INHALED CORTICOSTEROIDS (ICS)

DISCLOSURE

- Dr. Francisco has no financial interest in any commercial entity discussed in this presentation
- Dr. Francisco will not discuss experimental or off-label use of medications or devices

CREDITS

- **The first AAE Asthma Pharmacology workshop was first presented in 2008. Slide set have been edited several times over the last 7 years, however much of the content was originally developed by presenters who participated in the 2008 course. Credit is given to the following individuals:**
  - **Maureen George - "Inhaled Corticosteroids"**
  - **Tim Op't Holt - "Long-acting Beta 2 Agonists"**
  - **Nina Evans - "ICS/LABA Combinations" & "Leukotriene Modifiers"**

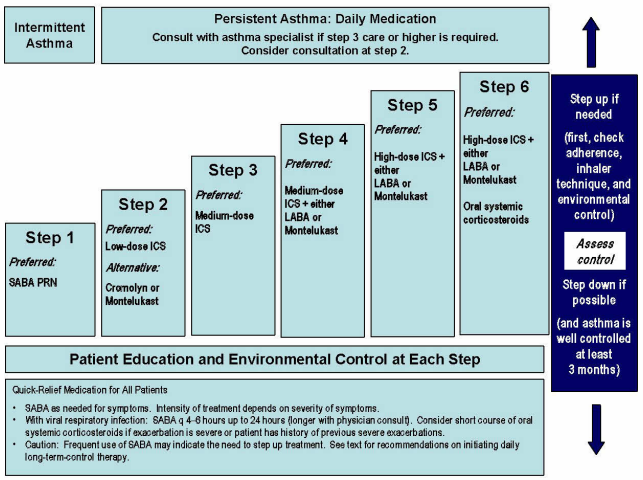
OBJECTIVES

1) Describe the mode of action, therapeutic value and role in the management of asthma.

2) Identify potential adverse effects and strategies for managing patients to minimize side effects

3) Evaluate the cost, barriers and potential benefit of this class of medications.

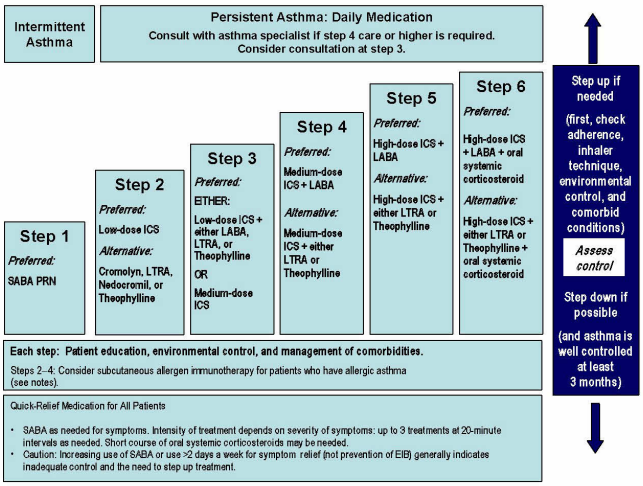
FIGURE 4–1a. STEPWISE APPROACH FOR MANAGING ASTHMA IN CHILDREN 0–4 YEARS OF AGE



Key: **Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy.** ICS, inhaled corticosteroid; LABA, inhaled long-acting beta$_2$-agonist; SABA, inhaled short-acting beta$_2$-agonist

Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma
NIH Publication No. 08-4051

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



Key: **Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy.** ICS, inhaled corticosteroid; LABA, inhaled long-acting beta$_2$-agonist, LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta$_2$-agonist

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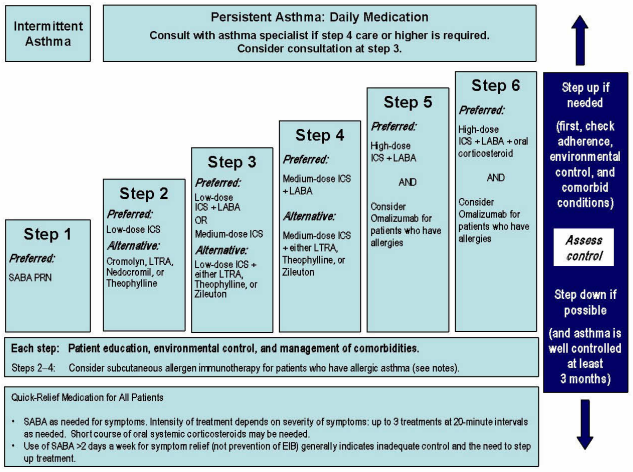
FIGURE 4–5. STEPWISE APPROACH FOR MANAGING ASTHMA IN YOUTHS ≥12 YEARS OF AGE AND ADULTS



Key: **Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy.** EIB, exercise-induced bronchospasm; ICS, inhaled corticosteroid; LABA, long-acting inhaled beta$_2$-agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta$_2$-agonist

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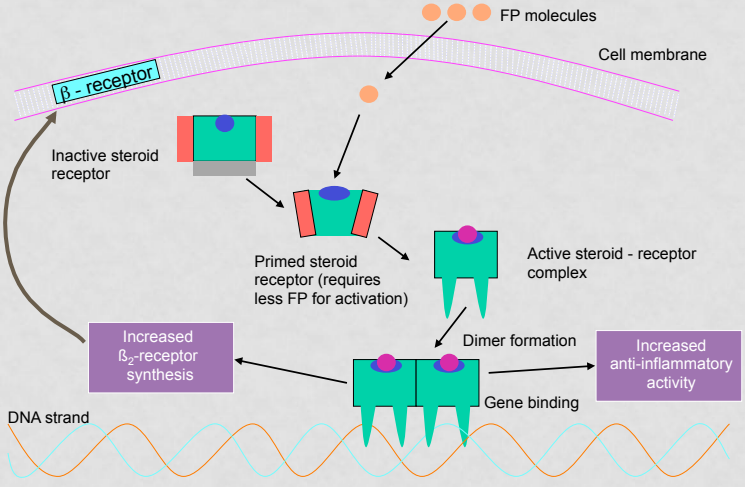
NIH Publication No. 08-4051

Proposed Mechanism of Action of Steroids



INHALED CORTICOSTEROIDS (ICS): MOST EFFECTIVE LONG-TERM CONTROLLER FOR ASTHMA

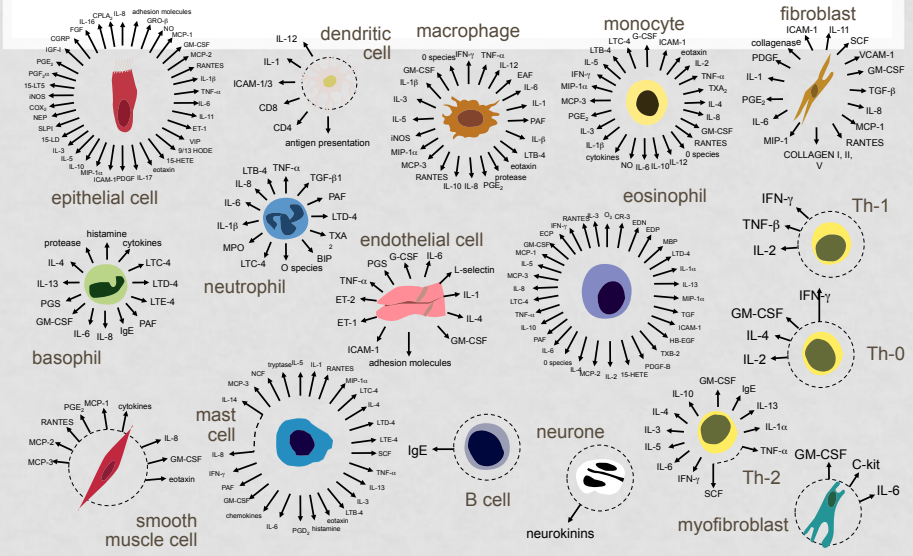
The daily use of ICS results in the following:

