ASTHMA

Symptomatic vs Preventative

	Symptomatic 	Preventative 
Asthma	Acute asthma attack/ symptoms	Exercise-induced Asthma exacerbations
COPD	Acute exacerbation/ symptoms	Smoking cessation COPD exacerbations Pneumonia

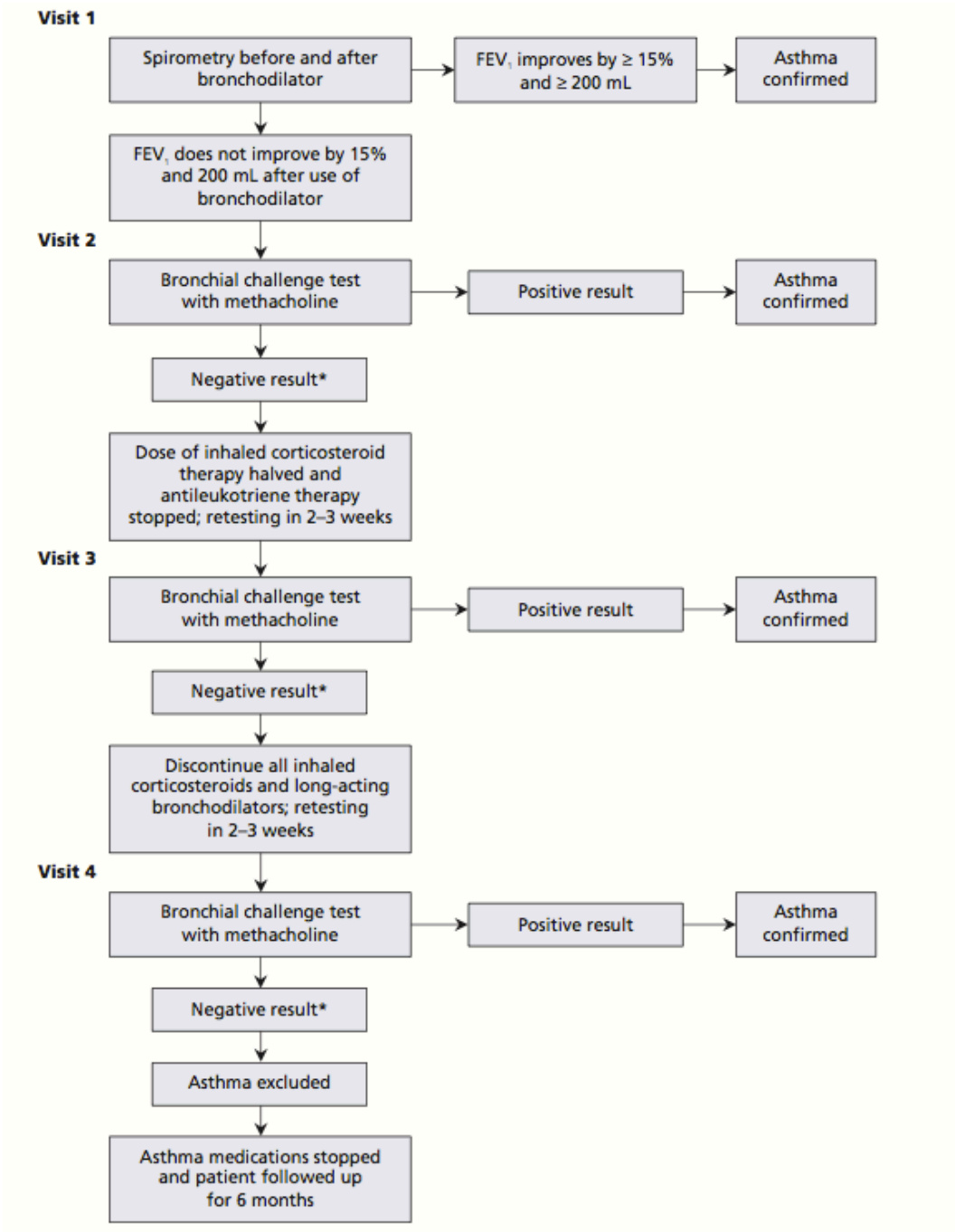
CMAJ RESEARCH

Overdiagnosis of asthma in obese and nonobese adults

Shawn D. Aaron MD, Katherine L. Vandemheen BScN, Louis-Philippe Boulet MD,
R. Andrew McIvor MD, J. Mark FitzGerald MD, Paul Hernandez MD, Catherine Lemiere MD,
Sat Sharma MD, Stephen K. Field MD, Gonzalo G. Alvarez MD, Robert E. Dales MD,
Steve Doucette MSc, Dean Fergusson PhD, for the Canadian Respiratory Clinical Research Consortium

Interpretation: "About one-third of obese and non-obese individuals with physician-diagnosed asthma did not have asthma when objectively assessed. This finding suggests that, in developed countries such as Canada, asthma is overdiagnosed."

CMAJ 2008;179(11):1121-31


Visit 1
Spirometry before and after bronchodilator
FEV1 improves by ≥ 15% and ≥ 200 mL
Asthma confirmed
FEV1 does not improve by 15% and 200 mL after use of bronchodilator
Visit 2
Bronchial challenge test with methacholine
Positive result
Asthma confirmed
Negative result*
Dose of inhaled corticosteroid therapy halved and antileukotriene therapy stopped; retesting in 2–3 weeks
Visit 3
Bronchial challenge test with methacholine
Positive result
Asthma confirmed
Negative result*
Discontinue all inhaled corticosteroids and long-acting bronchodilators; retesting in 2–3 weeks
Visit 4
Bronchial challenge test with methacholine
Positive result
Asthma confirmed
Negative result*
Asthma excluded
Asthma medications stopped and patient followed up for 6 months

"Thus, almost all patients with asthma include wheezing as one of their symptoms compared with about three out of four patients with chronic obstructive pulmonary disease and about three out of ten patients with heart disease."

