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"**

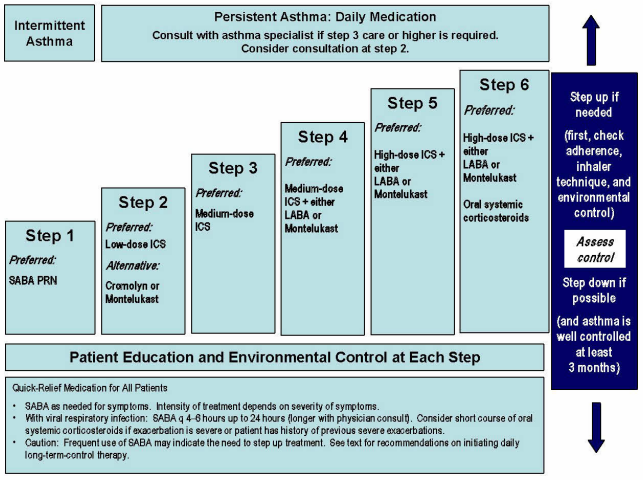
OBJECTIVES

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.

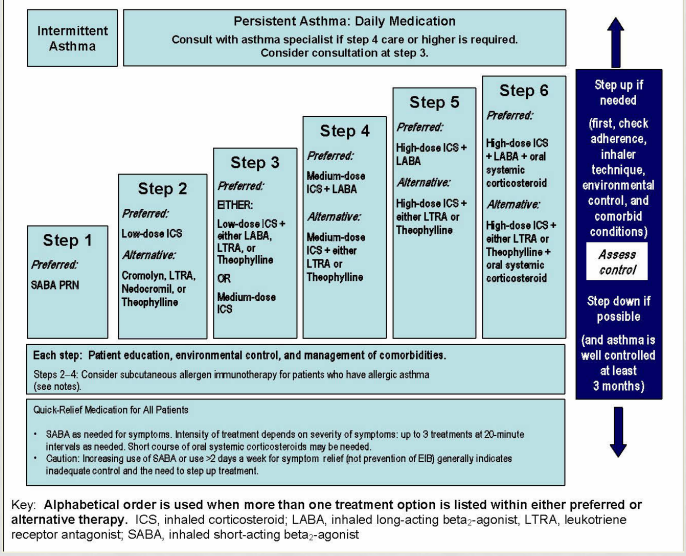
FIGURE 4–1a. STEPWISE APPROACH FOR MANAGING ASTHMA IN CHILDREN 0–4 YEARS OF AGE



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

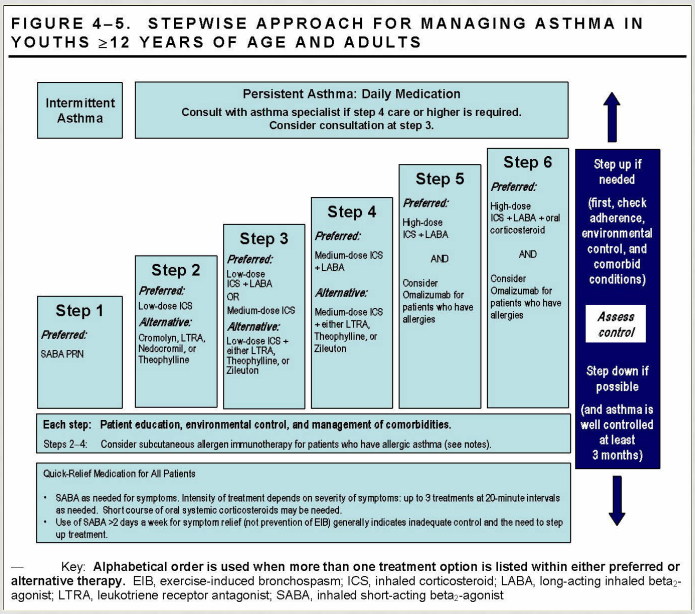
Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma
NIH Publication No. 08-4051