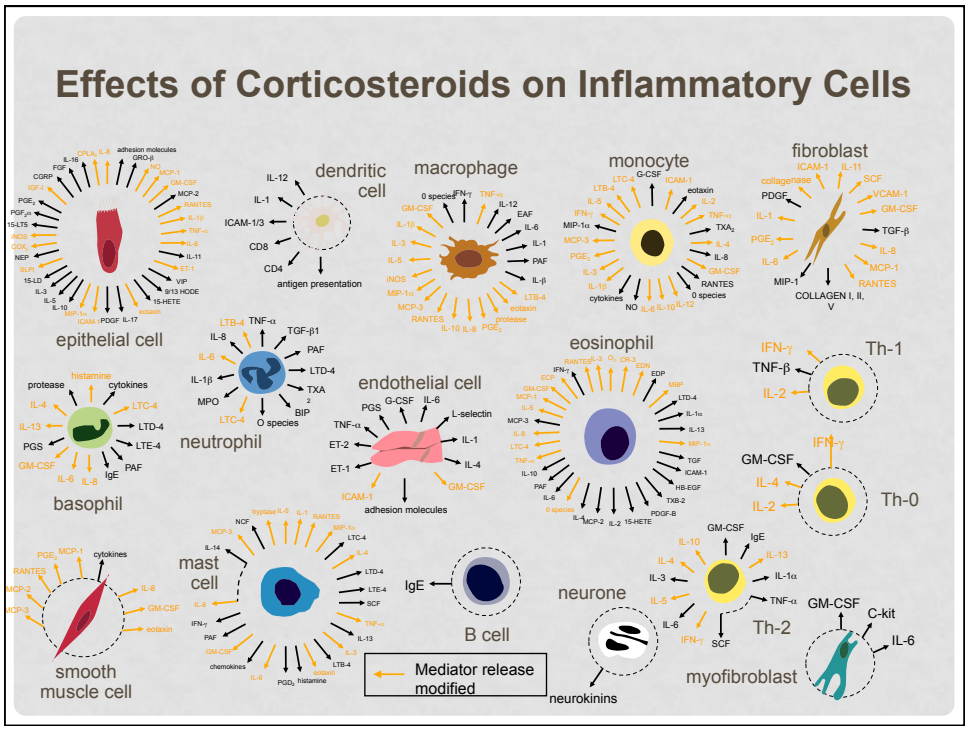
- **Asthma symptoms will diminish. Improvement will continue gradually over 60-90 days**
- **Occurrence of severe exacerbations is greatly reduced**
- **Need for quick-relief medication decreases**
- **Lung function improves significantly, as measured by FEV_1, FEV_1/FVC, PEF(?) & airway hyperresponsiveness**

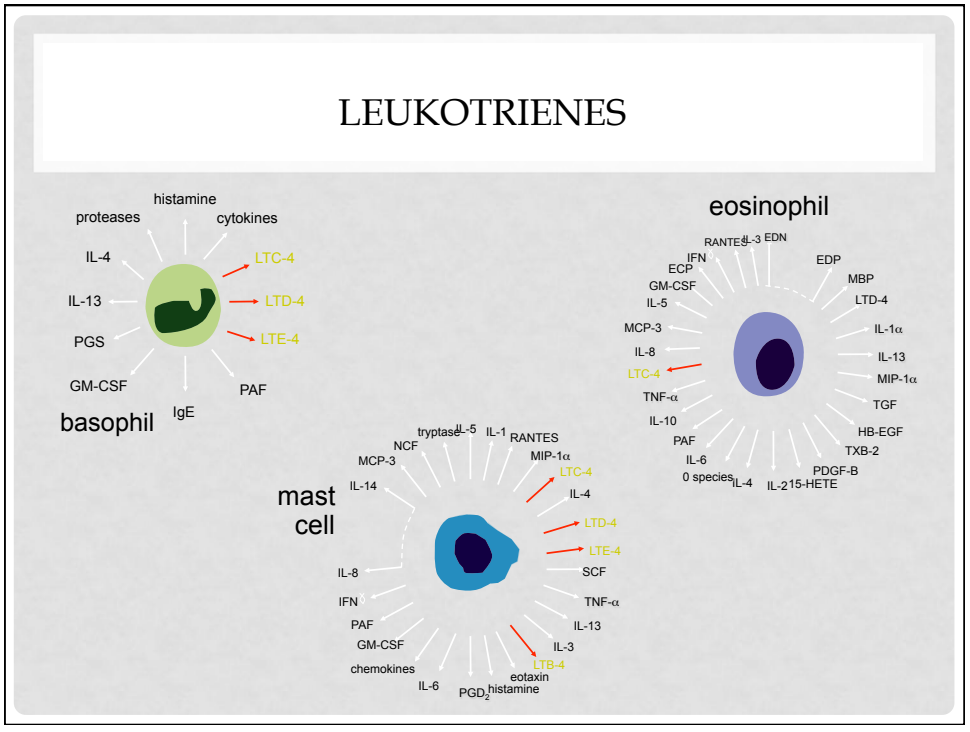
Problems due to asthma may return if patients stop taking ICS

***Guidelines for the Diagnosis and Management of Asthma.* 2007.**

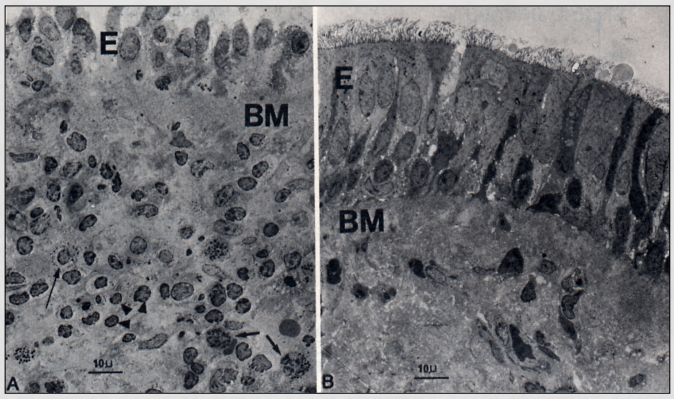
Mechanisms involved in inflammation




Effects of Corticosteroids on Inflammatory Cells
epithelial cell
dendritic cell
antigen presentation
macrophage
monocyte
fibroblast
neutrophil
endothelial cell
eosinophil
basophil
Th-1
Th-0
Th-2
mast cell
B cell
IgE
neurone
neurokinins
myofibroblast
smooth muscle cell
Mediator release modified


LEUKOTRIENES
basophil
histamine
proteases
cytokines
IL-4
IL-13
PGS
GM-CSF
IgE
PAF
LTC-4
LTD-4
LTE-4
eosinophil
mast cell
tryptase
NCF
MCP-3
IL-14
IL-8
IFN
PAF
GM-CSF
chemokines
IL-6
PGD2
histamine
eotaxin
IL-3
IL-13
TNF-α
SCF
IL-5
IL-1
RANTES
MIP-1α
IL-4
EDN
EDP
MBP
ECP
IFN
IL-10
HB-EGF
TGF
TXB-2
PDGF-B
15-HETE
0 species

EFFECTS OF INHALED CORTICOSTEROIDS ON INFLAMMATION



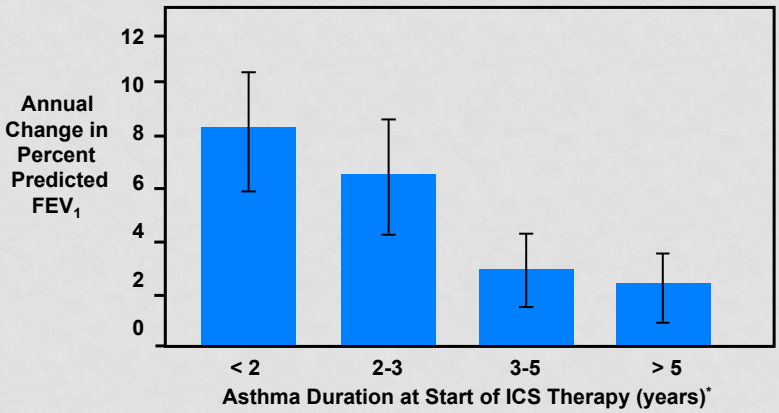
Pre– and post–3-month treatment with budesonide (BUD) 600 mcg b.i.d.

E = Epithelium

BM = Basement Membrane

Laitinen et al. *J Allergy Clin Immunol.* 1992;90:32-42.

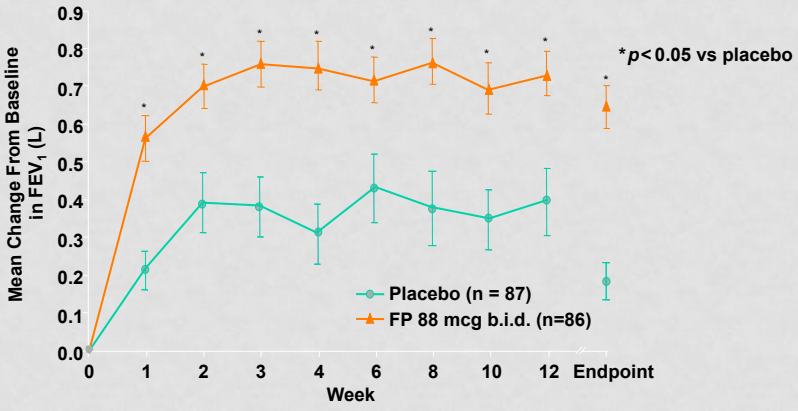
MEAN ANNUAL INCREASE IN FEV_1 DURING ICS THERAPY IN PEDIATRIC PATIENTS



*Mean values and 95% confidence intervals are shown.