"The idea that cough can be the sole symptom of patients with asthma is closely linked to the demonstration of nonspecific bronchial hyperresponsiveness in these individuals."

"Sixty percent of patients showed no significant correlation between subjective asthma scores and peak expiratory flow rate measurements."

Clinical vs Surrogate vs Symptomatic outcomes

Symptoms

1. Description

   wheeze, breathlessness, cough, chest tightness, etc.

2. Onset

3. Progression

Severity

A. Severity of symptoms

1. Frequency, number of episodes per day or week

2. Duration

3. Description of typical exacerbation

4. Response to treatment

B. Limitations of daily activity

Walking, distance, pace

Stairs, number of flights

Exercise, sports

Sleep disturbance, early morning symptoms

Daily activity

C. Hospitalizations

Number, frequency, length of stay

Intubation

Intensive care

D. Emergency visits

1. Number, frequency

2. Other unscheduled visits

E. Days lost from work or school

1. School or work performance

F. Medication requirements

1. Systemic corticosteroid use

2. Beta-adrenergic agonist use

   number of puffs per day

   number of canisters per month

3. Inhaled corticosteroids, LABAs, anticholinergics, leukotriene antagonists, cromolyn, theophylline use

4. Changes in medication requirements

G. Tests

1. Previous or home peak flow measurements

2. Previous spirometry

3. Blood gases

4. Pulse oximetry (O2 sat')

Adapted from
Ann Allergy Asthma
Immunol 1996;76:1–14

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3. Progression

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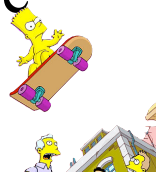
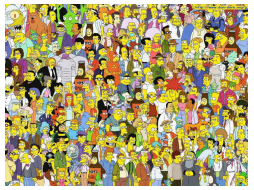
Clinical trial evidence vs Experience



No treatment vs Treatment



Relative vs Absolute benefit

THESE ARE ALSO THE MONITORING PARAMETERS!!!!