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

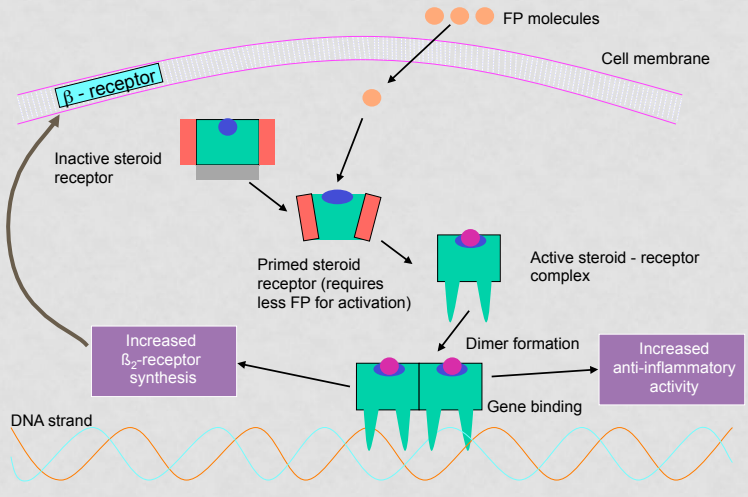


Key: **Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy.** ICS, inhaled corticosteroid; LABA, inhaled long-acting beta$_2$-agonist, LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta$_2$-agonist

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



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

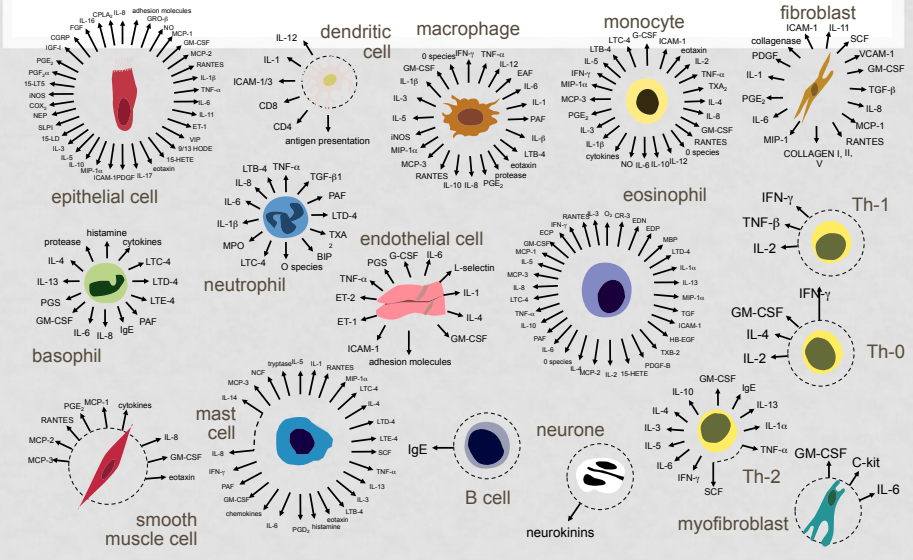
The daily use of ICS results in the following:

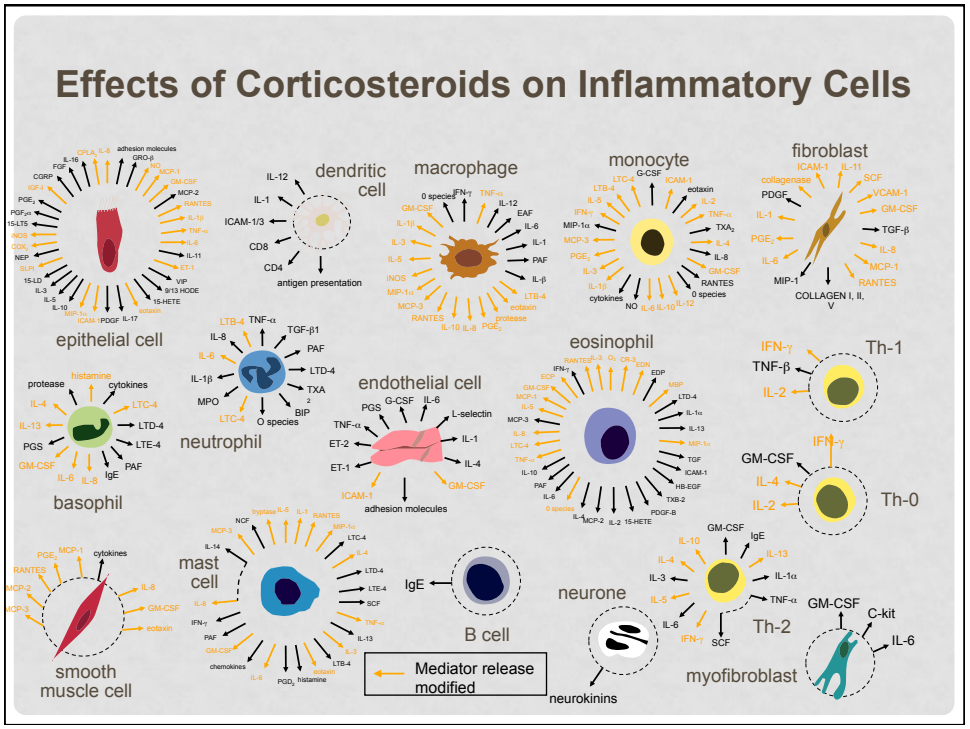
- **Asthma symptoms will diminish. Improvement will continue gradually over 60-90 days**
- **Occurrence of severe exacerbations is greatly reduced**
- **Need for quick-relief medication decreases**
- **Lung function improves significantly, as measured by FEV_1, FEV_1/FVC, PEF(?) & airway hyperresponsiveness**