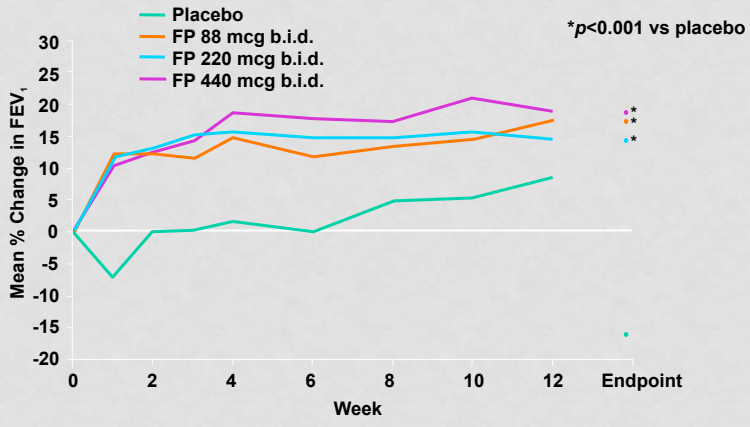
Agertoft L, Pedersen S. *Respir Med.* 1994;88:373-381.

PATIENTS INADEQUATELY CONTROLLED ON BRONCHODILATORS ALONE: MEAN CHANGE FROM BASELINE (±SEM) IN FEV_1 (LITERS) PRIOR TO AM DOSE



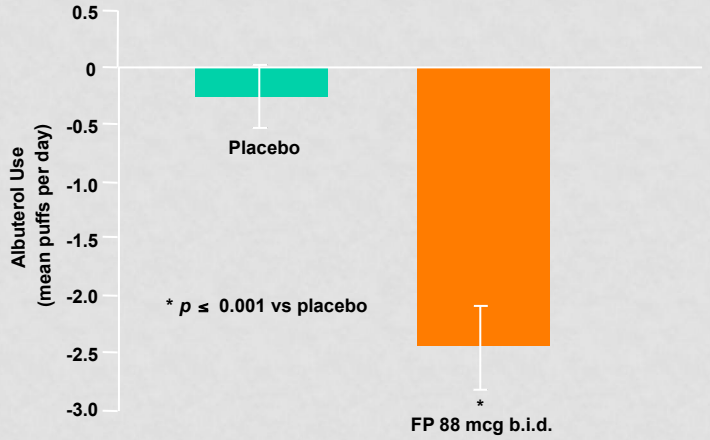
Adapted from Galant SP et al. *Ann Allergy Asthma Immunol.* 1996;77:112-118.

PATIENTS PREVIOUSLY RECEIVING DAILY INHALED CORTICOSTEROIDS – MEAN PERCENTAGE CHANGE FROM BASELINE IN FEV_1 PRIOR TO AM DOSE



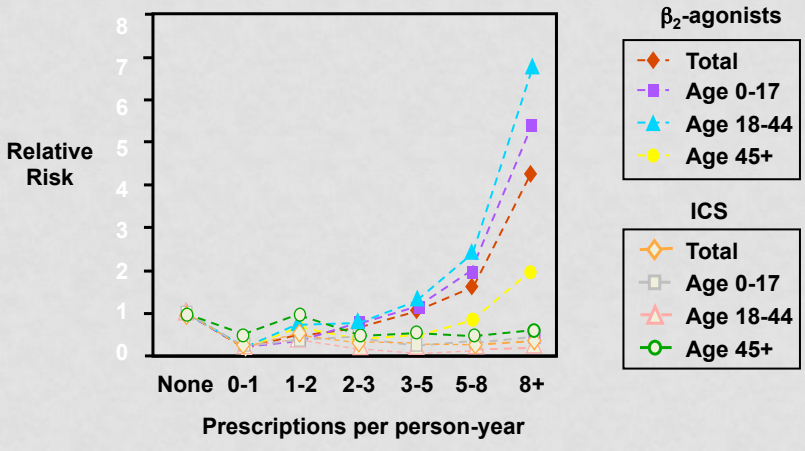
Adapted from Wolfe JD et al. *Clin Ther.* 1996;18(4): 635-646.

PATIENTS INADEQUATELY CONTROLLED ON BRONCHODILATORS ALONE: MEAN DECREASE FROM BASELINE (±SEM) TO ENDPOINT IN ALBUTEROL USE



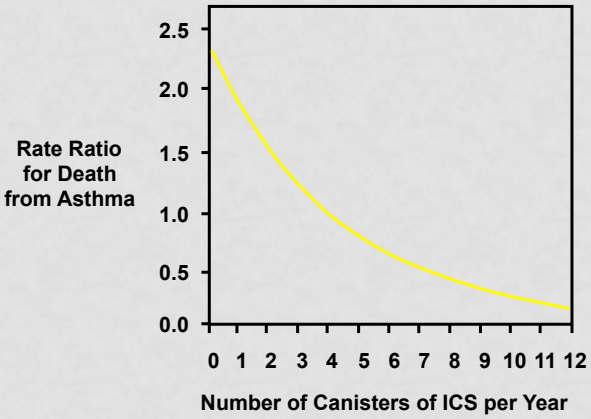
Galant SP et al. *Ann Allergy Asthma Immunol.* 1996;77:112-118.

Relative Risk of Hospitalization in the United States



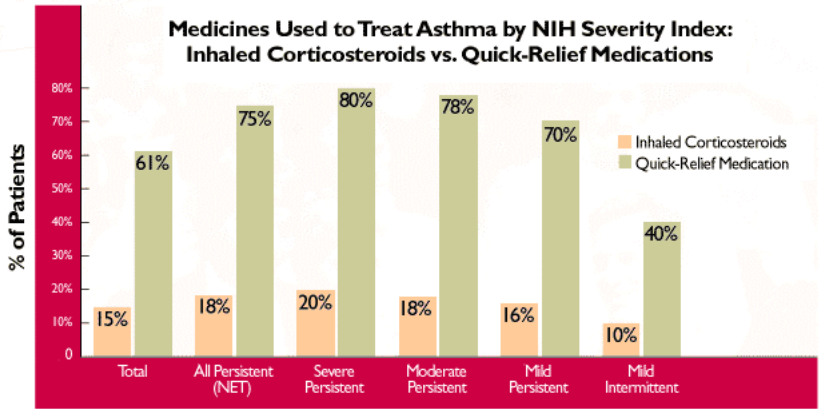
Donahue et al. *JAMA.* 1997;277:887-891.

Low-dose ICS and the Prevention of Death from Asthma in Canada



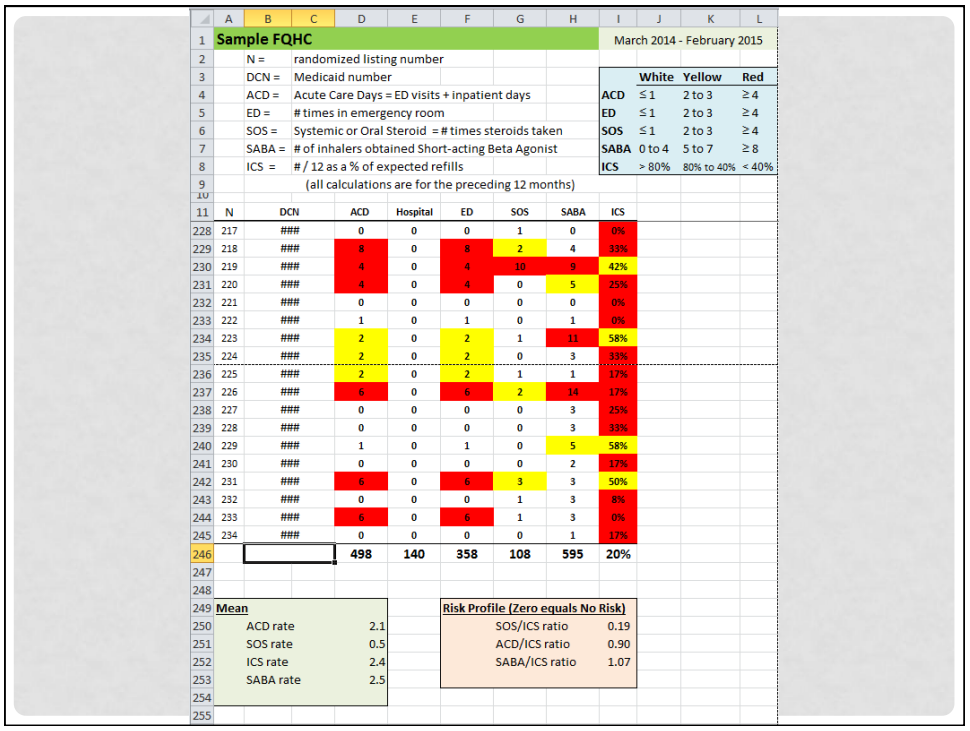
Suissa et al. *N Engl J Med.* 2000;343:332-336.