Benefit vs Harm vs Cost vs inconvenience

Non-drug

Provoking or triggering factors

1. Exercise
   - timing, duration, severity
   - effect on work, school, recreation
2. Infection
   - frequency, severity
   - response to treatment
3. Allergens
   - seasonal

animals, pets

occupational/home

risk factors for dust mite exposure

related to hobbies, recreation

associated rhinoconjunctivitis

previous allergy testing

4. Irritant

fumes, dust, pollution, smoking, environmental smoke

5. Cold air
   - exercise in cold air
6. Medications

beta-adrenergic blocking agents, aspirin and non-steroidal anti-inflammatory drugs medications for co-morbid medical condition

7. Emotional stress
   - hyperventilation
   - panic attacks
8. Foods
   - sulfites

Alleviating factors

1. Rest, avoidance of physical activity
2. Avoidance of allergens, irritants

"Chemical and physical methods aimed at reducing exposure to house dust mite allergens cannot be recommended. It is doubtful whether further studies, similar to the ones in our review, are worthwhile."

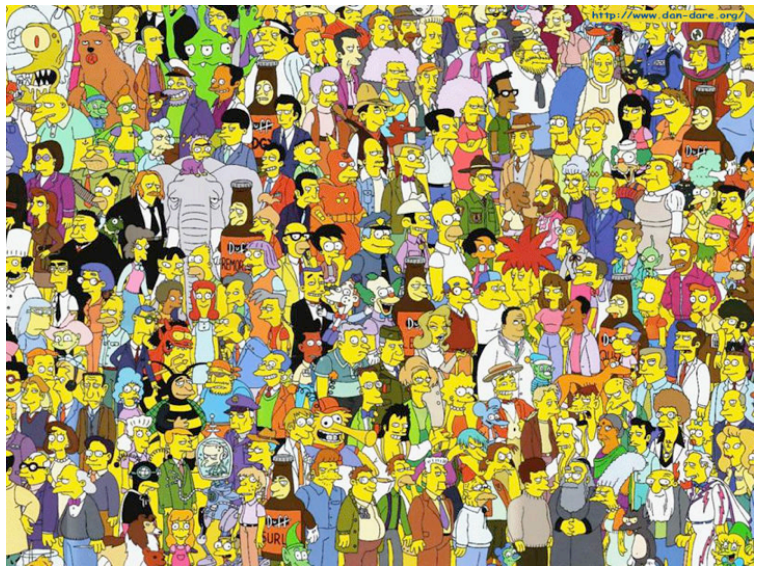
"Whilst recent epidemiological studies suggest that feather bedding is associated with less frequent wheeze than man-made fibre fillings, the evidence currently available is insufficient to assess the clinical benefits of feather bedding in the management of asthma"

Cochrane Library

Most Numbers on the slides are RELATIVE RISK/ODDS RATIO and almost all from the Cochrane Library

VERY ROUGHLY

Baseline = 50%
RR = 0.8
Treatment = 40%
Absolute difference = 10%



Baseline = 10%
RR = 2.5
Treatment = 25%
Absolute difference = 15%

Baseline = 20%
RR = 0.25
Treatment = 5%
Absolute difference = 15%

Benefit vs Harm vs Cost vs inconvenience

ACUTE ASTHMA - baseline 30-50% hospitalization

	BENEFIT	HARM	Costs (choose least expensive)	Inconvenience
O_2	Titrate to achieve O2 sat of at least 93%	100% O_2 - damages lungs over 7-10 days	N/A	Nasal prongs Mask
Short-acting Beta-agonists	Immediate relief	Hypotension, tachycardia, tremor, hypokalemia	Salbutamol Fenoterol Terbutaliine	MDI, Spacer, Nebulized, IV
Short-acting Anticholinergics	Hospitalizations 0.75 RR	Dry mouth	Ipratropium	MDI, Spacer Nebulized
Corticosteroids	3-6 hours izations 0.50 RR	Short term - CNS, glucose	Prednisone Hydrocortisone Methylprednisolone	Oral, IM, IV
	ns 0.81 RR ;24:823–830	Epigastric or facial warmth, flushing, pain, numbness at the infusion site, dry mouth, malaise, hypotension	N/A	IV, Nebulized
	work	Seizures, arrhythmias, GI upset		