Problems due to asthma may return if patients stop taking ICS

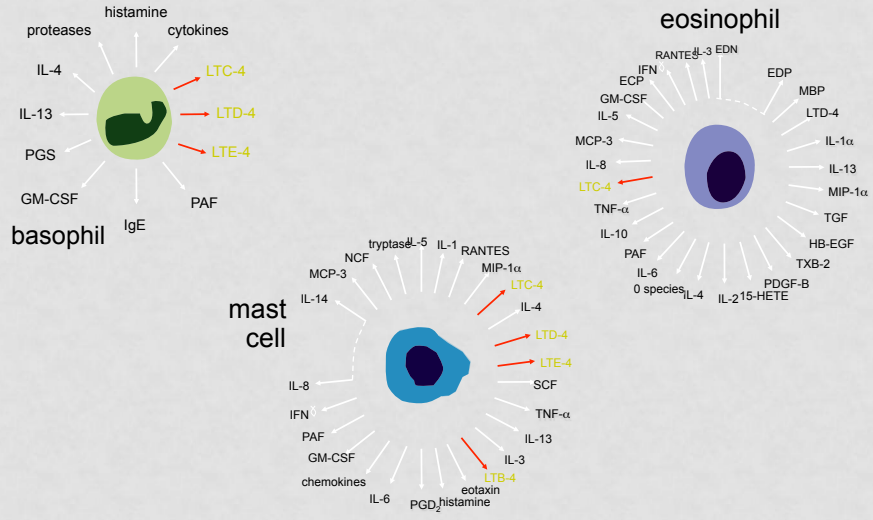
***Guidelines for the Diagnosis and Management of Asthma.* 2007.**