Patients and inhaled corticosteroids



Base: All patients (unweighted N=2509).

Asthma in AMERICA
A LANDMARK SURVEY
An Executive Summary



Sample FQHC — March 2014 - February 2015

N =	randomized listing number
DCN =	Medicaid number
ACD =	Acute Care Days = ED visits + inpatient days
ED =	# times in emergency room
SOS =	Systemic or Oral Steroid = # times steroids taken
SABA =	# of inhalers obtained Short-acting Beta Agonist
ICS =	# / 12 as a % of expected refills

(all calculations are for the preceding 12 months)

	White	Yellow	Red
ACD	≤ 1	2 to 3	≥ 4
ED	≤ 1	2 to 3	≥ 4
SOS	≤ 1	2 to 3	≥ 4
SABA	0 to 4	5 to 7	≥ 8
ICS	> 80%	80% to 40%	< 40%

N	DCN	ACD	Hospital	ED	SOS	SABA	ICS
217	###	0	0	0	1	0	0%
218	###	8	0	8	2	4	33%
219	###	4	0	4	10	9	42%
220	###	4	0	4	0	5	25%
221	###	0	0	0	0	0	0%
222	###	1	0	1	0	1	0%
223	###	2	0	2	1	11	58%
224	###	2	0	2	0	3	33%
225	###	2	0	2	1	1	17%
226	###	6	0	6	2	14	17%
227	###	0	0	0	0	3	25%
228	###	0	0	0	0	3	33%
229	###	1	0	1	0	5	58%
230	###	0	0	0	0	2	17%
231	###	6	0	6	3	3	50%
232	###	0	0	0	1	3	8%
233	###	6	0	6	1	3	0%
234	###	0	0	0	0	1	17%
		498	**140**	**358**	**108**	**595**	**20%**

Mean

ACD rate	2.1
SOS rate	0.5
ICS rate	2.4
SABA rate	2.5

Risk Profile (Zero equals No Risk)

SOS/ICS ratio	0.19
ACD/ICS ratio	0.90
SABA/ICS ratio	1.07

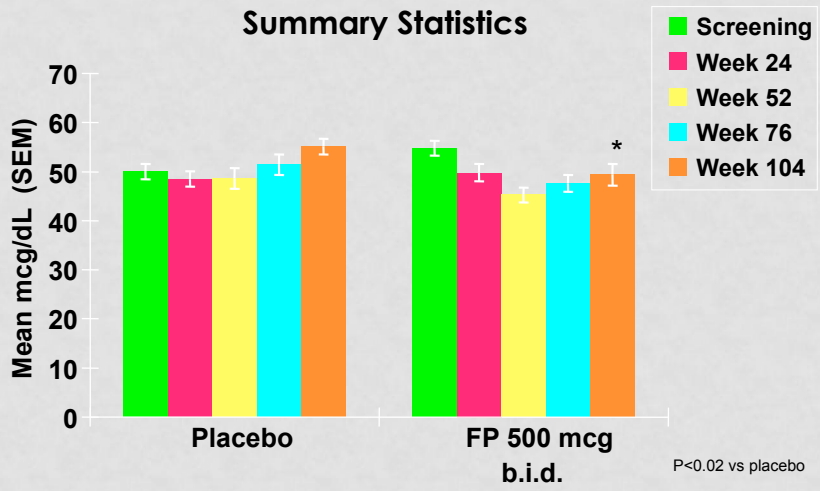
Underutilization of ICS

- 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

INHALED CORTICOSTEROIDS: POTENTIAL THERAPEUTIC RISKS

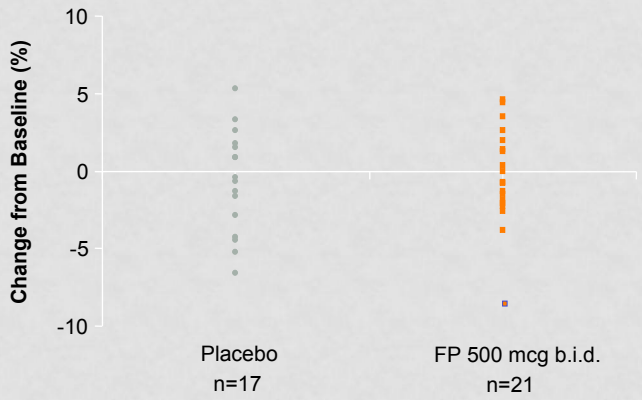
- HPA axis suppression
- Decreased bone mineral density
- Ophthalmic changes
- Growth Suppression
- Bruising

6-HOUR COSYNTROPIN TEST: PEAK PLASMA CORTISOL



Li JT et al. J Allergy Clin Immunol 1999;103:1062-1068

LONG-TERM SAFETY IN ADULTS MEAN LUMBAR SPINE BONE LOSS



Li JT et al. J Allergy Clin Immunol 1999;103:1062-1068

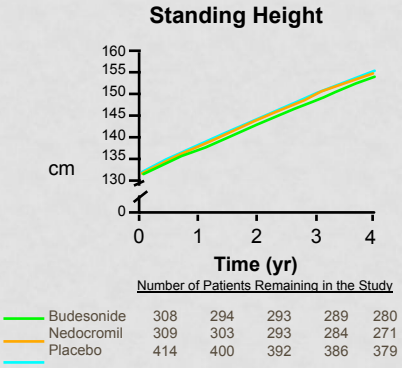
LONG-TERM SAFETY IN ADULTS OPHTHALMIC EXAMINATION

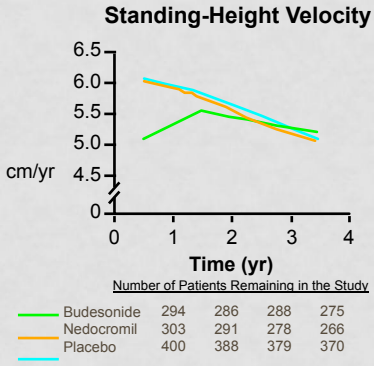
- No posterior subcapsular cataracts
- No new cortical cataracts; 1 placebo patient had a nuclear cataract (18 mos.)
- No diagnosis of glaucoma or increased IOP.

Rare incidences of glaucoma, increased intraocular pressure, and cataracts have been reported with inhaled corticosteroids

Li JT et al. J Allergy Clin Immunol 1999;103:1062-1068

LONG-TERM EFFECTS OF BUDESONIDE AND NEDOCROMIL ON GROWTH





Number of Patients Remaining in the Study

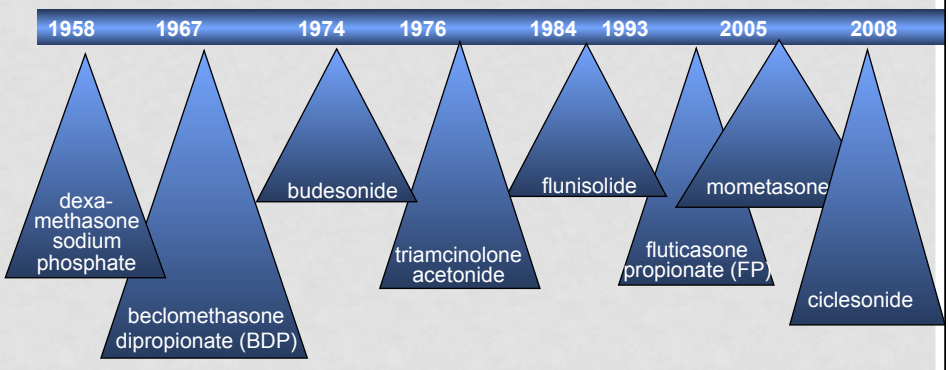
Budesonide	308	294	293	289	280
Nedocromil	309	303	293	284	271
Placebo	414	400	392	386	379

Number of Patients Remaining in the Study

Budesonide	294	286	288	275	
Nedocromil	303	291	278	266	
Placebo	400	388	379	370	

Childhood Asthma Management Program Research Group. *N Engl J Med* 2000;343:1054-1063.

History of Worldwide Glucocorticoid Development in the Treatment of Asthma



IMS MIDAS Database

PHARMACOLOGIC PROFILE OF NEWER ICS

- High topical anti-inflammatory activity
- High lipophilicity
- High glucocorticoid receptor selectivity/affinity
- Systemic bioavailability of approximately 30% with less than 1-5% available through the oral route

The clinical relevance of these pharmacologic properties has not been established.

LIPOPHILICITY OF NEW ICS

- Increased uptake in lung tissue
- Slow release from lung lipid compartment
- Increased affinity for steroid receptor
- Prolonged receptor occupancy/action

The clinical relevance of these pharmacologic properties has not been established.

Johnson M. J Allergy Clin Immunol 1996;97:169-176.