ACUTE ASTHMA

	Dose
O_2	not 100% as this may increase PC02 use 40-60% (4-10L/min) Chest 2003;124:1312-17, Thorax doi:10.1136/thx.2010.155259
Short-acting Beta-agonists (SABA	MDI - four puffs over 2 minutes followed by one puff each minute until side effects or until breathing improves - titrate to response
	Nebulized - salbutamol 5 mg repeated every 20 minutes x 3 doses then every 1-2 hours until stable Use 2.5 mg if patient experiences tremor or tachycardia Maintain with 2.5 mg every 4 hours Dilute dose in 4 ml of saline, place in nebulizer with an air flow rate of 6-8 L/min
Short-acting Anticholinergics (SAAC)	Nebulized - 0.5 mg every 20 minutes for three doses followed by 0.5 mg every 2 to 4 hours
Corticosteroids	50mg prednisone PO NOT 40mg 125 mg - 250 mg hydrocortisone IV Q8H 100 mg methylprednisolone IV Q8H

Chronic Asthma
Levels of Asthma Control

TABLE 3 Levels of asthma control

Characteristic	Controlled (all of the following)	Partly controlled (any measure present in any week)	Uncontrolled
Daytime symptoms	None (twice or less per week)	More than twice a week	Three or more features of partly controlled asthma present in any week
Limitations of activities	None (twice or less per week)	Any	Three or more features of partly controlled asthma present in any week
Nocturnal symptoms/ awakening	None	Any	Three or more features of partly controlled asthma present in any week
Need for reliever/rescue treatment	None (twice or less per week)	More than twice a week	Three or more features of partly controlled asthma present in any week
Lung function (PEF or FEV_1)#	Normal	<80% pred or personal best (if known)	Three or more features of partly controlled asthma present in any week
Exacerbations	None	One or more per year¶	One in any week+

PEF: peak expiratory flow; FEV_1: forced expiratory volume in one second; % pred: % predicted. #: lung function is not a reliable test for children aged ⩽5 yrs; ¶: any exacerbation should prompt review of maintenance treatment to ensure that it is adequate; +: by definition, an exacerbation in any week makes that an uncontrolled asthma week.

ALSO SEE www.ginasthma.com

Eur Respir J 2008;31:143-78

Regular terbutaline vs regular budesonide for new-onset asthma

Patients

RDBCT - 103 patients with asthma - mean age 38
- new-onset asthma in last 12 months

Treatment

600 micg budesonide BID or terbutaline 375 micg BID

Duration

2 years

NEJM 1991;325:388-92

	Asthma score (1-10)	Terbutaline (PRN puffs per day)	Withdrew due to lack of effect (%)
Budesonide	2.5 → 1.5	1.25 → 0.5	2
Terbutaline	2.5 → 2.5	1.25 → 1.5	19

Changes seen in first 1-2 weeks

NEJM 1991;325:388-92

Benefit vs Harm vs Cost vs inconvenience

CHRONIC ASTHMA

	BENEFIT	HARM
SABA	**Regular vs intermittent salbutamol** Exacerbations - no difference in major exacerbations Regular - less rescue medication -0.8 puffs/24 hours – also 7% fewer days with asthma symptoms	Hypotension Tachycardia Tremor
Inhaled corticosteroids (ICS) low doses (400 mcg of beclomethasone dipropionate or equivalent)	**Beclomethasone, budesonide** Baseline exacerbations - 50% of patients per year? Baseline withdrawal due to exacerbations - approx 10% over 2-3 months Beclomethasone 0.29 RR Budesonide 0.26 RR PRN puffs salbutamol/day Beclomethasone minus 2.32 Budesonide minus 1.6 “there is currently no evidence to support differences in efficacy [of inhaled corticosteroids] when they are administered at equipotent dosages” Ann Allergy Asthma Immunol 2003;91:326-34, Cochrane Library, issue 2, 2005	LOW DOSES Candidiasis 1-5% Dysphonia 1-5%