Mechanisms involved in inflammation

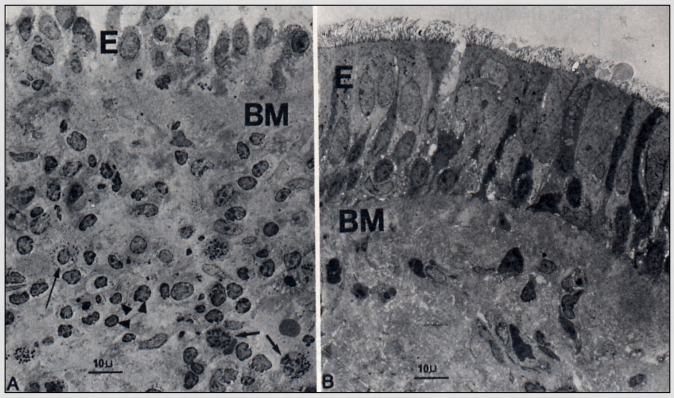




LEUKOTRIENES



EFFECTS OF INHALED CORTICOSTEROIDS ON INFLAMMATION



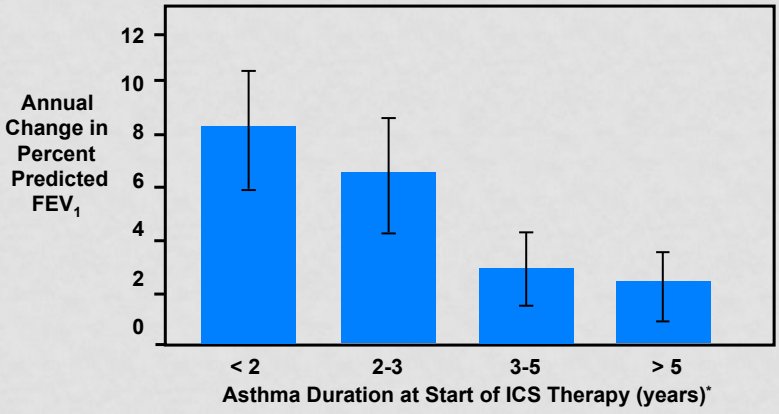
Pre– and post–3-month treatment with budesonide (BUD) 600 mcg b.i.d.

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

E = Epithelium

BM = Basement Membrane

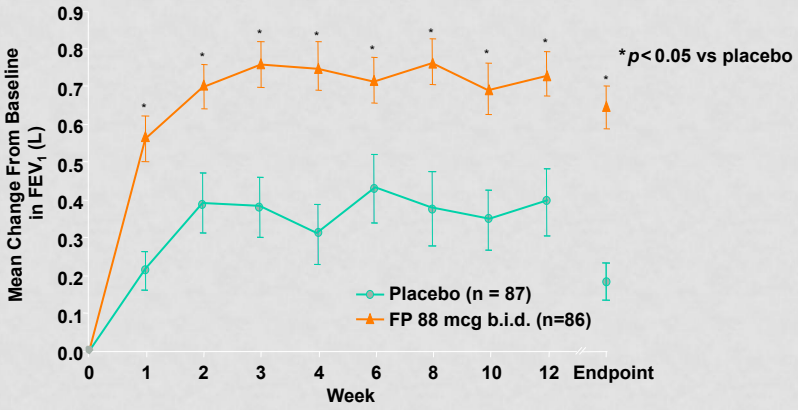
MEAN ANNUAL INCREASE IN FEV_1 DURING ICS THERAPY IN PEDIATRIC PATIENTS



*Mean values and 95% confidence intervals are shown.

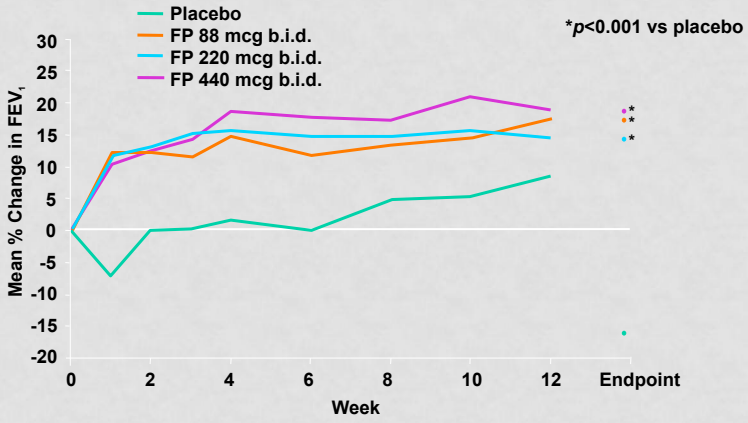
Agertoft L, Pedersen S. *Respir Med.* 1994;88:373-381.

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



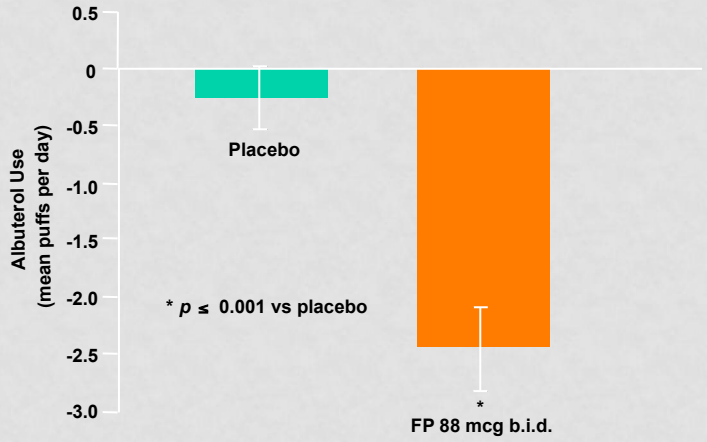
Adapted from Galant SP et al. *Ann Allergy Asthma Immunol.* 1996;77:112-118.