Relative potency of inhaled corticosteroids

Medication	Topical Potency (Skin Blanching)*	Corticosteroid Receptor Binding Half-Life	Receptor Binding Affinity
Fluticasone propionate (FP)	**1,200**	**10.5 hours**	**18.0**
Budesonide (BUD)	**980**	**5.1 hours**	**9.4**
Beclomethasone diprop (BDP)	**600**	**7.5 hours**	**13.5**
Triamcinolone acetonide (TAA)	**330**	**3.9 hours**	**3.6**
Flunisolide (FLU)	**330**	**3.5 hours**	**1.8**

*Numbers are assigned in reference to dexamethasone, which has a value of "1" in the MacKenzie test.

National Asthma Education and Prevention Program. *Expert Panel Report 2:*

INHALED ANTI-INFLAMMATORIES

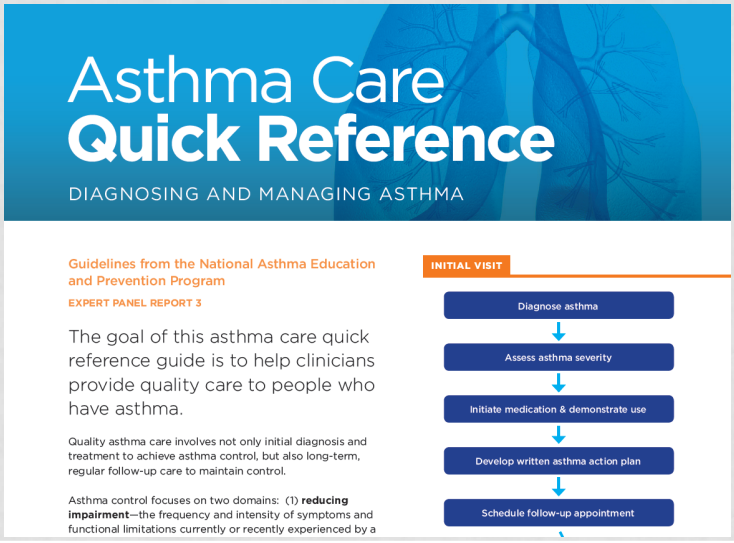
The provider/educator action is:

- Teach patient about delay onset of action
- Teach patient to take EVERY DAY (twice?)
- Demonstrate proper technique
- Have patient demonstrate technique
- Instruct patient to use a spacer for MDI
- Instruct patient to rinse & spit (eat or drink) after use
- Teach patient days supply per canister
- Calendar cues to check counter
- Consider reasons for non-response

	0–4 years of age			5–11 years of age			≥12 years of age		
Daily Dose	**Low**	**Medium***	**High***	**Low**	**Medium***	**High***	**Low**	**Medium***	**High***
MEDICATION									
Beclomethasone MDI†	N/A	N/A	N/A	80–160 mcg	>160–320 mcg	>320 mcg	80–240 mcg	>240–480 mcg	>480 mcg
40 mcg/puff				1–2 puffs 2x/day	3–4 puffs 2x/day		1–3 puffs 2x/day	4–6 puffs 2x/day	
80 mcg/puff				1 puff 2x/day	2 puffs 2x/day	≥3 puffs 2x/day	1 puff am, 2 puffs pm	2–3 puffs 2x/day	≥4 puffs 2x/day
Budesonide DPI†	N/A	N/A	N/A	180–360 mcg	>360–720 mcg	>720 mcg	180–540 mcg	>540–1,080 mcg	>1,080 mcg
90 mcg/inhalation				1–2 inhs† 2x/day	3–4 inhs† 2x/day		1–3 inhs† 2x/day		
180 mcg/inhalation					2 inhs† 2x/day	≥3 inhs† 2x/day	1 inh† am, 2 inhs† pm	2–3 inhs† 2x/day	≥4 inhs† 2x/day
Budesonide Nebules	0.25–0.5 mg	>0.5–1.0 mg	>1.0 mg	0.5 mg	1.0 mg	2.0 mg	N/A	N/A	N/A
0.25 mg	1–2 nebs†/day			1 neb† 2x/day					
0.5 mg	1 neb†/day	2 nebs†/day	3 nebs†/day	1 neb†/day	1 neb† 2x/day				
1.0 mg		1 neb†/day	2 nebs†/day		1 neb†/day	1 neb† 2x/day			
Ciclesonide MDI†	N/A	N/A	N/A	80–160 mcg	>160–320 mcg	>320 mcg	160–320 mcg	>320–640 mcg	>640 mcg
80 mcg/puff				1–2 puffs/day	1 puff am, 2 puffs pm–2 puffs 2x/day	≥3 puffs 2x/day	1–2 puffs 2x/day	3–4 puffs 2x/day	
160 mcg/puff				1 puff/day	1 puff 2x/day	≥2 puffs 2x/day		2 puffs 2x/day	≥3 puffs 2x/day
Flunisolide MDI†	N/A	N/A	N/A	160 mcg	320–480 mcg	≥480 mcg	320 mcg	>320–640 mcg	>640 mcg
80 mcg/puff				1 puff 2x/day	2–3 puffs 2x/day	≥4 puffs 2x/day	2 puffs 2x/day	3–4 puffs 2x/day	≥5 puffs 2x/day

	0–4 years of age			5–11 years of age			≥12 years of age		
Daily Dose	**Low**	**Medium***	**High***	**Low**	**Medium***	**High***	**Low**	**Medium***	**High***
MEDICATION									
Fluticasone MDI†	176 mcg	>176–352 mcg	>352 mcg	88–176 mcg	>176–352 mcg	>352 mcg	88–264 mcg	>264–440 mcg	>440 mcg
44 mcg/puff	2 puffs 2x/day	3–4 puffs 2x/day		1–2 puffs 2x/day	3–4 puffs 2x/day		1–3 puffs 2x/day		
110 mcg/puff		1 puff 2x/day	≥2 puffs 2x/day		1 puff 2x/day	≥2 puffs 2x/day		2 puffs 2x/day	3 puffs 2x/day
220 mcg/puff								1 puffs 2x/day	≥2 puffs 2x/day
Fluticasone DPI†	N/A	N/A	N/A	100–200 mcg	>200–400 mcg	>400 mcg	100–300 mcg	>300–500 mcg	>500 mcg
50 mcg/inhalation				1–2 inhs† 2x/day	3–4 inhs† 2x/day		1–3 inhs† 2x/day		
100 mcg/inhalation				1 inh† 2x/day	2 inhs† 2x/day	>2 inhs† 2x/day		2 inhs† 2x/day	≥3 inhs† 2x/day
250 mcg/inhalation						1 inh† 2x/day		1 inh† 2x/day	≥2 inhs† 2x/day
Mometasone DPI†	N/A	N/A	N/A	110 mcg	220–440 mcg	>440 mcg	110–220 mcg	>220–440 mcg	>440 mcg
110 mcg/inhalation				1 inh†/day	1–2 inhs† 2x/day	≥3 inhs† 2x/day	1–2 inhs† pm	3–4 inhs† pm or 2 inhs† 2x/day	≥3 inhs† 2x/day
220 mcg/inhalation					1–2 inhs†/day	≥3 inhs† divided in 2 doses	1 inh† pm	1 inh† 2x/day or 2 inhs† pm	≥3 inhs† divided in 2 doses

- ICS comparable dose chart by age group, Pages 8 and 9



Asthma Care Quick Reference

DIAGNOSING AND MANAGING ASTHMA

Guidelines from the National Asthma Education and Prevention Program

EXPERT PANEL REPORT 3

The goal of this asthma care quick reference guide is to help clinicians provide quality care to people who have asthma.

Quality asthma care involves not only initial diagnosis and treatment to achieve asthma control, but also long-term, regular follow-up care to maintain control.