Benefit vs Harm vs Cost vs inconvenience

CHRONIC ASTHMA

	BENEFIT	HARM
Long-acting beta agonists (LABA)	Adding to inhaled corticosteroids Baseline risk of exacerbations requiring oral steroids - 15% LABA 0.77 RR Baseline hospitalizations - 1% LABA ND Baseline withdrawals due to poor asthma control or exacerbation - 5% LABA 0.5 RR Change in 24 hour symptom score; PRN puffs salbutamol/day 0.58 less puffs per day	Hypotension Tachycardia Tremor
Leukotriene antagonists (LTRA)	Adding to inhaled corticosteroids - no difference in exacerbations, addition of anti-leukotrienes is associated with superior asthma control after glucocorticoid tapering - fewer withdrawals due to poor asthma control 0.64 RR	Increased LFTs diarrhea, rash abdominal pain Drug Int
SAAC	"this review provides no justification for routinely introducing anticholinergics as part of add-on treatment for patients whose asthma is not well controlled on standard therapies"	Dry mouth
Vaccinations	"very limited evidence to support the routine use of pneumococcal vaccine in people with asthma" "Uncertainty remains about the degree of protection vaccination affords against asthma exacerbations that are related to influenza infection"	

Benefit vs Harm vs Cost vs inconvenience
CHRONIC ASTHMA

	Benefit	Harm
LABA vs LTRA	In adults with asthma that is inadequately controlled on low doses ICS Baseline exacerbations 10% - 0.83/year Steroid treated exacerbations LABA vs LTRA 0.83 RR in favour of LABA AQLQ -0.11 in favour of LABA - 0.5 is the minimally important difference	1.3% increase in serious adverse events with LABA
LABA vs increasing ICS dose	In adolescents and adults with sub-optimal control on low dose ICS Baseline exacerbations 10% Steroid treated exacerbations 0.88 RR in favour of LABA Hospitalization - no difference in hospitalization Baseline withdrawals due to poor asthma control - 3% 0.71 RR in favour of LABA Change in daytime symptom score -0.26 (Score 0-4) , 9% greater symptom free days	LABA increased tremor 1-2% reduced thrush by 1-2%
LTRA vs ICS	In patients with mild to moderate asthma Baseline exacerbations - 5% on ICS Steroid treated exacerbation LTRA 1.65 RR Other significant benefits of ICS were seen for symptoms, nocturnal awakenings, rescue medication use, symptom-free days, and quality of life. Baseline withdrawal due to poor asthma control exacerbations – 2% LTRA 2.58 RR	No difference in side effects

Benefit vs Harm vs Cost vs inconvenience

CHRONIC ASTHMA

	Costs (choose least expensive)	Inconvenience
SABA	Salbutamol, Fenoterol, Terbutaliine	MDI, Spacer
ICS	Beclomethasone, Budesonide, Fluticasone, Ciclesonide	MDI, Spacer, Dry powder
LABA	Salmeterol, Formoterol (also for acute symptoms)	Dry powder
LTRA	Montelukast, Zafirlukast	Oral
ICS/LABA	Fluticasone/salmeterol Budesonide, formoterol	"The seven identified studies in adults did not show any significant difference in safety between formoterol and budesonide in comparison with salmeterol and fluticasone." "The current evidence does not support use of combination therapy with LABA and ICS as first line treatment in adults and children with asthma, without a prior trial of inhaled corticosteroids."