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



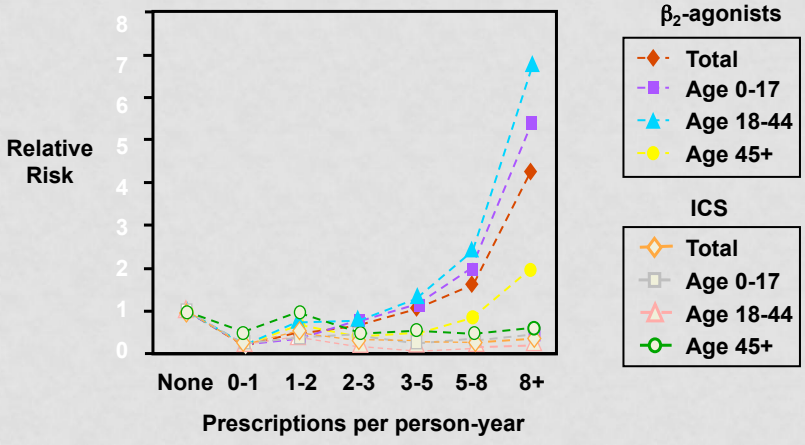
Adapted from Wolfe JD et al. *Clin Ther.* 1996;18(4): 635-646.

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



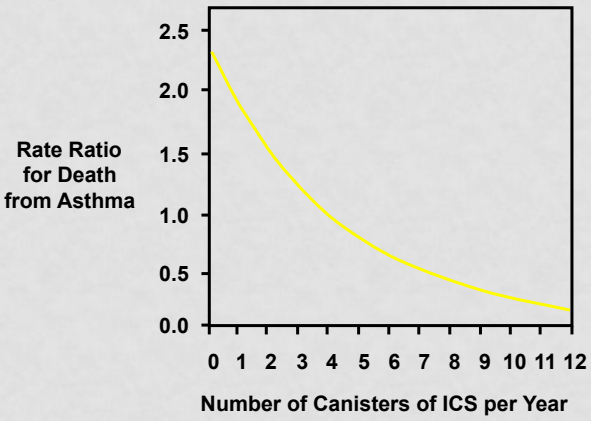
Galant SP et al. *Ann Allergy Asthma Immunol.* 1996;77:112-118.

Relative Risk of Hospitalization in the United States



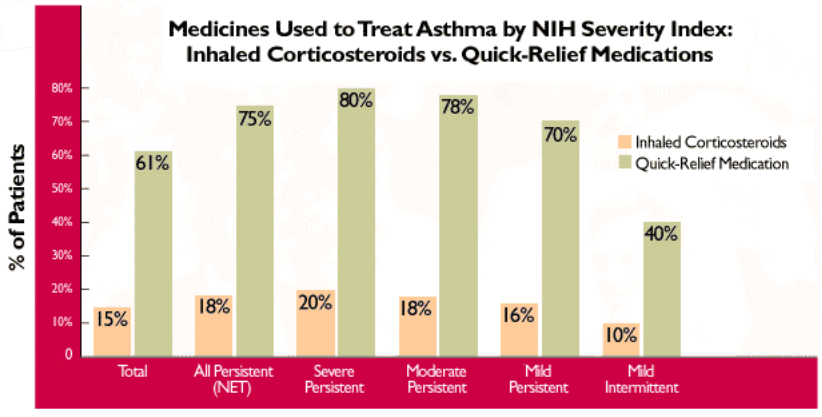
Donahue et al. *JAMA.* 1997;277:887-891.