Asthma control focuses on two domains: (1) **reducing impairment**—the frequency and intensity of symptoms and functional limitations currently or recently experienced by a

INITIAL VISIT

Diagnose asthma

Assess asthma severity

Initiate medication & demonstrate use

Develop written asthma action plan

Schedule follow-up appointment

JOINT TASK FORCE PRACTICE PARAMETERS

AAAAI, ACAAI, JCAI

Ann Allergy Asthma Immunol 113 (2014) 143–159

Contents lists available at ScienceDirect

ELSEVIER

Practice Parameter

Management of acute loss of asthma control in the yellow zone: a practice parameter

CrossMark

Chitra Dinakar, MD; John Oppenheimer, MD; Jay Portnoy, MD; Leonard B. Bacharier, MD; James Li, MD; Carolyn M. Kercsmar, MD; David Bernstein, MD; Joann Blessing-Moore, MD; David Khan, MD; David Lang, MD; Richard Nicklas, MD; Christopher Randolph, MD; Diane Schuller, MD; Sheldon Spector, MD; Stephen A. Tilles, MD; and Dana Wallace, MD

Chief Editors: Chitra Dinakar, MD; John Oppenheimer, MD; Jay Portnoy, MD

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Practice Parameter Workgroup: Chitra Dinakar, MD; John Oppenheimer, MD; Jay Portnoy, MD; Leonard Bacharier, MD; James Li, MD; Carolyn Kercsmar, MD

WHAT TO DO IN THE "YELLOW ZONE"

Summary Statement 6: Advise patients currently treated with daily low-to-moderate dose inhaled corticosteroid (ICS) therapy to consider increasing the total ICS dose per 24 hours (ie, quadrupling) for managing loss of asthma control in the yellow zone. (Option: B Evidence)

Summary Statement 7: For children younger than 6 years with recurrent wheezing and risk factors for subsequent asthma (ie, positive modified asthma predictive index), consider initiating high-dose ICS or oral montelukast at the early signs of wheezing illnesses to decrease intensity of symptoms. (Option: B Evidence)

Summary Statement 8: For patients with mild to moderate asthma, consider recommending symptom-driven use of ICS with concomitant inhaled β agonist for control of yellow zone symptoms. (Option: B Evidence)

Asthma Topics

1. **Role of Adjustable Medication Dosing in Recurrent Wheezing and Asthma**
2. **Role of Long Acting Anti-Muscarinic Agents (LAMAs) in Asthma Management as Add-on to ICSs**
3. **Role of Bronchial Thermoplasty in Adult Severe Asthma**
4. **Role of Fractional exhaled Nitric Oxide (FeNO) in Diagnosis, Medication Selection, and Monitoring Treatment Response in Asthma**
5. **Role of Remediation of Indoor Allergens (e.g., House Dust Mites/Animals/Pests) in Asthma Management**
6. **Role of Immunotherapy in Treatment of Asthma**

NHLBI Advisory Council Asthma Expert Working Group, January 2015

NIH National Heart, Lung, and Blood Institute

LONG-ACTING BETA AGONISTS

AND ICS/LABA COMBINATIONS

DISCLOSURE

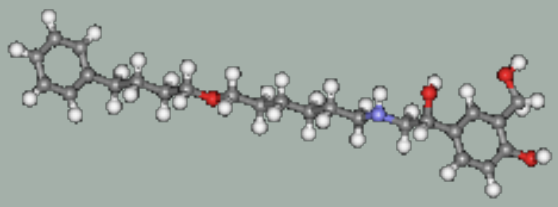
- Dr. Francisco has no financial interest in any commercial entity discussed in this presentation
- Dr. Francisco will not discuss experimental or off-label use of medications or devices

OBJECTIVES

1) Describe the mode of action, therapeutic value and role in the management of asthma.

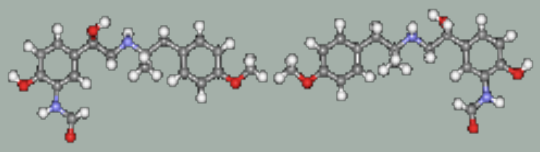
2) Identify potential adverse effects and strategies for managing patients to minimize side effects

3) Evaluate the cost, barriers and potential benefit of this class of medications.



Salmeterol (Serevent)

Racemic
Lipophilic: anchors in the cell wall to prolong effect
Onset 20-40 min
Duration 12 hours



Formoterol (Foradil)

Racemic
Onset 15 min
Duration 12 hrs

LONG-ACTING B2 AGONIST MECHANISM OF ACTION

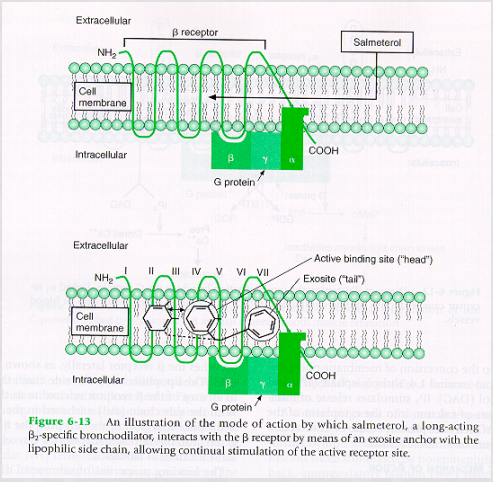


Figure 6-13 An illustration of the mode of action by which salmeterol, a long-acting β_2-specific bronchodilator, interacts with the β receptor by means of an exosite anchor with the lipophilic side chain, allowing continual stimulation of the active receptor site.

From: Rau JL. Respiratory Care Pharmacology 6th ed. 2002. p.124.

Long-acting β_2 adrenergic receptor agonists

- Relax airway smooth muscle
- Cause bronchodilation
- Same mechanisms as SABA

Chronic treatment with a receptor agonists often leads to receptor desensitization and a diminution of effect.

Goodman & Gilman's The Pharmacological Basis of Therapeutics - 11th Ed. (2006)

LABA POTENTIAL ADVERSE EFFECTS

- Tachycardia, skeletal muscle tremor, hypokalemia
- Diminished broncho-protective effect within 1-6 weeks of chronic therapy
- Increase risk of severe, life-threatening exacerbations

LABA CONTROVERSY

- Increased risk of life-threatening and fatal exacerbations related to LABA in asthma
  - Castle et al, BMJ 1993;306:1034
- Respiratory related death or life-threatening experiences in all patients(1.98/1000 person-years)
  - 0.48/1000 for all persons with asthma
- Disparate increase in combined asthma- related death or life-threatening experience
  - Increase in respiratory related deaths and life threatening experiences in African-Americans (5.8 vs. 1.2 /1000 person-years for Caucasians)
    - Nelson et al Chest 2006;129:15-26.
    - (SMART study)

CAUSE OF DEATH RELATED TO LABAS

- Worsened asthma control
  - Repeated stimulation of β receptors results in desensitization
    - Uncoupling and internalization of receptors
  - Followed by downregulation
    - Decrease in receptor density and receptor gene expression
  - Increased bronchial hyperreactivity
  - Reduced response to rescue inhaler

LABA CONTROVERSY: WHY THE RACIAL DIFFERENCE?

At screening, African Americans:

- Had a lower PEF (78% vs. 85%)
- Had more nocturnal sx. (59% vs. 67%)
- Had increased hospitalizations, ED visits
- Had less ICS use (38% vs. 49%)
- Different patient behaviors?
- Genetic variation in β adrenergic receptor?

B_2–ADRENOCEPTOR POLYMORPHISM

- Variant of the β_2 adrenergic receptor in which glycine replaces arginine at position 16 (Gly 16) shows an increased rate of down-regulation in response to agonist exposure.
- Polymorphism occurs with equal frequency in asthmatic and non-asthmatic populations.
- Some evidence that asthmatics who are homozygous for Gly 16 receptors are less responsive to β_2-agonist therapy than wild-type controls

Martinez, F.D., Graves, P.E., Baldini, P.E., *et al.* Genetic polymorphisms of the β_2 adrenoceptor and response to albuterol in children with and without a history of wheezing. *J. Clin. Invest.*, 1997, *100*:3184-3188.

Tan, S., Hall, I.P., Dewar, J., *et al.* Association between β_2 -adrenoceptor polymorphism and susceptibility to bronchodilator desensitization in moderately severe stable asthmatics. *Lancet,* 1997, *350*:995-999.

β_2 –adrenoceptor polymorphism

- Polymorphism of the β_2 receptor did not appear to determine the response to long-term inhaled β_2–agonist treatment[1]
- The complexity of the genotype by response effects makes clinical application of the ADRbeta$_2$ variations limited[2]

[1] Hancox, R.J., Sears, M.R., and Taylor, D.R. Polymorphism of the β_2-adrenoceptor and the response to long-term β_2 -agonist therapy in asthma. *Eur. Respir. J.*, 1998, *11*:589-593.

[2] Hawkins GA, Weiss ST, Bleecker ER. Clinical consequences of ADRbeta2 polymorphisms. *Pharmacogenomics.* 2008 Mar;9(3):349-58

LABA CONTROVERSY

- Meta-analysis of 19 trials and 33,826 participants
- LABA increases risk for hospitalization for an asthma exacerbation (OR=2.6), life-threatening asthma attack (OR=1.8), and asthma–related death (OR=3.5)
- Increase in asthma-related death of 0.06% - 0.07%/6 months
- Salmeterol may be responsible for 4000 of the 5000 asthma deaths/year!

Salpeter et al. Ann Int Med 2006;144:904-912.