Equipotent daily doses adults

children - about 2/3 of these doses - inconsistent recom'

	Low daily dose (microg)	Med daily dose	High daily dose
Beclomethasone	200-500	"published data provide little support for dose titration above 400 mcg/d in patients with mild to moderate asthma" Cochrane Library	
Budesonide	200-400	X2	X4
Fluticasone	100-250		
Ciclesonide	80-160		5-10 mg? Prednisone

Eur Respir J 2008;31:143–78

Specific Label Changes for Long-Acting Beta-Agonists (LABAs).

1. Contraindicate the use of LABAs for asthma in patients of all ages without concomitant use of an asthma-controller medication such as an inhaled corticosteroid.
2. Stop use of the LABA, if possible, once asthma control is achieved and maintain the use of an asthma-controller medication, such as an inhaled corticosteroid.
3. Recommend against LABA use in patients whose asthma is adequately controlled with a low- or medium-dose inhaled corticosteroid.
4. Recommend that a fixed-dose combination product containing a LABA and an inhaled corticosteroid be used to ensure compliance with concomitant therapy in pediatric and adolescent patients who require the addition of a LABA to an inhaled corticosteroid.

NEJM 2010 - 10.1056/nejmp1002074

Data from 110 trials (60,954 pts) including 11% adolescents and 6% children.
For the primary end-point of asthma-related death, intubation, and hospitalization
Statistically significant increase of 2.8 extra events per 1000 asthmatic patients treated with LABA inhalers - Number needed to harm (NNH) was 358
Tools For Practice - Edmonton, Alberta

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tiotropium Bromide Step-Up Therapy for Adults with Uncontrolled Asthma

Three-way double blind triple dummy crossover - funded by NHLBI

210 patients with asthma

On ICS (80 mcg beclomethasone BID) and randomized to

1.LABA (salmeterol)

2.doubling of ICS

3.tiotropium

14 weeks on each therapy

Predetermined secondary outcome measures

the number of asthma-control days, asthma symptoms, rescue-bronchodilator use, asthma exacerbations, use of health care services, biomarkers of airway inflammation, and results of validated questionnaires

NEJM 2010;Sept 19

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tiotropium Bromide Step-Up Therapy for Adults with Uncontrolled Asthma

Tiotropium – of the clinical endpoints all but the albuterol use was improved from baseline

LABA - all were improved for salmeterol

Double dose ICS – only improvement was proportion of asthma controlled days

The average change in the questionnaires were all less than the minimum importance difference

Tiotropium=salmeterol >double dose of ICS

Not enough patients to see a difference in exacerbations

NEJM 2010;Sept 19

Two studies - real world effectiveness - open label

2 years - average age 45-50 - 40-50% male

Initiation - LTRA or ICS

Add-on - ICS (12 weeks) then LTRA or LABA

LTRA (montelukast or zafirlukast); inhaled glucocorticoid (beclomethasone, budesonide, or fluticasone); LABA (salmeterol or formoterol)

"Study results at 2 months suggest that LTRA was equivalent to an inhaled glucocorticoid as first-line controller therapy and to LABA as add-on therapy for diverse primary care patients. Equivalence was not proved at 2 years"

"Exacerbation rates and ACQ scores did not differ significantly between the two groups."

N Engl J Med 2011;364:1695-707

288 patients with mild persistent asthma - 44 week trial - average age 11- 55% male

4 treatments - placebo controlled

Beclo = beclomethasone 80 micrograms a day total

1 - COMBINED - BID beclo PLUS beclo/salbutamol for rescue

2 - DAILY - BID beclo PLUS salbutamol for rescue

3 - RESCUE - No maintenance PLUS beclo/salbutamol for rescue

4 - NO MAINTENANCE - just salbutamol for rescue

Rescue for all groups was two puffs as needed for symptom relief

Lancet 2011, 377:650-7

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Lancet 2011, 377:650-7

	Exacerbations (%) - required prednisone	Treatment failure (%) - two courses of prednisone
Combined	31	5.6
Daily	28	2.8
Rescue	35	8.5
No maintenance	49	23