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



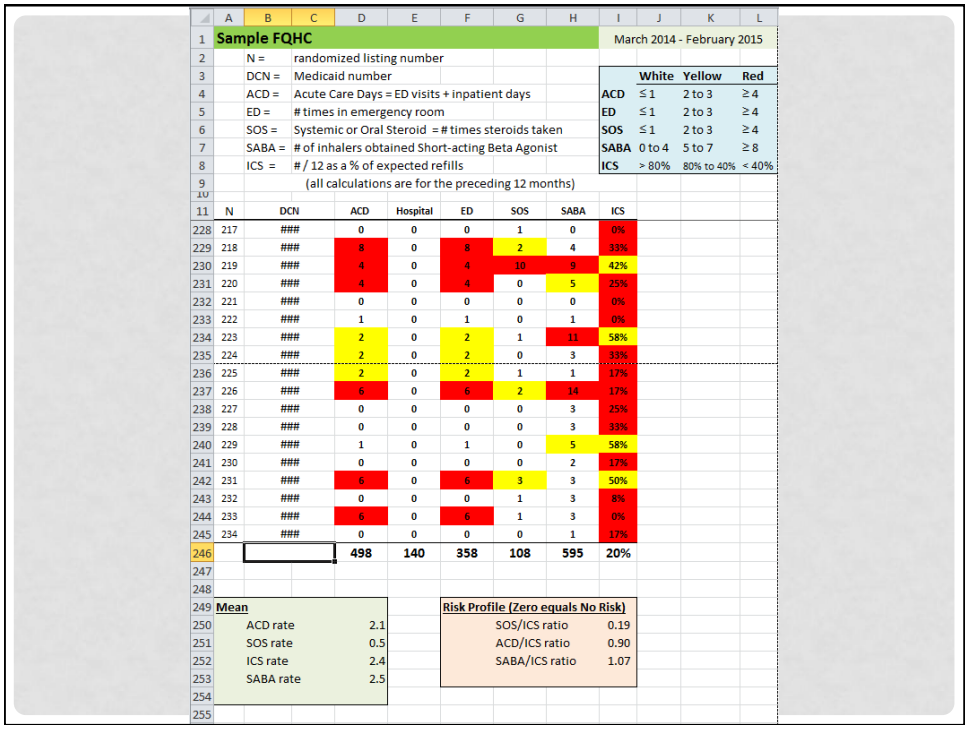
Suissa et al. *N Engl J Med.* 2000;343:332-336.

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

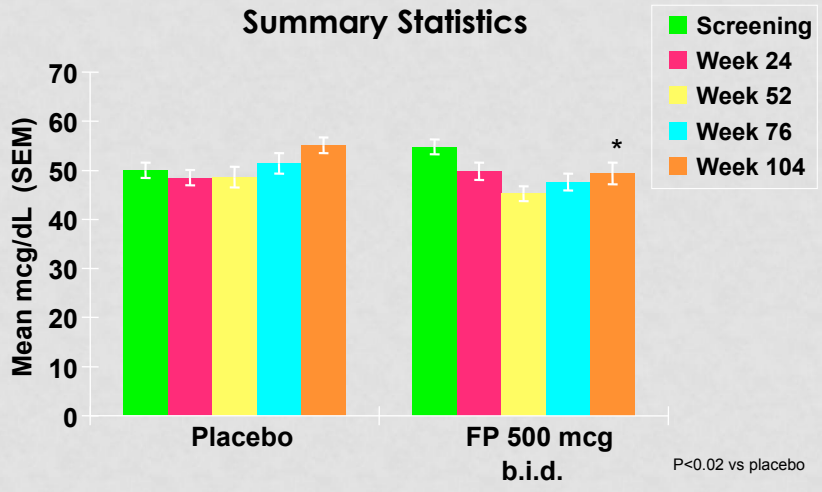
Underutilization of ICS

- 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

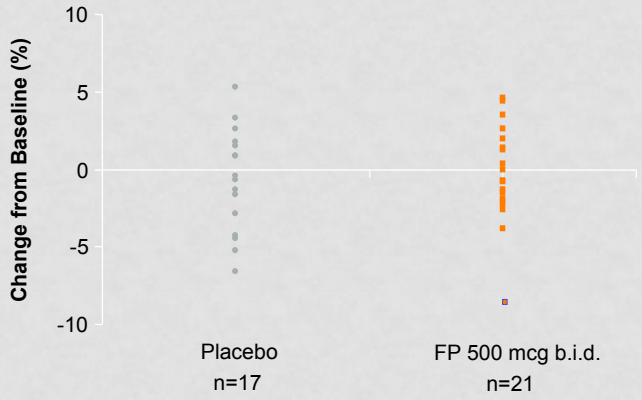
- HPA axis suppression
- Decreased bone mineral density
- Ophthalmic changes
- Growth Suppression
- Bruising