LABA CONTROVERSY

Pro

- Reduction in asthma exacerbations
- Widely-used to treat COPD as well
  - Still, β agonists increased respiratory deaths (rr=2.5)

    vs. decreased respiratory deaths with anticholinergics (rr=0.3)

Con

- Increase asthma deaths after LABAs were introduced
- Similar risks for morbidity and mortality exist for salmeterol vs formoterol
- Associated with unnecessary hospitalization, ICU admission and death

SALMETEROL WARNING

WARNING

Long-acting beta$_2$-adrenergic agonists, such as salmeterol, the active ingredient in SEREVENT DISKUS, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, SEREVENT DISKUS should only be used as additional therapy for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies, including SEREVENT DISKUS. Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT® Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo) (see WARNINGS and CLINICAL TRIALS: Asthma: *Salmeterol Multi-center Asthma Research Trial*).

"This information could be used to reassess whether these agents should be withdrawn from the market" Salpeter et al.

EPR-3 CONCLUSIONS ABOUT LABA USE

- **ALWAYS** use adjunctively to ICS
- **DO NOT** use as monotherapy for asthma
- Not to be used for quick relief
- May be used before exercise to prevent EIB

EPR-3: SAFETY OF LABA

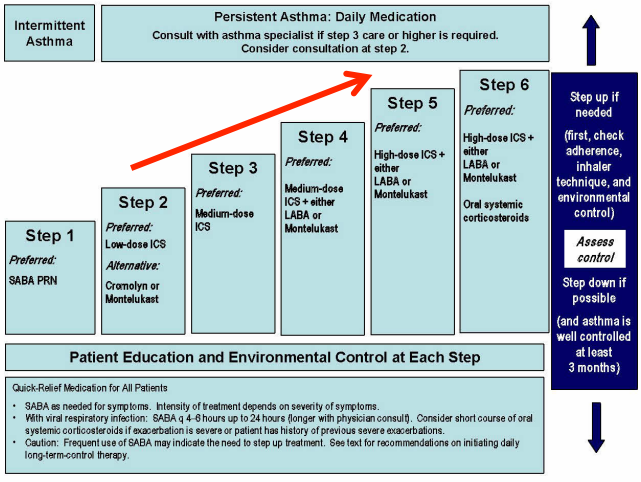
- Addition of LABA when asthma is not well controlled on low-medium dose ICS decreases symptoms, exacerbations and SABA use
- Black box warning warranted
- Recognize the risk
- Give equal weight to increasing ICS or addition of LABA (note step 3 in age group 0-4 years)

EPR3 Guide to Stepping Therapy Up or Down

- **Step up IF** needed
- FIRST, check adherence
- THEN, check inhaler technique
- AND, check environmental control
- **Step Down**, IF asthma is well controlled for 3 months or longer

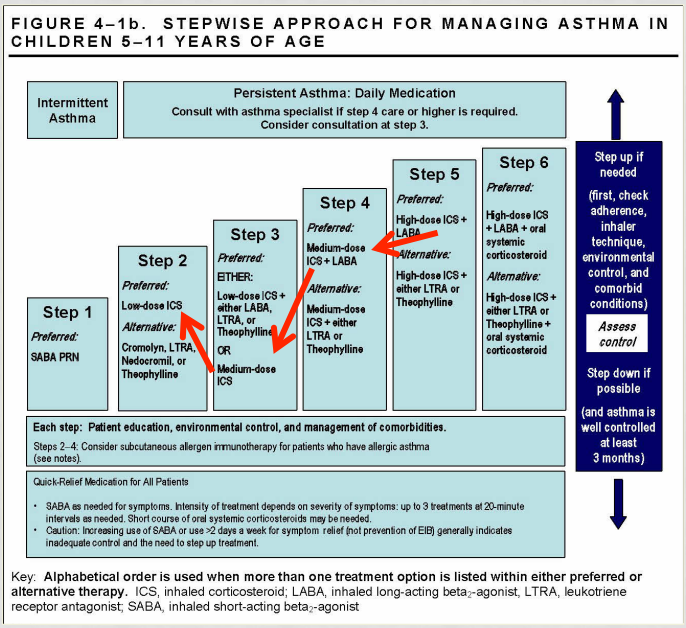
Must base therapy step changes on assessment of adherence, inhalation technique and triggers

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



Key: **Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy.** ICS, inhaled corticosteroid; LABA, inhaled long-acting beta$_2$-agonist; SABA, inhaled short-acting beta$_2$-agonist

Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma
NIH Publication No. 08-4051



Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma
NIH Publication No. 08-4051

CHILDREN 5 TO 11 YEARS OLD

Moderate persistent asthma or asthma inadequately controlled by low dose ICS

Step 3 care equal weight given to:

- Increasing dose to medium dose ICS
- Add LABA to low dose ICS

CHILDREN 5 TO 11 YEARS OLD

LABA/ICS combinations are the preferred therapy for long term control in moderate to severe persistent asthma (Step 4 care or higher)

[Evidence B]

CHILDREN 5 TO 11 YEARS OLD

Severe persistent asthma or asthma inadequately controlled on Step 3 Care

The combination of LABA & ICS is preferred

YOUTHS ≥ 12 YEARS AND ADULTS

LABA/ICS combinations are the preferred therapy for long term control in moderate to severe persistent asthma (Step 4 care or higher)

[Evidence A]

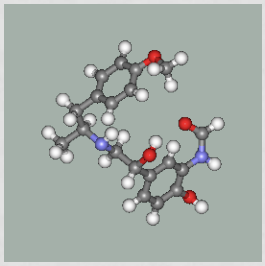
LABA/ICS ADVERSE REACTIONS

- Nasopharyngitis
- Dysphonia
- Headache
- Upper respiratory tract infection
- Pharyngo-laryngeal pain
- Sinusitis
- Stomach discomfort
- Tremor
- Dysrhythmias

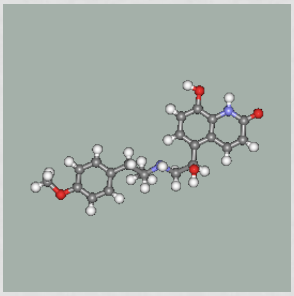
ICS/LABA THERAPY DOSING- APPLYING EPR3 GUIDELINES

- Which ICS/LABA products can be used in step 5 for ages 12 years and older
- Which ICS/LABA products can be used for step 4 for children ages 5-11?
- What other considerations are important in selecting an ICS/LABA product?

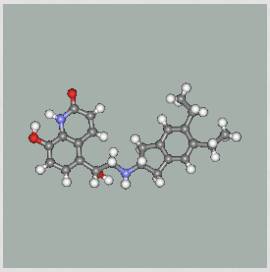
OTHER LABA AGENTS (COPD)



R,R Formoterol



Carmoterol



indacaterol

SUMMARY

- Anchorage of LABAs in lipophilic receptors gives them their long duration of action
- The addition of LABA to ICS should be given equal weight to increasing ICS
- Do not use LABA as monotherapy
- Several LABAs are under development that may offer once daily dosing lipiphilic ICS

LEUKOTRIENE MODIFIERS:

LEUKOTRIENE RECEPTOR ANTAGONISTS (LTRA) AND 5-LIPOXYGENASE INHIBITOR

OBJECTIVES

1) Describe the mode of action, therapeutic value and role in the management of asthma.

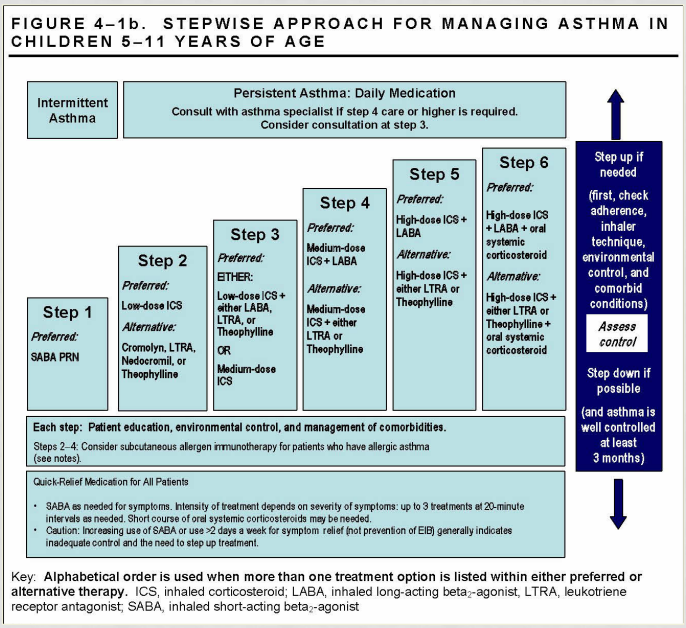
2) Identify potential adverse effects and strategies for managing patients to minimize side effects

3) Evaluate the cost, barriers and potential benefit of this class of medications.

"PREFERRED" VS. "ALTERNATIVE"

- "If alternative treatment is used and response is inadequate, DISCONTINUE it and use the preferred treatment BEFORE stepping up."