Asthma control days - no difference between the groups

Children in the regular beclomethasone group grew 1.1 cm less

Children in the rescue group used 15-25% of the total beclomethasone used in the daily group

ASTHMA ACTION PLAN (EXAMPLE 1)

Name_____ Date_____

It is important in managing asthma to keep track of your symptoms, medications, and peak expiratory flow (PEF).
You can use the colors of a traffic light to help learn your asthma medications:

A. **GREEN means Go** Use preventive (anti-inflammatory) medicine
B. **YELLOW means Caution** Use quick-relief (short-acting bronchodilator) medicine in addition to the preventive medicine.
C. **RED means STOP!** Get help from a doctor.

A Your **GREEN ZONE** is_____80 to 100% of your personal best. GO!
Breathing is good with no cough, wheeze, or chest tightness during work, school, exercise, or play.

ACTION:

☐ Continue with medications listed in your daily treatment plan.

B. Your **YELLOW ZONE** is_____50 to less than 80% of your personal best. CAUTION!
Asthma symptoms are present (cough, wheeze, chest tightness).
Your peak flow number drops below_____or you notice:

☐ Increased need for inhaled quick-relief medicine
☐ Increased asthma symptoms upon awakening
☐ Awakening at night with asthma symptoms
☐ _____

ACTIONS:

☐ Take _____ puffs of your quick-relief (bronchodilator) medicine_____.
Repeat _____ times.
☐ Take _____ puffs of _____ (anti-inflammatory) _____ times/day.
☐ Begin/increase treatment with oral steroids:
Take _____ mg of _____ every a.m. _____ p.m._____ .
☐ Call your doctor (phone) _____ or emergency room _____.

C. Your **RED ZONE** is _____50% or less of your best. DANGER!!
Your peak flow number drops below _____ , or you continue to get worse after increasing treatment according to the directions above.

ACTIONS:

☐ Take _____ puffs of your quick-relief (bronchodilator) medicine_____. Repeat _____ times.
☐ Begin/increase treatment with oral steroids. Take _____ mg now.
☐ Call your doctor now (phone _____). If you cannot contact your doctor, go directly to the emergency room (phone _____).
Other important phone numbers for transportation_____.

AT ANY TIME, CALL YOUR DOCTOR IF:

☐ Asthma symptoms worsen while you are taking oral steroids, or
☐ Inhaled bronchodilator treatments are not lasting 4 hours, or
☐ Your peak flow number remains or falls below _____ in spite of following the plan.