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

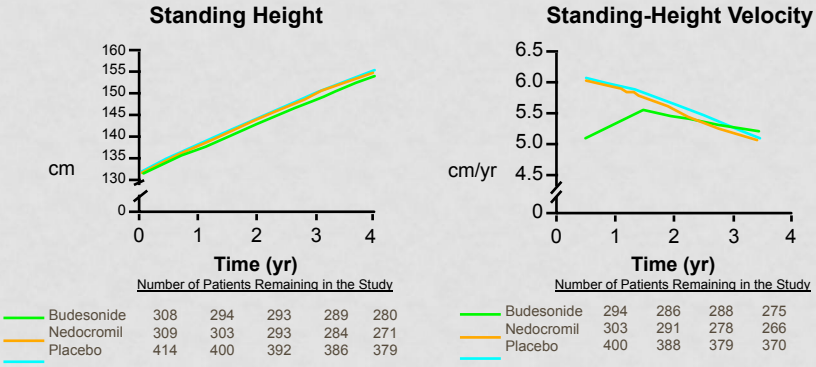
LONG-TERM SAFETY IN ADULTS OPHTHALMIC EXAMINATION

- 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

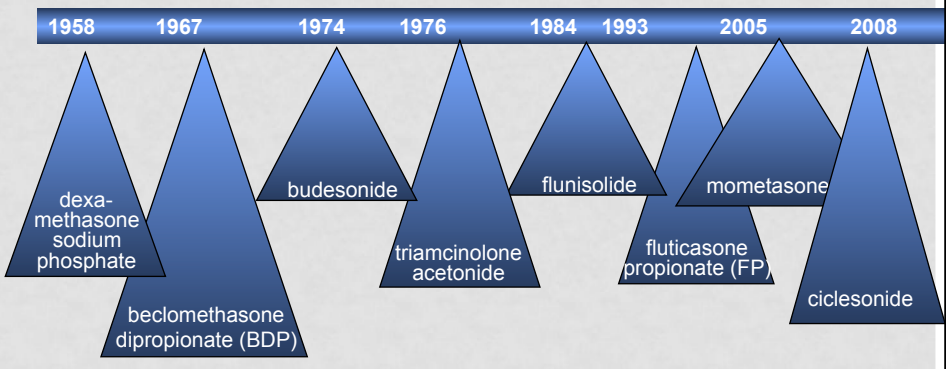
Budesonide	308	294	293	289	280
Nedocromil	309	303	293	284	271
Placebo	414	400	392	386	379

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

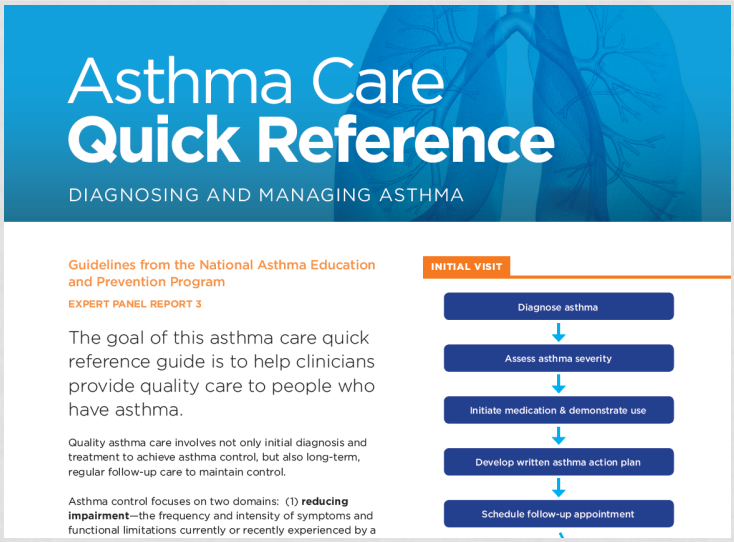
The provider/educator action is:

- 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



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

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