  (EPR3, p. 305, 306 & 343)



Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma
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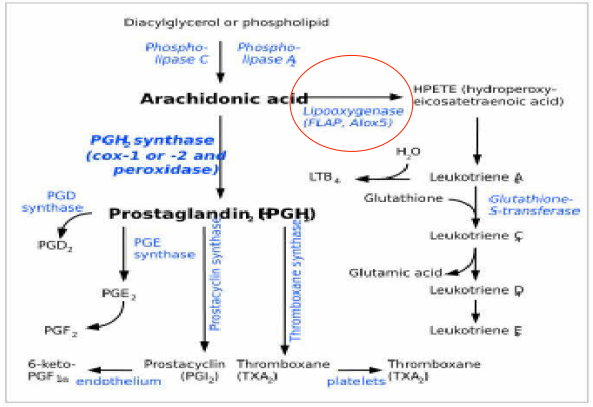
CYSTEINYL LEUKOTRIENES

- 1982 Bengt Samuelsson and his team in Stockholm elucidated the formation of cysteinyl leukotrienes and the 5-lipoxygenase pathway
- Products of arachidonic acid metabolism
- Abundantly produced in mast cells, eosinophils and alveolar macrophages

LEUKOTRIENE SYNTHESIS



Leukotrienes are synthesized in the cell from arachidonic acid by 5-lipoxygenase.

CYSTEINYL LEUKOTRIENES

- LTC4, LTD4, LTE4
- Bind to CysLT receptors
  - in the airways
  - on other proinflammatory cells
- Important mediators of inflammation and modulate inflammatory response in asthma

CYSTEINYL LEUKOTRIENES

- LTC4, LTD4, and LTE4 are released in the airways after exposure to allergens and are associated with changes in airway hyperresponsiveness
- LTC4 and LTD4 are considerably more potent than LTE4 as a cause of airway smooth muscle constriction

CYSTEINYL LEUKOTRIENES

Increased concentrations of CysLTs were not substantially reduced by treatment with inhaled corticosteroids (ICSs), suggesting that the LT pathway is relatively independent of regulation by corticosteroids

Mondino C, et. al, Effects of inhaled corticosteroids on exhaled leukotrienes and Prostanoids in asthmatic children. *J Allergy Clin Immnol.* 2004;114:76-767.

Louis R, et. al., The relationship between airways inflammation and asthma severity,. *Am J Respir Crit Care Med.* 2000;161:9-16

INITIAL THERAPY: ICS VS LTRA

- Two cohorts: patients on ICS or on LTRA as initial therapy
- 31,860 patients
- Asthma related charges included
  - ED visits and hospitalizations
  - Office visits
  - Asthma medication use

O'Connor, et. al., Inhaled corticosteroids vs. leukotriene receptor antagnoists: health care costs across varying asthma severities. *Ann Allergy Asthma Immunol.* 2006 Aug;97 (2):236-243

INITIAL THERAPY: ICS VS LTRA

Conclusion:

Across varying degrees of severities, treating asthma with an ICS as initial controller therapy leads to less healthcare resource utilization than does using an LTRA s initial therapy

O'Connor, et. al., Inhaled corticosteroids vs. leukotriene receptor antagnoists: health care costs across varying asthma severities. *Ann Allergy Asthma Immunol.* 2006 Aug;97 (2):236-243

EPR-3 RECOMMENDATIONS

- LTRAs are alternative, but not preferred, therapy for the treatment of mild persistent asthma (Step 2 care) [Evidence A]
- LTRAs can also be used as adjuctive therapy with ICS, but in youths ≥ 12 years & adults they are not preferred compared to adding LABA [Evidence A]

MONTELUKAST

Montelukast is a selective leukotriene receptor antagonist that inhibits the CysLT1 receptor, specifically inhibiting the physiologic actions of LTD4 at the CysLT1 receptor

DOSE OF MONTELUKAST

- Adults and children over 15 years old
  - 10 mg p.o. Q HS
- Children 6 to 14 years old
  - 5 mg, chewed, Q HS
- Children 2 to 5 years old
  - 4mg, chewed, Q HS
- Children 6 to 23 months old
  - 4mg oral granules, mixed, Q HS

DOSE OF MONTELUKAST

- Exercise induce bronchospasm (EIB) in adults and in children over 15 years old
  - 10mg Q HS

Review

Pharmacology

Pharmacology 2014;94:60–70
DOI: 10.1159/000366164

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Montelukast-Induced Adverse Drug Reactions: A Review of Case Reports in the Literature

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LITERATURE REVIEW OF CASE REPORTS
MONTELUKAST-INDUCED REACTIONS

Key Words
Montelukast · Adverse drug reaction · Anti-leucotrienes · Allergy · Asthma · Hypersensitivity · Pharmacovigilance · Churg-Strauss syndrome · Toxicity

Abstract
Background: Montelukast, a leucotriene receptor antagonist, binds the cysteinyl leucotriene type 1 receptor. Montelukast is commonly prescribed to asthma patients as add-on therapy to inhaled corticosteroids. Several clinical trials emphasized that montelukast can be considered a safe drug. However, recent evidence reconsidered the benefit/risk ratio of the use of montelukast for both paediatric and adult patients. ***Summary:*** The present review analyzed the previous published case reports regarding montelukast-induced adverse drug reactions (ADRs). They included agitation, anxiety, depression, sleep disturbance, hallucinations, suicidal thinking and suicidality, tremor, dizziness, drowsiness, neuropathies and seizures. The immune system can be involved, in particular, cases of Churg-Strauss syndrome have been published. Furthermore, it can induce hypersensitivity reactions, including anaphylaxis and eosinophilic infiltration. In addition, hepatobiliary, pancreatic and uropoietic disorders have been observed. Some of these cases are characterized by severe prognosis (i.e. neurological deficit and fatal hepatotoxicity). ***Key Message:*** The use of montelukast can be burdened by several ADRs, of which physicians should be aware in their clinical practice. A better understanding of the mechanisms causing ADRs after using montelukast could help researchers and clinicians in defining a risk-reduction strategy aimed to lessen montelukast toxicity. More accurate epidemiological studies, in order to discover risk factors favouring montelukast-associated ADRs, are demanded.

Introduction

Montelukast sodium is a selective leucotriene receptor antagonist (LTRA) that specifically blocks the cysteinyl leucotriene type 1 (CysLT1) receptor. CysLTs (LTC 4, LTD 4 and LTE 4) are important pro-asthmatic lipid mediators binding to CysLT receptors. The CysLT1 receptor is localized in the human airways and synthesized by a variety of cells, including mast cells, eosinophils, baso-

ZARFIRLUKAST

Zafirlukast is a selective and competitive receptor antagonist of LTD4 and LTE4

DOSE OF ZARFIRULAST

- Adults and children over 12 years old
  - 20mg p.o. BID on an empty stomach, 1 hr ac or 2 hr pc
- Children 5 to 11 years old
  - 10mg p.o. BID on an empty stomach, 1 hr ac or 2 hr pc

ADVERSE REACTIONS

- GI: abdominal pain, dyspepsia, nausea, vomiting and diarrhea
- Headache
- Fever
- Asthenia
- Generalized pain

PRECAUTIONS

- May increase liver enzymes
- Coadministration with warfarin increases Prothromin Time (PT)

ZILEUTON

Zileuton is a specific inhibitor of 5-lipoxygenase and thus inhibits LTB4, LTC4, LTD4, and LTE4 formation.

Both the R(+) and S(−) enantiomers are pharmacologically active as 5-lipoxygenase inhibitors in vitro and in vivo.

DOSE OF ZILEUTON

Adults and children over 12 years old

1200mg (2 x 600mg extended release tablets) p.o. BID on an empty stomach 1hr ac or 2 hr pc

ADVERSE REACTIONS

- GI: abdominal pain, dyspepsia, nausea
- Headache
- Myalgia
- Asthenia
- Unspecified pain

PRECAUTIONS

- Elevation of ALT, use with caution in patients with significant alcohol consumption and in patients with history of liver disease
- Monitor liver enzymes once a month x 3 months, then every 2 to 3 months
- Pregnancy category C

DRUG INTERACTIONS

- Metabolized by CYP3A4
- Known to increases levels of
  - theophylline
  - warfarin
  - terfenadine
  - propranolol
  - pimozide

EPR-3 RECOMMENDATIONS

- Zileuton can be used as an alternative, but not preferred adjunctive therapy in adults [Evidence D]
- Zileuton is less desirable due to limited data on efficacy and the need for liver function monitoring

IMMUNOMODULATORS
OMALIZUMAB AND IMMUNOTHERAPY

PUBLIC DOMAIN, OPEN SOURCE (SEE ORIGINAL FILES)

- http://www.worldallergy.org/educational_programs/gloria/slides/US/Immunotherapy.ppt
- http://www.worldallergy.org/UserFiles/file/Monoclonal%20antibodies%20-%20El-Gamal.pdf