Physician Signature_____ Patient's/Family Member's Signature_____

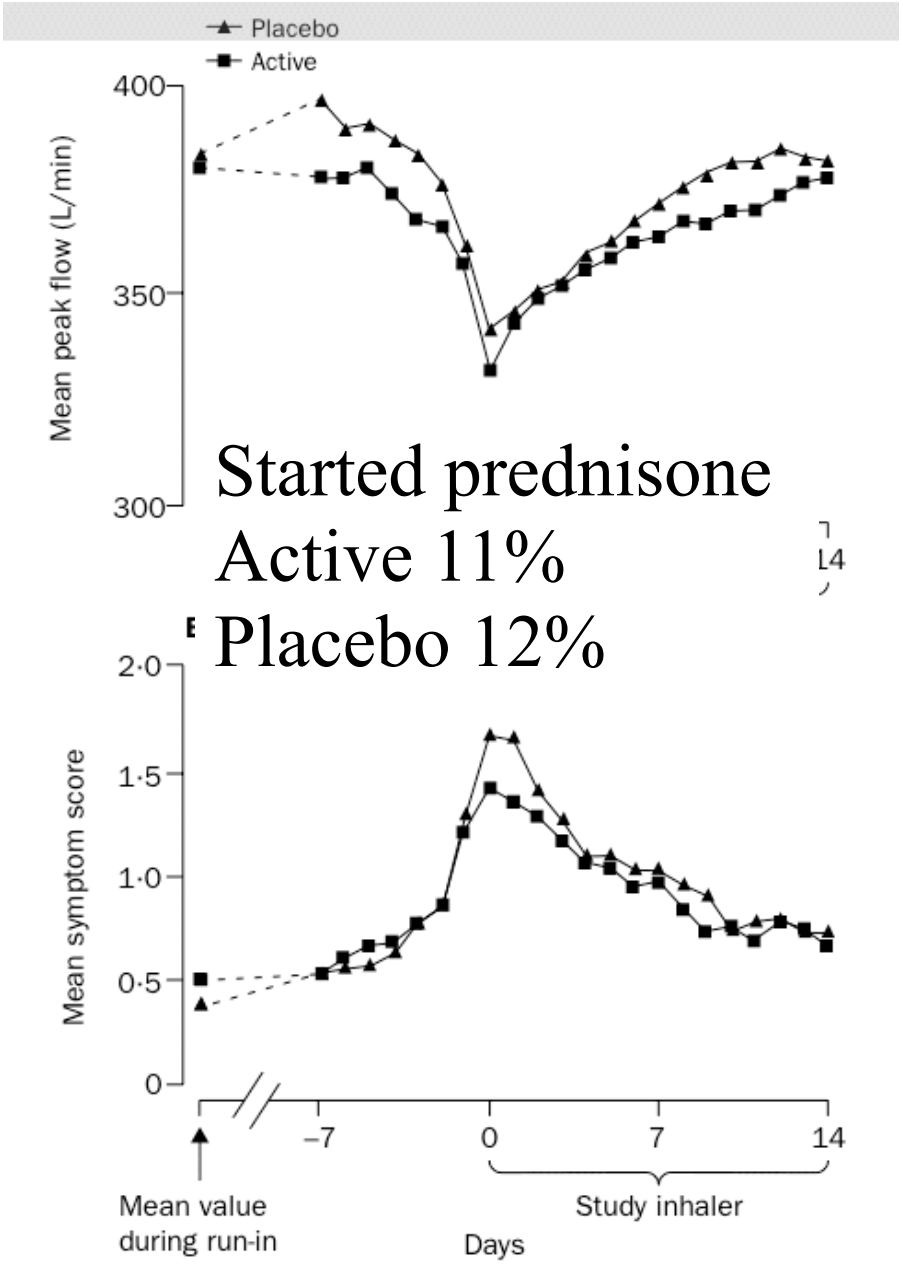
390 patients with asthma followed for 1 year

Instructed to double their dose if FEV dropped by >15% or symptoms increased by more than 1 point on a 4 point scale

Approx - 50% had an "exacerbation"

Lancet 2004; 363: 271-5

"In adults with asthma on daily maintenance ICS, a self-initiated ICS increase to 1000 to 2000 mcg/day at the onset of an exacerbation is not associated with a statistically significant reduction in the risk of exacerbations requiring rescue oral corticosteroids" Cochrane Library



Quadrupling the Dose of Inhaled Corticosteroid to Prevent Asthma Exacerbations: A Randomized, Double Blind, Placebo Controlled, Parallel Group, Clinical Trial

Am J Respir Crit Care Med. 2009 Jul 9. [Epub ahead of print

The right approach?

Salbutamol used when symptomatic and preventing exercise-induced asthma

"all patients with mild persistent asthma deserve the opportunity to decide whether the benefit from their use (ICS) is worth the effort of taking a very safe medication, usually once daily" Am J Res Crit Care Med 2005;172:410-2

Maybe use ICS seasonally or situationally?

Start with a low dose of inhaled corticosteroids - 200-400 mcg beclomethasone equiv - daily, twice daily? - always reassess

Then a LABA - but maybe LTRA/tiotropium - INDIVIDUALIZED

Combination product used if individual agents used together improved control

Exacerbations - use more salbutamol - maybe quadruple dose of ICS?