% predicted</li> <li>• FEV<sub>1</sub>/FVC reduced &gt;5%</li> </ul>
<b>Risk</b>  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.				
<b>Recommended Step for Initiating Treatment</b>  (See figure 4-5 for treatment steps.)		<b>Step 1</b>	<b>Step 2</b>	<b>Step 3</b> and consider short course of oral systemic corticosteroids	<b>Step 4 or 5</b>
		In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

**FIGURE 4-1a. STEPWISE APPROACH FOR MANAGING ASTHMA IN CHILDREN 0-4 YEARS OF AGE**

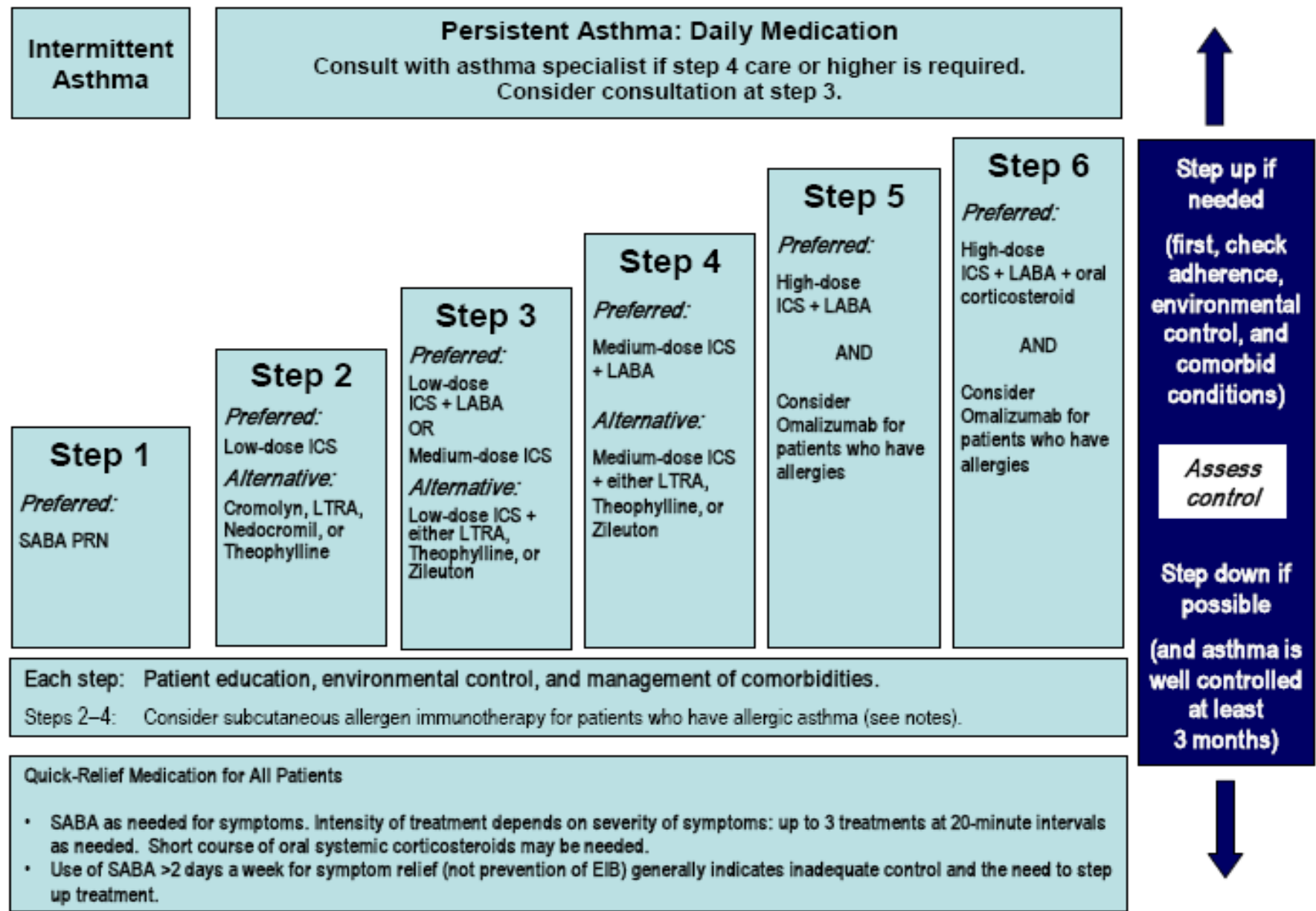


**FIGURE 4-1b. STEPWISE APPROACH FOR MANAGING ASTHMA IN CHILDREN 5-11 YEARS OF AGE**



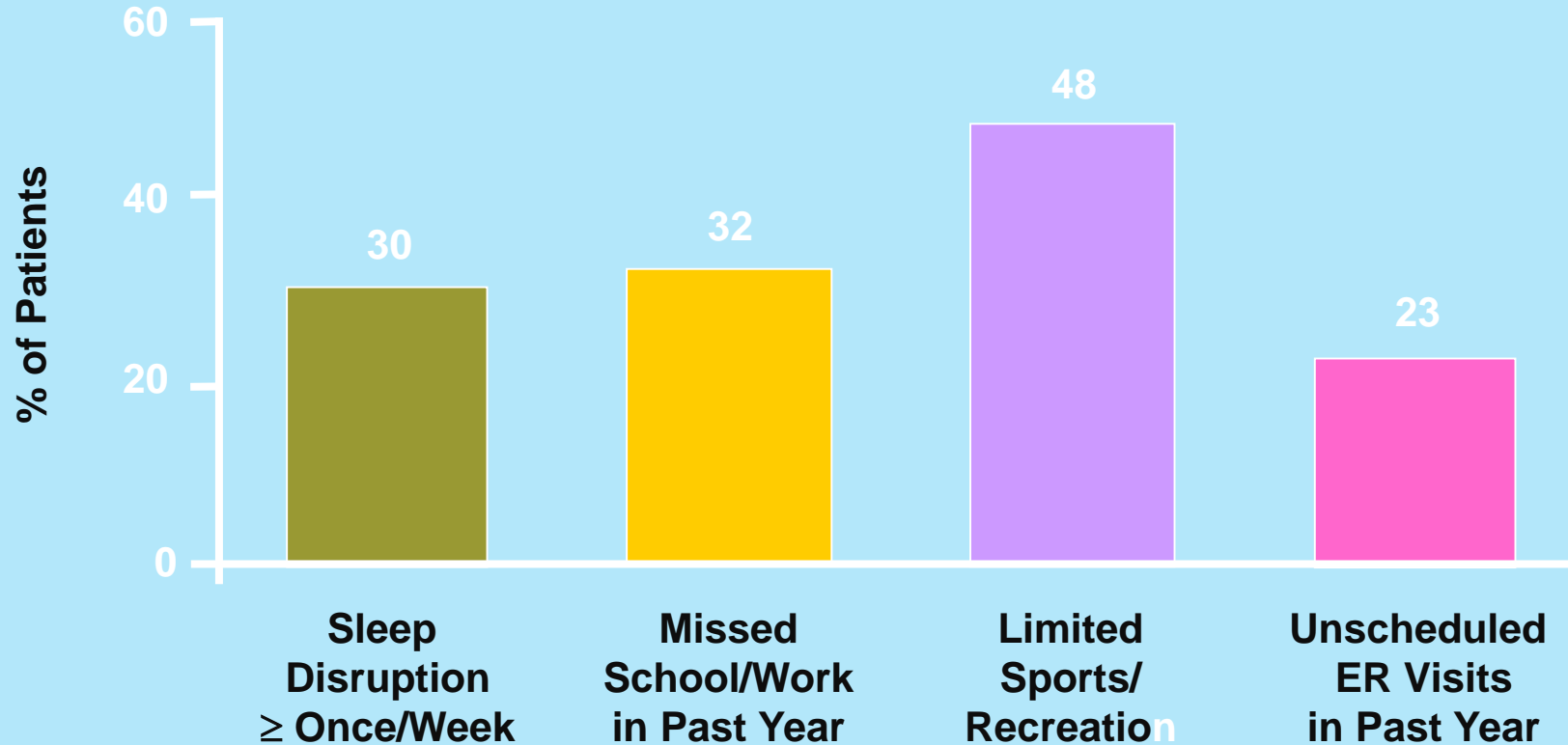


**FIGURE 4-5. STEPWISE APPROACH FOR MANAGING ASTHMA IN YOUTHS ≥12 YEARS OF AGE AND ADULTS**





# Many Patients Fail to Meet the Goals of Asthma Therapy



Results of a large, national survey of adults with asthma or parents of children under 16 years with asthma. A total of 2509 interviews were conducted.

Adequate studies with ADVAIR DISKUS have not been conducted to evaluate these parameters.

*Asthma in America™. A Landmark Survey. Executive Summary. SRBI. 1998.*

**PRACTICE QUESTIONS NEXT**

A 28 year old female has been advised by her physician that she requires a mast cell stabilizer to help control her asthma. The physician tells the patient she will phone the prescription to the local pharmacy. Which of the following medications should the patient expect to pickup at the pharmacy?

- A. Albuterol
- B. Flumisolide
- C. Cromolyn Sodium
- D. Montelukast

**Cromolyn sodium**

The asthma educator is interviewing a 20 year old male patient who has not started taking the oral corticosteroid prescribed by his allergist. The physician asks the educator to determine why the patient has not started the medication. The patient tells the educator that he has concerns about taking steroids because he has heard there are consequences associated with taking this type of medication.

Consequences of oral steroids include all of the following EXCEPT

- A. Airway remodeling
- B. Diabetes
- C. Weight gain
- D. Hypertension

**Airway remodeling**

A 16 year old girl is concerned that her asthma interferes with her ability to play on the school basketball team. She informs the asthma educator that during basketball practice, she often has to stop playing when she feels an onset of her asthma. She tells the asthma educator that her short-acting bronchodilator helps temporarily. What should the asthma educator recommend?

- A. Xopenex MDI 30 minutes before practice and games.
- B. Add Atrovent to the bronchodilator and use 1 hr. before practice
- C. Foradil Aerolizer 15 minutes before practice and games
- D. Alupent MDI 15 minutes before practice and games.

**Foradil Aerolizer**



**Thank  
You!!!**